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Protocol

Concordance between urine and self-collected vaginal samples for high-risk HPV detection in cervical cancer screening

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ABSTRACT

Background: A system comprising of screening for pre-cancerous lesions succeeded by therapeutic interventions can greatly reduce the incidence of cervical cancer. High risk HPV detection in urine has proven itself as a potential primary screening tool. However, only a few studies have showed it's concordance with matched self-collected vaginal samples while screening for high risk HPV infection in the community. Objective of the study was to determine the concordance between first void urine sample and self-collected vaginal sample for high risk HPV detection using Cobas 4800. The sensitivity and positive predictive value of screening by urine HPV testing for CIN 2+ detection would also be done along with its acceptability and cost analysis in community screening.
Methods: This study will include women between 30-60 years with intact cervix and no precancerous lesions. Self-sampling will be provided by participants in the form of urine and vaginal swab collection by the Collipee device and vaginal swab stick respectively. This will be followed by high risk HPV testing using Cobas 4800 technology. The participants will also be asked to fill up a questionnaire about the acceptability of urine sampling for cancer screening.
Conclusions: Screening tools can perhaps be diversified in order to suit the needs of low and middle income countries. Research and development of cervical cancer screening tools could hence bring to light feasible alternatives that could further improve compliance of non-attenders.
Trial registration: The trial is registered with clinical trials registry (CTRI/2023/01/049322).

Keywords: Human papilloma virus, Cervical cancer, Urine sampling, Cobas 4800, High risk HPV detection, CIN 2+ detection, Vaginal sampling

INTRODUCTION

Cancer cervix is the second leading cause of cancer related mortality among Indian women. In India, the numbers of newly diagnosed women with cervical cancer are 1,23,907 numbers per year and about 77,348 women die from this disease every year.[1] In the World Health Organization (WHO)'s global strategy for elimination of cervical cancer, that has been endorsed by the World Health Assembly in 2020, there has been a call for regular screening of 70% of women with a high-performance test and among those requiring it 90% should receive appropriate treatment.[2] In developed countries with effective traditional cytology-based cervical cancer screening and treatment programmes, the mortality from cervical cancer has been reduced fivefold over the past 50 years. However, this screening approach has not been as successful in low and middle-income countries.

Visual inspection of the cervix with acetic acid and Pap smear test have been the two main modalities of traditional screening so far. Keeping in view that in most developing countries, lack of necessary manpower, infrastructure and quality control; high-quality cytology

screening may not be feasible for wide-scale implementation of cervical cancer screening programs. Hence it has been recommended that visual screening tests such as VIA could be adopted, till a low-cost reliable HPV test is made available in India.[3]

Recently, several HPV testing based screening strategies have been adopted in India as a primary screening test, based on the current WHO recommendations due to its improved diagnostic accuracy.[2] In India the cervical cancer screening test currently recommended in the national cancer screening program is VIA. However, this test has several limitations such as moderate sensitivity, low specificity and subjectivity. In India a nationwide uniform government sponsored screening program is absent. Hence a springboard for scaling up affordable, acceptable, sustainable cervical cancer screening services at the level of primary health centres is required, in order to reach the global targets by 2030.

Originally cervical sample was collected by a health provider after a speculum examination was required for HPV detection tests. Subsequent studies have shown that self-collected upper vaginal sample is as good as provider-collected cervical sample for the detection of high-risk (HR) HPV infection.

As an alternative to traditional screening methods, we are proposing a screening strategy using self-collected first void urine for high risk HPV detection by Cobas 4800 technique First-void urine contains washed away mucus and debris from exfoliated superficial cell layers and has shown to contain higher concentrations of HPV DNA. Therefore collection of this fraction is important to increase sample sensitivity.[5] In addition, several studies reported that first-void urine sampling, using a first-void urine collection device was preferred over a physician-collected cervical sample.[6]

Besides being a primary screening tool, urine-based HPV testing can also be used for monitoring the impact of vaccination.[9-11] The World Health Organization (WHO) also used HPV-self sampling through urine collection to evaluate the impact of HPV vaccination in Rwanda and Bhutan. HPV testing by urine also offers possibilities for the follow-up after cervical precancer treatment.[12,13]

As vaginal sample collection has an invasive element, urine testing, which is non-invasive may be more acceptable to some women or cultures. Self-collected vaginal samples are not always culturally and socially feasible in conservative societies. However, the incorporation of non-invasive sampling modalities into existing cervical cancer screening programme may improve the participation rate in developing countries. This approach may be more cost effective, acceptable and less embarrassing to the women from the low-income countries who demonstrate the lowest cervical cancer screening compliance despite being at a higher risk of HPV-associated malignancies.

METHODS

Type of study

This will be a prospective observational study.

Research setting

The study will be conducted at Chittaranjan National Cancer Institute, Kolkata, India from March 2023 to March 2025.

Objectives

The primary objective of the study is to determine the concordance between first void urine sample and self-collected vaginal sample for high risk HPV detection using Cobas 4800.

The secondary objectives of the study are: to evaluate the sensitivity of urine sample for detection of underlying CIN2+, to evaluate the positive predictive value of urine and vaginal self-sample for detection of CIN 2+, to determine the acceptability of urine testing for cervical cancer screening, and to collect data on the costs associated with implementation of HPV screening by self-sampling and urine analysis with a payer perspective to compare them.

Novelty

The present study is in line with the updated WHO recommendation for screening and treatment of cervical cancer by HPV DNA detection in a screen-triage-treat approach and is the need of the hour for initiating and upscaling screening services. Irrespective of HPV vaccination, women must continue with screening. It is necessary to close the cancer care gap especially for women among whom access to screening has been an issue due to socio-cultural, geographical or occupational reasons. Access to cervical cancer screening remains a major problem in rural areas and amongst working women resulting in reduction in follow up and failure to achieve the desired benefit of screening, as a continued screening program is required especially in unvaccinated women. HPV testing by urine in the community can upscale the cervical cancer screening in low middle income countries (LMIC) as it will probably be more acceptable to the participants. A urine assay for detection of the virus could be a boon in a setting where more traditional means of screening for cervical cancer are and there is also a scope for it to be used to see the impact of HPV vaccination in young girls.

Review of literature

The recent update in cervical cancer screening was the 2015 US FDA approval of Roche Cobas HPV testing for women above 25 years without concurrent Pap testing.[14] HPV testing is much more sensitive with a high negative

predictive value compared to cytology and visual inspection with acetic acid. Another advantage is that urine as well as vaginal samples, can be tested by molecular assays. The first void urine can be collected by Collipee device by Novosanis company which is a single use urine collection device which can be used to collect first void urine at any time of the day because the first flush urine contains high concentrations of DNA from human papillomavirus rather than mid-stream urine.

Evidence on accuracy of urine testing for detection of HPV

As early as 2006, before the publication of the first meta-analysis on urine HPV assessment, Daponte et al utilized polymerase chain reaction (PCR) methods and concluded that the detection of HPV in urine correlates well with the detection of concomitant cervical HPV even during pregnancy, while also stressing the importance of testing first-void urine (FVU) and quantifying viral load levels.[15-18]

Later, in 2014, the first important meta-analyses of 14 studies (1,443 women) confined to urine self-sample had been published; Pathak et al conclusively regarded urine HPV testing as a feasible and acceptable alternative in established cervical screening modalities suggesting it as a possible complementary organized screening method. For high risk HPV detection, urine had a pooled sensitivity of 77% (68% to 84%).[19]

The Predictor 5.1 study by Cadman et al studied the comparison of different vaginal self-sampling devices and also urine sampling using Collipee device for human papilloma virus testing. About 620 women were referred for colposcopy and also invited to provide an initial stream of urine. Urine sample was collected with Collipee device and vaginal samples were taken using either dry or wet swab. Similar positivity rates and sensitivities for CIN2+ and CIN3+ were seen between dry swab and urine. Women found urine easiest to collect and were more confident about sample collection. The study concluded that urine, dry swab and wet swab all performed well and easily accepted by women. The concordance between urine and the four vaginal samples was found to be 0.568-0.646.[20]

The EVAH study was conducted on 84 women to study the correlation between HPV detection using self-collected urine and physician taken cervical smears also showed high concordance between HPV detection in first-void urine and clinician-taken smears illustrated by kappa values ranging from 0.75 to 0.85. The study also stated that the detection of CIN2+ lesions for HPV testing by first void urine is feasible and has a sensitivity and specificity to physician collected sample.[21]

Arbyn et al in 2019 designed the VALHUDES protocol as a diagnostic test to compare the clinical sensitivity and specificity of hrHPV assay on vaginal self-sample and first void urine collected in agreement with standardized protocols with hrHPV testing on matched clinician taken samples. 500 women referred to colposcopy clinic were invited to give their samples. The first-void urine collected at home showed similar accuracy for detecting CIN2+ as compared to cervical samples taken by a clinician. These results are pivotal to improve sampling strategies and reach women who do not participate in traditional screening programs by offering urine self-collection at home.[22]

Sensitivity and specificity of urine test to detect CIN 2+

In the study by Cadman et al, similar positivity rates and sensitivities for CIN2+ and CIN3+ were seen between dry swab and urine. Sensitivity of urine for detection of CIN2+ and CIN3+ was 87% and 89.7%.[20]

In the study by Maged et al, to assess the sensitivity of urine test for detection of hrHPV on 1375 women referred to a medical school in Cairo, 87 women had positive urine test for high-risk HPV and 82 had pathologic findings of CIN 2 or CIN 3.[23]

In a cross sectional study by Sargent et al, to compare the sensitivity of hrHPV testing for detection of CIN2+ in matched urine and cervical samples, the sensitivity of urine for detection of CIN2+ lesions was 83% for urine and 89% for cervical sample.[24]

Ornskov et al conducted a study between paired urine, cervical and vaginal specimen. The sensitivity for CIN2+ and CIN3+ detection with urine sample was 93% and 95% respectively. Between urine and self-collected vaginal samples, kappa was 0.77. Regarding the acceptability of the screening method used, they concluded that the majority of women identified urine as the sampling method of choice, especially when they were asked about the expected preference for women not attending the screening programme.[25]

Through earlier studies, self-sampling and HPV detection through urine are proven to be acceptable methods of screening and feasible for large epidemiological surveys in India.[26,27] However, it would be ideal if a test like urine analysis for cervical screening can be proven to be cost-effective compared to self-sampling. While cost is a critical component that is necessary to be assessed with the intervention benefits to analyze cost-effectiveness, there is a scarcity of studies on the data related to implementation costs of HPV testing through urine analysis. This study will therefore assess the cases detected and generate information on the cost of implementation of the two interventions.

Pilot work

Around 25 women with histo-pathologically proven cervical cancer, attending the Gynecology oncology department of Chittaranjan National Cancer Institute,

Kolkata have given their first void urine and vaginal swab which has then been tested by Cobas 4800 test for high risk HPV detection. The results of the preliminary work are as follows.

Among the 25 women who were tested, 84% of the women were positive for either HPV 16 or 18 on both the urine and vaginal self-swab and 4 women were positive for other HPV type. The cycle threshold value for urine and vaginal swab were almost similar.

Research plan, methodology and data collection

The proposed study plan is diagrammatically represented in Figure 1.

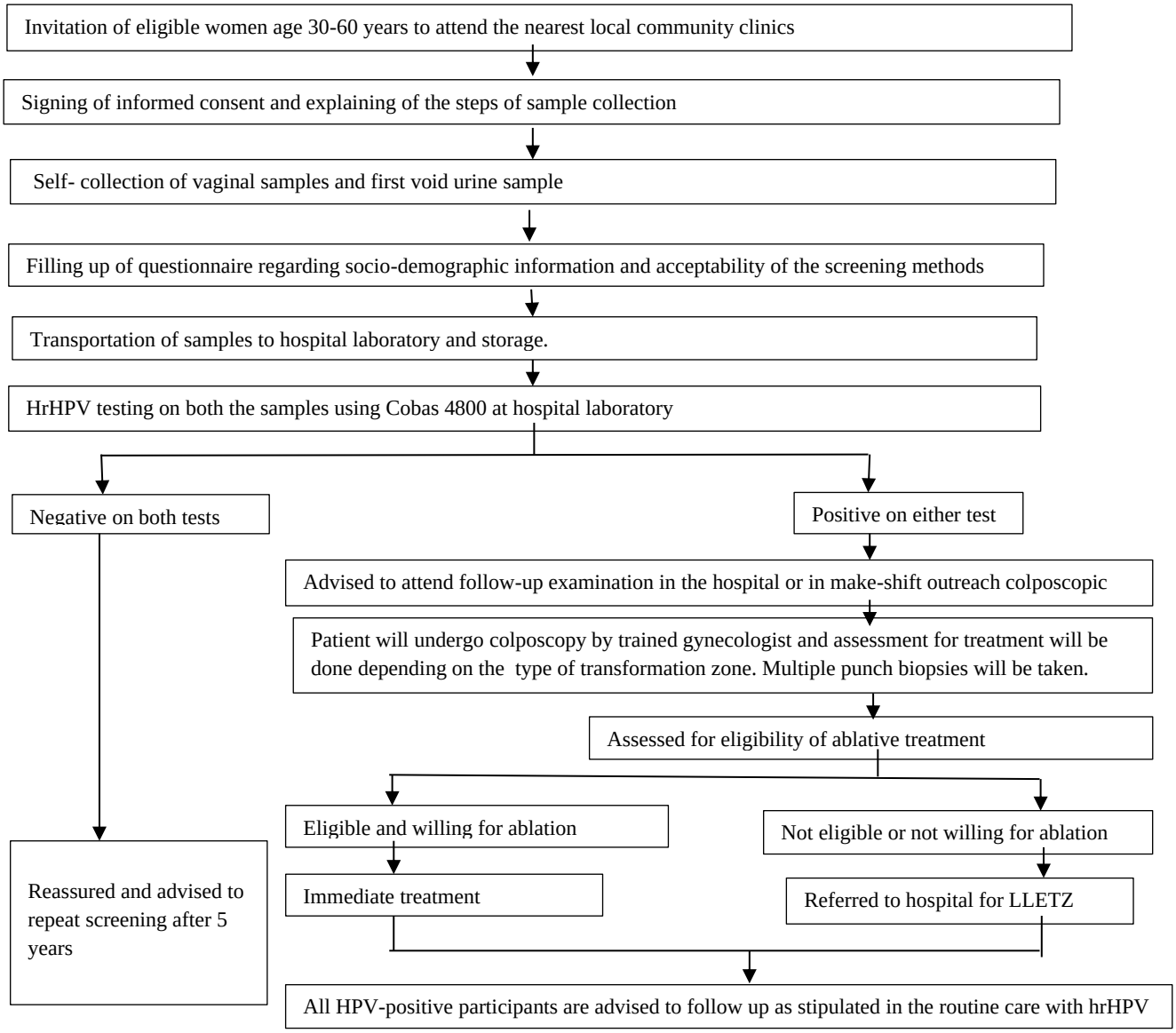

Figure 1: Study plan.

Table 1: Preliminary results of the pilot study conducted on carcinoma cervix patients.

Carcinoma cervix patients	High risk HPV positive	Other HPV positive	Vaginal swab positive	Urine sample (with medium) positive
1	HPV 16		31.4	32.3
2	HPV 16		36.3	37.1
3	-	Other HPV positive		
4	HPV 16		28.1	31.5
5	HPV 16		35.2	37.3
6	HPV 16		40.1	42.2
7	HPV 16		36.3	37.2

Continued.

Carcinoma cervix patients	High risk HPV positive	Other HPV positive	Vaginal swab positive	Urine sample (with medium) positive
8	HPV 18		27.4	25.4
9	HPV 16		35.1	33.1
10	HPV 16		31.4	32.4
11	HPV 16		24.1	26.2
12	HPV 16		36.3	37.1
13	HPV 16		29.3	31.4
14	HPV 18		31.2	33.4
15	HPV 18		37.8	39
16	-	Other HPV positive		
17	HPV 18		29.2	31.2
18	HPV 16		31.4	33.4
19	-	Other HPV positive		
20	HPV 16		37.1	40
21	HPV 6		35.2	37.1
22	HPV 18		28.2	25.3
23	-	Other HPV positive		
24	HPV 16		31.4	30.4
25	HPV 16		25.3	26.1

Study population

Selection of sample population

The participants will be recruited among women attending the community based cervical cancer screening camp organised by Chittaranjan National Cancer Institute in areas of South 24 Parganas. All the participants have to sign informed consent forms voluntarily before being enrolled into the study. Complete project information will be provided to all the eligible women and women who are willing to participate will be included in the study..

Participant inclusion criteria

Asymptomatic women aged 30-60 years with intact cervix will be included.

Participant exclusion criteria

Women with previously hysterectomies, previously diagnosed as cervical cancer or precancerous lesions, and pregnancy will be excluded.

Biological materials to be used

Biological materials to be used include vaginal swab and first void urine sample.

Questionnaire filling

After completing both procedures, the participants have to answer the questions in the questionnaire by themselves and hand it over to the investigator in the end.

The questionnaire will be in 2 parts: part one is general information of the participants such as age, occupation, marital status, parity, and monthly income.

Part two is the acceptability questions to assess the acceptability of urine for hrHPV testing. Likert scale will be used for scoring each aspect of the questions ranging from 1 to 5. The meaning of the score number is written at the heading of the questionnaire. Score 1 means highly dissatisfied. Score 2 means dissatisfied. Score 3 is neutral. Score 4 is satisfied and score 5 means highly satisfied. The score 4 and 5 are classified as acceptance. Score 3 or less are verified as poor acceptability. The questions are based on ease of use of the devices, embarrassment, pain, privacy and social stigma. The participants will be given a visual analogue scale to record their responses.

Sample collection

The study will be conducted on around 2500 patients .The participants will be assigned to collect their first void urine sample in a in a standardized way using the user friendly Collipee device which contains a urine conservation medium. Self-collection of vaginal sample will be done by a brush by the participants under guidance of a health worker.

The instruction of self-sampling HPV and urine test and the consent form will be handed over to the participants as a leaflet. The volume of the samples collected using ColliPee device lie in the range of 8-12 ml (10 ml nominal volume) and include a prefilled volume of 3.4 ml urine conservation medium.

Method of sample collection

Urine collection

General procedure

The procedure for the collection of urine sample will be as follows. The participants will be advised to hold urine for 3-4 hours. They should not to clean their private parts with soap solution before giving the sample. ColliPee urine collection device will be used to collect first void urine. It consists of a housing, a floater within a tube, and a cap for final sealing of the tube. When collecting urine, the collator tube is screwed onto the ColliPee housing and the volume of urine needed is then collected. The device is then disconnected from the tube, which is then capped.

Participant should then present the collected urine specimen to the study coordinator. The date and time of collection should be recorded.

Collection device

First-void urine will be collected in a user-friendly and standardized way, using ColliPee device containing urine conservation medium to allow for instant mixing with the preservative and thus stabilization of the urinary analytes.[28,29]

Time of collection

Anytime during the clinic hours will be used for collection.

Volume of sample

The device has a capacity to hold around 10 ml of urine.

Urine specimen preservation

It is preserved in a prefilled volume of 3.4 ml urine conservation medium preservative (UCM).

Storage

Due to the presence of the UCM preservative, collected samples can be stored at room temperature (21°C – 25°C) for a period of maximum of 7 days, before downstream processing. Prolonged storage of the urine samples is possible at 4°C for up to 14 days, and at -20°C for up to 90 days.

Vaginal swab collection

General procedure

The woman should be in a comfortable position, preferably in standing posture with one foot on a stool. She would be advised to spread open the folds of skin at the vaginal opening with the other hand. The brush should be inserted into the vagina upto the mark provided, approximately half the length of the finger and rotated gently 360 degrees 5-6 times for 10-30 seconds. Once the sample is collected, the brush should be placed in the collection tube with the preservative solution, and the cap should be tightly screwed and handed to the health worker.

Storage and transport

The sample collected can be kept at room temperature for up to two weeks after which the specimens can be stored for an additional week between 2-8 degree Celsius. A preservative has been added to specimen transport medium to retard bacterial growth and retain the integrity of DNA.

Hr-HPV testing

The samples will be then transported to hospital laboratory on the same day, while maintaining cold chain of 4-8° C. High risk HPV testing will be done for both vaginal and urine sample by Cobas 4800. The Cobas HPV Assay is an automated test for qualitative detection and differentiation of HPV DNA.

The assay is performed on the Cobas 4800 Instrument System. The collector tube of Colli-Pee small Volumes is compatible with the cobas 4800 system. Therefore, the sample can be placed directly into the rack of the Cobas system, without any further sample preparation need.

Sample analysis

The Cobas test is a HPV detection test that is clinically validated and FDA approved. It utilizes amplification of target DNA by the polymerase chain reaction (PCR) and nucleic acid hybridization for the detection of 14 high-risk HPV (hrHPV) types in a single analysis. The Cobas HPV Test is based on two major processes: automated specimen preparation to simultaneously extract HPV and cellular DNA; PCR amplification of target DNA sequences using both HPV and β-globin specific complementary primer pairs and real-time detection of cleaved fluorescent-labelled HPV and β-globin specific oligonucleotide detection probes. The concurrent extraction, amplification, and detection of β-globin in the Cobas HPV test monitors the entire test process. The master mix reagent for the Cobas HPV test contains primer pairs and probes specific for the 14 high-risk HPV types and β-globin DNA.

Evaluation of HPV viral load

The hr-HPV viral load in vaginal samples and their correlation with the viral presence in the corresponding urine samples will be analysed. Such analysis can also explain hr-HPV discordant cervical and urine samples.

Samples with invalid test results for both urine and vaginal swab will be retested.

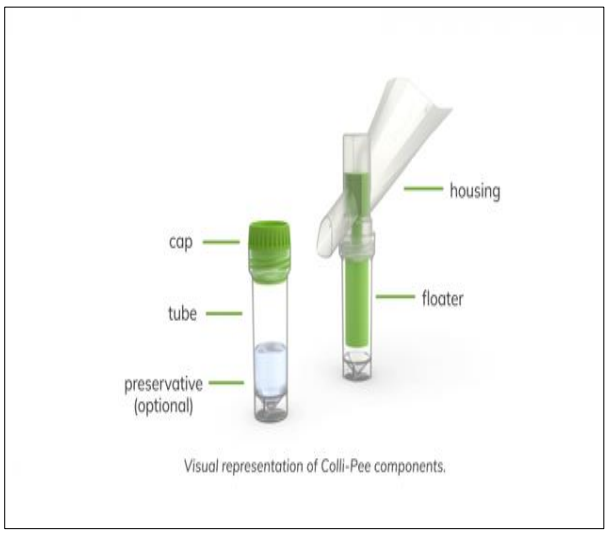

Figure 2: Collipee device containing the preservative with the collector and tube.

Figure 3: Vaginal swab collection tube.

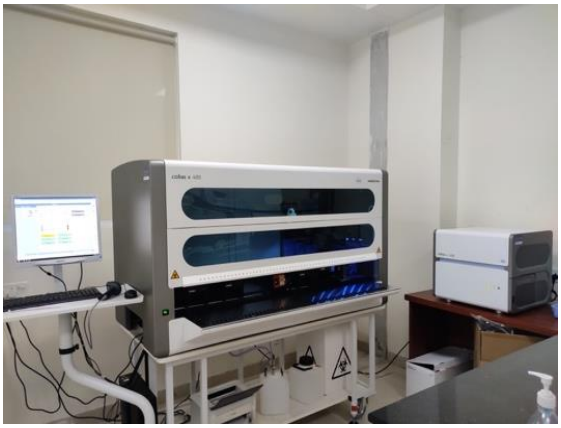

Figure 4: Cobas machine for processing vaginal swab and urine samples.

Statistical analysis

The distribution of socio-demographic characteristics of the participants will be presented as proportions. For analysis, only women with valid hrHPV results from paired urine and vaginal samples will be included. The results will be categorized as positive or negative. The agreement between the two tests will be presented as proportions. Cohen's kappa (κ) will be used to measure concordance in for urine and vaginal samples by the COBAS assay. Concordance is defined as "poor" ($\kappa \leq 0.20$), "fair" ($0.21 \leq \kappa \leq 0.40$), "moderate" ($0.41 \leq \kappa \leq 0.60$), "good" ($0.61 \leq \kappa \leq 0.80$), or "very good" ($\kappa \geq 0.81$).[30] The positive predictive value will be calculated using the standard formulas.

All these measures will be provided with their 95% confidence interval. For comparison of secondary objectives like positive predictive value between the two tests will be done using McNemars test. For the quantitative data, the scores from Likert scale will be added to find the total score of each person.

Cost analysis

Micro-costing analysis will be conducted from the provider perspective to determine the unit cost of informing and inviting women from community, conducting HPV self-sampling and urine sampling and detecting and follow-up care and treatment related to both the interventions.

DISCUSSION

Implementation of triage and treat model in community based cervical screening

The participants who have abnormal results with HPV testing will be called back for colposcopy and treatment. At the time of colposcopy, cervical biopsy will be taken from multiple sites. Patients will undergo treatment by thermal ablation or large loop excision of the transformation zone depending on the transformation zone type.

Primary outcome measure

By the end of this study, we will be able to analyse the concordance between first void urine and self-collected vaginal sample.

Secondary outcome measures

We will be able to assess the secondary outcome measures like the sensitivity of urine to detect underlying CIN2+, positive predictive value of urine and vaginal self-sample for detection of CIN 2+, acceptability of urine sampling as a method of cervical cancer screening tool, and understand the costs associated with

implementation of HPV self- sampling between vaginal swab and urine.

Potential risks and benefits

Potential benefits

The potential benefits include enhanced uptake of cervical cancer screening among women, reduced mortality and morbidity related to cancer cervix and costs incurred for screening and treatment in a large-scale community- based project. This would perhaps be more feasible in the long run when compared to the costs involved in the investigation, treatment, palliation, and rehabilitation of cervical cancer patients and also year's lost to unemployment.

Potential risks

There can be of possible bleeding at the time of self-swab sampling which may be a very small possibility. This will be addressed by excluding the women with history of contact bleeding and intermenstrual bleeding. Also, women will be instructed about the safe length of the swab that can be inserted up to lower mid vagina. Women who experience bleeding will be managed appropriately. As the study includes only screening activities and as no screening activity is 100% sensitive, there is small possibility of missing the abnormalities despite screening. There can be possibilities of overtreatment when HPV DNA test is used as a single test.

CONCLUSION

Current cervical cancer screening methods have drawbacks resulting in poor attendance. Women would prefer easy and non-invasive techniques that are not clinician dependent. Urine as a sample type has the potential to reach a wider population**,** especially women who do not participate in screening.

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Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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