**Manuscript Title:**

**A Sequential Explanatory Mix Methods Design to understand the Awareness, Opinion on Cervix** **Cancer, Compare the Acceptance of Self Sampling Versus Assisted Sampling on HPV Screening and Barriers for HPV Vaccination among Women - Study Protocol**

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**Abstract**

Cancer is one of the leading causes of adult deaths worldwide. In contrast to developed countries, cervical cancer is a public health problem in developing countries like India, so much so that India alone accounts for one-quarter of the worldwide burden of cervical cancers the breasts and the cervix. Screening for cancer is known to reduce mortality by early detection and treatment. However, despite availability of various screening method for cervical cancer, women are not showing interest to participate in screening in regions where programme are available.it is predicted that the number of women in India will die due to cervical cancer will reach to 13 million by 2120. Providing screening programs is in place a major obstacle for women across many countries and culture has been the requirement to undergo a speculum based pelvic examination, limited sources to care and lack of awareness about disease and preventive tools. In this protocol study we provide an assessment of opinion and experiences regarding self-sampling versus assisted sampling for HPV screening and noncompliance of HPV vaccine among women at selected villages of Puducherry as a mixed methods study.

**Keywords:**

**Cervix** **cancer.** **HPV screening. HPV vaccination. Pilot study. Study protocol**

**Background**

Cervix cancer is the major public health issue among middle aged women. World analysis report on cervical cancer mentioned that highest number of deaths happened in India in year 2018, nearly 60,000 [1]. A research report projected that in India there will be approximately 225,000 new cases by 2025 [2]. It stated that alone cervical cancer credits 17% of cancer deaths among women aged of 30 to 69 years [3]. HPV 16 and 18 main virus causing cervical cancer, yet prevention is achievable with systematic and advance hpv screening [4]. Epidemiological studies evidenced that 40% of young women have evidence of HPV infection with peaks during the teens and early twenties, soon after first coitus [5] .

The cervical cancer screening is very low (22% to 36%) in India among women, [6]but a study from Tamil Nadu reported the screening coverage for cervical cancer to be around 63% [7]. Pondicherry is “the Union Territories” in India has high and promising in structure of healthcare facility. Even though Pondicherry has high incidence of cervical cancer compared to neighbouring districts of Tamil Nadu [8,9].pap smear and VIA is the primary cervical cancer screening used to detect precancerous lesion and early-stage cervical cancer[10,11]. However, studies from Delhi (25%) and Tamil Nadu (29%) reported low level of willingness to go under pap screening[12,13].

A community-based pilot study on screening of cancer conducted under Tamil Nadu health system project suggests large proportion of women did not return for follow up and screening services represent the existence of other individual-, community- and health system level barriers such as lack of familial support, cancer-related belief, and inadequate referral systems, unpleasant experience with speculum examination. Study also stated that there is low acceptability of screening by women due to fear and inaccessibility [14]. Hpv testing has been shown to be more sensitive than pap smear exam [15]. Several evidences proved that self collection of sample for cervical cancer screening can increase the participation and follow up as well. Self-sampling also provides the feasibility in verity of setting such as home, workplace etc. Self-collected sample (where women collected sample by her own) for hpv testing have been found as sensitive as clinically collected sample[16].In the year 2020 world health organization recommended that self-collection can help to meet global target of 70% coverage of screening by 2030. Women may feel more feasible to collect their own samples, rather than going to visit a health worker for cervical cancer screening[17]. HPV vaccine has significant impact on prevention of HPV infection or prevention of cervical cancer as it was very well mentioned that HPV vaccine has prophylactic strategy for prevention of HPV-16 and HPV-18 sub-types of HPV infection (approximately all cervical cancer caused by these two sub-types of HPV infection) [18]. It has mentioned invariably that in-spite of huge alarming statistic about cervical cancer (21) including the fact that in India the private health facilities are the solo facilitator for providing HPV vaccination [18].India alone accounts for one-quarter of the worldwide burden of cervical cancers (Fig1). It is the one of the leading cause of cancer mortality, accounting for 17% of all cancer deaths among women aged between 30 and 69 years. It is estimated that cervical cancer will occur in approximately 1 in 53 Indian women during their lifetime compared with 1 in 100 women in more developed regions of the world [3].Cervix cancer estimated to be increased among females (fig.2), and highly increased in Asian countries (Fig 3). Cancer cervix mortality is remaining high among women, which was evident in a worldwide analysis mentioned that approximately 570000 case of cervical cancer and 311000 deaths from the disease occurred in 2018. India alone contributes 97000 case burden and 60000 deaths due to cervical cancer (Fig4). Study further interoperated that cancer cervix continue to be a major public health issue affecting women, the global scale-up of hpv vaccination and hpv based screening has potential to reduce the burden of cancer cervix or mortality and morbidity due to cervical cancer [21].Prevalence of cervical cancer is most common in rural population in India. Demographic factors also play a very important role. Adequate screening measures and health awareness activities are helping in cancer identification and adequate prevention of cervical cancer [22].Screening for cancer is plays important role to reduce mortality and morbidity by early detection and treatment. However, despite availability of various screening method for cervical cancer, women are not showing interest to participate in screening in regions where programme are available. Where programme are in place a major obstacle for women across many country and culture has been the requirement to undergo a speculum based pelvic examination, limited sources to care and lack of awareness about disease and preventive tools.With the emergence of HPV-based primary screening, the option of self-collection (where the woman takes the sample from the vagina herself) may overcome this barrier, given that such samples when tested using a PCR-based HPV assay have similar sensitivity for the detection of cervical pre-cancers as practitioner-collected cervical specimens. Other advantages of HPV-based screening using self-collection, beyond the increase in acceptability to women, it is feasible, invasive, involving and promising method to detect hpv [23].Cervical cancer is affected by socio-economic inequalities and health disparities across and within countries. While 81% of countries have cervical cancer screening policies and strategies, only 48% have an operational plan with funding. In many countries, a majority of women do not have access to screening services. Women aged 30 and above need to be screened regularly, as pre-cancerous lesions can take many years to develop. For some groups, including women living with HIV, screening should be done earlier, as soon as they know their HIV status and have been sexually active. When good services are available, women may not get screened regularly. Barriers include fear or shame, cultural or religious considerations, time in and distance to services [17].

A longitudinal descriptive design evaluated a community-based pilot study conducted in a rural setting (Tirunelveli and Tuticorin districts) in Tamil Nadu and reviewed the completion of care continuum.All women underwent conventional cytology-based screening (Pap smear) and Visual Inspection with Acetic Acid (VIA). Of 2192, 807 were eligible for referral. Among the 807 women referred, only 74 (9.2%) women visited the referral center. Study concluded that the follow-up rate was very poor accounting to portion of care continuum [24]. New methods are required to increase the uptake for screening. DNA testing for high-risk HPV (hrHPV) provides improved, more reliable identification of women with cervical pre-cancer and cancer than Pap (i.e., cytology) testing . For women who are not coming to the clinic for recommended screening, it has been shown that self-sampling for HPV testing (“self-sampling”) yields comparable results to HPV testing performed by a health care provider at the clinic. While passive strategies (e.g., sending the self-sampling kit in the mail) increase screening uptake, active engagement through a door-to-door approach by trusted individuals in the community yields greater screening adherence. Among un/under-screened women, women’s preference is also an important consideration [25]. Many evidence supports hpv testing as an alternative to the Pap test [26].The sensitivity of the hpv test is greater than that of the Pap test, detecting persistent hpv infections that can lead to cervical cancer for women. Molecular dna testing for hpv detects oncogenic hpv types that can cause cervical cancer and its precursors. The technology can also be used as part of a screening program in the form of a self-sampling kit for hpv that might be more appealing to under-screened and unscreened women in hard to reach, underserved populations. Study concluded that Self-collection has been shown to increase participation in never or under screened population [26]. Self-sampling is generally associated with increased participation of cervical cancer screening services: self-sampling nearly doubled the use of cervical cancer screening services and also it is seen as highly acceptable for its privacy, convenience, time and effort saved, cost effectiveness, ease, comfort (including decreased embarrassment, pain and anxiety), speed, safety and user-friendliness [17].

In this present scenario an effective vaccine against the high-risk strains of HPV shows great promise The combination of HPV vaccination and cervical screening can provide the greatest protection against cervical cancer, by reducing the risk of developing cancers caused by HPV at sites other than the cervix [18]. In this regards, ignorance, and less acceptability of screening as well as of vaccination is a big challenge in the prevention of the disease. In India many studies have either addressed knowledge, compliance rate of participant specially existing screening programmes or have been done in hospital or urban settings. Here, researcher found that self-sampling has potential to enhance the screening uptake but there are no proved evidences in this regard in India even though WHO has recommended self-sampling to increase the uptake for screening. Therefore, researcher thought to take up this research to understand the opinion and experience of self-sampling versus assisted sampling and non-compliance to hpv vaccine.

**Objectives and study design**

**Primary objectives:**

To assess the level of awareness, opinions and acceptance rate of self-sampling versus assisted sampling for HPV screening among women at selected villages of Puducherry.

**Secondary objectives:**

1. To compare the level of awareness regarding cervical cancer, opinions and prevalence of hpv infection with the acceptance rate of self-sampling Vs assisted sampling among women of selected villages of Puducherry.
2. To explore the level of experiences with acceptance of self-sampling Vs assisted sampling among women of selected villages of Puducherry.
3. To correlate the level of awareness regarding cervical cancer, opinions and experiences with acceptance rate for HPV screening in self-sampling versus assisted sampling technique.
4. To associate the level of awareness regarding cervical cancer and opinion for hpv screening with selected baseline variables.
5. To explore associations with the level of experiences, awareness regarding cervical cancer and opinions with non-compliance of HPV vaccine with their selected baseline variables.

**Data collection and participants**

The study will be conducted among women at selected villages of Puducherry (union territory). Data will be collected from the 80 women per group. This study will be divided in to two phase first phase will be quantitative followed by qualitative in second phase. This will be the subsequent phase. In-depth interviews will be conducted among women to explore the experience and non-compliance factors for hpv vaccination and for furthermore explanation focus group discussions will be conducted among health workers to elicit the factors for non-compliance of hpv vaccine. This outcome will make us to know ground realities of their cultural context, belief’s, values, attitudes, behavioral patterns and other factors of non-compliance of HPV vaccine among women of selected village of Pondicherry. The study contains two data collection Phases.

**Phase one study:**

**Step I**

Researcher will be selecting the sample as per inclusion criteria. Target women will get invitation to participate in the study. Prior to data collection written consent will be obtained from each participant. Further the researcher will collect the baseline information with the help of interview guide related to their demographic and obstetrics variable, along with information related to hpv vaccine coverage, awareness and opinion regarding cervical cancer and self sampling and assisted sampling screening technique respectively.

**Step II**

Insecond step of data collection researcher will conduct the sensitization pregame for both self sampling group and assisted sampling group. The sensitization programme will be provided by the researcher with the help of Power Point presentation which contains the content on definition of cancer, cervical cancer, signs and symptoms, complications, prevention measures, screening methods and hpv vaccination etc. Sensitization programme includes the need for self sampling, procedure for self sampling, advantages etc. for self sampling group and content regarding assisted sampling will be included for assisted sampling group. Further the leaflet will be distributed with the same content.

For self sampling group after sensitization programme, eligible women will be offer a cotton swab to collect sample from cervix. Women will collect samples in any private area. After taking Samples, it will be immediately placed in a plastic container (filled with preservative medium) provided by the researcher with a unique ID. Samples will store and transport by end of the day to the Laboratory for testing. After receiving the results back, it will be communicated to the health center of that village. Women who tested positive will be cautiously counsel and appoint for further screening for VIA for confirmation to the concern study village health center. The steps will be followed for self collection procedure for self sampling will be as fellow; hand Wash with soap and water, the cotton swab is inserted into the vagina and gently rotated for 10-30 second, the cotton swab is removed and transferred to a provided collection container and Container is sealed and labeled, Sample is sent to the laboratory.

For assisted sampling group after sensitization programme women will be informed to visit the health centre for screening test on any of 15 consecutive days. Assisted sampling will be done with the help of cotton swab for all participants who will visit the hospital and eligible for the procedure by the Researcher. All women who tested positive will counsel for VIA for confirmation.

**Step III**

HPV TESTING – HPV testing will be perform using the GeneXpert hpv assay for the swab samples of self sampling groups and assisted sampling group. Briefly, the Xpert hpv assay (Cepheid, Sunnyvale, CA, USA) is PCR amplification assay to detects the following hr HPV types: 16, 18/45, 31, 33, 35, 51, 52, 56, 58, 39, 66, 68 and 59 and sample adequacy control confirms that the samples contain sufficient amounts of cellular material for the test to be informative. The result will be intimated to the concerned health centres for further process.

**Phase** **two study - procedure for data collection (qualitative phase)**

Participants receive a verbal explanation of the objectives and general structure of the study. All the participants assured of confidentiality. Only willing participants and those who will give written informed consent will be included in the study. They will further apprised that participation will anonymous and they will have full right of withdrawal after reading the interview guide. During interviews, the researchers will encourage participants to express their views and experiences freely. For qualitative data collection the Researcher will conduct the structured open ended face to face in-depth interviews (IDIs) with the help of Interview guide, for twenty randomly selected women ten from self sampling group and ten from assisted sampling group to explore the experience regarding self sampling, assisted sampling and factors for non compliance to hpv vaccine etc.

**Data Analysis plan:**

Quantitative analysis will be conducted for the Descriptive statistics which will be explained in terms of percentages and proportions with chi square test for difference while inferential statistics will be used for the interpretation of any difference between level of acceptance and other parameters between the self-sampling and assisted screening techniques while appropriate descriptive statistics like Mean and SD and statistical tests viz., t test will be applied to estimate the significance. For all statistical purposes p value <0.05 will be considered as significant.

Qualitative analysis, Data analysis of the IDIs will be done inductively following the steps - free listing, domain identification, coding, and cross tabulation. The translations will be examined for emergent themes. The transcripts will be examined to identify relevant texts segments which will be summarized and labelled with a code. These codes will be then compared for identifying the connections between categories (axial coding) and grouped into fewer categories (selective coding). Categories with similarity will be further assembled under key themes. An effort will be made to minimize the bias by free listing, coding, category creation, and thematic analyses, and discrepancies will be resolved to minimize bias.

**Conclusion:**

The study provides a tool to study the level of awareness and training for self-sampling and assisted sampling for HPV screening plus providing awareness regarding Cervical cancer among women in Puducherry villages the study will gain beneficial outcome for women, villages and to the country plus it can be applied any where around the world. Benefits for women as they can find cancer cervix by early detection to get chance to treat before symptoms. If the cancer is already present, early detection due to screening women can get chance of better survival. Women screening status will improve and they will get chance to know about their own health status. Benefits to Villages as Reduction the prevalence of cervical cancer by early detection in selected villages. Project will provide the awareness regarding cancer cervix and hpv vaccination in selected villages. Less financial burden will be offered to women and their families as improving health screening of women will reduce the chances of cancer cervix. Benefits for the Country as the women mortality due to cervical cancer statistic will be reduced by early detection. Estimation the coverage of HPV vaccine and understand noncompliance factors. Work as formative research to develop preventive interventional packages based on non-compliance factors of HPV vaccine. Used to draft health protection scheme for prevention of cervical cancer for state and central government in addition to the women morbidity rate will be improved early identification and preventive treatment of cervical abnormalities and more women get chance to aware and screened.

**Funding:**

No funding got received

**Declarations:**

**Availability of Data and Materials**

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

**Conflict of Interest:**

The authors report there are no competing interests to declare.

**Trial Registration:**

Trial has been registered in clinical trial Registry- India, Trial number is CTRI/2022/09/045714

**Consent and publication**

Participant consent for study and publication will be obtained.

**Ethical Approval**

This study is authorized by the institute ethics committee, INDIRA GANDHI MEDICAL COLLEGE & RESEARCH institute (A Govt. of Puducherry institution) on 22/03/2022, no. 385 /IEC – 33 / IGMC&RI / PP-19 / 2022. The subjects will be asked for voluntary participation and written consent will be obtained before study.

**Author Contribution**

Ankita Jacob contributed in designing the work and collecting the literature and interpretation of data. Manjubala dash proposed the idea and supervised the work. Jeyastri Kurushev, Malar Vizhi and Felicia Chitra did reading and grammar checking of the manuscript.

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