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# Cervical screening awareness week integrating cervical cancer screening and precancer treatments

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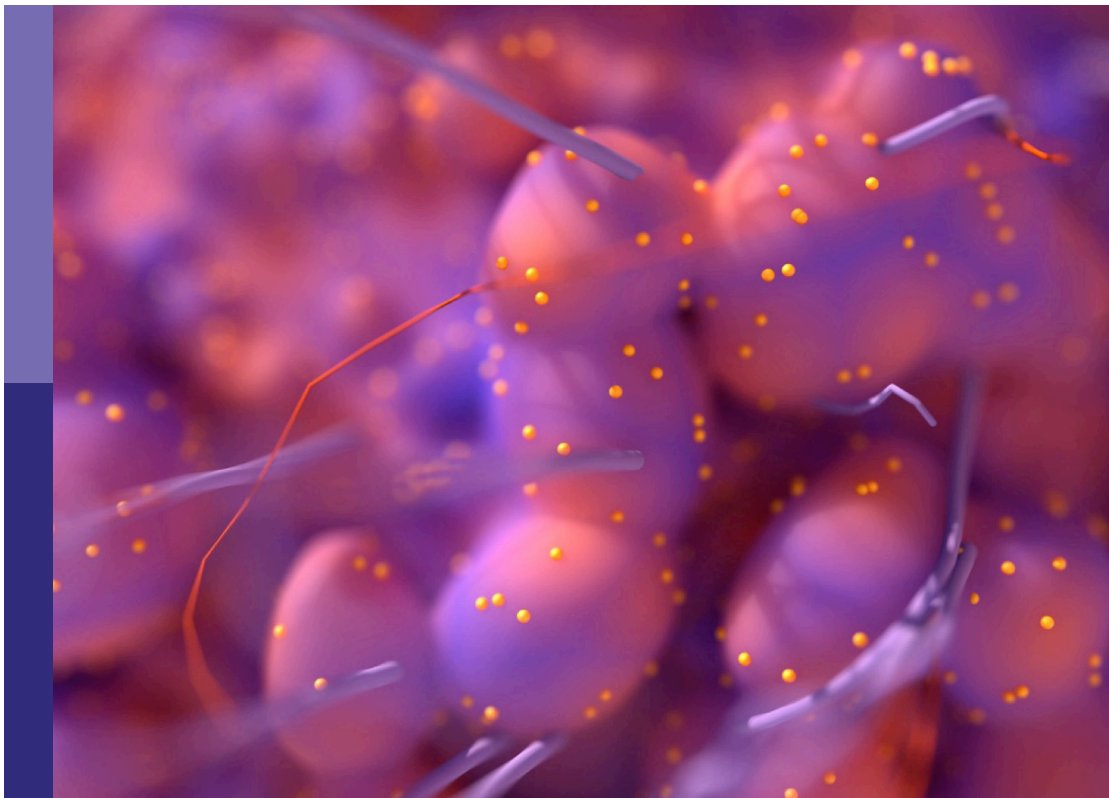

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# Cervical screening awareness week 2023: integrating cervical cancer screening and precancer treatments

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# Editorial: Cervical screening awareness week 2023: integrating cervical cancer screening and precancer treatments

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Editorial on the Research Topic
Cervical screening awareness week 2023: integrating cervical cancer screening and precancer treatments

## Introduction

Despite effective methods to both prevent and screen for cervical cancer, invasive cervical cancer (ICC) remains a leading cause of morbidity and mortality globally. While the incidence of ICC and mortality secondary to ICC has declined dramatically in high-income countries (HICs) – these gains are not universal. Indeed, ICC is the most common cause of cancer-related death in many low-and-middle-income countries (LMICs). As such, there is an urgent need to develop and implement locally relevant interventions to achieve the World Health Organization (WHO) 90-70-90 cervical cancer elimination targets. The WHO aims to vaccinate 90% of girls, screen 70% of women, and treat 90% of women with cervical disease by 2030, however novel efforts are necessary to achieve these ambitious goals (1). Here, we highlight strategies which target cervical cancer awareness, screening, prevention, and treatment – in an economically sustainably fashion.

## Awareness

Given the relatively low rates of cervical cancer screening in Ethiopia, Yosef et al. via a hospital-based case-control study demonstrated that knowledge of cervical cancer screening and proximity to the health facility were associated with cervical cancer screening. Recognizing the vital need of cancer awareness, Ouedraogo et al. organized a workshop, consisting of representatives from the relevant stakeholders-including government, non-governmental organizations, civil society organizations, and academic/research organizations, to craft and tailor effective health education and communication strategies.

## Screening

To assess the availability and capacity of cervical cancer screening and treatment services in Kenya, Mwenda et al. conducted a sub-national survey of healthcare workers in over 3,000 hospitals. Only 5% of hospitals provided both cervical cancer screening and treatment services – a disparity which will need to be addressed in order to achieve the WHO targets.

## Prevention

The prevention of cervical cancer incorporates both primary prevention strategies, via an effective vaccine, as well as secondary prevention, via treatment of pre-cancerous lesions. To inform the implementation of the most effective vaccine, Kebede et al. describe the prevalence and variation of HPV genotypes. Given that prevalence of genotypes which are not included in the commonly used bivalent or quadrivalent HPV vaccine, such information can help advocate for nonavalent vaccine.

Hypothesizing that with increased utilization of the HPV vaccines, the genotypes of HPV may vary among those vaccinated and those unvaccinated Yang et al. conducted a study among women with atypical squamous cells of undetermined significance (ASCUS). These researchers concluded that genotype identification may inform the choice of triage options for women identified to have ASCUS lessions on cervical cytology screening. Although the goal to increase HPV remains, cost-effective triage strategies are particularly necessary in resource-limited regions.

Lee et al. explored the feasibility and acceptability among women undergoing various HPV-based screen-triage-treatment options, including self-collected vaginal samples. These researchers offer specific strategies, including the need for health education to optimize perspectives and utilization of cervical cancer prevention services. To minimize the invasive procedures, Qian et al. investigated the safety and efficacy of the non-invasive 5-aminolevulinic acid photodynamic therapy (ALA-PDT) in the treatment of high-grade squamous intraepithelial lesions. Although ALA-PDT has been used in low-grade squamous intraepithelial lesions, these researchers found that the treatment was safe – with no severe adverse effects, as well as effective – with a 12-month complete regression rate of over 80%.

Mungo et al. conducted focus group discussions to learn of men's perspectives on their female partner's use of topical therapies for pre-cancerous lesions. These colleagues also encourage health education strategies which reach the partners of patients undergoing cervical precancer treatment.

Given the need for cost-effective strategies for the diagnosis and treatment of cervical cancer and pre-cancerous lesions and recognizing the pathogenesis of cervical cancer, Gong et al. developed a Classification of Lesion Stages (CLS) algorithm to predict the risk of cervical cancer. The use of such technology may optimally triage patients with pre-cancer lesions, reduce the number of unnecessary procedures, and potentially alleviate the burden on health systems.

Although the screening modalities vary among resource-abundant and resource-limited regions, the benefits of resource-relevant screening are clear. An obvious challenge of cervical cancer screening programs is the limited funds dedicated to cancer prevention. Tran et al. utilized a simulation model of the current standard of care (i.e. cytology and colposcopy triage) with various scenarios calculated the disability-adjusted life-years (DALYs) averted for each scenario. These researchers demonstrated that repeat HPV DNA testing was associated with the highest DALY averted.

Clinical services in LMICs are often funded and provided in a vertical fashion with the appropriate integration of relevant infrastructure (2, 3). Because many health systems do not have a primary care model of service delivery, there has been increased recognition of the need to leverage and incorporate non-communicable disease (NCDs) care, including cancer care, within the existing routine services. The benefit of such integration has been demonstrated for certain NCDs, including hypertension and diabetes (4, 5). However, despite the clinical burden, such an integrated approach has not been fully implemented for the early detection of cervical cancer and precancer care treatment.

The articles in this Research Topic highlight the burden of cervical cancer as well as necessary strategies to decrease the toll which disproportionately impacts LMICs. Although effective vaccines to prevent cervical cancer and screening techniques to identify pre-cancerous lesions exist, disparities persist with regard to clinical access. As such, the unnecessary burden cervical cancer remain. Further cost-effective efforts to incorporate the findings demonstrated in this Research Topic and specifically integrate cervical cancer screening and precancer treatment programs within existing health care programs are necessary to achieve the WHO cervical cancer elimination targets.

## Author contributions

NM: Writing – original draft, Writing – review & editing. LP: Writing – review & editing. MM: Writing – review & editing, Writing – original draft.

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# Predicting cervical intraepithelial neoplasia and determining the follow-up period in high-risk human papillomavirus patients

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**Purpose:** Despite strong efforts to promote human papillomavirus (HPV) vaccine and cervical cancer screening, cervical cancer remains a threat to women's reproductive health. Some high-risk HPV types play a crucial role in the progression of cervical cancer and precancerous lesions. Therefore, HPV screening has become an important means to prevent, diagnose, and triage cervical cancer. This study aims to leverage artificial intelligence to predict individual risks of cervical intraepithelial neoplasia (CIN) in women with high-risk HPV infection and to recommend the appropriate triage strategy and follow-up period according to the risk level.

**Materials and methods:** A total of 475 cases were collected in this study. The sources were from the Department of Gynecology and Obstetrics in a tertiary hospital, a case report on HPV from the PubMed website, and clinical data of cervical cancer patients from The Cancer Genome Atlas (TCGA) database. Through in-depth study of the interaction between high-risk HPV and its risk factors, the risk factor relationship diagram structure was constructed. A Classification of Lesion Stages (CLS) algorithm was designed to predict cervical lesion stages. The risk levels of patients were analyzed based on all risk factors, and follow-up periods were formulated for each risk level.

**Results:** Our proposed CLS algorithm predicted the probability of occurrence of CIN3—the precancerous lesion stage of cervical cancer. This prediction was based on patients' HPV-16 and -18 infection status, age, presence of persistent infection, and HPV type. Follow-up periods of 3–6 months, 6–12 months, and 3- to 5-year intervals were suggested for high-risk, medium-risk, and low-risk patients, respectively.

**Conclusion:** A lesion prediction model was constructed to determine the probabilities of occurrence of CIN by analyzing individual data, such as patient lifestyle, physical assessments, and patient complaints, in order to identify high-risk patients. Furthermore, the potential implications of the calculated features were mined to devise prevention strategies.

KEYWORDS

**follow-up period, human papillomavirus, cervical intraepithelial neoplasia, prediction, genotype, cervical cancer**

# 1 Introduction

Global statistics on cancer in women indicate that cervical cancer ranked fourth in both incidence and mortality rate in 2012 (1). In 2020, there were over 604,000 cervical cancer cases and 341,000 deaths worldwide (2). The efficacy of vaccination and screening in preventing cervical cancer has been established, leading to increased awareness and participation in prevention programs among women. However, globally, the incidence and mortality rates of cervical cancer remain substantially higher in low-income and middle-income countries than in high-income countries; this is attributed to the lack of vaccination coverage, high-quality screening, timely treatment, and follow-up care services. A priority for public health managers worldwide is to take proactive measures to address the need for continuous and improved prevention and monitoring of cervical cancer. This aligns with the targets of the World Health Organization elimination initiative launched in 2020 to reduce cervical cancer incidence to below four cases per 100,000 women-years in every country (3). Furthermore, advancements in effective disease prediction and diagnosis are crucial for accurately identifying the target population.

Persistent high-risk HPV infection is recognized as the primary cause of CIN and cervical cancer. The pathogenesis of cervical cancer involves a prolonged period of development of precancerous lesions, such as the CIN1, CIN2, and CIN3 stages. The risk of developing invasive cervical cancer associated with CIN 1, CIN2, and CIN3 is 4 times, 14.5 times, and 46.5 times, respectively, higher than that of non-CIN. While most CIN 1 lesions resolve naturally, CIN2 and CIN3 incur the risk of malignant transformation (4–6). Studies, including randomized clinical trials, have indicated that HPV-based screening—characterized by high sensitivity and long-term negative predictive value—plays a significant role in primary screening methods, along with cervical cytology, in identifying potential cervical cancer cases and triage (7–9). Additionally, electronic colposcopy of the cervix and cervical biopsy are employed to determine the cervical lesion stage based on primary screening results. However, it is not advisable for all patients to directly undergo biopsy due to its associated low detection rate, wastage of medical resources, and invasive nature of biopsies. Therefore, accurate prediction of the risk of cervical lesions holds crucial clinical implications for early diagnosis and prevention of cervical cancer.

There are still some challenges in predicting cervical cancer, such as missing data in medical records and transient HPV infection. Poor data quality affects the accuracy of prediction. The uncertainty of the prediction model and the deficiencies in the data would lead to poor performance of the model during prediction and affect the reliability of the prediction results. In recent years, artificial intelligence (AI) has been gradually applied in the field of clinical medicine, especially in disease diagnosis and detection, for greater ability of learning and strong potentials in data processing (10–12). The application of AI is conducive to reducing the rate of missed diagnoses, saving more time, and improving accuracy for clinicians. AI technology has greatly improved the diagnostic accuracy of lung cancer and breast cancer through training CT and ultrasound images (13, 14). AI liquid-based cytology has resulted in efficient referrals to colposcopy, with higher specificity than manual screening methods (15). The Colposcopic Artificial Intelligence Auxiliary Diagnostic System has been explored to classify colposcopic impressions and suggest biopsies (16). AI technology can not only overcome the limitations of doctors' subjective judgment and personal biases in diagnosis but also improve the accuracy of diagnosis and help to locate the lesion site (17–20). In the context of driving continuous progress in medical technology, there is an urgent need for an efficient and accurate method to determine the probabilities of occurrence of CIN through analysis of individual data such as information on lifestyle, physical assessments, and complaints so that high-risk patients can be identified and the potential implications of calculated features can be mined for further prevention strategies.

# 2 Materials and methods

## 2.1 Study design

The pathogenesis of cervical cancer usually involves a long period during which precancerous lesions (such as CIN3) form, mainly caused by persistent infection with high-risk HPV. The aim of this research is to achieve early detection of the predisposing factors for precancerous lesions, based on high-risk HPV infection, and implementation of preventive patient interventions. Data preprocessing—including dataset construction and mapping and mining of impact factors, along with the CLS algorithm proposed in our research—enabled prediction of cervical lesions, exploration of predictive indicators, and risk classification of CIN. The findings yield valuable suggestions for the formulation of guidelines for patient follow-up periods at all levels and for advance implementation of preventive interventions, to effectively enable precise prevention strategies and reduce the probability of occurrence of cervical cancer (Figure 1).

## 2.2 Data preprocessing

### 2.2.1 Datasets

The experimental environment is as follows: Python 3.7, Neo4j, and NetworkX 2.1 are configured under a Windows 10 operating system. Three Hadoop-distributed clusters of the CentOS 7 operating system were built, namely, HDFS, YARN, and Spark on YARN. A dataset constructing structure of the diagram for risk factors was collected by using crawler tools from the PubMed website, searching high-risk HPV, cervical cancer, HPV risk factor, and other similar terms, as literature retrieval words. The search yielded 2,221 pieces of medical literature.

The case data were collected mainly on the basis of cases with high-risk HPV infection and lesions, cases with high-risk HPV infection but no lesions, cases without high-risk HPV infection but lesions (i.e., cases that tested HPV-negative, but with lesions), and cases without high-risk HPV infection and no lesions.

A total of 475 cases were collected in this study. The sources were as follows: the Department of Gynecology and Obstetrics at

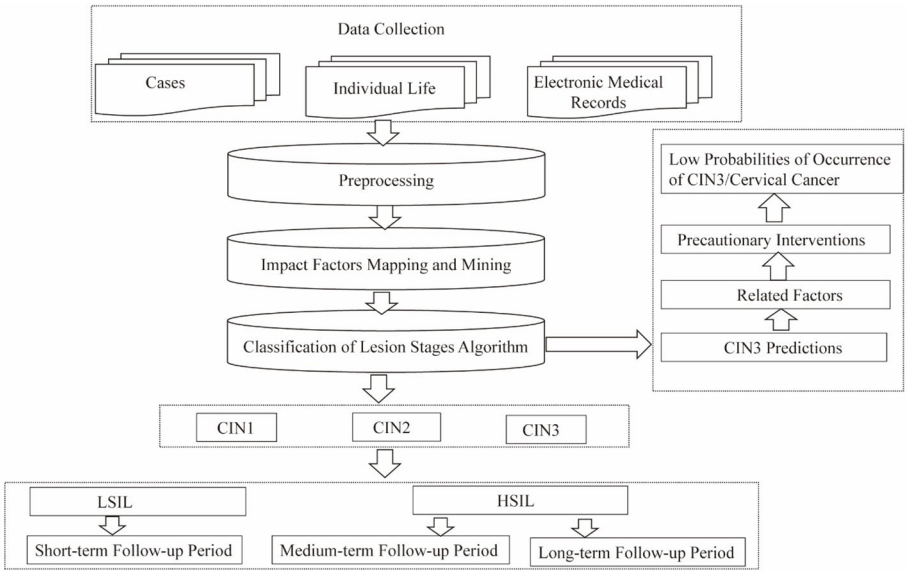


FIGURE 1
Mapping and mining of impact factors.

Jilin Central General Hospital, case report articles about HPV on the PubMed website, and clinical data for cervical cancer in The Cancer Genome Atlas (TCGA) database.

### 2.2.2 Mapping of key risk factors

The electronic medical record text, which is different from ordinary text, usually has a relatively complete structure, including patients' personal information, main complaints, personal history, physical examination results, and auxiliary examination results, with little noise data. Examples of the style of entries include "the patient had vaginal bleeding one month ago," "denied history of drug allergy," and "denied familial inherited diseases". Therefore, the set of keywords for patient case data can be obtained by natural language processing methods. Key words representing textual information were directly extracted—e.g., "vaginal bleeding" for "the patient had vaginal bleeding one month ago"—and numerical information was extracted according to the rules shown in Table 1.

TABLE 1 Extraction Rules for Abnormality of Risk Factors.

| Risk Factors | Extraction Rules for Abnormality |
|---|---|
| Age | > 30 years |
| Age at Menarche | > 14 years or <12 years |
| Age at First Sexual Intercourse | < 18 years |
| Number of Sexual Partners | >2 |
| Age at First Full-term Pregnancy | <18 years |
| Number of Vaginal Births | > 2 |
| Number of Pregnancies | > 2 |

## 2.3 Method

### 2.3.1 Classification of the lesion stage algorithm

The challenges involved in predicting lesion stage by machine learning methods involve determining what kind of data and what kind of features to analyze and calculate. The corresponding test values for patients are commonly used for training and analysis in machine learning methods, which poses great obstacles due to insufficient amount of data. The larger the amount of data and the more values available in machine learning, the more accurate the training is. However, there are many missing values and few positive samples when collecting data, which causes failures of application of many disease prediction models. Therefore, the mechanism of the disease should be fully considered when selecting features to enable more accurate prediction. The Classification of Lesion Stages (CLS) algorithm proposed in this study gives full consideration to the pathogenic mechanism and selects appropriate features for analysis, which has practical significance for the prediction of cervical lesions.

### 2.3.2 Types of high-risk HPV and classification of lesion stages

There are more than 100 types of high-risk HPV; 16 common types, namely, HPV-16, -18, -58, -52, -31, -51, -33, -35, -56, -26, -39, -53, -66, -67, -70, and -45, were analyzed and used for the calculations in this study, as nodes in the structure of the risk factor graph and connected with many other factors.

Cervical lesions are divided into three grades: CIN1, CIN2, and CIN3. The CIN3 stage has a high probability of transformation into cervical cancer. In 2014, the World Health Organization reclassified it into low-grade squamous intraepithelial lesion (LSIL) and high-grade squamous intraepithelial lesion (HSIL), further simplifying the original classification. LSIL refers to the original CIN1 stage, and HSIL includes the original CIN2 and CIN3 stages. In this study,

both classification methods were adopted in the analysis and calculation stage, which was conducive to more detailed analysis. We described the differences in neighbor risk factor nodes and neighbor HPV genotypes between CIN1, CIN2, and CIN3. The factors with node relation value greater than 3 were selected as close factors, among which differences were compared and the degree of difference was calculated.

### 2.3.3 Prediction of lesion stages

Based on the set of key risk factors, we extracted the risk factors that were abnormal in case history and the HPV types with which the patient was infected by natural language processing. According to the principle of abnormal extraction of risk factors, we identified key risk factors for patients with abnormal p collection $AF_p = \{af_1, af_2, \ldots\ldots, af_n\}$, including patients' HPV types and their risk factors that were abnormal. The predictive value of a patient's classification relative to CIN1 was calculated by the following Equation 1.

$$CIN1_p = \sum_{m=1}^{n} W_{(AF_m, cin1)} \quad (1)$$

When the abnormal factors for a patient included those in *cin2Element* or *cin3Element*, it indicated that the patient had factors unique to CIN2 or CIN3. To describe this difference, the degree of difference was introduced to calculate the extent of difference of CIN2 or CIN3 relative to CIN1 in the current situation for each patient, using Equation 2. Abnormal factors as unique ones that appeared in CIN2 or CIN3 were remembered as $CIN2ELE_p = \{cin2Ele_{(p,1)}, cin2Ele_{(p,2)}, \ldots\ldots, cin2Ele_{(p,n)},\}$, $CIN3ELE_p = \{cin3Ele_{(p,1)}, cin3Ele_{(p,2)}, \ldots\ldots, cin3Ele_{(p,n)},\}$。

$$Diff_{(p,\ cin2)} = \frac{\sum_{m=1}^{n} W_{(cin2Ele_{(p,m)}, cin2)}}{n} \quad (2)$$

$W_{(cin2Ele_{(p,m)}, cin2)}$—connected edge weights of factor *of cin2Ele*$_{(p,m)}$ and CIN2 in risk factors—figure structure.

*n*— number of elements in $CIN2ELE_p Diff_{(p,cin2)}$—degree of difference in patients' p between CIN2 and CIN1.

The degree of difference in patients with p between CIN3 and CIN1 $Diff_{(p,cin2)}$ was calculated in the same way.

The degree of difference calculation should be introduced into the classification predicted value of CIN2 or CIN3, which is calculated by Equations 3, 4.

$$CIN2_p = Diff_{(p,\ cin2)} * \sum_{m=1}^{n} W_{(AF_m, cin2)} \quad (3)$$

$$CIN3_p = Diff_{(p,\ cin3)} * \sum_{m=1}^{n} W_{(AF_m, cin3)} \quad (4)$$

From the above calculation, the three classification predictive values of patient "p" can be obtained. In order to more accurately determine which category the patient belongs to, the risk level of the patient is introduced into the analysis. Patients at a low-risk level—which means that their risk of infection with high-risk HPV is very low—have low possibility of cervical lesion. Therefore, we predict that patients at a low-risk level will be disease-free (CIN−). In high-risk patients, i.e., those with a high risk of infection with high-risk HPV, the likelihood of lesions is also high. The prediction result with the largest predictive value of the three-stage classification is selected as the final prediction result. If the maximum value is the predicted value FOR CIN2 or CIN3, it is classified as HSIL; if the maximum value is the predicted value FOR CIN1, it is classified as LSIL. For intermediate-risk patients, this analysis is somewhat difficult, because for these patients, the risk level value is around 0.5, which represents an almost risk of occurrence of HSIL or LSIL. Patients in this category require more cautious management. In order to reduce the rate of missed diagnoses rate, degree of difference analysis is conducted in the present study. If the value of the degree of difference of patients with CIN2/CIN3 is greater than 2 at any stage, it is identified as a large difference and directly classified as HSIL because the possibility of CIN2/CIN3 stage is stronger. If the value of degree of difference is not greater than 2 at either stage of CIN2/CIN3, the patient does not have a high stage difference. In this scenario, identification as CIN1 and classification as LSIL is more likely.

## 3 Results

### 3.1 Follow-up period

After calculating risk levels for all patients, follow-up periods for patients at different risk levels were statistically analyzed (Figure 2). Each blue circle represents the suggested follow-up period for a patient at a high level of risk, green ones show follow-up periods for patients at medium risk, and beige ones represent suggested follow-up periods for patients at low risk. There was a clustering of data at different levels.

After summarizing the data for the above groups, the follow-up periods for patients at different risk levels were obtained. Respectively, for high-risk, medium-risk, and low-risk patients, follow-up at 3 to 6 months, 6 to 12 months, and 3 to 5 year intervals was suggested (Table 2).

### 3.2 Prediction of CIN

The 16 types of high-risk HPV, CIN1, CIN2, and CIN3 exist in the risk factor graph structure as nodes connected with many other factors, and the weight of the edge represents the closeness between them and the risk factors. The neighbor nodes in the graph structure were used to observe the relevant factors for different disease stages and the nodes' characteristics. The names and edge weights of key risk factors and high-risk HPV types that were directly related to CIN1, CIN2, and CIN3 were the output. CIN3 node's top-5 neighbor nodes and their relationship values are addressed as below (Table 3).

The risk classification of each patient warranted consideration. In addition, for lesions at different stages, their close risk factor neighbor nodes and the relationship value was different. Consideration of the difference of factors at different stages was conducive to better classification and prediction of patients' lesions.

The values of the relationship with the CIN3 weight of all the top-5 neighbor nodes were between 3 and 3.005, which means that

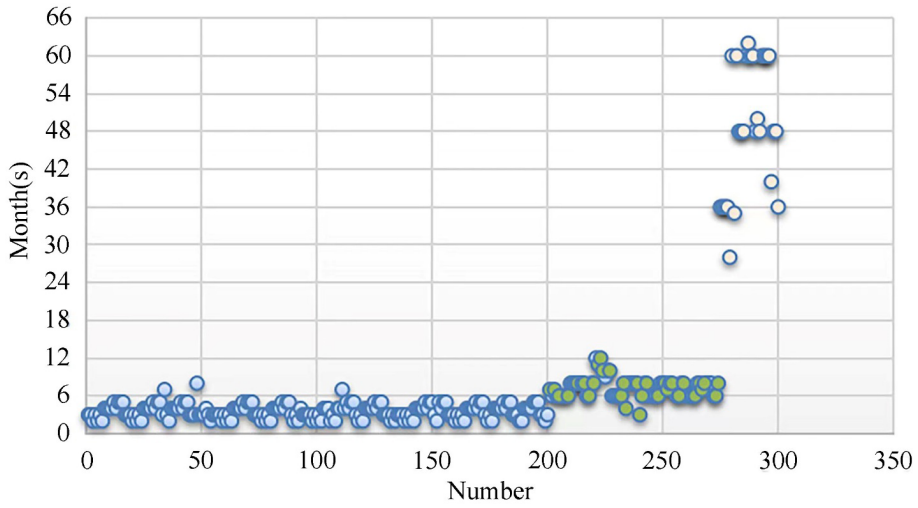


FIGURE 2
Follow-up periods for patients at the three risk levels (Blue: Low-risk Level, Green: Medium-risk Level, Beige: High-risk Level).

the factors were reliable predictive parameters for CIN3; in order, they were HPV-16, HPV-18, age, persistent HPV infection, and HPV type. HPV type and infection represent four of the five closest neighbor nodes of CIN3. Obviously, factors closely related to HPV made a large contribution to precancerous progression. The top two factors were the two high-risk genotypes 16 and 18, in line with current studies that consider them the predominant causes of precancer or cervical squamous cell carcinoma. In recent years, extant works have yielded similar results as our study: HPV subtypes in different age groups and different regions have different characteristics, according to epidemiological statistical data. Moreover, the differences also reflect the different levels of cervical lesions (21).

When analyzing the CLS and identifying related risk factors and high-risk HPV types, we found that different lesion stages had different correlations with high-risk HPV types. Three genotypes, mentioned in Table 4, describe CIN1-related high-risk HPV and relation value with CIN1. In descending order of risk, they are HPV-18, -16, and -45. The top two values are above 3.0, which is remarkably higher than the value for HPV 45. It is suggested that HPV 18 has the closest relationship with CIN1 and HPV 45 takes the third place with a relatively low value.

As shown in Table 5, CIN2-related high-risk HPV genotypes include those found in CIN1 as well as HPV 31. HPV 16 is the primary type. The relation values with CIN2 for HPV-16 and -18 are greater than 3.0, although the values for HPV-31 and -45 are just over 1.0. Evidently, HPV-16 and -18 are predominant factors leading to CIN2 among high-risk HPV genotypes. Despite the values for the other genotypes not being as high, HPV-31 and -45 emerge, among many other genotypes, as CIN2-relevant high-risk HPV genotypes.

Calculations implicate 14 genotypes as causes of CIN3 from the perspective of high-risk HPV (Table 6). They can be divided into three echelons according to relation value with CIN3 ≥3.0, ≥2.0 and<3.0, and ≥1.0 and<2.0. In the first echelon, HPV-16 and -18 display the most intimate relationship with CIN3. HPV-58 and -31 appear in the second echelon and HPV-52, -56, -66, -51, -39, -35, -33, -45, and -26 emerge in the third echelon, in descending order.

CIN3 was correlated with multiple high-risk HPV types; in other words, when these high-risk HPV types occur, there is a greater probability of development of CIN3. At the same time, we found that HPV-16 and -18 have a strong impact on each of the three stages. A number of studies over the years have also shown that these two HPV genotypes are associated with the highest risk of occurrence of lesions and even cervical cancer, and the three common types of cervical cancer vaccines inevitably cover these two genotypes. Compared with the CIN1 stage, it was found that the HPV31 genotype was a unique high-risk type for the CIN2 stage, indicating that upon infection with HPV31, the likelihood of development into the CIN2 stage is higher. High-risk HPV

TABLE 2 Follow-up Periods for Patients of Different Risk Levels.

| Risk Level | Follow-up Period |
|---|---|
| Low-Risk | 3-5 years |
| Medium-Risk | 6-12 months |
| High-Risk | 3-6 months |

TABLE 3 CIN3 Node's Top 5 Neighbor Nodes.

| Neighbor Nodes | Value of the Relationship with CIN3 Weight |
|---|---|
| HPV 16 | 3.004129552 |
| HPV 18 | 3.00267266 |
| Age | 3.001884209 |
| Persistent HPV Infection | 3.001449165 |
| HPV Type | 3.000758473 |

TABLE 4 CIN1 Relevant High-risk HPV and Value.

| Type of High-risk HPV | Relation Value with CIN1 |
|---|---|
| HPV 18 | 3.001518086 |
| HPV 16 | 3.000897878 |
| HPV 45 | 1.000011528 |

infection warrants more attention. It also indicates that multiple genotypes of infection leads to greater likelihood of high-grade lesions.

## 3.3 Experimental analysis

We introduced an experimental evaluation index and conducted evidence-based analysis based on the diagram structure of risk factors. Finally, classification to predict the cervical lesion stage of patients and experimental verification through a total of 125 collected case data, excluding the data for cases that have developed into cervical cancer, was carried out. Comparative experimental analysis between the CLS algorithm proposed in this study and SMOTE-LSTM (22) was conducted.

At a statistical level, the results of disease diagnosis are described in terms of sensitivity and specificity. Sensitivity refers to the ability of diagnostic tests to detect disease when people are sick, as shown in the calculation Equation 5. Specificity refers to the ability of diagnostic tests to exclude disease when people are not sick, as shown in the calculation Equation 6.

TP (true positive): The prediction corresponds to the number of people diagnosed with a certain stage of the disease.

FP (false positive): The prediction does not correspond to the number of people diagnosed with a certain stage of the disease.

FN (false negative): The prediction does not correspond to the number of people free from disease.

TN (true negative): The prediction corresponds to the number of people free from disease.

$$sensitivity = \frac{TP}{TP + FN} \tag{5}$$

$$specificity = \frac{TN}{TN + FP} \tag{6}$$

TABLE 5 CIN2 Relevant High-risk HPV and Value.

| Type of High-risk HPV | Relation Value with CIN2 |
|---|---|
| HPV 16 | 3.003927177 |
| HPV 18 | 3.003502006 |
| HPV 31 | 1.00005263 |
| HPV 45 | 1.000007755 |

Sensitivity and specificity are often used to evaluate the authenticity of outpatient results. In order to evaluate the classification results of disease prediction more accurately, the definition of true positive in this study has been modified. In general, true positive indicates the condition of finding disease and predicting disease; that is, patients with the disease are correctly predicted to be patients with the disease. However, in the study, true positive is to predict not disease but accurate disease stage. These changes were made to improve the accuracy of CLS.

The CLS algorithm put forward in this research and the SMOTE-LSTM algorithm were compared based on the two aspects of specificity and sensitivity. Sensitivity represents the ability to identify patients, and specificity represents the ability to identify non-patients, i.e., the ability to be assessed as disease-free.

The experimental results of lesion prediction are shown in Figure 3. It can be clearly seen that the sensitivity and specificity of the CLS algorithm proposed in this study are higher than those of the comparison algorithm. This is because we have fully considered the principle of disease application, that is, the relationship between high-risk HPV infection and cervical lesions. A comprehensive analysis of the infection risk level of the patients themselves was carried out, so as to avoid missed diagnoses of those patients who have not tested positive for high-risk HPV but do have lesions. Degree of difference analysis was introduced to analyze the differences between related risk factors at different disease stages, so as to classify and predict the disease stages of patients better. In addition, the specificity of the CLS algorithm proposed in this study reached 92.7%, which indicates that our algorithm shows good ability to distinguish non-patients from patients. The CLS algorithm is therefore a tool for medically assisted decision-making that can effectively reduce the occurrence of overexamination.

TABLE 6 CIN3 Relevant High-risk HPV and Value.

| Type of High-risk HPV | Relation Value with CIN3 |
|---|---|
| HPV16 | 3.004129552 |
| HPV 18 | 3.00267266 |
| HPV 58 | 2.000134558 |
| HPV 52 | 1.000043481 |
| HPV 31 | 2.000129077 |
| HPV 51 | 1.000015006 |
| HPV 33 | 1.000014283 |
| HPV 35 | 1.000014325 |
| HPV 56 | 1.000015488 |
| HPV 26 | 1.000007551 |
| HPV 39 | 1.000014413 |
| HPV 66 | 1.00001536 |
| HPV 45 | 1.000007829 |

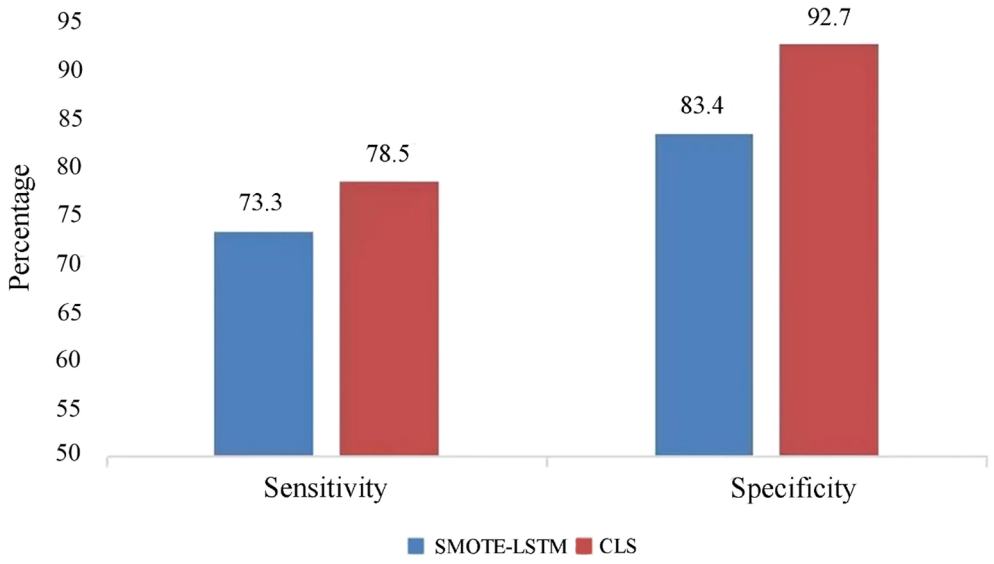


FIGURE 3
Comparison of sensitivity and specificity of prediction methods for cervical lesions.

## 4 Discussion

Accurate decision-making regarding the appropriate follow-up period for a target population with high-risk HPV infection can be time-consuming and challenging for clinicians, given the multitude of factors to consider. Prolonging the follow-up period increases the risk of missing the occurrence of cervical lesions, potentially leading to missed diagnostic opportunities before lesions develop. If the follow-up period is set too short, it may result in excessive examination, wasting medical resources and posing harm to patients' health. In 2020, the American Cancer Society updated its guidance to extend HPV screening intervals to 5 years based on accumulated evidence (23). However, disparities exist in recommendations from different academic organizations. According to the ATHENA trial, colposcopy is recommended if the patient tests positive for either HPV 16 or 18. Unfortunately, HPV testing can detect viral subtypes rather than persistent infection, which is an important factor in carcinogenesis. Girls and women tested positive for HPV subtypes -35, -39, -51, -56, -59, -66, or -68 are advised to undergo rescreening in 12 months (24). HPV infection genotype is important in detecting cancer and should be considered in triage management (25). To avoid excessive examinations and reduce the burden on patients, a more personalized diagnosis is recommended based on individual conditions. Physicians often manage patients according to their practical experience, acquired knowledge, guidance from predecessors, or research reports in journals, mainly relying on their subjective judgment. Evidence-based medicine not only focuses on doctors' clinical experience but also emphasizes the use of scientific evidence to guide clinical practice. Computers, as tools for data mining and knowledge discovery, can extract scientific evidence, providing an auxiliary support to doctors in clinical diagnosis. Therefore, evidence-based analysis of medical evidence can not only validate the accuracy of research but also play a relevant and conclusive role in clinical decision-making.

According to our study, patient risk was divided into three levels based on calculation of their total risk through the CLS algorithm. Then, every patient was assigned a serial number and a follow-up period. Follow-up periods were based on different risk levels. Individuals comprehensively understood to provide suggestions for the follow-up period compared with considering only single or several aspects. A reasonable and sufficient recommendation was expected.

Although studies published in 2006 and later show that fewer cases progressed to CIN3+, on average, in high-risk HPV-positive women compared with studies before 2006 (26), it remains critical to identify high-risk individuals to minimize the risk of their developing high-grade precancerous lesions. CIN3+ has been shown to be predominantly attributed to persistent HPV-16 and -18 infection, in line with the present study. However, it is difficult to identify the variations in the trends of the distribution of HPV genotypes in the target population due to the effects of vaccination and other factors such as patient age.

In extant studies of HPV, patient age has not received sufficient attention. Actually, age is non-negligible as one of other factors in present and potential CIN3 cases regardless of including or excluding HPV genotype. In our study, age was found to play a key role in CIN3 risk, ranking in significance only after HPV-16 and -18 infection status. Because of the limitations of the study, we did not analyze how or why age affects the infecting HPV genotypes and CIN risk. Extant studies show that the characteristics of distribution of high-risk HPV types differ with increasing age in patients with CIN2+. For instance, HPV-16 and -18 types cause CIN more often in younger women than in older women who are affected by genotypes other than those associated with non-high-risk HPV (27, 28). The reason for the atypical age-related distribution of HPV

genotypes in older women is immunological status (29). Changes in the immunological status of older women weaken their immune systems, resulting in less effective immune clearance of uncommon HPV genotypes. Persistent infection may occur for the same reason and lead to high-grade cervical lesions. In the meanwhile, the incidence of CIN2 and CIN3 in the 20–29-year age group has doubled relative to the >60-year age group (30). Approximately 50% of cervical cancer cases in older women result in non-high-risk-HPV (31). Age and immunological status ought to be fully considered when investigating the distribution of HPV genotype.

The emergence and development of HPV vaccines, from bivalent to nonavalent, as the primary prevention method, has effectively protected more and more women of the appropriate age from HPV infection with certain genotypes, with well-established safety (32). The bivalent vaccine covers the HPV genotypes 16 and 18; the quadrivalent vaccine covers the low-risk genotypes 6 and 11 that contribute to most cases of genital warts (33, 34) and the two high-risk genotypes mentioned above. In addition to all these abovementioned genotypes, high-risk HPV genotypes 31, 33, 45, 52, and 58 are the other genotypes covered by the nonavalent vaccine (35).

Extant studies describe high efficacy (>90%) of the HPV vaccine against high-grade CIN-related genotypes and persistent high-risk HPV infection, and an efficacy of 64.6% against cross-protective types (HPV-31, -33, and -45). Additionally, the HPV vaccine shows robust and long-acting clinical efficacy in terms of protection and prevention (36, 37). Due to the effects of the uptake of the HPV vaccine, changes of prevalent HPV genotypes in women of different age groups have appeared globally. However, the unequal uptake of HPV vaccination program step by step in the world has led to variations in HPV genotype among countries and regions at a given time. Studies indicate the role of the HPV vaccine in preventing the occurrence of CIN2 and CIN3 in some countries (36, 37). Although the proportion of CIN3 due to genotypes covered by the nonavalent vaccine is high in the age group of 45 years and above, it seems that older women have significantly higher risk of high-grade CIN associated with the genotypes of HPV that are not covered by the nonavalent vaccine as well as non-high-risk HPV precancerous lesions.

In the present study, we find that HPV-16, -18, and -45 are the common types leading to all stages of CIN; this is consistent with a study that considers HPV-16 and -18 as the main types of cervical squamous carcinoma and HPV-18 and -45 as the primary types of cervical adenocarcinoma (38).The HPV types at the secondary level leading to CIN did not appear to be common features, likely because of the differences in race, region, and vaccination status.

In the future, the rates of HPV-16 and -18 infection are expected to gradually decrease, especially in young women, as a result of the effectiveness of bivalent and quadrivalent HPV vaccination programs. The influence of nonavalent vaccine on other prevalent high-risk genotypes is deemed to come out in a long term for relatively late implementation and stipulated younger age group between 9 and 26. Therefore, traditional high-risk HPV types may not be predictive of CIN or lesions. Conversely, the specific HPV genotypes excluded in the nonavalent vaccination, such as -56, -66, -51, -39, -35, and -26, are expected to be predictive of CIN3 and CIN3+.

Therefore, HPV genotyping test is a valuable screening method to predict risk value and guide individual management. Clinical decision-makers should regard age as a factor, together with HPV genotype, when managing CIN3 patients (39). Overall, these findings highlight the importance of regular cervical cancer screening throughout a woman's lifetime and tailoring management strategies based on individual risk profiles. This would allow unnecessary interventions to be minimized while ensuring early detection and treatment of precancerous lesions before they progress to invasive disease.

The HPV vaccine—an effective preventive strategy against HPV infection, related genital warts, and cervical cancer (40–42)—combined with HPV testing is expected to reduce cervical cancer rates. HPV testing has gradually become the main screening method due to its good sensitivity, and HPV self-sampling programs will be an available supplement to improve screening coverage. Although HPV self-sampling projects have been carried out only in a small number of countries, because of its advantages as a safe, simple, and private method, HPV self-sampling may have more widespread application in the future in additional countries (43). In addition, the vaccination status of girls and women should be taken into account during triage and to determine the frequency of HPV screening; these considerations should be explored in future studies (42).

## 5 Conclusion

Through in-depth study of the interactions between the risk factors for high-risk HPV, a risk factor relationship diagram structure was constructed. The risk level of patients was analyzed based on all risk factors, and a follow-up period for each risk level was formulated. According to the correlation between high-risk HPV genotypes and CIN, a lesion prediction model was constructed to predict the stage of cervical lesions within a reasonable follow-up period, provide a basis for pathological diagnosis, effectively reduce the risk of lesions, and even cancerization, and achieve primary prevention of cervical cancer.

In this study, we mined potential key risk factors, identified high-risk HPV patients, formulated follow-up periods for each risk level, and predicted cervical lesions, providing a new technological basis and ideas for related fields. Through evidence-based analysis, we demonstrated that the construction of a cervical cancer knowledge base and the structure of the risk factor relationship graph in this study play a key role in the evidence-based analysis of diseases and provide convenience and a scientific basis for evidence-based medicine. Furthermore, the findings offer time savings to doctors by enabling to assess and conduct decision making more efficiently. At the same time, the potential risk factors mined based on the structure of the risk factor map are also of significance for guiding clinical diagnosis and disease prevention. Altogether, the findings of this study can help the medical community to identify high-risk HPV patients more accurately, arrange follow-up more effectively, and improve the accuracy of cervical lesion prediction, thus providing more effective strategies for the prevention and treatment of cervical cancer.

## Data availability statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found in the article/supplementary material.

## Ethics statement

The studies involving humans were approved by Ethics Committee of Jilin Central General Hospital. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin because the local legislation and institutional requirements.

## Author contributions

LG: Project administration, Writing – original draft, Conceptualization. YT: Data curation, Methodology, Writing – original draft. HX: Conceptualization, Investigation, Writing – original draft. LZ: Investigation, Resources, Writing – review & editing. YS: Formal analysis, Writing – review & editing, Supervision.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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# Experiences of women participating in a human papillomavirus-based screen-triage-and treat strategy for cervical cancer prevention in Malawi

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**Objective:** To explore the experiences of Malawian women who underwent a human papillomavirus (HPV)-based screen-triage-treat algorithm for cervical cancer (CxCa) prevention. This algorithm included GeneXpert® HPV testing of self-collected vaginal samples, visual inspection with acetic acid (VIA) and colposcopy for HPV-positive women, and thermal ablation of ablation-eligible women.

**Method:** In-depth interviews were conducted with participants of a trial that evaluated the feasibility of a HPV-based screen-triage-treat algorithm among women living with HIV and HIV negative women in Lilongwe, Malawi. Participants were recruited from 3 groups: 1) HPV-negative; 2) HPV-positive/VIA-negative; 3) HPV-positive/VIA-positive and received thermal ablation. Interviews explored baseline knowledge of CxCa and screening, attitudes towards self-collection, and understanding of test results. Content analysis was conducted using NVIVO v12.

**Results:** Thematic saturation was reached at 25 interviews. Advantages of HPV self-collection to participants were convenience of sampling, same-day HPV results and availability of same-day treatment. There was confusion surrounding HPV-positive/VIA-negative results, as some participants still felt treatment was needed. Counseling, and in particular anticipatory guidance, was key in helping participants understand complex screening procedures and results. Overall, participants expressed confidence in the HPV screen-triage-treat strategy.

**Discussion:** HPV testing through self-collected samples is a promising tool to increase CxCa screening coverage. A multi-step screening algorithm utilizing HPV self-testing, VIA triage and thermal ablation treatment requires proper

counseling and anticipatory guidance to improve patient understanding. Incorporating thorough counseling in CxCa screening programs can change women's perspectives about screening, build trust in healthcare systems, and influence healthcare seeking behavior towards routine screening and prevention.

KEYWORDS

HPV self-collection, VIA triage, thermal ablation, cervical cancer screening experience, Malawi (MeSH [Z01.058.290.175.500])

# Introduction

Malawi has the highest cervical cancer (CxCa) mortality rate in the world (51.5 deaths/100,000 per year), seven times higher than the global rate (1). This disease burden is largely due to the high prevalence of HIV (>9% for women 15-50 years of age) (2) and low CxCa screening coverage (3). For the last two decades, the national CxCa screening program in Malawi has been using visual inspection with acetic acid (VIA) for screening and cryotherapy for treatment of VIA-positive lesions amenable for ablative therapy. However, a comprehensive evaluation of this program in 2015 showed that screening coverage has remained low (<27%) and less than half of those who required treatment received treatment (3).

Lack of trained staff was cited as the main challenge in offering CxCa screening by service providers in Malawi (4). Pelvic exam-based screening for cervical cancer, such as VIA, requires trained providers, adequate facilities, and patient acceptability of exams, thus limiting screening efficiency, access, and uptake. Human papillomavirus (HPV) screening by self-collection can bypass some of these challenges. The detection of high-risk types of HPV associated with CxCa has improved the accuracy of detecting cervical precancer (5) and was recommended by the World Health Organization (WHO) in 2021 to be the primary screening method, when available (6). Recent advancements in technology, such as GeneXpert® HPV tests (Cepheid Inc, Sunnyvale, CA, USA), has made HPV testing available in low-resource settings and allow the possibility of same-day treatment because of the quick result turnaround (about 1-2 hours with GeneXpert®). Self-collection of vaginal sample for HPV testing has been validated as an effective and sensitive method for CxCa screening if highly sensitive assays are utilized, with notably lower provider burden compared to provider-collected tests (5). HPV self-collection has been shown to increase CxCa screening compared to VIA (7) and is acceptable to women all over the world (8), including in Sub-Saharan Africa (SSA) (9).

The biggest limitation to same-day treatment of cervical precancerous lesions in Malawi was maintaining functional cryotherapy machines and sustaining the supply of refrigerant gas (3). Thermal ablation, a battery-powered, portable, and less time-intensive treatment modality is replacing cryotherapy as the preferred treatment modality in low- and middle-income countries (LMICs). With increasing evidence of safety, efficacy, and the ability to increase same-day screening and treatment (10, 11), the Malawi Ministry of Health (MoH) added thermal ablation as a treatment option in the national screening guidelines (12).

In line with WHO and Malawi MoH recommendations, we implemented a HPV-based screen-triage-treat algorithm that incorporates the strategies of HPV self-collection and same-day thermal ablation treatment. Our single-arm prospective trial evaluated the feasibility and performance of this algorithm in Lilongwe, Malawi among women living with HIV (WHIV) and HIV-negative women (13). This manuscript focuses on the study's secondary aim, which was to explore the experiences of the participants. Perceptions of HPV-based screening have primarily been evaluated in HPV/Pap smear algorithms among patients in high income countries (14, 15). This study uniquely evaluated the experience of women undergoing a HPV/VIA screen-triage-treat algorithm, including acceptance of HPV self-collection, understanding of results, and challenges posed by a multistep screening process.

# Methods

## Study setting and participants

Participants for this qualitative sub-study were recruited from a single-arm prospective study that investigated a novel HPV screen-triage-treat strategy among 1,250 women (625 WHIV and 625 HIV-uninfected) in Lilongwe, Malawi. The strategy consisted of 1) GeneXpert® HPV testing of self-collected cervicovaginal samples; 2) VIA and colposcopy for HPV-positive women; and 3) thermal ablation for HPV-positive/ablation-eligible women. Colposcopy was conducted following VIA to determine final eligibility for thermal ablation, and additional samples (endocervical curettage and cervical biopsy or pap smear) were collected based on colposcopy results for other study objectives (see protocol paper for details) (13). For this qualitative sub-study, we focused on the HPV self-collection screening, VIA triage, and thermal ablation treatment components of the algorithm.

The parent study and this qualitative sub-study were conducted at UNC Project-Malawi's Tidziwe Centre clinic in Lilongwe,

Malawi. UNC Project-Malawi is a collaboration between the University of North Carolina at Chapel Hill and the Malawi MoH. Recruitment of participants for the parent study are detailed in the protocol paper (13). Briefly, study staff provided educational talks about cervical cancer screening and the study in waiting areas of outpatient clinics that provided reproductive health and HIV care services. Women who were interested in the study were scheduled for screening at the UNC Project-Malawi research clinic. On arrival, informed consent began with a summary of study goals and introduction to the new approach to cervical cancer screening employed in the study. Specifically, counseling was focused on HPV, its relationship to cervical cancer and detailed descriptions of each screening step. For those who continued to be interested, the remainder of the informed consent was completed, which further included counseling on what to expect at each step of screening and after each result. During screening, participants' understanding of procedures and results was continually assessed and counseling was reiterated as needed. Study eligibility criteria included: femal1es between 25-50 years of age; non-pregnant; at least 12 weeks postpartum; and able and willing to provide written informed consent. Exclusion criteria included: current or prior history of cervical, vaginal, or vulvar cancer; current symptomatic sexually transmitted infection (STI) requiring treatment; prior HPV vaccination; allergy to acetic acid; or history of total hysterectomy.

At the enrollment visit of the parent study, participants were asked if they were interested in joining the qualitative sub-study. Convenience sampling was used among those who expressed interest and the sub-study participants were recruited via phone call by study staff. Those interested were asked to come back to Tidziwe Centre to consent and enroll in the sub-study. We planned to enroll up to thirty women for in-depth-interviews (IDIs) across 3 groups of screening outcomes: 1) those who screened negative on self-collection HPV test (HPV-negative); 2) those who screened positive on self-collection HPV test but had a negative VIA (HPV-positive/VIA-negative) and did not receive treatment; and 3) those who screened positive on HPV self-collection, had a positive VIA triage exam (HPV-positive/VIA-positive) and received same-day thermal ablation. All participants received transport reimbursement, as approved by the local ethics committee.

## Data collection

Semi-structured IDIs were developed around four main domains of inquiry: 1) baseline knowledge and perception of CxCa and CxCa screening; 2) attitudes towards self-collection; 3) experience with the screen-triage-treat procedures; and 4) understanding of screening results. Domains were developed based on existing literature that assessed acceptability of and perspectives on HPV-based screening (9, 16, 17). Interviews were conducted in Chichewa, the local language, by study staff experienced in qualitative data collection methods (WD). Interviews were audiotaped and then translated and transcribed into English. Completed transcripts were reviewed immediately by study investigators and analyzed for emerging and/or new themes to inform the questions for subsequent interviews. This iterative process ensured saturation of themes and depth of content within the predetermined domains of inquiry.

Additionally, five survey questions specific to participants' HPV self-collection experience were administered after IDIs. The survey asked participants to rank whether they felt embarrassed, experienced discomfort, experienced pain, had privacy, and felt confident that they self-collected correctly on a three-point scale of 1) not at all; 2) somewhat; and 3) very much.

## Data analysis

Three qualitative investigators (FL, SM, JC) independently reviewed and coded three transcripts at a time using thematic analysis, followed by a group discussion, to identify relationships between emerging themes and ensure relevance to research questions. This was repeated until the code book was finalized. The code book and IDIs were uploaded to NVIVO 12 software. To ensure validity of coding and robustness of analysis, nine interviews were coded by all three investigators and the remaining 16 were doubly coded. The code book was refined as analysis progressed. An Excel spreadsheet was used to structure and compile all extracted quotes for each code. The quotes were reviewed by all three coders and themes were revised until it was felt that they accurately reflected the data.

Survey data on HPV self-collection experience was entered into an Excel spreadsheet, and descriptive statistics were used for analysis.

## Ethical considerations

This study was approved by Malawi National Health Sciences Research Committee and the University of North Carolina at Chapel Hill Institution Review Board. All participants underwent informed consent and provided written consent.

# Results

Between July 2020 – March 2021, we interviewed 25 women across the three groups of screening outcomes. Thematic saturation was reached at seven for Group 1, twelve for Group 2, and six for Group 3 (Figure 1).

## Baseline characteristics of participants

Participants were between 25-49 years old, with a median age of 34 (Table 1). Overall, ten (40%) of participants were WHIV (one in Group 1, five in Group 2, and four in Group 3). Most participants (84%) reported no prior CxCa screening; for those who did, the prior screening method reported was VIA. The majority of participants (72%) report a travel time between 30-60 minutes to reach the nearest clinic that offered CxCa screening. Of note, participants in Group 3 had a longer time between initial HPV

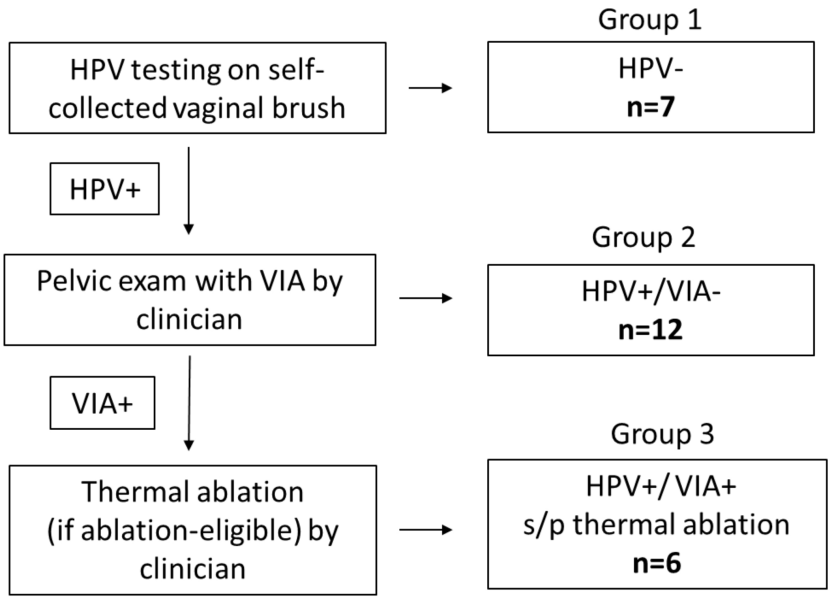


FIGURE 1
Screening algorithm, screening outcomes (Group 1: HPV-negative; Group 2: HPV-positive/VIA-negative; Group 3: HPV-positive/VIA-positive and underwent thermal ablation) and number of participants interviewed in each group. HPV, Human papillomavirus (testing for high risk HPV); VIA, Visual inspection with acetic acid s/p: status post. Healthcare provider included nurses and clinicians.

screening and their IDI (median of 7 weeks vs. 3-4 weeks for Groups 1 & 2). Baseline socioeconomic characteristics were similar across the three groups. Most (60%) had at most some secondary school education, most (68%) were married or living with their partner, and most (64%) worked outside the house. Half of the participants (48%) made less than the equivalent of about $2 per day (<K49,999 per month), and the others (52%) made the equivalent of about $2-6 per day (K50,000-K150,000 per month). The median age at first vaginal intercourse among participants was 17 years, with a range of 15-22 years. The median number of lifetime partners was two, with a range of 1-3. Most (76%) reported using condoms at least some of the time.

## Knowledge and perception of CxCa

All participants had heard of CxCa, predominantly from CxCa screening messages on the radio, at clinics (antenatal, family planning and HIV), and/or from other women in the community (Table 2). Participants' reported that CxCa is associated with sexual transmission, early sexual debut, and having multiple sexual partners, specifically with uncircumcised men. Some participants described CxCa as asymptomatic in the early stage. Others described gynecological symptoms, such as vaginal discharge, abnormal vaginal bleeding, abdominal pains, and genital sores, as associated with CxCa. Several participants reported that CxCa can spread to the womb and treatment involves hysterectomy, which leads to the inability to give birth again. The general perception of CxCa was that it is dangerous and deadly when detected in advanced stages when it is too late for treatment (Table 2). All felt that CxCa can be prevented; some reported prevention through lifestyle changes, such as limiting number of sexual partners, male circumcision, and vaginal hygiene. Several participants also specifically reported that CxCa can be prevented with screening.

## Perceptions about CxCa screening

Participants reported that in their communities, screening is associated with the embarrassment and painful speculum exams (Table 2) and that these fears hinder screening attendance. Many had heard about screening through clinics (e.g., antenatal or family planning), and some were encouraged by clinicians or other women to attend screening. Some expressed initial hesitancy towards screening based on hearsay from the community, however, all participants had a positive perception of screening and believed that screening can prevent disease. The predominant reason participants decided to undergo screening was to know about their health and to catch abnormalities at an early stage when treatment was still available.

## Experience of self-collection

All participants reported a positive overall experience with self-collection of vaginal samples for HPV testing (Table 3). All expressed understanding of the self-collection process and many were able to describe the steps in detail even weeks after screening. They felt well-counseled on the collection steps, described it as an easy procedure, and valued the quick turn-around of HPV results. When participants were asked to rate a series of experiences during self-collection, all 25 participants reported no embarrassment, only one reported

TABLE 1 Baseline demographic of participants by self-collection HPV screening and VIA triage result.

| Characteristics | Total N=25 n(%) | Group 1 HPV- n=7 n(%) | Group 2 HPV+ / VIA- n=12 n(%) | Group 3 HPV+ / VIA+ n=6 n(%) |
|---|---|---|---|---|
| Age median (range) in years | 34 (25-49) | 36 (27-49) | 31 (26-40) | 28 (25-36) |
| HIV positive* | 10 (40%) | 1 (14%) | 5 (45%) | 4 (57%) |
| No prior cervical cancer screening† | 21 (84%) | 6 (86%) | 9 (75%) | 6 (100%) |
| Median length of time (range) in weeks between screening and in-depth-interview | 8 (1.3-24) | 3.6 (1.3-9.1) | 4.7 (2.0-24.0) | 7.1 (3.4-17.1) |
| Educational attainment‡ | | | – | |
| Some secondary or less | 15 (60%) | 5 (71%) | 4 (33%) | 6 (100%) |
| Completed secondary or more | 8 (32%) | 1 (14%) | 7 (58%) | 0 |
| Marital Status | | | | |
| Single (never married, widowed, divorced or separated) | 8 (32%) | 1 (14%) | 4 (33%) | 3 (50%) |
| Married or living with partner | 17 (68%) | 6 (86%) | 8 (67%) | 3 (50%) |
| Monthly income§ | | | | |
| Less than $65 (K49,999) | 12 (48%) | 3 (43%) | 6 (50%) | 3 (50%) |
| $65-$195 (K50,000-K150,000) | 13 (52%) | 4 (57%) | 6 (50%) | 3 (50%) |
| Distance to nearest clinic that offers cervical cancer screening services (CCS) | | | | |
| <30 min | 14 (56%) | 4 (57%) | 6 (50%) | 4 (67%) |
| 30-60 min | 11 (44%) | 3 (43%) | 6 (50%) | 2 (33%) |
| Parity median (range) | 3 (0-5) | 3 (2-4) | 2 (0-5) | 3 (1-4) |
| Age at first vaginal intercourse: median (range) | 17 (15-22) | 19 (15-20) | 17 (16-22) | 15 (15-21) |
| Number of lifetime sexual partners: median (range) | 2 (1-3) | 2 (1-2) | 1 (1-3) | 2 (2-2) |
| Uses condoms | 19 (76%) | 7 (100%) | 9 (75%) | 6 (100%) |

* All WHIV are on ART and have been taking it for over 6 months.
† All 4 participants with prior screening had VIA screening.
‡ No response = 2.
§ Malawi Kwacha(K) to United States Dollar ($) exchange at the time of study was 1K to $0.0013; K49,999= ~$65; K150,000 = ~$195.
**Participants reported between 1-4 family planning methods used, most commonly used was Depo provera IM (n=16), followed by Jadelle (n=8), Depo provera SC (n=6), Levoplant (n=4), birth control pills (n=4), and Implanon (n=2).

discomfort (rated as mild), and only four reported pain (rated as mild by all four) (Figure 2). On further inquiry, mild pain was described as more of a "discomfort" or "sensation" or "pinch" by participants (Table 3). All participants reported they had very good privacy, and all but one reported being very confident in collecting the sample correctly (Figure 2). Many suggested that this method could be more acceptable to women who feel embarrassed to undress for speculum-based screening (Table 3).

## Understanding HPV results

All participants, except one, reported that they had never heard of HPV prior to being involved in the research study. After undergoing screening and counseling, participants were able to describe HPV as a virus that can cause CxCa or lesions on the cervix (Table 4). Regardless of their own HPV result, participants reported that a HPV-positive test is associated with increased risk of CxCa, which requires further evaluation and/or treatment. Participants also recognized that while HPV-negative result was reassuring, regular screening is still necessary since the infection could occur later. The concept of routine screening was compared to HIV testing by both WHIV and HIV-negative women.

## Experience of VIA triage and thermal ablation treatment

Several participants who underwent VIA triage (Groups 2 and 3) reported negative experiences during pelvic exams (Table 3). Some reported discomfort related to the insertion and removal of the speculum, and others reported feeling embarrassed, especially when male providers were present. One participant did not like having to go for another test after the initial HPV self-collection. The discomfort and embarrassment were ameliorated by ongoing counseling during the exam process (Table 5). When thermal

TABLE 2 Participants' prior knowledge and perception of cervical cancer and cervical cancer screening before undergoing self-collection HPV-based screen-triage-and treat program.

| Area of inquiry | Themes | Quotes |
|---|---|---|
| Participants' prior knowledge of cervical cancer | Heard about cervical cancer screening | I didn't know anything [about cervical cancer]. What cancer looks like, or what happens. I would just hear that people are getting screened for cancer. (P0003) |
| | Cervical cancer is sexually transmitted, transmitted from uncircumcised men and the risk is increased with having multiple sexual partners | If you have unprotected sex whilst still young, you are bound to contract HPV. They [family planning clinic] also said that an uncircumcised man harbors HPV, because the virus thrives in warm places. They further went on to say all men have HPV, they have it from a young age, they are born with it. So if young men have sex with young women, they transmit the virus easily. (P0685) |
| | Gynecologic symptoms are associated with cervical cancer | I heard that when you have cervical cancer, you experience abdominal pains, and you also develop sores. Likewise, your vaginal discharge has a foul smell, and is watery with a yellowish color. (P0007) |
| | Treatment associated with hysterectomy and infertility | [At antenatal clinic] they would just say that there is cervical cancer, and if it spreads, a hysterectomy is performed, and a person will never be able to give birth again after that. (P0322) |
| Participants' perception of cervical cancer | Cervical cancer is perceived as dangerous and deadly | I knew that cervical cancer is very dangerous...They said if you have cervical cancer, it is only detected when it's too late. (P0131) |
| | Asymptomatic in early stages | With cancer, you do not feel any pain, as opposed to malaria where you feel body pains. That is why I made a decision to get screened for cancer so I know what my health is like. You can just wake up one day and you have cancer. (P0310) |
| | Cervical cancer can be prevented | When you go to get screened and you hear your results, if the cancer is in its early stages, it is preventable (P0003) |
| Participants' prior knowledge of cervical cancer screening | Community stigma of screening: fear of speculum exams | I knew that cervical cancer is very dangerous...They said if you have cervical cancer, it is only detected when it's too late, due to the method that we have in Malawi, the one where a metal is placed on the opening of the vagina. A lot of women we are afraid of this. So we only know when we are sick, that it is cancer.(P0131) |
| | Many understood that screening was a key part of cervical cancer prevention | You can prevent it [cervical cancer] by getting screened at the hospital, hearing the results, and following what the doctors tell you. (P0684) |
| | Heard about screening at health facilities, radio, community and friends | I just heard people talking about it, even in hospitals, in here about it. (P0687) |
| Participants' perception of cervical cancer screening | Decision to get screening overall despite fear of screening | Made the decision to get screened so that I know about my health where cervical cancer is concerned. However, I was afraid to go and get screened because women would often talk about how painful it is, and would get me scared.(P0478) |
| | Screening can help catch abnormalities early when treatment may still be available. | I know that if we get screened for cervical cancer then we know about our health. Whether we have cervical cancer or not. If we have it, then we have to follow procedures so that the disease can be cured. If we don't have, then we ought to go and take care of ourselves so that we don't get it. (P0112) |

ablation was recommended, some participants reported having anxiety about the treatment procedure and others reported mild discomfort during treatment. However, overall, most expressed that thermal ablation itself was quick, painless, and well tolerated. Many participants who underwent treatment expressed gratitude for the treatment.

## Understanding VIA triage and thermal ablation treatment

Participants reported understanding that the purpose of VIA was to examine the cervix for "damage" caused by the virus or "lesions" that need treatment (Table 4). Even those who were HPV-negative and did not undergo VIA described VIA triage as a "confirmatory test," to see if one has the disease or not. However, there was confusion in Group 2 about the significance of a positive screening test (HPV) with VIA-negative result. One participant expressed concern that the HPV will develop again if not treated, and others felt they still needed some kind of treatment for a positive HPV result, despite the VIA-negative result. One participant reported that the vinegar used in VIA was used to kill the HPV. The majority of Group 2 however viewed a negative VIA triage as an overall negative screening result and expressed relief.

All Group 3 participants understood that an HPV-positive/VIA-positive result meant that treatment was indicated. Many reported initial concerns when lesions were seen on exam, however, they also reported being counseled to not worry, as treatment was available right away (Table 5). Participants in this group predominantly expressed acceptance of the results and gratitude that they could proceed with immediate treatment. Participants who underwent treatment with thermal ablation correctly explained that the purpose was to treat lesions and prevent worsening of disease. Of note, we found no differences in understanding between WHIV and HIV-negative participants (Table 4).

TABLE 3 Participants' experience with self-collection HPV-based screen-triage-and treat program.

| Area of inquiry | Themes | Sub-themes | Quotes |
|---|---|---|---|
| HPV self-collection | Participants reported being well counseled, which was reflected in their ability to remember steps of self-collection well, and felt that avoiding pelvic exams was a strength of self-collection. | Remembered the steps of self-collection well | When I went in a private room to self-collect... I inserted the brush slowly, then I felt that I had reached the cervix, and I swirled the brush 4 times and pulled it out. I looked at the brush if the sample was visible, I saw it, I then put the brush in the tube (without touching it). After that, I handed it over. (P0478) [*Participant was interviewed 8.4 weeks after screening]* |
| | | Valued counseling about screening process | What I liked most was they started by taking us through what happens. So we knew what happens, before it took place. This was so we should make a personal decision whether to go ahead or not.. (P0409) |
| | | Valued doing the collection herself and quick turn-around of HPV results after collection | I liked that I collected the brush, and I got my results after the brush had been tested. (P0467) |
| | | Avoiding pelvic exams decreases fear, is more private, and can reach more women | I was also one of the people who would be embarrassed with the other method, where there would be undressing, and male doctors would see that nakedness. A lot of people do not like that. (P0322) |
| | Most initial concerns about self-collection resolved after counseling and/or performing the self-collection | Worried about treatment after a positive result | I was worried because I thought I will be found with a problem, which will result in a hysterectomy on my part. I was very worried that if they remove my womb, I will never give birth again. (P0131) |
| | | Worried it might be painful or uncomfortable, relieved by seeing/touching the brush | Before I collected the swab, my worry was whether the brush would really be inserted and if I would feel pain, and also if the brush would wound me. But when I touched it, I concluded that it wasn't the case. When I inserted it into my vagina, I realized there was no pain and everything they told me to do was possible. (P0007) |
| | | Worried about collecting sufficient sample. | Yes, I had worries. I was told that if the sample will be insufficient on the brush, then I would have to repeat the process. So I was worried about that. So I made sure I did it right the first time. (P0118) |
| Visual Inspection with Acetic Acid (VIA) triage | Despite fear and discomfort of pelvic exam performed for VIA triage, most felt comfortable due to the counseling they received throughout the exam process | Discomfort during the pelvic exam was mostly due to speculum (insertion of the metal) | I was scared when I saw the speculum…But I was well assisted, and I was being told what was happening the whole time... I felt a bit of pain, but I think that was caused by a mishap…But when the speculum was inside and they were doing the exam, I didn't feel anything, I was just conscious that there is a foreign body inside me. Only when they were taking out the speculum did I feel a bit of pain. (P0322) |
| | | Pelvic exam was embarrassing, especially with male provider | Embarrassment is very likely being a male [doctor] was present. (P0310) |
| | | Did not like additional test following HPV positive self-test result | I didn't like when the doctors told me I needed to go for another test. (P0682) |
| | | Active counseling during the exam was helpful | They were telling me everything that was happening. Some don't tell you what is happening, you just realize it has happened. That is very heartbreaking, but here, it was a delight to be told what was happening. And they addressed us with warmth.(P0322) |
| Thermal ablation treatment | Some women reported initial anxiety about the treatment, others had mild discomfort during the treatment. But overall, thermal ablation was painless and well tolerated. Many participants expressed gratitude for the treatment. | Some had anxiety about the treatment procedure | When they told me that they were going to perform thermal ablation, I was anxious. The hot air got me worried. (Chuckles), but I accepted the situation and went on ahead. (P0629) |
| | | Some experienced mild pain but no severe discomfort | It was a bit painful… When they finished, they gave me cotton wool to use. I got off the bed with no problems. I was able to walk, I got home just fine, I did not encounter any problems further than that. (P0118) |
| | | Grateful for availability of quick treatment following initial screening | The treatment was instantaneous. From the pelvic exam to the thermal ablation. And then I went back home. There was no postponement of anything. I really liked that (P0629) |
| Post-screening and treatment experience | Post-treatment symptoms were minor and mostly consisted of vaginal discharge | Several described vaginal discharge after the procedure that stopped spontaneously, most were not alarmed as they were counseled that this may be a side effect of treatment. | The complication I experiences happened when I got home, but they had already warned me about it. They told me that I'd produce dark vaginal discharge. It seemed like a menstrual flow, but it was very dark. That went on for a week. But after it stopped, it never happened again until now. (P0467) |

*(Continued)*

TABLE 3 Continued

| Area of inquiry | Themes | Sub-themes | Quotes |
|---|---|---|---|
| | The post-treatment abstinence recommendation* was difficult for participants.<br>*Post-procedural abstinence counseling changed from 6 to 4 weeks over the interview period. | The need to discuss abstinence with male partner caused anxiety | I kept thinking the whole way back home, about how I was going to explain this [abstinence] to my husband. Because as it was, I wasn't given any medication for me to show him that maybe he can believe me. It was only I who knew of how I had been assisted, and what to do afterwards. So for me to go and tell him about the 6 weeks. It was a problem." (P0131) |
| | | Many were not able to abstain from sex due to lack of partner support | They just told me not to indulge in sexual intercourse in the time being. Should it happen that I really want, I should use protection. But because my husband was away, I managed to stay without sexual intercourse for 3 weeks. (P0310) |
| | | Desired male partner or couples counseling | It was better that I be sent back home and come back together on a day that he [my husband] can manage to come…To screen and treat me, then explain to both of us of what is to happen. Then after, to stay away from each other sexually for such and such a long time. Explain everything, just as they did to me. (P0131) |
| | Participants were excited to their experiences with friends and family | Sharing experiences address misconceptions and encourages screening uptake by friends | I told my friends, almost 10 of them if I'm not mistaken. I told them to go and get screened for cervical cancer… They asked if it was scary. I explained to them the process I went through, and the method. I explained to them that I was given a brush, you self-collect, and it is not painful when it is inserted to collect the sample. (P0578) |

## Experiences post-thermal ablation and post screen-and-treat

Those who experienced symptoms after ablation viewed these as minor side effects (Table 3). The major post-treatment challenge participants reported was having to explain the need for several weeks of abstinence to their male partners. One participant reported that she did not know how to explain the treatment to her husband, as there was no medication that she could show him and felt the conversation would not go well. Other participants reported they were not able to abstain from sex due to the lack of male partner support. Some participants desired male partner counseling to be incorporated in the screen-and-treat program so that their husbands could understand and be supportive of abstinence recommendations. Some felt that same-day screen-and-treat did not allow them the opportunity to discuss treatment with their husbands before receiving it.

Many participants reported that after screening, they shared their experiences with others in their communities, including family, friends, and male partners (Table 3). Several participants reported answering questions from other women about screening and addressing misconceptions that kept women from presenting for CxCa screening. Almost all participants felt it was important to share their own experiences with the community and encourage screening uptake (Table 5).

# Discussion

The 25 participants of this study, including both WHIV and HIV-uninfected women, exhibited a higher baseline knowledge of CxCa and CxCa screening than reported in prior studies (18). Despite the introduction of several new factors and concept in our study's screening algorithm – including HPV test, self-collection, a triage step and same-day treatment – participants reported accurate understanding of each step and an overall positive experience. The process of self-collection was highly acceptable, and participants demonstrated understanding and trust towards the HPV test result. Confusion did occur when the VIA result was discordant with the HPV result, indicating the need for additional targeted counseling in this group. Participants demonstrated confidence in their knowledge and expressed desire to share these experiences with their community so that other women are encouraged to attend screening. Counseling, and in particular anticipatory guidance, was key in helping participants understand complex screening procedures and results (Table 5).

## Understanding of CxCa and CxCa prevention

Participants demonstrated a higher baseline knowledge of CxCa (e.g. association with sexual transmission, gynecological symptoms, infertility after treatment) and screening awareness (i.e. majority have heard of screening) than previously seen in Lilongwe district (19). This likely was due to recruitment of participants from clinics where women are already engaged in health care, compared to rural populations reached by mobile campaigns (20).

Notably, study participants displayed an understanding of the importance of screening for prevention. While fatalistic views of CxCa still existed (19, 21, 22), they were associated more with late diagnosis. In this study, screening was generally viewed positively and recognized as the way to find disease at a treatable stage and prevent fatal disease progression. Recent studies among women in southern Malawi also captured similar sentiment around the importance of early detection in CxCa screening (23). However, despite adequate knowledge of the disease and understanding of prevention, fears

TABLE 4 Participants' overall impression and major take away messages from the self-collection HPV-based screen-triage-and treat strategy.

| Theme | Sub-theme | Quotes |
|---|---|---|
| Thorough counseling contributed to their positive overall experience | Thorough counseling minimizes negative emotions, built trust with the providers and leads to satisfaction with the screening and treatment services | I understood what they were trying to say. I was not afraid when they explained to me. Everything that I felt, fear and doubt, it all went away. I was relieved. I went back home happy. I realized that if I had just stayed at home and not gotten screened, it could have been disastrous. But this time around, everything was fine. (P0478) |
| | Anticipatory guidance helps participants know what to expect to limit the confusion of a multi-step or multi-result screening method | What I liked most was they started by taking us through what happens. So we knew what happens, before it took place. This was so we should make a personal decision whether to go ahead or not. The second thing was when we heard that, it was good because we were told everything beforehand. Yes, that's what we encountered on that day. (P0409) |
| | Ongoing active counseling throughout exams and treatment procedures is reassuring for participants | They were telling me everything that was happening. Some don't tell you what is happening, you just realize it has happened. That is very heartbreaking, but here, it was a delight to be told what was happening. And they addressed us with warmth. (P0322) |
| | Counseling extended to health maintenance and routine screening for prevention | I was treated well; I was told what I needed to hear. They told me there is no problem at the moment, but it could develop in the future. So we needed to do such and such. (P0068 |
| Participants felt it was important to share their screening experiences, addresses misconceptions and encourages screening | Many participants already shared their experience with others (family and friends) in the community, addressed misconceptions and encouraged other women to go for screening | First, [I told] my husband. Second, my friends. I was encouraging them to go and get screened for cervical cancer….I was the one encouraging them due to the questions they were asking me…I was explaining to them that you self-collect the sample…Don't be afraid of a pelvic exam. It is better here because of the self-sample collection. I was encouraging them in that manner. (P0112) |
| | Sharing their screening and treatment experiences was important | Also that a lot of us women are usually hesitant to come to the hospital, but that is not good. If you're summoned to come to the hospital, you should do just that. You only have one life. If you lose it, there's no getting it back. So personally, I just want to encourage women to take part in this, because it is a good thing. And it is simple. (P0004) |
| | Many participants themselves came for screening due to hearing about it from other women in the community | I'd just hear about how some women had gone for cervical cancer screening. These women testifying about their experiences is what prompted me to come as well (P0467) |

around pelvic exams (e.g. pain and embarrassment) hindered women from previously seeking out screening services; similar acceptability-related barriers have been identified in other studies from low- and middle-income countries (18).

## Self-collection was well accepted

Self-collection of vaginal samples for HPV testing was well-received and valued among our participants for ease of collection, avoidance of embarrassment or discomfort from speculum exams, and quick turnaround time of results. Many felt that self-collection could mitigate the fear and stigma surrounding speculum exams. These findings are consistent with existing literature over the last couple of decades that has shown self-collection to be acceptable across a variety of geographic locations, cultures and age groups (8, 9). Studies specific to African populations showed that women are willing to collect their own samples and that it is a more socially acceptable and feasible method than pelvic exam-based screening methods, such as Pap smear or VIA (24, 25).

Major concerns surrounding self-collection were worry about not collecting it correctly, fear of receiving a positive result, and fear

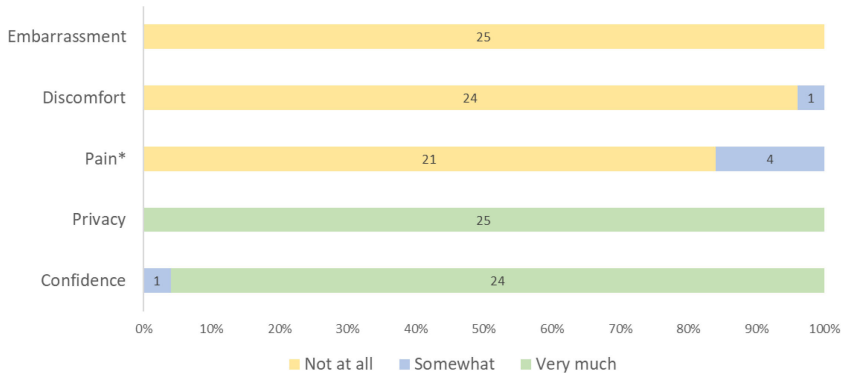


FIGURE 2
Participants' reported HPV self-collection experience on a three point scale (N=25). *Of those who reported "somewhat" pain during HPV self-collection, 3 had HPV negative and 1 had HPV positive results.

TABLE 5 Participants' understanding of results and purpose of screening, triage and treatment steps stratified by HPV result.

| Area of Inquiry | Themes | HPV- participants Quotes | HPV+ participants Quotes |
|---|---|---|---|
| Understanding HPV in the context of cervical cancer | HPV is a virus; HPV causes cervical cancer; HPV causes lesions* on the cervix.<br>No major differences in understanding between HIV-positive or HIV-negative participants | It [HPV positive test] means she has a virus that causes cervical cancer. So that means she has to receive treatment at the hospital in order to kill the viruses so that they don't cause cervical cancer. (P0003) *HPV negative, HIV negative* | They told me that testing HPV positive does not directly mean that you have cervical cancer. It is merely the virus that causes cervical cancer, but if the virus has caused lesions on the cervix, then you likely have cervical cancer. (P0685) *HPV positive, VIA negative, HIV positive* |
| Understanding HPV results in the context of cervical cancer | HPV negative result does not need treatment, but still needs routine screening because there is still risk in the future | Not that I am above others, but at this particular time, it meant that I am okay. However, this does not mean it is forever, maybe at some point I may be diagnosed with it. But I am okay for now. (P0490) *HPV negative, HIV negative* | That [HPV negative] means that woman does not have cervical cancer….Yes, she needs further testing after some time… No. She does not need any treatment. Only if she was later on tested and the test results, positive. Only then. (P0409) *HPV positive, VIA negative, HIV positive* |
| | HPV positive result is associated with risk and needs follow-up and/or treatment | In my understanding, when that [HPV positive result] happens, then she is supposed to be screened again, this time around, a pelvic exam...And then she undergoes thermal coagulation. (P0007) *HPV negative, HIV negative* | It [HPV positive result] meant that chances of me getting cancer in the future were high. (P0068) *HPV positive, VIA negative, HIV negative* |
| Understanding implication of HPV result in the context of cervical cancer prevention | Continued routine periodic screening is necessary for prevention, even if HPV screening is negative | Maybe the virus may come back, but I should not stop getting screened, so that I know the status of my health. (P0628) *HPV negative. HIV negative* | Yes [she needs further testing if she is HPV negative ] Because even though at that particular time she tested negative, she can test positive at a later date. (P0467) *HPV positive, VIA positive, HIV positive*) |
| | Some compared routine cervical cancer screening to HIV screening.<br>No major differences between HIV positive versus negative participants | You are supposed to get tested for HIV every 3 months. At this moment I am fine, but how about 3 or 4 months down the line…I find it to be a good thing to get screened (for cervical cancer) again. (P0490) *HPV negative, HIV negative* | It is like HIV, you cannot get tested once and think you are in the clear. (P0684) *HPV positive, VIA negative, HIV negative* |
| Understanding the role of VIA in this screening algorithm | VIA is to examine the cervix , to see if there is damage caused by the virus. VIA detects lesions that would require treatment. VIA is a confirmatory test. | So that they confirm if I have the disease or not. (P0682) *HPV negative. HIV negative* | They told me I had tested HPV positive and needed a pelvic exam so that they check my cervix, to see if there it had lesions. (P0409) *HPV positive, VIA positive, HIV positive* |

| Area of inquiry | Themes | Quotes: HPV+ participants |
|---|---|---|
| Understanding HPV +/VIA- (positive HPV-screen, negative VIA triage) result | A positive screening (HPV) followed by negative triage (VIA) and therefore no treatment was confusing for some | I am worried that one day if I don't get screened again, maybe the HPV will develop again. (P0478) *HPV positive, VIA negative, HIV positive*<br>I was a bit worried, because I was HPV positive, and then I was told I am VIA negative. I was a bit confused, but I accepted it. After they said that in the future, a problem can develop and we ought to fix now what we can, I agreed to that, before anything gets bad. I accepted that. (P0068) *HPV positive, VIA negative, HIV negative* |
| | Some participants felt they still needed some kind of treatment, another thought they were treated | *This participant expressed need for treatment despite VIA negative exam:* The treatment in the sense that I am worried that HPV may reoccur on the cervix. And if so, how can it be managed? (P0684) *HPV positive, VIA negative. HIV negative.*<br>They told me I do not have any lesions, so they are going to smear vinegar so as to kill the HPV. (P0685) *HPV positive, VIA negative. HIV negative* |
| Understanding of HPV +/VIA+ result (positive HPV-screen, positive VIA triage) and need for thermal ablation treatment | Understood that a positive VIA meant treatment was indicated | I was told that I have lesions that could lead to cervical cancer. I was also told not to worry and that I would be treated the same day, and I was. (P0131) *HPV positive, VIA positive, HIV negative*<br>I accepted it, because I got treatment for it, as opposed if I had just neglected the situation, it could have been disastrous. But it was a good thing that I came to the hospital and I was assisted. (P0467) *HPV positive, VIA positive. HIV positive* |
| Understanding the purpose of thermocoagulation | Thermal ablation was understood to treat lesions and prevent worsening of disease<br>*No major differences in answers between HIV pos and HIV neg participants | To treat the lesions so that the situation doesn't get worse. (P0467) *HPV positive, VIA positive, HIV positive*<br>They said they wanted to treat the HPV that was on the cervix…To fight the disease… The lesions come about because of HPV, so the thermal ablation treats the lesions. (P0629) *HPV positive, VIA positive, HIV positive* |

that screening would reveal cancer. These are also well-documented concerns in studies on self-collection HPV testing (26, 27) and have been identified as barriers to screening (28). Factors mitigating these concerns, reported by our participants, were anticipatory guidance of what came next after each step of the screening process, quick results, and availability of same-day treatment. Knowing what to expect with a positive result, and knowing there is treatment right away if the result was positive, were identified as two reassuring factors by participants.

## Understanding of HPV-based multi-step CxCa screening

VIA has been the primary screening method, followed by cryotherapy in Malawi's screen-and-treat national strategy for CxCa prevention (12). In our study screening algorithm, several concepts including HPV screening, self-collection of vaginal samples, and thermal ablation treatment were new. Additionally, none of the participants (except one) had heard of HPV or its association with CxCa. A large part of the initial recruitment and consent process for the parent study was spent on explaining the relationship between HPV, cervical dysplasia, and CxCa. When this understanding was assessed though IDIs weeks or even months after screening, most participants accurately described that HPV is a virus that causes cervical lesions, and if untreated, can lead to CxCa. This likely is evidence of successful pre-enrollment education, but also suggests that perhaps participants were already familiar with the concept of a virus causing significant illness (e.g., HIV). Exposure to HIV knowledge could have helped make new disease concepts more understandable. Participants engaged in HIV care may have greater knowledge in this area, but in our study, both WHIV and HIV-negative participants displayed good understanding of HPV (Table 4).

HPV testing has been shown to be difficult to comprehend for women more accustomed to pelvic exams for screening, with the main challenge being failure to understand why a positive HPV test may not lead to immediate treatment (14, 15). We found similar sentiments among three (of twelve) HPV-positive/VIA-negative participants (Table 4). Thematic saturation was reached later with this group due to the variability in understanding. A major hinderance in understanding HPV screening results identified in literature is that patients do not feel that healthcare professionals provide sufficient or understandable information during results delivery (14). When confusion was identified through IDIs, the clinic study staff increased anticipatory guidance of what to except with the VIA triage step and emphasized counseling for those with discordant results so that patients understood why they did not need treatment. The IDIs that occurred after increased counseling efforts revealed less confusion among participants (data not shown).

## Counseling was key to an overall positive screening experience

Ongoing counseling throughout the screening process and anticipatory guidance on what to expect with varying outcomes were key in creating a positive screening experience. Proper counseling leads to understanding, which can increase acceptability, uptake and adherence to routine screening. Counseling can also lead to trust with the healthcare team and mitigates negative psychological effects such as worry and fear, which are well identified barriers to accessing preventative care (29).

Anticipatory guidance was especially helpful in this multi-step screening process. Participants specifically described how knowing what to expect at each step of screening and anticipating what came next after each outcome was helpful in minimizing confusion and reducing negative emotions (Table 5). Anticipatory guidance is most practiced in pediatrics to prepare parents on the expected growth and development of their children (30), but not readily employed in cancer screening. Anticipatory guidance is also naturally present through the informed consent process of research, where each step of the study after each potential outcome is clearly reviewed, and the understanding of participants is assessed. While time can be a limitation in real-world cancer screening programs, our study suggests that the time spent on anticipatory guidance, especially if it involves a multi-step screening process, is invaluable for women to prepare for the emotional challenges of CxCa screening.

## Thermal ablation experience

Thermal ablation was well tolerated by the six participants who underwent treatment. Consistent with prior studies, post-treatment side-effects were minimal and most expressed gratitude for being able to receive treatment right away (13, 31). The major challenge reported was difficulty communicating with their male partners at home. Participants felt that because a period of sexual abstinence was recommended post-treatment, they had to inform their male partners of the procedure, which could lead to misunderstandings, conflicts, and for many, inability to comply with post-treatment abstinence. We saw similar challenges in our prior VIA and thermal ablation study (32) that identified male partners as a barrier to returning for follow-up. However, the prior study also identified male partners as a potential source of support in CxCa screening. Including male partners counseling in screen-and-treat services may be vital for women's safety and acceptance, especially when treatment is indicated.

## Strengths and limitations

This study was successful in reaching and unscreened women. However, being facility-based resulted in a selection of women with access to care. Familiarity with the health system and exposure to health concepts can favorably skew acceptability of the screening procedures. Perspectives from women in rural, hard-to-reach areas need to be considered for successful expansion of this strategy. Notably, a recent study in Malawi that implemented community-based self-collection for HPV screening found that it increased screening uptake (compared to facility-based screening alone) and was acceptable to both clients and health workers (33–35). A strength of this study is that we included both WHIV and HIV-uninfected

women and found no differences in their ability to understand results or perspectives on screening steps. Timing of our IDIs weeks to months after screening allowed us to cover topics such as how women had shared their experiences with their community and barriers faced in remaining abstinent for the recommended period following thermal ablation. On the other hand, the delay between the experience and the IDI could have resulted in some recall bias.

HPV-based screen-and-treat experiences through a research study may differ from real-world clinical settings where providers have higher volumes of patients with more limited staffing and resources. For example, good counseling was overwhelmingly identified as being valued by participants in our study, but time may be more constrained in actual clinical practice, limiting provider time to thoroughly counsel patients about potentially confusing results. In addition, our study utilized additional procedures that would not be routinely implemented in non-study settings, such as colposcopy, Pap smear, and/or biopsy, which could have confounded participant's experiences. However, most patients did not mention the additional procedures, and it did not seem to negatively affect their experiences.

## Conclusion

Self-collection HPV primary screening is a promising method to expand CxCa screening access and increase cervical precancer detection (5, 6). However, the lower specificity of the HPV assay requires a triage test for HPV-positive results to prevent overtreatment (36). As HPV-based multi-step screening is being implemented, our findings provide rich insight for healthcare providers and policymakers surrounding women's experiences undergoing a same-day HPV-based screen-triage-treat algorithm. We captured what was important to women: convenience of self-collection, quick result turnaround, availability of same-day treatment, and thorough counseling. HPV self-collection can overcome barriers to pelvic exams including discomfort, embarrassment and need for trained providers. While a multi-step screening process with VIA triage can lead to confusion about required follow-up procedures, proper counseling and anticipatory guidance can improve understanding. Incorporating thorough counseling in CxCa screening programs can change women's perspective of screening, build trust with healthcare systems, and influence healthcare seeking behavior towards routine screening and prevention.

## Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

## Ethics statement

The studies involving humans were approved by Malawi National Health Sciences Research Committee, University of North Carolina at Chapel Hill Institution Review Board. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

## Author contributions

FL: Data curation, Formal analysis, Investigation, Methodology, Project administration, Validation, Writing – original draft, Writing – review & editing. SM: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Writing – original draft, Writing – review & editing. JC: Data curation, Formal analysis, Investigation, Writing – original draft, Writing – review & editing. WD: Data curation, Investigation, Writing – review & editing. JT: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Supervision, Writing – original draft, Writing – review & editing. MN: Project administration, Writing – review & editing. LM: Project administration, Writing – review & editing. VM: Supervision, Writing – review & editing. JS: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Supervision, Validation, Writing – original draft, Writing – review & editing. LC: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Supervision, Writing – original draft, Writing – review & editing.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## Publisher's note



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# "There is nothing that can prevent me from supporting her:" men's perspectives on their involvement and support of women's use of topical therapy for cervical precancer treatment in Kenya

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**Purpose:** Cervical cancer disproportionately impacts women in low- and middle-income countries (LMICs). The World Health Organization's (WHO) 90/70/90 strategy aims to eliminate cervical cancer by 2030 by increasing HPV vaccination coverage to 90%, screening 70% of eligible women, and effectively treating 90% of those with abnormal results by 2030, potentially preventing 62 million deaths in LMICs. LMICs, however, struggle with limited access to cervical precancer treatment, in part due to a lack of trained professionals and weak health systems. Effective non-surgical, self-administered, which have demonstrated efficacy in high-income countries, could bridge the treatment gap in LMICs and may be more scalable and cost-effective than provider-administered therapies. To inform feasibility studies in LMICs, data are needed on the role of male partners in influencing the acceptability and uptake of self-administered topical therapies, including their support of recommended abstinence and contraception guidelines associated with these therapies.

**Methods:** Between November 2022 and April 2023, we conducted five focus group discussions (FGDs) with men aged 25 to 65 years in Kenya to explore their perspective and perceived support regarding their female partners using topical self-administered therapies for cervical precancer treatment. The FGDs were moderated by local qualitative research assistants and conducted in local languages, transcribed, coded, and analyzed using qualitative description.

**Results:** Thirty-nine male participants meeting the eligibility criteria participated in five FGDs. The mean age of participants was 42.5 years. Most participants,

79.5%, had a female partner with a history of cervical precancer treatment, 5.1% did not, and 15.4% were unsure of their female partner's prior precancer treatment history. The study aimed to assess men's support of their female partners' use of topical therapies for treating cervical precancer. We find that male participants strongly express acceptance and willingness to support their wives or partners in using such therapies, if available. Reported supportive behavior included permitting the use of the therapies and support of maintaining abstinence during the recommended times. Additionally, participants desired male involvement in clinic and community-based education about topical therapies to facilitate widespread support.

**Conclusion:** The use of self-administered topical therapies for cervical precancer treatment, if supported by efficacy studies in LMICs, may support achieving the WHO's 2030 goal of 90% treatment access. We find that with adequate education, men express overwhelming support of their female partner's use of topical therapies, including adherence to abstinence and contraception guidelines.

KEYWORDS

**cervical cancer prevention, cervical cancer screening, low-and middle-income countries, topical therapy, precancer treatment, male involvement, self-administered therapies, human papillomavirus**

## 1 Introduction

In 2018, the World Health Organization (WHO) launched the 90/70/90 global strategy to eliminate cervical cancer, the first-ever global commitment to eliminate a cancer (1). This strategy recognizes that cervical cancer can be prevented through a combination of primary and secondary prevention and calls for 90% human papillomavirus (HPV) vaccination of all girls by age 15 years, 70% of all women receiving cervical cancer screening with a high-performance test at least twice in their lifetime, and 90% of those with an abnormal screening result adequately treated by 2030 (1). Reaching these targets would achieve an elimination threshold of 4 or fewer cases of cervical cancer per 100,000 women globally. Nowhere will these targets make a difference, as in low-and middle-income countries (LMICs), where women bear a dire and unequal burden of cervical cancer. In 2020, it is estimated that of the approximately 600,000 new cervical cancer cases and 342,000 deaths, 85% of the cases and 90% of the deaths occurred in LMICs (2). The burden of cervical cancer is particularly pronounced in sub-Saharan Africa, a reflection in part lack of established health systems (3) and the dual epidemics of human immunodeficiency virus (HIV) and HPV (4) Malawi, in Eastern Africa, has the world's highest mortality from cervical cancer, with 51.5 deaths per 100,000 per year, twice the rate in Eastern Africa (28.6/100,000/year), and seven times the global rate (7.3/100,000/year) (5). As a result, cervical cancer is the leading cause of preventable premature cancer deaths in LMICs, accounting for 26.3% (1.83 million/6.93 million) of the total preventable premature years of life lost from cancer in 2020 (6).

While increasingly more LMICs have established HPV vaccination programs (7) and progress is being made in launching population-based screening programs (8), access to cervical precancer treatment remains significantly limited (9–13). Cervical precancer, also known as cervical intraepithelial neoplasia (CIN), the premalignant lesion caused by persistent infection with HPV, is treatable if identified through screening, preventing progression to cervical cancer (14). Cervical precancer can be diagnosed through various methods, such as visual inspection with acetic acid, colposcopy and biopsy (15), or with the aid of molecular markers (16). However, following screening and identification of precancerous lesions, most women in LMICs lack access to treatment. In a study from Kenya, following community-based HPV screening, only 52% of those who tested HPV-positive and were referred to a health facility for treatment ultimately received treatment within six months (17). Similarly, in a retrospective study on the treatment completion following cervical cancer screening among women living with HIV in South Africa, among 2072 women with abnormal pap smears between 2013 and 2018, only 174 (25.6%) underwent guideline-indicated management within 18 months (11). Between 2011 and 2015 in Malawi, only 43.3% and 31.8% of women with precancer who required cryotherapy or excision, respectively, received treatment (18). Challenges associated with precancer treatment in LMICs include a significant loss-to-follow-up rate, as high as 40-50%, when women screened in rural facilities are required to visit central

referral facilities to access treatment (13), lack of or non-functional treatment devices at referral facilities (18), and fragile health systems with high patient to provider ratio, resulting in significant delays in treatment access due to few or lack of trained personnel (12). In a study from the national referral hospital in Kenya, the median time to excisional treatment among those who successfully made it to the referral facility was 167 days (interquartile range 101-276 days) (19), further increasing the risk of loss-to-follow-up. To achieve the WHO target of 90% of women with cervical precancer receiving treatment globally by 2030, there is an urgent need for scalable, innovative, yet resource-appropriate strategies to close the precancer treatment gap in LMICs, including the use of patient-administered topical therapies.

While no non-surgical therapies are currently approved for the treatment of cervical precancer, the use of topical, non-excisional therapies for cervical precancer is an area of active investigation (20–26). The feasibility (22, 23, 27), acceptability (21, 28), and efficacy of several topical self- or provider-administered therapies for cervical precancer treatment have been demonstrated in several studies in high-income countries (23, 28–30), including randomized trials (20, 21, 24, 31, 32). In a randomized U.S. trial of women with cervical intraepithelial neoplasia grade 2 (CIN2), participants were randomized to 6-month observation or self-administered intravaginal 5-Fluorouracil (5FU) for primary treatment (21). Under intention-to-treat analysis, participants in the 5FU arm had a 1.62 relative risk of CIN2 disease regression (95% CI 1.10-2.56) compared to the observation arm (p=0.01), demonstrating the efficacy of self-administered 5FU cream for treating CIN2 disease. In this study, intravaginal 5FU, used once every other week for eight applications, was safe and highly acceptable, with no moderate or severe adverse events observed. In a 2020 U.S.-based single-arm Phase I study on the use of self-administered intravaginal Artesunate suppositories for primary treatment of cervical intraepithelial neoplasia grade 2 or 3 (CIN2/3), 67.9% of participants had disease regression within 15 weeks of Artesunate self-treatment (23) compared to an observed spontaneous regression rate of 28% over a similar period (33). Similarly, in this study, self-administered intravaginal Artesunate was safe and well-tolerated, with mild and self-limited adverse events. Both topical 5FU and Artesunate are on the WHO Model List of Essential Medications (34)and could feasibly be repurposed as self-administered cervical precancer treatment (21) if backed by feasibility, acceptability, and efficacy studies from LMICs. Compared to the standard-of-care provider-administered cervical precancer treatment methods, which are often inaccessible in LMICs, patient-administered topical therapies with cytotoxic or antiviral properties may be a highly scalable and cost-effective method to bridge the current precancer treatment gap in LMICs. Additionally, excisional precancer treatment methods are associated with obstetric complications, including preterm birth (35), which are particularly consequential in LMICs where access to neonatal care is limited (36).

To inform feasibility and efficacy studies on the use of topical therapies for cervical precancer treatment among women in LMICs, data are needed on the role of male partners in influencing their acceptability and uptake of such an intervention. Sexual and reproductive health (SRH) experts have long speculated about the importance of involving male partners in the SRH of women around the world (37–40). To increase women's participation in cervical cancer screening, the WHO recommends engagement of male partners through targeted health education about cervical cancer, underscoring the crucial role of men in prevention efforts (41). Similarly, to understand the potential impact of self-administered topical therapies for cervical precancer treatment in LMICs, the role of men as decision-makers in this context should be considered (42). Recent research in Uganda and Ghana shows that, contrary to some studies that view male partners as obstacles, male partners actually support cervical cancer prevention for their wives and daughters (43–45). Such discrepancies indicate that more research is needed to understand the beliefs underlying male support of cervical cancer prevention, especially as novel treatments such as self-administered topical precancer treatments may have requirements such as contraception use or abstinence for short time frames. For many women, negotiating SRH interventions requires permission and cooperation from their male partner.

To fill this gap in the literature, the objective of this study is to examine men's perspectives on their female partners' use of topical, self-administered therapies for cervical precancer treatment, including their intentions to support their female partner's use of such therapies and the roles of male partners as facilitators to treatment uptake and adherence were they to become available for public use.

# 2 Methods

## 2.1 Study design and recruitment

This cross-sectional study sequentially recruited men ages 25 to 65 years attending outpatient clinics in Kisumu County, Kenya, between November 2022 and April 2023 to participate in focus group discussions (FGDs). Inclusion criteria required that all participants have a current female partner. We used a stepped recruitment approach for the FGDs. Participants in the focus group were a subset of men who had previously participated in a survey. This survey assessed men's views on the use of self-administered therapies for the treatment of cervical precancer in their female partners, should such treatments be recommended. All men participating in the survey were invited to participate in FGDs, but a focus was placed on recruiting men whose female partners had a history of cervical precancer treatment. A total of 39 men participated in five FGDs. A sample size of five focus groups was determined *a priori* based on evidence suggesting most themes are captured in three to six focus groups (46).

We adopted a constructivist paradigm to understand men's views regarding cervical cancer screening and prevention, including the treatment of HPV and cervical precancer. We also explored their opinions, perceived acceptability, and support of their female partners' use of self-administered topical therapies for cervical precancer treatment were it to be recommended by a health provider. Constructivism posits that understanding is derived (i.e., constructed) based on one's perceptions, experiences, and social

contexts (47). Therefore, we hypothesized that men's acceptability of topical, self-administered therapies is based, in part, on their experiences (such as having a female partner who had ever been diagnosed with HPV or cervical precancer or cancer and prior experiences with the health system) and their social contexts (such as relationships with sexual partners).

## 2.2 Research team

The research team included the principal investigator (CM), a Kenyan-born practicing obstetrician/gynecologist with seven years of experience, graduate students in medicine, social work, and public health (KA, SKG, GZ), a senior qualitative investigator with nearly 20 years of experience in qualitative methods and health services research (RMF), and a senior gynecologist with over 15 years experience studying topical therapies in the U.S context (LR). The focus groups were moderated and transcribed by two qualitative research assistants from the local community who spoke local languages and were conversant with the local culture (EA, JO). The moderators had training in qualitative research, prior experience conducting FDGs, familiarity with the local context, and fluency in the local languages. The moderators also received additional training from the principal investigator on the study topic, protocol, and informed consent.

## 2.3 Data collection, transcription, and translation

FGDs included five to eight participants each and were held in facilities that were geographically convenient to the recruiting clinics. The FGDs were conducted in the two most spoken local languages (*Swahili* and *Dholuo*) and were guided by several domains of inquiry: 1) baseline knowledge of HPV and cervical cancer screening and prevention, 2) perception of the female partner's risk of HPV or cervical cancer, 3) prior experience of a female partner undergoing cervical precancer treatment, 4) perceived support of and acceptability of female partners using self-administered topical therapies for HPV or cervical precancer treatment, 5) perceived barriers and facilitators of the use of topical therapies among female partners. During the FGDs, participants were introduced to two potential self-administered, intravaginal topical therapies for precancer treatment for which data are available: 5FU and Artesunate. Details provided included potential usage frequency (5FU once every other week for eight applications, Artesunate daily for five days for three cycles), abstinence requirements (two to three days of abstinence after each 5FU application and none for Artesunate), and the recommendation of consistent contraception use while using both therapies. The FGD participants' perceptions and perceived support of their female partner's use of topical therapies were explored in a hypothetical scenario in which the participants' female partners needed precancer treatment and a topical therapy was recommended, with discussions about male partner support of the various requirements including abstinence or contraception requirements. Each FGD lasted approximately 90 minutes. To promote a certain degree of anonymity, participants identified themselves by respondent number (e.g., R1, R2…R8). All FGDs were audio recorded and transcribed verbatim and translated from *Swahili* and *Dholuo* to *English* by the FGD moderators. The two moderators crosschecked the translations to confirm that the translations captured all discussions that were recorded (48).

## 2.4 Data analysis

A codebook was created during the coding process through agreement among two coders (GZ, SKG) who read and coded two of the five FGD transcripts to gain a sense of topics covered and group discussions. All FGD transcripts were coded using the developed codebook. To ensure inter-coder agreement, a subset of transcripts was randomly selected, and codes were compared for agreement; discrepancies were resolved through discussion and consensus, with revisions documented in the codebook. Content analysis was performed using NVivo V1.71.

Because the proposed topical treatment is novel in this context, our analysis involved using qualitative description, which is well-suited for increasing understanding in an area with limited knowledge (49). As this approach stays 'close' to the data with minimal interpretation, qualitative description supported our intent of straightforward description of participant experiences that included describing and relaying perspectives using participants' own experiences and language. Coding reports were generated from NVivo and carefully reviewed to identify themes relating to male involvement and support of cervical precancer treatment. Themes included: 1) participants' knowledge and awareness of cervical cancer, 2) reasons behind their intention to support their partners in the uptake of self-administered topical treatment were it to become available, 3) their perceptions of themselves as facilitators to care, and 4) education as a facilitator to male partner support.

## 2.5 Ethical considerations

The study was approved by the ethics review boards at Maseno University School of Medicine in Kenya (MUSERC/01136/22) and the University of North Carolina at Chapel Hill in the U.S (22-1978). All participants provided consent prior to participation in the study.

# 3 Results

Thirty-nine male participants meeting the eligibility criteria participated in five FGDs. The mean age of participants was 42.5 years (standard deviation 6.3). Most participants, 31 (79.5%), had a female partner with a history of cervical precancer treatment, 2 (5.1%) did not, and 6 (15.4%) were unsure of their female partner's prior precancer treatment history.

## 3.1 Knowledge of cervical cancer

Most of the participants had some previous knowledge of or exposure to cervical cancer. Sources of knowledge included family or community members who had had cervical precancer or cancer, as well as television, radio, and community education sessions.

> There was a time when we were called for a brief meeting, and we were told to encourage our wives and partners to be going for cervical cancer screening and treatment. - (R4, FGD1)

Some participants mentioned having known someone who *"suffered"* from cervical cancer. One participant cited his previous exposure to cervical cancer as the driver for permitting his wife to get screening, while another cited it as motivation to learn more about the disease.

> What I have heard is that one of my relatives had her womb removed, that is hysterectomy for her to survive. She is still alive but cannot bear children, and so, whenever I hear anything to do with cancer, that memory comes to my mind and I imagine how serious the disease is. I am usually interested in knowing what type of cancer it is, and thus my curiosity to join this group and even allowed my wife to come for screening for cervical cancer. I saw my relative suffer from it and I know it is a serious thing. - (R2, FGD1)

> Cervical cancer is such a great problem, my sister-in-law succumbed to it … So, whenever I hear about cancer having seen my in-law suffer, I am usually keen on [learning] anything about cancer, regardless of the type. - (R3, FGD1)

Though participants had several questions about cervical cancer, and cancer in general, including questions about its acquisition, most believed that cancer was deadly, screen-able, and preventable.

> I have heard that cervical cancer, when screened or tested early, it is easy to manage, but when it has advanced, it becomes very difficult to treat. It will worsen and may not be cured. So, I usually hear that people should know their status as far as cancer is concerned early enough, so that you be put on treatment or you be sure that you do not have it. - (R8, FGD5)

## 3.2 Male partner involvement

### 3.2.1 Intention to support female partner's use of self-administered precancer therapy

The focus group discussions involved brief education sessions on the relationship between HPV and cervical cancer, the efficaciousness of two topical treatments currently being studied (5FU and Artesunate) as self-administered cervical precancer treatments, the treatment protocol of both drugs (including condom use and abstinence requirements for each), and the recommendation for women to use a tampon during treatment and why. When asked, all the FGD participants reported a willingness and intention to support their wife's or female partner's uptake of and adherence to topical, self-administered therapies for cervical precancer treatment, were it to be recommended by a healthcare provider. The beliefs underlying their intention to support were related to 1) their beliefs about cancer, 2) their understanding of the effectiveness of topical therapies presented (after it was explained to them by the FGD moderator), and 3) their perception of partner and family dynamics.

As previously mentioned, most men in the study had some baseline understanding of, or prior exposure to, cervical cancer or cancer in general. When asked if they would support their wives through cervical precancer treatment, including the use of topical, self-administered therapies, some participants stated that they would support her because they believed that cancer was deadly. However, they also believed that a cancer diagnosis was preventable if discovered and treated early. This belief was a driving factor for support.

> I can support her [to use topical self-administered therapies for precancer treatment] because cancer is a killer disease, and if it is discovered early, it can be prevented, so, I can support my wife to use the cream. - (R3, FGD3)

Men also cited believing in the effectiveness of the drugs to prevent cervical cancer as a primary reason for their acceptance and support of their use.

> I will definitely agree [to support her to use the topical therapies discussed] and she will take it too because once a disease sets in, treatment is the only remedy and cream will do it very well. - (R2, FGD5)

Men also cited their interpersonal family dynamics as reasons to support their female partner or wife's screening and precancer treatment uptake. Some men mentioned believing that a cancer diagnosis impacted all the members of the family, including the male partner himself, while others believed that mutual support and knowing about each other's health was an integral part of the partnership.

> There is nothing that can prevent me from supporting her, if the two of you [male and female partner] sit and talk things [through] together. - (R1, FGD4)

> Our wives or partners should be screened for cervical cancer so that they get treatment early enough. You see, in case our wives have cervical cancer, we as their husbands are also affected. - (R1, FGD1)

> Yes, I want to say that when couples live together, they live as a unit and so, they know each other's issues and details. Even today as I came for my ARV (antiretroviral therapy) refill, she knows that I came for my drugs and so, why should she keep anything off from me, or why should I refuse that she doesn't use the cream, yet I know it is for her own good? - (R5, FGD5)

### 3.2.2 Male partner's perception of themselves as facilitators to uptake and adherence

Beyond an intention to support their partner, participants believed that if they supported their partner, she would be more likely to take up and adhere to cervical precancer treatment, including the use of self-administered topical therapy. Participants emphasized that if male partners were educated about cervical cancer prevention, they would be able to present the information to their wives, positively influencing their decision to use recommended cervical precancer treatment.

Participants also emphasized the importance of their partner's agency, stating that they would not or could not force her to use treatment, choosing to focus on support through encouragement and education.

> She will agree, after full and thorough explanation [from the male partner]. It will not be me forcing her to use the cream, but she will voluntarily accept because it is [a] source of healing. I will also take my time and explain to her the importance of this cream now that I have also understood it. I know that she will definitely agree to use it. - (R1, FGD5)

Nevertheless, most participants believed that their own (male partner) involvement would influence their female partner's decisions to use a self-administered topical therapy, like a cream, for cervical precancer treatment.

> I would say that women usually are hesitant to use certain things because they are not sure of their husband's reaction to whatever it is that they want to use. And so, they keep asking themselves whether the husband would be in agreement with new ideas she has learnt from elsewhere. But if there is openness in the family more so between husband and wife, then there will be free communication and the wife will use the cream fully without any fear. If the wife see[s] that you [male partner] are understanding what is going on and understanding her position, definitely she cannot refuse to use the cream. I know that men's fear of new ideas or their failure to accept new methods would push the women into refusing to use cream. - (R8, FGD5)

> Once the woman is taught the importance of this cream, she will definitely use it, because as her husband, if I have come for the teaching and I now understand what it takes to use the cream and I give her my full support, she will agree to use the cream for treatment of HPV or precancer of the cervix. - (R6, FGD1)

### 3.2.3 Ways that male partners perceive themselves to be facilitators to uptake and adherence

Participants stated ways that they intended to support their partner who may need to use self-administered therapies. Intended support highlighted ways in which men perceived themselves as facilitators of treatment uptake and adherence. This included: 1) maintaining abstinence as part of adhering to treatment protocol, 2) providing emotional support such as permission or encouragement to uptake treatment, 3) and providing financial support. Though maintaining sexual abstinence during periods of use of topical therapies has been considered a potential barrier to male partner support of topical therapies, the FGD participants unanimously asserted that they themselves were willing and able to maintain abstinence or condom use as needed if their partner were using a topical therapy, citing their understanding of the reason for the topical treatments as a key motivator of support.

> For those who have been taught like ourselves, [maintaining] abstinence is not a challenge, because we know what should be done. It will be a great challenge to those who have not been taught about cervical cancer. - (R5, FGD1)

> I don't think there is any challenge in that [maintaining abstinence or using condoms]. You know the reason why you should use condoms. Also, you that there are specific times you should not have sex with your wife. If you don't then its fine. When you see your wife applying that cream, you know why. If you know, I don't think if there can be any problem. - (R3, FGD4)

Second to maintaining abstinence, emotional support emerged as the greatest male support-related theme throughout the FGDs. Emotional support practices cited by participants included providing their female partners permission to receive cervical cancer screening and treatment, encouraging their partner to take up treatment if they needed it, reminders to adhere to treatment timing in case of self-administered treatment used at home, maintaining open communication, and general encouragement including maintaining hope during the treatment course.

> I would allow her [to use topical therapies], and I know that she will definitely go for it [if] she was found to be positive with HPV or precancer. The use of cream is good since it will help clear the precancer and so, she will not have cancer of the cervix - (R5, FGD5)

> I heard it in [the] Radio station when they were announcing it. I used to hear it keenly and know what the disease is. It attacks

> any part of the body whether throat or private parts, so when I heard that. I did not take it seriously, it just something that is there. So later, when my wife went for screening, she [came] back and told me. They told me I had precancer, and I told her that precancer is treatable and she should [not] have stress. She became emotional and I told her that is part of life, so just be calm. You have been told you just have precancer but there are some people who have cancer. Just be calm and follow the direction that you will be given by the doctor. Later she was calm and even asked for a reassurance to know if she will be fine. She has been coming for some health talk in the hospital and she is fine now. - (R6, FGD2)

One participant noted the ways in which open communication dynamics between male and female partners could support adherence to use of self-administered topical therapies, in which case the male partner can remind his female partner to use the cream if she has forgotten.

> Just like R7 has mentioned it needs being open. Even if she forgets to apply it then you can remind her to use the cream. I don't see any challenge in supporting them. Because if we have been supporting each other, I can't fail to support her in that. - (R3, FGD2)

Most participants expressed a willingness to pay for the treatment, while some mentioned a willingness to pay for transportation to health facilities to receive treatment.

> I would facilitate her going to hospital like giving her fare for boda boda [bicycle] or bus fare. You also look into and arrange how the household chores that she could have executed will be performed. - (R2, FGD5)

## 3.3 Facilitators to male partner support

Male partner education emerged as the greatest facilitator of male partner support of women's topical therapy use. Men emphasized the need for education in helping other men understand the importance of maintaining abstinence as needed when their female partner was using topical therapies.

> My wife told me about the cream but I want to learn more about it so that we, as men also get enlightened and thereby eliminating disagreement between couples. Through that [male partner education], gender-related violence will be eliminated, otherwise this thing is likely to cause chaos within marriages because the woman will want her partner or her husband to abstain because she is on medication and yet, the man doesn't understand why he must abstain from sex for a certain period. - (R2, FGD1)

> The partner may resist the idea of abstinence from sex because he has not been inducted [educated] fully. The wife will tell him that they cannot have sex because she is on medication, but the husband will not understand. Therefore, it is better for men to be taught about all the information concerning cervical cancer. - (R6, FGD1)

Suggestions for male partner education included: 1) male involvement within a clinical context and 2) male partner targeted community-based education. Some participants suggested that men attend clinic visits with their partner to receive information about topical treatment from a health care provider, citing that this would make maintaining abstinence *"easier"*.

> If possible, the health care provider should tell her to come with the husband and explain things to him. So, we come together and I also listen as she is being explained to. So that is if she is given the cream then it is easier. - (R6, FGD4)

Other suggestions included providing women with educational material or *"newsletters"* from the clinic or calling male partners on the phone.

> Women go with their husbands when going to the clinic or they be given newsletters to take home for the husbands to read. - (R6, FGD3)

> In my view we [male partners] should just be given these forms to read. After here I will also sit down with my wife and talk about it. The best thing is to first give the women that form to take home. - (R5, FDG4)

Community-targeted education suggestions included *"group counseling"* such as having education meetings at chief barazas (meetings), providing information on the radio, providing cervical cancer treatment education in people's homes, and male peer education.

> I would say that proper and wide information reach should be enhanced in order to include every [person] in the community. - (R3, FGD1)

Participants suggested that community-targeted education about new self-administered cervical precancer treatment could mitigate potential interpersonal conflicts or *"violence"* that may

arise from the need to maintain abstinence or general ignorance about topical therapies were they to be prescribed to women.

> It can bring violence in the house, what l would request that before the use of this cream, there should be advertisements through chief barazas[meetings] or radios for us to have prior knowledge that even one day if your wife decides to do [use a self-administered treatment] it then we have a knowledge about it. - (R2, FGD3)

Another participant referenced how previous HIV/AIDs *"awareness"* campaigns that helped reduce stigma around HIV/AIDs to highlight the importance of community-targeted education methods in normalizing cervical pre-cancer treatment and increasing awareness of self-administered treatments.

> [I] am very thankful for this because it something that saves life. What we should know is how to it should be accessible to everybody. My plea is that you involve also village elders, also door to door. Distributing the health care providers as they teach people around. It [door to door teaching] can [be] easier because gathering people is also not easy. Also, there are people who are shy because they are afraid of questions that might pop in. like HIV/AIDs, when it started there were some who would not even sit here that they are hiding from people they know. For us to overcome the fear just like when HIV was here. They [healthcare workers] would come even at the house to do awareness so that people are comfortable. So, like this if it [education] can be done also in the house, where both partners are sitting together. - (R8, FGD4)

Another participant highlighted the ways in which male partners themselves could be facilitators to male partner education.

> To use [male partners] who have learnt this [cervical precancer treatment] and have been taught on this it is not hard. But for those who have [not] received the information [maintaining abstinence and using condoms] will be hard for them … We will also go outside and teach others…. There are men who will not use condoms [with] their wives. There are men who when they will see that their wife is applying that cream, it will be like there is something that woman is not telling him. We should fight this and even tell our neighbors, friends what this [topical treatment] is. Even if he [finds] - his wife using, he will say that is true. His neighbor told him. - (R7, FGD4)

# 4 Discussion

In this study evaluating men's perspectives of their female partners' use of topical, self-administered therapies for cervical precancer treatment in Kenya, we found that men were highly supportive of topical treatments after the treatment's importance, efficacy, and use were explained to them. We also found that many participants perceived themselves to be key facilitators of their female partner's ability and willingness to use topical self-administered therapies. All the participants reported an intention to support their partner were she to be prescribed a topical therapy. Proposed supportive behaviors included giving their partner permission to use topical therapy and adherence to abstinence and condom use requirements associated with topical therapies. Participants also highlighted the importance of male partner education, both in the clinic and in the community, to facilitate male support of topical therapies and to mitigate any potential violence resulting from not understanding the need for abstinence during treatment. Proposed education strategies included explanations about treatment from a health professional when men accompany women to the clinic, distributing educational materials to women during clinic visits to take home, and initiating community-targeted awareness campaigns to raise public awareness about topical treatments.

To our knowledge, this is the first qualitative study to explore men's perspectives on self-administered therapies for cervical precancer treatment in an LMIC setting and their perceived support of their female partner's use of them, should they become available. We found that men believed that male partners understanding, acceptance, and support of novel treatment methods, including self-administered therapies, would increase the likelihood of their female partner adopting and adhering to the proposed treatment. They believed that this was due, in part, to a woman's ability to use the treatment without fear of male partner disapproval. Though they emphasized that they would not force their partners to use such a treatment, the ways in which men defined their intention to support their partners highlighted the ways that male partners may be gatekeepers to a woman's ability to use topical, self-administered therapies (42). For instance, we found that participants viewed giving their partner permission to seek treatment as a form of support. Therefore, in settings where men are viewed as primary decision-makers of the family, a woman's ability to use self-administered therapies for cervical precancer treatment may depend on the involvement of her male partner if she has one (42).

These findings are consistent with studies examining women's perspectives on how male partner involvement influences their ability and likelihood of utilizing sexual and reproductive health services in LMICs (42, 50–53). For example, one study found that women who attended their post-treatment follow-up visit as part of an HPV-based cervical cancer screening program in Western Kenya more often identified their male partners as supportive, compared to women who did not return and were considered "lost to follow-up" (43). This suggests that the lack of male partner support contributes to women's inability to adhere to follow-up recommendations in this setting. In the context of self-administered therapies, a Zimbabwean study evaluating the effect of male involvement on women's adherence to female-initiated HIV prevention methods, such as microbicide gels, found that women were more likely to use the study products if they believed their male partner supported their use (54).

Because of the pro-inflammatory nature of potential intravaginal therapies for cervical precancer, including 5FU, abstinence for specific periods around their use is recommended (20–22, 24, 55).Use of these therapies is associated with acute inflammatory changes, including transient erythema and edema of the vaginal mucosa, and mild side effects, including increased discharge, spotting, or irritation, are common (20, 21, 24, 28). In a few cases, superficial, self-limited erosions of the vaginal or epithelial mucosa have been observed (22). Inability to adhere to abstinence recommendations while using these therapies may be associated with worse side effects, potentially increasing a woman's risk of contracting sexually transmitted infections, including HIV (21) and may expose the partner to the agent in case of barrierless intercourse. Similarly, as some topical agents are teratogenic when used systemically, women must use contraception during their use to avoid pregnancy. Therefore, women's ability to negotiate abstinence and contraception use with their male partners is a critical aspect of the safety and feasibility of widespread use of these therapies in contexts where women may have less agency (56). Studies generally advise two to three days of sexual abstinence following each application of 5FU and contraception throughout the treatment to prevent pregnancy.

In exploring men's willingness to maintain abstinence for recommended periods of time when their female partners use these therapies, we found that an overwhelming majority of the FGD participants reported a willingness to maintain abstinence in support of their partner's treatment. Participants said that following appropriate teaching or education "*abstinence or condom use is not a challenge because we know [why] it should be done*." Participants added that maintaining abstinence may be a "*great challenge among those who have not been taught*," emphasizing that *"as men get enlightened,"* it would help *"[eliminate] disagreement between couples*." One participant highlighted that through male partner education around abstinence and condom use requirements, "*gender-based violence*" can be prevented; "*otherwise, this is likely to cause chaos within marriages*." This is particularly important when condom use is recommended among married couples, as "*there are men who will not use condoms with their wives*," and without adequate education, seeing a female partner using a topical therapy, some may feel like "*there is something [she] is not telling him*." Though all participants claimed that they themselves could maintain abstinence, their strong emphasis on male partner "*education*" to promote treatment acceptance, especially as it pertained to abstinence and condom use, sheds light on the importance of male partner involvement in facilitating male support of topical therapies like 5FU. Despite using "*education*" as an all-encompassing term, participants' suggestions were indicative of a desire for (1) male involvement in the treatment-seeking behaviors of their female partner and (2) awareness-raising campaigns that normalize the existence and use of topical precancer treatments. Further, participants' emphasis on the inability of "*other men*" to maintain abstinence and the need to educate "*other men*" on abstinence requirements may be indicative of an unwillingness to acknowledge abstinence as a personal barrier to female partner support within an FGD setting.

The ability of women receiving cervical precancer treatment in LMICs to adhere to post-treatment abstinence recommendations remains a question in the literature (57). Following conventional cervical precancer treatment, guidelines recommend avoiding sexual intercourse for four to six weeks to allow healing of the cervix or using condoms for those who cannot abstain (58). Research in LMICs has found male partners to be both a perceived and experienced barrier to adherence to post-treatment abstinence recommendations (43, 51). A study in Malawi assessing barriers to follow-up after an abnormal cervical cancer screening result found that although some women cited their partners as supportive of treatment, they were still unable to maintain abstinence for the recommended period (51). Another study found that women who underwent cryotherapy in Peru felt pressure from their male partners to engage in sex sooner than recommended, though this was a small minority (59). A Kenyan study found that 16% of women reported not adhering to abstinence recommendations after undergoing an excisional procedure for cervical precancer treatment (60). This discrepancy between our FGD participants' expressed willingness to maintain abstinence was their partner to use a topical therapy requiring intermittent abstinence and women's concerns or experiences to the contrary in the literature needs further study. It may highlight men's preference for therapies that have shorter abstinence requirements (e.g., 2-3 days after each use of a topical therapy, compared to 4-6 weeks after an ablative or excisional procedure), providing an additional advantage of topical therapies in this context. Alternatively, the FGD participant's responses may be affected by social desirability bias. To inform this, data are needed from LMIC-based studies on adherence to abstinence requirements among couples when a female partner is using topical therapies for cervical precancer treatment.

Suggestions for male involvement in the supporting use of topical therapies among their female partners included having male partners accompany their wives or female partners to clinic visits to seek information from healthcare professionals or sending women home with written educational materials directed towards their male partner, explaining the diagnosis and treatment requirements. This is consistent with a study in Kenya that found that male partners were willing and interested in accompanying their partner to maternal and child health to help facilitate uptake (50). Although women highly value and perceive the presence of male partners at clinical services as supportive, several SRH studies have identified obstacles to such accompaniment, including transportation costs, a need to work during clinic hours, and a lack of interest from male partners (42, 53, 54, 61, 62). Research on methods to encourage male partner participation in counseling sessions for topical precancer treatment, along with the use of education messages customized to local contexts, can shed light on how these strategies can impact the uptake of topical therapies in LMICs. Additionally, the impact of community-focused campaigns to raise awareness about possible new precancer treatments, like the topical therapies, as recommended in the FGDs, can be investigated to help normalize these treatments should they become available.

Supported by the expressed desire for male partner education, we believe that the unanimous intention to support and the general acceptance of the topical therapies reported in the FGDs was due, in part, to the information about topical therapies, including their

potential use and efficacy that participants received in the focus groups. This provides further indication that medical information about topical therapies for precancer treatment, provided by a trusted "*health professional*," is an important facilitator towards male partner involvement in the uptake and adherence to topical precancer treatment among women in LMICs.

This study has several strengths. To our knowledge, it is the first study to qualitatively evaluate the perception of African men on their female partner's use of self-administered topical therapies for cervical precancer treatment. As such, the study addresses a potential key barrier to the use of such therapies in low-resource settings, demonstrating significant support of this novel intervention among an important group. Our findings highlight important issues that can be addressed in future studies to support successful implementation of the use of topical therapies. There are several limitations to this study. Since participants were explicitly asked if they were willing to support their partner through treatment, it is possible that the responses were influenced by perceived pressure to provide a socially desirable response within a group setting. Further studies in non-group settings, including individual interviews or anonymous surveys, may further inform whether responses may differ outside a group setting. Another potential limitation is that participants in this study may not be representative of the general population due to the intentional recruitment of men whose partners had disclosed their cervical precancer treatment history, accounting for 80% of participants. Prior research suggests that an inability to seek treatment or fears about male partners as barriers to treatment often involve an inability to disclose their screening results to male partners for fears of repercussions such as accusations of promiscuity (63). Therefore, our study participants may be more likely to support topical therapies than men in the general population or those whose partners did not disclose their precancer treatment. While future studies can include a more representative sample of men, we believe that our sampling strategy is suitable for an initial study on men's perceptions of topical therapies in this context.

In summary, in this study evaluating men's perceptions of their female partner's use of self-administered topical therapies for cervical precancer treatment in an LMIC, we find that, after a brief explanation of topical therapies and their potential role in precancer treatment, male study partners, all of whom had a current female partner, and a majority of whom had a partner with a history of cervical precancer treatment, were overwhelmingly accepting of their female partner's use of self-administered topical therapies for the treatment of cervical precancer. Additionally, after receiving the said explanation, participants stated that they were willing to maintain abstinence and use condoms as necessary for treatment, though their emphasis was that "*other men*" (who may not be educated about topical therapies) may not be as willing to maintain abstinence without adequate education. Men's perception of their influence over their partner's ability and willingness to use such therapies highlights the ways in which male partners may be the gatekeepers of their female partner's reproductive health in this context. These findings highlight an opportunity for studies to engage male partners in ongoing and future studies investigating the use of topical therapies to help close the cervical precancer treatment gap in LMICs.

## Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

## Ethics statement

The studies involving humans were approved by Maseno University School of Medicine in Kenya and the University of North Carolina at Chapel Hill in the United States. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

## Author contributions

CM: Writing – original draft, Writing – review & editing, Conceptualization, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision. KA: Writing – original draft, Writing – review & editing, Validation. EA: Writing – original draft, Writing – review & editing, Formal analysis, Methodology. GZ: Writing – original draft, Writing – review & editing, Formal analysis, Validation. SG: Writing – original draft, Writing – review & editing, Formal analysis, Validation. CO: Writing – original draft, Writing – review & editing, Project administration, Supervision. JO: Writing – original draft, Writing – review & editing, Project administration, Supervision. RF: Writing – original draft, Writing – review & editing, Formal analysis, Methodology. LR: Writing – original draft, Writing – review & editing, Conceptualization.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## Publisher's note



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# The efficacy and safety of local 5-aminolevulinic acid-based photodynamic therapy in the treatment of cervical high-grade squamous intraepithelial lesion: a single center retrospective observational study

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**Background:** Typical treatments for cervical high-grade squamous intraepithelial lesion (HSIL) are invasive procedures. However, these procedures often come with several severe side effects, despite their positive effects on cervical HSIL. 5-aminolevulinic acid photodynamic therapy (ALA-PDT) is a non-invasive treatment that has been successfully used to treat cervical low-grade squamous intraepithelial lesion (LSIL). In this study, we aimed to further investigate the clinical efficacy and safety of ALA-PDT in the treatment of patients with cervical HSIL.

**Methods:** A total of 40 patients aged 20 - 41 years with cervical HSIL and high-risk Human Papilloma Virus (HR-HPV) infections were enrolled in this retrospective study from January 2019 to December 2022. Patients were treated with six times of ALA-PDT at intervals of 7–14 days. Three months after the treatment, the efficacy was evaluated through HPV genotyping and cervical cytology examination. If the cytological result was worse than ASC -US, the patient underwent colposcopy-directed biopsy immediately. Otherwise, patients would receive rigorous follow-up observation.

**Results:** Three months after receiving ALA-PDT treatment, 65% (26/40) of cervical HSIL patients at our center showed complete regression (cytological result: normal; HR-HPV: negative). This rate increased to 82.5% (33/40) at the 12-month follow-up. None of the patients experienced disease progression after ALA-PDT therapy. The risk of persistent HR-HPV infection was 32.5% (13/40) at the 3-month follow-up after ALA-PDT. Multivariate analyses identified cervical canal involvement as an independent risk factor for persistent HR-HPV infection at the 3-month follow-up after ALA-PDT treatment. During the treatment of the 40 patients with ALA-PDT, there were no reports of severe adverse reactions. Only a limited number of patients experienced slight discomfort symptoms.

**Conclusion:** ALA-PDT is safe and effective noninvasive therapy for patients with cervical HSIL and HR-HPV infections. It is particularly suitable for young women, who have been confirmed with cervical HSIL and have demand for fertility protection. Three months after ALA-PDT treatment, if a patient still has either ASC-US cervical cytological result and/or HR-HPV infection, rigorous observation is considered safe for her. Cervical canal involvement is an independent risk factor for persistent HR-HPV infection at the 3-month follow-up after ALA-PDT treatment.

KEYWORDS

**photodynamic therapy, 5-aminolevulinic acid, cervical high-grade squamous intraepithelial lesion, high-risk HPV, cervical cancer**

# 1 Introduction

Cervical cancer is a highly prevalent and severe life-threatening malignancy among women worldwide. More than 85% of cervical cancer cases take place in developing countries (1). Notably, in China alone, there were approximately 150,700 new cases and 55,700 deaths in 2022 (2). Hence, cervical cancer is a major public health problem affecting women in China. Histologically confirmed cervical HSIL, a precursor to cervical cancer, occurs as a result of persistent HR-HPV infection, has a risk of 20-30% to progress into invasive carcinoma within 10 years (3). Conventionally, managements for cervical HSIL including cold knife conization, laser conization, laser ablation and loop electrosurgical excision procedure (LEEP) (4), which can lead to cervical distortion, excessive destruction of tissue, and subsequent obstetric complications such as preterm labor, premature rupture of amniotic membranes, chorioamnionitis, low birth weight, and increased morbidity in the newborns (5–7). In China, with the gradual liberalization of fertility policies and the younger onset age of the female lower genital tract diseases, there is an increasing demand to protect normal cervical structure and preserve fertility. Therefore, there is a desirable need to explore effective conservative treatments with minimal damage and fewer adverse reactions for managing cervical HSIL.

Photodynamic therapy (PDT) is an emerging alternative technique for the treatment of squamous intraepithelial lesions. It works through the interaction of photosensitizing agents, light and oxygen, providing a non-invasive, effective and targeted treatment (8). 5-aminolevulinic acid (5-ALA), as a second-generation photosensitizer, can accumulate in higher concentrations in pathological cells and absorb light of the appropriate wavelength. This initiates the photodynamic reactions and selective destruction of inappropriate tissues (8, 9). In recent years, several studies have reported the satisfactory efficacy and safety of PDT in treating cervical LSIL (10–13). Chinese experts in gynecology and obstetrics unanimously recognized the importance of 5-aminolevulinic acid-based photodynamic therapy and reached a consensus on its clinical application in female lower genital tract diseases in 2022 (14). However, there are insufficient studies evaluating the efficacy of ALA-PDT for patients with cervical HSIL.

Our center, being one of the early adopters of ALA-PDT for treating female lower genital tract disorders, implemented this program in 2019. In this retrospective observational survey, we aimed to investigate the effectiveness and safety of ALA-PDT as a potential option for patients with cervical HSIL, as well as identify factors that impact its efficacy.

# 2 Materials and methods

## 2.1 Patients

The ALA-PDT treatment for female lower genital tract diseases was approved by the Ethics Committee at Hangzhou First people's Hospital (Reference Number: 2021-010-01). A total of 40 patients with pathologically confirmed cervical HSIL who had undergone ALA-PDT at Hangzhou First people's Hospital from Jan 2019 to Dec 2022 were enrolled in this study. Biopsies were taken under colposcopy guidance from the acetowhite and iodine unstained areas to obtain pathological tissues. All participants should have a strong desire to preserve the integrity and function of the cervix and voluntarily agreed to undergo ALA-PDT treatment with good compliance. Most of the patients selected had a pathologic diagnosis of CIN II. In our institution, we generally recommended surgical treatment for CIN III, unless the patient was fully informed and insisted on PDT. Histological results were assessed according to the 2014 World Health Organization Classification of female genital tumors (15): (1) normal, (2) low-grade squamous intraepithelial lesion, (3) high-grade squamous intraepithelial lesion (CIN II or CIN III), and (4) squamous cell carcinoma. All the enrolled patients had satisfactory colposcopy examination and their cervical transformation zones were required of entire visibility. Patients with type 3 transformation zones were

not recommended for inclusion in the study. During the treatment and 3-month follow-up period, patients were required to abstain from intercourse. Informed consents were obtained from all participants before treatment. Patients with suspected invasive cancers or other kinds of lower tract disorders were excluded. Women in pregnancy and lactation should not be included in this study.

## 2.2 Cytological tests

Cytology tests were performed using a fully automated liquid-based cytology assay technology method (BD SurePath™) to evaluate abnormal cells. The cervical cytology results were then reported according to the Bethesda System 2014 (16).

## 2.3 HPV genotyping

HPV genotyping was performed using the PCR reverse dot hybridization method kit (Yaneng BIO science Co., Ltd., Shenzhen, China. REG. NO: CFDA 20233400811), to identify HPV infection with 17 high-risk types (HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68, 73, 82) and 6 low-risk types (HPV 6、11、42、43、81、83) (17).

## 2.4 5-ALA PDT procedure

All patients were placed in the lithotomy position, and then their vagina and cervix were cleaned by sterile 0.9% sodium chloride before treatment. Lesions of the cervix and cervical canal were completely covered with a sterile and thin cotton soaked in freshly prepared 20% 5-ALA solution (Fudan-Zhang Jiang Bio-Pharmaceutical Co., Ltd., Shanghai, China) for 3 hours. After cervical topical application of 5-ALA, a condom filled with medical gauze was inserted into the vagina to fix the cotton. Patients were then free to move during the waiting time.

Subsequently, a red light with an energy density of 80 mw/cm$^2$ at a wavelength of 635 nm was applied to the cervical surface using an intravaginal light scattering cylindrical head (LED- IBS; Wuhan Yage Photo-Electronic Co., Ltd., Wuhan, China) (Figure 1A). Simultaneously, another red light was applied to the cervical canal using an optical fiber (LD600-C; Wuhan Yage Photo-Electronic Co., Ltd., Wuhan, China) (Figure 1B) for a duration of 30 minutes. The ALA-PDT procedure was scheduled 6 times for cervical HSIL patients. Interval between each time was one week, but postponed for one week during menstruation.

## 2.5 Follow up and clinical assessment

The treatment efficacy was evaluated by HPV genotyping and cervical cytology test at the 3-month follow-up post-treatment. If the HR-HPV turned negative and cytological result was normal, the treatment efficacy can be defined as complete remission (CR). If the cervical cytological result was worse than ASC -US, the patient should undergo colposcopy-directed biopsy immediately to evaluate the degree of cervical lesions, regardless of HR-HPV status. For other abnormalities, patients were advised to repeat HPV and cytology tests after 3 months, and if the abnormal results persisted or even progressed, timely colposcopy-guided biopsy is necessary to assess cervical lesions. ALA-PDT related symptoms and adverse events were also recorded.

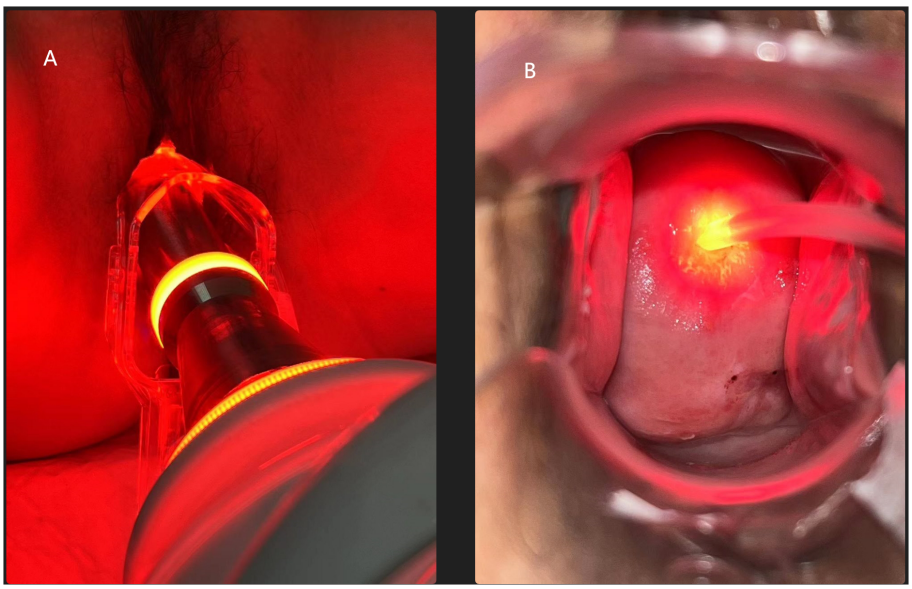


FIGURE 1
**(A)** An intravaginal light scattering cylindrical head applies to the cervical surface. **(B)** An optical fiber applies to the cervical canal.

## 2.6 Statistical analysis

The R software (Version 4.1.3) was used for data analysis. Chi-square and Fisher's exact tests were performed to compare HPV clearance rates at 3-month follow-up after ALA-PDT for cervical HSIL among different groups based on various factors. Multiple Linear Regression was used to mitigate the impact of different variables. P value less than 0.05 was considered statistically significant.

# 3 Results

## 3.1 Clinical characteristics of the patients before treatment

A total of 40 patients with a pathological biopsy result of cervical HSIL were treated with ALA-PDT. Among them, 38 (38/40, 95%) had CIN II, and 2 (2/40, 5%) had CIN III. The average age of the patients was 28.25 years old (20 - 41 years old), and all of them wanted to preserve their cervical structure. Notably, among these patients, 26 were ≤ 30 years old, while 14 were older than 30 years. All patients were infected with HR-HPV before treatment. Among them, 23 patients were infected with subtype HR-HPV 16/18 and 17 patients were infected with other types. 27 patients had only one type of HR- HPV infection, while 13 patients had more than 2 types of HR-HPV infections. Before ALA-PDT, 19 patients had cytology evaluation ≥ LSIL, whereas 21 patients exhibited cytology evaluation < LSIL. 11 patients exhibited cervical canal lesions, while the remaining 29 patients had no cervical canal lesions. 24 patients had multiple sites lesions and the other 16 patients had only a single site lesion. The lesion involved the cervical glands in 10 patients. The detailed clinical characteristics of these patients are presented in Table 1.

TABLE 1 Baseline characteristics of the study population.

| | Characteristics | Cases (n=40) % |
|---|---|---|
| Age | ≤ 30<br>>30 | 26(65)<br>14(35) |
| Lesion grade | CIN II<br>CIN III | 38(95)<br>2(5) |
| HR-HPV subtype | HPV16/18 related<br>Other types of HR-HPV | 23(57.5)<br>17(42.5) |
| Number of HR-HPV | Only one<br>More than two | 27(67.5)<br>13(32.5) |
| Cytology | ≥ LSIL<br>< LSIL | 19(47.5)<br>21(52.5) |
| Cervical canal lesions | Yes<br>No | 11(27.5)<br>29(72.5) |
| Multiple lesions | | |
| | Yes | 24(60) |
| | No | 16(40) |
| Gland involvement | | |
| | Yes | 10(25) |
| | No | 30(75) |

## 3.2 The effect of photodynamic therapy in HSIL at follow-up

The follow-up flowchart of the studied population is illustrated in Figure 2. All of the patients were evaluated for cervical cytological result and HR-HPV at the 3-month follow-up. Both cervical cytology and HR-HPV returned to normal in 26 out of the 40 cases. Therefore, the CR rate of ALA-PDT in cervical HSIL patients at our center was 65% (26/40) assessed at the 3-month follow-up. Six patients with cervical cytologic findings greater than ASC-US at the 3-month follow-up were directly referred for colposcopy-guided biopsy. The biopsy results indicated two cases of CIN II, which underwent LEEP; three cases of CIN I, of which two were treated with laser ablation and one received an additional course of PDT; and one case was confirmed to have chronic inflammation of the cervical mucosa. Additional details about these six patients were provided in Table 2. The remaining 8 patients had cervical cytology result of ASC-US and/or positive HR-HPV at the 3-month follow-up. In this group of patients, further evaluation was performed at 6 months after ALA-PDT to determine whether they should be referred for colposcopy-guided biopsy or kept under observation. Out of the eight patients, four had normal cervical cytology as well as negative HR-HPV at the 6-month assessment. Two patients had their cervical cytological and HR-HPV results normalized at the 12-month evaluation after ALA-PDT. Two patients underwent biopsy according to the 6-month evaluation, 1 was diagnosed with CIN II and underwent LEEP, while the other was diagnosed with CIN I and underwent laser ablation. The details on these 8 patients were provided in Table 3. Among the 38 patients with CIN II, 25 achieved CR after 3 months of treatment, with cervical cytology and HR-HPV completely turning negative. In addition, there were 6 CIN II patients who although did not achieve CR after 3 months of treatment, but 4 of them, and 2 of them, respectively, achieved CR at 6-month and 12-month follow-up. 81.6% (31/38)of CIN II patients achieved CR within one year of ALA-PDT in our study. Our study included two CIN III patients who strongly insisted ALA-PDT treatment. Their clinical and prognostic data are detailed in Table 4. One of the patients showed negative results in cervical cytology and HR-HPV infection after 3 months of treatment, achieving CR. Another patient was with cervical cytology indicating HSIL and HR-HPV persistent infection at the 3-month follow up. Further colposcopy biopsy revealed CIN II. The patient undergone LEEP surgery ultimately.

In summary, none of the patients showed disease progression during the observation period after ALA-PDT. At the 3-month follow-up, 4 patients received other surgical methods because of incomplete remission of the disease on biopsy, and another 2 patients underwent surgical treatments at the 6-month follow-up for the same reason. Actually, among these six patients who underwent surgical treatment, four experienced partial lesion

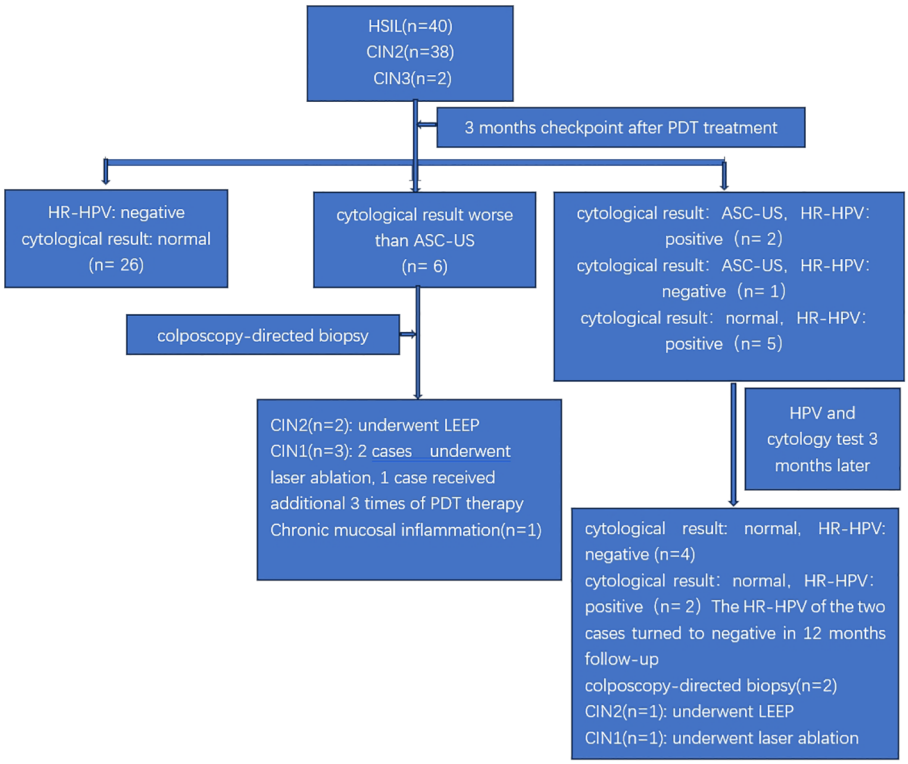


FIGURE 2
The follow-up flowchart of the study subjects.

regression after ALA-PDT, while only two remained lesions that were consistent with pre-treatment. None of them experienced disease progression. The CR rate of ALA-PDT in cervical HSIL patients at our center was 65% (26/40) at the 3-month follow-up and reached 82.5% (33/40) at the 12-month follow-up.

## 3.3 Representative cases

Case A was a 20-year-old lady, G0P0, who had a history of abnormal vaginal bleeding after intercourse for 2 years. Her cervical cancer screening showed HPV 16,51 infection and normal cervical

TABLE 2 Characteristics of the 6 patients with cytological result worse than ASC -US at 3-month follow up.

| No | Age | Lesion Grade | Before PDT | | GI | CI | Single lesion/ multicentric lesions | 3-month follow up | | Biopsy results | Further managements |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Cytology | HR-HPV | | | | Cytology | HR-HPV | | |
| 1 | 20 | CIN II | NILM | 16+ other | No | No | multicentric lesions | LSIL | Other type | Chronic mucosal inflammation | Cytology and HR-HPV turned to be normal at 1-year follow-up |
| 2 | 21 | CIN II | ASC-US | 16+ other | Yes | Yes | multicentric lesions | HSIL | 16+ other | CIN II | LEEP |
| 3 | 22 | CIN II | LSIL | Other type | No | No | multicentric lesions | LSIL | Other type | CIN I | Laser ablation |
| 4 | 24 | CIN II | NILM | 16 | No | No | multicentric lesions | LSIL | Other type | CIN I | Laser ablation |
| 5 | 27 | CIN III | LSIL | Other type | Yes | Yes | Single lesion | HSIL | Other type | CIN II | LEEP |
| 6 | 30 | CIN II | NILM | 16+ other | Yes | No | multicentric lesions | LSIL | 16+ other | CIN I | Additional one course of PDT, Cytology and HR-HPV turned to be normal at 1-year follow-up |

GI, gland involvement; CI, cervical involvement.

TABLE 3 Characteristics of the 8 patients with either cytological result ASC -US and/or HR-HPV positive at 3-month follow up.

| No | Age | Lesion Grade | Before PDT | | GI | CI | Single lesion/ multicentric lesions | 3-month follow up | | 6-month follow up | | Additional information |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Cytology | HR-HPV | | | | Cytology | HR-HPV | Cytology | HR-HPV | |
| 1 | 22 | CIN II | LSIL | 16 | No | No | multicentric lesions | NILM | Other type | NILM | negative | |
| 2 | 23 | CIN II | LSIL | 16 | No | No | multicentric lesions | ASC-US | Other type | NILM | negative | |
| 3 | 28 | CIN II | NILM | 16 | Yes | Yes | Single lesion | NILM | 16 | NILM | negative | |
| 4 | 30 | CIN II | LSIL | Other type | No | No | multicentric lesions | NILM | Other type | NILM | Other type | Cytology and HR-HPV turned to be normal at 1-year follow-up |
| 5 | 31 | CIN II | ASC-H | 16 | No | Yes | multicentric lesions | NILM | 16 | NILM | 16 | Cytology and HR-HPV turned to be normal at 1-year follow-up |
| 6 | 31 | CIN II | ASC-H | Other type | No | No | multicentric lesions | ASC-US | negative | NILM | negative | |
| 7 | 32 | CIN II | ASC-US | Other type | Yes | Yes | multicentric lesions | ASC-US | Other type | LSIL | Other type | Further biopsy showed CIN II, LEEP was conducted |
| 8 | 32 | CIN II | LSIL | 16+ other | No | Yes | multicentric lesions | NILM | 16 +other | NILM | 16 | Further biopsy showed CINI, laser ablation was conducted |

GI, gland involvement; CI, cervical involvement.

cytology result. The biopsy results of colposcopy indicated CIN II. Cervical cancer screening was repeated 3 months after the completion of 6 times of ALA-PDT, and the cervical cytological result showed LSIL and HPV 16 infection. The patient then received a repeated colposcopy-guided biopsy, which revealed chronic mucosal inflammation. Further observation found that her cytology and HR-HPV returned to normal at the 1-year follow-up. The colposcopy images before ALA-PDT and 3 months after ALA-PDT of this case are provided in Figure 3.

Case B was a 24-year-old woman, G0P0, who was asymptomatic but tested positive for HPV 16,18,59,68 infection during a cervical screening. Her cervical cytological result was normal. The colposcopy biopsy results suggested CIN II with glandular involvement. The patient underwent six times of ALA-PDT treatment, and a repeated cervical screening 3 months later showed the disappearance of HR-HPV and normal cervical cytology. Meanwhile, colposcopy images before and 3 months after ALA-PDT of this case were provided in Figure 4.

## 3.4 Factors affecting the rate of HPV clearance 3 months after PDT

We found that the persistent HR-HPV infection risk was 32.5% (13/40) in the 3-month follow-up. To evaluate the factors influencing the rate of HPV clearance 3 months after ALA-PDT, we conduct both univariate and multivariate analyses on age, lesion grade, HPV subtypes, number of HPV types, cervical cytological

TABLE 4 Characteristics and outcomes of the 2 patients diagnosed with CIN III.

| No | Age | Lesion Grade | Before PDT | | GI | CI | Single lesion/ multicentric lesions | 3-month follow up | | Biopsy results | Further managements |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Cytology | HR-HPV | | | | Cytology | HR-HPV | | |
| 1 | 26 | CIN II-III | NILM | 16+ | Yes | No | multicentric lesions | NILM | negative | / | Routine follow-up |
| 2 | 27 | CIN III | LSIL | Other type | Yes | Yes | Single lesion | HSIL | Other type | CIN II | LEEP |

GI, gland involvement; CI, cervical involvement; NILM, No Intraepithelial Lesion or Malignancy; HSIL, high-grade squamous intraepithelial lesion; LSIL, low-grade squamous intraepithelial lesion; LEEP, Loop Electro surgical Excision Procedure.

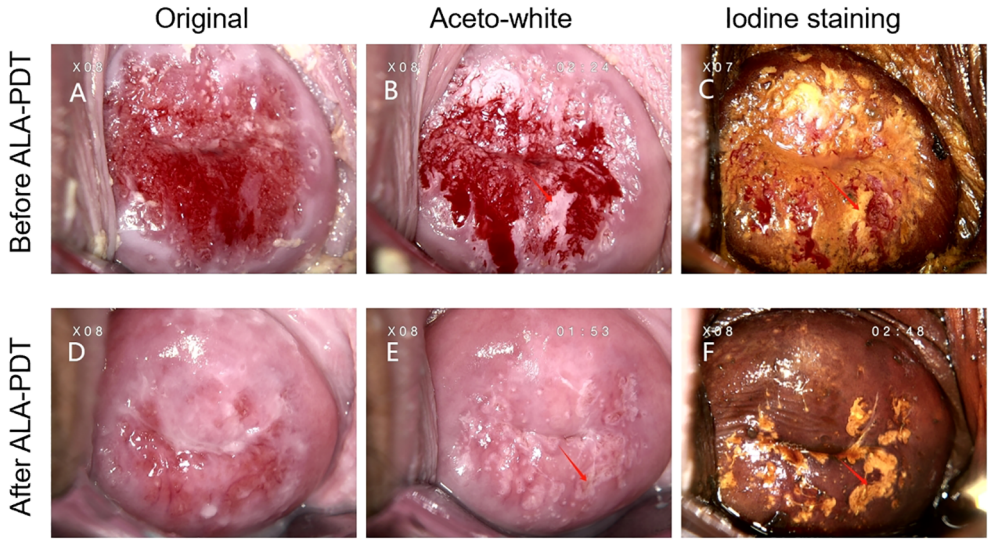


FIGURE 3
**(A–C)** Colposcopy images from case A who was diagnosed with CIN II before ALA-PDT. **(D–F)** Colposcopy images from case A who was diagnosed with cervical chronic mucosal inflammation 3 months after ALA-PDT treatment. The left column shows the initial performance of the cervical surface. The middle column depicts the aceto-white dysplastic lesion areas after the application of 3% acetic acid. The right column shows atypical epithelium after the use of iodine solution in the same patient. Arrows point to the appearances of the cervical high-grade squamous intraepithelial lesion before and after ALA-PDT.

results before treatment, cervical involvement, glandular involvement, as well as the number of lesions. Univariate analyses results showed that the HPV clearance rate was significantly lower in patients with cervical canal involvement (36.36% vs 79.31%, $p<0.05$), multiple lesions (54.17% vs 87.5%, $p<0.05$) and infection with more than one species of HPV (46.15% vs 77.78%, $p<0.05$) when compared to those without cervical canal or glandular involvement. The analysis revealed that factors such as age, lesion grade, HPV subtype, cytology results before treatment, and number of lesions before ALA-PDT have no impact on the HPV clearance rate (Figure 5). However, after multivariate regression analyses, we found that cervical canal involvement was the only independent risk factors affecting the clearance rate of HPV 3 months after completion of PDT (Table 5).

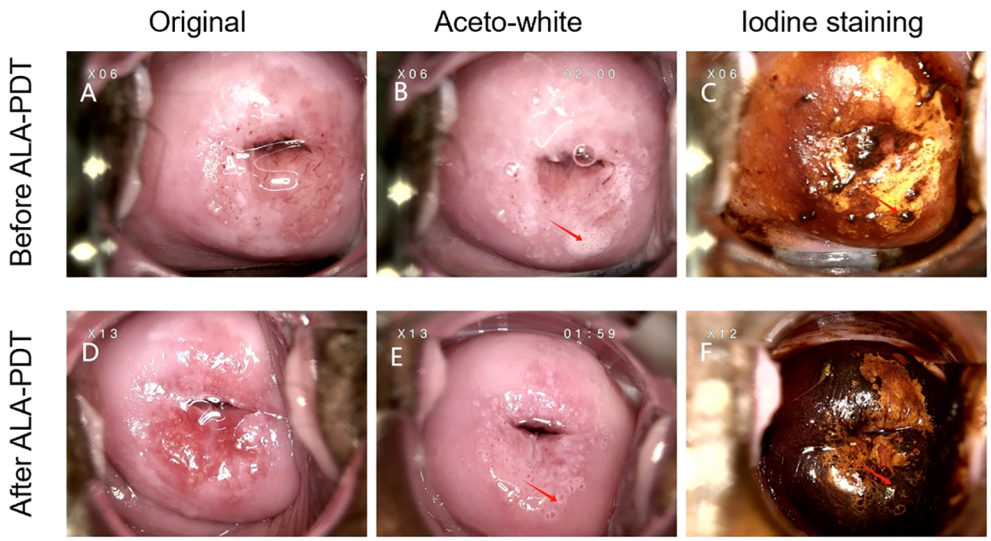


FIGURE 4
**(A–C)**. Colposcopy images from case B who was diagnosed with CIN II before ALA-PDT. **(D–F)** Colposcopy images from case B whose cervical cytology and HR-HPV turned to be normal 3 months after ALA-PDT treatment. The left column shows the initial performance of the cervical surface. The middle column depicts the aceto-white dysplastic lesion areas after the application of 3% acetic acid. The right column shows atypical epithelium after the use of iodine solution in the same patient. Arrows point to the appearances of the cervical high-grade squamous intraepithelial lesion before and after ALA-PDT.

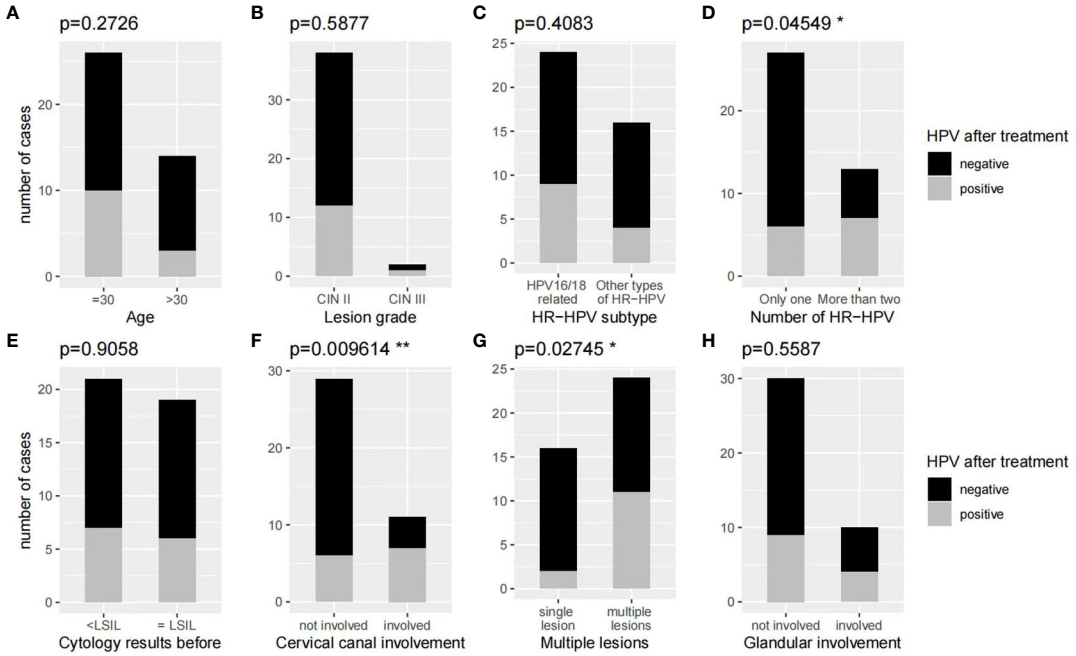


FIGURE 5
**(A, B, C, E, H)** Univariate analyses results showed that age, lesion grade, HR-HPV subtype, cytology, and cervical gland involvement before treatment of ALA-PDT have no effect on the HR-HPV clearance rate at the 3-month follow-up. **(D, F, G)** Univariate analyses results showed that cervical canal involvement, cervical multiple sites lesions, and more than one type of HR-HPV infection are risk factors for persistent HR-HPV infection at the 3-month follow-up.

## 3.5 Incidence of side effects

No patients experienced severe side effects on vital signs such as blood pressure, heart rate and breath. Most patients were observed mild local adverse effects during of a few days after ALA-PDT. These effects included increased vaginal discharge, slight abnormal pain, slight vaginal bleeding and burning sensations. Fortunately, these side effects were bearable and relieved within one-week post-treatment. Notably, some patients were observed to have mental disorders such as anxiety or insomnia during the follow-up period. This may be attributed to the fear of the disease and concerns about the efficacy of the treatment.

# 4 Discussion

Currently, cervical cancer is the fourth most common malignancy in women worldwide, and it is still a major cause of cancer-related death in some of the world's poorest countries (18). In 2018, the World Health Organization issued a global call for the elimination of cervical cancer as a public health problem (19). The strategies for eliminating cervical cancer included primary prevention via HPV vaccination, secondary prevention via cervical screening, and the third prevention of timely management of precancerous lesions. HSIL of the cervix, which is induced by HR-HPV, is a premalignant disease. In the past, surgical excision using methods like cold knife conization, laser conization/ablation, or LEEP was the gold standard treatment for cervical HSIL (4). Because of young women's low-acceptance of surgical procedures and the associated complications, as well as their strong desire for complete preservation of cervical tissues, it is imperative to explore a non-invasive and effective method for the management of cervical HSIL. ALA-PDT seems to be a good choice for this specific group of patients.

ALA-PDT involves the selective accumulation of 5-aminolevulinic acid in the CIN tissues (20), which are then illuminated to generate ROS that destroy tumor cells by inducing apoptosis and necrosis. The success of the process relies on three key points: oxygen-induced activation of photosensitizer, appropriate utilization of visible light, and proper selection of the photosensitizer (21). This process is highly tissue selective, non-invasive, and carries a low risk of severe complications, making it an ideal method for treating cervical HSIL, especially for young women. Compared to traditional surgical excisions, ALA-PDT is characterized by elimination of precancerous lesions and potential HPV infection (22) without causing damage to the normal anatomy.

Our study showed that ALA-PDT was highly effective in treating a cervical HSIL, leading to a complete remission rate of 65% at 3 months after completion of ALA-PDT. Furthermore, with an extended observation period, the complete remission rate could reach as high as 82.5% at 12 months after the completion of ALA-PDT. These findings are consistent with previous studies. Wu et al. reported a histological complete remission rate of 77.78% for CIN II after PDT at 12-month follow-up (23). Tang et al. revealed that the cervical HSIL complete remission rate after PDT was 88.9%, 92.5% at 6-months,12-months follow-up respectively (24). Qu et al. found that the total lesion regression rate of cervical HSIL after PDT was

TABLE 5 Multiple linear regression analysis of HPV clearance rate after ALA-PDT.

| | Ratio of HPV positive patients | | Effect on HPV Clearance (P Value) |
|---|---|---|---|
| Age | <=30 | 10/26 | 0.1823 |
| | >30 | 3/14 | |
| Lesion grade | CIN II | 12/38 | 0.9848 |
| | CIN III | 1/2 | |
| HR-HPV subtype | HPV16/18 related | 9/24 | 0.6338 |
| | Other types of HR-HPV | 4/16 | |
| Number of HR-HPV | Only one | 6/27 | 0.1525 |
| | More than two | 7/13 | |
| Cytology | ≥ LSIL | 6/19 | 0.2858 |
| | < LSIL | 7/21 | |
| Cervical canal lesions | Yes | 7/11 | **0.0066*** |
| | No | 6/29 | |
| Multiple lesions | Yes | 11/24 | 0.0537 |
| | No | 2/16 | |
| Gland involvement | Yes | 4/10 | 0.4994 |
| | No | 9/30 | |
| Total | 13/40 | | **0.0248*** |

Values with P<0.05 are marked in bold, which mean significant difference between groups.

89.58% at 3-months follow-up (25). Hu et al. reported that the disappearance rate of cervical HSIL after PDT was 81.82%, 90.91% at 3-month,6-month follow-up respectively (26). Although the above studies reported a satisfactory efficacy of PDT for HSIL treatment, there are still some limitations. The application of ALA-PDT in cervical HSIL is still in the initial exploration stage, and the included cases in the above studies were limited, which might limit the generalizability and robustness of the conclusions. Further studies with high-level of evidence, such as multicenter, large-sample, randomized controlled clinical trials, are necessary to be conducted to validate our findings. Additionally, it should be noted that our study primarily focused on patients with CIN II, only 2 patients with CIN III were included. One patient was diagnosed with CIN II-III and responded positively to ALA-PDT treatment, showing normal cervical cytological and HPV test results after three months. Conversely, the second patient, diagnosed with CIN III, did not benefit from this therapy and instead achieved recovery through LEEP. This discrepancy in treatment efficacy may be attributed to the greater lesion depth associated with CIN III, which renders non-invasive treatments such as ALA-PDT less effective than they are for CIN I and CIN II cases. Due to the lack of sufficient data, we cannot make some rigorous suggestions for CIN III patients. Further research including larger subjects is needed to demonstrate the effectiveness of PDT for patients with CIN III.

There is no consensus on the follow-up strategy after PDT. In our study, we evaluate the combination of HPV genotyping and cervical cytological results as an initial evaluation at the 3-month follow-up. Cases were then triaged according to the results. The stratification protocol in our study was to immediately refer to colposcopy-guided biopsy if the cytologic result was worse than ASC-US at the 3-month follow-up. If the cervical cytological result was ASC-US and/or there was HR-HPV infection, observation could continue with repeated cervical screening at 6-months follow-up. We designed this stratification protocol based on previous studies reporting that PDT could enhance local and systemic immunity, which plays a crucial role in clearing lesions (27–29). Therefore, we have implemented a relatively conservative observation protocol for patients with either cytology result ASC-US or HR -HPV infection 3 months after PDT treatment. We hypothesized that the activated immune response by PDT would have a long-term effect on the clearance of lesions or HR-HPV, thus ensuring the safety of this group of patients. In our study, 8 cases that met this criterion(either cytologic result ASC-US and/or HR-HPV infection). Among them, 6 patients returned to normal cytology and negative HPV within 1 year by observation, one patient regressed from CIN II to CINI, and one patient persisted in CIN II. None of the patients had a history of disease progression during the course of observation. Therefore, we consider our triage program to be reasonable.

In our study of single factor analysis, we found that cervical canal involvement, multiple lesions and infection with more than one species of HR-HPV can cause persistent viral infection at the 3-month follow-up after ALA-PDT treatment. However, multiple linear regression analysis revealed that only cervical canal involvement was an independent risk factor. These findings suggest that the effects of multiple lesions and HR-HPV species are secondary to the difference in cervical canal involvement. Consequently, even if a patient has numerous lesions and HR-HPV infection, if there is no disease in the cervical canal, ALA-PDT can effectively eliminate her HR-HPV infection. We infer that the reason maybe the optical fiber is not as efficient as the intravaginal light scattering cylindrical head. Thus, we recommend to prolong the time of irradiation by the optical fiber for patients with cervical canal lesions. The underlying association between cervical involvement and persistent HR-HPV infection requires further research. It is important to monitor women with persistence of HR-HPV infection who have underwent PDT therapy as it greatly impacts the prognosis. Our findings emphasize the need to pay extra attention to the patients with cervical involvement.

During the treatment of the 40 patients with ALA-PDT, there were no severe adverse reactions. A few patients presented with discomfort symptoms, such as burning sensations, slight pain, slight discomforts in the lower abdomen and increased vaginal discharge. These adverse reactions were bearable and were relieved within a few days after treatment, indicating the safety of ALA-PDT.

During our research, patients underwent a treatment regimen of ALA- PDT with a frequency of once per week, typically completing six sessions. The entire course of treatment spanned approximately 7 weeks to 2 months, which is notably longer than the single-session requirement of other non-invasive therapies such

as laser, cryotherapy, and thermal ablation. Despite the extended duration, ALA-PDT offers the advantage of being less painful in comparison to these alternatives. Moreover, the satisfactory outcomes observed in this study can be partly attributed to the regularity of the ALA-PDT treatment sessions.

Non-invasive physical plasma (NIPP), which inhibit pathological cell growth through rapid and transient DNA damage, is another emerging approach for cervical precancerous lesions. Like ALA-PDT, NIPP is a tissue-preserving and easy-to-apply method, which can be performed in outpatient settings without the need for local or general anesthesia and is more cost-effective than ALA-PDT. Previous studies have reported that the complete remission rate of NIPP to CINI/II reached 86.2% -95% at 3-6 months after treatment (30, 31). However, these studies were single arm prospective studies and included a small sample size. Further studies are expected to include larger population and reveal the efficacy of NIPP in CINII/III patients. NIPP may be an underlying alternative to ALA-PDT for the treatment of cervical HSIL.

## 5 Conclusion

1. ALA-PDT is a highly effective, non-invasive, and safe therapeutic intervention for cervical HSIL. Compare to surgical procedures, it has the advantage of preserving the structural and functional integrity of the cervix. Therefore, it is an optimal choice for young women with cervical HSIL who have fertility requirements. 2. We suggest continuous observation instead of performing a colposcopy-guided biopsy in patients who have either a cervical cytological result of ASU-US and/or a HR-HPV infection at 3-month follow-up after ALA-PDT therapy. 3. Cervical canal involvement is an independent risk factor for persistent HR-HPV infection at the 3-month follow-up after PDT treatment.

## Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding authors.

## Ethics statement

The studies involving humans were approved by Ethics Committee of Hangzhou First people's Hospital. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

## Author contributions

JQ: Writing – review & editing, Writing – original draft, Formal analysis, Data curation, Conceptualization. YW: Writing – review & editing, Supervision, Investigation. GW: Writing – review & editing, Resources, Data curation. JL: Writing – review & editing, Resources. LS: Writing – review & editing, Supervision, Conceptualization. SX: Writing – review & editing, Software, Methodology, Formal analysis, Conceptualization.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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# Cost-effectiveness of single-visit cervical cancer screening in KwaZulu-Natal, South Africa: a model-based analysis accounting for the HIV epidemic

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**Introduction:** Women living with human immunodeficiency virus (WLHIV) face elevated risks of human papillomavirus (HPV) acquisition and cervical cancer (CC). Coverage of CC screening and treatment remains low in low-and-middle-income settings, reflecting resource challenges and loss to follow-up with current strategies. We estimated the health and economic impact of alternative scalable CC screening strategies in KwaZulu-Natal, South Africa, a region with high burden of CC and HIV.

**Methods:** We parameterized a dynamic compartmental model of HPV and HIV transmission and CC natural history to KwaZulu-Natal. Over 100 years, we simulated the status quo of a multi-visit screening and treatment strategy with cytology and colposcopy triage (South African standard of care) and six single-visit comparator scenarios with varying: 1) screening strategy (HPV DNA testing alone, with genotyping, or with automated visual evaluation triage, a new high-performance technology), 2) screening frequency (once-per-lifetime for all women, or repeated every 5 years for WLHIV and twice for women without HIV), and 3) loss to follow-up for treatment. Using the Ministry of Health perspective, we estimated costs associated with HPV vaccination, screening, and pre-cancer, CC, and HIV treatment. We quantified CC cases, deaths, and disability-adjusted life-years (DALYs) averted for each scenario. We discounted costs (2022 US dollars) and outcomes at 3% annually and calculated incremental cost-effectiveness ratios (ICERs).

**Results:** We projected 69,294 new CC cases and 43,950 CC-related deaths in the status quo scenario. HPV DNA testing achieved the greatest improvement in health outcomes, averting 9.4% of cases and 9.0% of deaths with one-time screening and 37.1% and 35.1%, respectively, with repeat screening. Compared to

the cost of the status quo ($12.79 billion), repeat screening using HPV DNA genotyping had the greatest increase in costs. Repeat screening with HPV DNA testing was the most effective strategy below the willingness to pay threshold (ICER: $3,194/DALY averted). One-time screening with HPV DNA testing was also an efficient strategy (ICER: $1,398/DALY averted).

**Conclusions:** Repeat single-visit screening with HPV DNA testing was the optimal strategy simulated. Single-visit strategies with increased frequency for WLHIV may be cost-effective in KwaZulu-Natal and similar settings with high HIV and HPV prevalence.

KEYWORDS

cervical cancer screening, cervical cancer prevention, economic evaluation, human papillomavirus, human immunodeficiency virus

## 1 Introduction

Cervical cancer is the fourth most commonly diagnosed cancer globally, and it disproportionately impacts women in low- and middle-income countries (LMIC) where screening coverage is low. While effective screening strategies are available and have been successfully implemented in high income countries, lack of infrastructure, specialized equipment, and trained health and laboratory personnel remain structural barriers to scale-up in LMICs (1, 2). In 2020, the World Health Organization (WHO) unveiled a worldwide strategy aimed at eradicating cervical cancer and achieving the ambitious 90-70-90 targets by 2030 which encompass: fully vaccinating 90% of girls against HPV by 15 years old, screening 70% of women twice with high performance tests by age 35 and 45 years old, and treating 90% of women with pre-cancerous lesions or cervical cancer (3).

South Africa has one of the highest cervical cancer incidence and mortality rates globally, with over 10,000 new cervical cancer cases and nearly 6,000 cervical cancer-related deaths in 2020 (4). The South African province of KwaZulu-Natal stands as a microcosm of these broader global health challenges, with a disproportionate burden of cervical cancer and high prevalence rates of human immunodeficiency virus (HIV). These two public health issues converge in this region because women living with HIV (WLHIV) are at increased risk of acquiring human papillomavirus (HPV), the primary cause of cervical cancer, and their HPV infections are more likely to progress to cancer (5–8).

With approximately 4.8 million WLHIV in South Africa as of 2022, the burden of HPV and cervical cancer is high, despite high coverage of antiretroviral therapy (7, 9, 10). In 2017, HIV prevalence in KwaZulu Natal was estimated to be 37%, reaching a peak of 59% among women 30 to 49 years old (11–13). The region has historically high HPV prevalence, with estimates 2.5 times higher in WLHIV compared to women without HIV (14). Stelzle et al. estimated that 63.4% of new cervical cancer cases in South Africa were WLHIV in 2018 (5), highlighting the impact of HIV on cervical cancer incidence. Although recent data suggest a decline in HIV incidence in KwaZulu-Natal (12, 13, 15), cervical cancer incidence continues to rise (16), emphasizing the need for greater cervical cancer prevention and screening, particularly among WLHIV.

Coverage of cervical cancer prevention programs in South Africa remains low, reflecting challenges with resource allocation for screening, diagnosis, and access to adequate care (17, 18), in addition to individual and societal barriers such as lack of awareness and misconceptions of cervical cancer (19–21). Barriers to effective scale-up persist at each step of the current South African multi-visit standard of care, in which women undergo cytology screening and are required to return to the clinic multiple times for results, triage, and pre-cancer treatment, if necessary. First, widespread implementation of cytology and triage demands critical infrastructure, equipment, and adequately trained personnel in clinics and laboratories, all of which are lean in-country in the public-sector healthcare network (1, 2, 21, 22). Meeting supply and cold chain requirements for cryotherapy treatment of cervical lesions proves challenging (23), and the need for multiple clinic visits results in notable loss to follow-up (23, 24). These barriers emphasize the imperative for more efficient and less resource-intensive screening strategies such as single-visit screening and treatment approaches that employ high performance technologies like HPV DNA testing and genotyping.

A multi-pronged approach and scale-up of appropriate interventions is needed to reach WHO 90-70-90 cervical cancer elimination goals. However, prevention and management of cervical cancer are associated with considerable clinical and economic costs with implications for accessing effective care in LMICs (25–28). The interaction between HIV and HPV compounds the health and economic burden and underscores the urgent need for prevention and early intervention strategies. We aimed to estimate the potential health outcomes, economic costs,

and cost-effectiveness of single-visit cervical cancer screening strategies among women in KwaZulu-Natal, South Africa.

# 2 Materials and methods

## 2.1 Overview

To project future outcomes of multiple cervical cancer screening interventions, we utilized the Data-driven Recommendations for Interventions against Viral InfEction (DRIVE) model, which simulates HPV and HIV transmission, co-infection, and natural history. Output from the DRIVE model were used to estimate future costs associated with screening, testing, and treatment. Health and economic outcomes were jointly evaluated to assess cost-effectiveness.

## 2.2 Transmission model

The DRIVE model is a compartmental model that has been calibrated and described in previous publications (29, 30). The model simulates an open population of men and women aged 0-79 years, stratified by sex, 5-year age group, sexual risk group, and HIV- and HPV- associated health states. HIV health states are stratified by CD4 cell count and viral load (Supplementary Figure S3), while HPV health states are stratified by pre-cancerous lesions and stages of cervical cancer (Supplementary Figure S2). The model simulates demographic dynamics; heterosexual transmission of oncogenic HPV and HIV infection; HIV-related interventions such as ART, voluntary male medical circumcision, and condoms; HPV vaccination; natural history of HPV infections; and cervical cancer screening, diagnosis, treatment, and mortality. The model represents interactions between HIV and HPV, in that HPV acquisition and progression risks increase with declining CD4 count among individuals with untreated HIV, and screening and treatment performance vary by HIV status.

Model dynamics are governed by a system of ordinary differential equations solved in MATLAB (version R2022a) using a $4^{th}$ order Runge-Kutta numerical method. HPV is introduced in 1925 to allow HPV transmission dynamics and cervical cancer incidence to equilibrate prior to the introduction of HIV infection in 1980. At each 2-month time step, differential equations were evaluated to estimate population demographics and the number of persons in each infection, disease, or treatment state for the following time step. The dynamic nature of the model captured population-level effects such as herd immunity. Description of model processes, calibration, parameters, and data sources are in the Supplementary Material and previous publications (29, 30).

## 2.3 Strategies and scenarios

We used the 25 best-fitting parameter sets from model calibration to simulate seven primary scenarios (Table 1). We evaluated the status quo and six comparator strategies with nonavalent HPV (9vHPV) vaccine coverage and varying screening modalities, frequencies, and loss to follow-up between screening and treatments. In the status quo scenario, we simulated one-time screening between the ages of 35 and 39 with a multi-visit screening and treatment strategy and 57% 9vHPV vaccine coverage, based on a 2020 observation (31). The multi-visit strategy reflects the current South African standard of care of cytology screening, triage with colposcopy, and treatment with cryotherapy or large loop excision of the transformation zone (LLETZ). The need for multiple visits results in an estimated 64% of screen-positive women who are lost to follow-up for treatment (23, 24, 32).

Our comparator scenarios assumed sustained 57% coverage of 9vHPV and a switch to single-visit strategies, where both screening and pre-cancer treatment occur during the same visit. In these single-visit scenarios, we assumed lower loss to follow-up compared to the status quo, with rates reduced to 5% for thermal ablation and 20% for LLETZ. We evaluated three screening strategies: 1) HPV DNA testing, 2) HPV DNA testing with genotyping, and 3) HPV

TABLE 1 Primary screening strategies and scenarios.

| Scenario | | Number of visits for screening and treatment | Loss to follow-up between screening to treatment | Screening strategy | Screening frequency |
|---|---|---|---|---|---|
| 1 | Status quo | Multi-visit | 28% for colposcopy;<br>50% for cryotherapy or LLETZ | Cytology + colposcopy triage | One-time[1] |
| 2 | Comparators | Single-visit | 5% for thermal ablation;<br>20% for LLETZ | HPV DNA testing | One-time[1] |
| 3 | | | | | Repeat[2] |
| 4 | | | | HPV DNA genotyping | One-time[1] |
| 5 | | | | | Repeat[2] |
| 6 | | | | HPV DNA testing + AVE triage | One-time[1] |
| 7 | | | | | Repeat[2] |

AVE, automated visual evaluation; HIV, human immunodeficiency virus; HPV, human papillomavirus; LLETZ, large loop excision of the transformation zone.
[1]Once-per-lifetime screening between ages 35 to 39.
[2]Repeated screening every 5 years for women living with HIV and twice-per-lifetime for women without HIV.

DNA testing and triage with automated visual evaluation (AVE), a new machine learning-based technology with demonstrated high performance (33–36). Each strategy was implemented either: 1) once-per-lifetime between ages 35 to 39 years for all women ("one-time" screening) or 2) twice-per-lifetime between ages 35 to 39 and 45 to 49 for women without HIV and every 5 years for WLHIV, starting from age 25 ("repeat" screening).

## 2.4 Outcomes

Model outcomes included cervical cancer cases and deaths averted, life-years saved, and disability-adjusted life-years (DALYs) averted. Disability weights for cervical cancer health states were derived from Global Burden of Disease (Table 2) (48). We adopted the South African Ministry of Health perspective for costs, encompassing direct medical expenses. Aggregated costs of cervical cancer screening, triage, and the treatment and care of pre-cancer, cervical cancer, and HIV were derived from published studies (37–39, 41, 43–47, 49–51). HPV vaccination costs accounted for the 9vHPV vaccine product, with an additional 5% for wastage, 4.5% for transportation and handling, and 15% for distribution and delivery, based on prior studies (43, 44, 50, 51). Costs were converted and inflated to 2022 US dollars. Costs and outcomes were projected over lifetime time horizon of 100 years from 2023 to 2122 to capture the full impacts of the interventions and were discounted at a rate of 3% per year (52, 53). We reported our results according to HPV-FRAME, a consensus statement and quality framework for modelled evaluations of HPV prevention, and Consolidated Health Economic Evaluation Reporting Standards (CHEERS) 2022, the guidance for reporting health economic evaluations (54, 55) (Supplementary Sections VII.a and VII.b, respectively).

## 2.5 Statistical analysis

The comparative performance of each scenario was evaluated using the incremental cost effectiveness ratio (ICER), computed as the additional cost divided by the additional health benefit (in DALYs) of one strategy compared with the next less costly strategy. Strategies that were more costly and less effective than an alternative (strongly dominated) or had higher ICERs compared to a more effective alternative (weakly or extended dominated) were considered inefficient and removed from the calculations in that analysis following standard practice. For all non-dominated scenarios, we report the median ICER from simulations using the 25 best-fitting parameter sets, along with the minimum and maximum values. We adopted a commonly utilized willingness to pay threshold (or cost-effectiveness threshold) of South Africa's gross domestic product (GDP; $6,776 per capita in 2022) to determine the most optimal strategy (56). However, given the lack of consensus on which thresholds are most appropriate in LMICs, we applied several additional thresholds ranging from

TABLE 2 Key cost-effectiveness analysis inputs.

| Parameter | Estimate (Range) | Source |
|---|---|---|
| **Costs (2022 USD)** | | |
| **Screening & Triage** | | |
| Cytology | $12.78 ($10.22 – $17.85) | (37, 38) |
| Colposcopy | $105.91 ($84.73 – $127.09) | (37) |
| HPV DNA testing | $47.17 ($37.74 – $56.60) | (37, 39) |
| HPV DNA genotyping | $93.96 ($75.17 – $112.75) | (37, 39) |
| AVE | $5.74 ($4.59 – $6.89) | Assumption based on (37) |
| **Pre-cancer Treatment** | | |
| Cryotherapy | $5.95 ($4.76 – $7.14) | (40) |
| LLETZ | $76.28 ($52.15 – $206.25) | (38, 40, 41) |
| Thermal ablation | $10.02 ($8.02 – $12.02) | (41, 42) |
| **HPV Vaccination** | | |
| Nonavalent vaccine cost (per dose) | $106.98 ($85.58 – $128.38) | In-country source (43, 44) |
| **Cervical Cancer** | | |
| Staging | $293.91 ($235.13 – $352.69) | (45) |
| Hysterectomy - radical | $1,829.23 ($1,463.38 – $2,195.08) | (45) |
| Local cervical cancer | $10,795.77 ($8,636.62 – $12,954.92) | (45) |
| Regional cervical cancer | $10,795.77 ($8,636.62 – $12,954.92) | (45) |
| Distant cervical cancer | $10,763.99 ($8,611.19 – $12,916.79) | (45) |
| **HIV** | | |
| On ART, virally suppressed | $52.23 ($41.78 – $62.68) | (46) |
| CD4 > 500 | $37.32 ($26.13 – $44.78) | (46, 47) |
| CD4 350 - 500 | $39.57 ($31.66 – $47.48) | (47) |
| CD4 200 - 350 | $39.98 ($31.98 – $47.98) | (47) |
| CD4 <=200 | $98.89 ($79.11 – $118.67) | (47) |
| **Additional Inputs** | | |
| **Disability weights** | | |
| Local cervical cancer | 0.288 (0.193-0.399) | (48) (proxy: diagnosed cancer and primary therapy) |
| Regional cervical cancer | 0.451 (0.307-0.6) | (48) (proxy: metastatic cancer) |
| Distant cervical cancer | 0.54 (0.377-0.687) | (48) (proxy: terminal phase) |

*(Continued)*

TABLE 2 Continued

| Parameter | Estimate (Range) | Source |
|---|---|---|
| **Disability weights** | | |
| Hysterectomy | 0.049 (0.031-0.072) | (48) (proxy: controlled phase) |
| **HPV vaccination** | | |
| Number of doses | 2 (1 – 3) | Assumed |
| Additional cost for waste (% of vaccine product cost) | 5% (4% – 6%) | (49) |
| Additional cost for transportation and handling (% of vaccine product cost) | 4.5% (2% – 7%) | (50) |
| Additional cost for delivery/distribution (% of vaccine product cost) | 15% (10% – 20%) | (44, 51) |

AVE, automated visual evaluation; HIV, human immunodeficiency virus; HPV, human papillomavirus; LLETZ, large loop excision of the transformation zone; USD, US dollars.

$2,221 to $8,909 based on health opportunity costs ($2,221 and $8,909) and 50% of the GDP per capita ($3,388) (57, 58). The cost-effectiveness analyses were conducted using R (version 4.2.1).

## 2.6 Sensitivity analysis

We conducted one-way sensitivity analyses of costs and disability weights, informed by published literature or by adjusting by 20% when no data were available. Additional scenario analyses were conducted in which we introduced: a more optimistic estimate of 90% 9vHPV vaccine coverage, increased loss to follow-up in single-visit strategies (30% for thermal ablation and 50% for LLETZ), and a shortened time horizon of 50 years. We also explored the impact of AVE as a primary screening strategy 1) at optimal test performance and 2) with 20% reduction in test sensitivity and specificity.

# 3 Results

Clinical and economic outcomes for our primary scenarios are summarized in Table 3 and Supplementary Table S34. Over the 100-year time horizon, the status quo scenario was estimated to result in 69,294 cervical cancer cases, 43,950 cervical cancer-related deaths, and 188.13 million life-years. All comparator scenarios in the base and sensitivity analyses demonstrated improved health outcomes and were therefore more effective than the status quo. Relative to the status quo, repeat screening achieved lower cervical cancer incidence (29.5% to 37.1% reduction) and mortality (25.8% to 35.1% reduction) compared to one-time screening (7.1% to 9.4% and 6.0% to 9.0%, respectively). Further, repeat screening with HPV DNA testing was associated greater reduction in cervical cancer cases (37.1%) and mortality (35.1%) compared to HPV DNA genotyping (29.5% and 25.8%, respectively) and HPV DNA testing with AVE triage (32.6% and 31.2%, respectively).

The status quo screening scenario was associated with $12.79 billion in direct medical costs over the next 100 years (Table 3). Among the single-visit strategies, we found greater increases in costs of repeat screening (1.8% to 3.3%) compared to one-time screening (0.4% to 0.9%) across all technologies. HPV DNA testing

TABLE 3 Health and cost impact of cervical cancer screening strategies in South Africa[1].

| Description | CC Cases Averted, % Change[2] | CC Deaths Averted, % Change[2] | Total Costs, 2022 USD | DALY Averted, Count | ICER[3], $ per DALY averted |
|---|---|---|---|---|---|
| Status quo[4] | – | – | 12.786 B (11.25 B-13.78 B) | – | – |
| One-time HPV DNA testing[5] | 9.4 (7.9-11.1) | 9.0 (7.5-10.5) | 12.83 B (11.30 B-13.82 B) | 34,080 (14,221-112,877) | Dominated |
| One-time HPV DNA genotyping[5] | 7.1 (5.5-8.4) | 6.0 (4.5-7.5) | 12.89 B (11.37 B-13.88 B) | 25,657 (10,044-85,820) | 1,398 (442-3,478) |
| One-time HPV DNA testing with AVE triage[5] | 7.9 (6.3-9.6) | 7.4 (6.2-9.1) | 12.83 B (11.30 B-13.82 B) | 26,387 (11,717-95,033) | Dominated |
| Repeat HPV DNA testing[6] | 37.1 (30.7-41.7) | 35.1 (29.2-39.5) | 13.00 B (11.47 B-13.99 B) | 91,590 (37,522-254,599) | 3,194 (1,488-7,599) |
| Repeat HPV DNA genotyping[6] | 29.5 (25.6-36.7) | 25.8 (22.8-33.1) | 13.19 B (11.67 B-14.19 B) | 68,623 (29,258-203,559) | Dominated |
| Repeat HPV DNA testing with AVE triage[6] | 32.6 (27.1-38.1) | 31.2 (25.9-35.6) | 13.00 B (11.47 B-13.99 B) | 75,615 (32,214-226,500) | Dominated |

%, Percent; AVE, automated visual evaluation; B, billion; CC, cervical cancer; DALY, disability-adjusted life-year; HIV, human immunodeficiency virus; HPV, human papillomavirus; ICER, incremental cost-effectiveness ratio; USD, US dollar.
[1]We report the median estimates across the 25 best fitting parameter sets, along with the minimum and maximum in parentheses. All costs and outcomes were discounted at 3% annually. [2]Reflects the percent reduction in CC cases and CC-related deaths compared to the status quo. [3]ICER is reported for nondominated strategies. Dominated strategies, which exhibited higher costs and lower effectiveness than an alternative or higher ICERs compared to a more effective alternative, were deemed inefficient. [4]Multi-visit screening and treatment strategy between ages 35 to 39. [5]Single-visit screening and treatment strategy once per lifetime between ages 35 to 39. [6]Single-visit screening and treatment strategy every 5 years for women living with HIV and twice at ages 35-39 and 45-49 for women without HIV for women without HIV.

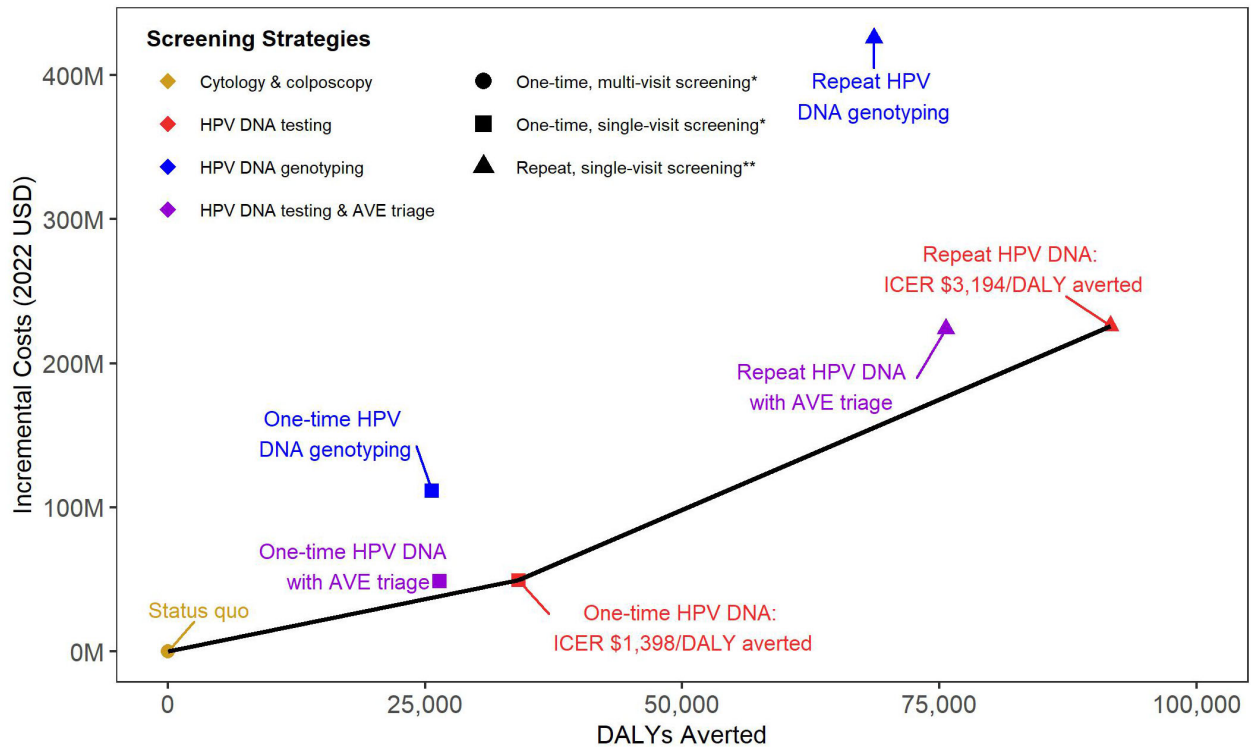
with genotyping was more costly than HPV DNA testing alone and with AVE triage. Figure 1 shows the efficiency frontier with the incremental costs and DALYs for each scenario compared to the status quo. Repeat screening with HPV DNA testing was the most effective strategy below the willingness to pay threshold of South Africa's GDP per capita (ICER: $3,194 per DALY averted). However, when we assumed the lowest bound threshold of $2,221, one-time screening with HPV DNA testing became the optimal strategy (ICER: $1,398 per DALY averted).

In the one-way sensitivity analyses (Figures 2, 3), the parameters with the greatest impact on both ICERs were the discount rate and cost of HPV DNA testing. In the scenario analyses (Table 4, Supplementary Table S35), increasing 9vHPV vaccine coverage to 90% with single-visit screening and treatment strategies had notable impact on cervical cancer outcomes, averting up to 44.3% of cervical cancer cases and 41.2% of deaths, and increasing costs up to 6.3%. At our base willingness to pay threshold, the optimal strategy remained repeat screening with HPV DNA testing when assumptions of vaccine coverage and loss to follow-up were increased and when the time horizon was shortened to 50 years, but AVE became optimal when we assumed its use as a primary screening strategy.

# 4 Discussion

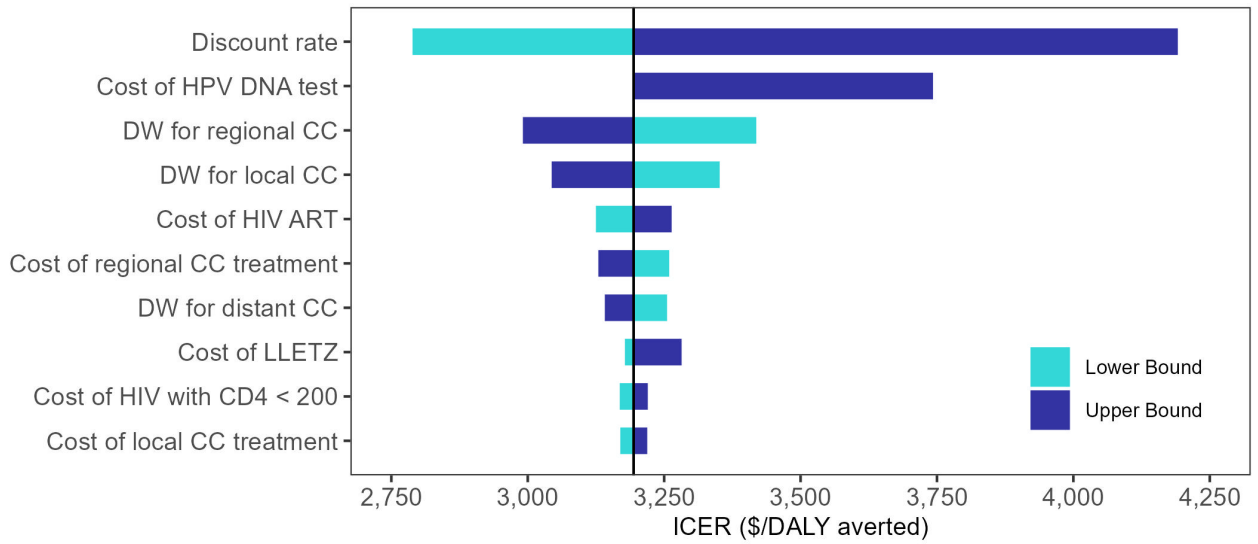
Our paper contributes to the limited literature evaluating the economic and clinical benefits of cervical cancer screening interventions, while accounting for the impact of HIV (59). To our knowledge, this is the first cost-effectiveness analysis in the South African context to incorporate DALYs averted as part of the cost-effectiveness measure evaluating cervical cancer screening and interventions. The use of a standardized outcome such as DALYs allows policy and decision makers to weigh costs and outcomes across disease states and interventions. Given funding and resource constraints in LMICs, implementing cost-effective cervical cancer prevention strategies is imperative to achieving WHO 90-70-90 cervical cancer elimination goals.

We found that repeat single-visit screening with HPV DNA testing was the most effective strategy under our willingness to pay threshold; one-time single-visit screening with HPV DNA testing also had an ICER under our threshold but was less effective than repeat screening. Although more frequent screening was associated with increased costs, our model substantiates its added clinical benefits of reduced cervical cancer incidence, mortality, and DALYs, and its cost-effectiveness, particularly among WLHIV, as




AVE, automated visual evaluation; CC, cervical cancer; DALY, disability-adjusted life year; DNA, deoxyribonucleic acid; HIV, human immunodeficiency virus; HPV, human papillomavirus; *One-time screening between ages 35-39; **Every 5 years for women living with HIV and twice for women without HIV between ages 35-39 and 45-49

FIGURE 1
Cost-effectiveness of primary cervical cancer screening strategies.

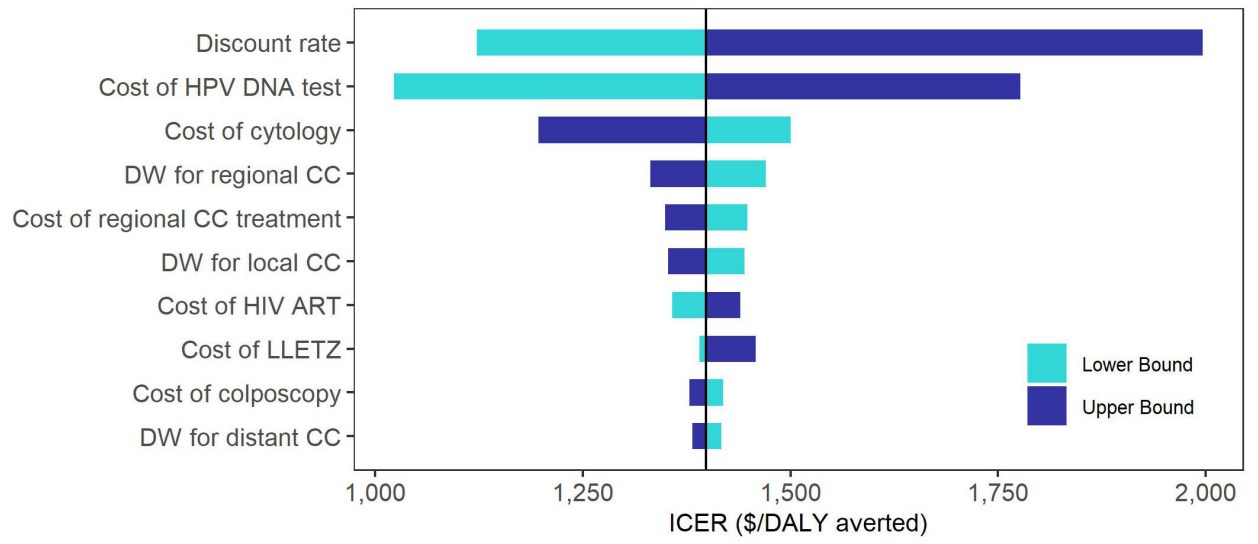



ART, antiretroviral therapy; CC, cervical cancer; DALY, disability-adjusted life-year; DNA, deoxyribonucleic acid; DW, disability weight; HIV, human immunodeficiency virus; HPV, human papillomavirus; ICER, incremental cost-effectiveness ratio; LLETZ, large loop excision of the transformation zone; See Table 2 for parameter ranges

FIGURE 2
One-way sensitivity analysis – Repeat single-visit screening with HPV DNA testing.

recommended by WHO (60). Previous studies found that same-day screening and treatment could improve cervical cancer screening uptake and reduce the burden in South Africa (29, 61), and our findings suggest that implementing single-visit strategies could yield greatly improved health outcomes at comparatively modest increases in costs.

We demonstrate both the effectiveness and cost-effectiveness of screening with HPV DNA testing, further supporting WHO cervical cancer screening recommendations (60). However, as evident by prior studies and our analysis, HPV DNA testing is associated with higher costs (0.4% and 1.8% increase with one-time and repeat screening, respectively) (37, 38, 45, 62), and real-world implementation and public sector scale-up of HPV DNA testing in KwaZulu-Natal will require substantial financial investment, resources, and time. Drivers of these additional costs may be attributed to more women receiving pre-cancer treatment because




ART, antiretroviral therapy; CC, cervical cancer; DALY, disability-adjusted life-year; DNA, deoxyribonucleic acid; DW, disability weight; HIV, human immunodeficiency virus; HPV, human papillomavirus; ICER, incremental cost-effectiveness ratio; LLETZ, large loop excision of the transformation zone; See Table 2 for parameter ranges

FIGURE 3
One-way sensitivity analysis – One-time single-visit screening with HPV DNA testing.

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TABLE 4 Optimal screening strategy under different assumptions across varying willingness to pay thresholds.

| | Base value | Willingness to Pay Threshold | | | |
|---|---|---|---|---|---|
| | | $2,221 | $3,388 (50% of GDP) | $6,776 (GDP) | $8,909 |
| Primary scenarios | –– | One-time HPV DNA testing: $1,398/ DALY averted | Repeat DNA testing: $3,194/DALY averted | Repeat DNA testing: $3,194/ DALY averted | Repeat DNA testing: $3,194/ DALY averted |
| LTFU increased to 30% for TA/50% for LLETZ | 5%/20% | Dominated | One-time HPV DNA testing: $2,193/ DALY averted | Repeat DNA testing: $4,134/ DALY averted | Repeat DNA testing: $4,134/ DALY averted |
| Time horizon of 50 years | 100 | One-time HPV DNA testing: $1,615/ DALY averted | Repeat DNA testing: $3,326/DALY averted | Repeat DNA testing: $3,326/ DALY averted | Repeat DNA testing: $3,326/ DALY averted |
| AVE for primary screening | Not included | Repeat AVE: $915/DALY averted | Repeat AVE: $915/DALY averted | Repeat AVE: $915/DALY averted | Repeat AVE: $915/DALY averted |
| AVE for primary screening with 20% lower sensitivity and specificity | Not included | Repeat AVE: $984/DALY averted | Repeat AVE: $984/DALY averted | Repeat AVE: $984/DALY averted | Repeat AVE: $984/DALY averted |
| 90% HPV vaccine coverage | 57% | Dominated | Dominated | Repeat DNA testing: $4,605/ DALY averted | Repeat DNA testing: $4,605/ DALY averted |
| 90% HPV vaccine coverage with increased LTFU: 30% for TA/50% for LLETZ | 57%/ 5%/20% | Dominated | Dominated | Repeat DNA testing: $5,740/ DALY averted | Repeat DNA testing: $5,740/ DALY averted |
| 90% HPV vaccine coverage with AVE for primary screening | 57%/ Not included | Dominated | Repeat AVE: $3,222/DALY averted | Repeat AVE: $3,222/ DALY averted | Repeat AVE: $3,222/ DALY averted |
| 90% HPV vaccine coverage with AVE for primary screening with 20% lower sensitivity and specificity | 57%/ Not included | Dominated | Dominated | Repeat AVE: $3,554/ DALY averted | Repeat AVE: $3,554/ DALY averted |

AVE, automated visual evaluation; DALY, disability-adjusted life-year; GDP, gross domestic product; HIV, human immunodeficiency virus; HPV, human papillomavirus; LLETZ, large loop excision of the transformation zone; USD, US dollar.
The strategies listed were the most effective under the specified willingness to pay threshold among non-dominated strategies. These strategies were not dominated in 100% of our 25 best-fitting parameter sets, and the ICERs listed are the median values.

of HPV DNA's higher test sensitivity and lower loss to follow-up from the single-visit strategies, but it is also noted that costs may be offset by averting cervical cancer cases and the need for cervical cancer treatment.

Our findings are consistent with several economic evaluations that have demonstrated the cost-effectiveness of single-visit screening and treatment, HPV DNA testing, and HPV vaccination in Sub-Saharan Africa (44, 45, 62–65). For example, a prior study by Zimmermann et al. found that the cost of single-visit screening strategies at an HIV clinic in Kenya was lower than two-visit strategies, and HPV DNA testing was the most effective strategy when screening and treatment were provided in a single visit (66). Conversely, alternative strategies such as HPV genotyping and visual inspection with acetic acid may be optimal in other contexts (37, 67–70). Lew et al. identified repeat HPV screening with partial genotyping to be the optimal and cost-saving strategy in New Zealand (67), highlighting the potential benefits of newer technologies while emphasizing the importance of repeat screening. However, when comparing strategies and economic evaluations across resource settings, it is important to consider differences in the burdens of cervical cancer and HIV as well as barriers such as limited infrastructure, resources, and trained personnel (19, 71)

Given the interaction of HPV and HIV, mathematical models have also been used in numerous studies to evaluate cervical cancer interventions among WLHIV (59), and our results align with previous cost-effectiveness studies that modeled coinfection in South Africa (37, 45, 72–75). Similar to our findings, Campos et al. and Goldie et al. concluded that HPV DNA test and treat was the most cost-effective strategy (45, 76). In contrast, Lince-Deroche et al. found visual inspection with acetic acid to be most cost-effective, attributing the increased colposcopy triage costs to HPV DNA testing's higher sensitivity and lower specificity (37); however, their analysis focused on programmatic screening and triage costs and did not account for costs of pre-cancer treatment, cervical cancer, and cervical cancer treatment. While visual inspection with acetic acid may demonstrate short-term cost-effectiveness, our study highlights the importance of incorporating downstream costs and benefits and suggests that HPV DNA testing would be cost-effective long-term. Our findings build upon these prior economic analyses by

emphasizing the cost-effectiveness of single-visit screening with HPV DNA testing in South Africa and highlighting the benefits of more frequent screening, particularly among WLHIV.

Our results were sensitive to assumptions about loss to follow-up. In our primary scenarios (base case), we assumed a loss to follow-up rate of 5% for thermal ablation treatment and 20% for LLETZ. In sensitivity analyses, we applied more conservative estimates, increasing loss to follow-up to 30% and 50%, respectively. Despite the higher ICERs with increased loss to follow-up, repeat screening with HPV DNA testing persisted as the most effective strategy under the base willingness to pay threshold.

To assess the potential impact of scaling 9vHPV vaccination, we considered a more optimistic vaccine coverage of 90%. Our findings suggest that vaccine scale-up would prevent substantially more cervical cancer cases and cervical cancer-related deaths, and repeat HPV DNA testing remained the optimal screening strategy. It is important to note that the 9vHPV vaccine in our model covers nine HPV types compared to two and four types in the bivalent and quadrivalent HPV vaccine, respectively, but the 9vHPV vaccine has not been widely rolled out in South Africa. The cost of the 9vHPV vaccine can be up to 20 times more expensive than the bi- and quadrivalent alternatives and the costs of vaccine delivery may be lower than estimated in our model (44, 77, 78). Our assumption of switching to 9vHPV vaccine coverage may overestimate the effectiveness and cost of HPV vaccination and, consequently, diminish the estimated health impact and cost-effectiveness of cervical cancer screening and treatment strategies, which address the residual burden of cases not prevented by vaccination. Therefore, our ICERs are conservative.

Our choice of willingness to pay thresholds and discount rate had notable impact on our conclusions of cost-effectiveness. We find repeat single-visit screening with HPV DNA testing is the most optimal strategy at all study thresholds equal to or higher than 50% of GDP per capita ($3,388). However, one-time HPV DNA testing was the most effective strategy at our lowest threshold of $2,221, emphasizing how recommendations and decisions may differ depending on the willingness to pay threshold employed by policy makers. Further, applying a higher discount rate of 6% yield an ICER exceeding $3,388 for repeat HPV DNA testing, and the strategy would no longer be deemed cost-effective.

We employed a 100-year lifetime time horizon to capture the full health and economic impact of the interventions simulated. However, because longer time horizons inherently introduce greater uncertainty, the projected long-term health and economic outcomes may be less reliable. We conducted a sensitivity analysis using a 50-year time horizon, and our conclusions remained consistent, with repeat screening with HPV DNA testing emerging as the most effective strategy under the cost-effectiveness threshold.

Our analysis highlights potential cost-effective opportunities for recent innovations with high sensitivity and specificity such as HPV genotyping and AVE. Although our findings demonstrate the clinical benefits of HPV DNA genotyping, the ICER exceeded our threshold, likely due to the increased costs from testing and treatment, but newer technologies for genotyping have the potential to lower testing prices. Moreover, while AVE was not cost-effective for triage in our two primary scenarios, it became the optimal strategy when we assumed its use as a primary screening strategy, highlighting its potential future role in cervical cancer screening. However, it should be noted that the costs and performance of AVE are currently highly uncertain, and additional data will be needed to generate more reliable cost-effectiveness estimates.

A key strength of this analysis is the use of a dynamic HIV-HPV transmission model, allowing us to simulate the natural history of HIV, HPV, and cervical cancer, along with their interaction and transmission. We also assessed numerous strategies ranging from current South African standards (cytology with colposcopy), single-visit screening and treatment approaches, WHO's current recommendations (HPV DNA testing with and without genotyping), scaled 9vHPV vaccine coverage, and a promising novel technology leveraging machine learning (AVE).

Our study is subject to several limitations. First, we use the Ministry of Health perspective and do not include societal costs such as productivity and travel time costs, which would likely increase our ICERs if the societal costs associated with the screening and treatment strategies are substantial. However, this approach may also have the potential to decrease ICERs if averting cervical cancer and death would have profound improvement on productivity costs. Further, we did not collect primary cost data but rather derived our cost-estimates from published costing studies and input from in-country experts in South Africa. Lastly, when calculating DALYs averted, we included only disability from cervical cancer because disability weights for coinfection of HIV and HPV/cervical cancer have not yet been estimated. We considered the quality-of-life impacts for cervical cancer to be of greater interest since our interventions focused on cervical cancer prevention.

In conclusion, we find that adopting single-visit strategies with high performance HPV DNA testing will improve the impact of cervical cancer prevention resources. In KwaZulu-Natal and similar LMIC settings with high HIV prevalence, repeat screening every five years for WLHIV and twice between ages 35 to 39 and 45 to 49 for women without HIV would be the optimal cervical cancer screening and treatment approach. Our findings can inform resource allocation and policy deliberations regarding optimal strategies to reach the WHO 90-70-90 cervical cancer elimination goals by 2030.

## Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

## Author contributions

JT: Conceptualization, Formal analysis, Methodology, Software, Visualization, Writing – original draft, Writing – review & editing. CH: Data curation, Formal analysis, Methodology, Software, Writing – review & editing. CB: Data curation, Formal analysis,

Methodology, Software, Writing – review & editing. TP-P: Resources, Writing – review & editing. RB: Conceptualization, Methodology, Supervision, Writing – review & editing, Funding acquisition. DR: Conceptualization, Methodology, Supervision, Writing – review & editing, Funding acquisition. MS: Methodology, Supervision, Writing – review & editing, Funding acquisition.

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## Conflict of interest

Outside of the submitted work, CB acknowledges past part-time employment by Merck & Co., Inc for a summer graduate research assistantship.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## Publisher's note



## Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2024.1382599/full#supplementary-material

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# Cervical cancer prevention in Burkina Faso: a stakeholder's collaboration for the development of awareness messaging

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**Background:** Cervical Cancer stands as the second leading cause of both incident female cancers and deaths in Burkina Faso. Unfortunately, the prevention, early detection, and care of cervical cancers are suboptimal at individual, institutional, and national levels. In October 2023, we organized a stakeholder's workshop to develop cervical cancer awareness messaging for disease control in the country.

**Methods:** A one-text workshop was organized with stakeholders working toward improving health in general or women's health and well-being. A participatory, learning, and adaptive approach was used to facilitate discussions and activities, ensuring the contribution of all participants. Contextual evidence-based and empirical elements about cervical cancer burden and preventive strategies were presented to the participants by key informants. These served as the foundation for a collaborative formulation of messaging content that aimed at raising awareness about cervical cancer.

**Results:** Sixty-two participants from 28 organizations attended the workshop. They work mainly at local and international non-governmental organizations, civil society organizations, universities, university hospitals, research centers, and the Ministry of Health. During the first and second days of the workshop, the participants explored cervical cancer data, its preventive and treatment options available in Burkina Faso, communication strategies for behavioral change, and determinants of the use of prevention and health promotion services. During the

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following three days, 3 working groups were formed to define strategies, and key messages adapted to diverse tools and targeted audiences. All information was validated during plenary sessions before the end of the workshop and available to all participants and their organizations for cancer awareness activities.

**Conclusion:** Upon conclusion of the workshop, the participants provided insightful information for the development of cervical awareness messaging in Burkina Faso. They formed the first community of practice to serve as a dynamic platform for implementation, monitoring, evaluation, and continued learning activities.

KEYWORDS

cancer prevention, cervical cancer, cancer awareness, stakeholder engagement, Burkina Faso

# 1 Introduction

In 2022, it is estimated that 1,308 cases and 1,018 deaths due to CC occurred in Burkina Faso, positioning this disease as the second most prevalent cancer and an important public health challenge (1). The burden of CC in Burkina mirrors the broader context of Sub-Saharan Africa (SSA) and is influenced by many factors such as i) a higher risk of Human Papilloma Virus (HPV) infection due to poverty, risky sexual behavior, and low socioeconomic status, coupled with inadequate HPV vaccination coverage ii) an absence of effective screening programs; iii) a lack of awareness about CC prevention and early detection benefits, iv) an inequitable access to healthcare services (2–8). Yet, as part of a national policy of free healthcare for children under five and women launched in March 2016, cervical cancer screening and treatment have been decreed free for all women in Burkina Faso (9). Moreover, on April 26, 2022, the Ministry of Health and Public Hygiene introduced the HPV vaccine in the country's Expanded Program on Immunization (EPI) targeting nine-year-old girls (10, 11). These strategies align with the World Health Organization's (WHO) global strategy aimed at eliminating cervical cancer within generations. Indeed, the WHO strategy delineates specific objectives, including achieving a 90% HPV vaccination rate among girls by age 15, a 70% screening rate among women at key ages, and a 90% treatment rate for those identified with cervical disease, all by 2030 (12). Many research has already shown the importance of the WHO strategy in contributing to CC elimination (7, 13–16). But to meet these WHO targets, effective dissemination of information and promotion of preventive measures are vital. An impactful communication strategy development for consistent messaging should include collaboration among all stakeholders interested in CC elimination such as researchers, health professionals, advocacy groups, journalists, etc (9, 17–23). It encompasses: i) accessible HPV vaccination and cervical screening information for all population segments; ii) comprehensive and tailored information matching the literacy levels of the target audience; iii) client-centered communication addressing the needs of diverse sub-groups; iv) health professionals' proficiency in screening and communication.

This paper outlines the planning process and key findings of a stakeholder workshop in Burkina Faso, designed to foster effective awareness messaging for cervical cancer control. The workshop brought together healthcare professionals, government officials, community leaders, patient advocates, non-governmental and civil society organizations, cancer survivors, caregivers, and advocates. It represents a concerted effort to address the unique challenges of CC elimination in Burkina Faso and highlights collaborative approaches that could serve as a model for similar initiatives in other SSA countries.

# 2 Materials and methods

## 2.1 Study type

The work consisted of a participatory approach involving a diverse group of stakeholders who are directly or indirectly interested in/(affected by) cervical cancer. The data collected were qualitative information generated during active engagement and dialogue between participants who attended a five-day workshop.

## 2.2 Workshop participants

From October 2 to 6, 2023, we convened a diverse group of key stakeholders in Burkina Faso to discuss communication strategies for cervical cancer awareness. This group included healthcare professionals, government health officials, community leaders, patient advocates, representatives from non-governmental and civil society organizations specializing in women's health, as well as cancer survivors, caregivers, and advocates. Stakeholders were encouraged to extend invitations to other interested parties, broadening the workshop's reach and diversity of perspectives.

The list of stakeholders invited to this workshop was prepared with the support of the Non-Governmental Organization Permanent Secretary in Burkina Faso. It included non-governmental organizations (NGOs) and civil society organizations (CSOs) that were active in communication and sensitization at the community level during the Corona Virus-19 (COVID-19) pandemic as well as those with known interest in cancer, women's health and well-being, and mental health. Governmental organization representatives were represented mainly by healthcare workers from the main university hospitals of the country (one gynecological medical doctor and two nurses, two oncologists, a pediatrician, two anatomopathologists, and three general practitioners).

We sent special invitations to researchers and clinicians with renowned work experience on cancer in Burkina Faso to present the theoretical concepts of cancer, and the focus of their work and contribute to the workshop discussions. We also invited a cervical cancer survivor identified among our close relatives to bring her experience and voice to the discussion. A detailed list of the organizations invited is presented in Table 1.

TABLE 1 List of stakeholders invited to a workshop for the development of awareness messaging for cervical cancer prevention in Burkina Faso.

| Category | Organization |
|---|---|
| Governmental organizations | Ministry of health and Public Hygiene |
| | National Public health Institute |
| | Yalgado Ouedraogo University Hospital in Ouagadougou |
| | Charles De-Gaulle Pediatric University Hospital in Ouagadougou |
| | Sourô Sanou University Hospital in Bobo |
| | Bogodogo University Hospital in Ouagadougou |
| Academic | Joseph KI-ZERBO University in Ouagadougou |
| | Saint Thomas d'Aquin University in Ouagadougou |
| Private sectors | Language and design Communication Agency |
| | Mousso News |
| | Webactubf.info |
| Local non-governmental organizations | KIMI Foundation |
| | Pananetugri Initiative for the Well-being of Women |
| | Organization for New Initiatives in Development and Health |
| Civil society organizations | Access to Essential Medicines Network |
| | Association Noug Yen Ka Woukd Zoom |
| | African Youth Health and Development Network in Burkina Faso |
| | Action group against cancer |
| | Women in Global Health Francophone West Africa |
| | Brigade rose |
| | The Support Network for Health Mutuals in Burkina Faso |
| | Union of Religious and Traditional Leaders of Burkina for Health and Development |
| International non-governmental organizations | U.S. Agency for International Development |
| | Union for International Cancer Control |
| | Médecins du Monde |
| | Jhpiego |
| | Marie Stopes International |
| Cancer patients | Two cancer patients, two survivors |
| Experts (Moderators) | 4 experts in public health and social behavior change |

## 2.3 Organization and process

Invitations for the workshop were issued on August 12, 2023, to the official email address or contact person of all identified stakeholders. The email included a request to confirm the organization's interest in attending the workshop through the completion of an online registration form which included the names, roles in the organization, and contact details of their representatives. To maintain engagement and ensure a high turnout, we sent weekly reminder emails leading up to the event. The last reminder included a formal invitation letter, the reference terms of the workshop, and a tentative agenda for the meeting (Figure 1).

## 2.4 Workshop setting and logistics

The workshop took place physically at Joseph KI-ZERBO University's main location in Ouagadougou. We used an online platform on the afternoon of the first day to allow a representative of the International Union for Cancer Control (IUCC) to present their work.

During small group working sessions, we provided a handout (Table 2 template) to guide the discussion and collect the outputs.

## 2.5 Workshop moderators and main speakers

The workshop moderators were four resource persons - two females and two males - identified for their expertise in health and their work with multiple stakeholders:

- The first moderator was a senior public health consultant, trained as a medical doctor with experience in communication for behavior change. He has worked for diverse national and international institutions and organizations in many countries for decades;

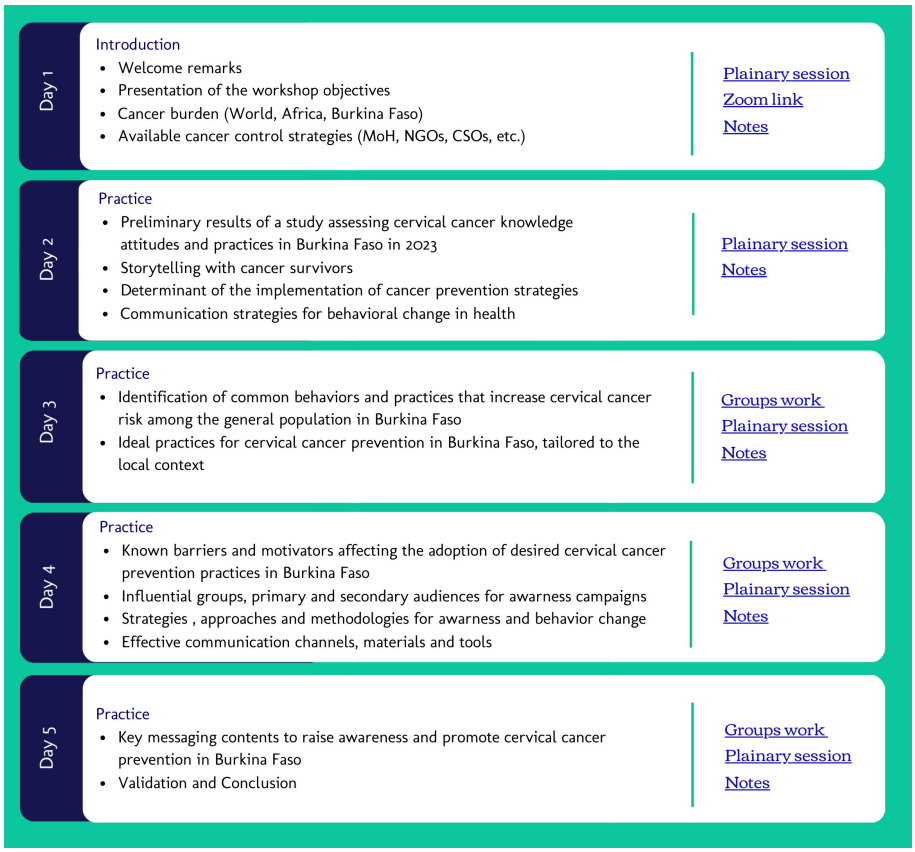


FIGURE 1
Agenda for a stakeholder's collaboration workshop for the development of awareness messaging on cervical cancer prevention in Burkina Faso.

- The second moderator was a researcher and lecturer with a master's and Ph.D. in public health focus on cancer issues and almost 15 years of work experience;
- The third moderator was a researcher and lecturer in sociology and anthropology, with expertise in research ethics and stakeholder collaborations;
- The fourth moderator was a senior consultant with extensive experience in communication for behavior change who provides facilitation services to local and international organizations.

We also invited guest speakers to present general cancer information and discuss their work related to the disease:

- An epidemiologist who presented CC statistics (in the world, in Africa, and Burkina Faso), risk factors, and the strategy for its elimination;
- A gynecologist and specialist in female cancer who provided information on the most frequent female cancers and available treatment options in Burkina Faso;
- A representative of the Ministry of Health and Public Hygiene from Burkina Faso presented the national HPV immunization strategy;
- Representatives from, the Coalition Against Cancer in Burkina Faso, the KIMI Foundation, Médecins du Monde France, and the IUCC presented their organization's cancer control strategies;
- A researcher who presented the preliminary result of a research on the general population and health professional Knowledge, attitude, and practice about cervical cancer prevention;
- A communication expert who presented on communication strategies for behavioral change;
- A public health expert who presented on the determinants of the use of prevention and health promotion services.

## 2.6 Workshop structuration

The workshop was structured into three main sessions. The initial session provided an overview of the epidemiology of cervical cancer in Burkina Faso, including current control strategies.

The subsequent session was multi-faceted, encompassing:

- Presentations on the barriers and facilitators influencing the adoption of best practices for cervical cancer prevention;

- Discussions on the contextual evidence underlying the development of intervention strategies, content, communication messages, and educational materials;
- A storytelling session where breast, cervical, and ovarian cancer patients and survivors along with their relatives, shared personal experiences related to their journey and battles with the disease.

The latter part of the workshop consisted of four alternating working group sessions, each culminating in a plenary session. The working group sessions focused on the multifaced steps that should be considered for raising awareness for cervical cancer prevention in Burkina Faso and include:

- Common behaviors and practices that increase cervical cancer risk among the general population in Burkina Faso;
- Ideal practices for cervical cancer prevention in Burkina Faso, tailored to the local context;
- Known barriers and motivators affecting the adoption of desired practices;
- Influential groups for primary and secondary audiences for awareness campaigns;
- Strategies, approaches, and methodologies for awareness and behavior change;
- Effective communication channels, materials, and tools;
- Key messaging content to raise awareness and promote cervical cancer prevention.

## 2.7 Data collection and validation

Each working group was led by a moderator and a note-taker. Each group session lasted a minimum of 3 hours and was followed by a plenary session the same or the following day.

The plenary sessions aimed at sharing, discussing, synthesizing, and validating the information presented by the working groups. This strategy aimed at fostering a cohesive and comprehensive understanding among participants and the validation of the content by all.

## 2.8 Ethical considerations

The cancer survivors and their relatives provided their verbal consent to share their stories and experiences and to be audio-recorded for a faithful transcription of the storytelling session. To ensure their confidentiality, no picture was captured.

## 2.9 Feedback mechanisms

At the end of the workshop, all participants were asked to provide verbal and open written feedback regarding the workshop.

## 2.10 Follow-up actions

The workshop ended with all participants agreeing to be part of a virtual Community of Practice for Cancer Control in Burkina Faso.

# 3 Results

## 3.1 Participation in the workshop

Sixty-two participants from 28 organizations (Table 1) working toward improving health in general or women's health and well-being attended the workshop. They were from diverse backgrounds and levels of implication in cancer control and health improvement at local, national, and international levels.

## 3.2 Summary of the discussions of a stakeholder's workshop for the development of awareness messaging for cervical cancer prevention in Burkina Faso

The five-day discussion resulted in a consensus strategy in line with multifaced steps that should be considered for raising awareness for cervical cancer elimination in Burkina Faso and reflects the global strategy. A summary of the discussion is presented in Figure 2.

# 4 Discussion

Unlike resource-rich settings where CC elimination strategies are well-established with access to vaccines, regular screening, and treatment for patients, the nascent CC elimination program in Burkina Faso is defined with limited infrastructure and resources, necessitating innovative, context-specific approaches. This workshop aimed to develop a consensus strategy to enhance public awareness of CC, leveraging a participatory approach. By gathering a diverse group of stakeholders, the event fostered a collaborative environment conducive to generating innovative, context-specific solutions for CC awareness and prevention (24).

Through the five-day discussions, we gained comprehensive insights and developed practical, stakeholder-driven solutions for cervical cancer awareness. These solutions are innovative and creative, adapted to the local context, and represent a significant step in advancing communication for cervical cancer elimination in Burkina Faso.

## 4.1 Addressing communication challenges with innovative solutions

The workshop highlighted several communication issues: 1) the lack of continuous mass media communication about cervical cancer prevention options available in Burkina Faso and their

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FIGURE 2
Summary of the discussions of a stakeholders workshop for the development of awareness messaging for cervical cancer prevention in Burkina Faso.

accessibility; 2) the lack of communication between caregivers (clinicians, oncologists, radiologists, nurses, psychologists, etc.) for optimal patient care; 3) the fact that communication with patients is not adapted to their needs and cultural habits and 4) the challenges related to communication on social networks, particularly in terms of authenticity and fact-checking. To address these challenges, an effective and low-cost strategy discussed during the workshop consists of inclusive and integrative communication and healthcare programs for cancer prevention. These programs should be designed to be innovative and practical, ensuring they can be easily integrated into everyday healthcare practices (25). Lessons learned from other disease areas, such as HIV/AIDS, can provide effective inspiration, working models to build capacity, and communication strategy to improve access, increase efficiency, and ultimately contribute to better health outcomes in vulnerable populations. The following practical approaches that can be easily integrated into everyday healthcare practices, drawing inspiration from successful HIV/AIDS strategies, were recommended:

- Comprehensive education campaigns that address both men and women across different life stages. It should leverage lessons from HIV/AIDS education by emphasizing the importance of regular screenings, and HPV vaccination and use testimonials from survivors and patients to personalize the message and increase its impact. These communications should emphasize the importance of CC early detection which improves cancer outcomes by enabling care at the earliest possible stage and potentially better outcomes for patients (26, 27).
- Active engagement of male partners in CC prevention programs similar to HIV/AIDS strategies, educating them on the importance of supporting their partners in getting screened and vaccinated, and on their role in preventing HPV transmission. Encourage men to get their daughters vaccinated against HPV and like strategies used in HIV prevention, encouraging them in condom use and regular testing.
- Integration of CC screening and HPV vaccinations into routine health services, such as family planning, prenatal visits, and HIV testing and counseling sessions to mirror the HIV model where testing is often integrated into other health services to reduce stigma and increase accessibility. Use mobile clinics and outreach to offer CC screening and HPV vaccinations in remote or underserved areas, drawing from the HIV/AIDS strategy of reaching out to populations with limited access to healthcare facilities.

A systematic review has shown that integration of cervical cancer screening and treatment with HIV services using different models of service delivery is feasible as well as acceptable to women living with HIV (28). An innovative project for health promotion by primary healthcare professionals was tested in primary healthcare centers of the Basque Healthcare Service. It focuses on promoting multiple healthy habits and demonstrates the feasibility of implementing health promotion programs in routine primary health care (29). In a scarce resource setting like Burkina Faso, inclusive and integrative healthcare programs may not generate extra costs for the health sector (30). However, it requires investment in nationally led and evidence-based capacity-building activities in participatory approaches to cancer policies for civil society organizations like cancer patients' organizations (31, 32).

During the workshop, the participants agreed on community awareness strategies tailored to the country's socio-cultural context using relevant and accessible content, age-appropriate language, and mediums such as:

- Mass communication primarily aims to reach a broad audience: social networks, billboards, theaters, fairs, flyers, posters, informational booklets, advice cards, models, pamphlets, interactive radio talks, television series, and films.
- Interpersonal communication that involves establishing a direct relationship between a health professional and a patient, or between two patients. This allows for providing emotional support, giving advice, explaining different treatments, and answering patient questions. The communication tools also include brochures, fact sheets, documents, flipcharts, roll-up banners, etc.
- Digital communication is very widespread and can reach a wide audience but it can also be personalized to meet individual needs. The communication tools for this strategy include social networks, websites, mobile apps, chatbots, etc.
- A community-based approach that requires community involvement in CC elimination activities. This can involve raising awareness, disseminating information among community members, recommending health centers or specialists, etc. The communication tools for this strategy include theater and sketches, community radio talks, brochures, and posters.

## 4.2 Meaningful engagement with patients

Meaningful engagement with cancer patients and their relatives was highlighted during the workshop to help them understand their disease, and treatment options through the different phases of their treatment for improved quality of life. This was reported to be important for the patients' medical outcomes and also the overall well-being of their support systems (32). Indeed, the meaningful engagement of patients, survivors, caregivers, or families forms a vital part of the lived experience of those affected by cancer. It is essential to meet the information needs of cancer patients and their caregivers. It can reduce caregiver burden, improve physical and mental health, and promote intimacy. According to Samson et al. (2022) (30), cancer patients' organizations should be recognized and considered as a critical voice in national cancer policies in LMICs as part of the right to health but also as a prerequisite to quality cancer policies.

## 4.3 Next steps

Follow-up meetings are planned to validate and monitor the dissemination of developed messages. The workshop aligns with WHO's strategy for CC elimination and emphasizes the critical role of localized health initiatives.

It was also suggested to create a network of health professionals to facilitate communication among them, with the community and the patients. This can be facilitated with the following approaches:

- Digital tools that could be developed to allow more efficient collaboration: data-sharing platforms, and online discussion spaces, among others, would be of great benefit.
- Continuous public awareness campaigns on local radio, television, and social networks around the HPV vaccine, CC screening, and the importance of fact-checking could be carried out to combat the spread of fake news.
- Development and implementation of training programs for health professionals, teaching them to tailor their communication to the needs and cultural sensibility of their patients.

## 5 Conclusion

This stakeholder's workshop aligns with WHO's strategy for CC elimination (12) and emphasis on community-level interventions. It contributes to the global efforts in combating cervical cancer, emphasizing the critical role of localized health initiatives. Participants in the workshop came from various backgrounds and had varying levels of understanding about cervical cancer elimination strategy and different perspectives and opinions. This led to multiple challenges during the discussions. However, the group sessions provided each participant with an equal opportunity to voice their opinions. The four skilled moderators also played an important role in guiding the group discussions and finding common ground among differing viewpoints. Despite potential participant selection biases, the collaborative approach provided comprehensive insights for CC awareness strategies in Burkina Faso, offering valuable guidance for national health authorities. It represents a significant step towards CC elimination in Burkina Faso. The next steps should be the development and dissemination of the messages initiated during the workshop involving all stakeholders, an assessment of their impact over time, and an evaluation of their effectiveness for CC control. The collaborative efforts initiated during the workshop must be sustained and expanded upon to make significant strides in the strategy for CC elimination in the region.

## Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

## Author contributions

SO: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal Analysis, Data curation, Conceptualization. AB: Writing – review & editing, Writing – original draft, Visualization, Validation, Investigation. GT: Writing – review & editing, Writing – original draft, Visualization, Validation, Resources, Methodology, Investigation, Data curation, Conceptualization. SK: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Project administration, Methodology, Formal Analysis, Conceptualization. AT-T: Writing – review & editing, Visualization, Validation, Methodology, Investigation. MM: Writing – review & editing, Visualization, Validation, Methodology, Investigation. SK: Writing – review & editing, Visualization, Supervision, Project administration, Investigation. BS: Writing – review & editing, Visualization, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization. MD: Writing – review & editing, Validation, Resources, Project administration, Methodology, Investigation, Funding acquisition, Data curation. OL: Writing – review & editing, Visualization, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization. NM: Writing – original draft, Visualization, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal Analysis, Data curation, Conceptualization. JS: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Formal Analysis, Data curation, Conceptualization.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## Publisher's note



## Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2024.1383133/full#supplementary-material

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# Baseline assessment of cervical cancer screening and treatment capacity in 25 counties in Kenya, 2022

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**Background:** Cervical cancer is the leading cause of cancer deaths among women in Kenya. In the context of the Global strategy to accelerate the elimination of cervical cancer as a public health problem, Kenya is currently implementing screening and treatment scale-up. For effectively tracking the scale-up, a baseline assessment of cervical cancer screening and treatment service availability and readiness was conducted in 25 priority counties. We describe the findings of this assessment in the context of elimination efforts in Kenya.

**Methods:** The survey was conducted from February 2021 to January 2022. All public hospitals in the target counties were included. We utilized healthcare workers trained in preparation for the scale-up as data collectors in each sub-county. Two electronic survey questionnaires (screening and treatment; and laboratory components) were used for data collection. All the health system building blocks were assessed. We used descriptive statistics to summarize the main service readiness indicators.

**Results:** Of 3,150 hospitals surveyed, 47.6% (1,499) offered cervical cancer screening only, while 5.3% (166) offered both screening and treatment for precancer lesions. Visual inspection with acetic acid (VIA) was used in 96.0% (1,599/1,665) of the hospitals as primary screening modality and HPV testing was available in 31 (1.0%) hospitals. Among the 166 hospitals offering treatment for precancerous lesions, 79.5% (132/166) used cryotherapy, 18.7% (31/166) performed thermal ablation and 25.3% (42/166) performed large loop excision of the transformation zone (LLETZ). Pathology services were offered in only 7.1% (17/238) of the hospitals expected to have the service (level 4 and above). Only 10.8% (2,955/27,363) of healthcare workers were trained in cervical cancer screening and treatment; of these, 71.0% (2,097/2,955) were offering the services. Less than half of the hospitals had cervical cancer screening and treatment commodities at time of survey. The main health system strength

was presence of multiple screening points at hospitals, but frequent commodity stock-outs was a key weakness.

**Conclusion:** Training, commodities, and diagnostic services are major gaps in the cervical cancer program in Kenya. To meet the 2030 elimination targets, the national and county governments should ensure adequate financing, training, and service integration, especially at primary care level.

KEYWORDS

cervical cancer, screening, Kenya, baseline assessment, service readiness

# Introduction

Cervical cancer is the second leading cause of cancer incidence and the leading cause of cancer deaths among women in Sub-Saharan Africa (SSA). In 2020, an estimated 117,316 cases of cervical cancer were diagnosed in Africa, and more than 76,000 women died from the disease in the continent, representing 22% of global deaths from cervical cancer (1). Majority of cervical cancer deaths occur among socio-economically disadvantaged women, especially those with poor access to quality health services (2, 3). While cervical cancer deaths continue falling in countries with organized screening programs and high human papillomavirus (HPV) vaccination coverage, the burden in SSA is increasing (4). In Kenya, cervical cancer is the leading cause of cancer deaths, with approximately 3,200 deaths reported in 2020 (1).

Cervical cancer has very effective modalities for screening, early diagnosis and treatment (5). To reduce the global burden of disease from cervical cancer, the World Health Organization (WHO) launched the Global strategy to accelerate the elimination of cervical cancer as a public health problem in 2020 (6). This strategy identifies key interventions and targets for countries globally by 2030: vaccination against HPV, screening with a high precision test and linkage to treatment. However, innovative strategies and collaborations are necessary to address low HPV vaccination coverage, low screening uptake and high loss to follow-up from screening programs, if low and middle-income countries are to move towards cervical cancer elimination (7). Health system strengthening and effective organization of cervical cancer screening programs have been identified as critical ingredients for success (8). Unfortunately, majority of SSA countries have not implemented and/or sustained high quality cervical cancer screening programs, due to health system deficiencies as well as socio-cultural influences (3, 9–11).

Cervical cancer screening coverage in Kenya was estimated at 16% in 2015 (12). One possible explanation for this low coverage is service availability; only a quarter of hospitals were offering cervical cancer screening services in 2018 (13). In order to move towards cervical cancer elimination, Kenya is implementing a national cervical cancer screening and treatment scale-up, targeting 25 priority counties since 2021. The scale-up involves healthcare workers training, supply of screening and treatment commodities and equipment as well as setting-up governance and coordination structures for the national cervical cancer program. Before the scale-up was launched, a baseline assessment of the cervical cancer screening and treatment service readiness was conducted in the 25 focus counties. The main objective of the baseline assessment was to provide an objective situational analysis of the national cervical cancer program, inform the planning of the scale-up and provide a basis for evaluating future successes of the targeted health system interventions. We present the findings from this assessment and its implications for cervical cancer elimination efforts in Kenya.

# Methods

## Study design and population

This was a cross-sectional survey, conducted in 25 of the 47 counties in Kenya, which were earmarked for the first phase of the national scale-up of cervical cancer screening and treatment. The counties were selected on the basis of HIV burden, regional representation, and sites where a previous pilot on cervical cancer screening scale-up had been carried out. The assessment was carried out over 12 months, from February 2021 to January 2022. The study population was hospitals, from level two (dispensaries) to level six (national referral hospitals) in the target counties. Screening using visual inspection with acetic acid (VIA), HPV sample collection, cryotherapy and thermal ablation are the modalities expected at level two and three hospitals; additional services like large loop excision of the transformation zone (LLETZ), HPV and cytology sample processing, biopsy and histology are expected from level four and above. All eligible hospitals in the selected counties were assessed. Two critical areas for cervical cancer screening programs were assessed in the hospitals: the screening service points and the laboratory. The specific areas assessed are shown in Table 1.

TABLE 1 Domains assessed at the hospitals during the study.

| Domain | Items assessed |
|---|---|
| Hospital demographics | Name |
| | Sub-county |
| | County |
| | Level as per the Kenya Essential Package for Health (KEPH): level two (dispensary), three (health centre), four (sub-county hospital), five (county referral hospital) and six (national referral hospitals) |
| | Ownership: public, private, faith-based |
| | Catchment population |
| Service availability | Screening using visual inspection with acetic acid (VIA) |
| | Screening using human papillomavirus (HPV): sample collection |
| | Screening using HPV testing: sample processing |
| | Screening using cytology: sample collection |
| | Screening using cytology: sample processing |
| | Treatment: cryotherapy, thermal ablation, large loop excision of the transformation zone (LLETZ) |
| | Biopsy, endocervical curettage, colposcopy, histopathology<br>Health products and supplies: acetic acid, cryotherapy gas, HPV, and pap smear kits |
| Service provision sites | Maternal and child health clinic |
| | Comprehensive care centres for HIV |
| | Outpatient department |
| | Gynaecologic clinic |
| | Theatre clinic |
| | Laboratory |
| Human resources for health | Number of healthcare workers per cadre, trained and/or deployed at cervical cancer screening and treatment service points |
| Minimum equipment for cervical cancer screening and treatment and commodities | White light source |
| | Examination room |
| | Examination couch |
| | HPV, cytology kits |
| | Acetic acid |
| | Applicator sticks |
| Infection prevention | Waste disposal bins |
| Awareness and advocacy | Methods used and frequency |
| Health information system | Electronic medical records systems (EMR), screening registers |
| Laboratory | Availability of a GeneXpert machine |
| | Sample referral mechanisms |
| | Backlogs |
| | Commodity stock outs |

## Survey procedures

Two healthcare workers from each sub-county, who had already been identified and trained as peer trainers for cervical cancer screening and treatment, were utilized as data collectors for the survey. The trainers/data collectors had been selected from a pool of nurses/clinical officers/medical officers stationed at cervical cancer screening service provision points in their respective hospitals. A module on the survey tools and procedures was part of their training of trainers (TOT); it included administration of the questions, maneuvering through the electronic tools and data transmission procedures. This approach was deemed to be both efficient and provided an opportunity for the trainers to undertake hospitals mapping before they commenced their cascaded trainings. Each pair was then required to visit and administer the survey tools to hospitals managers, screening, and laboratory staff in all hospitals in their sub-county.

## Data collection and analysis

Data collection approaches included both interviewing key informants in various departments at the hospitals, as well as direct observation of hospitals/processes of interest. Data collection was conducted using two questionnaires: one for cervical cancer screening and treatment services and one for laboratory services. The questionnaires were created electronically using the SurveyCTO© application and loaded into android tablets. Data was transmitted instantaneously to a central database, domiciled at the National Cancer Control Program (NCCP), for processing. Data cleaning and analysis were conducted using Epi-Info software (US CDC, Atlanta, GA). Descriptive statistics were calculated, in terms of the availability and readiness of various components of the cervical cancer screening and treatment program, across various strata including hospitals type and KEPH level.

# Findings

A total of 3,150 hospitals in 25 counties were assessed; majority 3,021 (95.9%) were public hospitals. Majority of the hospitals (3,122 [99.1%]) were primary health care hospitals (level 2-4). Cervical cancer screening was available in 1,665

hospitals (52.6%); however, only 166 (5.3%) were offering both screening and treatment for cervical cancer. The bulk of the health workforce available in the surveyed hospitals was made up of nurses (63.6% [18,639/29,326]). Awareness creation on cervical cancer screening services available was reported by 67.6% of the hospitals; (2,128/3,150); use of community health workers (86.2% [1,835/2,128]) and community outreaches (48.6% [1,035/2,128]) were the most popular methods for awareness creation (some facilities were using multiple approaches). Mass media was the least used approach (3.8%) even though it has the greatest capacity to reach many people. Clinical breast examination (CBE) was available at 78.3% (2,467/3,150) of the hospitals. Only 19.2% (606/3,150) had cervical cancer screening data capture and reporting tools at the time of the survey. Approximately 60% (1,905/3,150) of the hospitals had some form of EMR systems available at some service provision points; however, none had integrated cervical cancer screening data capture in the EMR. Other facility variables are shown in Table 2.

TABLE 2 Summary statistics of the hospitals surveyed.

| Variable | Frequency | Proportion |
|---|---|---|
| **Hospital tier (n=3,150)** | | |
| Level 2 | 2,264 | 71.9 |
| Level 3 | 648 | 20.6 |
| Level 4 | 210 | 6.7 |
| Level 5 | 25 | 0.8 |
| Level 6 | 3 | 0.1 |
| **Facility ownership (n=3,150)** | | |
| Public | 3,021 | 95.9 |
| Faith-based | 69 | 2.2 |
| Private/NGO | 60 | 1.9 |
| **Cervical and breast cancer services offered (n=3,150)** | | |
| Awareness creation | 2,128 | 67.6 |
| Breast cancer screening | 2,467 | 78.3 |
| Cervical cancer screening only | 1,499 | 47.6% |
| Cervical cancer screening and treatment | 166 | 5.3% |
| Pathology (biopsy and histology) | 17 | 0.5 |
| **Cadres of HCWs available (n=29,326)** | | |
| Nurses | 18,639 | 63.6 |
| Clinical officers | 4,286 | 14.6 |
| Laboratory technologists | 3,050 | 10.4 |
| Public Health Officers | 1,935 | 6.6 |
| Medical officers | 1,215 | 4.1 |
| Gynaecologists | 134 | 0.5 |
| Histo-technicians | 28 | 0.1 |
| Pathologists | 20 | 0.1 |
| Cytologists | 19 | 0.1 |
| **Health information system (n=3,150)** | | |
| Data tools available | 606 | 19.2 |
| IEC materials available | 774 | 24.6 |
| **Electronic health systems (n=1,905)** | | |
| EMR | 240 | 12.6% |
| Internet | 289 | 15.2% |
| **Demand generation approaches (n=2,128)** | | |
| Cancer awareness months | 540 | 25.4 |
| Places of worship | 432 | 20.3 |
| Community Health Workers | 1,835 | 86.2 |
| Community Leaders | 559 | 26.3 |
| Mass media | 80 | 3.8 |
| Community Outreaches | 1,035 | 48.6 |
| Others | 419 | 19.7 |

Some percentages may not be exactly 100% due to rounding-up to one decimal place.

## Service delivery per level of care

Cervical cancer screening service availability was highest at level 3 (70.5% [457/648]) and level 4 (67.1% [141/210]) (Table 3). However, availability of both screening and treatment was highest at level 5 hospitals (76% [19/25]). Majority of levels 2 and 3, which formed the bulk of the hospitals, did not have cervical pre-cancer treatment services.

The primary screening method used in most hospitals with screening services was VIA in 96.0% (1,599/1,665) of the hospitals. Among hospitals offering pre-cancer treatment, the modality commonly used was cryotherapy, available in 79.5% (132/166) of these hospitals; 63.9% (106/166) offered single visit approach. In diagnostics, cervical biopsy was available in 21.8% (52/238) of level four and above hospitals and histology in 7.1% (17/238). Among hospitals offering the service, the median cost of histopathology was $ 12.46 [IQR; 5.81–20.76]; the cost was borne by the patients in all the hospitals. Availability of other services across hospitals as per level of where the service is expected, is shown in Figure 1.

Most of the screening, diagnostic and treatment services were offered in the maternal and child health (MCH) clinic and comprehensive clinics (CCC) for people living with HIV; for instance, 66.5% (1,108/1,665) of the hospitals offering VIA were providing it at MCH only, 1.9% (32/1,665) at CCC alone and 24.7% (412/1,665) at both MCH and CCC.

## Screening and treatment health workforce

Only 10.8% (2,955/27,363) of all the HCWs were trained in cervical cancer screening and treatment, with nurses contributing 74.9% (2,212/2,955) of the trained workforce. Among those who are trained, 72.2% of nurses, 66.4% of clinical officers, 41.0% of medical officers, and 65.7% of gynecologists were deployed at cervical cancer screening and treatment service provision points at their hospitals (Table 4).

TABLE 3 Screening and treatment service availability per facility level.

| Facility Level | Number of hospitals (N) | Screening alone available n (%) | Both screening and pre-cancer treatment available n (%) |
|---|---|---|---|
| 2 | 2,264 | 896 (39.6) | 12 (0.5) |
| 3 | 648 | 457 (70.5) | 51 (7.8) |
| 4 | 210 | 141 (67.1) | 83 (39.5) |
| 5 | 25 | 4 (16.0) | 19 (76.0) |
| 6 | 3 | 1 (33.3) | 1 (33.3) |
| **Total** | 3,150 | 1,499 (47.6) | 166 (5.3) |

## Screening commodities availability

Among hospitals that had included cervical cancer screening in their service charter, half (830/1,665) had acetic acid available while 48.9% (815/1,665) had the recommended light source for pelvic examination at the time of the assessment. Other critical commodities like HPV tests and pap smear kits were available in less than five percent of the hospitals offering screening (Figure 2).

## Health system readiness

We noted some key strengths and weaknesses in the health system readiness in moving towards cervical cancer elimination (Table 5). Multiple service delivery points offer opportunities for a better reach and exploitation of efficiencies of service integration. Having multiple cadres offering cervical cancer screening and treatment offers a larger pool for service provision and skill-set strengthening for an effective cervical program. Cervical precancer lesions treatment availability is limited in the hospitals surveyed, which may reduce successful care linkage for women with positive screening results. Another major weakness is the erratic and inefficient supply chain for the screening and treatment commodities, especially cryotherapy gas that limited the number of hospitals able to offer both screening and treatment. Primary care hospitals offer free services, but are limited in service readiness for both screening and treatment.

# Discussion

## Summary of findings

We found that primary health care (PHC) hospitals form the bedrock of cervical cancer service provision in the 25 Counties surveyed. While more than half of all the hospitals offer cervical cancer screening, only 5.0% offer both screening and treatment. Only one in 10 of HCWs in the surveyed hospitals were trained in cervical cancer screening and treatment. Less than half of the hospitals had available stock of cervical cancer screening and treatment commodities at the time of the survey. Presence of multiple screening points at the hospitals was the main health system strength, but commodity stockouts was identified as the main weakness.

## Cervical cancer screening service readiness in Kenya

Majority of the surveyed hospitals were PHC level (2 and 3). This agrees with the structure of the overall health system in Kenya, where PHC hospitals form the bulk of the available public hospitals countrywide. Therefore, strengthening PHC system would be a major step in increasing access to cervical cancer screening and treatment, to make progress towards the 2030 elimination targets.

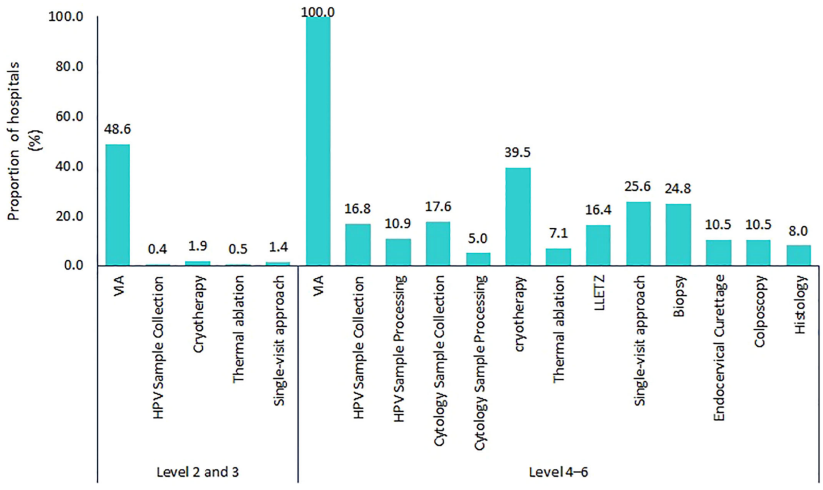


FIGURE 1
Proportion of assessed hospitals, offering various services along the cervical cancer screening and treatment continuum (level 2 and 3, n=2,912; level 4 and above, n=238). LLETZ: Large loop excision of the transformation zone; VIA: visual inspection with acetic acid. Single visit approach: both screening and treatment offered during the same visit.

TABLE 4 Cervical cancer screening and treatment health workforce.

| Cadre | Total number in the hospitals (N) | Number trained* on cervical cancer screening n1 (n1/N %) | Number offering cervical cancer screening and treatment n2 (n2/n1%) |
|---|---|---|---|
| Nurses | 18,639 | 2,212 (11.9) | 1,598 (72.2) |
| Clinical officers | 4,286 | 381 (8.9) | 253 (66.4) |
| Medical officers | 1,215 | 134 (11.0) | 55 (41.0) |
| Gynecologists | 134 | 108 (80.6) | 71 (65.7) |
| Laboratory technologists | 3,050 | 94 (3.1) | 94 (100.0) |
| Pathologists | 20 | 11 (55.0) | 11 (100.0) |
| Cytologists | 19 | 10 (52.6) | 10 (100.0) |
| Histo-technologist | 28 | 5 (17.9) | 5 (100.0) |

*Any form of focused training on cervical cancer screening and treatment, whether pre-service, formal, or on-job training in the previous three years.

Levels 2 and 3 also have service provision at no cost to patients, implying that they can be avenues for removing financial barriers to cervical cancer screening uptake. PHC, especially within the context of Universal Health Coverage (UHC), is important for increasing access to cervical screening (14).

Unfortunately, more than half of the PHC hospitals do not offer cervical cancer screening, and even those that do, fail to provide treatment. One reason may be inadequate trained and competent personnel; while some HCWs reported that they had received training in the past, some did not feel competent enough to offer treatment. Another reason could be erratic provision of screening and treatment health commodities and unavailability of treatment equipment. For instance, despite a country-wide distribution of cryotherapy equipment over a decade ago, we found that many were either broken, or had run out of cryotherapy gas and never replenished. PHC hospitals, while offering free services, have no financial planning autonomy, and rely on secondary level hospitals for procurement of supplies; in such circumstances health promotion interventions like cancer screening may be deprioritized when financial resources are very limited. Even where trained personnel were available at some point, they are lost by either transfer to other hospitals/departments or retirement from service and no regular replacements done. These findings are similar to a recent national service readiness survey in Kenya, which showed higher readiness in referral hospitals compared with PHC hospitals (15).

MCH and CCC/HIV clinics are the main cervical cancer screening service points in the surveyed hospitals. Traditionally, cervical cancer screening in Kenya was domiciled under the reproductive health services, hence services were offered either at MCH or family planning clinics. Organized cervical cancer screening also served as an integral component of HIV care, due to the epidemiological and biological linkage between HIV and cervical cancer. Integration is an efficient policy direction for increasing cervical cancer screening uptake; lessons from integration at MCH and CCC can enable incorporation of more service provision points at hospitals, including outpatient departments (OPD) and gynecological clinics. More hospitals were offering CBE than cervical cancer screening, proving another opportunity for integration. Ample evidence exists on the efficacy of integrating cervical cancer screening in reproductive, HIV and vaccination programs in SSA (16–23).

We found frequent unavailability of critical supplies for cervical cancer screening and treatment, especially acetic acid, cryotherapy gas and HPV kits. Procurement of such commodities may not be prioritized at the county level, compared with diagnostic commodities and medicines. In addition, screening commodities are not available at the Kenya Medical Supplies Authority (KEMSA), the main medical supplier for the County Departments of Health in Kenya, possibly due to policy or resource constraints. NHIF does not cover preventive or promotive health services like cancer screening, which severely limits the financing component of the national cervical cancer control program. However, this may change with the ongoing UHC reforms in the health sector. Lack of screening commodities

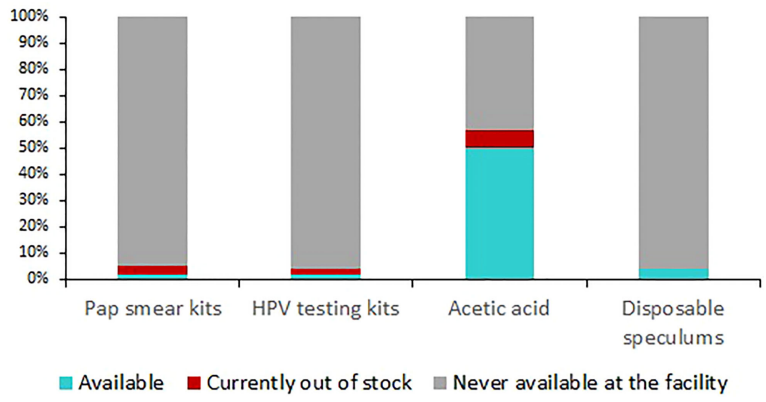


FIGURE 2
Availability of critical cervical cancer screening commodities in hospitals in 25 Kenyan counties, 2022. (n=3,150).

TABLE 5 Strengths and weaknesses of the healthcare system to support cervical cancer screening and treatment in Kenya.

| Health system building block | Strength | weakness |
|---|---|---|
| Leadership and governance | Some form of governance structure exists, with either reproductive health or non-communicable disease coordinator taking charge of cervical cancer screening and treatment planning at county level and sitting in the County Health Management Team. | Data-driven decision making has not been adequately embraced at facility and county level. |
| Service delivery | Services, where available, are spread out in multiple delivery points. | Treatment of cervical pre-cancerous lesions is available in very few hospitals. Primary health care hospitals, which constitute the majority of hospitals, have in sufficient service availability and readiness. |
| Health system financing | At health centre and dispensary level (level 2 and 3), cervical cancer screening and treatment is offered free of charge. | Cervical cancer screening is not covered under the National health Insurance Fund (NHIF); funding for screening is relegated to the background and priority given to curative programs. While screening is free at primary care hospitals (dispensaries and health centres), service provision is limited by trained workforce and health products stock-outs in these hospitals since they lack planning and budgeting autonomy. |
| Health workforce | Screening and treatment services are provided by multiple cadres, including nurses, clinical officers, medical officers, and gynaecologists. | High attrition rate of HCWs trained on cervical cancer screening and treatment makes it impossible to sustain highly trained and motivated teams. |
| Medical products, vaccines, and technologies | Most hospitals had the bare minimum screening commodities; speculums, gloves, and acetic acid. | Screening commodities supply is not prioritized, making it erratic and prone to frequent stock-outs. For instance, cryotherapy gas is commonly unavailable even where the equipment is available, therefore making many screening hospitals unbale to offer treatment. |
| Health information systems | A comprehensive cancer screening register has been developed and disseminated. Aggregated cervical cancer screening and treatment data is collected using primary and summary registers at facility level and uploaded into the Kenya Health Information System (DHIS2). | The paper-based system is inefficient in ensuring proper follow-ups and linkage to further evaluation/treatment. This is especially critical when clients with positive tests are referred for treatment in a different hospital. |

was also identified as a key gap in an evaluation of the Zimbabwe cervical cancer program (24).

Multiple service provision points, by different cadres were identified as key strengths in the cervical cancer program in the surveyed hospitals; unavailability of treatment services, erratic commodity supply chain and few numbers of trained personnel were the major weaknesses. Availing multiple screening points at hospitals minimizes lost opportunities and increase screening uptake. Health service provision in Kenya is based on the Kenya Essential Package for Health (KEPH) levels; cervical cancer screening ideally is supposed to be offered across all the levels, but especially PHC hospitals (2–4). All the HCW cadres in these levels are eligible for training on cervical cancer screening and treatment, as guided by the respective schemes of service. Accessibility of screening and integrating with other services offered at the hospitals were noted as drivers of cervical cancer screening uptake in Malawi (25). In Uganda, building capacity among PHC health workers in cervical cancer screening and treatment has been adopted as a strategy to address unmet needs in the population (26). In addition to commodities supply chain, the Zimbabwean study also identified staffing challenges, lack of equipment, limited funding and ineffective leadership and governance structure (24). A similar approach, including training PHC personnel, adapting screening approaches to practical local contexts and enhancing local infrastructure to perform various screening tests, has been suggested for two West-African countries (27).

## Strengths and limitations

A particular strength of this study was that we conducted a census of all the hospitals in the 25 Counties, spread out in the 10 regions of Kenya; therefore, the findings are likely representative of the true state of cervical cancer control service readiness. The assessment also comprehensively examined the main health system building blocks, therefore provides critical insights for areas in need of strengthening for Kenya to move towards elimination. A weakness of the study was that the survey did not undertake an exploratory angle, to find out the possible underlying reasons to some of the identified gaps. Such an undertaking would have provided more information for planning and focusing the interventions in a more effective and efficient manner and is planned for subsequent program evaluations.

# Conclusion and recommendations

We identified major gaps in the service readiness for an effective cervical cancer program in the 25 Counties, but also some opportunities, which if explored can provide a path towards elimination. We recommend a more efficient supply for cervical cancer screening and treatment commodities at PHC, primarily through public financing. Since level 2 and 3 hospitals constitute the majority of the hospitals, they should be enabled to offer cervical cancer screening and treatment by ensuring adequately trained staff

and essential health commodities. Availability of screening services in nearby hospitals has been identified as one of the determinants of screening uptake (28). Additional service provision points at hospitals need to integrate cervical cancer screening to their routine service provision, to reduce missed opportunities for screening when women visit for other services. A study in Ethiopia identified restricting screening to a single service point as a barrier to screening uptake (29). A cervical cancer human resource development plan is necessary to guide recruitment, training, mentorship, retention, and replacement of personnel at the county level; sustained capacity-building of HCWs is necessary for success of programs (30). Cervical cancer screening and treatment should be included in the ongoing health financing reforms, especially at PHC; recent evidence shows adequate financing will be necessary for cervical cancer elimination (31). Regular similar assessments should be conducted to inform the efficacy of ongoing investments in the strengthening of the national cervical cancer control program.

## Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

## Ethics statement

Since the unit of assessment was the hospitals, we collected data on service availability and readiness; no personal information was obtained. The study was approved by the Ministry of Health (MoH) and the respective County Departments of Health. Specifically, the assessment was modelled on a broader health system service availability and readiness assessment, usually conducted for all health services in Kenya every five years. However, in this case, we focused on readiness for the country to implement selected interventions within the cervical cancer elimination strategy. Being a routine component of health system evaluation and strengthening, this assessment did not require an Institutional Review Board (IRB) clearance process as per relevant stipulations by the Ministry of Health. All methods were carried out in accordance with the Monitoring and Evaluation guidelines of MoH. Even though the data collected was not personal in nature, safety was ensured during transmission and archiving through password-protected files.

## Author contributions

VM: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. DM: Formal analysis, Methodology, Validation, Writing – original draft, Writing – review & editing. CK: Formal analysis, Writing – original draft, Writing – review & editing. J-PB: Conceptualization, Investigation, Validation, Writing – original draft, Writing – review & editing. PN: Conceptualization, Funding acquisition, Project administration, Resources, Supervision, Validation, Writing – original draft, Writing – review & editing. LO: Conceptualization, Investigation, Validation, Writing – original draft, Writing – review & editing. MN: Conceptualization, Funding acquisition, Investigation, Project administration, Supervision, Writing – original draft, Writing – review & editing. MA: Writing – original draft, Writing – review & editing. PT: Writing – original draft, Writing – review & editing. MT: Writing – original draft, Writing – review & editing.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## Publisher's note



## Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2024.1371529/full#supplementary-material

DATA SHEET 1
Screening and treatment services assessment dataset.

DATA SHEET 2
Laboratory services assessment dataset.

DATA SHEET 3
Screening and treatment services assessment codebook.

DATA SHEET 4
Laboratory services assessment dataset codebook.

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# Comparative study of triage strategies for women with atypical squamous cells of undetermined significance in the post-vaccine era

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**Objective:** The research focused on a comparative analysis of triage strategies for women with Atypical Squamous Cells of Undetermined Significance (ASC-US) before and after receiving the HPV vaccine, aiming to optimize cervical cancer prevention strategies, especially in resource-limited healthcare settings.

**Materials and methods:** Between September 2018 and December 2023, 7,511 women aged 21 years or older who underwent liquid-based cytology for cervical cancer screening were recruited. Women diagnosed with ASC-US were included in the study. All participants underwent HPV testing and liquid-based cytology examination, and those with abnormal results were referred for colposcopy. Women with abnormal colposcopy findings underwent further histopathological examination. The gold standard for diagnosis was pathological, with cervical intraepithelial neoplasia grade 2 or higher (CIN2+) on histology as the endpoints. In the final analysis, 933 women with ASC-US were enrolled as the unvaccinated group, with 179 of them testing positive for HPV 16/18. Assuming that all women would receive the bivalent vaccine targeting HPV 16/18 in the post-vaccine era, and given that the vaccine protection rate is 100% against HPV 16/18, then 754 women excluding those of HPV 16/18 positive would comprise the vaccinated group.

**Results:** In the unvaccinated group, the overall HPV positivity rate was 59.27% among ASC-US women, with a 100% HPV prevalence rate among those with CIN2+ lesions. The combination genotyping model of HPV16/18 showed the highest specificity (81.77%) and the lowest referral rate (32.37%). In the vaccinated group, the HPV positivity rate was 49.61% among ASC-US women, with a 100% HPV prevalence rate among those with CIN2+ lesions. The specificity of HPV33/

58 was the highest (86.99%), and the colposcopy referral rate was lowest (27.54%), with statistical significance. Sensitivity, positive predictive value, and negative predictive value were not statistically significant.

**Conclusion:** HPV16/18 demonstrated a more efficacious triaging effect in the unvaccinated group. HPV33/58 will potentially replace HPV16/18 as the priority screening genotyping among vaccinated populations.

KEYWORDS

**human papillomaviruses, atypical squamous cells of undetermined significance, cervical cancer, resource-limited areas, the post-vaccine era**

# 1 Introduction

Cervical cancer is the most common malignancy among female reproductive tract tumors, posing a significant disease burden, particularly in areas with limited health resources (1, 2). Screening for cervical cancer primarily relies on cytology tests and HPV testing. ASC-US, an important cytological diagnosis in cervical cancer screening, is not definitive, and its histopathology results can range from inflammation and cervical intraepithelial neoplasia (CIN) to cervical cancer. Approximately, 3%-10% of women are diagnosed with atypical squamous cells of undetermined significance (ASC-US) (3). The interpretation of cytological results can be influenced by the skill level of the physician, leading to a degree of bias. Over the past period, the integration of HPV testing into clinical practice, including HPV mRNA and HPV DNA testing, has significantly improved the management of ASC-US cases, with HPV testing (4–6). More precise triaging of ASC-US women is crucial for cervical cancer prevention, especially when implementing a stratified management approach tailored to different high-risk human papillomaviruses (HR-HPV) types.

HPV vaccines are the most effective primary prevention measure against cervical cancer (7). The bivalent vaccine offers a protection rate exceeding 95% (8–11), while it is significantly less expensive than the quadrivalent and nine-valent HPV vaccines. Despite this, vaccination coverage remains relatively low in many developing countries (12, 13). Considering the balance between cost and preventive effectiveness, the bivalent HPV vaccines is recommended for the general population in limited health resources settings. In China, National People's Congress deputies and health experts have called for inclusion of domestically produced bivalent HPV vaccines in the national immunization program to enhance accessibility and affordability for the eligible population.

With the gradual popularization of the HPV vaccine, we will eventually enter the post-vaccine era, where vaccinated and unvaccinated women will coexist for an extended period, and the types of HPV infections will also change. Currently, follow-up data from real-world studies on the HPV-vaccinated population are not readily available or lacking in resource-limited settings, particularly for those with ASC-US. As a result, the specific gene combination that best triages the ASC-US population in the post-vaccine era is rarely reported, the differential triage strategies for ASC-US women who are vaccinated and unvaccinated are worth exploring. In this study, based on an earlier large real-world population undergoing cervical cancer screening, we make the hypothetical assumption that in the future, all women who were initially unvaccinated against HPV have subsequently received the HPV bivalent vaccine. Under this assumption, the subgroup of these women who are not HPV 16/18 positive were considered as the 'vaccinated group' for the purpose of our analysis. By comparing the triage efficacy of the vaccinated and unvaccinated groups, we identified different management approaches for ASC-US women in the post-vaccine era in countries with limited healthcare resources.

# 2 Materials and methods

## 2.1 Study design and participants

Since 2009, the "Two Cancers Screening" program for rural women has been implemented in China. This project provides free or subsidized screenings within the rural female population to enhance women's health status and reduce the incidence and mortality rates of cervical cancer and breast cancer. The cervical cancer screening used co-testing with cytology and HPV testing. This cohort study was based on the "Two Cancer Screening" program in Wuxiang County, Shangdang District, and Zezhou County, Changzhi City, Shanxi Province. Women diagnosed with ASC-US, aged≥21 years, and with sexual experience were included in the study. Exclusions were: 1) pregnant women or women within 8 weeks after delivery; 2) women with a history of hysterectomy, cervix surgery, or cervical cancer treatment; 3) women with cognitive impairment.

Of the 7,511 women enrolled from 2018 to 2023 for cervical cancer screening, 933 women diagnosed with ASC-US were categorized as the unvaccinated group. Assuming that all women in the unvaccinated group would receive the bivalent vaccine targeting HPV 16/18, and given that the protection rate of this bivalent vaccine is 100% against HPV 16/18, the subgroup of 754 women who excluded 179 HPV 16/18 positive women were considered as the vaccinated group. Additionally, 754 women were included as the bivalent vaccinated group, which excluded 179 HPV 16/18-positive women from the 933 ASC-US women. All included ASC-US women were followed up for the next 3 years with HPV DNA testing and liquid-based cytology (LBC) examinations. Women who tested HPV-positive or had ASC-US or and higher results were referred for colposcopy. Those with abnormal colposcopy findings underwent further histopathological examination. Pathological diagnosis was the gold standard, with cervical intraepithelial neoplasia grade 2 or higher (CIN2+) as endpoints. The screening flowchart is shown in Figure 1.

## 2.2 Data and specimen collection

Demographic information was collected through questionnaires, including marital status, education level, smoking and alcohol consumption history, menstrual history, and reproductive history. Trained gynecologists conducted gynecological examinations of the vulva, vagina, and cervix for all participants, and speculum examinations were also performed. The specimens of cervical exfoliated cells were collected for liquid-based cytology (LBC) classification and HPV genotyping tests.

## 2.3 Laboratory testing

### 2.3.1 HPV testing

A commercial assay was used for HPV DNA testing. The HPV testing method was the Biochip Method, manufactured by Beijing Bohui Innovative Optoelectronic Technology, with approval from the China Food and Drug Administration (CFDA) (registration certificate no: 20163401108). This method can detect 14 types of HPV DNA (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68) from the cervical exfoliated cells, and distinguish all HPV types individually. Quality control probes and detection probes are distributed on the hybrid membrane of HPV nucleic acid detector. The quality control probes include blank, negative, color rendering, and internal reference quality control points. The positive quality control is used to verify the validity of the detection method, while the negative quality control is used to exclude the possibility of false positive results.

### 2.3.2 Cytology examination

Cytology slides were reviewed by two pathologists, and results were reported according to the Bethesda 2014 classification. The cytological results included: negative for intraepithelial lesion or malignancy (NILM), atypical squamous cells of undetermined significance (ASC-US), low-grade squamous intraepithelial lesion

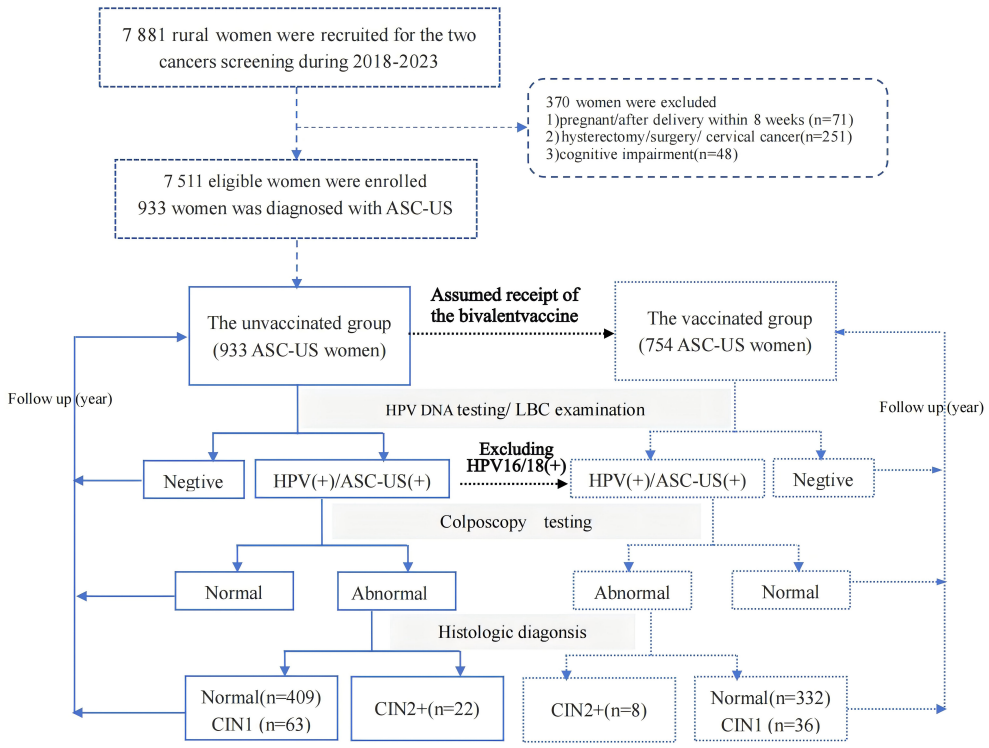


FIGURE 1
The flowchart of subject enrollment in this study.

(LSIL), atypical squamous cells-cannot exclude high-grade squamous intraepithelial lesion (ASC-H), high-grade squamous intraepithelial lesion (HSIL), atypical glandular cells, and cervical cancer cells. Diagnoses were reported if the diagnoses by two cytologists were consistent. Otherwise, a third cytologist was consulted.

#### 2.3.3 Cytology and histology

All women with positive HPV results or abnormal cytology (ASC-US or worse) were referred for colposcopy. If the colposcopy provided full visibility and a lesion was identified, a biopsy was performed on the abnormal area, with the specific location of the specimen clearly marked. If the colposcopy exposure was insufficient, cervical curettage was performed. Two pathologists independently made diagnoses, if the diagnoses were concordant, they were reported as the pathological diagnosis. Otherwise, a third pathologist also reviewed all positive results and 10% of negative slides. The final diagnosis was based on the agreement between the three doctors, and in cases of disagreement, a consensus decision was made by all three. According to the 2014 WHO Classification of Tumors of the Female Genital Tract (14), histological diagnoses of cervical lesions were categorized as normal, LSIL/CIN1 (including the condylomatous variant), HSIL/CIN2, HSIL/CIN3 (including adenocarcinoma *in situ*) and carcinoma (squamous cell carcinoma or adenocarcinoma).

### 2.4 Quality control

Investigators, gynecologists, and pathologists were trained according to a standardized manual of operation. All technicians, cytologists, and pathologists involved in HPV testing and cytology slide reading were blinded throughout the study. Experienced physicians conducted gynecological and colposcopy examinations. Pathologists with more than 30 years of experience provided the final decisions for cytological and pathological diagnoses. HPV detection probe and quality control probe be used throughout the whole process of HPV detection, and quality control probe be distributed on each chip. Positive and negative quality controls were implemented to ensure the quality of HPV testing.

### 2.5 Statistical analysis

SPSS version 20.2 (IBM Corp, New York, USA) was used for data analysis. Quantitative variables were expressed as medians and interquartile ranges, while categorical variables were represented by numbers and percentages. The pathological diagnosis served as the gold standard, with CIN2+ on histology as the endpoint. A receiver operating characteristic (ROC) curve was plotted, and the sensitivity, specificity, positive predictive value, negative predictive value, area under the curve (AUC) of the ROC, and referral rate of HPV genotyping were calculated. The referral rate was calculated as the number of participants with ASC-US and positive HR-HPV dividing by the total number of participants with ASC-US. The chi-square test and Fisher's exact probability test were applied to compare diagnostic effects. Statistical significance was set at a two-sided *P* value of less than 0.05. The Attribute Fraction (AF) was used to calculate the proportion of CIN2+ lesions caused by specific HPV genotypes: AF= (contribution coefficient of target HPV genes × number of infections)/(CIN2+) ×100%. Based on the normal group, the relative risk (RR) of CIN1 and CIN2 was calculated as RR=AF (+)/AF (-).

## 3 Results

### 3.1 Characteristics of the study population

Of the 7,511 women were enrolled, 933 (12.42%) were diagnosed with ASC-US and categorized as the unvaccinated group. In this group, the average age was 47.42 ± 8.88 years, with around 70% having a junior middle school degree or below. The median ages of menarche and first pregnancy were 14 (13-16) and 23 (22-26) years, respectively. Almost all women in this group did not smoke or drink alcohol. In the vaccinated group, 754 women were induced, with an average age of 47.39 ± 8.92 years. There were no significant statistical differences between the two groups in terms of age, education level, marital status, alcohol consumption, smoking status, menarche age, and fertility history. Detailed results are shown in Table 1.

### 3.2 Pathological diagnosis and attributable risk stratification analysis of CIN2+ by different HPV infection types in women with ASC-US

In the unvaccinated group, histopathology confirmed that 90.88% (848/933) of participants had a normal cervix. The proportions of participants with CIN1 and CIN2+ were 6.75% (63/933) and 2.35% (22/933), respectively. Among participants with ASC-US, the prevalence of HR-HPV was 59.27% (553/933). The prevalence of HR-HPV in participants with normal pathology, CIN1, and CIN2+ were 56.25% (477/848), 85.71% (54/63), and 100% (22/22), respectively. In the vaccinated group, histopathology confirmed that 94.16% (710/754) of participants had a normal cervix, while the proportions of participants with CIN1 or CIN2+ were 4.77% (36/754) and 1.06% (8/754), respectively (Table 2).

In the unvaccinated group, the five most common HPV genotypes among normal participants were HPV16, 52, 58, 39 and 51. For those with CIN1, the top five HPV genotypes ranked by AF value were HPV16, 52, 58, 66, and 33, with HPV35 having the same AF as HPV39. Among participants with CIN2+, the five most common HPV types were HPV16, 33, 18, 58, and 31. In the vaccinated group, the incidence of HR-HPV infection increased with the severity of the pathological diagnosis. Among normal participants, the five most common types of HPV infections indicated by AF were HPV58, 52, 51, 31, and 56. The ranking of risks for CIN1, from high to low, was 52, 58, 66, 31, 33, 35,and 39. Among them, HPV types 33, 35, and 39 share the same rank. Among the CIN2+ population, the risk attribution of HPV from

TABLE 1 Characteristics of the study population (n/%).

| Characteristics | Group | Unvaccined group | Vaccined group | $\chi^2$ | *P* |
|---|---|---|---|---|---|
| Age (yrs) | 21~29 | 26 (2.78) | 21 (2.78) | 0.000 | 1.000 |
| | 30~39 | 157 (16.82) | 127 (16.84) | | |
| | ≥40 | 750 (80.40) | 606 (80.38) | | |
| Level of education | Primary school and below | 248 (26.58) | 202 (26.79) | 1.350 | 0.717 |
| | Junior middle school | 419 (44.91) | 320 (42.44) | | |
| | High school | 101 (10.83) | 86 (11.40) | | |
| | ≥University | 165 (17.68) | 146 (19.37) | | |
| Marital status | Yes | 918 (98.39) | 744 (98.67) | 0.140 | 0.707 |
| | No | 15 (1.61) | 10 (1.33) | | |
| Smoking | No | 933 (100) | 754 (100) | 18.99 | <0.01 |
| | Yes | 0 (0) | 0 (0) | | |
| Drinking | No | 893 (95.71) | 720 (95.49) | 0.05 | 0.824 |
| | Yes | 40 (4.29) | 34 (4.51) | | |
| Age of menarche (yrs) | ≤14 | 486 (52.09) | 403 (53.44) | 0.308 | 0.578 |
| | >14 | 447 (47.91) | 351 (46.56) | | |
| Contraception measures | Sterilization Surgery | 500 (53.59) | 405 (53.71) | 0.067 | 0.999 |
| | Intrauterine Contraceptive Device | 134 (14.36) | 110 (14.58) | | |
| | Oral Contraceptive Pills | 1 (0.00) | 1 (0.00) | | |
| | Condom | 75 (0.08) | 59 (0.07) | | |
| | No | 223 (31.97) | 179 (0.23) | | |
| Age of the first pregnancy* | ≤23 | 565 (60.56) | 443 (59.06) | 0.571 | 0.450 |
| | >23 | 363 (39.44) | 307 (40.94) | | |
| Times of pregnancy | ≤3 | 664 (71.16) | 536 (71.08) | 0.001 | 0.971 |
| | >3 | 269 (28.84) | 218 (28.92) | | |
| Times of reproduction* | ≤2 | 671 (72.15) | 554 (73.86) | 0.619 | 0.431 |
| | >2 | 259 (27.85) | 196 (26.14) | | |

*indicates missing data.
χ, Chi-square test.

TABLE 2 The prevalence of infection with different HPV genotypes in women with ASC-US (n,%).

| HPVgenotypes | Unvaccined group | | | | Vaccined group | | | |
|---|---|---|---|---|---|---|---|---|
| | Normal | CIN1 | CIN2+ | Total | Normal | CIN1 | CIN2+ | Total |
| HPV16 | 103 (12.14) | 23 (36.50) | 10 (45.45) | 136 (14.57) | – | – | – | – |
| HPV18 | 40 (4.41) | 3 (4.76) | 4 (18.18) | 47 (5.03) | – | – | – | – |
| HPV31 | 33 (3.89) | 6 (9.52) | 2 (9.09) | 41 (4.39) | 30 (4.23) | 2 (5.56) | 2 (25.00) | 34 (4.51) |
| HPV33 | 31 (3.65) | 4 (6.34) | 5 (22.72) | 40 (4.28) | 21 (2.96) | 2 (5.56) | 3 (37.50) | 26 (3.45) |
| HPV52 | 100 (11.79) | 11 (17.46) | 3 (13.63) | 114 (12.21) | 78 (10.99) | 6 (16.67) | 2 (25.00) | 86 (11.41) |
| HPV58 | 93 (10.96) | 9 (14.28) | 4 (18.18) | 106 (11.36) | 72 (10.15) | 6 (16.67) | 3 (37.50) | 81 (10.75) |
| HPV51 | 72 (8.49) | 8 (12.69) | 2 (9.09) | 82 (8.78) | 54 (7.61) | 2 (5.56) | 2 (25.00) | 58 (7.7) |

*(Continued)*

TABLE 2 Continued

| HPVgenotypes | Unvaccined group | | | | Vaccined group | | | |
|---|---|---|---|---|---|---|---|---|
| | Normal | CIN1 | CIN2+ | Total | Normal | CIN1 | CIN2+ | Total |
| HPV66 | 34 (4.00) | 9 (14.28) | 1 (4.54) | 44 (4.71) | 22 (3.10) | 7 (19.45) | 0 (0) | 29 (3.85) |
| HPV68 | 28 (3.30) | 1 (1.58) | 1 (4.54) | 30 (3.21) | 22 (3.10) | 1 (2.78) | 1 (12.50) | 24 (3.19) |
| HPV35 | 19 (2.25) | 2 (3.17) | 0 | 21 (2.25) | 10 (1.41) | 2 (5.56) | 0 (0) | 12 (1.6) |
| HPV39 | 36 (4.25) | 2 (3.17) | 2 (9.09) | 40 (4.28) | 28 (3.95) | 1 (2.78) | 0 (0) | 29 (3.85) |
| HPV45 | 11 (1.30) | 1 (1.58) | 0 | 12 (1.28) | 9 (1.27) | 1 (2.78) | 0 (0) | 10 (1.33) |
| HPV59 | 29 (3.42) | 1 (1.58) | 0 | 30 (3.21) | 22 (3.10) | 0 (0) | 0 (0) | 22 (2.92) |
| HPV56 | 52 (6.13) | 4 (6.34) | 0 | 56 (6.00) | 36 (5.08) | 2 (5.56) | 0 (0) | 38 (5.04) |
| HR-HPV | 477 (56.25) | 54 (85.71) | 22 (100.00) | 553 (59.27) | 339 (47.74) | 27 (75.00) | 8 (100.00) | 374 (49.61) |
| Total | 848 (90.88) | 63 (6.75) | 22 (2.36) | 933 (100.00) | 710 (94.16) | 36 (4.77) | 8 (1.06) | 754 (100) |

HPV, human papillomavirus; CIN 1/2/3, cervical intraepithelial neoplasia grade 1/2/3; "-", negative.

high to low was HPV33, 58, and 31. More details are shown in Table 3.

## 3.3 The triaging value of different HPV genetypes in women with ASC-US

In the unvaccinated population, with CIN2+ histology of cervical lesions was the endpoint, the sensitivity and colposcopy referral rate of the combination HPV16/18 was the lowest compared to HPV16/18/31, HPV16/18/31/33, and HPV16/18/31/33/58 (63.63% vs. 77.27% vs. 86.36% vs. 95.45%; 32.37% vs. 37.97% vs. 42.86% vs. 56.06%). However the missed diagnosis rate of HPV16/18/31/33/58 (4.55%) was the lowest. In the vaccinated population, with CIN2+ histology of cervical lesions as the endpoint, the sensitivity and colposcopy referral rate of different combination models of HR-HPV increased with the inclusion of HPV33/58, HPV31/58, HPV31/33/58, and HPV31/33/52/58. However, the specificity of the combination HPV31/33/52/58 was the lowest compared to HPV33/58, HPV31/58, and HPV31/33/58 (72.92% vs. 85.52% vs. 86.99% or 83.11%). The ROC AUC of HPV33/58, HPV31/58, HPV31/33/58, and HPV31/33/52/58 were similar, while the referral rate of HPV33/58 was the lowest (27.54%), as shown in Figures 2, 3 and Table 4.

# 4 Discussion

In regions with scarce resources and low hygiene levels, cervical cancer prevention and control are currently at a pivotal stage. This stage involves transforming vaccination strategies and confronting the dual responsibilities of advancing vaccine coverage and ensuring adequate screening for both vaccinated and unvaccinated groups. ASC-US is a common cytological abnormality in cervical cancer screening in the post-vaccine era, with histopathology that varies greatly (15). Due to the relatively limited diagnostic capabilities of cytologists, relying solely on TCT testing methods presents certain limitations. To optimize screening outcomes, introducing HPV testing can effectively compensate for the shortcomings of cytological screening.

Currently, there is a lack of substantial real-world datasets in China for reference purposes. We hypothesize that the bivalent vaccine was received by the study population to make a cautious estimation of post-immunization outcomes. In this study, the reporting rate of ASC-US among 7,511 rural women was about 12% in the unvaccinated group. The incidence rate of ASC-US in the population after vaccination was about 10%, similar to the range of 3.7-10% observed in Chinese women (16, 17). In the unvaccinated group, the study identified that the prevalence rate (59.27%) of HR-HPV in the ASC-US population was higher than the proportions reported by Zhang J (18) (43.79%) and Wang L (19) (49.76%) in rural Chinese areas, but lower than the figure reported by White C (20) (62.2%) in Ireland. This discrepancy may be due to differences in HPV infection rates among various regions. The CIN2+ is an important outcome endpoint in this study, with routine fertility-sparing treatments for early-stage cervical cancer including Loop Electrosurgical Excision Procedure (LEEP) and laparoscopic-assisted vaginal trachelectomy (21, 22). The CIN2+ detection rate among ASC-US individuals was 2.35% (22/933), which was similar to the rate reported by Ittiamornlert P (2.74%) (23) but lower than the rate reported by Tao X (5.5%) (15). This discrepancy might be attributed to the fact that our investigation carried out screening assessments within the general populace, whereas Tao X's study enlisted participants through opportunistic screening procedures conducted at outpatient clinics. However, the detection rate of CIN2+ was only 1.06% (8/754) in the vaccinated group, significantly lower than in the unvaccinated group. Consistent with Teoh D's (24) study, our findings showed that the probability of cervical precancerous lesions was lower in the vaccinated population compared to their unvaccinated counterparts.

In the unvaccined group, HPV16 had the highest infection rate and pathogenicity. HPV16 was the most prevalent genotype, with 44% of the risk of CIN2+ attributed to it (25). In addition to HPV16, the AF values for HPV33, 18, 58, and 31 were also high in CIN2+

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TABLE 3 Attributable risk analysis of different HPV types on CIN2+ (%,95%CI).

| HPV genotype | Unvaccined group | | | | | Vaccined group | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Normal | CIN1 | CIN2+ | RR (A) | RR (B) | Normal | CIN1 | CIN2+ | RR (A) | RR (B) |
| HPV16 | 0.11 (0.09,0.13) | 0.32 (0.21,0.45) | 0.44 (0.32,0.58) | 2.90 | 4.00 | – | – | – | – | – |
| HPV18 | 0.02 (0.01,0.04) | 0.02 (0.00,0.13) | 0.13 (0.02,0.39) | 1.00 | 6.50 | – | – | – | – | – |
| HPV33 | 0.02 (0.01,0.03) | 0.04 (0.03,0.06) | 0.22 (0.07,0.53) | 2.00 | 11.00 | 0.01 (0.01,0.03) | 0.02 (0.00,0.15) | 0.37 (0.07,1.09) | 2.00 | 37.00 |
| HPV52 | 0.09 (0.07,0.11) | 0.11 (0.10,0.12) | 0 | 1.22 | 0 | 0.06 (0.05,0.09) | 0.13 (0.04,0.32) | 0 | 2.16 | 0 |
| HPV58 | 0.08 (0.06,0.10) | 0.09 (0.08,0.09) | 0.13 (0.09,0.17) | 1.12 | 1.62 | 0.07 (0.05,0.10) | 0.11 (0.03,0.28) | 0.33 (0.00,1.85) | 1.57 | 4.71 |
| HPV31 | 0.03 (0.02,0.04) | 0.02 (0.01,0.03) | 0.06 (0.00,0.21) | 0.66 | 2.00 | 0.03 (0.02,0.04) | 0.03 (0.00,0.15) | 0.16 (0.00,0.92) | 1.00 | 5.33 |
| HPV35 | 0.00 (0.00,0.01) | 0.03 (0.00,0.11) | 0 | – | 0 | 0.00 (0.00,0.01) | 0.02 (0.00,0.15) | 0 | – | 0 |
| HPV39 | 0.05 (0.04,0.07) | 0.03 (0.01,0.09) | 0 | 0.60 | 0 | 0.01 (0.00,0.02) | 0.02 (0.00,0.15) | 0 | 2.00 | 0 |
| HPV45 | 0.00 (0.00,0.01) | – | 0 | – | 0 | 0.00 (0.00,0.01) | – | 0 | – | 0 |
| HPV51 | 0.05 (0.03,0.06) | – | 0 | – | 0 | 0.05 (0.03,0.07) | – | 0 | – | 0 |
| HPV56 | 0.03 (0.02,0.05) | – | 0 | – | 0 | 0.03 (0.02,0.05) | – | 0 | – | 0 |
| HPV59 | 0.01 (0.01,0.02) | – | 0 | – | 0 | 0.02 (0.01,0.03) | – | 0 | – | 0 |
| HPV66 | 0.02 (0.01,0.03) | 0.08 (0.08,0.09) | 0 | 4.00 | 0 | 0.01 (0.00,0.02) | 0.08 (0.01,0.24) | 0 | 8.00 | 0 |
| HPV68 | 0.01 (0.00,0.02) | 0 | 0 | 0 | 0 | 0.01 (0.01,0.03) | 0 | 0 | 0 | 0 |

AF, Attribution score; RR, Relative risk; RR(A), $AF_{(CIN1)}/AF_{(Normal)}$; RR(B), $AF_{(CIN2+)}/AF_{(Normal)}$; "-", negative.

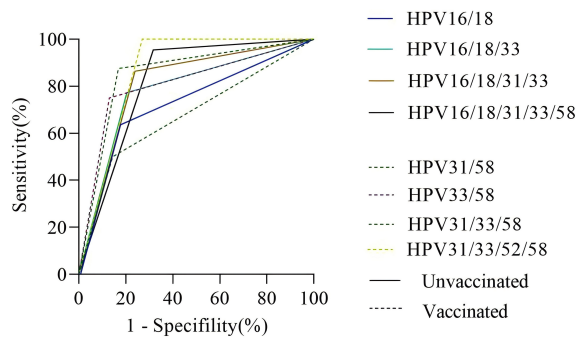


FIGURE 2
The ROC curve of different HR-HPV genotype combinations. Notes: The vertical axis represents the sensitivity of CIN2+ detection in different HPV genotype combinations, and the horizontal axis represents 1-specifility of CIN2+ detection in different HPV genotype combinations. The solid line represents the unvaccinated group, and the dotted line represents the vaccinated group.

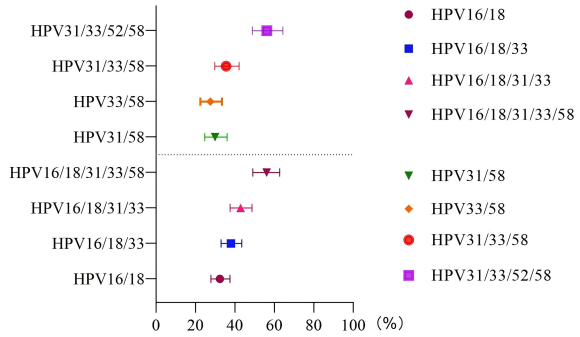


FIGURE 3
Referral rate in the unvaccinated and vaccinated groups. The vertical axis represents different HR-HPV genotype combination patterns, and the horizontal axis represents the probability of referral for colposcopy under different genotype combination patterns.

TABLE 4 The triaging effect of different HPV genotype on CIN2+ in women with ASC-US.

| Group | HPV genotype | Sensitivity | Specificity* | PPV | NPV | Missed diagnosis rate | ROC AUC | Colposcopic referral rate* |
|---|---|---|---|---|---|---|---|---|
| Unvaccined group | HPV16/18 | 63.63 (40.65,82.80) | 81.77* (79.11,84.23) | 7.82 (5.67,10.69) | 98.93 (98.16,99.38) | 36.37 (17.20,59.35) | 0.728 (0.698,0.756) | 32.37* (27.80,37.47) |
| | HPV16/18/33 | 77.27 (54.63,92.17) | 79.58* (76.81,82.15) | 8.37 (6.58,10.60) | 99.31 (98.53,99.68) | 22.73 (7.83,45.37) | 0.784 (0.756,0.810) | 37.97* (33.01,43.47) |
| | HPV16/18/31/33 | 86.36 (65.08,97.09) | 76.07* (73.16,78.80) | 8.01 (6.64,9.64) | 99.56 (98.77,99.84) | 13.64 (2.91,34.92) | 0.812 (0.786,0.836) | 42.86* (37.57,48.67) |
| | HPV16/18/31/33/58 | 95.45 (77.15,99.88) | 68.27* (65.14,71.29) | 6.77 (5.98,7.65) | 99.83 (98.92,99.97) | 4.55 (0.12,22.85) | 0.819 (0.792,0.843) | 56.06* (49.09,62.66) |
| Vaccined group | HPV33 | 37.5 (8.52,75.51) | 96.91# (95.41,98.03) | 11.53 (4.66,25.80) | 99.31 (98.83,99.59) | 62.50 (24.49,91.48) | 0.672 (0.637,0.706) | 6.95# (4.54,10.18) |
| | HPV58 | 37.5 (8.52,75.51) | 89.54# (87.12,91.64) | 3.70 (1.51,8.79) | 99.25 (98.73,99.56) | 62.50 (24.49,91.48) | 0.635 (0.600,0.670) | 21.66# (17.2,26.92) |
| | HPV31 | 25.00 (3.18,65.08) | 95.71# (93.99,97.04) | 5.88 (1.76,17.86) | 99.16 (98.76,99.44) | 75.00 (34.52,96.82) | 0.604 (0.568,0.639) | 9.09# (6.29.12.70) |
| | HPV33/58 | 75.00 (34.91,96.81) | 86.99* (84.37,89.32) | 5.82 (3.82,8.77) | 99.69 (98.98,99.90) | 25.00 (3.19,65.09) | 0.810 (0.780,0.837) | 27.54* (22.48.33.40) |
| | HPV31/58 | 50.00 (15.70,84.29) | 85.52* (82.79,87.97) | 3.57 (1.78,7.03) | 99.37 (98.76,99.68) | 50.00 (84.30,15.71) | 0.687 (0.643,0.711) | 29.95* (24.66,36.03) |
| | HPV31/33/58 | 87.50 (47.34,99.68) | 83.11* (80.22,85.73) | 5.26 (3.92,7.01) | 99.83 (99.00,99.97) | 12.50 (0.32,52.64) | 0.853 (0.826,0.878) | 35.56* (29.77,42.14) |
| | HPV31/33/52/58 | 100.00 (63.05,100.00) | 72.92* (69.58,76.08) | 3.81 (3.40,4.26) | 100.00 | 0 | 0.865 (0.838,0.888) | 56.15* (48.81,64.28) |

HPV, human papillomavirus; PPV, positive predictive value; NPV, negative predictive value; ROC AUC, the area under ROC curve; *, it means that there is $P$ <0.05 between the combinational HPVgenotypes; #, it means that there is $P$ <0.05 between the single HPV genotype.

cases. This contrasted with Li L's study (26), where AF values were relatively higher for HPV16, 58, 52, 18, and 51, likely because our study population consisted of ASC-US individuals, whereas her research was conducted in the general population. Due to the protection provided by vaccination, the proportion of HPV genotypes has changed. In the vaccinated group, the AF values of HPV33, 58, and 31 ranked in the top three among individuals with CIN2+. HPV33, 58, and 31 should also be followed up in a short period. A similar study revealed that different types of HPV play distinct roles in cervical precancerous lesions (27). Previous studies (5, 28, 29) by domestic and foreign scholars analyzed the triage strategy of HPV16/18 and HR-HPV genotypes in ASC-US populations. A previous study found that the sensitivity and specificity of HPV16/18 genotyping in detecting CIN2+ lesions in 329 Chinese women with ASC-US were 82% and 91% (30). Another study in Shanxi province of China demonstrated that the sensitivity and specificity of HPV16/18/33/52/58 were 72.46% and 81.57%, respectively, for detecting CIN2+ lesions in women with ASC-US (31). In the current study, we evaluated the possibility of using a combination of the five most common HPV genotyping (HPV16/18/31/33/58). The sensitivity of HPV16/18 for ASC-US population in our study was similar to Li X's findings (58.3%) (32). Our study also suggested that HPV16/18 (81.77%) saw the highest specificity in detecting CIN2+ in ASC-US compared to HPV16/18/33 (79.58%), HPV16/18/31/33 (76.07%), and HPV16/18/31/33/58 (68.27%), with significant difference. Moreover, the referral rate of HPV16/18 (32.37%) was the lowest, almost half of that of HPV16/18/31/33/58 (33.23%), which might avoid the waste of medical resources.

The incidence of HPV16/18 strains that lead to cervical cancer and its precursor lesions had declined with the onset of the vaccine era (33, 34). Studies conducted in India suggested that the HPV vaccine was more than 90% effective against HPV16/18 (35–37). In countries with high vaccine coverage, such as the United States and Australia, there had been a significant reduction in high-grade cervical lesions after the introduction of the HPV vaccine. In developing nations, the administration of bivalent vaccines had been extensively carried out among age-appropriate females under the auspices of local health policies. This measure contributed to reducing the future burden on both societal and familial levels and fostered improved female health. We assumed that the protection rate of post-bivalent vaccines would reach 100% in the vaccinated group. We evaluated the sensitivity, specificity, positive predictive value, and negative predictive value of other HPV genotype combinations excluding HPV16/18. Among single-genotype infections, HPV33 demonstrated relatively high specificity (96.91%) and the lowest referral rates (6.95%), demonstrating statistical significance against HPV31 and HPV58. It emerged as an excellent marker for assessing ASC-US triage within vaccinated populations. The sensitivity of HPV33/58 reached 75%, and the specificity was close to 90%, with a significant difference ($P$<0.05). In particular, the colposcopy referral rate (27.54%) was the lowest,

and the difference was statistically different. Despite the unavoidable examination of colposcopy, the HPV vaccine will reduce the number of colposcopy referrals by 10% (38). HPV33/58 may be a new combination for the triage of ASC-US populations in the future. Consequently, this gene-specific genotyping test might help avoid unnecessary examinations and treatments.

This study has several limitations. Firstly, this hypothetical scenario disregards real-world variables affecting HPV vaccination's impact, including coverage, compliance, and non-targeted HPV types. But the assumption grounded in comprehensive data of a large, real-world population that has undergone cervical cancer screening, can still offer valuable insights value for the triage of ASC-US women post-vaccination in the absence of comprehensive real-world research data on HPV vaccines. Secondly, only bivalent vaccines were considered, not quadrivalent and nine-valent vaccines. The bivalent vaccine was an economical option, and this research has carried out a cautious evaluation. The efficacy would be further improved if quadrivalent and nine-valent vaccines were employed.

## 5 Conclusion

In conclusion, in the unvaccinated group, HPV16, 18, 33, 58, and 31 genotypes require significant attention. The HPV16/18 genotyping strategy is a feasible for triaging participants with ASC-US in resource-limited areas. In the vaccinated group, HPV33, 58, and 31 genotypes require significant attention. The combination of HPV33/58 would be highly sensitive and specific for triaging the ASC-US population in the vaccinated group.

## Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

## Ethics statement

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

## Author contributions

HY: Investigation, Writing – original draft, Writing – review & editing. YH: Software, Writing – original draft, Writing – review & editing. MN: Investigation, Data curation, Writing – original draft. JZ: Investigation, Data curation, Writing – original draft. XJ: Writing – original draft, Writing – review & editing. SZ: Conceptualization, Writing – review & editing. LW: Methodology, Writing – original draft. XZ: Methodology, Writing – original draft. QP: Methodology, Writing – original draft. XF: Conceptualization, Writing – original draft. YQ: Supervision, Writing – review & editing. ZL: Conceptualization, Methodology, Writing – original draft, Writing – review & editing.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## Publisher's note



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# Prevalence and distribution of human papillomavirus genotypes in women with abnormal cervical cytology in Ethiopia: a systematic review and meta-analysis

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**Background:** Cervical cancer is the 4th most common cancer in women globally. Determining the prevalence of the high-risk human papillomavirus (HR-HPV) and low-risk (LR-HPV) genotypes and the distribution in abnormal cervical cytology will be essential in a future population-based cervical cancer prevention program.

**Method:** Primary studies with women with abnormal cervical cytology were systematically searched for in Medline, CINHAL, Google Scholar, African Journal Online, and the University of Antwerp repository from 19-30 May 2023. A weighted inverse-variance random effects model was used. Variations across the studies were checked using a forest plot, $I^2$ statistics, and Egger's test. Group analysis was performed for evidence of heterogeneity.

**Results:** The pooled prevalence of human papillomavirus (HPV) genotypes with abnormal cervical cytology of a precancerous cervical lesion was 38.74% (95% CI: 27.56-49.93). The leading pooled prevalence estimates by subgroup analysis were 18% (95% CI: 13-26), 14% (95% CI: 111-16), and 66% (51-79) for women with retroviral infection (RVI), DNA genotyping with amplification, and central parts of Ethiopia respectively. There were 25 HPV variants identified by genotyping techniques with the five most prevalent HPV genotypes being HPV-16 and HPV-18 coexisting at 54%; HPV-16 alone at 29%; HPV-51 at 16%; HPV-52 at 13%; and HPV-31 and HPV-33 each contributing approximately 12%.

**Conclusion:** The pooled prevalence of HPV genotypes was higher than in other countries. HPV-51, HPV-52, HPV-31, and HPV-33 are the most prevalent genotypes. Hence, the nonavalent vaccine type would be the one that includes all the most prevalent HPV genotypes, but HPV-51in Ethiopia. Additional data on similar DNA test techniques for comparisons with

precancerous lesions and invasive cancer are needed. Cervical cancer prevention and control programs in Ethiopia should be aligned with the most prevalent genotypes.

**Systematic review registration:** https://www.crd.york.ac.uk/prospero/, identifier CRD42023428955.

KEYWORDS

HPV genotypes, cervical lesion, abnormal cervical cytology, pap smear test, cervical cancer screening

## Background

Cervical cancer is the most prevalent type of cancer affecting the reproductive organs of women and the primary cause of cancer-related deaths in low- and middle-income countries (LMICs), such as Ethiopia. For instance, the ten African countries with the highest rates of cervical cancer were all above the global average, at 13.30 per 100,000 women and 604,127 cases (1–3).

Africa has the highest incidence of cervical cancer worldwide with rates of 31.6 cases per 100,000 people which is above the global incidence of 13.3 cases per 100,000 people (2, 4).

A systematic population-based program with pap tests has been reducing the incidence of invasive cervical cancer in high-income countries by detecting and treating cervical lesions. However, screening is limited in low-income countries as it is being performed in public or private laboratories in urban areas for only approximately 5% of eligible women. In addition, the absence of a well-organized surveillance and review system results in poor screening or lack of follow-up (2, 5–7).

Evidence suggests that less than 5% of all eligible women in developing countries receive cytology-based screening within 5 years. This is because there are few healthcare providers and professionals involved in such analyses or because of the limited availability of medical facilities available to accommodate the demand for screening and treatment. Moreover, in LMICs, cytology services are limited to teaching hospitals or private clinics in larger cities and are not accessible to all eligible women (5, 6).

The Bethesda system is a standardized model for reporting cervicovaginal cytology by which there are low-grade squamous intraepithelial lesions (LSILs), high-grade squamous intraepithelial lesions (HSILs), or atypical squamous cells [of undermined significance (ASCUS) or cannot rule out HSIL (ASC-H)] (8–10). Approximately 15% of human papillomavirus (HPV) infections progress to low LSILs within 3-4 years, and 30-70% of LSILs advance to HSILs in 10 years (11–13). The most common HPV types identified in previous studies were 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 68, and 59, which were considered high risk. Several groups, including HPV types 53, 66, 70, 73, and 82, have been classified as potential or high-risk types. Approximately seven types of high-risk human papillomavirus (HR-HPV) are associated with approximately 87% of cervical cancer cases worldwide. Forty types of papillomaviruses, which tend to spread to the genitals, usually infect the cervix, genitals, urethra, and anus in both sexes (1, 7, 14).

According to the WHO global strategy to accelerate the elimination of cervical cancer as a public health problem by 2030, 90% of girls will be fully vaccinated against HPV by the age of 15 (5). There are currently two types of HPV vaccines licensed in many countries, and these vaccines have been proven to prevent more than 95% of HPV infections caused by HPV types 16 and 18, which cause 70% of cancer cases (15). However, there is no consistent information on which type of vaccine is better at preventing HPV-related cervical cancer in Ethiopia. This review aimed to determine the prevalence, most specific type, and distribution of HPV genotypes among women with abnormal cervical cytology.

## Materials and methods

### Reporting

The results of this review were reported in accordance with the MOOSE checklist for meta-analyses of observational studies (16). Supplementary File 1 shows the MOOSE checklist.

The review has been registered with PROSPERO ID: CRD42023428955.

### Search strategy and source of information

Data searching was conducted from 19-30 May 2023. The articles retrieved were published from 2006 to 2023, were written in English, and had cross-sectional and cohort study designs. The MEDLINE, Web of Science, Scopus, Google Scholar, Africa Online Journals, University of

**Abbreviations:** DNA, Deoxyribonucleic acid; HPV, human papillomavirus; RNA, Ribonucleic acid; RVI, retroviral infection; VIA, visual inspection via acetic acid.

Antwerp repository, and gray literature databases were searched. The key search terms and phrases used were "human papillomavirus", "human papillomavirus DNA tests", "human papillomavirus investigating", "cervical cancer", "precancerous cervical lesion", "cervical tumor", "cervical malignancy", "reproductive women", "adolescent girls", "mothers", and "Ethiopia". The search strategy was developed using various Boolean operators. Hence, to fit the advanced PubMed database, the following search strategies were applied on 29 March 2023: [(human papillomavirus screening [MeSH Terms]) AND (human papillomavirus testing [MeSH Terms] AND (human papilloma investigating [MeSH Terms] AND (cervical neoplasms [MeSH Terms]) OR (cervical cancer [MeSH Terms]) OR (precancerous cervical lesion [MeSH Terms]) OR (cervical tumor [MeSH Terms]) AND (reproductive women [MeSH Terms]) OR (adolescent girls [MeSH Terms]) AND (Ethiopia).

## Study selection

The studies were imported into Mendeley Desktop using data management software to eliminate duplicate data. Two independent reviewers reviewed the title and abstract. Differences between reviewers were checked by article-based analysis. Abstract and full-text analyses were performed by two independent authors in three groups. All reviewers screened all studies with discussions on inconsistency amendments among the reviewers.

## Eligibility criteria

### Inclusion criteria

The primary studies included were those that reported both high-risk HPV (HR-HPV) and low-risk HPV (LR-HPV) genotype prevalence and distribution in women with LSILs or HSILs in Ethiopia.

### Exclusion criteria

Articles without full text available and qualitative studies were excluded.

## Outcome measurement

The overall HPV prevalence was defined as the number of women with positive HPV tests among all women with LSIL or HSIL cytology reports, expressed as a percentage.

Similarly, the prevalence of HPV type specificity was defined as the number of women with positive HPV type-specific tests among all women with LSIL or HSIL cytology reports, expressed as a percentage.

## Quality assessment

The JBI quality appraisal criteria were used (17). The tool has nine main features. The first feature is suitability for the sample frame. The second is using the convenient sampling technique. Third, the sample size should be large enough. Fourth is a description of the research object and environment. Fifth, the data analysis program was sufficient. The sixth is the validity of the situation analysis method. The seventh feature is being reliable for all participants. Eight is the necessity of statistical analysis. The final feature is being reasonable and cost-effective.

Studies were considered low risk when five or more were positive out of the nine criteria. Two independent authors evaluated the quality of the studies. Disputes are resolved with the intervention of a third-party moderator. Supplementary File 2 shows the JBI quality assessment of the included studies.

## Data extraction

The adapted PICO format was used to explicitly review the pieces of literature and clear specifications for the inclusion and exclusion criteria. The adapted PICO comprises Population (P), Exposure (E), Outcome (O), and Context (Setting) as described below.

a. Population: women with abnormal cervical cytology
b. Exposure: human papillomavirus (HPV)
c. Outcome: prevalence and distribution
d. Context (Setting): Ethiopia

Both authors (SD and TM) extracted the data using a standard method. The author, year, study area, study design, setting, sample size, and HPV type on abnormal cervical cytology were extracted. This step was repeated every time a change was found in the extracted data. If inconsistencies between the extracted data persisted, a third reviewer (SZ) was included.

## Statistical analysis

Statistical pooling for the prevalence proportion of estimates was performed according to the random effects model using Statistical software for Data Science (STATA V17). The random effects model of analysis was used since the studies identified were observational and had both clinical and methodological variability. The heterogeneity of the studies was evaluated based on Cochrane's Q and I2 tests as well as the Q/df (degree of freedom) ratio. Thus, Cochrane's Q test ($p = 0.1$), $Q/df = 1$, and $I2 = 50\%$ were considered cutoff points for identifying heterogeneity and selecting an effective model for analysis.

Forest plots were generated to present the pooled prevalence of HPV genotypes in women with precancerous cervical lesions. In line with this, subgroup analyses were carried out to explain HPV DNA variant distributions in subgroups with the potential to account for the differences in the effect sizes of the HPV genotypes. Egger's regression tests were performed to objectively test for the presence of a small study effect.

# Results

## Selection of studies for review

A total of 1,779 research citations that met the requirements of the National Institute of Health (NIH) quality assessment tool for

observational cohort and cross-sectional study guidelines were retrieved. Following the removal of duplicates and the screening of titles and abstracts, 35 studies were retrieved for full-text review. Of these, a further 17 were excluded as they were not full-length articles or did not report outcomes of interest. The remaining 18 full-text articles were assessed for eligibility and two were excluded as they did not report the outcome of interest. This left 16 studies included in the review and meta-analysis. Data were extracted by title before beginning the systematic screening using the PRISMA flow diagram for the final review of the included studies. Figure 1 shows the PRISMA flow diagram of the study selection process.

## Characteristics of the included studies

For the systematic review, 16 studies were included from which three studies were from the Oromia region (18–20), three from Addis Ababa in central Ethiopia (21–23), two studies from northwest Ethiopia (15, 24), and one in each of Amhara region, Tigray, Southern nations nationalities, south-central Ethiopia, southwest Ethiopia, eastern Ethiopia, Armauer Hansen Research Institute, and gynecology referral hospitals in Ethiopia, respectively (4, 14, 15, 24–30). The age range of the women studied was 15-85 years (14, 19, 21, 22, 26, 27, 29, 30). The mean age of the women was 32 years in one study (18), and the mean age was 15- ≥ 44 years in another study (16).

A total of 5,276 study participants were included. Of these, 2,621 were infected with one or more HPV genotypes. Table 1 shows the characteristics of the included studies.

Regarding the type of HPV genotyping tests and techniques, two studies used DNA testing with direct genomic detection with hybrid capture (4, 24), eight used DNA testing with amplification for HR genotyping (14, 21, 22, 25–31), and RNA amplification of an E6/E7mRNA HPV assay was used in three studies (18, 19, 23).

## Meta-analysis

The pooled prevalence of HPV in abnormal cervical cytology.

The absence of publication bias was assessed with Egger's regression test analysis (p = 0.125), which showed no publication bias. Table 2 shows the Egger's regression results.

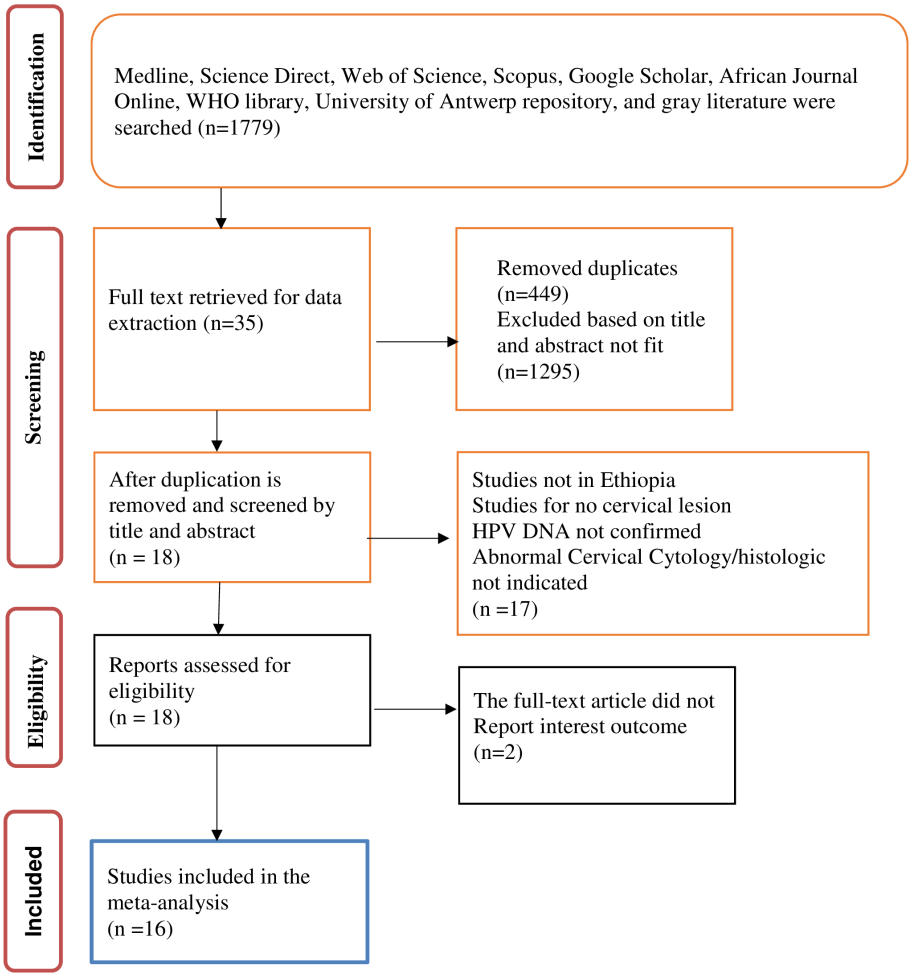


FIGURE 1
The study selection process.

TABLE 1 Characteristics of the included studies.

| First author and year | Participants age range or mean | Health facility | Study area/region | Study design | Sample size | Population outcome | Prevalence | Quality status |
|---|---|---|---|---|---|---|---|---|
| Ali et al. (2019) (21) | 18-64 | Addis Ababa | Central Ethiopia | Cross-sectional | 50 | 38 | 76.00 | Low risk |
| Bartholomeusz and Locarnini (2006) (29) | 21-85 | Central | Armauer Hansen Research Institute, | Cross-sectional | 149 | 136 | 91.28 | Low risk |
| Bekele et al. (2010) (27) | 32-65 | Jimma | Southwest Ethiopia | Cross-sectional | 83 | 68 | 81.93 | Low risk |
| Bogale et al. (2022) (22) | 25-49 | Addis Ababa | Central Ethiopia | Cross-sectional | 130 | 24 | 18.46 | Low risk |
| Derbies et al. (2022) (31) | — | Bahir Dar | Amhara | Cohort | 3633 | 1950 | 53.67 | Low risk |
| Derbies et al. (2023) (14) | 30-67 | Gynecology referral clinics | Northwest Ethiopia | Cross-sectional | 154 | 77 | 50.00 | Low risk |
| Gebremariam (2016) (25) | — | Mekele | Tigray | Cohort | 86 | 21 | 24.42 | Low risk |
| Haile et al. (2019) (18) | 32 | Adama | Oromia | Cross-sectional | 27 | 6 | 22.22 | Low risk |
| Kiros et al. (2021) (24) | …… | Debre Tabor Comprehensive Hospital | Northwest | Cross-sectional | 109 | 14 | 12.84 | Low risk |
| Lemma et al. (2022) (19) | 30-35 | Adama | Oromia | Cross-sectional | 66 | 6 | 9.09 | Low risk |
| Leyh-Bannurah et al. (2014) (4) | 15-64 | gurage zone | southern nations | Cross-sectional | 86 | 21 | 24.42 | Low risk |
| Megersa et al. (2023) (20) | 15-≥44 | hashemite | Oromia | Cross-sectional | 143 | 21 | 14.69 | Low risk |
| Mekuria et al. (2020) (23) | 18-70 | Addis Ababa | Central Ethiopia | Cross-sectional | 164 | 28 | 17.07 | Low risk |
| Seyoum et al. (2023) (28) | 30-60 | Harara, Dire Dawa and Jigjiga | Eastern Ethiopia | Cross-sectional | 152 | 35 | 23.03 | Low risk |
| Teka et al. (2021) (26) | 30-49 | Butajira rural | South-central Ethiopia | Cross-sectional | 205 | 117 | 57.07 | Low risk |
| Wolday et al. (2018) (30) | 40.1-43.2 | Gynecology referral clinics | Ethiopia | Cross-sectional | 134 | 59 | 44.03 | Low risk |
| | Total | | | | 5276 | 2621 | | |

The overall pooled prevalence of HPV genotypes among women screened and identified with precancerous cervical lesions, either LSIL or HSIL, was 38.75%, with a 95% CI of 25.69-51.8 (4, 14, 18–31). Figure 2 shows a forest plot of the pooled prevalence of HPV variants in Ethiopia.

## Subgroup analysis

Subgroup analysis was performed based on the study's geographical region, HPV genotyping testing technique, and characteristics of the women. Based on the pooled effect of two or more studies, the three most common genotyping testing techniques identified were acetowhite changes by visual inspection with acetic acid (VIA) and HPV DNA testing for specimens in women with retrovirus infection (RVI) at 18%, all women screened for HPV at 12%, and women with RVI at 10% (4, 18, 19, 21, 23, 25, 26, 28, 29, 31). The least prevalent HPV type, at 6%, was found in two studies (24, 30). Among the genotyping test techniques used, the DNA test with amplification was the most commonly used test modality (14, 21, 22, 25–31). Central Ethiopia was the highest contributor to the HPV genotyping evidence, accounting for 66%, and the lowest were Oromia and southern Ethiopia, which accounted for 5% of the studies (4, 18–20). Table 3 shows a subgroup analysis of the characteristics of the women, HPV testing technique, and region of Ethiopia.

Among the 16 studies, there were 25 HPV variants identified by genotyping techniques in this review. The most prevalent HPV type

TABLE 2 Egger's regression results.

| Std.-Eff. | Coef. | Std. Err | t | p>t | 95% confidence interval | |
|---|---|---|---|---|---|---|
| Slope | 5.022488 | 9.950689 | 0.50 | 0.622 | -16.31962 | 26.36459 |
| Bias | 30.05708 | 18.41711 | 1.63 | 0.125 | -9.443692 | 69.55784 |

was HPV-16 and HPV-18 coexisting (14) at 54%. The second most prevalent type was HPV-16 alone, accounting for 29% of the total number of studies. The third and fourth most common HPV types were HPV-51 and HPV-52, accounting for 16% and 13% (4, 14, 18, 19, 21–23, 25, 28–31) respectively. The fifth most prevalent HPV type were HPV-31 and HPV-33, each contributing approximately 12% of all HPV variant burdens in Ethiopia in previous studies (4, 14, 18, 19, 21, 22, 25–31). Table 4 shows the prevalence of HPV DNA test results by subgroup analysis of HPV DNA genotypes in Ethiopia.

## Sensitivity analysis

Two studies (27), and (29), had an impact on the overall estimation of the meta-analysis results. Supplementary File 3 shows the sensitivity analysis.

# Discussion

According to our review and meta-analysis, the prevalence any HPV genotype being detected among women who had a precancerous cervical lesion in health facilities was 38.75% (25.69-

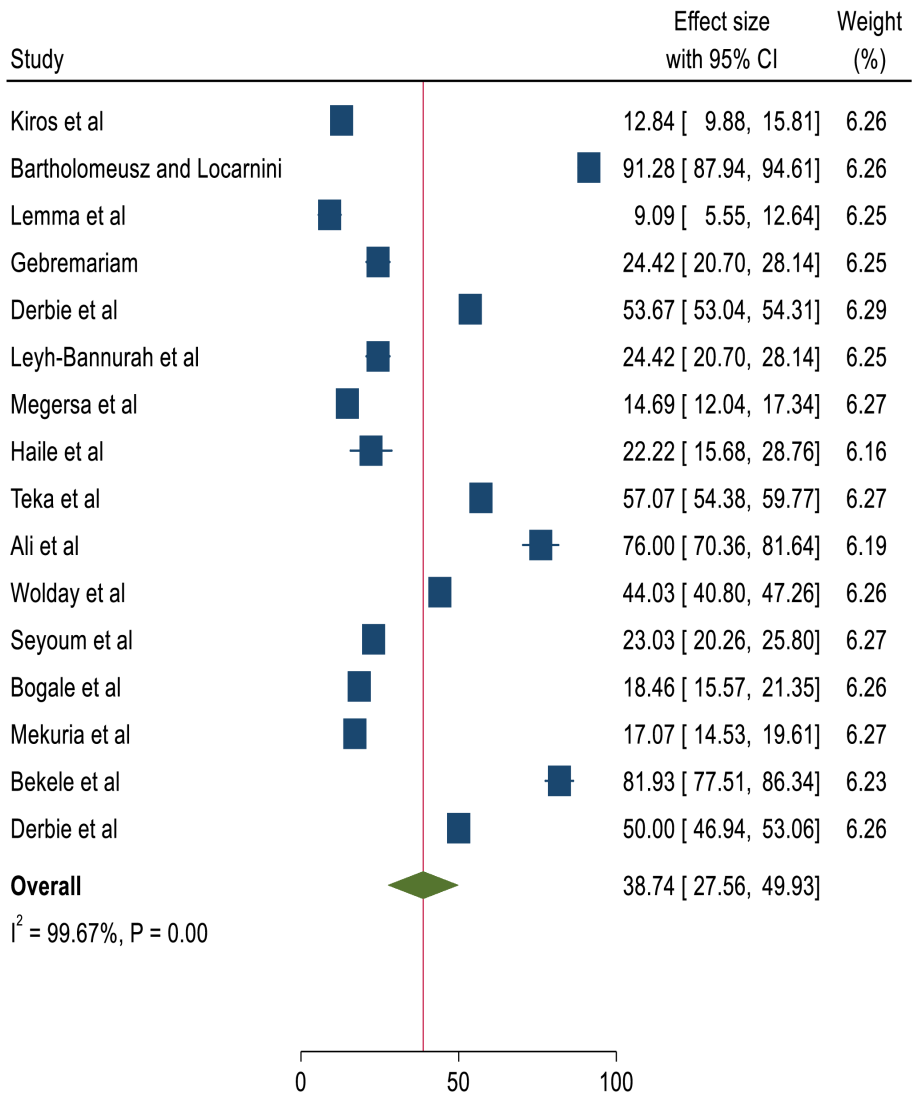


FIGURE 2
Forest plot of the pooled prevalence of HPV variant with abnormal cytology in Ethopia.

TABLE 3 The subgroup analysis of the characteristics of the women, HPV testing technique, and region of Ethiopia.

| Variable | Characteristics | Pooled prevalence (95% CI) | $I^2$(P value) |
|---|---|---|---|
| **Characteristics of the women** | With abnormal cervical cytology | 6%(3-13) | – |
| | Women screened for HPV | 12%(10-15) | 98.86(0.00) |
| | With abnormal cervical cytology and RVI | 10%(7-14) | – |
| | With abnormal cervical cytology, but no RVI | 6%(2-12) | 93.74(0.00) |
| | With abnormal cervical cytology and acetowhite changes | 18%(13-26) | 82.44(0.00) |
| | With abnormal cytology and other STI complaints | 7%(3-12) | 95.55(0.00) |
| **Genotyping testing techniques** | Direct genome detection | 5%(3-7) | 68.90(0.00) |
| | DNA with amplification | 14%(11-16) | 98.97(0.00) |
| | RNA amplification of E6/E7 | 6%(4-8) | 35.29(0.02) |
| **By region of Ethiopia** | Northwest | 6%(2-10) | 93.99(0.00) |
| | Armauer Hansen Res Center | 12%(4-24) | 98.08(0.00) |
| | Oromia | 5%(3-7) | 43.57(0.02) |
| | Tigray | 9%(5-14) | 71.14(0.00) |
| | Amhara | 7%(3-13) | 99.84(0.00) |
| | Southern Ethiopia | 5%(3-7) | 71.87(0.00) |
| | Central Ethiopia | 66%(51-79) | 93.66(0.00) |
| | South-central Ethiopia | 22%(11-36) | 96.64(0.00) |
| | Gynecology referral clinics | 7%(4-10) | 84.93(0.00) |
| | Eastern Ethiopia | 7%(4-9) | 79.93(0.00) |
| | Central Ethiopia | 16%(12-20) | 81.20(0.00) |
| | Southwest Ethiopia | 8%(1-20) | 96.41(0.00) |

TABLE 4 The prevalence of HPV DNA test results by subgroup analysis of HPV DNA genotypes in Ethiopia.

| Variable | HPV type | Pooled prevalence (95% CI) | $I^2$(P value) |
|---|---|---|---|
| HPV DNA genotype | 16 | 29% (19-41) | 97.69(0.00) |
| | 18 | 5%(3-7) | 78.72(0.00) |
| | 31 | 12%(7-18) | 94.75(0.00) |
| | 33 | 12%(3-26) | 96.12(0.00) |
| | 35 | 11%(6-18) | 95.20(0.00) |
| | 39 | 11%(4-22) | 94.69(0.00) |
| | 45 | 10%(5-16) | 94.16(0.00) |
| | 52 | 13%(7-19) | 94.98(0.00) |
| | 58 | 10%(4-17) | 95.90(0.00) |
| | 66 | 10%(1-26) | 96.67(0.00) |
| | 68 | 11%(4-19) | 95.86(0.00) |
| | 39 and 68 | 3%(1-7) | – |
| | 56 and 74 | 1%(0-4) | – |
| | 6 | 5%(1-11) | 86.23(0.00) |
| | 51 | 16%(6-31) | 94.14(0.00) |
| | 56 | 10%(5-17) | 94.44(0.00) |
| | 59 | 7%(7-14) | 94.61(0.00) |
| | 53 | 2%(0-5) | – |
| | 35 and 39 | 6%(3-13) | – |
| | 45 and 68 | 5%(2-11) | – |
| | 16 and 18 | 54%(52-55) | – |
| | 11 | 7%(0-24) | – |
| | 42 | 2%(1-2) | – |
| | 70 | 2%(0-6) | – |
| | 68 and 73 | 2%(1-8) | – |

51.81). A recent meta-analysis showed that the proportion of patients infected with HR-HPV was 42.2% in Eastern Africa (32). Similarly, the prevalence of HPV in women with precancerous cervical lesions and cervical cancer was between 13.7% and 93%. A globally based review showed that the prevalence of HPV genotype was between 11% and 12% (with higher rates, 24%, in sub-Saharan Africa) in women without cervical abnormalities (15, 31, 33).

The detection of HPV increases in women with abnormal cervical cytology in proportion to the severity of the lesions, which supports our findings (33). Based on a global review, HPV was detected 90% of the time in abnormal cervical cytology, which is relatively higher than that reported in this review and meta-analysis (33). This might be because developed nations use more sophisticated DNA testing techniques than Ethiopia. In addition, a review showed that the prevalence of HPV was 84.8% among Asian patients with atypical squamous cell lesions (34).

The predominant genotypes identified in this review were HPV-16 and HPV-18, accounting for 9.52% and 8.33%, respectively; HPV-31 and HPV-48, each accounting for 7.74%; HPV-52 and HPV-56, each accounting for 7.14%; and HPV-35, HPV-58, and HPV-59 with an average of 6.55% of all HPV variant burdens in Ethiopia. These findings are essential for predicting how HPV vaccination and HPV-based screening will impact cervical cancer prevention in Ethiopia. This infers that further HPV vaccine studies in Ethiopia should mainly target the most predominant

genotypes as the current vaccine type only targets HPV-6, HPV-11, HPV-16, and HPV-18.

Based on similar review reports in different parts of the globe, the genotype distributions of HPVs in different countries from different kinds of cervical lesions were compared with this review. HPV-16 is the most common genotype consistently reported globally as an important cause of cervical abnormalities (35–37). The pooled prevalence of HPV-16 sub genotypes in this review and meta-analysis was found to be 29% which was relatively comparable with the overall incidence in Africa (35). The pooled prevalence of subgroup HPV genotypes 31 and 33 were 12% each, which was comparable to (35), which found 8.2% and 10.3%, respectively. However, HPV types 51 and 52 were not reported as prevalent genotypes, but in this study, they were the most prevalent cases, accounting for 16% (6–31) and 13% (7–19), respectively. HPV genotype 18 was among the lowest at 5% and HPV genotype 35 was among the dominant at 11% in this review.

This variation in HPV genotype distribution across the studies is likely attributable to differences in the population, severity of cervical lesions, age at screening initiation, frequency, coverage, and follow-up rates of women with cervical abnormalities (38). In addition, the difference might also be associated with ethnic differences, geographical location, and the sexual behavior of their male partners (39).

Globally, HPV type-specific prevalence varies. A study in Asia (40) indicated that HPV-16 was most prevalent at 23.9%, which was comparable with the findings of this review. In contrast, the prevalence of HPV type 52 was lower than that in this review. However, studies in North America (37) found the prevalence of HPV types 16, 31, and 51 to be 26%, 11.5%, and 10.6%, respectively. These findings are comparable to those of this review and meta-analysis. Similarly, in a study in Israel (41), the most prevalent HPV type was HPV-16 (46.5%), which is higher than that of this review and meta-analysis. However, the prevalence of HPV type 31 was comparable at 7%. These differences among the studies and this review might be due to variations in population, DNA testing technique, and sampling technique.

According to the results of this review and meta-analysis, the pooled prevalence of HPV 16/18 in the combined subgroup was 54%. Similarly, other reviews showed that 45.1% of HPV16/18 combined were from high-grade cervical lesions, while 67.7% were from abnormal cervical cytology among African women and 605 Israeli women (15, 31, 35, 41). Among HPV-positive patients, the co-existing prevalence of HPV 16/18 was reported differently in different countries, as it was 87.5% in Central and Eastern Europe (42) and 80% in India among those with high-grade cervical lesions (43).

HPV-16 was the most prevalent type in this review at 29% (19%-41%), and HPV-18 was not among the five most prevalent types at 5% (3%-7%). These findings were comparable to those of studies in Italy on HPV-18 (7%). However, HPV-16 (64%) was much more prevalent than this review finding (44). A review by Guan et al. revealed that HPV-16 positivity increased steeply from normal to high-grade cervical lesions (44). Accordingly, vaccine mixes and HPV-based screening tests should always include this genotype, although some low-grade cervical lesions associated with certain other HPVs may preferentially progress to cervical cancer (3, 15). Our review envisages a future impact of the broadly identified subgroup pooling of the genotypes (HPV-16 and HPV-18 coexisting, HPV-16, HPV-51, HPV-52, HPV-31, and HPV-33) on vaccination and HPV-based screening in Ethiopia.

The Ethiopian Ministry of Health started vaccinating schoolchildren aged 14 years using Gardasil-4™ (HPV-6, HPV-11, HPV-16, HPV-18) in 2018. However, in this review, in addition to the genotypes covered by the current vaccine, there were other genotypes found to be prevalent in Ethiopia, such as HPV-51, HPV-52, HPV-31, and HPV-32. Hence, HPV-based screening based on the detection of HPV16/18 oncoproteins and, most recently, the use of the HPV DNA test has been employed. This finding suggests that vaccinating girls using Gardasil-4TM and screening women for cervical lesions using HPV16/18 oncoproteins significantly reduces the number of girls who might be protected.

The vaccine for girls would be more effective if the most prevalent genotype distribution was included. This is because women might be missed by screening programs for the most dominant HPV genotypes circulating in the country. For this reason, most developed countries are currently using other vaccine types of the monovalent Gardasil®9 (6, 11, 16, 18, 31, 33, 45, 52, and 58) vaccine that targets close to 90% of all HR-HPVs (45), which is essentially an ideal type of vaccine for Ethiopians based on our review findings. However, this vaccine type might not cover all the top five highly distributed HPV genotypes, except for HPV-52. Even though there is a financial limitation, the nonavalent vaccine type would be the one that includes all the most prevalent HPV genotypes, including HPV-51, for the Ethiopian setting.

## Strengths and limitations

This systematic review and meta-analysis was the first to analyze results from women with abnormal cervical cytology, and important input will be obtained to revise the current vaccination and HPV-based screening program in Ethiopia. The review included studies from different health facilities and geographical areas, with a wide range of study participants and different DNA tests and techniques, which enabled us to obtain a better picture of the HPV genotype burden in Ethiopia. This review and meta-analysis result should be interpreted in light of several limitations. Because of the absence of articles on women's abnormal cervical cytology test results in some parts of the country, our findings could compromise the overall picture of the HPV genotype distribution in Ethiopia.

# Conclusion

In this review and meta-analysis, HPV genotypes were predominantly identified from different kinds of cervical samples via abnormal cervical cytology. There are currently two types of HPV vaccines licensed in many countries, and these vaccines have been proven to prevent more than 95% of HPV infections caused by HPV types 16 and 18, which cause 70% of cancer cases, but the

HPV genome distribution is not uniform across the country. The pooled prevalence of HPV genotypes in Ethiopia was greater than that in the other countries. HPV-16 and HPV-18 coexist, and HPV-16, HPV-51, HPV-52, HPV-31, and HPV-33 are the most prevalent HPV genotypes which require special attention when designing vaccination and HPV-based cervical cancer screening programs. Additional data on similar DNA test techniques among women with cervical cancer are needed. It is important to place emphasis on the nationwide HPV distribution in the prevention and control strategies.

## Data availability statement

The data will be available upon reasonable request to corresponding author. Requests to access these datasets should be directed to SK, solomondemis@gmail.com.

## Author contributions

SK: Investigation, Supervision, Writing – original draft, Writing – review & editing. SZ: Methodology, Writing – original draft, Writing – review & editing. AK: Formal analysis, Writing – original draft, Writing – review & editing. TM: Conceptualization, Writing – original draft, Writing – review & editing. DK: Software, Writing – original draft, Writing – review & editing. WA: Formal analysis, Methodology, Writing – original draft, Writing – review & editing.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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## Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2024.1384994/full#supplementary-material

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# Determinants of cervical cancer screening uptake among reproductive-age women in southwest Ethiopia: a case-control study

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**Background:** Cervical cancer is a major global health issue, with 604,000 diagnoses and 342,000 deaths in 2020. Despite the importance of early detection, only 5% of eligible women in Ethiopia are screened. Therefore, this study aimed to assess the determinants of cervical cancer screening uptake among reproductive-age women at selected public hospitals in southwest Ethiopia.

**Methods:** A case-control study involving 392 women (98 cases and 294 controls) aged 15-49 was conducted across three hospitals. Cases were women aged 15 to 49 who had cervical cancer screening, while controls were reproductive-age women seeking antenatal care or family planning but not screened. Data were collected via face-to-face interviews with pretested questionnaires and analyzed using SPSS 25. Bivariate analysis identified candidate variables with P-values < 0.25, and a multivariable logistic regression model determined factors with P-values < 0.05 as significant for cervical cancer screening uptake.

**Results:** Determinants of cervical cancer screening uptake included high knowledge of screening (AOR=6.23; 95%CI: 1.96, 19.79), a positive attitude toward screening (AOR=6.12; 95%CI: 2.40, 15.58), women aged 30-39 (AOR=3.94; 95%CI: 1.79, 8.63) and 40-49 (AOR=3.54; 95%CI: 1.52, 8.22), and those who reached health facilities within 60 minutes (AOR=2.32; 95%CI: 1.21, 4.45).

**Conclusion:** The study pinpointed age, knowledge, attitude toward cervical cancer screening, and accessibility to health facilities within a 60-minute radius as pivotal factors impacting cervical cancer screening uptake among reproductive-age women. These findings highlight the importance of targeted education, promoting positive attitudes, and enhancing healthcare accessibility to improve screening uptake and reduce the burden of cervical cancer.

KEYWORDS

**cervical cancer, screening uptake, reproductive-age women, knowledge, attitude, Ethiopia**

# Introduction

Cervical cancer, a major global health issue, involves uncontrolled cell growth in the uterine cervix (1). It's the leading cause of maternal illness and death worldwide, with 604,000 diagnoses and 342,000 deaths in 2020 (2, 3). According to Global Cancer Statistics 2020, it's the fourth most common cause of cancer-related deaths among women, with a death occurring every two minutes, mostly in developing countries (4). In 2020, sub-Saharan Africa saw about 110,300 new cervical cancer cases, with cervical cancer being the second most common cancer among women in the region (5). In Ethiopia, it accounts for 10% of new cases in sub-Saharan Africa, making it the most prevalent cancer there and the second leading cause of death among reproductive-age women. Ethiopia reported approximately 7,445 new cases and 12,492 prevalent cases in 2020 (4).

Most cervical cancers are caused by persistent infection with high-risk HPV strains. While many HPV infections resolve on their own, persistent infections can lead to cervical pre-cancer, which, if untreated, may develop into cervical cancer over 10 to 20 years (6). Cervical cancer is preventable and curable if detected early, requiring more intensive prevention, detection, and treatment efforts than other gynecological cancers. Effective interventions in developed countries have reduced mortality rates (7). In August 2020, the WHO launched a strategy to eliminate cervical cancer, aiming to vaccinate 90% of eligible women against HPV, screen 70% at least twice, and treat 90% of those with positive results (6).

A study found that cervical cancer screening is the most effective prevention strategy, reducing deaths by 70% (8). Screening aims to detect and remove abnormal cells before cancer develops. Globally, methods include HPV testing, cytology (Pap test), and VIA (9). In resource-limited countries like Ethiopia, VIA is preferred and recommended for women, especially between ages 30-49. Evidence suggests that including younger women in screening and treatment strategies may also be beneficial (2, 6, 10). Studies show that cervical cancer affects patients in many ways, including societal discrimination, body image issues, sexual function impairment, income loss, financial strain, and employment challenges (11, 12). Despite these impacts, cervical cancer screening rates remain low, particularly in sub-Saharan Africa (13).

A 2021 review found cervical cancer screening uptake in sub-Saharan Africa was only 12.87% (3). In Ethiopia, the 2020 HSTP-I report indicated a screening rate of just 5%, with other studies showing a range from 2.5% to 38.7% (14–18), and another meta-analysis found 14.79% (19). In early 2022, screening rates at Mizan Tepi University, Gebretsadik Shewa General, and Bachuma Primary Hospitals were 0.5%, 0.3%, and 2.3%, respectively, all below the national average. Despite the low uptake, there's a gap in understanding the factors affecting cervical cancer screening in Ethiopia. Therefore, this study aimed to assess the determinants of cervical cancer screening uptake among reproductive-age women at selected public hospitals in southwest Ethiopia.

# Methods

## Study design, setting, and period

A hospital-based unmatched case-control study was conducted at Mizan-Tepi University Teaching Hospital, Gebretsadik Shewa General Hospital, and Bachuma Primary Hospital in the southwest region of Ethiopia. This region, located 449 km from the capital city, consists of six zones. Among the 12 hospitals in the region, these three hospitals collectively serve over one million people.

Mizan Tepi University Teaching Hospital, located in Ethiopia's southwest Bench Sheko Zone, serves communities in Bench Sheko, West Omo, Sheka, and Gambela regions. Established in 1986 as Mizan Teferi Hospital and integrated into Mizan Tepi University in 2016, it is situated 580 kilometers southwest of Addis Ababa. Gebretsadik Shewa General Hospital is situated in Bonga town, Kaffa Zone, and is 449 kilometers from Addis Ababa. Bachuma Primary Hospital, located in the West Omo Zone, was upgraded from a health center in 2017 and is approximately 660 kilometers from Addis Ababa and 180 kilometers from Bonga town. These hospitals provide cervical cancer screening services for reproductive-age women. The study was conducted from June 10 to August 25, 2022.

## Populations

The source population included all reproductive-age women seeking antenatal care, family planning services, and cervical cancer screening in the obstetrics and gynecology outpatient departments during the study period. Cases were women aged 15 to 49 who underwent cervical cancer screening, while controls were reproductive-age women visiting the hospitals for antenatal care or family planning services but not screened for cervical cancer. Exclusion criteria included women with known mental illness, those previously screened, those currently diagnosed and on follow-up, and women unable to provide written informed consent.

## Sample size determination

The study's sample size was determined using Epi-info version 7.1, assuming a control-to-case ratio of 3, 80% power, and a 95% confidence level. The proportion of advanced age among controls (38.8%), with an odds ratio of 2.15, was based on a similar study in Ethiopia (20). To address non-response bias, an extra 10% was included, yielding a final sample size of around 420 participants (105 cases and 315 controls).

## Sampling procedure

Mizan Tepi University Teaching Hospital, Gebretsadik Shewa General Hospital, and Bachuma Primary Hospital were purposively selected for their routine cervical cancer screening services. Sample allocation to these hospitals was based on the proportion of women screened monthly, as reported in the first quarter of 2022 (Figure 1). Cases were sampled consecutively until the required number was reached, with three controls selected for each case on the same day from the obstetrics and gynecology outpatient department using consecutive sampling.

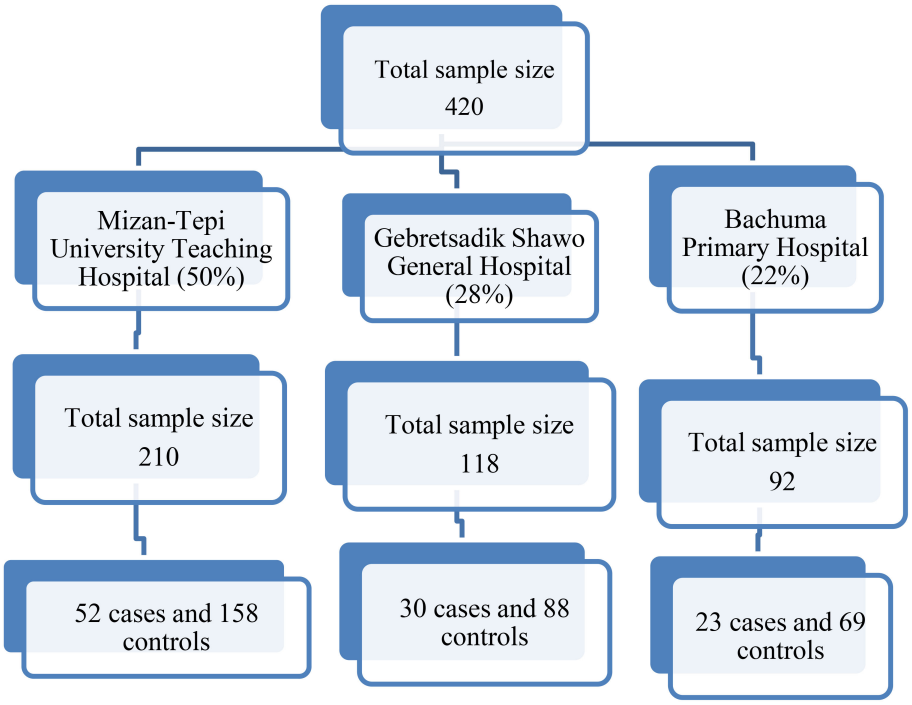


FIGURE 1
Sample size allocation for the three hospitals.

## Study variables

The outcome variable was cervical cancer screening uptake, while the independent variables encompassed socio-demographic factors (age, education, marital status, occupation, income, religion, and residence), access to healthcare (travel time, transport means, cost of travel and perceived cost), knowledge of cervical cancer, knowledge and attitude toward screening, and medical and behavioral determinants (number of sexual partners, history of STDs, smoking, and HIV status).

## Operational definitions

Knowledge of cervical cancer: Knowledge levels were categorized based on Bloom's cut-off points as follows: High level: Knowledge scores of 7 and 8 (80 – 100%). Moderate level: Knowledge scores of 5 and 6 (60 – 79.9%). Low level: Knowledge scores of 0 – 4 (<60%) (21).

Knowledgeable about cervical cancer screening: Knowledge levels were categorized based on Bloom's cut-off points as follows: High level: Knowledge scores of 4 and 5 (80 – 100%). Moderate level: Knowledge score of 3 (60 – 79.9%). Low level: Knowledge scores of <3 (<60%) (21).

Attitude toward screening: The responses were categorized into three levels according to Bloom's cut-off points: Positive attitude: Attitude scores ranging from 28 to 35 (80 – 100%). Neutral attitude: Attitude scores ranging from 21 to 27 (60 – 79.9%). Negative attitude: Attitude scores below 7 to 20 (<60%) (21).

Accessibility to the health facility: It was categorized as follows: Accessible: Time taken less than 60 minutes (distance <5 km). Not accessible: Time taken greater than 60 minutes (distance ≥5 km) (20).

## Data collection tools, and quality management

An interviewer-administered questionnaire, adapted from previous studies (20, 22), was utilized in the three selected hospitals. The questionnaire, originally prepared in English, was translated into Amharic by an experienced translator and back-translated into English by an independent translator to ensure consistency. In this study, attitude was evaluated using questions based on a Likert scale, with responses ranging from strongly disagree to strongly agree. The scoring system assigned: 5 for strongly agree, 4 for agree, 3 for neither agree nor disagree, 2 for disagree, and 1 for strongly disagree. Seven questions were utilized to assess attitude, and the responses were categorized into three levels based on Bloom's cut-off points: 1 for negative, 2 for neutral, and 3 for positive. The minimum score was 7, and the maximum score was 35. Knowledge of cervical cancer was assessed through eight knowledge assessment questions, with each question having multiple responses. The responses were computed and recorded as either correct (1) or incorrect (0). The scores ranged from 0 to 8. Knowledge about cervical cancer screening was assessed using five knowledge

assessment questions, each with multiple responses. The responses were computed and recorded as either correct (1) or incorrect (0), resulting in scores ranging from 0 to 5. Accessibility was measured by the total time taken to reach the health institution to access cervical cancer screening services in minutes when study subjects arrived on foot, or the distance in kilometers. Before actual data collection, the tools underwent pretesting with 21 study participants (5 cases &16 controls), which constituted 5% of the total sample size, to assess response accuracy, language clarity, and tool appropriateness. Six midwives, two from each hospital, underwent one-day training on data collection tools. Following training, these data collectors interviewed women visiting the hospitals for cervical cancer services after their appointments, while controls were interviewed after completing their visits. Each interviewed client received a sign on their card to prevent interview redundancy.

## Data processing and analysis

The data were cleaned, coded, and entered into EpiData version 4.6 before being exported to SPSS version 25 for analysis. Descriptive statistics, including frequencies and percentages, were computed and the results were presented in text, graphs, and tables. The model's independent variables had an acceptable variance inflation factor (VIF < 2), indicating low multicollinearity. The model fit the data well, as confirmed by the Hosmer-Lemeshow test ($p = 0.656$). Candidate variables with a p-value below 0.25 in the bivariate regression were included in the multivariable logistic regression model to control for confounding effects. Predictors for cervical cancer screening uptake were identified based on a p-value < 0.05 and presented as adjusted odds ratios (AOR) with a 95% confidence interval.

# Results

## Socio-demographic characteristics

The study included 98 cases and 294 controls, achieving a 93.3% response rate. Among cases, 50% were aged 30-39 years, while 28.6% of controls. Education levels showed 13.2% of cases and 12.6% of controls with no formal education. Additionally, 12.3% of cases and 7.1% of controls were single, with 75.5% of cases and 71.8% of controls being married. Residence-wise, 81.6% of cases and 67.7% of controls lived in urban areas (Table 1).

## Access to healthcare facilities

Fifty percent of cases reached the health facility within 60 minutes, compared to 34% of controls. Among cases, 81.6% used public transportation, while 18.6% walked on foot (Figure 2).

## Medical and behavioral characteristics

Thirteen point three percent of cases and 15.7% of controls reported having multiple sexual partners. Regarding smoking status, 4.1% of cases and 9.5% of controls were smokers. Among cases, 5.1% had a history of sexually transmitted diseases (STDs), compared to 4.4% of controls. Additionally, 8.2% of cases and 4.4% of controls tested positive for HIV (Supplementary Figure S1).

## Knowledge of cervical cancer

Among the cases, 87.8% were aware of cervical cancer, compared to 50.7% of controls. Among those aware of cervical cancer, 75.6% of cases and 65.1% of controls recognized viruses as the cause. For symptoms, 59.3% of cases and 27.9% of controls identified vaginal bleeding. Overall, 81.6% of cases had high knowledge, compared to 38.4% of controls (Supplementary Table S1).

## Knowledge about cervical cancer screening

Ninety cases (91.8%) and 39.5% of controls were aware of cervical cancer screening. Public media was the primary source of information for 60% of cases and 55.2% of controls. Overall, 83.7% of cases and 32% of controls demonstrated high knowledge about cervical cancer screening (Supplementary Table S2).

## Attitude towards cervical cancer screening

Seventy-one cases (72.4%) and 46.2% of controls agreed that cervical cancer is deadlier than other cancers. Eighty-eight cases (85.6%) and 36% of controls were willing to undergo screening. Overall, 71% of cases and 24% of controls had a positive attitude toward cervical cancer screening (Supplementary Table S3).

## Factors associated with cervical cancer screening uptake

After adjusting for confounding variables, women aged 30–39 (AOR=3.94; 95% CI: 1.79, 8.63) and those aged 40–49 (AOR=3.54; 95% CI: 1.52, 8.22) were more likely to undergo cervical cancer screening. Additionally, women with a high knowledge of screening (AOR=6.23; 95% CI: 1.96, 19.79), a positive attitude toward screening (AOR=6.12; 95% CI: 2.40, 15.58), and those who reached health facilities within 60 minutes (AOR=2.32; 95% CI: 1.21, 4.45) were also more likely to participate in screening (Table 1).

TABLE 1 Factors associated with cervical cancer screening uptake among the study participants.

| Variables | Categories | Cases | Controls | COR (95% CI) | AOR (95% CI) | *P-value* |
|---|---|---|---|---|---|---|
| | | n (%) | n (%) | | | |
| Age (y) | 20 – 29 | 19 (19) | 140 (47.6) | 1 | 1 | |
| | 30 – 39 | 49 (50) | 84 (28.6) | 4.31 (2.42, 7.83)** | 3.94 (1.79, 8.63) | **0.001** |
| | 40 – 49 | 30 (31) | 70 (23.8) | 3.22 (1.61, 6.13)* | 3.54 (1.52, 8.22) | **0.003** |
| Religion | Orthodox | 52 (53.1) | 119 (40.5) | 1 | 1 | |
| | Muslim | 17 (17.3) | 37 (12.6) | 1.05 (0.53, 2.24) | 0.78 (0.31, 1.96) | 0.601 |
| | Protestant | 24 (24.5) | 111 (37.8) | 0.49 (0.36, 0.92) | 0.62 (0.29, 1.29) | 0.199 |
| | Catholic | 5 (5.1) | 27 (9.1) | 0.42 (0.16, 1.24) | 0.32 (0.09, 1.07) | 0.065 |
| Education | No formal education | 13 (13.2) | 37 (12.6) | 1 | 1 | |
| | Primary school | 31 (31.6) | 55 (18.7) | 1.64 (0.72, 3.52) | 1.31 (0.44, 3.91) | 0.628 |
| | Secondary school | 27 (27.6) | 71 (24.1) | 1.11 (0.53, 2.34) | 0.64 (0.21, 1.98) | 0.440 |
| | College and above | 27 (27.6) | 131 (44.6) | 0.62 (0.35, 1.25) | 0.39 (0.12, 1.25) | 0.113 |
| Marital status | Single | 12 (12.3) | 21 (7.1) | 1 | 1 | |
| | Married | 74 (75.5) | 211 (71.8) | 0.63 (0.34, 1.35) | 1.13 (0.43, 2.94) | 0.802 |
| | Divorced | 7 (7.1) | 35 (11.9) | 0.44 (0.17, 1.02) | 1.32 (0.33, 5.27) | 0.696 |
| | Widowed | 5 (5.1) | 27 (9.2) | 0.38 (0.09-1.06) | 1.33 (0.27, 6.59) | 0.726 |
| Residence | Rural | 18 (18.4) | 95 (32.3) | 1 | 1 | |
| | Urban | 80 (81.6) | 199 (67.7) | 2.12 (1.26, 3.71)* | 0.67 (0.29, 1.55) | 0.349 |
| Occupation | Government employee | 29 (29.6) | 99 (33.7) | 1 | 1 | |
| | Private employee | 37 (37.8) | 135 (45.9) | 0.94 (0.51, 1.62) | 0.74 (0.33, 1.69) | 0.480 |
| | Housewife | 30 (30.6) | 48 (16.3) | 2.10 (1.23, 3.94)* | 1.79 (0.71, 4.56) | 0.220 |
| | Others[#] | 2 (2) | 12 (4.1) | 0.57 (0.12, 2.69) | 0.75 (0.08, 6.76) | 0.798 |
| Travel time to healthcare facilities | ≥60 minutes | 49 (50) | 194 (66) | 1 | 1 | |
| | <60 minutes | 49 (50) | 100 (34) | 1.94 (1.22, 3.08)* | 2.32 (1.21, 4.45) | **0.011** |
| Cervical cancer knowledge | Low level | 8 (8.2) | 149 (50.7) | 1 | 1 | |
| | Moderate level | 10 (10.2) | 32 (10.9) | 13.2 (6.10, 28.4)* | 1.66 (0.40, 6.85) | 0.483 |
| | High level | 80 (81.6) | 113 (38.4) | 5.82 (2.15, 15.9)* | 1.64 (0.45, 6.00) | 0.454 |
| Knowledge of screening | Low level | 10 (10.2) | 182 (61.9) | 1 | 1 | |
| | Moderate level | 6 (6.1) | 17 (5.8) | 15.7 (7.81, 31.7)* | 3.88 (0.89, 16.9) | 0.071 |
| | High level | 82 (83.7) | 95 (32.3) | 6.43 (2.08, 19.8)** | 6.23 (1.96, 19.8) | **0.002** |
| Attitude towards screening | Negative | 12 (12.3) | 169 (57.5) | 1 | 1 | |
| | Neutral | 16 (16.3) | 55 (18.7) | 14.1 (7.22, 27.6)* | 1.71 (0.65, 4.49) | 0.278 |
| | Positive | 70 (71.4) | 70 (23.8) | 4.18 (1.84, 9.24)** | 6.12 (2.40, 15.6) | **<0.001** |

N.B, AOR, Adjusted odds ratio; CI, Confidence interval; COR, Crude odds ratio; n, frequency; *p-value<0.05; **p-value<0.001; Others[#]: Merchant, daily labor and student.
The bold values used to show statistical significance.

## Discussion

Cervical cancer screening is vital for the early detection and treatment of precancerous lesions (23). This study sought to identify the factors influencing cervical cancer screening uptake among women of reproductive age in southwest Ethiopia. It found that key determinants include women's age, their level of knowledge about cervical cancer screening, their attitude towards screening, and the time required to reach health facilities.

The study revealed that women aged 30 – 39 and 40 – 49 were respectively 3.9 and 3.5 times more likely to undergo cervical cancer screening compared to those aged 20 – 29. This finding aligns with

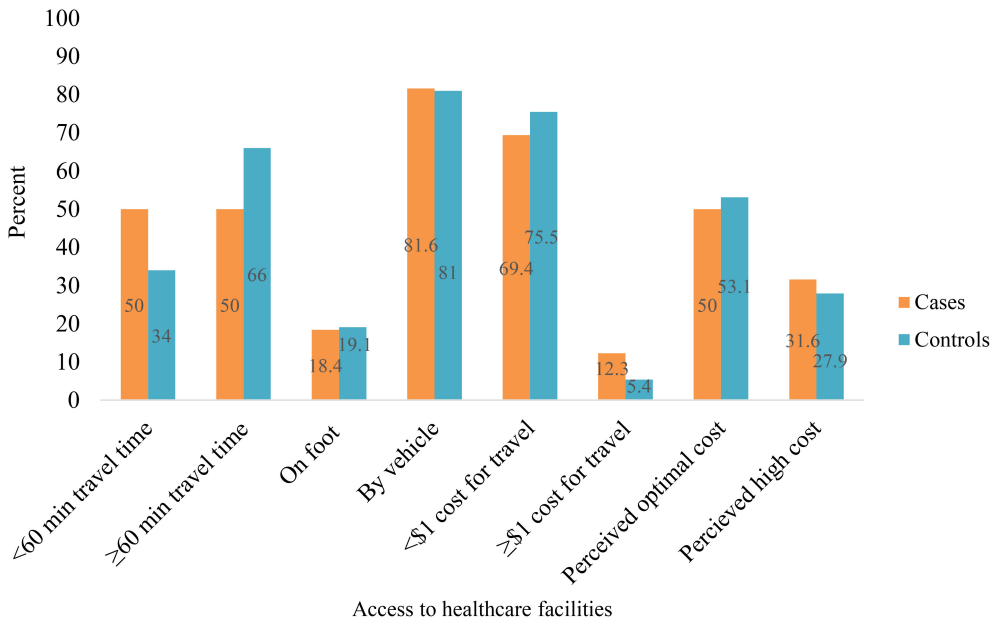


FIGURE 2
Access to healthcare facilities among participants.

similar studies conducted in various Ethiopian regions like Ambo, Diredawa, Mekele, and Finoteselam, which also observed higher screening rates among older age groups (16, 20, 24, 25). Older women may be more inclined to undergo cervical cancer screening due to a perceived higher risk associated with their age. Moreover, increased exposure to healthcare facilities as women age could contribute to higher screening rates among older age groups. Indeed, a study conducted in India revealed that younger women were more inclined to undergo cervical cancer screening compared to older age groups (26). This discrepancy could stem from differences in information availability and variations in the study participants' characteristics.

This study found that having a high knowledge of cervical cancer screening was a significant predictor of uptake. Women with a high of knowledge screening were 6 times more likely to undergo cervical cancer screening compared to those with low knowledge of screening. This finding aligns with studies conducted in various regions of Ethiopia, such as Mekele, Ambo, Addis Ababa, Jimma, and Adigrat. These studies also demonstrated that women with a high knowledge of cervical cancer screening were more inclined to utilize screening services compared to those with lower knowledge of screening (20, 22, 25, 27, 28). Studies conducted worldwide have consistently shown that women with a high knowledge of cervical cancer screening are more likely to utilize screening services compared to those with low knowledge (29, 30). This trend suggests that informed women may exhibit higher health-seeking behavior and intentions to undergo screening. Access to various sources of information, such as media, may contribute to their increased awareness and motivation to seek healthcare services, including cervical cancer screening. Consequently, women with a good understanding of cervical cancer are more likely to uptake screening services than those with poor knowledge levels.

A positive attitude toward cervical cancer screening significantly increased the likelihood of uptake, as women with a positive attitude were 6 times more likely to undergo screening compared to those with a negative attitude toward screening. The findings of this study align with previous research conducted in various regions of Ethiopia (20, 31, 32). Similarly, a study conducted in Gondar, Ethiopia, found that women with a favorable attitude were more inclined to utilize cervical cancer screening services compared to those with an unfavorable attitude (33). Women with a positive attitude towards screening may possess a stronger sense of self-care and respect for their well-being, potentially leading to better health-seeking behaviors. Moreover, this positive attitude may drive them towards seeking a healthier lifestyle, thus making them more likely to engage in preventive healthcare practices such as cervical cancer screening.

In this study, the time taken to reach health facilities emerged as a predictor of cervical cancer screening uptake. Women who reached health facilities within 60 minutes had 2 times higher odds of being screened compared to their counterparts. This study aligns with research conducted in Uganda and South Africa, indicating that women who had access to health facilities offering cervical cancer screening services were more likely to undergo screening compared to those who lacked such accessibility (30, 34). The evidence suggests that proximity to health facilities plays a crucial role in facilitating cervical cancer screening uptake. Women residing closer to health facilities have greater opportunities to access various services and information from healthcare professionals, thereby increasing their likelihood of undergoing screening. Additionally, accessibility is influenced by travel costs, with women living nearer to health facilities incurring lower expenses. This affordability may enhance their willingness to seek healthcare, consequently leading to a higher uptake of cervical cancer screening.

## Limitations of the study

As a hospital-based study, the results may not apply to the general population. The small sample size limits the ability to generalize the findings to a larger population because it decreases the statistical power and reliability of the results. Recall bias and social desirability bias could affect the findings, particularly for variables like STI history and smoking status. Additionally, establishing a clear temporal relationship between factors such as attitude, knowledge, and cervical cancer screening uptake is challenging.

## Conclusion

The research identified age, knowledge, and attitude regarding cervical cancer screening, along with proximity to health facilities within a 60-minute radius, as key factors influencing cervical cancer screening uptake among women of reproductive age. These findings highlight the importance of targeted education, promoting positive attitudes, and enhancing healthcare accessibility to improve screening uptake and reduce the burden of cervical cancer.

## Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, upon reasonable request.

## Ethics statement

The studies involving humans were approved by Mizan-Tepi University Institutional Review Board (PGC/061/2022). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

## Author contributions

TY: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Software, Writing – original draft, Writing – review & editing. BB: Formal analysis, Funding acquisition, Methodology, Project administration, Resources, Software, Supervision, Validation, Writing – original draft, Writing – review & editing. NS: Formal analysis, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. BBB: Investigation, Formal analysis, Project administration, Supervision, Resources, Funding acquisition, Writing – original draft, Writing – review & editing. AA: Conceptualization, Data curation, Funding acquisition, Investigation, Project administration, Resources, Supervision, Validation, Writing – original draft, Writing – review & editing.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## Publisher's note



## Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2024.1424810/full#supplementary-material

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