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Implementing Community-based Cervical Cancer Screening Programs using Visual Inspection with Acetic Acid in India: A Systematic Review

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Abstract

The objective of this review was to systematically appraise the existing published literature about community-based cervical cancer screening programs that have used visual inspection methods using acetic acid (VIA) in India. All peer reviewed journal articles till December 2015 were searched per PRISMA guidelines. Articles reporting results from cervical cancer screening programs in community-based settings, conducted in India, and using VIA were included in this review. The search resulted in 20 articles to be included in the review with a total of 313,553 women at 12 unique urban and rural sites across India. Seventeen (85%) studies were cross-sectional and three studies were randomized controlled trials; most studies compared accuracy of VIA with other screening tests such as visual inspection using Lugol's Iodine (VILI), HPV DNA, and cytology. Of studies that reported test accuracy for CIN Grade 2+, the VIA sensitivity values ranged from 16.6 – 82.6% and specificity ranged from 82.1 – 96.8%. Women between age groups of 30–59 years were recruited using motivational one-on-one counseling and local support staff. All studies conducted diagnostic follow-up using colposcopy and guided biopsies, when necessary. Three major themes were identified that facilitated implementation of screening programs in a community-based setting: standardized training that maintained competency of test providers; collaborations with community-based organizations that used health education for recruitment of participants; and employing the screen-and-treat method to reduce loss to follow-up. Summarized

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evidence presented in this review could substantially influence future implementation and sustainment of cervical cancer screening programs at a national level.

Keywords

Cervical Cancer; Screening; Acetic Acid; Visual Inspection; Health Planning; Implementation; India

Introduction

According to the World Health Organization estimates, approximately 122,844 new cases and 67,544 deaths were due to cervical cancer in India, accounting for nearly 1/3rd of the global cervical cancer deaths in 2014.[1] Epidemiological and laboratory research has clearly established that a persistent infection with Human Papillomavirus (HPV) causes most cases of cervical cancer and the past decade has focused on primary prevention using HPV vaccinations, which have shown promising results.[2, 3] Although there has been substantial progress in primary prevention strategies, an optimal effect on incidence and mortality due to cervical cancer can only be achieved by the addition of secondary prevention strategies, which include screening for precancerous and cancerous cervical lesions in women above 30 years of age.[4] For developing countries like India, it is critical that they achieve relatively high screening coverage rates as well as ensure that screen-positive women receive appropriate diagnostic and treatment services.

Establishing a quality assured cytology screening program, with national coverage can prove to be very challenging and probably beyond the capacity and resources available for India.[5] Moreover, underlying pelvic infections resulting in cervical smear abnormalities along with inherent difficulties in efficiently performing the different steps in cytology screening, which requires significant training and experience, can result in low sensitivity for the performance of Pap smears.[6] Repeated, yearly testing can improve the sensitivity of the Pap smears as seen in the US but can require significant resources.[7] Accumulating evidence on HPV testing as a screening strategy, highlights the test to be the most objective and reproducible of all cervical screening tests.[8] The test however, is expensive (approximately $20 US Dollars per test) and requires a sophisticated laboratory infrastructure which can be difficult to setup in primary care settings in India. On the other hand, visual inspection methods using acetic acid (VIA) and Lugol's iodine (VILI) have shown to be well accepted by women in India and the incidence of discomfort and pain during VIA is less than that reported for when Pap smears are conducted.[9, 10]

For large scale screening of populations, visual inspection methods have been extensively studied and proven to be effective, especially in the low- and middle-income countries. Visual methods involve the application of acetic acid (VIA) or Lugol's iodine (VILI) on the cervix to enhance the ability to detect the presence of pre-cancerous lesions thereby enabling the detection of cervical cancer at earlier stages.[11] It is now well established that with training, a physician or even a healthcare worker can identify acetowhite (with VIA) or mustard yellow (with VILI) lesions on the cervix, which are indicative of cancerous or precancerous tissue. Several studies in India have demonstrated that VIA and VILI have

comparable sensitivity and specificity to cytology while offering the advantages of being simple to perform and cost-effective for large scale implementation.[12] A randomized controlled trial in India has shown a 30% reduction in cervical cancer incidence [11] and a modeling study showed that even a single VIA test at 35 years of age can significantly decrease the risk of mortality from and incidence of advanced cervical cancer when compared to no screening.[13]

The Government of India's Ministry of Health and Family Welfare, recently launched the Operational Framework for the Management of Common Cancers which includes the use of VIA in primary care settings across India.[14] However, awareness about cervical cancer among the public is very low and there are only a few centers with cancer screening facilities throughout the country, which makes early detection and treatment very difficult. Furthermore, to move forward on this framework, it is important to consider the existing evidence in a critical manner. Public health evidence is usually the result of observation, theory and experiments, and the usefulness of this evidence may vary by the stakeholder type. Three distinct categories of scientific evidence have been proposed: (a) type 1 focuses on the causes of disease and the magnitude of risk factors, (b) type 2 on the relative impact on specific interventions, but Brownson and colleagues specifically emphasize (c) type 3 evidence, which shows how and under which "contextual" conditions, were the interventions implemented and how they were received.[15]

In promoting evidence-based public health, contextual information is information that is needed to adapt and implement an evidence-based intervention in a setting or population. Contextual information can be critical for moving clinical interventions to population-level and policy level interventions. To date, there have been no systematic reviews of published literature on community based cervical cancer programs in India that could provide this contextual information. For this review, we sought to answer two specific questions concerning the context in which cervical cancer screening is delivered: How were community-based cervical cancer screening programs implemented in India and what were the barriers and facilitators to implementing community-based cervical cancer screening programs using VIA methodology in India?

Methods

Protocol and registration

The protocol for this review was registered with the PROSPERO International Prospective Register of Systematic Reviews (No. CRD42016032601). This review was conducted and is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[16]

Information sources and search strategy

The initial database search was conducted by one author (PA) and the search strategy is provided in Appendix A. The electronic databases included Medline, Embase, PsychInfo and Cochrane Database of Systematic Reviews searched using the OVID platform up to December 31st, 2015. Gray literature was not included, as they did not meet the standards

associated with peer-reviewed publications. Conference abstracts were excluded since complete information about the implementation of the project was not available. We also excluded case studies, commentaries, proposed studies, protocol papers and editorials. Reference lists for all retrieved studies and table of contents for high-yield journals were also searched. English language restrictions were applied to the search. The search strategy was first created for Medline, which was then adapted for other database searches.

Eligibility criteria and study selection

Two authors (PA and NM) independently screened all the citations. Titles and abstracts were first screened for inclusion; when eligibility could not be ascertained, full-text articles were screened. Disagreements were resolved by consensus. To be included in the review, peer-reviewed journal articles had to report results from cervical cancer screening programs, which were community-based, conducted in India, and used visual inspections methods using acetic acid (VIA). Hospital-based studies, studies that did not include VIA as one of the screening methods and those that were conducted outside India, were excluded.

After removal of duplicates, abstracts were screened according to the eligibility criteria and a total of 20 research papers were found eligible to be included in this review.[5, 6, 9, 10, 17–32] We included observational, program effectiveness, acceptability and feasibility studies so as to provide a rich discussion about implementation of VIA in community-based settings in India. An additional 10 papers provided details about the 20 unique studies and were deemed to be critical for this review.[8, 11, 12, 22, 33–37]

Data collection process

When an article reported studies done in different locations, only information pertinent to India was extracted. Implementation data was primarily extracted from the discussion section in the articles that spoke about the authors experience in implementing the study. Data were extracted using a standardized form, which included the following variables: authors, year of publication, screening coverage, recruitment strategies, study methods and infrastructure, screening test accuracy and outcomes, diagnosis and treatment follow-up and implementation factors.

Risk of bias in individual studies

Methodological quality was assessed independently by two reviewers using the Effective Public Health Practice Project Group’s tool.[38] Disagreements were resolved by consensus. The tool allows studies to be rated on the following components: participation selection, study design, control of confounders, blinding, data collection methods, loss to follow-up, intervention integrity and analyses. Cumulative scores were reported as: strong (no component rated weak), moderate (one component rated weak), and weak (two or more components rated weak).

Results

Study characteristics

Figure 1 describes the literature search strategy, and characteristics of the studies included in this review are summarized in Table 1. The initial search of the databases resulted in 1,228 citations. From a manual search, an additional 18 abstracts were identified resulting in 1,246 citations in total. Of these, 42 were duplicates. The final selection of 20 studies included a total of 313,553 women at 12 unique sites across India.[5, 6, 9–11, 17–22, 24–30, 32, 39]. Seventeen were cross-sectional studies [5, 6, 9, 10, 17–21, 24–30, 39] and three were randomized controlled trials.[11, 22, 32]

Synthesis of results from individual studies

Screening coverage—Of the 20 studies, 10 were conducted in rural areas [5, 9, 11, 22, 24–26, 28–30], four in urban areas [6, 10, 20, 32], three in urban and rural areas [19, 21, 27], while three studies did not specify the type of community where the study was conducted. [17, 18, 39] As seen in Fig 2, the twenty studies included 12 unique study sites all across India. Eleven studies did not provide information on the number of eligible women in the communities being studied.[6, 9, 10, 17, 19–21, 27, 29–31] Gravitt *et al.*[24] used census lists to enumerate the target population in the community, while four other studies [5, 8, 11, 26] conducted household surveys to enumerate the eligible population. Shastri *et al.*[32] used both census lists and conducted household surveys of the 20 clusters included in their trial. Of the nine studies [5, 11, 12, 22, 24–26, 28, 32] that provided the number of eligible women in the communities being studied, the participation rates ranged from 41.6% to 78.6%.

Seventeen studies included women in the age groups of 30–59 years.[5, 6, 9, 10, 17–24, 26, 28–31] Of the remaining three, one study [32] included 35–64 year old women while two other studies [25, 27] set their inclusion age group to be from 30–49 years. Overall, among the 20 studies included in this review, six studies [5, 18–20, 24, 30] included women below 30 years of age (starting at 25 years) and nine studies [6, 9, 10, 18–20, 24, 26, 32] included women above the age of 60 years. All studies recruited women who were asymptomatic and/or apparently healthy, ever married, non-pregnant, intact uterus, and with no previous history of cervical cancer. However, two studies noted the presence of symptomatic women in their study sample. One study reported 83.1% of the total study sample to be symptomatic [28], whereas another reported some women to be symptomatic (with symptoms such as persistent vaginal discharge, post-coital bleeding and irregular bleeding) without specifying the actual number.[31]

Recruitment strategies

Of the 20 studies, four studies did not describe their recruitment strategies nor provide any information on who conducted the recruitment.[17, 21, 26, 31] The remaining 16 studies, used motivational and/or health education campaigns that were either group or one-on-one counselling for recruiting women into the study. Nine studies used audiovisual (e.g. radio, films, etc.) or written (e.g. pamphlets, brochures, etc.) information media for recruitment.[6, 18–20, 22, 27–29, 32] Eight studies [10, 11, 20, 22, 24, 27, 30, 32] collaborated with local

organizations (e.g. NGO's, women's self-help groups, etc.) and/or involved local leaders (e.g. social or religious leaders, village *panchayat*s, civic leaders, etc.) during recruitment, and only one study conducted by Nene, *et al.* included family members and husbands when recruiting women from the communities.[22] For recruitment, nine studies used health workers (e.g. Auxiliary Nurse Midwives (ANMs) or ASHA workers), [5, 6, 11, 19, 20, 22, 25, 28, 30], seven studies used social workers [6, 9, 10, 18, 28, 29, 32], and seven studies used field workers and/or volunteers [6, 11, 22, 24, 27–29].

Study methods and infrastructure

As shown in Table 1, 17 studies were cross-sectional [5, 6, 9, 10, 17–21, 24–31] and three studies were randomized controlled trials. [22, 23, 32] Of the 17 cross-sectional studies, 11 compared VIA with other screening methods such as VILI, VIA with low-level magnification, Pap smears and HPV DNA tests.[5, 6, 17–21, 25, 27–29] One study measured the prevalence of Human Papillomavirus (HPV) infection and Cervical Intraepithelial Neoplasia (CIN) in a previously unscreened population, [26] and another study evaluated the performance of colposcopy in further evaluating VIA or HPV DNA positive women in the community.[31] Four observational studies were described as program effectiveness, acceptability and or feasibility of implementing a VIA screening program in a community-based setting.[9, 10, 24, 30]

Three studies did not provide any information on the screening site infrastructure.[18, 25, 31] Of the 17 studies that did provide information, Kumar *et al.* used mobile vans to provide screening services in the community [10], while Gravitt *et al.* provided transportation services for women from their villages to the medical center.[24] In the 15 remaining studies, seven studies [6, 20, 22, 26–29] used government public health setups (e.g. primary healthcare centers, urban health centers, district hospitals) and others used convenient locations to set-up temporary, open access screening clinics in target communities.[5, 9, 17, 19, 21, 23, 30, 32]

Screening test providers and performance

Two studies did not mention who conducted the screening test. [9, 28] Of the 18 studies that did provide the information, Gravitt *et al.* used physicians, 14 studies [5, 10, 17, 18, 21–23, 25–27, 29–32] used health workers (including nurses, ANM and cytotechnicians) and five studies [5, 23, 29, 30, 39] used both healthcare workers and physicians. These studies usually mentioned medical supervision or cross-examination by medical officers as a method of quality assurance in reporting of VIA results. The three remaining studies used non-health care workers such as high school or university graduates in arts and science.[6, 19, 20]

Among the 20 studies included in the review, six studies did not provide any information on the training provided to individuals conducting the screening.[9, 10, 26, 27, 29, 31] In 14 studies that provided training, 10 studies [5, 6, 17, 19, 20, 23–25, 30, 32] reported using the manual developed by the International Agency for Research on Cancer (IARC) [40] and most of these studies provided refresher training prior to starting the study or on an annual basis. Only four studies reported evaluating the training for screening providers.[5, 6, 21, 22]

Since Kumar *et al.* had the study objective of measuring the overall acceptance and satisfaction levels among women undergoing health education and screening in their program, the authors did not report screening test outcomes or screen positivity. The range for screen positivity was between 1.37% and 18.7% (Table 1). Only ten studies reported the sensitivity and specificity for VIA (Table 2).[6, 18–21, 24, 25, 27–29] Of the studies that reported test accuracy at CIN Grade 2+, the VIA sensitivity ranged from 16.6% to 82.6%, and specificity 82.1% to 96.8%. At CIN Grade 3+, the sensitivity ranged from 7.7% to 67.9%, and specificity from 87.4% to 96.7%.

Of the ten studies that provided information on test accuracy, four studies used histology [24, 25, 27, 28], five studies used histology and/or colposcopy[6, 18–20, 29], and one study used colposcopy [21] as their reference standard. For the five studies that used histology and/or colposcopy – study authors reported using colposcopy findings as the reference standard for women without a biopsy. Five of the 10 studies conducted a colposcopy on all the screened women, whereas four studies conducted colposcopy only on women who were VIA positive. Gravitt *et al.*[24] conducted colposcopy on a random sample of 20% of the women who screened negative to obtain data for correction of verification bias. Four of the six studies that used colposcopy findings as a reference standard, blinded the colposcopists to the VIA results. Seven studies used CIN Grade 2+ as the threshold to assess disease status. Kamal *et al.*[21] used colposcopy positivity as their disease threshold and defined it as dense, acetowhite epithelium with coarse punctations, thick leukoplakia, atypical vessels and colposcopically suspect invasive cancer or frank growth. Two studies used a histological diagnosis of High-grade Squamous Intraepithelial Lesion (HSIL) as their disease threshold.

Diagnosis and Treatment

All studies included in this review conducted the diagnostic follow-up using colposcopy and guided biopsies, when necessary (Table 3). Fourteen studies offered same-visit colposcopy and biopsies to women who needed them.[5, 6, 9, 10, 18–23, 25, 29, 30, 39] Basu *et al.*[26] did not report when colposcopy was performed, whereas Kamal *et al.*[21] conducted the study in two different sites (urban and rural) but did not have colposcopy available on the same day in the rural site. In these studies, the loss to follow-up ranged from 0 to 1.2%. In the five studies that did not conduct the diagnostic follow-up on the same visit, loss to follow-up for diagnosis ranged from 10% to 70.9%. Amongst the six studies that provided data on biopsies, the loss to follow-up ranged from 2.6% to 38% with participant refusal for biopsy, being the most commonly cited reason.[6, 9, 24–26, 39] Six studies did not provide any information on the number of women lost to follow-up for diagnostic evaluations.[5, 10, 19, 26, 27, 30]

Two studies reported providing cryotherapy during the same visit.[23, 30] Sankaranarayanan *et al.*[23] reported using nurses to provide cryotherapy during the same visit, whereas Poli *et al.*[30] provided cryotherapy in the same visit for the first two years but discontinued it for the remainder of the study citing logistical issues with gas supply needed for cryotherapy. Six studies did not provide information about the treatment given to women who tested positive on VIA.[18–21, 26, 31] Six studies reported referring women to further management to tertiary care centers.[9, 10, 23, 27, 28, 30] In the remaining eight studies,

compliance to treatment ranged from 58.2% to 100% for women diagnosed with CIN Grade 2, 3, or invasive cancer.[5, 6, 17, 22, 24, 25, 29, 32] Six studies provided details about treatment given to women diagnosed with CIN Grade 1/pre-invasive cancer, with reported treatment compliance rates of 39.4% to 80.6%.[5, 6, 22, 29, 30, 32]

Implementation barriers and facilitators

Six major themes were identified related to implementation barriers to community-based screening programs: 1) limitations of the VIA test performance in terms of sensitivity and specificity; 2) logistical and infrastructure challenges; 3) non-participation of women; 4) competency levels of healthcare workers providing the screening tests; 5) integration of cervical cancer screening with breast/oral cancer screening and delivery of other healthcare services; and 6) difficulties encountered in diagnostic and treatment follow-up.

Satyanarayana *et al.*[28] discussed the possibility of missing cases and reported a 50% sensitivity for VIA in a realistic rural community setting. Jeronimo *et al.*[27] reported lower specificity for VIA and as a consequence discussed the possibility ≥50% of the women being referred to either colposcopy or unnecessary treatment as compared to other screening tests like Pap smears or HPV DNA testing. A 2003 study reported the lack of criteria to define VIA positivity as a barrier to implementing cervical cancer screening programs.[18] Logistical issues in the studies included ensuring uninterrupted cryo gas supply in the field clinics for treatment,[30] to selecting screening study sites based on accessibility by road, availability of health centers and permission required from local health authorities.[26] Gravitt *et al.*[24] in their study in rural Andhra Pradesh reported that 58% of the eligible women refused to participate in the study. In the focus groups conducted by the authors, reluctance to participate was reported as being related to perception that there was no need to go to the clinic when they have no symptoms.[24]

While reporting on competency levels of individuals conducting the screening tests, Sankaranarayanan *et al.*[19] highlighted the heterogeneous service delivery conditions that play an important role in implementing cervical cancer screening programs in the real world settings. Specifically, they discussed the issues of variable educational backgrounds of test providers and variable lengths of experience of colposcopists and pathologists, which could impact the interpretation of subjective tests such as VIA. None of the studies included in this review described the colposcopy related experience levels of the colposcopists. In Basu *et al.* [9] study, women participating in the screening program expected treatment for other health problems they were experiencing and were disappointed to note that the program only provided cervical cancer screening. Thus, the study authors discussed that cervical cancer screening could not be run as a stand-alone program, and needed to be integrated with existing primary health services. The studies conducted by Kamal *et al.*[21] and Satyanarayana *et al.*[28] reported higher rates of loss to follow-up when diagnostic follow-up with colposcopy and/or biopsies were not provided on the same visit. Bhatla *et al.* in their study of 3,000 women, reported 2/3^{rds} of the VIA positive women received treatment within four months of diagnosis, thus highlighting a long delay between screening and treatment. [5] They discussed the possibility of minimizing delays with a single visit ‘screen and treat’ approach reducing the number of women not receiving treatment.

Three major themes were identified in this review that facilitated implementation of cervical cancer screening programs in a community-based setting: 1) standardization of training that maintained competency of test providers; 2) collaborations with community-based organizations and health education delivery for recruitment of participants; and 3) employing the 'screen and treat' method to reduce loss to follow-up. Several studies [5, 6, 17, 19, 20, 23–25, 30, 32] reported using the manual developed by the International Agency for Research on Cancer [40] to provide VIA screening training to healthcare providers. Using this manual and providing regular refresher trainings for the staff delivering the screening allowed the programs to maintain high levels of competency among test providers throughout the duration of the study. Studies in this review mentioned the importance of establishing collaborations with community-based organizations and local leaders in recruiting study participants.[10, 24, 27] Only one study [23] was able to provide evidence for the effectiveness, safety and acceptability of the 'screen and treat' method in a cervical cancer screening program in a low resource setting. Their study was able to achieve a relatively high compliance rate (74.8%) to treatment when compared to other studies not providing treatment at the same visit.

Risk of bias across studies

Table 4 presents the details of bias assessment. Three studies had a strong rating (no components rated weak), and one was assigned a moderate rating (one component rated weak), and 16 were assigned a weak rating (two or more components rated weak). The three studies that were rated strong were all randomized controlled trials. The most common risk of bias in all the studies reported was selection bias and non-randomization.

Discussion

Findings from this systematic review of 20 studies with a total of 313,553 women that were screened at 12 unique urban and rural sites across India that used VIA provides contextual information on how screening programs can be implemented in community-based settings across India. Studies that reported test accuracy for CIN Grade 2+, the VIA sensitivity values ranged from 16.6 – 82.6% and specificity ranged from 82.1 – 96.8%. Most studies provided same-visit colposcopy and biopsy with minimal loss to follow-up but only two studies described providing same-visit cryotherapy.

Almost 40% of the studies in our review used media, group and one-on-one counseling, and local social support to recruit women into the screening programs, which represents substantial investment prior to the implementation of screening programs in the community. The studies also reported substantial use of infrastructure in setting up screening programs in the communities including transportation and establishing screening sites, which required several collaborations. As evidence in the Tamil Nadu Cervical Cancer Screening Pilot Project, efforts to mobilize women for participation were restricted due to a lack of health education.[41] On the other hand Shastri *et al.* attributed high levels of participation, diagnosis and treatment compliance to effective health education programs.[32] When translating evidence from research studies into real world program settings, it is critical that

program planners consider the human and logistical capital required for successful implementation of cervical cancer screening programs.

Sauvaget *et al.* in their review reported that the screening provider's background (e.g. physicians, nurses, health workers) did not influence the test accuracy of VIA.[42] That cannot be addressed as the test providers in the studies included in this review had varying backgrounds and expertise, and none of the studies reported on the providers' experience levels, which may affect VIA test outcomes. Furthermore, authors frequently reported a learning curve, in the sense that VIA positivity rates were higher in the earlier stages compared to the later stages when conducting studies over a period of few years. VIA being a subjective test required the staff to develop some degree of experience prior to getting comfortable in delivering accurate test results.

An important consideration in this regard is the focus of screening programs to provide adequate training to the test providers. When studies reported providing training, the IARC manual was consistently used. However, not all studies provided refresher trainings or evaluated their training. Based on their experience in conducting screening programs, the Alliance for Cervical Cancer Prevention (ACCP) recommended providing screener training using a competency-based curriculum, combining both didactic and hands-on approaches, and conducting the trainings in a clinical setting similar to the service delivery conditions of the program site.[43] Studies included in this review did not provide information about the training of the test providers based on these criteria.

When screening tests such as VIA are being evaluated for large scale implementation, they need to be reliable and have good test characteristics in addition to being convenient, safe and acceptable by target community members.[44] Test reliability assesses the degree to which repeated measurements of the test yields the same result, and the accuracy of a test (specificity and sensitivity) is measured using cross-sectional studies with adequate sample size. Previous reviews, not focused on Indian or community-based settings, have reported sensitivity and specificity values of 79–82% and 91–92% by Sauvaget *et al.*[42], 79–83% and 84–85% by Arbyn *et al.*[45], 77% and 82% by Mustafa *et al.*[46], and 71.8% and 79.4% by Sritipsukho *et al.*[47] Compared to previous reviews, the sensitivity values reported in the included studies were lower and for specificity were in the same range when compared to previous reviews. Variation in test providers training, light source when conducting the VIA test in the field settings, and the preparation and storage of diluted acetic acid have previously been reported as possible explanations for wide variations in sensitivity and specificity for VIA conducted in community-based settings.[48]

According to Mahe & Gaffkin, several basic features are necessary to ensure internal validity in cross-sectional studies reporting test characteristics, including: a) final disease status data should be obtained for all subjects; b) all test results must be determined independently of previous results; c) the reference standard used to determine the disease status should be accurate; and d) the full "spectrum" of the disease should be included in the study.[49] In the cross-sectional studies that reported test accuracy, six used colposcopy as the reference standard and provided it to all screened women. However, the ability of colposcopy to categorize pre-cancer and cancers is poor and can cause inflation of the

sensitivity values of the tests.[39, 50] More importantly, abnormalities on colposcopy are likely to be correlated with VIA positivity since both tests are subjective and rely on the visual inspection.[42] Two of the six studies using colposcopy as a reference standard did not blind the colposcopists to the VIA findings, which may have introduced ascertainment bias in these studies. Five of the ten studies reporting test accuracy did not apply the reference standard test to all screened women indicating the possibility of verification bias in the included studies. Furthermore, the quality and accuracy of the disease definition could be substantially affected by the experience levels of the colposcopists or pathologists interpreting histology, which was not reported consistently in the studies included in this review.

In low resource settings, visual inspection approaches offer a distinct advantage of immediate availability of screening test results, which provides health care professionals an opportunity to offer treatment during the same visit; widely known as the same day “screen-and-treat” approach. This approach has shown to reduce the likelihood of failure to follow-up and prevent advanced disease as demonstrated in several studies from India and other low-and middle-income countries included in a review.[41] Only two studies included in this review reported using the ‘screen-and-treat’ approach, with Poli *et al.* having to discontinue the approach after the initial two years due to logistical issues of ensuring uninterrupted cryo gas supply. Furthermore, treating women without confirming the diagnosis can result in considerable overtreatment as demonstrated in a meta-analysis, which concluded that if VIA alone was used to screen women, compared to Pap smears, 58 more per 1000 women would receive treatment unnecessarily for CIN grade 2–3 lesions.[46] Furthermore, a meta-analysis reported that 14.8% (65/439) of the women treated with cryotherapy had infertility and 12 reported spontaneous abortions in 210 pregnancies.[51] Scaling-up programs will require planners to keep in mind that if diagnostic services are provided at the screening site, fewer women would need to be referred, thereby reducing loss to follow-up. In waiting for diagnostic confirmation, this model also prevents overtreatment by cryotherapy, which has been reported in the ‘screen and treat’ model.[52] This may require creative implementation strategies that involve a wide variety of stakeholders such as social scientists, family members, and both public and private healthcare partnerships.

Most of the evidence in this review was derived from cross-sectional studies conducted in controlled community settings with limited information on the adaptation and translation of an effective intervention in socially intact groups or communities. Two studies in this review [28, 31] included information from symptomatic women in their study, which may bias the evidence regarding VIA effectiveness. However, the information synthesized in this review will be critical as national programs are implemented and evaluated for sustainability. It is also possible that research studies using VIA methods with non-significant findings may not have been accepted for publication and might have led to publication bias. We also did not include any qualitative studies or conference abstracts since complete information about the screening programs was not available. Nonetheless, to the best of our knowledge, this is the only review that focused on reviewing VIA based cervical cancer screening programs in community-based settings across India.

Overall, VIA based screening programs implemented in these studies were found to be appropriate, acceptable and feasible in community-based settings in India. Implementation barriers and facilitators presented in this review could substantially influence the future implementation of cervical cancer programs at a national level in India. The lower test accuracy values highlight the challenges involved in providing VIA in a community-based setting. A concern for over-diagnosis resulting in psychological distress for the false positives and may lead to over-treatment is evident if the 'screen and treat' approach is implemented in future screening programs.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Appendix A. Medline through Ovid Search String

"Cervical Neoplasm, Uterine" OR "Cervical Neoplasms, Uterine" OR "Neoplasm, Uterine Cervical" OR "Neoplasms, Uterine Cervical" OR "Uterine Cervical Neoplasm" OR "Neoplasms, Cervical" OR "Cervical Neoplasms" OR "Cervical Neoplasm" OR "Neoplasm, Cervical" OR "Neoplasms, Cervix" OR "Cervix Neoplasms" OR "Cervix Neoplasm" OR "Neoplasm, Cervix" OR "Cancer of the Uterine Cervix" OR "Cancer of the Cervix" OR "Cervical Cancer" OR "Uterine Cervical Cancer" OR "Cancer, Uterine Cervical" OR "Cancers, Uterine Cervical" OR "Cervical Cancer, Uterine" OR "Cervical Cancers, Uterine" OR "Uterine Cervical Cancers" OR "Cancer of Cervix" OR "Cervix Cancer" OR "Cancer, Cervix" OR "Cancers, Cervix"

AND

"Early Detection of Cancer" OR "Cancer Early Detection" OR "Cancer Screening" OR "Screening, Cancer" OR "Cancer Screening Tests" OR "Cancer Screening Test" OR "Screening Test, Cancer" OR "Screening Tests, Cancer" OR "Test, Cancer Screening" OR "Tests, Cancer Screening" OR "Early Diagnosis of Cancer" OR "Cancer Early Diagnosis"

AND

"India"

Total search results = 1228

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Highlights

- Cervical cancer screening programs using visual inspection methods in India are reviewed
- Focus of the review is to understand implementation of community based screening programs
- For visual inspection, specificity and sensitivity values range from 82.1–96.8% and 16.6–82.6% respectively
- Standardized training for community health workers was critical to screening test accuracy
- Logistical and infrastructural challenges were identified as most common barriers to implementation

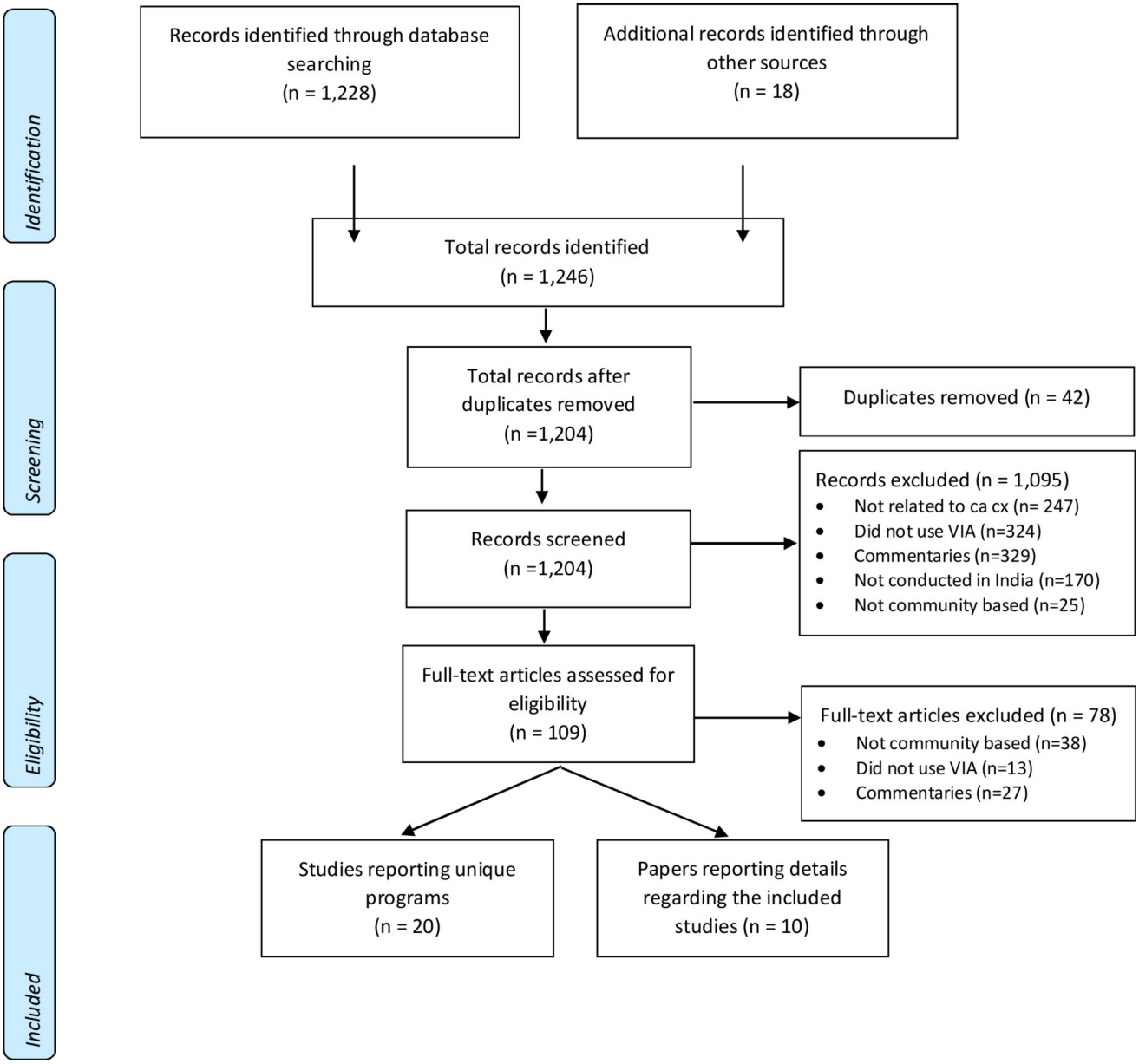

Fig 1. PRISMA 2009 Flow Diagram

Implementing Community-based Cervical Cancer Screening Programs using Visual Inspection Methods in India: A Systematic Review

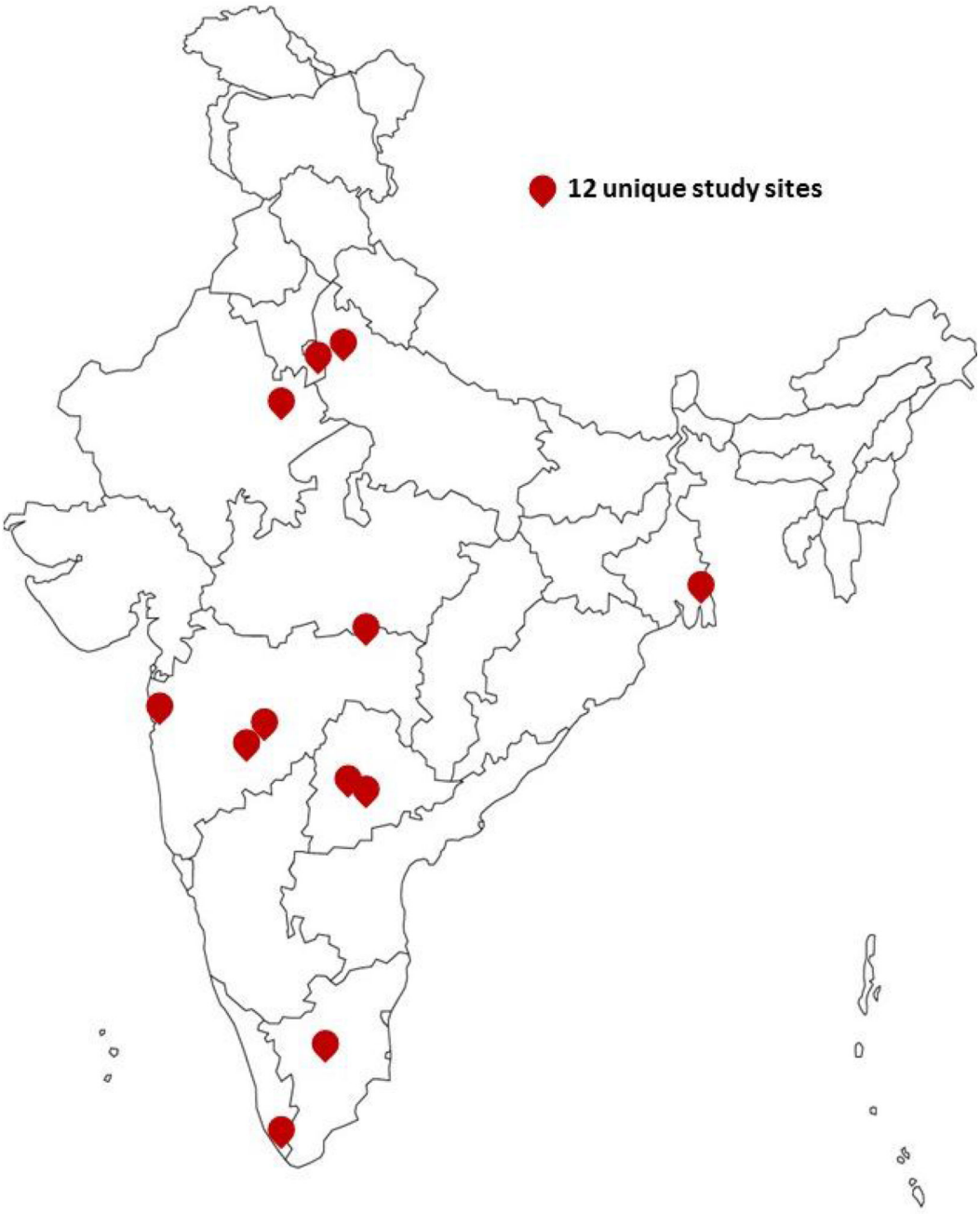

Fig 2.
Map of India showing the twelve unique study sites

Table 1

Characteristics of studies included in this review

First Author	Year	Duration of study	Community	Location	Age range	Screening tests	Screening conducted by	Number of screened women	Reference standard	Sensitivity	Specificity	Screen positivity
Cross Sectional Studies[5, 6, 9, 10, 17–21, 24–31]												
Sankaranarayanan *et al.*[17]	1998	2 years	Unclear	Thiruvanathapuram (KL)	Not Reported	VIA, Cytology	Cytotechnicians	3000	Not Reported	Not Reported	~92.2%	9.93%
Basu *et al.*[6]	2003	2 years 6 months	Urban	Kolkata (WB)	30 – 64 years	VIA, VIAM, Cytology	Female Health Workers	5843	Histology & Colposcopy	CIN II+: 55.7%	CIN II+: 82.1%	18.70%
Sankaranarayanan *et al.*[18]	2003	3 years	Unclear	Thiruvanathapuram (KL)	25 – 65 years	VIA, VILI, Cytology	Female Health Workers	4444	Histology & Colposcopy	CIN II+: 82.6%	CIN II+: 86.5%	HT: 15.8%
Sankaranarayanan *et al.*[19]	2004[a]	5 years	Urban & Rural	Kolkata (WB), Jaipur (RJ), Mumbai (MH), Thiruvanathapuram (KL)	25 – 65 years	VIA, VILI	Female Health Workers, Nurses, Cytotechnicians	31,154	Histology & Colposcopy	HSIL: 73%	HSIL: 84.8%	16.20%
Sankaranarayanan *et al.*[20]	2004[b]	4 years	Urban	Kolkata (WB) & Mumbai (MH)	25 – 65 years	VIA, VIAM	Female Health Workers	18,675	Histology & Colposcopy	HSIL: 60.3%	HSIL: 86.8%	14.10%
Basu *et al.*[9]	2006	1 year	Rural	Kolkata (WB)	30 – 65 years	VIA	Female Health Workers	2184	Not Reported	Not Reported	Not Reported	11.30%
Kamal *et al.*[21]	2007	7 years	Urban	Nagpur (MH)	*Repoductive age group	VIA, Cytology	Multipurpose Health workers	1347	Colposcopy	Colpo + : 29.6%	Colpo +: 92.1%	12.00%
			Rural					2392	Colposcopy	Colpo + : 26.2%	Colpo +: 88%	16%
Bhatla *et al.*[5]	2009	1 year 6 months	Rural	Faridabad (HR)	25 – 59 years	VIA, VILI, Cytology	Female Health Workers	3000	Not Reported	Not Reported	Not Reported	14.20%
Gravitt *et al.*[24]	2010	2 years 6 months	Rural	Medchal (AP)	> 25 years	VIA, Cytology, HPV DNA	Gynecologists	2331	Histology	CIN II+: 16.65% CIN III +: 31.56%	CIN II+: 87.36% CIN III +: 87.45%	12.90%
Kumar *et al.*[10]	2011	5 months	Urban	Mumbai (MH)	30 – 65 years	VIA, VILI, CBE, OVE	Primary Health Workers	182	Not Reported	Not Reported	Not Reported	Not Reported
Deodhar *et al.*[25]	2012	10 months	Rural	Solapur (MH)	30 – 49 years	VIA, VIL, Cytology	Nurses	5648	Histology	CIN II+: 64.5%	CIN II: 84.2%	16.90%
Basu *et al.*[26]	2013	i) 4 years ii) 2 years ii) 2 years	Rural	Kolkata (WB)	30 – 65 years	VIA, HC2	Female Health Workers	35,308	Not Reported	Not Reported	Not Reported	1.37%
Jeronimo *et al.*[27]	2014	Unclear	Urban & Rural	Dadri (UP) & Hyderabad (AP)	30 – 59 years 30 – 49 years	VIA, Cytology , CareHPV (Self collected), CareHPV (Physician collected)	Unclear	4925	Histology	CIN II+: 21.9% CIN III+: 7.69	CIN II+: 94.6 CIN III+: 94.5%	5.00%
Ghosh *et al.*[31]	2014	3 years	Unclear	Kolkata (WB)	30 – 60 years	VIA, HC2	Female Health Worker	30,773	Not Reported	Not Reported	Not Reported	7.50%

First Author	Year	Duration of study	Community	Location	Age range	Screening tests	Screening conducted by	Number of screened women	Reference standard	Sensitivity	Specificity	Screen positivity
Satyanarayana *et al.*[28]	2014	3 years	Rural	Dadri (UP)	30 – 60 years	VIA, VILI, Cytology	Not described.	4198	Histology	CIN-II+: 54.5% CIN III+: 50.%	CIN II+: 96.8% III+: 96.7%	9.70%
Basu *et al.*[29]	2015	4 years 4 months	Rural	Kolkata (WB)	30 – 60 years	VIA, HC2	Female Health Workers	39,740	Histology & Colposcopy	CIN II+: 61.0%; CIN III: 59.9%; CIN III+: 67.9%	CIN II+: 93.4%; CIN III: 93.1%; CIN III+: 93.2%	7.10%
Poli *et al.*[30]	2015	7 years	Rural	Hyderabad (AP)	26 – 60 years	VIA	Auxiliary Nurse Midwives	18,869	Not Reported	Not Reported	Not Reported	10.75%
Randomized Control Trials[11, 22, 32]												
Shastri *et al.*[32]	2013	16 years	Urban	Mumbai (MH)	35 – 64 years	VIA, CBE	Primary Health Workers	67070	Not Reported	Not Reported	Not Reported	1.75 – 1.91%
Sankaranarayanan *et al.*[11]	2007	3 years 6 months	Rural	Dindigul (TN)	30 – 59 years	VIA	Nurses	31,343	Not Reported	Not Reported	Not Reported	9.90%
Nene *et al.*[22]	2007	4 years	Rural	Osmanabad (MH)	30 – 59 years	VIA, Cytology, HPV DNA	Nurses	26,755	Not Reported	Not Reported	Not Reported	14%

*VIA = Visual Inspection with Acetic Acid, VILI = Visual Inspection with Lugol's Iodine, VIAM = Visual Inspection with Acetic acid under Magnification, CBE = Clinical Breast Examination, OVE = Oral Visual Examination, UP = Uttar Pradesh, MH = Maharashtra, WB = West Bengal, HR = Haryana, AP = Andhra Pradesh, RJ = Rajasthan, KL = Kerala, TN = Tamil Nadu.

Table 2

Criteria for test accuracy studies

Authors	Year	Reference Standard used	Colposcopy done on	Colposcopists blinded to VIA results	Disease threshold
Basu *et al.*[6]	2003	Histology/ colposcopy *	All women	No	CIN II+
Sankaranarayanan *et al.*[18]	2003	Histology/ colposcopy *	All women	Yes	CIN II+
Sankaranarayanan *et al.* [19]	2004	Histology/ colposcopy *	All women	Yes	HSIL
Sankaranarayanan *et al.*[20]	2004	Histology/ colposcopy *	All women	Yes	HSIL
Kamal *et al.* [21]	2007	Colposcopy	All women	Yes	Colposcopy +
Gravitt *et al.*[24]	2010	Histology	VIA +	No	CIN II+
Deodhar *et al.*[25]	2012	Histology	VIA +	No	CIN II+
Satyanarayana *et al.*[28]	2014	Histology	VIA +	No	CIN II+
Jeronimo *et al.*[27]	2014	Histology	VIA +	No	CIN II+
Basu *et al.*[29]	2015	Histology/ colposcopy *	VIA +	No	CIN II+

* Colposcopy results were used as the final diagnosis where histology was not available.

Table 3

Diagnostic and Treatment Follow-up

First Author	Year	Diagnostic follow-up	Same day diagnosis/Referred	Loss to follow-up for colposcopy	Loss to follow-up for biopsy	Reasons for loss to follow up	Information regarding treatment provided?	Same visit cryotherapy	Treatment strategy		
									CIN1	CIN2/3	Invasive cancer
Sankaranarayanan *et al.*[17]	1998	Colposcopy and Histology	Referred	10%	Not reported	Not reported	Yes	Not reported	77 cases of mild dysplasia were considered as false positives and not treated.		
Basu *et al.*[6]	2003	Colposcopy and Histology	Same day	0%	11.60 %	Biopsies were not obtained or inadequate or inconclusive in these cases	Yes	Unclear	Of 336 women detected with low grade lesions, 127 had cryotherapy and two had LEEP. A total of 207 (61.6%) did not receive treatment	Of the 122 women detected with high grade lesions, 48 had cryotherapy, 20 had LEEP, and three had conisation. A total of 51 (41.8%) women did not receive treatment.	
Sankaranarayanan *et al.*[18]	2003	Colposcopy and Histology	Same day	0%	Not reported	Not reported	Not reported	Not reported	Not reported		
Sankaranarayanan *et al.*[19]	2004	Colposcopy and Histology	Same day	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		
Sankaranarayanan *et al.*[20]	2004	Colposcopy and Histology	Same day	0%	Not reported	Not reported	Not reported	Not reported	Not reported		
Basu *et al.*[9]	2006	Colposcopy and Histology	Same day	0%	4.40 %	Women refused	Yes	No	Treated appropriately after biopsy results		
Kamal *et al.*[21]	2007	Colposcopy	Same day	0%	Not reported	Not reported	Not reported	Not reported	Not reported		
		Colposcopy	Referred	84%	Not reported	Referral	Not reported	Not reported	Not reported		
Nene *et al.*[22]	2007	Colposcopy and Histology	Same day	1.40%	Not reported	Not reported	Yes	No	80% of the women with CIN 1 received treatment	Women with moderate to severe CIN (CIN2+) were treated with cryotherapy as eligible and/or referred for further management. Overall, 85% with CIN 2 and 88% with CIN 3 received treatment and approximately 15% were lost to follow-up.	Not reported
Sankaranarayanan *et al.*[23]	2007	Colposcopy and Histology	Same day	1.20%	Not reported	Not reported	Yes	Yes	A central referral center was established at the CFCHC, Ambillikai, with facilities for treatment of detected lesions by loop electrosurgical excision procedure (LEEP) and cold knife conisation. When lesions were too extensive for cryotherapy, women were given an appointment to visit the referral center for LEEP or cold knife conisation by doctors.		Women with suspected invasive cancer were referred to the clinical oncology department of the CFCHC or to other cancer treatment facilities near the district for investigations, staging and treatment.

First Author	Year	Diagnostic follow-up	Same day diagnosis/Referred	Loss to follow-up for colposcopy	Loss to follow-up for biopsy	Reasons for loss to follow up	Information regarding treatment provided?	Same visit cryotherapy	Treatment strategy		
									CIN1	CIN2/3	Invasive cancer
Bhatla *et al.*[5]	2009	Colposcopy and Histology	Same day	Not reported	Not reported	Not reported	Yes	No	9/37 (24.3%) women diagnosed with CIN 1 were lost to follow up	All 20 women with CIN 2+ underwent treatment. 0% lost to follow-up	
Gravitt *et al.*[24]	2010	Colposcopy and Histology	Referred	44%	38%	Women refused	Yes	No	No info provided for CIN 1	Of the 19 women who had CIN2+, we provided LEEP for 2, hysterectomy for 9, and referral to the cancer hospital for radiation therapy for 4 women who had invasive cancer. Four women (21%) refused treatment despite several direct visits by the study gynecologist for direct counseling.	Not reported
Kumar *et al.*[10]	2011	Colposcopy and Histology	Same day	Not reported	Not reported	Not reported	Yes	No	Referred to tertiary care center		
Deodhar *et al.*[25]	2012	Colposcopy and Histology	Same day	0%	3.60 %	Refusal	Yes	Unclear	No info provided for CIN 1	Of 112, 98 received LEEP and 1 received LEEP + hysterectomy and 13 (11.6%) were lost to follow up.	Invasive cancers were referred to a tertiary hospital for further investigations and management.
Basu *et al.*[26]	2013	Colposcopy and Histology	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported		
Shastri *et al.*[32]	2013	Colposcopy and Histology	Referred	20.60 %	Not reported	Predictors of non-compliance: increasing age, manual labourers, illiteracy, language barriers, one time screening participation, women referred for both breast and cervical cancer	Yes	No	Compliance to treatment for pre-invasive cancer is 80.67%		Compliance to treatment for invasive cancer was 85.93%
Ghosh *et al.*[31]	2014	Colposcopy and Histology	Same day	0%	3.10%	Not reported	Not reported	Not reported	Not reported		
Jeronimo *et al.*[27]	2014	Colposcopy and Histology	Referred	Not reported	Not reported	Not reported	Yes	No	Not reported	Women with moderate to severe CIN (CIN2+) were treated with cryotherapy as eligible and/or referred for further management.	Not reported
Satyanarayana *et al.*[28]	2014	Colposcopy and Histology	Referred	70.90 %	Not reported	Maybe referral	Yes	No	Referred to tertiary care center		
Basu *et al.*[29]	2015	Colposcopy and Histology	Same day	0%	2.60%	Refusal	Yes	No	CIN1 = 1880 were advised for yearly f/ups	The total patients diagnosed with CIN 2 + were 230 of which 37 (16.1%) were loss to follow up at CNCI.	Of the 48 women diagnosed with invasive cancer, 6

First Author	Year	Diagnostic follow-up	Same day diagnosis/Referred	Loss to follow-up for colposcopy	Loss to follow-up for biopsy	Reasons for loss to follow up	Information regarding treatment provided?	Same visit cryotherapy	Treatment strategy		
									CIN1	CIN2/3	Invasive cancer
											(12.5%) were loss to follow up
Poli *et al.*[30]	2015	Colposcopy and Histology	Same day	Not reported	Not reported	Not reported	Yes	No (only first two years)	Cryotherapy where eligible	Women requiring treatment for HSIL other than cryotherapy or with invasive cancer were referred to a higher center for appropriate treatment.	Not reported

Table 4

Risk bias assessment in included studies.

No.	Author, year	Selection Bias	Study Design	Confounders	Blinding	Data collection methods	Withdrawals and drop-outs	Final rating
1.	Sankaranarayanan *et al.*, 1998[17]	+++	+++	+	+	+++	+	3
2.	Basu *et al.*, 2003[6]	+++	+++	+	+	+	+++	3
3.	Sankaranarayanan *et al.*, 2003[18]	+++	+++	+	+	+	+	3
4.	Sankaranarayanan *et al.*, 2004[19]	+++	+++	+	+	+	+++	3
5.	Sankaranarayanan *et al.*, 2004[20]	+++	+++	+	+	+	+	3
6.	Basu *et al.*, 2006[9]	+++	+++	+	+	+	+++	3
7.	Kamal *et al.*, 2007[21]	+++	+++	+	+	+	+++	3
8.	Nene *et al.*, 2007[22]*	++	+	+	+	+	+	1
9.	Sankaranarayanan *et al.*, 2007[11]*	++	+	+	+	+	+	1
10.	Bhatla *et al.*, 2009[5]	+++	+++	+	+	+	+++	3
11.	Gravitt *et al.*, 2010[24]	+++	+++	+	+	+	+++	3
12.	Kumar *et al.*, 2011[10]	+++	+++	+	+	+	+++	3
13.	Deodhar *et al.*, 2012[25]	++	+++	+	+	+	+	2
14.	Basu *et al.*, 2013[26]	++	+++	+	+	+	+++	3
15.	Shastri *et al.*, 2013[32]*	+	+	+	+	+	++	1
16.	Ghosh *et al.*, 2014 [31]	+++	+++	+	+	+	+	3
17.	Jeronimo *et al.*, 2014[27]	+++	+++	+	+	+	+	3
18.	Satyanarayanan *et al.*, 2014[28]	++	+++	+	+	+	+++	3
19.	Basu *et al.*, 2015[29]	+++	+++	+	+	+	+	3
20.	Poli *et al.*, 2015[30]	+++	+++	+	+	+	+++	3

+ strong;

++ moderate;

+++ weak;

* randomized controlled trial; 1= strong; 2=moderate; 3=weak