Self sampling HPV testing as cervical cancer screening approach among women living in low-middle-income -countries: Systematic review and Meta-analysis.

Research submitted to: CDT-Africa, College of health sciences, Addis Ababa University on the partial fulfillment of master's program on clinical trials.

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Abbreviations/Acronyms

CHW: Community Health Workers

DNA: Deoxyribonucleic acid

GNI: Gross National Income

HIV: Human Immunodeficiency virus

HPV: Human papilloma virus

hr-HPV: High risk human papilloma virus

LMIC: Low and middle income countries

VIA: Visualization with acetic acid

PICO: Participant, intervention, comparative, and outcome

RCT: Randomized controlled trial

RR: Relative risk

RNA: Ribonucleic acid

WHO: World health organization

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Abstract

Background: More than 85% of cervical cancer deaths occur in low-middle-income countries, and 90% of the mortality burden is primarily attributed to low coverage of cervical cancer screening. Self-sampling HPV could increase the overall cervical screening and contribute to alleviating the burden of cervical cancer in LMICs (low-middle-income countries)

Objective: The general objective of this review and meta-analysis was to see if self-sampling HPV screening method can increase uptake of cervical cancer screening in low-middle-income countries.

Methods: CENTRAL (Cochrane Central Registry of controlled trials), MEDLINE (through PubMed), Clinicaltrial.gov, WHO Global Health Library, and EMBASE were searched. Reference lists of the relevant studies found were assessed to further search for relevant studies. The MeSH terms for HPV (MeSH (DNA Probes, HPV) (Human Papillomavirus DNA Tests)) and cervical cancer MeSH term (uterine cervical neoplasms) were found and as for the term self-sampling, there was no MeSH term found therefore method of text words/synonyms (Self-sampling, Self-collection, Self-obtained) for self-sampling was used. For the LMIC, LMIC filter prepared by Cochrane from all LMIC countries listed by World bank was used. Where multiple studies reported the same comparable outcome of interest, we conducted a metaanalysis. Random-effects models was used to generate pooled effect size of relative risk with a 95% confidence interval using Rev-Man 5.4.

Results: Six RCTs (randomized control trials) were included in this review. The studies were from Ethiopia, Kenya, Nigeria, Uganda, Argentina, and Mexico. These studies included a total of 39,274 participants with in the age group ranged from 25 – 65 years**.** All the studies compared an interventional group of HPV self-sampling method with a control group of a standard of care. HPV self-sampling was reported to be acceptable, and participants stated the device was easy to use and they would use HPV self-sampling instead of the regular hospital screening in the future. There were no adverse events associated with the self-sampling device. In the meta-analysis, uptake of cervical cancer screening services showed that the likelihood of participants to use self-sampling HPV screening method was 75% higher than with standard of care (RR: 1.72, 95% CI 1.58 to 1.87, I-squared: 72%) with insignificant I2, (*MODERATE* quality of evidence). However, there was no difference between linkage to care between the two groups (RR=1.18, 95% CI 0.77 to 1.81, I2= 87%) (*VERY LOW* quality of evidence).

Conclusion: Self-sampling HPV screening technique has the potential to increase the uptake of cervical cancer screening in LMICs, and is acceptable by women. Moreover, this technique helps overcome many barriers to cervical cancer screening in LMICs such as lack of trained personnel, lack of laboratory supplies, infrastructure, socio-religious and cultural barriers to pelvic examination, limited physical access to patient populations, and the need for spousal permission. As this can

reduce social inequalities in access to cervical screening, it helps alleviate the cervical cancer burden in LMICs.

1. Introduction

1.1. Background and literature review

Cervical cancer holds a third place as the most common cancer globally and the second common cancer in low-middle income countries. Over half million women were diagnosed with this cancer in 2018 and 311,000 of these women died from the cervical cancer. **(1)** More than 85% of cervical cancer deaths occur in LMIC, and 90% of the mortality burden is primarily attributed to low coverage of cervical cancer screening.**(2)** It is anticipated that LMIC will jointly account for more than 95% of deaths attributed to cervical cancer by 2030.(3)Cervical cancer incidence and mortality differ across LMICs. In India, 20.2/100000 new cases of cervical cancer are diagnosed with 11.1/100000 deaths yearly, and this accounted for more than one fifth of the global deaths from cervical cancer.(4) In sub-Saharan Africa, 34.8/100000 women are diagnosed with cervical cancer annually and 22.5/100000 women die due to cervical cancer. (5) A woman from Thailand has a roughly 58% chance of survival, while the one in India has a fifty percent chance;. survival is worse in Sub-Saharan Africa. Sub-saharan women have only 20% chance to survive from cervical cancer. (6)

Very few LMIC countries have been able to fully implement cervical cancer screening programs. For the program to be successful, different requirements need to be met, for instance, the program has to ensure wide coverage, guarantee adequate follow-up of patients, be of low cost, and most importantly with minimum infrastructure requirement.(7) In the Middle East and North Africa, screening based on VIA (Visualization with acetic acid) national program is being implemented.(8)And in India,a VIA population-based screening program has been established.(9)Nonetheless, regardless of these introducions of cervical cancer guidelines, screening in low-middle-income countries is still low.(7) Comparing the rates with developed countries, cervical cancer has shown a 70% decline in countries like the USA from 1955 to 1992.(3) However, the rate in LMIC either remained unchanged or even got worse in some places.(10) For

example, in East Africa and South Asia, cervical cancer remains the most common type of cancer in women and the number one cause of death.[11] Nevertheless, cervical cancer is a potentially preventable and curable non-communicable disease if diagnosed and treated early. However, poor access to prevention, screening, and treatment contributes to 90% of deaths, hence different interventional approaches to eliminate this cancer as a public health concern should be immediately implemented. [12]

Cervical cancer arises from a woman's cervix located at the entrance of the vagina. [2] Initially, there might be no symptoms but symptoms like abnormal vaginal bleeding, vaginal discharge, pelvic pain, or moderate pain during sexual intercourse might be seen later. [13] Most cervical cancer cases (99%) are linked to high-risk human papillomaviruses (HPV) infections. [2] Currently, HPV is the most common sexually transmitted infection, and it is estimated that 80% of women will be infected with this virus at some point in their lifetime. [14]. Of the 100 serotypes of HPV, 15 serotypes are recognized as high-risk HPV types (hr-HPV) and are responsible for HPV-related malignancy development. HPV 16 and HPV 18 cause the majority (70%) of cervical cancers and pre-cancerous cervical lesions globally, while HPV 31 and HPV 45 cause about 10% of cervical cancer. [15] Other risk factors of cervical cancer include cigarette smoking, long term oral contraception use, multiple pregnancies, HIV infection, immune system suppression, past or current Chlamydia infection, being overweight, having a first full-term pregnancy before age 17, poverty, and family history of cervical cancer. [16]

Cervical cancer is unique in that it is almost 100% preventable. This can be done by ensuring that young girls get vaccinated with HPV vaccines, screening women, and when identified treatment of precancerous lesions. WHO recommends age-appropriate, cost-effective interventions as an approach to the prevention and control of cervical cancer. These range from preventing the disease (primary prevention through vaccination), screening for pre-cancer (secondary prevention) and early cancer to diagnosis, early treatment of cancer, and palliative care. [18] Although prophylactic HPV vaccines as a primary prevention technique may be the optimal cervical cancer prevention strategy, 2-3 generations of at-risk women are already highly exposed to HPV and would not gain from the HPV vaccine. [19] At the moment, particularly in LMIC, cervical cancer is mostly diagnosed when the disease has progressed to advanced stages. Recommended screening methods should be able to detect pre-cancer and include HPV DNA testing, visual inspection with acetic

acid (VIA) as well as Cytology test. These tests are simple to conduct in resource-poor settings and the results can be available almost immediately, thus ensuring that women who test positive can be treated almost immediately. [7]

Cytology test has been the most common test utilized for identifying cytological changes associated with cervical cancer. It is also called a Pap smear. [20] Cytology screening is one of the most successful screening programs, mostly in developed areas, however, it has failed to achieve the same outcomes in LMICs.[7] One of the downfalls of implementing a cytology-based screening program is that it requires repeated testing and visits to detect who need treatment. Another one is, a cytopathologist, a colposcopy specialist and a pathologist should also be involved. To guarantee the success of a screening program, training and continuing education are essential.[21] Even if implementing a high-quality cytology program in these LMICs is possible, it would only be moderately effective. The reason behind this is, cytology test misses almost 50% of precursor lesions and cancers with a single screening test. [22] This would be hindering in LMIC settings because women would only be screened once or twice in their entire life. [7] Visual inspection using acetic acid is another screening method that is done with a few tools and the naked eye. It is done by applying, diluted white vinegar to the cervix, after which the health professional checks for abnormalities in the cervix. This screening method is very beneficial in areas with limited medical services. [19] However VIA also has some drawbacks for the visual interpretation of the cervix specially in older women. The reason for this is due to aging, there is degeneration of the cervical tissue causing lack of visibility of the transition zone. Moreover, several studies have shown that VIA sensitivity declines substantially in women aged 40 years and older.[23][24]Another screening method is HPV test which tests for the HPV strain commonly linked to cervical cancer. This is done on a sample of cells obtained from the woman's cervix or vagina, which makes it convenient for the woman to collect her own sample. [19] The greatest challenge of HPV testing used to be the need for expensive laboratory infrastructure and the hours of time to process the test. However, the development of rapid tests (care HPV,GeneXpert) for HPV detection has changed that situation, and this is a great success in cervical cancer screening in low-resource settings. [7] There is an existing limitation of HPV screening, and that is HPV test has low positive predictive value because it detects HPV infection and not directly cervical cancer. Therefore, a triage test after a positive HPV result may be necessary to limit the rate of false-positive and

consequently reduce the harm of overtreatment. Integrating HPV screening with a VIA triage test may offer the double benefits of HPV screening to maximize the detection and VIA for treatment triage of HPV-positive women. [7] After a positive result of the single or sequence screening, the available treatments include cryotherapy, LEEP/ LLETZ, and CKC.[15]

The World Health Organization has recommended HPV testing as an alternative to cytology-based screening in LMIC, given that these tests are more sensitive than cytology and visual inspection methods in detecting high-grade cervical intraepithelial neoplasia and cancer. [15] Several studies support that HPV testing is feasible in LMIC settings and can be the best strategy for cervical cancer. [25][26][27] In addition, a RCT in India showed that, a single round of HPV testing significantly reduced cervical cancer mortality low-resource settings .[28] HPV tests also have the advantage that vaginal samples can be collected by the woman herself, which may increase coverage. For this reason, HPV testing is an attractive substitute for cytology-based screening in low-resource settings. [15]

As defined by WHO, HPV self-sampling is a procedure where a woman uses a kit to collect a sample from her vagina/cervix and sends it for analysis to check whether she has HPV infection or not. There are different methods of collecting the sample such as a swab, lavage, brush, and vaginal patch. HPV self-sampling will not be a direct diagnosis for cervical cancer, however, it will detect the women who are at high risk.[15]Self-sampling could help remove socio-religious and cultural barriers to HPV screening and provide privacy and autonomy in LMICs without bargaining test performance and could reduce the total time required during a screen-and-treat visit. [29] The advantage of self-sampling HPV screening is that it doesn't require training personnel and infrastructure inorder to do a pelvic examination. This makes the standards for a good quality sample less rigorous with self-sampling HPV compared with cytology.[7] Some studies have reported that offering self-sampling HPV can improve uptake of a screening program. Several studies have also shown that the accuracy of self-sampling HPV versus health professional-collected screening is comparable for identification of precancerous and cancerous lesions.[30][31][32]

A randomized trial conducted in a low-income population reported that there was a significant difference in the uptake of self-sampling HPV compared to the health professional collected group (18% vs 2% $p \leq 0.001$).[33] Another randomized study conducted in the Netherlands reported that

uptake was higher in self-sampling HPV compared with the standards of care (34.2 vs. 17.6%; p<0.001). [34]This result was also reflected in a study done in Somalian immigrants in Minnesota, USA which reported that uptake was significantly higher in the self-sampling than in the health professional collected group (65.6% vs 19.4% p<0.001), though linkage to care after a positive result was low in both groups (41% in self-sampling group and 55% in health professional-collected group). [35] In a systematic review and meta-analysis on 29RCT and 4 observational studies conducted by the WHO in HPV self-sampling in high-income countries, it was concluded that women who used HPV self-sampling were twice likely to get screened and benefit from the service without any negative effect on linkage to care. [36]Different observational studies conducted in LMICs assessed acceptance of self-sampling using different questions; ease of use of the device, the comfort, privacy, whether they would recommend it to a friend if they felt relaxed while using it, and if they felt confident on doing the test properly. A significantly higher number of women gave positive feedback in favor of self-sampling, however, when it comes to their confidence of doing the test properly higher number of women reported that they would feel more comfortable with the results if it was performed by a health professional. [37][38][39][40][41]Some of these studies tried to examine the association of these preferences to education and age, although there was no significant association to age, they found a significant association with education stating that the women who reported less confidence towards their sample are the ones with lower educational level. [37][42][43]

1.2. Problem statement

Cervical cancer brings about a significant threat to women in LMIC and the conventional way of screening (VIA, health professional collected HPV and Cytology test) women at risk have not been practical nor has it been accessible for the majority of women leaving in LMIC.[15] In low-resource settings, various barriers to implementing cervical cancer screening programs exist. These include: lack of trained personnel, lack of laboratory supplies, lack of laboratory infrastructure, socio-religious and cultural barriers to pelvic examination, limited physical access to patient populations, and the need for spousal permission contribute to the avoidance of cervical cancer screening by women. [29]An alternative screening method is in need to address access challenges as well as personal barriers in women living in LMIC.

According to the WHO, HPV DNA screening is the recommended screening method in LMIC [(15)], and HPV self-sampling is found to be more acceptable as it overcomes personal barriers such as shame, embarrassment, and reluctance in letting a doctor see or touch their genitals.[(31)(46)]Self-sampling HPV has been shown to be a cost-effective and convenient method of increasing cervical cancer screening participation among the hard-to-reach population. [(45)] A systematic review in Africa done on HPV self-sampling to compare the diagnostic accuracy comparing self-collected with physician collected HPV showed high concordance. Other studies from other LMIC had the same findings. [(32)(46)] Several other studies have also reported that the majority of women who are underscreened and tested positive for HPV in a self-sampled test may have the potential to visit a clinic for follow-up. [(34)(47)]

HPV self-sampling has the capability to overcome the common barriers to accessing cytology in LMICs. Self-sampling, in particular, can eliminate the need for a pelvic examination, infrastructure, and a trained health professional.[(48)] This strategy can potentially be highly advantageous to hard-to-reach and rural populations which have limitations in transportation services and distant health centers. [(49)] Therefore, this method of screening has the potential to increase uptake and improve access to screening in LMIC, specifically among underscreened women. [(48)] Because of the above, HPV self-sampling might reduce social inequalities in access to cervical screening services and contribute to alleviating the burden in LMIC.

1.3. Significance of the study

Based on a systematic review and meta-analysis on 29RCT and 4 observational studies conducted by the WHO on HPV self-sampling, it was concluded that women who used HPV self-sampling were twice likely to get screened and benefit from the service without any negative effect on linkage to care.[(50)(51)] However, this study was conducted mainly in high-income countries (93%), and hence is not representative of LMIC.HPV self-sampling is a promising strategy to overcome the multiple barriers to cervical cancer screening in low-resource settings. However, it is still unclear if this method will be suitable for LMIC settings. Therefore a systematic review and meta-analysis on HPV self-sampling need to be conducted in LMIC to assess its benefits on cervical screening. The study aimed to review the existing

randomized controlled trials on HPV self-sampling in LMICs and reach a consensus on their results whether it can potentially increase uptake of cervical cancer screening and linkage to care for positive results in women living in LMIC as opposed to the standard of care. The findings of this study will benefit researchers who want to further investigate the feasibility of HPV self-sampling in LMIC. This will also benefit policymakers in making evidence-based decisions regarding cervical cancer screening.

1.4. Objective

1.4.1. General objective

The general objective of this review and meta-analysis was to see if the self-sampling HPV screening method can increase uptake of cervical cancer screening in LMICs.

1.4.2. Specific objectives

- To compare the uptake of cervical cancer screening with HPV self-sampling with that of the standard of care
- To compare the linkage of care after positive screening result of HPV self-sampling group with the standard of care group.
- To evaluate the acceptance of self-sampling HPV
- To examine any adverse event associated with the screening device.

1.5. Operational definitions

- **Uptake**: From the women offered self-sampling HPV or other screening services, the proportion who accepted and completed screening.[50][51]
- **Linkage to care**: Among people who have a positive test result, the proportion who reach the next stage of management (treatment or recommendation). [50][51]

- **Self-sampling**: a woman takes her HPV sample using a sampling device and puts it in a plastic bag as directed and then it is taken for laboratory analysis.**(15)**
- **An adverse event**; is any pain or discomfort associated with the device of screening. (50)(51)
- **Acceptance:** It addresses after the screening, how the participants perceive the screening method. (50)(51)
- **Standard of care:** cervical screening by cytology, VIA testing services, health professional-collected HPV testing other than self-sampling. (50)(51)
- **Health professional-collected:** Sample for cervical cancer screening for standard of care collected by a trained nurse or a physician in a clinic or hospital. (50)(51)
- **Prior sensitization:** health education given on cervical cancer and the relationship of HPV to cervical cancer give to both arms
- **No prior sensitization**: only instructions on self- collection methods are given, no health education given.
- **Opt-in:** is a kit dissemination approach whereby the women takes the initiative to visit a nearby clinic or any health service providing site or takes the request for a self-sampling kit by mail, phone or website after randomization.
- **Opt-out:** is kit dissemination approach whereby a self-sampling kit is offered door-to-door to women by a health worker (this could be be a nurse, CMH or health volunteers) or is sent by a regular mail to the women after randomazation**.**
- **Community health workers:** sometimes refered as outreach workers, can be regular employees or volunteers that have assisted in the study by approaching, instructing or sensitizing eligible participants.

2. Methods

We followed the PRISMA-P(Preferred Reporting Items for Systematic Reviews and Meta-Analyses)2015 guidelines for the design and reporting of the results.**(52)** **Prospero Registration:**Hanna Amanuel Tesfahunei, Dr. Yimtubezinash Woldeamanuel and Prof Eyasu Makonnen: Self-sampling HPV testing as cervical cancer screening approach among women living

in low-middle-income -countries: Systematic review and Meta-analysis. In the process of registration. Prospero ID 238752.

2.1. Eligibility Criteria

2.1.1. Inclusion criteria

The studies should

(1) Have a compared women who screened with self-sampling HPV with women who screened with standard of care (cytology, VIA testing services, health professional-collected HPV testing)

(2) Evaluate one or more of the outcomes listed below,

(3) Be from low-middle-income countries listed by World Bank.

(4) Written in English

PICOS

Population: Women in LMIC

Intervention: Cervical screening with HPV self-sampling.

Comparison: Cervical screening with the standard of care (cytology, VIA testing services or health professional-collected HPV testing.)

Outcomes

Primary outcome

- Uptake of cervical cancer screening services

Secondary outcomes

- Linkage to care after positive diagnosis.
- Acceptance of screening.
- Adverse event associated with intervention (device-related harm)

Study design: Randomized controlled trial

2.1.2. Exclusion criteria

(1) Studies not published by peer-reviewed publisher or not yet published

(2) Studies lacking adequate methodologcal information.

(3) Studies that compared different modes of intervention in self-sampled HPV and didn't compare it to the standard of care.

N.B. No restriction was made on the date of publication to not lose relevant studies.

2.2. Information source and search strategy

In the attempt to answer our research question on HPV self-sampling, the following electronic databases were searched for journals: EMBASE, CENTRAL (Cochrane Central Registry of controlled trials), Clinicaltrial.gov, MEDLINE (through PubMed), and WHO Global Health Library. Search strategies that incorporate the population, intervention, and study design were developed in a way that keeps the balance between sensitive and precise searches. For MEDLINE (PubMed), search term was created in the "PubMed Advanced search" and MeSH (Medical Subject Headings) and text words (synonyms and related terms) were used to come up with the search terms. The MeSH terms for HPV (MeSH (DNA Probes, HPV) (Human Papillomavirus DNA Tests)) and for cervical cancer MeSH term (uterine cervical neoplasms) were found and as for the term self-sampling, there was no MeSH term found therefore method of text words/synonyms (Self-sampling, Self-collection, Self-obtained) for self-sampling was used. For the LMIC, EPOC LMIC filter prepared by Cochrane[56] from all LMIC countries listed by World bank [55] was used. From the EPOC filter options, we used the one that picks up records with the search terms in title, abstract, author keywords, MeSH, and non-MeSH keywords. Boolean operations were used in between to come up with our search term. The full search term is attached as Annex. Filters were put in Randomized controlled trials and Clinical trials. This search term generated was then pilot tested. For journals with limited search power, so as not to lose relevant studies, the following search terms were adapted: "HPV-screening developing countries", "papillomavirus AND self-collected OR self-test AND LMIC"; or "self-sampling HPV in LMIC." The term "Retracted publication" was added to the

terms to search for errors and retractions in the included studies. Reference lists of the relevant studies found were assessed to further search for relevant studies.

2.3 Study Selection

ENDNOTE software version X7 was used to import and filter the duplicates of the included studies. After initially screening the title and abstract obtained the full text of the potential articles, and relevant articles were retrieved and assessed further. Two reviewers assessed all full articles independently for study inclusion using the eligibility set above and settled any differences with a third responsible author through consensus. The study selection process is shown in figure 1. The final selected studies were then coded as "*name of the main author, et al (to mean 'and others'), year of publication*".

2.4. Data extraction

Two reviewers extracted data and conducted the quality assessments independently and settled differences with a third responsible author through consensus. Standardized data extraction forms including fields for study location, population setting (rural, urban), population characteristics, description of the intervention and control used, type of self-sampling device used, study design, sample size, reported outcomes, results, and inclusion and exclusion criteria used in each study prepared in Microsoft Excel was used for data extraction.

2.5. Risk of bias in individual studies

The Cochrane Collaboration's tool (ROB version 2) was used to assess risk of bias in individually randomized and cluster-randomized studies. [53] Two independent authors (DG and ED) reviewed it and resolved disagreement with a third responsible author (HAT). The ratings were "high risk", "unclear risk", and "low risk". The studies with at least one domain with a high risk of bias were considered "high-risk study" and a study with all its domains with low-risk bias was considered

"low-risk study". The risk of bias assessment was performed on the Rev-Man version 5.4 software and was presented in the risk of bias graph (Figure 2), summary (Figure 3), and also tables presenting each reasoning behind the judgement of each domain in each study (Table 2 in Annex section) .

2.6. Summary measure

The Meta-analyses was performed by computing relative risk (RR). The relative risk of the outcomes was presented along with a 95% confidence interval.

2.7. Method of analysis

The primary outcome of interest is the uptake of cervical cancer screening service defined as the proportion offered self-sampling HPV testing or standard screening who accepted and completed screening. We took the authors' reported proportion data on screening participation, attendance, response, and compliance on both the interventional (self-sampling HPV) group and the control group (using other methods for screening). For the outcome linkage to care, the proportion who reached this next stage of management after positive result were taken. As for the adverse event and acceptance, we took data on reported harm related to the device and reports describing acceptance by participants respectively. Where multiple studies reported the same comparable outcome of interest, we conducted a metaanalysis. Random-effects models was used to generate pooled effect size of relative risk with a 95% confidence interval using Rev-Man 5.4. The Cochrane Handbook for Systematic Reviews of Interventions was followed in the interpretation of the result [(54)]. All of the studies that conducted a cluster randomized trials used statistical analysis to appropriately adjust for clustering. Intention-to-treat data were taken and all the studies analyzed and reported intention-to-treat.

2.8. Risk of bias across studies

Publication bias could not be assessed as the number of studies was too low. However, the risk of bias across studies was assessed with selective reporting within studies.

2.9. Additional analysis

2.9.1. Heterogeneity

Heterogeneity was assessed using I-squared statistics and results were interpreted using the Cochrane Handbook Version 6.1.[54]

2.9.2. Subgroup analysis to investigate heterogeneity

Subgroup analysis was done to investigate the cause of heterogeneity in the uptake of cervical cancer screening services. Therefore conduct subgroup analysis on:

1. **Settings:** to compare "low-income countries", "lower-middle-income countries" and "upper-middle-income countries" to see if there is a significant difference in uptake and linkage to care by HPV self-sampling cervical screening between the two economically different regions.
2. **Prior sensitization:** Subgroup analysis was also done to assess if there is a significant difference between the group which had prior sensitization on cervical cancer and HPV infections and the ones that had no prior sensitization.
3. **Opt-in and Opt-out:** Subgroup analysis was done to assess if there is a significant difference between these two different approaches of getting self-sampling kits.

- Subgroups number 1 and 2 were both prespecified in the protocol, however, subgroup number 3 was a posthoc analysis**.**

2.9.2. Influence case and outlier analysis

To further investigate the between-study heterogeneity that may be caused by studies with extreme effect sizes (outliers) that did not quite fit in or if there were one or more studies heavily influencing the pooled result and hence majorly contributing to heterogeneity (influential case), outlier and influence case analysis was done. And then the heterogeneity was observed if it significantly shrinks after the removal of the outliers and the influential cases. This was performed using R-studio version 1.4.

2.9.3 Sensitivity analysis

Sensitivity analysis was conducted by influence analysis to explore the robustness of the meta-analysis results using the leave-one-out method. This method recalculates the results of the meta-analysis, each time leaving out one study. This was performed using R-studio version 1.4. Excluding

and including the study to check if there is a significant impact on the risk of bias and to check the effects of missing data was assessed using Rev-Man 5.4.

2.10. Certainty assessment

Two authors independently assessed the certainty of the evidence and resolved disagreement with a third responsible author. Five GRADE considerations: Study design, risk of bias, inconsistency of effect, indirectness, imprecision, and publication bias were used to evaluate the certainty of the evidence relating to the studies contributing to the meta-analysis of the outcome of interest. The certainty of evidence was assessed as high, moderate, low, very low recommendation in section 8.5 and 8.7 of chapter 11 and 12 of Cochrane Handbook [(54)] was followed throughout this assessment. GRADEpro GDT software was used in preparing a Summary of findings tables). An explanation was given for the judgments made. (Table 5, annex section)

3. Results

3.1. Study selection

Database searches retrieved 84 citations. Secondary searching retrived additional 11 citations (Figure 1). After removing duplicates, there were 64 unique citations. After an initial screening of titles and abstracts, 18 citations remained for full-text review. Of those, 6 studies were included in this review and meta-analysis. [(57-62)]

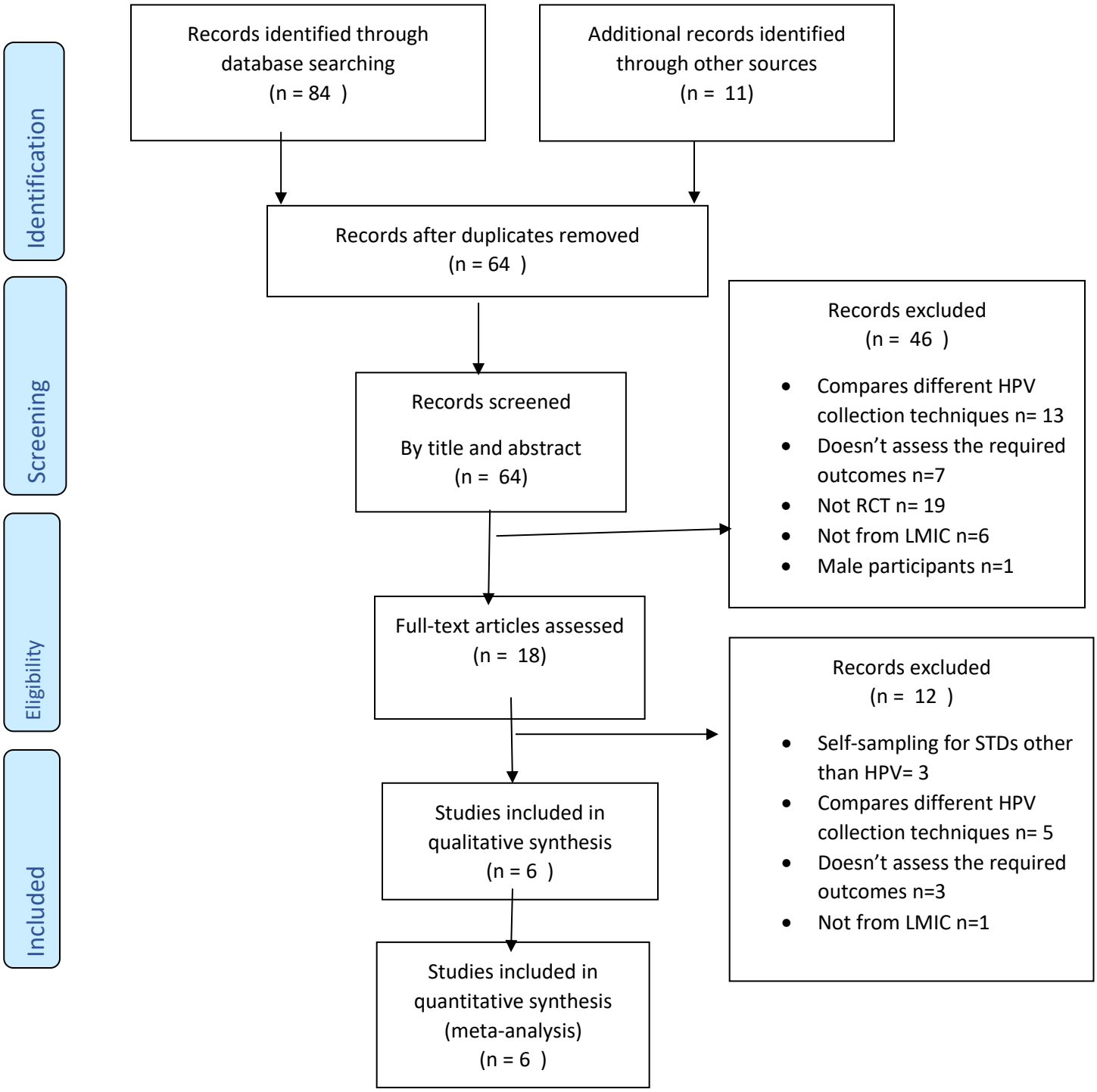

Figure. 1 Prisma Diagram: Study Selection process.

Table 1. Study characteristics of included studies

Author, Year	Characteristics	Sample size (in each group)	Intervention information	Methodology	Inclusion criteria	Exclusion criteria	Study Outcome
Gizaw et al, 2019 (57)	**Ethiopia, Rural and Urban** Population, Women around Butajira vicinity **Age: 30-49**	2356: Intervention arm: 1213 Control arm: 1143	**Intervention**: HPV self-sampling in the primary health care unit at their vicinity in a private area under active **Supervision** by a trained health professional **Prior Sensitization** on cervical cancer and HPV and instruction on self-sampling given. **Device**: Evalyn Brush (Rovers) **Specimen:** not specified **Control**: Standard of care: Butajira hospital for Health professional collected VIA screening. **Opt-in approach**	Cluster RCT Study: 22 clusters Randomization: 1:1	Age: 30-49 - Never been screened before	Women were excluded if they were pregnant, actively bleeding, had a previous hysterectomy, and refused to give consent before the screening.	**Uptake** and **Linkage to care**
Huchko et al, 2018 (59)	**Kenya**, **Rural setting**, women residing in Migori, western Kenya **Age, 25-65**	4944 intervention arm= 2898 control= 2046	**Intervention**: HPV self-sampling screening was offered in tents around villages Under **supervision** of community health volunteers (CHV). Self-screening **instruction** given by CHV **Prion sensitization** on cervical cancer and HPV. **Device**: not mentioned **Specimen**: Vaginal **Control:** Standard of care: Health professional- collected HPV screening was offered at government health facilities in Migori. **Opt-in approach**	Cluster RCT: 12 clusters. Randomization: 1:1	Individuals: women aged 25–65 years living in Migori County who had an intact uterus and cervix Communities: with at least one governmental health facility with the capacity to offer HPV testing and has support from community leaders for community outreach.	Individuals: women from urban settings. Communities: near Migori County hospital(Is considered Urban setting)	**Uptake** of screening, **Acceptance** and **linkage to care**.

Modibbo et al, 2017 (**58**)	**Nigeria**. **Semi-urban**. Women residing in Karu **Age: 30–65.**	400 intervention: 200 control: 200	**Intervention**: HPV self-sampling kits were mailed to participant's home **Unsupervised**. Collected at home. **Prion sensitization;** health education on cervical cancer, its risk factors**.** **Device**: Dry flocked Swab. **Specimen**; Cervicovaginal **Control**: Standard of care: Health professional- collected HPV testing appointment at hospital clinic. **Opt-out approach**	RCT.	Inclusion criteria were women aged between 30 and 65 years, living or working in Karu who do not plan to move out of the community over the next 6 months.	Pregnant, planning to relocate within six months, HIV positive, had unexplained cervical bleeding, history of hysterectomy, mental illness or cervical cancer from the study.	**Uptake** of HPV testing services and **Acceptance**.
Moses et al, 2015 (**60**)	**Uganda.** **Semi- urban**. Women residing in Kisenyi near Kampala **Age: 30–65**.	500 intervention: 250; control 250.	**Intervention**: HPV self-sampling. Women Were asked by the outreach worker to collect and provide specimens immediately where they were recruited, either in their home or in a private area in their place of work. **Instruction**, how to self-collect a vaginal specimen using a standard script and diagram by the outreach workers. **No prior sensitization** **Unsupervised**. At work place or home up on recruitment. **Device**: Dacron swab. **Specimen;** Cervicovaginal **Control**: Standard of care: Health professional-collected VIA, Screened in Kisenyi healthcare center **Opt-out approach**	RCT	Age between 30 and 65 years of age, lived or worked in Kisenyi, and had access to a mobile telephone. And who had an intact uterus and cervix.	Excluded if they had a previous hysterectomy or cervical cancer, if they did not meet the eligibility criteria or if they were unable to give consent	**Uptake of screening and Linkage to care**

Arrossi et al, 2012 **(61)**	**Argentina.** Jujuy, Women: 30 - 65	6013: Intervention: 3049 Control: 2964	**Intervention: self-sampling HPV** kit were offered by CHW in home visit. **Cervical specimen Unsupervised**. **Device:** Qiagen test kit **Prior sensitization**: the CHWs explained the aim of the study, And educated the women about cervical cancer prevention and HPV testing **Control:** Standard of care: Health professional-collected HPV test **Opt-out approach**	Study design: Cluster RCT. Randomization: 1:1 Study name: EMA study	30 -75: living in a household that is visited by community health workers.	Excluded if they had treatment for premalignant or malignant disease; they had a previous HPV test; a hysterectomy; were pregnant, or had a mental illness.	**Uptake of** screening services ,**Linkage to care**
Lazcano-Ponce et al, 2011 **(62)**	**Mexico.** Participants came from **rural** communities in Morelos, Guerrero, **Women** Age: 25–65.	25 061 intervention: 12 330; Control: 12 731	**Intervention: HPV self-sampling** kit offered at home by a nurse. **Vaginal specimen Supervised**.by nurse **No prior sensitization** **Device**: Digene conical-shaped brush **Control:** Standard of care: Health professional-collected cytology test at the nearest health center **Opt-out approach**	RCT.	Women aged 25-65, living in the medically underserved predominantly rural area in Morelos.	Exclusion criteria were previous hysterectomy and current pregnancy.	**Uptake** of screening services. **Adverse events**.

3.2. Study characteristics of included studies

Table 1 presents the summary characteristics of the six included articles. The studies were from Ethiopia [57], Kenya [59], Nigeria [58], Uganda [60], Argentina [61], and Mexico [62]. The studies included a total of 39,274 participants, with individual study sample sizes ranging from 400 – 25,061 and the age group ranged from 25 – 65 years. The majority of the women in the studies fell under the age group 30-39 years. The articles were published between 2011 and 2019, with the latest published in Ethiopia, Gizaw *et al* [57].

The studies had different settings: Gizaw *et al,* [57] and Arrossi *et al,* 2012 [61] both enrolled from both urban and rural, where Gizaw *et al* [57] enrolled majority (86%) from a rural setting and Arrossi *et al* [61] enrolled majority (85%) from an urban setting; Modibbo *et al* [58] and Moses *et al* [60] enrolled from semi-urban settings that were both near the city capital of their countries but with impoverished lifestyle; and Huchko *et al* [59] and Lazcano-Ponce *et al*, [62] enrolled only from rural settings. According to the World Bank classifications[55], studies by Gizaw *et al*, [57] and Moses *et al* [60] are classified as low-income countries; those by Modibbo *et al,* [58] and Huchko *et al* [59] are classified as lower-middle-income countries and Arrossi *et al* [61] and Lazcano-Ponce *et al* [62] are classified as upper-middle-income countries. Huchko *et al* [59]' study was conducted in a setting with the highest prevalence of HIV (15%) in Kenya and a higher prevalence of HPV among HIV-positive women. And on this study, women living with HIV were more likely to prefer the HPV standard of care sampling than HPV self-sampling (38% vs 25% $p < 0.001$). This was similar in Uganda, Moses *et al* [60], where women who were HIV positive and had chronic disease were more likely to attend standard of care compared to HPV self-sampling. Arrossi *et al* [61] conducted the study in Jujuy, a province in Argentina that had the highest mortality rate from cervical cancer and despite its continuous screening promotions, screening coverage was only 50% in this area.

The included studies had different methods of randomization. Gizaw *et al* [57] and Huchko *et al* [59] first divided their study villages into community clusters and randomized these clusters to either interventional group or control group. Community mobilization was conducted in each cluster by health extension workers (Gizaw *et al,* [57]) or community health volunteers (Huchko *et al* [59]). The clusters in the interventional arm were given self-sampling instructions, while those in the control group were informed to go to the nearby health facility for health professional sampling. In a study conducted by Arrossi *et al* [61] community health workers, who were each in charge of several

households for health-related visits were considered clusters and hence randomized as clusters. These CHWs who were trained on cervical cancer prevention and HPV testing, then identified eligible women upon their routine home visits, sensitized them, and obtained written consent from the individuals. CHW assigned to the intervention group offered the women self-sampling HPV with instruction and those assigned to control advised the women to go to any of the 270 provincial health centers and got screened by the standard screening method, which is a health-professional-HPV test. As for the Modibbo *et al* [58] study, they invited all women 30-65 to the king's palace and gave information on the research on cervical cancer and risk factors. And after consenting, the women were assigned to the intervention and control groups. In women randomized to the intervention arm, HPV self-sampling kit along with instructions was directly mailed to their home address, and those assigned to the standard of care group were appointed to visit the clinic. In the Moses *et al* [60] study, outreach workers approached women in their homes or places of work, invited them to participate in the study, and upon getting consent, they were randomized on spot. Those women randomized to the self-sampling group were given a Dacron swab and instructed on how to use it, and they provided specimens in a private room immediately at the place where they were recruited. And those who were randomized to the VIA arm were scheduled a date to attend the health unit to undergo VIA for screening. Participants were provided a reminder phone call the day before their scheduled visit. In Lazcano-Ponce *et al* [62], the participants came from 540 medically underserved rural communities in Morelos, Mexico. The population in the community was then randomized into intervention and control groups. The women in the intervention group were instructed by a nurse on self-sampling and the sample was then taken by the nurse, and those in the control group were told to visit the nearest clinic for cytology.

Two of the studies (Gizaw *et al* [57]) (Huchko *et al* [59]) used the opt-in approach where participants went to the nearby center to get their self-sampling kit and the rest four studies used the opt-out approach where the self-sampling kit was offered to participants door-to-door by CHW (Moses *et al* [60])(Lazcano-Ponce *et al* [62])(Arrossi *et al* [61]) or where kits were mailed to the participants(Modibbo *et al* [58]). The studies also had different approaches on the way they communicated the results to the participants. Modibbo *et al* [58] and Moses *et al* [60] used participant's phone to communicate their results via phone call and text messages, however on the control group of Moses *et al*, [60], participants were told of the result and treated if needed on the same visit following screen-and-treat policy. Participants in the Gizaw *et al* [57] and Arrossi *et al*

[61] studies were informed to visit the health center to get their results and participants in Lazcano-Ponce *et al* [62] were visited by the nurses for their results. Participants in Huchko *et al* [59] had all the options mentioned in the above studies, participants had the option of text message, phone call, clinic visit and if not comfortable with these options, a home visit by CHW was another option. Participants in the HPV self-sampling group from Gizaw *et al* [57] and Moses *et al* [60] who had positive results underwent VIA triage before treatment with cryotherapy, those with unsatisfactory VIA or lesion inappropriate for cryotherapy underwent further colposcopy then treatment. However, participants who were positive in the self-sampling group in Huchko *et al* [59] and Modibbo *et al* [58] didn't undergo triage, they were referred directly to treatment. This was similar in Arrossi *et al* [61] and Lazcano-Ponce *et al* [62] studies, where the participants didn't undergo triage with further screening, however, these participants who were HPV positive underwent colposcopy examination before treatment.

3.3. Risk of Bias in the included studies

3.3.1. Random sequence generation (Selection bias)

All six included studies had a low risk of bias in this domain as a random component was used in the sequence generation process. All included studies generated their random sequence using different software-generated random allocation which was described adequately. A computer-generated random number list was used in Modibbo *et al* [58] , Lazcano-Ponce *et a* [62], and Arrossi *et al* [61]. others also used different software such as research randomizer software (Gizaw *et al* [57]), SAS (Moses *et al* [60]), and Stata/MP (Huchko *et al*[59]). Details of the types and versions of the software used for generating a random number is shown in table 2 in Annex section. The risk of bias is shown in figures 2 and 3.

3.3.2 Allocation concealment (Selection bias)

Four of the included studies by Arrossi *et al* [61], Gizaw *et al* [57], Moses *et al* [60], and Huchko *et al* [59] were judged to have a low risk of bias on allocation concealment. Moses *et al*, [60] mentioned

that allocation was recorded on cards, which were concealed in an opaque envelope and kept in a locked cabinet. Arrossi *et al* [61], Gizaw et al [57], and Huchko *et al* [59] conducted cluster RCT, and they randomized their clusters at the same time; therefore, allocation concealment was not an issue and hence they were labeled as low-risk of bias. In Lazcano-Ponce et al [62], it was stated that the nurses visiting the participants were concealed of the random allocation, however, there was no further information to judge if the concealment was appropriate and hence was labeled as unclear risk. Modibbo et al [58] did not mention their attempt to conceal the allocation and hence was labeled as unclear-risk. However, there were no significant baseline differences between intervention groups to suggest a problem with the randomization process in both Modibbo *et al* [58] and Lazcano-Ponce *et al* [62] studies that had unclear risk. Detailed information of this allocation concealment process on the individual studies is shown in Table 2 in the Annex section.

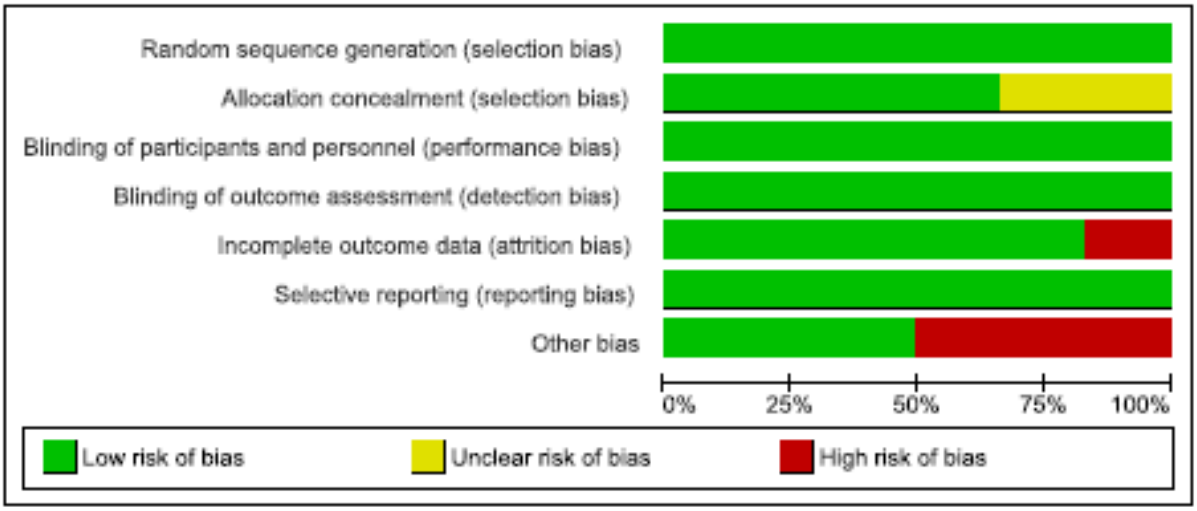

Figure 2: Risk of Bias Graph

3.3.3 Blinding of participants and personnel (performance bias)

Due to the intervention of interest, blinding the participants was not possible as participants had to be aware of the intervention they were to use. However, the outcomes measured were not likely to

be biased by the absence of blinding as uptake and linkage to care were measured as the number of kits sent to laboratory and medical records.

3.3.4 Blinding of outcome assessment (detection bias)

Blinding of outcomes assessors was not possible given the type of intervention, and this also was not likely to cause bias as outcomes were measured as the number of kits sent to lab and medical records.

3.3.5 Incomplete outcome data (attrition bias)

All included studies except that of Moses *et al* [60] had no missing data on the outcomes of interest and hence were judged as low-risk of bias in this domain. But Moses *et al* [60] had 53% missing individuals in the second outcome assessment of linkage to care on the HPV self-sampling group and was judged as high-risk of bias.

3.3.6 Selective reporting (reporting bias)

All four studies reported outcomes that were pre-specified in their protocol registered in Clinicaltrial.gov and had a low-risk of bias.

3.3.7 Other bias

There was potential recruitment bias detected in studies that had clusters as their unit of randomization [61], [57] [59]). Therefore this can lead to recruitment bias as they were recruited after knowledge of which cluster was the intervention group and which was control. Hence they were labeled as “high risk of bias”. In addition, it’s good to note that there was also a significant baseline imbalance despite randomization in Huchko *et al* study [59]. However, there was no significant difference in

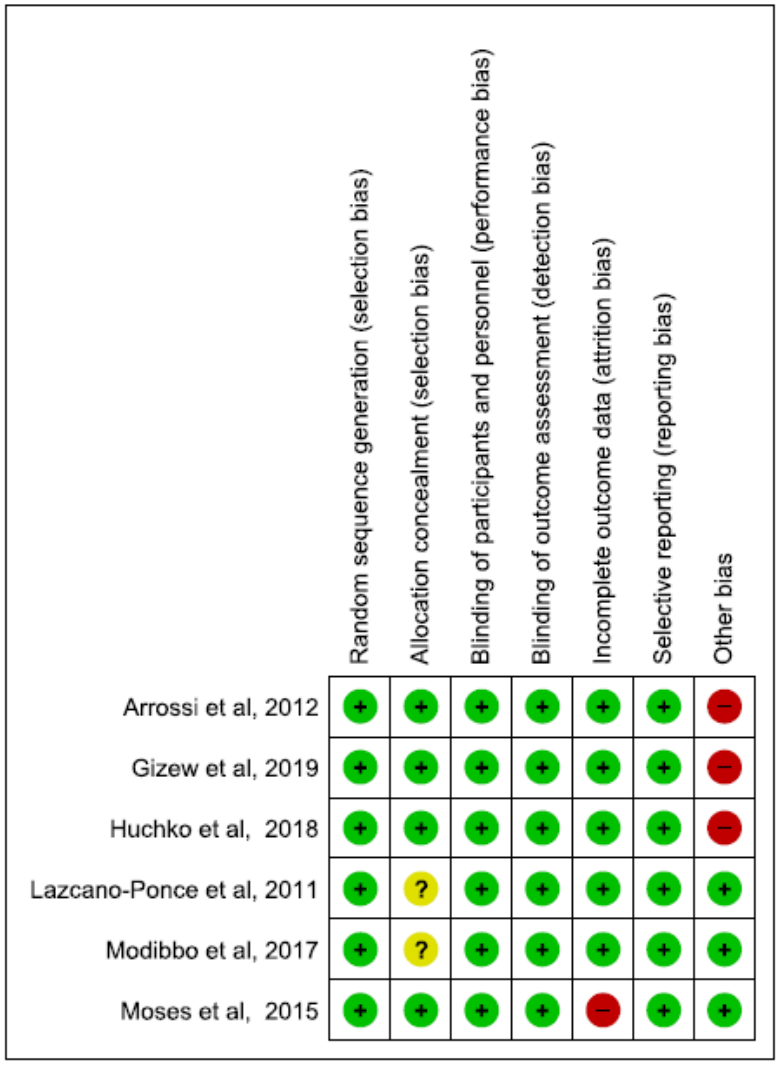

Figure 3: Risk of Bias Summary

Arrossi *et al* [61] and Gizaw *et al* [57] suggest a problem with the randomization process. All studies mentioned that the funder had no role in any study procedures and studies appear to be free of other biases. Hence the rest three studies by Modibbo *et al* [58], Lazcano-Ponce *et al* [62], and Moses *et al* [60] were judged as low-risk in this domain.

3.4 Results of individual studies

3.4.1 Uptake of cervical cancer services

All six included studies reported uptake proportions. Results of uptake of cervical cancer services on self-sampling HPV group and standard of care from the individual studies are presented in table 3. The effect estimate and its precision (95% confidence interval) are shown in Figure 4.

Table 3: Uptake of cervical cancer screening in individual studies

Uptake	Self Sampling HPV			Standard of care		
Studies	total n	uptake(proportion)	%	total n	uptake(proportion)	%
Gizew et al 2019	1213	1020	84.10%	1143	575	50.50%
Modibbo et al, 2017	200	185	93%	200	113	57%
Moses et al, 2015	250	248	99.20%	250	121	48.40%
Huchko et al, 2018	2898	1739	60%	2046	757	37%
Arrossi et al, 2012	3049	2618	85%	2964	599	20%
Lazcano-Ponce et al, 2011	12330	11812	95%	12713	8444	66.40%

3.4.2 *Linkage to care*

Four of the included studies reported linkage to care after positive results. Results on linkage to care on self-sampling HPV group and standard of care from the individual studies is presented in table 4, The effect estimate and its precision (95% confidence interval) is shown in figure 10.

Table 4: Linkage to care of individual studies

Linkage to care	Self Sampling HPV			Standard of care		
Studies	+ve result	linkage (proportion)	%	+ve result	linkage (proportion)	%
Gizew et al 2019	144	122	84.70%	22	5	22.70%
Moses et al, 2015	73	33	45.20%	16	12	75.00%
Huchko et al, 2018	567	222	39%	476	150	32%
Arrossi et al, 2012	298	238	80%	26	19	73%

3.4.3 Acceptance of self-sampling HPV screening

Two studies reported outcomes on acceptance of the screening method [58] [59]. In Modibbo *et al*, study [58], most of the women (95.2%, 177/185) found the self-sampling device easy to use, and 95.7% (177/185) stated it was convenient. In the present study, 83.2% (154/185) reported that they

would prefer self-sampling and 9.2% preferred health professional collected screening. The reason behind the majority who preferred self-sampling was comfort, 87% (134/154), privacy, financial convenience, less embarrassing , and a sense of independence. Self-sampling HPV was also accepted in Huchko *et al* [59] study, 99.1% (2872) said they would test again via self-collection and 99.4% (2881) said they would recommend testing via self-sampling to a friend.

3.4.4 Adverse event

This outcome was reported in one study only [62]. This study stated that after routinely collecting safety data on the participants, there was no adverse event associated with self-collection of vaginal samples.

3.5 Synthesis of results

3.5.1 Meta-analysis: Uptake of cervical cancer screening services

All the studies included in the review reported uptake as from those offered self-sampling HPV or standard of care, the proportion that accepted and completed screening. Self-sampling HPV in the intervention group and standard of care (either health professional - collected HPV or VIA) in the control group were compared in assessing uptake. The result of the meta-analysis of the six RCTs has substantial heterogeneity (RR: 1.95, 95% CI 1.39 to 2.75, I-squared: 100%), and we could not rely on this pooled result. Therefore it is better to consider the individual results of the included studies and it's good to note that all of the included studies are in the same direction in favor of self-sampling HPV, with RR above one. (Figure 4)

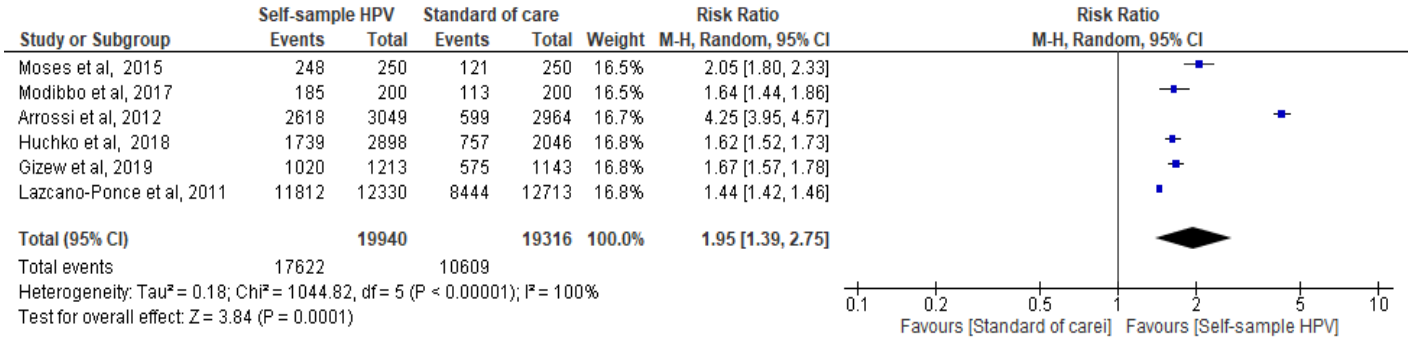

Figure 4: Meta-analysis: Uptake of cervical cancer screening services

3.5.1.1 Subgroup analysis

Subgroup analysis was done to investigate the cause of heterogeneity in the uptake of cervical cancer screening services.

3.5.1.1.1 Uptake: Sub-grouped by prior sensitization

Subgroup analysis prespecified in the protocol was done to assess if there was a significant difference between the group which had prior sensitization on cervical cancer and HPV infections and the ones that had no prior sensitization to explain the considerable heterogeneity in the uptake of cervical cancer screening services. However, there was no significant difference (I2=0%, P=0.52) between the subgroups, and hence the summary estimate of the two groups can not be considered. (Figure 5)

3.5.1.1.2. Uptake: Subgrouped by setting

Subgroup analysis was done to assess if there is a significant difference between the economically different regions of "low-income countries", "lower-middle-income countries" and "upper-middle-income countries" to explain the considerable heterogeneity in the uptake of cervical cancer screening services. However, there was no significant difference (I2=0%, P=0.75) between the subgroups, and hence the summary estimate of the groups can not be considered.

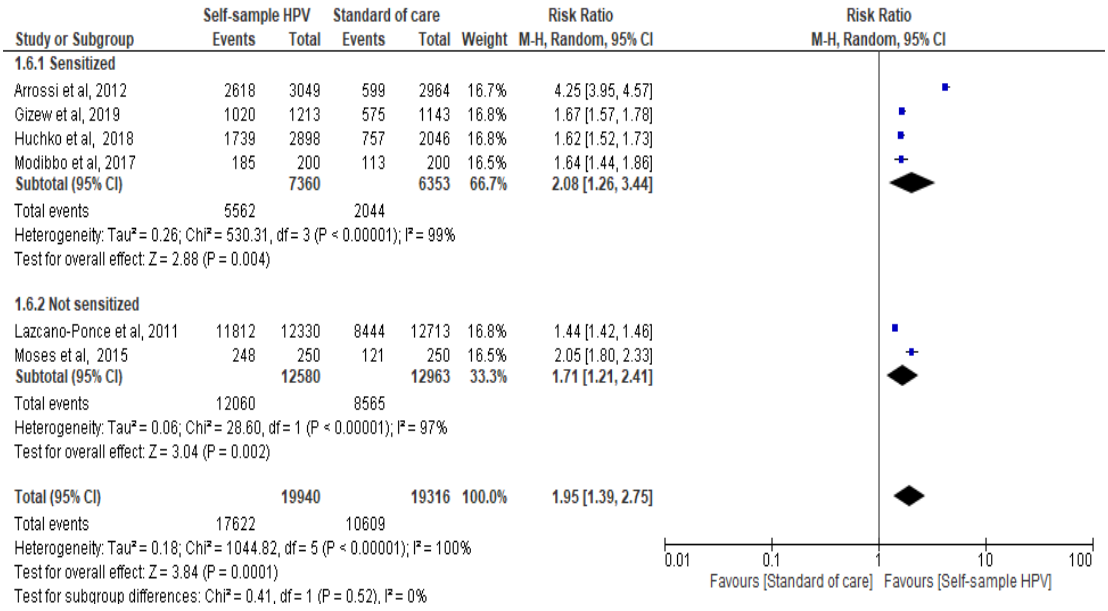

Figure 5: Uptake: Subgrouped by prior sensitization

3.5.1.1.3. Uptake: Subgrouped by opt-in vs opt-out approaches

Post hoc subgroup analysis was done to assess if there was a significant difference between the two different approaches of getting self-sampling kits opt-in and opt-out to explain the considerable heterogeneity in the uptake of cervical cancer screening services. However, there was no significant difference (I2=0%, P=0.45) between the subgroups, and hence the summary estimate of the groups can not be considered. (Figure 6)

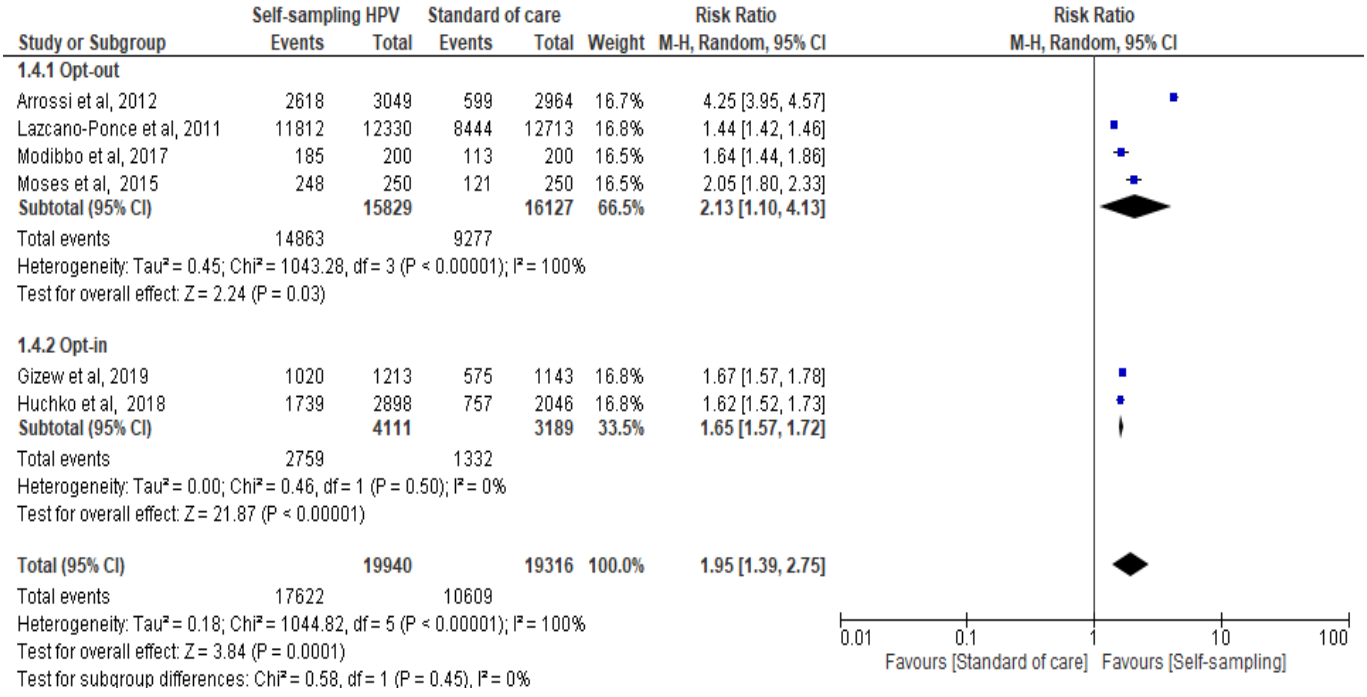

Figure 6: Uptake: Subgrouped by opt-in vs opt-out approaches

3.5.1.2 Sensitivity analysis

To further investigate the between-study heterogeneity that may be caused by studies with extreme effect sizes (outliers) or if there were one or more studies heavily influencing the pooled result contributing to heterogeneity (influential case), outlier and influence case analysis was done. After outlier analysis, The results of the study done by Arrossi *et al* **(61)** was found to be an outlier, however, after removing this study there was still considerable heterogeneity (RR=1.65, 95% CI 1.28 to 1.85, I^2= 93.9%). We conducted influence analysis and the leave-one-out analysis by

heterogeneity. As shown in figure 7, the lowest I2 was reached by omitting the studies done by Arrossi *et al*, [61] and Lazcano-Ponce *et al*, [62]. The influence analysis plot also showed these two studies heavily influenced the pooled result contributing to heterogeneity. (Figure 8) Hence, we conducted sensitivity analysis by excluding these studies, and this is reported in the forest plot in figure 9. The result of uptake of cervical cancer screening services showed that the likelihood of participants to screen with self-sampling HPV was 75% higher than the standard of care (RR: 1.72, 95% CI 1.58 to 1.87, I-squared: 72%) with insignificant I2 of 75%.

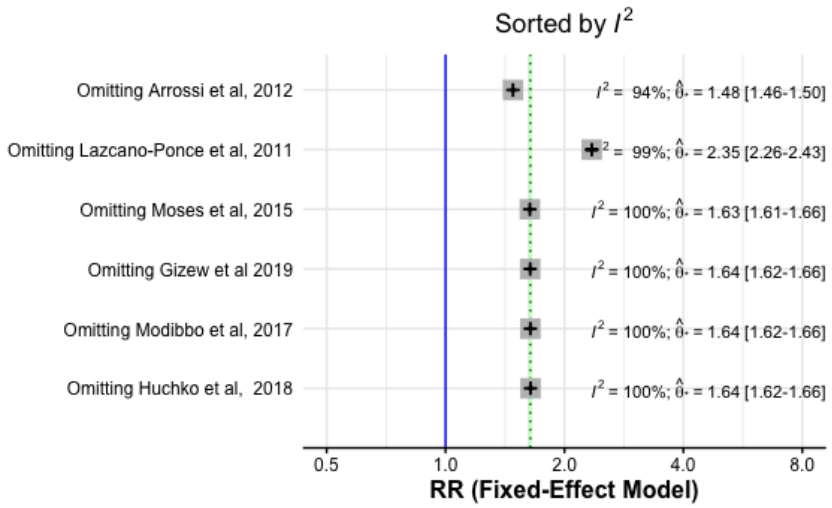

Figure 7: Leave-one-out analysis by heterogeneity.

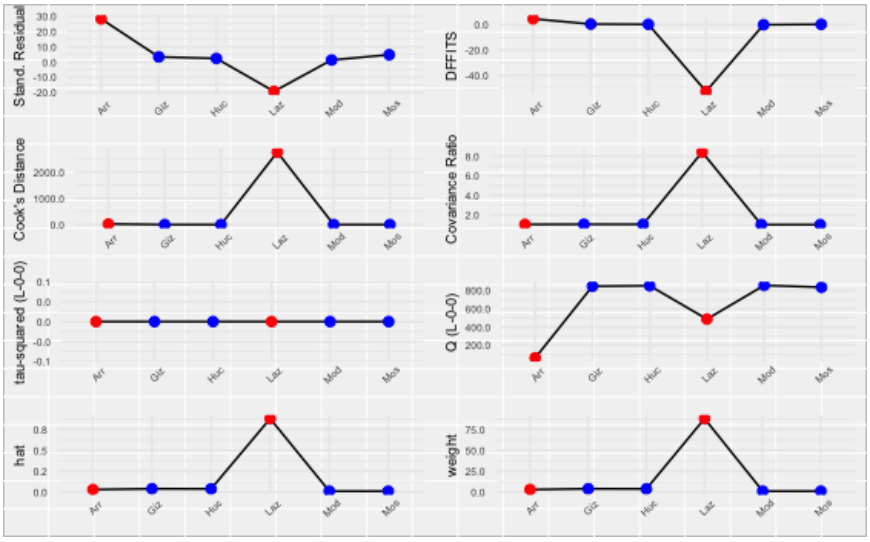

Figure 8: Influence analysis

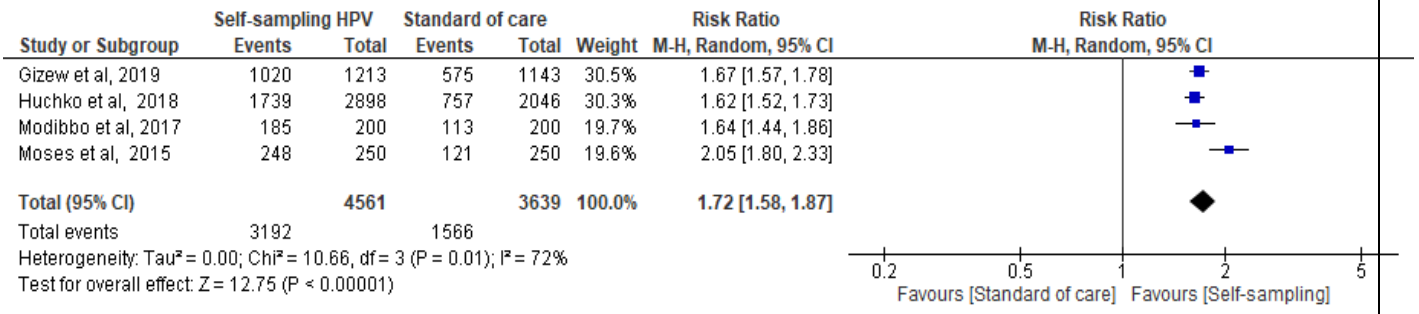

Figure 9: Meta-analysis 2: Uptake of cervical cancer screening services.

3.5.2 Linkage to care

Four studies reported the proportion of those women who got a positive result and reached a health center for further treatment or recommendation. [61],[59], [57], [60]. The meta-analysis found no significant difference in linkage to care in women who received a positive screening result between the two arms (RR=1.18, 95% CI 0.77 to 1.81, I^2= 87%) (Figure 10). Both Gizaw *et al* and Huchko *et al* [59] showed that linkage to care was higher in the intervention group however Moses showed that linkage of care was higher in the control group. This may be due to the high risk of bias that arises from the high missing participants in the intervention group.

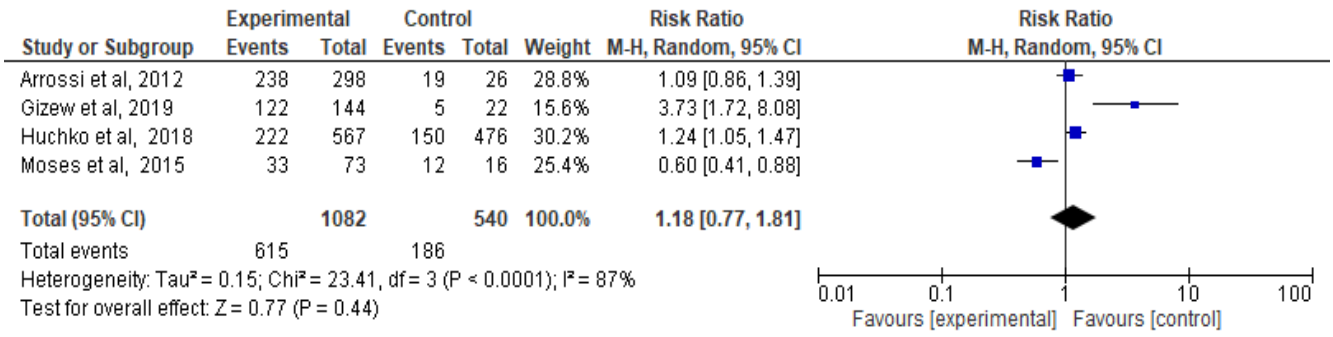

Figure 10: Linkage to care

3.5.3 Acceptability of HPV self-sampling method

Only one study [58] compared the acceptance of screening between the control and intervention arms, hence no meta-analysis was done. This was reported in the systematic review result summarized in narration.

3.5.4 Adverse events

No included study compared the adverse event related to the device between the control and intervention arms, hence no meta-analysis was done. This was reported in the systematic review result summarized in the narration

3.6 Risk of bias across studies

3.6.1 Publication bias

We could not assess publication bias as our studies were below 10, i.e., only 6 studies.

3.6.2 Selective reporting

Explained in the above section.(Section 3.3.6)

3.7 Additional analysis

Subgroup analysis was performed to investigate the heterogeneity, however, all three subgroup analyses failed to explain the heterogeneity. Sensitivity analysis was performed on the uptake outcome using influence analysis and leave-one-out analysis, and sensitivity analysis was done by excluding the influencing studies and this reduced the heterogeneity to an insignificant figure. Sensitivity analysis was performed to check the robustness of results by removing and adding the high risk of bias studies and there was no significant change. The results of the study done by Moses *et al,* [(60)] had significant missing values on measuring linkage to care and this study was removed to check if it affected the pooled outcome, however, the meta-analysis was still not significant.

3.8 Certainity assessment

The GRADE (Grading of Recommendations Assessment, Development, and Evaluation) report by outcomes (uptake and linkage to care) is presented in a summary of findings table along with the explanation of each judgement. Where the uptake outcome was rated as (RR: 1.72, 95% CI 1.58 to 1.87, I-squared: 72%)(*MODERATE* quality of evidence), and linkage to care (RR=1.18, 95% CI 0.77 to 1.81, I^2= 87%) (*VERY LOW* quality of evidence). (Table 5, Annex section.)

4. Discussion

4.1 Summary of evidence

Cervical cancer holds a third place as the most common cancer globally and the second common cancer in low-middle income countries. Over half million women were diagnosed with this cancer in 2018 and 311,000 of these women died from the cervical cancer. [(1)] More than 85% of cervical cancer deaths occur in LMIC, and 90% of the mortality burden is primarily attributed to low coverage of cervical cancer screening. [(2)] An alternative screening method is needed to increase screening coverage by addressing access challenges as well as personal barriers for women living in LMIC. HPV testing is a WHO recommended alternative screening in LMIC and it allows women to take their own samples, and this is found to be more acceptable as it overcomes personal barriers such as shame, embarrassment, and reluctance in letting a doctor see or touch their genitals. [(29)(15)]

Uptake of cervical cancer screening services shows that the likelihood of participants to screen with self-sampling HPV is 75% higher than with standard of care (RR: 1.72, 95% CI 1.58 to 1.87, I-squared: 72%)(*MODERATE* quality of evidence). The results of this review are in agreement with previous systematic review and meta-analysis done in high-income countries for WHO recommendation, showing uptake of self-sampling HPV to be more than twice higher, however, this had unexplained heterogeneity (RR: 2.13, 95% CI 1.89 to 2.40, I-squared: 99.34). Other individual randomized trials also support these findings where using self-sampling HPV significantly increases the uptake of cervical cancer screening compared to health-professional collected screening. **(33) (34) (35)** There was no significant difference in uptake between the group with prior sensitization and without prior sensitization, between studies from low-income,lower-middle-income, and upper-middle-income settings, and between using opt-in and opt-out kit dissemination approaches. However, different studies reported that the opt-out approach, where by HPV self-sampling kit is distributed by a CHW or directly by mail, was associated with increasing the likelihood of attending screening comparing with the opt-in approach, where the participants have to take the initiative to visit a clinic or request for HPV self-sampling. **(36)** Other studies reported that, although this opt-out approach can significantly increase screening uptake, it might not be financially feasible due to wastage. But this study was referring to an opt-out approach via direct mailing where kits might be lost and wasted.**(63)** Nevertheless, an opt-out approach using CHW or other health personnel to distribute kits might increase uptake in LMIC especially for those hard to reach communities, and this needs further assessment. In one of our included studies **(61)**, where they used CHW in kit dissemination in their routine home visits, it was reported that using CHW in sensitizing and kit dissemination showed high potential in increasing uptake of cervical cancer screening.**(61)**

The meta-analysis found no significant difference in linkage to care in women who received a positive screening result between the two arms (RR=1.18, 95% CI 0.77 to 1.81, I^2= 87%) (*VERY LOW* quality of evidence). All the included studies assessing linkage to care are in the same direction in favor of self-sampling HPV except Moses et al, 2015 **(60)**, which showed linkage of care higher in the control group. This may be due to the high risk of bias that arises from the high missing participants in the intervention group. Although it is encouraging that linkage to care is not lower in the self-sampling HPV group, the overall low rate of medical follow-up after positive

screening result is of concern. The results of this review are in agreement with that of previous systematic reviews and meta-analyses done in high-income countries for WHO recommendation, where there was no significant difference between the groups. [36]Another RCT also reported that linkage to care about positive result was low on both groups (41% in self-sampling group and 55% in standard of care). [35]. Only achieving high coverage will not lead to decreasing the disease burden, therefore linkage to care about positive result has to be improved. There is a need of research to assess different ways of improving this issue. One approach that was reported in a review of five different LMICs is, engaging CHW can increase follow-up rates. Arrossi *et al* [61] and Huchko *et al,* [59] reported that the median time between screening and treatment acquisition was 84 days (IQR 45-142) and 47 days (IQR 31-77), and this long time interval can be a barrier to adequate linkage to care, especially for those hard to reach participants or distant health facility.

The acceptability of HPV self-sampling was reported by Modibbo *et al* [58] and Huchko *et al,* [59]. Most of the women found the self-sampling device easy to use, said they would prefer self-sampling in the future than hospital screening and that they would recommend testing via self-sampling to a friend. The reason behind the majority who preferred self-sampling was comfort, privacy, financial convenience, less embarrassing, and a sense of independence. When the participants who chose health professionals collected screening were asked why they preferred, their reason was "to ensure the right sample was taken". Another review showed that HPV self-sampling was highly accepted as the participants found it easy and convenient [50]. This was also reflected in observational studies. [37][38][39][40][41] Different observational studies conducted in LMICs assessed acceptance of self-sampling using different questions; ease of use of the device, the comfort, privacy, whether they would recommend to a friend, if they felt relaxed while using it, and if they felt confident on doing the test properly. A significantly higher number of women gave positive feedback in favor of self-sampling, however, when it comes to their confidence of doing the test properly higher number of women reported that they would feel more comfortable with the results if it was performed by a health professional. [37][38][39][40][41] Their reasoning lies with the trust of the health professional's skills and their low confidence in the performance. Several observational studies tried to examine the association of these preferences to education and age, although there was no significant association to age, they found a significant association with education stating that the women who reported less confidence towards their sample are the ones with lower educational level. [37][42][43]

This may indicate that provision of instructions appropriate to each study population, literate and illiterate, on HPV self-sampling is essential to increase women's confidence in their ability to perform the test correctly and achieve a high uptake of HPV screening in LMICs. Advert events were reported by one study, Lazcano-Ponce et al, 2011 [62]. This study showed that there was no adverse event associated with the self-collection of vaginal samples.

4.2. Strength and limitations

This study has some limitations. Including only randomized controlled trials was both our strength and limitation. It was our strength as it had a higher degree of evidence however it had a limitation as there were a lot of observational studies that can address our research question. Three studies [61], [59] [57] that conducted cluster-randomized trials recruited after randomizing, and this might have led to recruitment bias and favored the intervention, hence more studies with more degree of evidence need to be conducted. The strength of this study is that it included different types of population (women with HIV, women with no prior screening) in different settings (different countries, urban, rural semi-urban). The other strength of this study is its large number of participants however, there were only six out of the 136 LMICs included in this study. Therefore, more studies need to be conducted in different LMICs to improve the generalizability of our results in different contexts.

5. Conclusion and recommendations

5.1 Conclusion

In conclusion, self-sampling HPV has the potential to increase the uptake of cervical cancer screening in LMICs and is an acceptable technique. Moreover, this technique is not associated with adverse events This technique helps overcome many barriers to cervical cancer screening in LMICs such as lack of trained personnel, lack of laboratory supplies, infrastructure, socio-religious and cultural barriers to pelvic examination, limited physical access to patient populations, and the need for spousal permission, which can reduce social inequalities in access to cervical screening services and contribute to alleviating cervical cancer burden in LMICs.

5.2 Recommendation

It is recommended;

- To promote self-sampling HPV for cervical cancer screening in LMIC as it increases the coverage of screening and is acceptable among women and to integrate it with the existing cervical cancer programme.
- Further assessment of the feasibility of integrating CHW in self-sampling HPV kit dissemination, sensitization, and linkage to care, as they already have different roles (malaria, TB, and other programs) in the community.
- More RCT to be conducted in LMICs to assess the usage of self-sampling HPV and improve generalizability.
- More researches are needed to assess the mechanism to increase linkage to care of the self-sampling women.
- Further studies need to address the cost-effectiveness of implementing this screening method.
- This study has shown an increase in uptake of screening with HPV self-sampling, but researchers need to assess which support material (health education, video illustrations or in-person training, or supervision), which kit dissemination approach (opt-in or opt-out) increases uptake and is feasible, which of these components can increase uptake among different populations such as the vulnerable (e.g. women with HIV or those with multiple sex partners), older women, illiterate women, and others.

6. Ethical considerations

This study did not require ethical approval and informed consent as participant's data for this systematic review and meta-analysis were exclusively extracted from published studies.

7. Dissemination of results

This manuscript will be published in a reputable journal and disseminated.

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9. Reference

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021 May;71(3):209-249. doi: 10.3322/caac.21660. Epub 2021 Feb 4. PMID: 33538338.
2. Denny L. Control of cancer of the cervix in low- and middle-income countries. Ann Surg Oncol. 2015 Mar;22(3):728-33. doi: 10.1245/s10434-014-4344-8. Epub 2015 Jan 21. PMID: 25605513.
3. LaVigne AW, Triedman SA, Randall TC, Trimble EL, Viswanathan AN. Cervical cancer in low and middle income countries: Addressing barriers to radiotherapy delivery. Gynecol Oncol Rep. 2017;22:16-20. Published 2017 Sep 1. doi:10.1016/j.gore.2017.08.004
4. Bruni L, Barrionuevo-Rosas L, Albero G, Aldea M, Serrano B, Valencia S, Brotons M, Mena M, Cosano R, Mu-oz J, Bosch FX, de Sanjosé S, Castellsagué X. ICO Information Centre on HPV and Cancer (HPV Information Centre). Human Papillomavirus and Related Diseases Reports. Available from: URL: http://www.hpvcentre.net/statistics/reports/XWX.pdf
5. LaMontagne DS, Barge S, Le NT, Mugisha E, Penny ME, Gandhi S, Janmohamed A, Kumakech E, Mosqueira NR, Nguyen NQ, Paul P, Tang Y, Minh TH, Uttekar BP, Jumaan AO. Human papillomavirus vaccine delivery strategies that achieved high coverage in low- and middle-income countries. Bull World Health Organ 2011; 89: 821-830B [PMID: 22084528 DOI: 10.2471/ BLT.11.089862]
6. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 2015; 136: E359-E386 [PMID: 25220842 DOI: 10.1002/ijc.29210]Organization, W.H Screening as well as vaccination is essential in the fight against cervical cancer. 2016.
7. Catarino R, Petignat P, Dongui G, Vassilakos P. Cervical cancer screening in developing countries at a crossroad: Emerging technologies and policy choices. World J Clin Oncol 2015; 6(6): 281-290 Available from: URL: http://www.wjgnet. com/2218-4333/full/v6/i6/281.htm DOI: http://dx.doi. org/10.5306/wjco.v6.i6.281
8. Sancho-Garnier H, Khazraji YC, Cherif MH, Mahnane A, Hsairi M, El Shalakamy A, Osgul N, Tuncer M, Jumaan AO, Seoud M. Overview of cervical cancer screening practices in the extended Middle East and North Africa countries. Vaccine 2013; 31 Suppl 6: G51-G57 [PMID: 24331820 DOI: 10.1016/j.vaccine.2012.06.046]
9. Department of Cytology and Gynaecological Pathology, Postgraduate Institute of Medical Education, and Research, Chandigarh, India. Guidelines for Cervical Cancer Screening Programme. [accessed 2006 Jun]. Available from: URL: http:// screening.iarc.fr/doc/WHO_India_CCSP_guidelines_2005.pdf

10. Chabra S. Cervical cancer preventable , treatable , but continues to kill women. Cerv. Cancer. 2016;1:1–2.
11. LaVigne, A. W., Triedman, S. A., Randall, T. C., Trimble, E. L., & Viswanathan, A. N. (2017). Cervical cancer in low and middle income countries: Addressing barriers to radiotherapy delivery. Gynecologic oncology reports, 22, 16–20. https://doi.org/10.1016/j.gore.2017.08.004
12. WHO:Cervical cancer. https://www.who.int/westernpacific/health-topics/cervical-cancer
13. Mboumba Bouassa RS;Prazuck T;Lethu T;Jenabian MA;Meye JF;Bélec L;. (n.d.). Cervical cancer in sub-Saharan Africa: A preventable noncommunicable disease. from https://pubmed.ncbi.nlm.nih.gov/28440679/
14. Projections of mortality and causes of death, 2016 to 2060. (2018, November 12), from https://www.who.int/healthinfo/global_burden_disease/projections/en/
15. Cervical Cancer Treatment (PDQ®)–Health Professional Version. (n.d, from https://www.cancer.gov/types/cervical/hp/cervical-treatment-pdq
16. WHO technical guidance and specifications of medical devices for screening and treatment of precancerous lesions in the prevention of cervical cancer. (2020, April 29). from 1https://www.who.int/medical_devices/publications/tech_specs_precancerous_Lesions_cervical_cancer_devices/en/
17. (PDF) Using the precaution adoption process model to(n.d.), fromhttps://www.researchgate.net/publication/330977505_Using_the_precaution_adoption_process_model_to_clarify_human_papillomavirus_vaccine_hesitancy_in_canadian_parents_of_girls_and_parents_of_boys
18. Melissa Conrad Stöppler, M. (2019, October 17). Cervical Cancer Symptoms, Causes, Stages, and Survival Rates. from https://www.medicinenet.com/cervical_cancer/article.htm
19. Cervical cancer. (n.d.). from https://www.afro.who.int/health-topics/cervical-cancer
20. Derbie A, Mekonnen D, Yismaw G, et al. Human papillomavirus in Ethiopia. Virusdisease. 2019 Jun;30(2):171-179. DOI: 10.1007/s13337-019-00527-4.
21. Denny L, Quinn M, Sankaranarayanan R. Chapter 8: Screening for cervical cancer in developing countries. Vaccine 2006; 24 Suppl 3: S3/71-S3/77 [PMID: 16950020 DOI: 10.1016/j.vaccine.2006.05.121]
22. Cuzick J, Clavel C, Petry KU, Meijer CJ, Hoyer H, Ratnam S, Szarewski A, Birembaut P, Kulasingam S, Sasieni P, Iftner T. Overview of the European and North American studies on HPV testing in primary cervical cancer screening. Int J Cancer 2006; 119: 1095-1101 [PMID: 16586444 DOI: 10.1002/ijc.21955]
23. Li N, Shi JF, Franceschi S, Zhang WH, Dai M, Liu B, Zhang YZ, Li LK, Wu RF, De Vuyst H, Plummer M, Qiao YL, Clifford G. Different cervical cancer screening approaches in a Chinese multicentre study. Br J Cancer 2009; 100: 532-537 [PMID: 19127262 DOI: 10.1038/sj.bjc.6604840]
24. Sankaranarayanan R, Esmy PO, Rajkumar R, Muwonge R, Swaminathan R, Shanthakumari S, Fayette JM, Cherian J. Effect of visual screening on cervical cancer incidence and

mortality in Tamil Nadu, India: a cluster-randomised trial. Lancet 2007; 370: 398-406 [PMID: 17679017 DOI: 10.1016/S0140-6736(07)61195-7]

25. Denny L, Kuhn L, Pollack A, Wainwright H, Wright TC. Evaluation of alternative methods of cervical cancer screening for resource-poor settings. Cancer 2000; 89: 826-833 [PMID: 10951346 DOI: 10.1002/1097-0142(20000815)89: 43.0.CO;2-5]
26. Basu P, Wesley RS, Mahe C, Keita N, Mbalawa CC, Sharma R, Dolo A, Shastri SS, Nacoulma M, Nayama M, Somanathan T, Lucas E, Muwonge R, Frappart L, Parkin DM. Accuracy of visual screening for cervical neoplasia: Results from an IARC multicentre study in India and Africa. Int J Cancer 2004; 110: 907-913 [PMID: 15170675 DOI: 10.1002/ijc.20190]
27. Ogilvie GS, Patrick DM, Schulzer M, Sellors JW, Petric M, Chambers K, White R, FitzGerald JM. Diagnostic accuracy of self collected vaginal specimens for human papillomavirus compared to clinician collected human papillomavirus specimens: a metaanalysis. Sex Transm Infect 2005; 81: 207-212 [PMID: 15923286 DOI: 10.1136/sti.2004.011858]
28. Cervical Cancer Diagnosis. from https://www.cancer.net/cancer-types/cervical-cancer/diagnosis
29. Guidelines for screening and treatment of precancerous lesions for cervical cancer prevention.fromhttps://www.who.int/reproductivehealth/publications/cancers/screening_and_treatment_of_precancerous_lesions/en/
30. Gravitt PE, Belinson JL, Salmeron J, Shah KV. Looking ahead: a case for human papillomavirus testing of self-sampled vaginal specimens as a cervical cancer screening strategy. Int J Cancer 2011; 129: 517-527 [PMID: 21384341 DOI: 10.1002/ijc.25974]
31. Nene, B., Shastri, S., Jayant, K., Muwonge, R., Budukh, A., . . . Dinshaw, K. (2009, April 2). HPV screening for cervical cancer in rural India. from https://www.ncbi.nlm.nih.gov/pubmed/19339719
32. Arbyn M;Verdoodt F;Snijders PJ;Verhoef VM;Suonio E;Dillner L;Minozzi S;Bellisario C;Banzi R;Zhao FH;Hillemanns P;Anttila A;. (n.d.). Accuracy of human papillomavirus testing on self-collected versus clinician-collected samples: A meta-analysis. https://pubmed.ncbi.nlm.nih.gov/24433684/
33. Sancho-Garnier H, Tamalet C, Halfon P, et al. HPV self-sampling or the Pap-smear: a randomized study among cervical screening nonattenders from lower socioeconomic groups in France. Int JCancer 2013;133:2681–7.
34. Bais AG, van Kemenade FJ, Berkhof J, et al. Human papillomavirus testing on self-sampled cervicovaginal brushes: an effective alternative to protect nonresponders in cervical screening programs.Int. J. Cancer 2007;120:1505–10.
35. Sewali B, Okuyemi KS, Askhir A, et al. Cervical cancer screening with clinic-based Pap test versus home HPV test among Somali immigrant women in Minnesota: a pilot randomized controlled trial.Cancer Med 2015;4:620–31.

36. Yeh, P. T., Kennedy, C. E., Vuyst, H. D., & Narasimhan, M. (2019). Self-sampling for human papillomavirus (HPV) testing: A systematic review and meta-analysis. *BMJ Global Health, 4*(3). doi:10.1136/bmjgh-2018-001351
37. Berner, A., Hassel, S. B., Tebeu, P.-M., Untiet, S., Kengne-Fosso, G., Navarria, I., … Petignat, P. (2013). Human Papillomavirus Self-Sampling in Cameroon. Journal of Lower Genital Tract Disease, 17(3), 235–241. doi:10.1097/lgt.0b013e31826b7b51
38. Mbatha, J.N., Galappaththi-Arachchige, H.N., Mtshali, A. *et al.* Self-sampling for human papillomavirus testing among rural young women of KwaZulu-Natal, South Africa. *BMC Res Notes* **10,** 702 (2017). https://doi.org/10.1186/s13104-017-3045-3
39. Esber A, Norris A, Jumbe E, et al. Feasibility, validity and acceptability of self-collected samples for human papillomavirus (HPV) testing in rural Malawi. Malawi Med J. 2018;30(2):61-66. doi:10.4314/mmj.v30i2.2
40. Taku O, Meiring TL, Gustavsson I, Phohlo K, Garcia-Jardon M, et al. (2020) Acceptability of self- collection for human papillomavirus detection in the Eastern Cape, South Africa. PLOS ONE 15(11): e0241781. https://doi.org/10.1371/journal.pone.0241781
41. Fall, N. S., Tamalet, C., Diagne, N., Fenollar, F., Raoult, D., Sokhna, C., & Lagier, J. (2019). Feasibility, Acceptability, and Accuracy of Vaginal Self-Sampling for Screening Human Papillomavirus Types in Women from Rural Areas in Senegal, The American Journal of Tropical Medicine and Hygiene, 100(6), 1552-1555. https://www.ajtmh.org/view/journals/tpmd/100/6/article-p1552.xml
42. Kohler RE, Elliott T, Monare B, et al. HPV self-sampling acceptability and preferences among women living with HIV in Botswana. *Int J Gynaecol Obstet*. 2019;147(3):332-338. doi:10.1002/ijgo.12963
43. Brandt, T., Wubneh, S.B., Handebo, S. *et al.* Genital self-sampling for HPV-based cervical cancer screening: a qualitative study of preferences and barriers in rural Ethiopia. *BMC Public Health* **19,** 1026 (2019). https://doi.org/10.1186/s12889-019-7354-4
44. Tjalma WA, Arbyn M, Paavonen J, van Waes TR, Bogers JJ. Prophylactic human papillomavirus vaccines: the beginning of the end of cervical cancer. International Journal of Gynecological Cancer : Official Journal of the International Gynecological Cancer Society. 2004 Sep-Oct;14(5):751-761. DOI: 10.1111/j.1048-891x.2004.014505.x.
45. Karjalainen, L., Anttila, A., Nieminen, P., Luostarinen, T., & Virtanen, A. (2016, March 15). Self-sampling in cervical cancer screening: Comparison of a brush-based and a lavage-based cervicovaginal self-sampling device. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4791879/
46. Bais, A., Van Kemenade, F., Berkhof, J., Verheijen, R., Snijders, P., Voorhorst, F., . . . Meijer, C. (2007, April 1). Human papillomavirus testing on self-sampled cervicovaginal brushes: An effective alternative to protect nonresponders in cervical screening programs. https://www.ncbi.nlm.nih.gov/pubmed/17205514

47. Nodjikouambaye, Z., Adawaye, C., Bouassa, R., Sadjoli, D., & Bélec, L. (2020, February 27). OBGYN. from https://obgyn.onlinelibrary.wiley.com/doi/full/10.1002/ijgo.13112
48. Crosby RA, Hagensee ME, Vanderpool R, et al. Community-based screening for cervical cancer: a feasibility study of rural Appalachian women. *Sex Transm Dis*. 2015;42(11):607-611.
49. Fokom Domgue J, Ngalla C, Kakute P, et al. Feasibility of a community-based cervical cancer screening with "test and treat" strategy using self-samples for HPV testing: experience from rural Cameroon, Africa [published online ahead of print October 21, 2019]. *Int J Cancer*.
50. Nelson, E. J., Maynard, B. R., Loux, T., Fatla, J., Gordon, R., & Arnold, L. D. (2016). The acceptability of self-sampled screening for HPV DNA: A systematic review and meta-analysis. *Sexually Transmitted Infections, 93*(1), 56-61. doi:10.1136/sextrans-2016-052609
51. WHO sexual and reproductive health: Self-sampling for human papillomavirus testing https://www.who.int/reproductivehealth/self-care-interventions/human-papillomavirus-testing/en/#:~:text=High%2Drisk%20HPV%20testing%20is,provider%20for%20cervical%20cancer%20screening.
52. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015.
53. RoB 2: A revised Cochrane risk-of-bias tool for randomized trials. (n.d.)., from https://methods.cochrane.org/bias/resources/rob-2-revised-cochrane-risk-bias-tool-randomized-trials
54. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, et al. Cochrane Handbook for Systematic Reviews of Interventions version 6.2 (updated February 2021). Cochrane, 2021 [Available from: www.training.cochrane.org/handbook]
55. The World Bank. World Bank Data and Lending group. 2019. https ://datah elpde sk.world bank.org/knowl edgeb ase/artic les/90651 9-world -bankcountry-and-lendi ng-group s.
56. LMICs Filters based on the World Bank list of countries (2019)https://epoc.cochrane.org/lmic-filters.
57. Gizaw, M., Teka, B., Ruddies, F., Abebe, T., Kaufmann, A. M., Worku, A., Kantelhardt, E. J. (2019). Uptake of Cervical Cancer Screening in Ethiopia by Self-Sampling HPV DNA Compared to Visual Inspection with Acetic Acid: A Cluster Randomized Trial. *Cancer Prevention Research, 12*(9), 609-616. doi:10.1158/1940-6207.capr-19-0156
58. Modibbo, F., Iregbu, K. C., Okuma, J., Leeman, A., Kasius, A., Koning, M. D. Adebamowo, C. (2017). Randomized trial evaluating self-sampling for HPV DNA based tests for cervical cancer screening in Nigeria. *Infectious Agents and Cancer, 12*(1). doi:10.1186/s13027-017-0123-z
59. Huchko, M. J., Ibrahim, S., Blat, C., Cohen, C. R., Smith, J. S., Hiatt, R. A., & Bukusi, E. (2018). Cervical cancer screening through human papillomavirus testing in community

health campaigns versus health facilities in rural western Kenya. *International Journal of Gynecology & Obstetrics*, *141*(1), 63-69. doi:10.1002/ijgo.12415

60. Moses, E., Pedersen, H. N., Mitchell, S. M., Sekikubo, M., Mwesigwa, D., Singer, J.Ogilvie, G. S. (2015). Uptake of community-based, self-collected HPV testingvs. visual inspection with acetic acid for cervical cancer screening in Kampala, Uganda: Preliminary results of a randomised controlled trial. *Tropical Medicine & International Health*, *20*(10), 1355-1367. doi:10.1111/tmi.12549
61. Arrossi S, Thouyaret L, Herrero R, et al. Effect of self-collection of HPV DNA offered by community health workers at home visits on uptake of screening for cervical cancer (the EMA study): a population-based cluster-randomised trial. Lancet Glob Health. 2015;3(2):e85-e94.
62. Lazcano-Ponce E, Lorincz AT, Cruz-Valdez A, Salmerón J, Uribe P, Velasco-Mondragón E, Nevarez PH, Acosta RD, Hernández-Avila M. Self-collection of vaginal specimens for human papillomavirus testing in cervical cancer prevention (MARCH): a community-based randomised controlled trial. Lancet. 2011 Nov 26;378(9806):1868-73. doi: 10.1016/S0140-6736(11)61522-5. Epub 2011 Nov 1. PMID: 22051739.
63. Ivanus U, Jerman T, Fokter AR, Takac I, Prevodnik VK, Marcec M, Gajsek US, Pakiz M, Koren J, Celik SH, Kramberger KG, Klopcic U, Kavalar R, Zatler SS, Kuzmanov BG, Florjancic M, Nolde N, Novakovic S, Poljak M, Zakelj MP. Randomised trial of HPV self-sampling among non-attenders in the Slovenian cervical screening programme ZORA: comparing three different screening approaches. Radiol Oncol. 2018 Sep 14;52(4):399-412. doi: 10.2478/raon-2018-0036. PMID: 30216191; PMCID: PMC6287183.

10. Annex

Search term for MEDLINE (through PubMed)

((("uterine cervical neoplasms"[MeSH Terms] OR "cervical cancer"[Text Word])AND ("DNA Probes, HPV"[Mesh] OR "Human Papillomavirus DNA Tests"[Mesh] OR hpv[All Fields]) AND "Self-collected" OR "Self-sampling" OR "Self-obtained" AND (afghanistan[Text Word] OR albania[Text Word] OR algeria[Text Word] OR american samoa[Text Word] OR angola[Text Word] OR antigua[Text Word] OR barbuda[Text Word] OR argentina[Text Word] OR armenia[Text Word] OR armenian[Text Word] OR aruba[Text Word] OR azerbaijan[Text Word] OR bahrain[Text Word] OR bangladesh[Text Word] OR barbados[Text Word] OR belarus[Text Word] OR byelarus[Text Word] OR belorussia[Text Word] OR byelorussian[Text Word] OR belize[Text Word] OR british honduras[Text Word] OR benin[Text Word] OR dahomey[Text Word] OR bhutan[Text Word] OR bolivia[Text Word] OR bosnia[Text Word] OR herzegovina[Text Word] OR botswana[Text Word] OR bechuanaland[Text Word] OR brazil[Text Word] OR brasil[Text Word] OR bulgaria[Text Word] OR burkina faso[Text Word] OR burkina fasso[Text Word] OR upper volta[Text Word] OR burundi[Text Word] OR urundi[Text Word] OR cabo verde[Text Word] OR cape verde[Text Word] OR cambodia[Text Word] OR kampuchea[Text Word] OR khmer republic[Text Word] OR cameroon[Text Word] OR cameron[Text Word] OR cameroun[Text Word] OR central african republic[Text Word] OR ubangi shari[Text Word] OR chad[Text Word] OR chile[Text Word] OR china[Text Word] OR colombia[Text Word] OR comoros[Text Word] OR comoro islands[Text Word] OR mayotte[Text Word] OR congo[Text Word] OR zaire[Text Word] OR costa rica[Text Word] OR cote d'ivoire[Text Word] OR cote d' ivoire[Text Word] OR cote divoire[Text Word] OR cote d ivoire[Text Word] OR ivory coast[Text Word] OR croatia[Text Word] OR cuba[Text Word] OR cyprus[Text Word] OR czech republic[Text Word] OR czechoslovakia[Text Word] OR djibouti[Text Word] OR french somaliland[Text Word] OR dominica[Text Word] OR dominican republic[Text Word] OR ecuador[Text Word] OR egypt[Text Word] OR united arab republic[Text Word] OR el salvador[Text Word] OR equatorial guinea[Text Word] OR spanish guinea[Text Word] OR eritrea[Text Word] OR estonia[Text Word] OR eswatini[Text Word] OR swaziland[Text Word] OR ethiopia[Text Word] OR fiji[Text Word] OR gabon[Text Word] OR gabonese republic[Text Word] OR gambia[Text Word] OR georgia[Text Word] OR georgian[Text Word] OR ghana[Text Word] OR gold coast[Text Word] OR gibraltar[Text Word] OR greece[Text Word] OR grenada[Text Word] OR guam[Text Word] OR guatemala[Text Word] OR guinea[Text Word] OR guyana[Text Word] OR guiana[Text Word] OR haiti[Text Word] OR hispaniola[Text Word] OR honduras[Text Word] OR hungary[Text Word] OR india[Text Word] OR indonesia[Text Word] OR timor[Text Word] OR iran[Text Word] OR iraq[Text Word] OR isle of man[Text Word] OR jamaica[Text Word] OR jordan[Text Word] OR kazakhstan[Text Word] OR kazakh[Text Word] OR kenya[Text Word] OR korea[Text Word] OR kosovo[Text Word] OR kyrgyzstan[Text Word] OR kirghizia[Text

Word] OR kirgizstan[Text Word] OR kyrgyz republic[Text Word] OR kirghiz[Text Word] OR laos[Text Word] OR lao pdr[Text Word] OR lao people's democratic republic[Text Word] OR latvia[Text Word] OR lebanon[Text Word] OR lesotho[Text Word] OR basutoland[Text Word] OR liberia[Text Word] OR libya[Text Word] OR libyan arab jamahiriya[Text Word] OR lithuania[Text Word] OR macau[Text Word] OR macao[Text Word] OR macedonia[Text Word] OR madagascar[Text Word] OR malagasy republic[Text Word] OR malawi[Text Word] OR nyasaland[Text Word] OR malaysia[Text Word] OR maldives[Text Word] OR indian ocean[Text Word] OR mali[Text Word] OR malta[Text Word] OR micronesia[Text Word] OR kiribati[Text Word] OR marshall islands[Text Word] OR nauru[Text Word] OR northern mariana islands[Text Word] OR palau[Text Word] OR tuvalu[Text Word] OR mauritania[Text Word] OR mauritius[Text Word] OR mexico[Text Word] OR moldova[Text Word] OR moldovian[Text Word] OR mongolia[Text Word] OR montenegro[Text Word] OR morocco[Text Word] OR ifni[Text Word] OR mozambique[Text Word] OR portuguese east africa[Text Word] OR myanmar[Text Word] OR burma[Text Word] OR namibia[Text Word] OR nepal[Text Word] OR netherlands antilles[Text Word] OR nicaragua[Text Word] OR niger[Text Word] OR nigeria[Text Word] OR oman[Text Word] OR muscat[Text Word] OR pakistan[Text Word] OR panama[Text Word] OR papua new guinea[Text Word] OR paraguay[Text Word] OR peru[Text Word] OR philippines[Text Word] OR philipines[Text Word] OR phillipines[Text Word] OR phillippines[Text Word] OR poland[Text Word] OR polish people's republic[Text Word] OR portugal[Text Word] OR portuguese republic[Text Word] OR puerto rico[Text Word] OR romania[Text Word] OR russia[Text Word] OR russian federation[Text Word] OR ussr[Text Word] OR soviet union[Text Word] OR union of soviet socialist republics[Text Word] OR rwanda[Text Word] OR ruanda[Text Word] OR samoa[Text Word] OR pacific islands[Text Word] OR polynesia[Text Word] OR samoan islands[Text Word] OR sao tome and principe[Text Word] OR saudi arabia[Text Word] OR senegal[Text Word] OR serbia[Text Word] OR seychelles[Text Word] OR sierra leone[Text Word] OR slovakia[Text Word] OR slovak republic[Text Word] OR slovenia[Text Word] OR melanesia[Text Word] OR solomon island[Text Word] OR solomon islands[Text Word] OR norfolk island[Text Word] OR somalia[Text Word] OR south africa[Text Word] OR south sudan[Text Word] OR sri lanka[Text Word] OR ceylon[Text Word] OR saint kitts and nevis[Text Word] OR st kitts and nevis[Text Word] OR saint lucia[Text Word] OR st lucia[Text Word] OR saint vincent[Text Word] OR st vincent[Text Word] OR grenadines[Text Word] OR sudan[Text Word] OR suriname[Text Word] OR surinam[Text Word] OR syria[Text Word] OR syrian arab republic[Text Word] OR tajikistan[Text Word] OR tadjikistan[Text Word] OR tadzhikistan[Text Word] OR tadzhik[Text Word] OR tanzania[Text Word] OR tanganyika[Text Word] OR thailand[Text Word] OR siam[Text Word] OR timor leste[Text Word] OR east timor[Text Word] OR togo[Text Word] OR togolese republic[Text Word] OR tonga[Text Word] OR trinidad[Text Word] OR tobago[Text Word] OR tunisia[Text Word] OR turkey[Text Word] OR turkmenistan[Text Word] OR turkmen[Text Word] OR uganda[Text Word] OR ukraine[Text Word] OR uruguay[Text Word] OR uzbekistan[Text Word] OR uzbek[Text Word] OR vanuatu[Text Word] OR new hebrides[Text Word] OR venezuela[Text Word] OR vietnam[Text Word] OR viet nam[Text Word] OR middle east[Text Word] OR west bank[Text Word] OR gaza[Text Word] OR palestine[Text Word] OR yemen[Text Word] OR yugoslavia[Text Word]

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gross domestic[Text Word] OR lmic[Text Word] OR lmics[Text Word] OR third world[Text Word] OR lami country[Text Word] OR lami countries[Text Word] OR transitional country[Text Word] OR transitional countries[Text Word] OR emerging economies[Text Word] OR emerging nation[Text Word] OR emerging nations[Text Word]))

Arrossi et al, 2012 [61]		
Domain	**Author's Judgment**	**Support for judgment**
Random sequence generation (selection bias)	Low risk	computer-generated random number list was used for the sequence generation
Allocation concealment (selection bias)	Low risk	All the clusters were randomized at once, so the concealment is less of an issue
Blinding of participants and personnel (performance bias)	Low risk	Because of the nature of the intervention of interest , blinding was impossible for participants and personnel..
Blinding of outcome assessment (detection bias)	Low risk	Because of the nature of the intervention of interest , blinding was impossible for outcome assessment. However, the measured outcomes are unlikely to be biazed by lack of blinding as they are measured through medical records and not self- report.
Incomplete outcome data (attrition bias)	Low risk	No missing outcome data on the outcomes of interest.
Selective outcome reporting	Low risk	Reported outcomes that were pre-specified in their protocol registered in Clinicaltrial.gov
Other bias	**High risk**	There is a chance of recruitment bias as enrollment occurred after knowledge of intervention and control group.

Gizaw et al, 2019 [57]		
Domain	**Author's Judgment**	**Support for judgment**
Random sequence generation (selection bias)	Low risk	The randomization list was created by using a unique allocation ID and randomized using Research Randomizer Software.
Allocation concealment (selection bias)	Low risk	All the clusters were randomized at once, so the concealment is less of an issue.
Blinding of participants and personnel (performance bias)	Low risk	Because of the nature of the intervention of interest , blinding was impossible for participants and personnel.
Blinding of outcome assessment (detection bias)	Low risk	Because of the nature of the intervention of interest , blinding was impossible for outcome assessment. However, the measured outcomes are unlikely to be biazed by lack of blinding as they are measured through medical records and not self- report.

Incomplete outcome data (attrition bias)	Low risk	No missing outcome data on the outcomes of interest.
Selective outcome reporting	Low risk	Reported outcomes that were pre-specified in their protocol registered in Clinicaltrial.gov.
Other bias	**High risk**	There is a chance of recruitment bias as enrollment occurred after knowledge of intervention and control group.

Huchko et al, 2018 [59]		
Domain	**Author's Judgment**	**Support for judgment**
Random sequence generation (selection bias)	Low risk	The 12 communities were randomized 1:1 using an allocation sequence generated by Stata/MP version 11.
Allocation concealment (selection bias)	Low risk	All the clusters were randomized at once, so the concealment is less of an issue.
Blinding of participants and personnel (performance bias)	Low risk	Because of the nature of the intervention of interest , blinding was impossible for participants and personnel.
Blinding of outcome assessment (detection bias)	Low risk	Because of the nature of the intervention of interest , blinding was impossible for outcome assessment. However, the measured outcomes are unlikely to be biazed by lack of blinding as they are measured through medical records and not self- report.
Incomplete outcome data (attrition bias)	Low risk	No missing outcome data on the outcomes of interest
Selective outcome reporting	Low risk	Reported outcomes that were pre-specified in their protocol registered in Clinicaltrial.gov
Other bias	**High risk**	There is a chance of recruitment bias as enrollment occurred after knowledge of intervention and control group. There was also significant baseline imbalance despite randomization.

Lazcano-Ponce et al, 2011 [62]		
Domain	**Author's Judgment**	**Support for judgment**
Random sequence generation (selection bias)	Low risk	By a computer-based random allocation process designed by study statisticians
Allocation concealment (selection bias)	Unclear risk	It was stated that the nurses visiting the participants were concealed of the random allocation, however there was no further information to judge if the concealment was appropriate.
Blinding of participants and personnel (performance bias)	Low risk	Because of the nature of the intervention of interest , blinding was impossible for participants and personnel.

Blinding of outcome assessment (detection bias)	Low risk	Because of the nature of the intervention of interest , blinding was impossible for outcome assessment. However, the measured outcomes are unlikely to be biazed by lack of blinding as they are measured through medical records and not self- report.
Incomplete outcome data (attrition bias)	Low risk	No missing outcome data on the outcomes of interest
Selective outcome reporting	Low risk	Reported outcomes that were pre-specified in their protocol registered in Clinicaltrial.gov
Other bias	Low risk	The funder had no role in any of the study procedure and writing of the report appears to be free of other bias.

Modibbo et al, 2017 [58]		
Domain	**Author's Judgment**	**Support for judgment**
Random sequence generation (selection bias)	Low risk	used random number table and randomized
Allocation concealment (selection bias)	Unclear risk	Information was not given to judge allocation concealment
Blinding of participants and personnel (performance bias)	Low Risk	Because of the nature of the intervention of interest, blinding was not possible for participants and personnel.
Blinding of outcome assessment (detection bias)	Low risk	Because of the nature of the intervention of interest , blinding was impossible for outcome assessment. However, the measured outcomes are unlikely to be biazed by lack of blinding as they are measured through medical records and not self- report.
Incomplete outcome data (attrition bias)	Low risk	No missing outcome data on the outcomes of interest.
Selective outcome reporting	Low risk	Reported outcomes that were pre-specified in their protocol registered in Clinicaltrial.gov
Other bias	Low risk	The funder had no role in study design, data collection,data analysis, data interpretation, or writing of the report. appears to be free of other bias.

Moses et al, 2015 [60]		
Domain	**Author's Judgment**	**Support for judgment**
Random sequence generation (selection bias)	Low risk	Using simple randomization, a randomisation list was generated using SAS 9.3 for 250 participants per arm, for a total of 500 participants.
Allocation concealment (selection bias)	Low risk	Unique study ID and allocation were recorded on cards, which were concealed in an opaque envelope and kept in a locked cabinet in the research office.

Blinding of participants and personnel (performance bias)	Low risk	Because of the nature of the intervention of interest, blinding was not possible for participants and personnel.
Blinding of outcome assessment (detection bias)	Low risk	Because of the nature of the intervention of interest , blinding was impossible for outcome assessment. However, the measured outcomes are unlikely to be biased by lack of blinding as they are measured through medical records and not self- report.
Incomplete outcome data (attrition bias)	**High risk**	53% missing individuals in the second outcome assessment of linkage to care.
Selective outcome reporting	Low risk	Reported outcomes that were pre-specified in their protocol registered in Clinicaltrial.gov
Other bias	Low risk	The funder had no role in the procedure of study. And Writing of the report appears to be devoid of other bias.

Table 5 Certainity assessment: Summary of Findings

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Human self sampling	standard of care	Relative (95% CI)	Absolute (95% CI)		
Linkage to care												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Human self sampling	standard of care	Relative (95% CI)	Absolute (95% CI)		
4	randomised trials	very serious [a,b]	serious [c]	not serious	serious [d]	none	615/1082 (56.8%)	186/540 (34.4%)	**RR 1.18** (0.77 to 1.81)	**62 more per 1,000** (from 79 fewer to 279 more)	⨁◯◯◯ VERY LOW	

Uptake of Screening LMIC

4	randomised trials	serious [e]	not serious	not serious	not serious	none	3192/4561 (70.0%)	1566/3639 (43.0%)	**RR 1.72** (1.58 to 1.87)	**310 more per 1,000** (from 250 more to 374 more)	⨁⨁⨁◯ MODERATE	

CI: Confidence interval; **RR:** Risk ratio

Explanations

a. Huchko et al, Gizaw et al and Arrosi et al conducted cluster RCT and enrolled participants after randomization of clusters to intervention and control arms and hence have potential recruitment bias.

b. Moses et al has 53% missing data on the intervention group and might favor standard of care.

c. There was unexplained heterogeneity between studies.

d. The outcome didn't exclude one.

e. Huchko et al, Gizaw et al conducted cluster RCT and enrolled participants after randomization of clusters to intervention and control arms and hence have potential recruitment bias and Moses et al has 53% missing on the intervention group and might favor standard of care.