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Advancing Cervical Cancer Prevention in India: Implementation Science Priorities

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ABSTRACT

Cervical cancer is the leading cause of cancer mortality in India, accounting for 17% of all cancer deaths among women aged 30 to 69 years. At current incidence rates, the annual burden of new cases in India is projected to increase to 225,000 by 2025, but there are few large-scale, organized cervical cancer prevention programs in the country. We conducted a review of the cervical cancer prevention research literature and programmatic experiences in India to summarize the current state of knowledge and practices and recommend research priorities to address the gap in services. We found that research and programs in India have demonstrated the feasibility and acceptability of cervical cancer prevention efforts and that screening strategies requiring minimal additional human resources and laboratory infrastructure can reduce morbidity and mortality. However, additional evidence generated through implementation science research is needed to ensure that cervical cancer prevention efforts have the desired impact and are cost-effective. Specifically, implementation science research is needed to understand individual- and community-level barriers to screening and diagnostic and treatment services; to improve health care worker performance; to strengthen links among screening, diagnosis, and treatment; and to determine optimal program design, outcomes, and costs. With a quarter of the global burden of cervical cancer in India, there is no better time than now to translate research findings to practice. Implementation science can help ensure that investments in cervical cancer prevention and control result in the greatest impact. ***The Oncologist*** 2013;18:1285–1297

Implications for Practice: Considerable research has been conducted on the prevention of cervical cancer in India. The majority of studies have focused on the feasibility, acceptability, and impact of secondary prevention of cancer through screening, early detection, and treatment. Despite this evidence, there have been few government-led public health programs to prevent and control cervical cancer. The primary goals of this review are to summarize the lessons learned from cervical cancer prevention research and pilot programs in India and to identify research priorities to facilitate the translation of existing knowledge into policies and programs that advance cervical cancer prevention.

INTRODUCTION

Cervical cancer is the most common cancer among women aged 15 years or older in India. Cervical cancer will occur in approximately 1 in 53 Indian women during their lifetime compared with 1 in 100 women in more developed regions of the world [1]. In 2010, there were nearly 74,000 new cases of cervical cancer in India. With 38% of cases occurring among women of reproductive age (15–49 years), the adverse social and economic impact of cervical cancer on families and communities is considerable [1].

Between 1980 and 2010, little progress was made in reducing cervical cancer mortality in India: 37 women died for every 100 new cases of cervical cancer in 1980 compared with 32 for every 100 new cases in 2010 [1]. High mortality rates are largely the result of nearly 70% of cervical cancer cases in India being diagnosed at an advanced stage (stage III or IV) [2]. Fewer than a third of Indian women diagnosed with stage III cervical cancer survive the first five years after their diagnosis, and the 5-year survival rate drops to nearly 6% among women diagnosed with stage IV disease [2].

In contrast to the United States and other high-income countries, where cervical cancer screening is offered as part of routine primary care, few large-scale screening programs exist in India [3]. Moreover, although primary prevention through human papilloma virus (HPV) vaccination is gaining acceptance in high-income countries and has been endorsed by the World Health Organization (WHO), vaccine awareness, access, and use are very low [4, 5]. However, cervical cancer prevention efforts appear to be gathering momentum. Coin-

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ciding with the United Nations High Level Summit on Non-Communicable Diseases in 2011, India's national government launched a program to address chronic and noncommunicable diseases (NCDs) that includes screening and treatment of cervical cancer. Simultaneously, several state governments decided to do a pilot test of their own NCD prevention efforts. In this context, we conducted a review of the cervical cancer prevention research literature and programmatic experiences to summarize the current state of knowledge and practice and recommend research priorities to facilitate the translation of existing knowledge into efficient, effective, and equitable public health action.

Methods

This paper is based on information gathered from a review of English-language peer-reviewed publications and gray literature (including unpublished program reports, white papers, and conference presentations) on cervical cancer prevention in India and interviews with individuals involved in the design and implementation of government-led cervical cancer prevention efforts in the southern state of Tamil Nadu.

The published literature was identified using ISI Web of Knowledge, PubMed, and Google Scholar using a broad time frame (1990 to the present). A combination of the following search terms was used: India, cervical cancer, screening, early detection, HPV, HPV vaccination, and visual inspection. The gray literature was identified using keyword search terms in Google's search engine, reviewing references of published papers, and searching Internet-based document repositories. Papers and reports were reviewed and key information regarding methods and findings was abstracted and organized thematically.

To better understand the translation of knowledge into practice, we conducted a case study of cervical cancer prevention efforts in the southern state of Tamil Nadu. Data sources included program reports and presentations, interviews, and field visits. Nine individuals (public health officials and cancer prevention experts) who were involved in program design and implementation were interviewed to ascertain factors that shaped program design, challenges faced in implementation, and strategies implemented to overcome those challenges. Field visits were made to a tertiary hospital where training in the diagnosis and treatment of cervical cancer is conducted for health care providers and to a district hospital and primary health center implementing cervical cancer screening, treatment, and referrals. Interviews and field notes were summarized thematically.

Research on Primary and Secondary Prevention of Cervical Cancer in India

Our review of the literature on cervical cancer prevention in India identified 44 peer-reviewed articles focused on the following themes: HPV prevalence and vaccination; performance of screening tools; and feasibility, acceptability, and effectiveness of screening and treatment interventions. Below we summarize the main findings by theme.

Primary Prevention Through HPV Vaccination

Available data indicate that HPV vaccination is a highly promising cervical cancer prevention method when used in conjunction with screening and treatment [6]. Approximately 70% of cervical cancers in India are caused by HPV types 16 and 18, which are targeted by the vaccine [7, 8]. However, there has been little empirical research on the feasibility, acceptability, and effectiveness of HPV vaccination in India. A qualitative study in the states of Gujarat and Andhra Pradesh identified three potential mechanisms for vaccine delivery: the existing national immunization program, adolescent health or cancer control services, and school- and community-focused campaigns [4, 9]. The study noted that successful introduction of the vaccine would depend on a communication strategy focused on raising community awareness, engagement with community gatekeepers, and advocacy to build political support for prevention. It also revealed that systems-level challenges associated with staffing, capacity, and coordination would have to be addressed [4]. Other research in southern India found that although parents held positive attitudes about vaccination, they were not in support of vaccinating pre-adolescent girls and felt that vaccination against HPV was more appropriate once girls had attained puberty [5].

Public provision of HPV vaccination has been debated in the mainstream press and in academic journals [4, 10–18]. Women's health activists and researchers in India have questioned the appropriateness of the HPV vaccination in light of limited data on safety and efficacy, the high cost, and the uncertain cost-effectiveness of the vaccine. They have argued that the government should focus on promoting awareness and ensuring access to comprehensive reproductive and sexual health services, including cervical cancer screening and treatment [14]. Others have challenged investments in HPV vaccination by disputing the data on India's cervical cancer burden, arguing that incidence rates are in fact on the decline in the country [15]. The deaths of four adolescent girls enrolled in a government-approved demonstration project in Gujarat and Andhra Pradesh escalated the controversy. Although an expert panel later concluded that the deaths were unrelated to the vaccine [9], the investigation revealed ethical violations related to the process of informed consent [11].

HPV vaccine debates in India raise several issues for consideration in future vaccination efforts. First is the need for systems to monitor, report, and respond to postvaccination adverse events. The Gujarat and Andhra Pradesh study found that although guidelines were available for postimmunization adverse event management, often they were not followed [4]. Additionally, the widely differing interpretations of the data on HPV vaccine safety among health activists, clinicians, public health practitioners, and journalists suggests that a more robust communication strategy is needed to disseminate evidence in support of vaccination. Research should identify effective ways to communicate information regarding the vaccines, including a focus on adolescent girls, partial efficacy, and the need for cervical cancer screening in adulthood.

Finally, cost and cost-effectiveness remain important considerations for India's HPV vaccination policy. A mathematic modeling study informed by empirical data from India found that pre-adolescent vaccination for HPV types 16 and 18 can reduce lifetime cervical cancer risk by 44%, assuming 70% vaccine coverage, and is more effective than screening alone, regardless of screening test, screening frequency, and target age groups [19]. Combining vaccination with screening was

cost-effective according to WHO benchmarks for developing countries at a vaccine cost of US$2 per dose or less.

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The Indian market price of the vaccine is approximately US$40 per dose. In 2013, the GAVI Alliance announced that it would offer the HPV vaccine at US$4.50 per dose to countries with a gross national income per capita below or equal to US$1520 [20]. The estimated total cost of vaccination per girl, taking into account three doses and vaccine delivery costs, is US$20.70 [21]. Eligible countries (of which there are 57, including India) can apply for support to introduce the vaccine nationwide or to conduct pilot projects that will enable them to prepare for national implementation. In light of the global evidence on HPV vaccination, pilot testing the vaccine and gathering empirical data on vaccine delivery costs and cost-effectiveness can significantly advance cervical cancer prevention efforts in India.

Secondary Prevention Through Screening

Secondary prevention through screening and treatment of precancerous and early stage cancerous cervical lesions can prevent disease progression and reduce subsequent morbidity and mortality. Substantial declines in cervical cancer incidence and mortality in high-income countries such as the United States have been attributed to screening. However, screening approaches used in high-income countries (namely, the annual Papanicolaou smear test) may not be appropriate in low- and middle-income countries where establishing laboratory infrastructure, training personnel such as cytotechnicians and pathologists, and implementing continuous quality assurance procedures have proven difficult [22]. Consequently, research has focused on evaluating visual inspection-based methods that use existing (or minimal additional) human resources and require less training and fewer clinic visits (Table 1).

Accuracy of Screening Tests

Over the past decade, 14 studies have been conducted in India to evaluate the accuracy and effectiveness of cervical cancer screening [23–34]. Studies have compared the specificity and sensitivity of visual inspection with acetic acid (VIA) or Lugol's iodine (VILI) and the Papanicolaou test and HPV DNA testing. These approaches have been implemented by health workers such as auxiliary nurse midwives (Table 2). The majority of these studies were cross-sectional in design and involved either community- or hospital-based samples [23–32, 35]; two studies were randomized controlled trials [33, 36–38]. To determine test sensitivity and specificity, most studies performed colposcopy for all participants and biopsy of abnormalities if indicated; in some, the colposcopist was blinded to the initial screening test results [24, 26, 27].

Salient findings of Indian studies on screening test performance are summarized in Table 3. Overall, research in India suggests that VIA and VILI have comparable sensitivity and specificity to Papanicolauo and HPV DNA test-based screening (Table 3). Studies have found that the sensitivity to detect cervical intraepithelial neoplasia (CIN) grade 2 or higher (CIN2+) is similar for VIA (range 64.5%–89.5%) and VILI (range 64.5%–100%) compared with Papanicolaou test (range 52.6%–62.3%). Research has found test specificity of VIA (76.4%–84.2%) to be lower than that of VILI (85.4%–93.4%) and HPV testing (80.7%–81.3%). Cytology testing has the highest specificity (76.1%–99.1%) [23–32, 35].

Studies have indicated that visual inspection-based approaches have lower test sensitivity when used with older women because of the migration of the transformation zone into the endocervical canal [37, 39]. Consequently, different screening strategies may be needed depending on the age group of the target population.

An advantage of visual inspection-based approaches is that the immediate availability of screening results provides the opportunity to conduct a biopsy or offer treatment at the same visit (a screen-and-treat approach), reducing the likelihood of loss to follow-up. That said, there is a risk for overtreatment in this context given that the specificity of visual inspection-based approaches is lower than that of the Papanicolaou test or HPV DNA testing. Although there is no clear evidence of harm arising from overtreatment [40, 41], some researchers contend that using the screen-and-treat approach entails risks that may only become apparent with longer follow-up [42]. The feasibility and effectiveness of the screen-and-treat method should be examined further in a patient program.

In conclusion, decisions regarding which screening strategy to use will largely depend on context, including the availability of infrastructure and human and financial resources. Studies on screening methods in India indicate that visual inspection-based approaches are feasible and reasonably accurate when compared with methods such as the Papanicolaou test and HPV DNA testing. However, training and quality assurance are especially important to ensuring acceptable test performance levels when using visual inspection. Thus, a key challenge is to create a system that is capable of effectively deploying the selected screening strategy. Establishing such a system and initiating screening can lay the foundation for the introduction of more optimal primary screening tests in the future.

Screening Coverage and Treatment Linkings

The effectiveness of screening is determined not only by the accuracy of the screening test, but also by screening coverage and linkages to diagnostic and treatment services. Several community-based studies have tracked participation and retention rates by first enumerating all eligible women in the target communities [25, 33, 36] or using census lists to determine the number of women eligible [29]. Even in the context of well-resourced studies, achieving high levels of screening participation and adherence to diagnostic and treatment recom-

Table 1. Overview of primary screening tools for cervical cancer

Screening Test[a]	Strengths	Limitations
VIA: *Acetic acid is applied to the cervix to identify precancerous and cancerous lesions.* *Process is often aided by a magnification tool.*	• Requires less training (5–10 days) than other methods • Cheaper than cytology/HPV testing • Immediate results • Potential for immediate treatment ("screen and treat")	• Variable (low to moderate) sensitivity and specificity for CIN2+ • Possibility for overtreatment • Acetic acid must be prepared directly before screen • Inappropriate for older women (>50 years) because of change in cervix position
VILI: *Lugol's iodine is applied to the cervix to identify precancerous and cancerous lesions.* *Process is often aided by a magnification tool.*	• Requires less training (5–10 days) than other methods • Cheaper than cytology/HPV testing • Immediate results • Potential for immediate treatment ("screen and treat") • Has a 1 month shelf life	• Variable (low to moderate) sensitivity and specificity for CIN2+ • Possibility for overtreatment
Cytology (Papanicolaou smear): *Sample of cells taken from transformational zone of the cervix. Sample is smeared onto a glass slide. Slide is sent to laboratory for reading by a cytologist.*	• High specificity for CIN2+	• Relatively low sensitivity • Requires laboratory and specialized technicians • Lag in test results can contribute to loss to follow up and delay treatment
HPV DNA test: *Sample of cells taken from the cervix by a provider or the woman herself. Sample is sent to laboratory for analysis by trained technicians.*	• High specificity and sensitivity for HPV infection • Requires minimal training • Woman can self-collect sample	• Has to be followed by a test for dysplasia • Requires laboratory and trained technicians • Lag in test results can contribute to loss to follow up and delay treatment

[a]Adapted from [55, 56].
Abbreviations: CIN2+, cervical intraepithelial neoplasia grade 2 or higher; HPV, human papilloma virus; VIA, visual inspection with acetic acid; VILI, visual inspection with Lugol's iodine.

mendations—without which it is difficult to justify screening—has been a challenge.

Studies that successfully recruited and retained participants in screening and treatment engaged with women, husbands, and family members; offered appointments and screening cards to women; and involved local government health workers and community leaders in mobilization efforts (Table 4) [25, 33, 36]. In Dindigul district, Tamil Nadu, accessibility was further enhanced by offering screening services at primary health centers, municipal offices, schools, women's clubs, and homes [33]. The study screened 63% of eligible women.

The importance of community engagement is underscored by the Community Access to Cervical Health study (CATCH), which despite using a fairly comprehensive approach involving community liaisons to promote screening, house-to-house visits, and transportation to a tertiary screening center, had among the lowest participation rates of published Indian studies: nearly three in five eligible women (59.4%) refused to undergo screening [29]. Reasons for refusal included lack of symptoms indicating a health problem; fear of the tests, the pelvic examination, and a cancer diagnosis; and community gossip and misconceptions.

Similar reasons for screening refusal were reported by Basu et al. [43] in their Kolkata study. Additionally, they found that some women were unable to attend screening clinics because of household responsibilities, family problems and illnesses, and refusal of husbands or other relatives to grant permission. A few women who made it to the clinic left prior to being screened because of apprehension about the process (after seeing the screening instruments), the long waiting times, and the presence of male doctors.

Facilitators of and barriers to patient adherence to diagnostic and treatment recommendations were generally similar to those for screening. Loss to follow-up tended to be lower in the case of more advanced disease, but did not vary consistently by location of diagnostic and treatment service provision [29, 33, 34, 36]. In the Dindigul study, trained nurses used a screen-and-treat approach for most precancerous lesions and referred women requiring loop electrosurgical excision procedure or cold knife conization or with invasive cancers to a tertiary center [33]. The study documented high loss to follow-up among women who did not choose to undergo screening and treatment at the same visit: 53% of women who were eligible for the screen-and-treat approach but decided to first consult their husband or other family members did not return for treatment. Diagnostic and treatment completion rates among women referred to a tertiary center were 80% and 75%, respectively [33]. In the Osmanabad, Maharashtra, trial, 85% of those referred to a central clinic for diagnostic and treatment procedures adhered to recommendations [36]. The CATCH study reported the lowest acceptance of diagnos-

Table 2. Health care workers trained to perform cervical cancer screening and treatment in studies in India

Study (location)	Personnel trained (qualifications)	Screening and treatment approach	Duration of training (curriculum)	Frequency of retraining
Sankaranarayanan et al., 2004 (Dindigul, Tamil Nadu) [33]	Nurses (3 years of nursing education after 10 years of schooling)	Training on VIA, colposcopy and cryotherapy	3 weeks (IARC)	Every 4 months
	Physicians (medical officers)	Training on VIA, colposcopy, cryotherapy, LEEP	NS	NS
	Surgeons	Training on cold knife conization	NS	NS
	Pathologists, laboratory technicians	Retraining on biopsy specimen processing and reporting	NS	NS
Sankaranarayan et al., 2004 (Mumbai, Maharashtra; Jaipur, Rajasthan; Kolkata, West Bengal; Thiruvananthapuram, Kerala) [35]	Female health workers with varying educational backgrounds (registered nurses, cytotechnicians, university graduates in science and arts, high school graduates)	Training on VIA and VILI	5 days (IARC)	1–2 days with unspecified frequency
	Physicians (gynecologists and non-gynecologists)	Training on colposcopy, cryotherapy, LEEP	15 days (IARC)	1 day every 4–6 months
	Pathologists, laboratory technicians	Retraining on biopsy specimen processing and reporting	1 day refresher	NS
Sankaranarayan et al., 2005 (Osmanabad, Maharashtra) [36]	Auxiliary nurse midwives	Training on VIA, cell sampling for cytology and HPV, cryotherapy	3 weeks (IARC)	2 brief refreshers over 4 years
	Physicians	Training on colposcopy, cryotherapy, and LEEP	(IARC)	
	Pathologists	Retraining on biopsy reporting	2 weeks (TMC)	Refresher after 9 months
	Laboratory technicians	Training on processing and reporting cytology slides, biopsy, HPV test	3 months (TMC)	Refresher after 9 months
Bhatla et al., 2009 (Faridabad district, Haryana) [25]	Auxiliary nurse-midwives	Training on VIA and VILI, cell sampling for cytology	(IARC)	Retrained, but frequency not specified
	Physicians	Training on cryotherapy, LEEP	(IARC)	
Deodhar et al., 2012 (Solapur district, Maharashtra) [27]	Nurses	Retraining on VIA, cell sampling for cytology and HPV, cryotherapy	NS (IARC)	Every 6 months after retraining
	Physicians (colposcopists)	Retraining on colposcopy, cryotherapy, and LEEP	NS (IARC)	Every 6 months after retraining
	Physicians (pathologists)	Retraining on cytology, biopsy reporting	NS (IARC)	Every 6 months after retraining
	Cytotechnicians	Retraining on processing and reporting cytology slides, biopsy	NS (IARC)	Every 6 months after retraining
Gravitt et al., 2010 (Medchal Mandal, Andhra Pradesh) [29]	Physicians (gynecologists)	VIA, VILI, HPV DNA, colposcopy	NS	NS

Abbreviations: HPV, human papilloma virus; IARC, International Agency for Research on Cancer; LEEP, loop electrosurgical excision procedure; NS, not specified; TMC, Tata Memorial Center, Mumbai; VIA, visual inspection with acetic acid; VILI, visual inspection with Lugol's iodine.

tic and treatment procedures, with 34% of women refusing colposcopy and biopsy after a positive screening test [29]. The relative role of factors such as cancer stigma, accessibility of services, and family support in shaping diagnostic and treatment adherence needs to be explored further.

The translation of evidence on cervical cancer screening and treatment approaches into effective prevention programs depends on a sound understanding of factors operating at the level of the individual, community, and health system that influence women's access to information/education, screening, diagnosis, and treatment. Further investigation of these factors and evaluation of strategies to improve service uptake can facilitate future program planning and implementation.

Quality of Service Provision

To date, researchers have assessed the quality of cervical cancer prevention services primarily in terms of screening test performance, and quality assurance has focused on training of health care providers (Table 5). Although studies have found it feasible to train frontline health workers such as auxiliary nurse midwives and staff nurses to implement visual inspection-based screening and treatment of precancerous lesions using cryotherapy, concerns have been raised about the quality and consistency of service provision [36, 44]. Auxiliary nurse midwives in the Osmanabad study received three weeks of training on cervical sample collection, VIA, and cryotherapy, but poor concordance on VIA results between the master

Table 3. Summary of Indian studies on accuracy of cervical cancer screening tests

				Sensitivity and specificity (respectively)				
Primary screening test	**Study location**	**Sample**	**Study design**	**CIN2+**	**CIN3+**	**All grades of CIN**	**HSIL or HSIL+ invasive cancer**	**Invasive cancer**
Visual Inspection with Acetic Acid (VIA)	Andhra Pradesh [29]	Population-based $n = 2,331$ 25 years+	Cross-sectional	26.3%, 6.4%	36.4%, 6.5%			
	Solapur District [27]	Population-based $n = 5,519$ 30–49 years	Cross-sectional	64.5%, 84.2%				
	Dindigul District [33]	Population-based $n = 80,269$ 30–59 years	RCT					71.1%, no specificity
	IARC multicentre [35]	Population-based $n = 104,061$ 26–65 years	Cross-sectional				76.8%, 85.5%, 79.3%, 85.5%	
	Lok Nayak Hospital, Delhi [28]	Opportunistic $n = 350$ 25–39 years	Cross-sectional			89.47%, 91.23%		
	Kolkata [23]	Population-based $n = 5,881$ 30–64 years	Cross-sectional	55.7%, 82.1%				
	New Delhi, Gyne OPD [24]	Opportunistic $n = 100$ 30+ years	Cross-sectional			100%, 53.3%		
	New Delhi Women's Clinic [32]	Opportunistic $n = 472$ 20–60 years	Cross-sectional	86.7%, 90.7%				
	Faridabad District [25]	Population-based $n = 3,000$ 25–59 years	Cross-sectional	No sensitivity, 86.1%				
	New Delhi Gyne OPD [26]	Opportunistic $n = 548$ 30+ years	Cross-sectional	82.5%, 66.9%				
	Mumbai, Kolkata (comparison with magnification) [30]	Population-based $n = 18,675$ 25–65 years	Cross-sectional	60.3%, 86.8% VIA with magnification: 64.2%, 86.8%				
	Kolkata, Mumbai, Trivandrum [31]	Opportunistic $n = 20,053$ 25–65 years	Cross-sectional	54.4%–78.7%, 88.6%–90.9%				
VILI	Solapur District [27]	Population-based $n = 5,519$ 30–49 years	Cross-sectional	64.5%, 85.5%				
	IARC multicenter [35]	Population-based $N = 104,061$ 26–65 years	Cross-sectional				91.7%, 85.4%; 92.2%, 85.5%	
	Lok Nayak Hospital, Delhi [28]	Opportunistic $n = 350$ 25–39 years	Cross-sectional			100%, 93.35%		
	Faridabad District [25]	Population-based $n = 3,000$ 25–59 years	Cross-sectional	84.7%				
	Kolkata, Mumbai, Trivandrum [31]	Opportunistic $n = 20,053$ 25–65 years	Cross-sectional	76.2%–76.9%, 86.3%–89.3%				
Cytology (Pap Smear)	Andhra Pradesh [29]	Population-based $n = 2,331$ 25+ years	Cross-sectional	63.2%, 76.2%	81.8%, 76.1%			
	Solapur District [27]	Population-based $n = 5,519$ 30–49 years	Cross-sectional	67.7%, 95.4%				
	Lok Nayak Hospital, Delhi [28]	Opportunistic $n = 350$ 25–39 years	Cross-sectional			52.6%, 99.1%		
	Kolkata [23]	Population-based $n = 5,881$ 30–64 years	Cross-sectional	29.5%, 92.3%				
	New Delhi, Gyne OPD [24]	Opportunistic $n = 100$ 30+ years	Cross-sectional			89.7%, 98.9%		
	New Delhi Women's Clinic [32]	Opportunistic $n = 472$ 20–60 years	Cross-sectional	91.4%, 86.6%				
	Faridabad District [25]	Population-based $n = 3,000$ 25–59 years	Cross-sectional	No sensitivity, 94.8% (ASCUS) 97.2% (LSIL)				
	New Delhi Gyne OPD [26]	Opportunistic $n = 548$ 30+ years	Cross-sectional	77.5%, 86.8% (ASCUS) 71.8%, 94.4% (LSIL)				
	Kolkata, Mumbai, Trivandrum [31]	Opportunistic $n = 20,053$ 25–65	Cross-sectional	36.6%–72.3% (ASCUS) 87.2%–98.6% (LSIL)				

(continued)

Table 3. (continued)

Primary screening test	Study location	Sample	Study design	Sensitivity and specificity (respectively) CIN2+	CIN3+	All grades of CIN	HSIL or HSIL+ invasive cancer	Invasive cancer
HPV DNA test	Andhra Pradesh [29]	Population-based $n = 2,331$ 25+ years	Cross-sectional	84.2%, 81.3%	100%, 80.72%			
	New Delhi, Gyne OPD [24]	Opportunistic $n = 100$ 30+ years	Cross-sectional			85.7%, 50%		
	New Delhi Women's Clinic [32]	Opportunistic $n = 472$ 20–60 years	Cross-sectional	97.1%, 84.2%				
	New Delhi Gyne OPD [26]	Opportunistic $n = 548$ 30+ years	Cross-sectional	Provider: 90%, 91.5% Self: 80%, 88.1%		Sensitivity: 45.7%–80.9% Specificity: 91.7%–94.6%		
	Kolkata, Mumbai, Trivandrum [31]	Opportunistic $n = 20,053$ 25–65 years	Cross-sectional					

Abbreviations: ASCUS, atypical squamous cells of undetermined origin; CIN, cervical intraepithelial neoplasia; HSIL, high-grade squamous intraepithelial lesion; IARC, International Agency for Research on Cancer; LSIL, low-grade squamous intraepithelial lesion; RCT, randomized controlled trial; VILI, visual inspection with Lugol's iodine.

Table 4. Strategies used to promote screening in India

• Mobilization efforts led by local health workers (medical officers, community health workers) who are known and respected in the community
• Involvement of community leaders (e.g., *panchayat* [village government], women's group members)
• Use of advertising campaigns through print and other media
• Promotion of "champions" such as cancer survivors or local celebrities
• Education of women, husbands, and families
• Recruitment through home visits by known health care workers
• Provision of screening appointments and informational cards
• Provision of screening and treatment services at locations close to the community
• Provision of screening by female health care providers
• Provision of screening and treatment in one visit
• Provision of transportation to referral clinic for diagnostic and treatment services
• Minimization of waiting times

Sources: [25, 33, 48, 57, 58].

trainer and the nurses led to two rounds of refresher training [36].

Prescreening and postscreening procedures, including informed consent for screening and postscreening counseling and monitoring patient follow-up rates for diagnostic confirmation and treatment, are important components of quality assurance that have not been discussed extensively in the research literature. It is unclear whether studies used electronic- or paper-based health information systems to monitor participant retention and follow-up, whether any specific actions were taken to minimize loss to follow-up, and which actions were most effective in promoting patient retention. Identifying best practices in quality assurance is a high priority.

Impact of Screening on Morbidity and Mortality

Three large-scale randomized controlled trials in India have found that screening can reduce cervical cancer morbidity and mortality [34, 37, 38]. In Dindigul, a single round of VIA-based screening led to a 25% reduction in cervical cancer incidence and a 35% reduction in mortality over seven years of follow-up [37]. Similar results (31% reduction in mortality) were reported recently by a trial that offered multiple rounds of VIA-based screening in Mumbai, Maharashtra [34]. A third randomized controlled trial in Osmanabad found that a single round of HPV testing led to reductions in mortality, whereas VIA and cytology did not [38]. Although screening uptake and treatment adherence did not differ between the study arms, questions have been raised about whether differences in diagnostic and treatment procedures across study arms may explain the observed outcomes [45].

Overall, data from India indicate that VIA, when offered under the controlled conditions of a trial with systems for following-up with women whose screening is positive and high adherence to diagnostic and treatment recommendations, leads to significant declines in cervical cancer mortality within a decade of intervention initiation, lending further support to the rationale for investment in secondary prevention. That said, the effectiveness of screening in less controlled programs and programs with potentially fewer resources remains unclear.

In Dindigul, a single round of VIA-based screening led to a 25% reduction in cervical cancer incidence and a 35% reduction in mortality over seven years of follow-up. Similar results (31% reduction in mortality) were reported recently by a trial that offered multiple rounds of VIA-based screening in Mumbai, Maharashtra.

Table 5. Quality assurance methods

Task	Personnel	Methods of quality assurance
Community mobilization	Health workers, primary health care nurses/staff, study staff, local resource persons	• None
Informed consent	Female health workers	• Training of staff [25, 27, 33]
Training	Health workers (auxiliary nurse midwives, nurses), technicians, doctors	• Training and periodic refresher training [36]
Screening implementation	Community health workers, gynecologists, nurses	• Comparison of different primary screening modalities implemented by different health workers who are blind to results of other tests [23] or by same health worker [27] • Colposcopy/biopsy conducted by a gynecologist blind to the results of the primary screening test [24]
Diagnostic confirmation	Physicians and laboratory technicians	• Quality control checks by master trainers/experts [36] • Review of a random sample of slides by master trainers/experts [36]
Counseling	Physicians [29], nurses [37]	• None
Treatment	Physicians	• Receipt of second opinion • Quarterly review of treatment outcomes (Tamil Nadu Health Systems Project)
Data collection	Staff nurses, statisticians	• Establishment of health information system • Training, queries, and monitoring by statistical assistants and district level managers (Tamil Nadu Health Systems Project)

Cost Effectiveness of Screening

Modeling studies using primary and secondary research data from India indicate that cost-effectiveness of vaccination is influenced by vaccine cost, efficacy, coverage, and duration of protection, whereas cost-effectiveness of screening depends on the linkages between screening and treatment, number of clinic visits, and laboratory infrastructure required [19, 46]. Strategies that targeted women in their mid-30s were the most cost-effective (compared with those that screened women less than 30 years old or more than 45 years old).

The Osmanabad randomized controlled trial, which estimated screening costs and cost-effectiveness, found that program implementation expenses (e.g., for monitoring patient recruitment and follow-up) were substantial—as high as one fifth of the total costs in the VIA arm [47]. VIA was the least expensive option, detecting 7.5 CIN2/3+ cases per 1,000 eligible women and costing $522 per case detected (compared with no screening), whereas cytology detected 10 cases per 1,000 and cost $659 per case. HPV DNA testing was nearly twice as expensive as cytology and detected fewer cases. Another modeling study recommended screening adult women two to three times per lifetime in addition to administering pre-adolescent vaccination, and found that this combination (assuming 70% coverage for both strategies) yielded a 56% to 63% reduction in cancer incidence [19].

Program data are needed to better understand cost and cost-effectiveness of available prevention strategies. Monitoring and evaluation of pilot programs in different settings (e.g., rural vs. urban) can yield important insights about the choice of prevention strategies. Finally, analyses should also account for treatment costs and longer-term benefits in terms of life years saved.

Translation of Research Into Practice

Tamil Nadu State's cervical cancer screening and treatment program designed and implemented by the World Bank-supported Tamil Nadu Health Systems Project (TNHSP) is among the few examples of large-scale government-led prevention efforts in India. In 2007, Tamil Nadu launched a pilot cervical cancer screening program in two predominantly rural districts, Theni and Thanjavur, to identify challenges and potential solutions prior to a state-wide scaling up of the program [48]. The goals of the cervical cancer program were to raise community awareness, promote early detection by offering routine VIA/VILI-based screening to 30- to 60-year-old women seeking public health services, and offer appropriate referrals and treatment (Table 6).

The pilot program, led by a senior bureaucrat and designed by technical experts, received administrative support from the government of Tamil Nadu, political backing, and the necessary financial resources. A team of public health physicians who were tasked with implementation coordination and oversight and staff nurses who were trained to provide NCD prevention services including VIA/VILI, and data management personnel were hired. Consultations were held with experts in NCD screening, diagnosis, and treatment to finalize clinical protocols and operations manuals, and a detailed capacity-building process was developed to train and equip staff to implement the program. In addition, the program commissioned an external monitoring and evaluation and cost analysis of the program.

Between 2007 and 2010, the program screened nearly 500,000 women, which translates to about 74% of the eligible population [48]. However, VIA/VILI positivity was lower than reported in the literature: 5.4% in Thanjavur and 2.6% in Theni

compared with approximately 15% to 20% in published Indian studies [35, 39, 48]. Follow-up rates were also relatively low, with approximately half of women with a positive screen undergoing diagnostic investigations. The program detected relatively few precancerous lesions (103 CIN2/3 lesions) compared with invasive cancers (887), although this may be in part because the population was largely unscreened. Notably, the overall proportion of women treated was low; only 13% of women needing treatment received it through the program [48].

A number of implementation challenges are likely to have led to these program outcomes (Table 6). Efforts to mobilize women to undergo screening were constrained by a limited evidence base to guide information, education, and communication efforts and outreach, which was initially carried out by contractual workers hired by nongovernmental organizations, was inconsistent and often of poor quality. The high coverage achieved by the program despite these limitations was likely the result of Tamil Nadu's strong primary health care system combined with the concerted efforts of the staff of the pilot program. However, that a large proportion of women did not return for diagnostic and treatment services suggests the existence of other individual-, community- and health system-level barriers such as lack of transportation or resources to travel to higher-level facilities for diagnostic confirmation and treatment, lack of familial support, cancer-related stigma, and inadequate referral systems. TNHSP subsequently hired a communications agency to conduct formative research and develop an information, education, and communication plan. However, administrative issues prevented the deployment of the plan within the pilot implementation period, and the effectiveness of the information, education, and communication strategy has not been evaluated.

Program outcomes such as relatively low VIA/VILI positivity, high loss to follow-up, and low levels of treatment provision were likely the result of several factors within the health system. Ensuring adequate, consistent, and high-quality training is one factor. Staff nurses received two days of training on VIA/VILI, which may not have been sufficient. In fact, similarly low VIA/VILI positivity was reported in Bangladesh, highlighting the need for refresher training [49]. Moreover, training quality could have been improved by greater standardization of the number of VIA/VILI tests done, the number of positive cases observed, and structured post-training assessments of knowledge and skills. Anecdotal evidence also suggests that refresher training may have been needed to increase physician confidence to conduct cryotherapy, conization, and loop electrosurgical excision procedure and to promote adherence to program protocols.

Several additional human resource-related issues may have also influenced the level and consistency of program implementation. Frequent changes in personnel at the local, district, and state levels because of transfers and staff attrition meant that program-related knowledge and experiences had to be continuously reestablished. In addition, accuracy of data reporting may have been reduced because nurses felt pressured by the pilot program's target-oriented approach; each center had fixed targets for the number of women they had to screen each month regardless of the sociodemographic profile of the communities they served. In many health centers, the newly hired nurses were tasked with provision of routine health care services, despite having been recruited specifically for the NCD prevention program. This situation was exacerbated because existing health department staff were reluctant to provide NCD-related services. Finally, difficulties in ensuring the availability of sufficient numbers of pathologists and obstetrician/gynecologists may have contributed to delays in reporting of biopsy results and treatment provision. These challenges were further compounded by infrastructural and logistic issues such as lack of availability of drugs and reagents (e.g., drugs to treat reproductive tract infections) and infrastructural deficiencies (e.g., lack of electricity, which made visualization of the cervix difficult).

Perhaps the most important challenges faced by the TNHSP pilot program had to do with the establishment of mechanisms to facilitate patient follow-up and quality assurance. Although screening was promoted at all primary care facilities, diagnostic confirmation and treatment were offered only at select secondary and tertiary facilities where related infrastructure and human resources were already available. In this scenario, communication and coordination of referrals between levels of the health care system were especially difficult. Moreover, the reliance on "village link volunteers" to facilitate patient follow-up may have been ineffective because these individuals were hired by local nongovernmental organizations and did not have sufficient familiarity with the health system. The volunteers had a poor rapport with existing health department staff such as the village health nurses, and they were offered only an honorarium (which was not always paid on time by their nongovernmental organization employer). Inaccurate and inconsistent data reporting such as incomplete or false addresses and lack of clarity regarding the definition of clinical terms and outcomes also hampered follow-up of patients and program monitoring, preventing timely responses to program deficiencies.

Similar to early stage screening programs in other low- and middle-income countries, the TNHSP pilot emphasized strengthening the health care infrastructure and training health care workers to deliver cancer prevention services [49]. Establishing a comprehensive quality assurance program, identifying strategies to promote communication and coordination between different levels of the health care system, and strengthening systems to facilitate identification and monitoring of cases for follow-up are issues that need to be addressed in the next phase of the program [50–52].

Recognition of these challenges has led to a range of responses in the design of the statewide scale up of the program (Table 7). These include the provision of refresher training for all health care workers; the introduction of an electronic health information system, with patient records accessible at different levels of the health care system; and the use of novel strategies to improve patient follow-up, such as cell phone reminder calls. Ongoing analyses of data captured by this system are shared by state-level program officials with district-level staff through monthly videoconferences and with community-level staff (mainly nurses) through weekly meetings at the district hospital. A variety of quality assurance methods, including facility checklists, exit interviews, and structured observations, are being used.

Table 6. Tamil Nadu Health Systems Project cervical cancer program by level of care

Level	Services provided	Method	Health institutions	Staff (in pilot)	Staff (in scale up)
Primary	Screening	VIA/VILI (with magnification)	Primary health centers, government hospitals, government medical colleges and hospitals	Female medical officers, obstetrician/gynecologists, female paramedical staff; village link volunteers	Dedicated noncommunicable disease program staff nurse
Secondary	Further evaluation and diagnosis	Colposcopy and biopsy	Government hospitals, government medical colleges and hospitals	Obstetrician/gynecologists (specifically trained for the task)	Same as in pilot
Tertiary	Treatment	Depends on severity	Government medical colleges and hospitals	Specialists	Same as in pilot
District/region	Monitoring and evaluation	Not applicable	Not applicable	Cancer control officers	Statistical assistants, regional medical officers, regional consultants

Source: Tamil Nadu Health Systems Project.
Abbreviations: VIA, visual inspection with acetic acid; VILI, visual inspection with Lugol's iodine.

The TNHSP pilot program has demonstrated the feasibility and acceptability of introducing cervical cancer prevention into the Indian public health system when there is adequate and consistent political and administrative support. It has also highlighted several implementation challenges related to service uptake and program delivery. Although few conclusions can be drawn about the outcomes and impacts of the pilot program given the lack of evaluation data, these pilot experiences and systematic documentation and analysis of the scale-up program can provide important insights for future prevention efforts in the country. Experiences in countries such as Zambia [51] and El Salvador [52] have revealed that focused efforts to improve quality of service provision, including follow-up rates, entail a strong commitment to quality improvement, dedicated resources, and a defined methodology. Based on these criteria, TNHSP is well positioned to successfully improve cervical cancer prevention across the state of Tamil Nadu.

Conclusion

Implementation Science Priorities

The availability of primary and secondary prevention tools has accelerated global efforts to prevent and control cervical cancer. In India, qualitative research has identified factors that influence the feasibility and acceptability of HPV vaccination. Cross-sectional studies and randomized controlled trials have shown that visual inspection-based screening approaches can achieve sensitivity and specificity comparable to that of cytology-based screening, that this screening can be implemented by frontline health workers, and that it can reduce cervical cancer incidence and mortality. The TNHSP pilot program has demonstrated the feasibility of applying research insights to public health policy and practice. However, our review of research and program experiences has revealed a number of critical gaps in the translation of the available evidence for public health action. Implementation science, which may be defined as research that supports the uptake, implementation, and sustained use of evidence-based interventions in routine practice and program settings, can help bridge these gaps [53].

Implementation science can provide evidence on program effectiveness, efficiency, and sustainability [54], and involves the use of a wide range of methods, data sources, and study designs. For example, implementation science research can entail the use of data from program monitoring and evaluation systems to better understand factors that explain the gap between desired and observed program outputs and outcomes. It can involve experimental and quasiexperimental approaches to assess the comparative advantages and cost-effectiveness of different intervention packages. Alternatively, it can use qualitative and quantitative methods to identify ways to enhance service uptake, improve implementation quality and efficiency, and ensure that a continuum of services is being delivered.

Below, we put forth implementation science priorities for advancing cervical cancer prevention and control in India:

- Understanding individual and community-level barriers to uptake of screening, diagnostic, and treatment services can lead to the identification and testing of strategies to increase program coverage and improve outcomes. For example, research is needed to determine how best to communicate the benefits and limitations of available prevention and control strategies to key stakeholders such as women and their husbands and to explore the role of cultural beliefs, stigma, gender inequities, and other factors in shaping health care decisions. Available evidence suggests that women who are older and have fewer socioeconomic resources are less likely to undergo cervical cancer screening and to have poorer outcomes. Program monitoring data can be analyzed to assess whether specific groups of women are underserved and why, leading to appropriate programmatic responses.
- Improving health care worker performance by identifying effective methods for training, supporting, and supervising providers is a priority. This includes the use of quality improvement tools such as "plan, do, study, act" cycles, telemedicine, simulation-based training, and financial and nonfinancial incentives.
- Strengthening links among screening, diagnosis, and treatment is critical to program success. The TNHSP program integrated cervical cancer prevention into a broader initiative focused on NCDs, with screening taking place at the primary health care level and diagnostic confirmation and treatment taking place at the secondary and tertiary levels. Although screening coverage was high, patient follow-up rates for diagnostic confirmation and treatment were poor. Implementation science research can be used to identify and evaluate strategies to increase patient retention and improve communication and coordination across levels of the health care system.

Table 7. Lessons learned from implementation of a pilot cervical cancer screening program in Tamil Nadu

Challenges during pilot implementation	Actions to address challenges during scale up
Community mobilization	
• Lack of strategic mobilization plan that detailed formative research, staff/community involved, methods, and levels of outreach, which adversely affected screening coverage	• Agency hired to conduct formative research and develop information, education, and communication strategy and materials
• Difficulty building awareness and buy-in to screening program in rural areas	• Use of multipronged strategy (television, radio, print, etc.)
	• Awareness created at four levels: clinical, school, community, and workplace
	• Advertisements targeted at all eligible women and men
Project staffing/training	
• Task shifting: Medical officers initially charged with screening, but tasks eventually fell to nurses and even counselors	• Appointment of staff nurses specifically for NCD
• Role creep: Nurses engaged in provision of routine services rather than services related to NCD	• NCD training for all nurses to keep services running in absence of NCD staff nurse
• Village level volunteers (contractual workers given honorarium) ineffective in mobilizing women and doing follow-up	• Reliance on village health nurses (health department staff) to mobilize women and support follow-up
• Staff turnover at all levels of care	• Regular payment of salaries and building staff relationships
• Subjective nature of screening tests, making quality assurance difficult and leading to large number of false positive results	• Expanded training program with adequate exposure to positive and negative cases
	• Periodic refresher trainings
Procurement/maintenance	
• Lack of regular supply of drugs/reagents	• Separate budget created and approved for purchases
• Malfunctioning equipment	• Central procurement by NCD coordinating site to ensure timely supply of drugs and other consumables
	• Ensure staff trained on stocking equipment and monitoring orders
	• System to monitor and maintain equipment
Protocols and guidelines	
• Nonadherence to protocols	• Simplification and refinement of protocols and reduced number of conditions requiring referrals
• Reluctance by staff to document and report service provision	• Staff supported to estimate case load based on local conditions and to monitor actual case load
• Inability to meet targeted screening goals	
Data collection	
• Poor data quality	• NCD staff nurse responsible for data entry
• Lack of analysis/corrections of reports at district level	• Dedicated statistical assistant to monitor data quality and compilation
• Incorrect information provided by patients (i.e., addresses)	• Routine reporting of data through monthly videoconferences
Access to treatment	
• Few centers equipped to do colposcopy and biopsy	• Village health nurses responsible for following up with patients and facilitating links to tertiary level services
• Poor follow up of patients needing diagnostic and treatment services; small proportion (13%) of women obtained treatment	• Coordination with state health insurance scheme for cashless tertiary care services for individuals belonging to households below the poverty line
• Weak linkage among health system levels	• Improved tracking of cases through the health information system

Source: Tamil Nadu Health Systems Project, personal communication.
Abbreviation: NCD, noncommunicable disease.

Potential strategies include the provision of transportation, employment of patient navigators, and/or the use of mobile communication technologies.

● Determining optimal program design, outcomes, and costs is important given the number of competing public health priorities facing the Indian government, including the growing burden of NCDs such as diabetes, hypertension, and cancer. In their 2013 guidance note, WHO emphasized the importance of taking a comprehensive approach to cervical cancer prevention and control by implementing vaccination programs as well as screening and treatment in conjunction with education and social mobilization at appropriate points

across the life course [21]. Research is needed to identify the optimal way to implement cervical cancer prevention in India, taking into account cost, human resources, and infrastructural elements. For example, should cervical cancer screening be packaged along with NCD prevention or family planning services? What are the best entry points for HPV vaccination? Data on cost and cost-effectiveness of primary and secondary prevention strategies are also important to ensure that limited resources are used most strategically. Key stakeholders such as program managers and policy makers should be engaged in this process to ensure policy relevance.

With a quarter of the global burden of cervical cancer in India, there is no better time than now to translate research findings into practice. Implementation science can help ensure that investments in cervical cancer prevention and control result in the greatest impact.

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Disclosures

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References

1. Institute for Health Metrics and Evaluation. The challenge ahead: Progress in breast and cervical cancer. Institute of Health Metrics and Evaluation, 2011. Available at http://www.healthmetricsandevaluation.org/publications/policy-report/challenge-ahead-progress-and-setbacks-breast-and-cervical-cancer. Accessed July 2, 2013.

2. Nandakumar A, Anantha N, Venugopal TC. Incidence, mortality and survival in cancer of the cervix in Bangalore, India Br J Cancer 1995;71:1348–1352.

3. Vallikad E. Cervical cancer: The Indian perspective. Int J Gynaecol Obstet 2006;95(suppl 1):215–233.

4. Jacob M. Assessing the environment for introduction of human papillomavirus vaccine in India. Open Vaccine J 2010;3:96–107.

5. Madhivanan P, Krupp K, Yashodha MN et al. Attitudes toward HPV vaccination among parents of adolescent girls in Mysore, India Vaccine 2009;27:5203–5208.

6. World Health Organization. Weekly epidemiological record. WHO, 2009. Available at http://www.who.int/wer/2009/wer8415.pdf. Accessed January 14, 2013.

7. Singh A, Datta P, Jain SK et al. Human papilloma virus genotyping, variants and viral load in tumors, squamous intraepithelial lesions, and controls in a North Indian population subset. Int J Gynaecol Cancer 2009;19:1642–1648.

8. Sowjanya AP, Jain M, Poli UR et al. Prevalence and distribution of high-risk human papilloma virus (HPV) types in invasive squamous cell carcinoma of the cervix and in normal women in Andhra Pradesh, India BMC Infect Dis 2005;5:116.

9. PATH. Update: Path's HPV vaccine project in India. Available at: http://www.path.org/news/press-room/333/. Accessed October 11, 2013.

10. Rathod SD. Commentary on HPV screening for cervical cancer in rural India. Ind J Med Ethics 2011;8:180–182.

11. Srinivasan S. HPV vaccine trials and sleeping watchdogs. Ind J Med Ethics 2011;8:73–74.

12. Kang G. HPV vaccines: Separating real hope from drug company hype. Ind J Med Ethics 2010;7:56–57.

13. Ramanathan M, Varghese J. The HPV vaccine demonstration projects: We should wait, watch and learn. Ind J Med Ethics 2010;7:43–45.

14. Dabade G, Abhiyan JS, Madhavi Y et al. Concerns around the human papilloma virus (HPV) vaccine. Ind J Med Ethics 2010;7:38–41.

15. Mattheji I, Pollock A, Brhlikova P. Do cervical cancer data justify HPV vaccination in India? Epidemiological data sources and comprehensiveness. JR Soc Med 2012;105:250–262.

16. Mudur G. Human papillomavirus vaccine project stirs controversy in India. BMJ 2010;340:c1775.

17. Mudur G. Row erupts over study of HPV vaccine in 23 148 000 girls in India. BMJ 2012;345:e4930.

18. Tsu V. Should the ideal be the enemy of the good? JR Soc Med 2012;105:366.

19. Diaz M, Kim JJ, Albero G et al. Health and economic impact of HPV 16 and 18 vaccination and cervical cancer screening in India. Br J Cancer 2008;99:230–238.

20. Alliance G. Human papillomavirus vaccine support. 2013. Available at: http://www.gavialliance.org/support/nvs/human-papillomavirus-vaccine-support/. Accessed July 2, 2013.

21. World Health Organization. WHO guidance note: Comprehensive cervical cancer prevention and control: A healthier future for girls and women. 2013. Available at: http://apps.who.int/iris/bitstream/10665/78128/3/9789241505147_eng.pdf. Accessed July 3, 2013.

22. Saxena U, Sauvaget C, Sankaranarayanan R. Evidence-based screening, early diagnosis and treatment strategy of cervical cancer for national policy in low- resource countries: Example of India. Asian Pac J Cancer Prev 2012;13:1699–1703.

23. Basu P, Sankaranarayanan SR, Mandal R et al. Visual inspection with acetic acid and cytology in the early detection of cervical neoplasia in Kolkata, India Int J Gynaecol Cancer 2003;13:626–632.

24. Bhatla N, Mukhopadhyay A, Kriplani A et al. Evaluation of adjunctive tests for cervical cancer screening in low resource settings. Ind J Cancer 2007;44:51–55.

25. Bhatla N, Gulati A, Mathur SR et al. Evaluation of cervical screening in rural North India. Int J Gynaecol Obstet 2009;105:145–149.

26. Bhatla N, Puri K, Kriplani A et al. Adjunctive testing for cervical cancer screening in low resource settings. Austr NZ J Obstet Gynaecol 2012;52:133–139.

27. Deodhar K, Sankaranarayanan R, Jayant K et al. Accuracy of concurrent visual and cytology screening in detecting cervical cancer precursors in rural India. Int J Cancer 2012;131:E954–62.

28. Ghosh P, Gandhi G, Kochhar PK et al. Visual inspection of cervix with lugol's iodine for early detection of premalignant and malignant lesions of cervix. Ind J Med Res 2012;136:265–271.

29. Gravitt PE, Paul P, Katki HA et al. Effectiveness of via, pap, and HPV DNA testing in a cervical cancer screening program in a peri-urban community in Andhra Pradesh, India PloS One 2010;5:e13711.

30. Sankaranarayanan R, Shastri SS, Basu P et al. The role of low-level magnification in visual inspection with acetic acid for the early detection of cervical neoplasia. Cancer Detect Prev 2004;28:345–351.

31. Sankaranarayanan R, Chatterji R, Shastri SS et al. Accuracy of human papillomavirus testing in primary screening of cervical neoplasia: Results from a

multicenter study in India. Int J Cancer 2004;112: 341–347.

32. Sodhani P, Gupta S, Sharma JK et al. Test characteristics of various screening modalities for cervical cancer: A feasibility study to develop an alternative strategy for resource-limited settings. Cytopathology 2006;17:348–352.

33. Sankaranarayanan R, Rajkumar R, Theresa R et al. Initial results from a randomized trial of cervical visual screening in rural South India. Int J Cancer 2004;109:461–467.

34. Shastri S, Mittra I, Mishra G et al. Effect of visual inspection with acetic acid (via) screening by primary health workers on cervical cancer mortality: A cluster randomized controlled trial in Mumbai, India. J Clin Oncol 2013;31(suppl):abstr 2.

35. Sankaranarayanan R, Basu P, Wesley RS et al. Accuracy of visual screening for cervical neoplasia: Results from an IARC multicentre study in India and Africa. Int J Cancer 2004;110:907–913.

36. Sankaranarayanan R, Nene BM, Dinshaw KA et al. A cluster randomized controlled trial of visual, cytology and human papillomavirus screening for cancer of the cervix in rural India. Int J Cancer 2005;116: 617–623.

37. Sankaranarayanan R, Esmy PO, Rajkumar R et al. Effect of visual screening on cervical cancer incidence and mortality in Tamil Nadu, India: A cluster-randomised trial Lancet 2007;370:398–406.

38. Sankaranarayanan R, Nene BM, Shastri SS et al. HPV screening for cervical cancer in rural India. N Engl J Med 2009;360:1385–1394.

39. Sankaranarayanan R, Nessa A, Esmy PO et al. Visual inspection methods for cervical cancer prevention. Best Pract Res Clin Obstet Gynaecol 2012; 26:221–232.

40. Sankaranarayanan R. 'See-and-treat' works for cervical cancer prevention: What about controlling the high burden in India? Indian J Med Res 2012; 135:576–579.

41. Chamot E, Kristensen S, Stringer JS et al. Are treatments for cervical precancerous lesions in less-developed countries safe enough to promote scaling-up of cervical screening programs? A systematic review. BMC Women's Health 2010;10:11.

42. Szarewski A. Cervical screening by visual inspection with acetic acid. Lancet 2007;370:265–366.

43. Basu M. The relevance of cervical cancer screening and the future of cervical cancer control in India in the light of the approval of the vaccine against cervical cancer. Indian J Cancer 2006;43: 139.

44. Blumenthal PD, Lauterbach M, Sellors JW et al. Training for cervical cancer prevention programs in low-resource settings: Focus on visual inspection with acetic acid and cryotherapy. Int J Gynaecol Obstet 2005;89 (suppl 2):S30–37.

45. Austin RM, Zhao C. Test group biases and ethical concerns mar New England Journal of Medicine articles promoting HPV screening for cervical cancer in rural India. Cytojournal 2009;6:12.

46. Goldie SJ, Gaffikin L, Goldhaber-Fiebert JD et al. Cost-effectiveness of cervical-cancer screening in five developing countries. N Engl J Med 2005;353: 2158–2168.

47. Legood R, Gray AM, Mahe C et al. Screening for cervical cancer in India: How much will it cost? A trial based analysis of the cost per case detected Int J Cancer 2005;117:981–987.

48. Tamil Nadu Health Systems Project. Prevention and care for women: Cervical cancer screening pilot program. Available at: http://www.tnhsp.org/files/Cervical%20Cancer.pdf. Accessed October 14, 2013.

49. Basu P, Nessa A, Majid M et al. Evaluation of the national cervical cancer screening programme of Bangladesh and the formulation of quality assurance guidelines. J Fam Plann Reprod Health Care 2010;36:131–134.

50. Moon TD, Silva-Matos C, Cordoso A et al. Implementation of cervical cancer screening using visual inspection with acetic acid in rural Mozambique: Successes and challenges using HIV care and treatment programme investments in Zambézia Province. J Int AIDS Soc 2012;15:17406.

51. Mwanahamuntu MHS, Kapambwe VV, Pfaendler S et al. Advancing cervical cancer prevention initiatives in resource-constrained settings: Insights from the cervical cancer prevention program in Zambia. PLOS Med 2011;8:e1001032.

52. Agurto I, Sandoval J, De La Rosa M et al. Improving cervical cancer prevention in a developing country. Int J Qual Health Care 2006;18:81–86.

53. Rubenstein LV, Pugh J. Strategies for promoting organizational and practice change by advancing implementation research. J Gen Intern Med 2006;21 (suppl 2):S58–64.

54. Padian NS, Holmes CB, McCoy SI et al. Implementation science for the US president's emergency plan for aids relief (pepfar). JAIDS 2011;56: 199–203.

55. Denny L, Quinn M, Sankaranarayanan R. Chapter 8: Screening for cervical cancer in developing countries. Vaccine 2006;24 (suppl 3):71–77.

56. World Health Organization. Cervical cancer screening in developing countries: Report of a WHO consultation. 2002. Available at: http://whqlibdoc.who.int/publications/2002/9241545720.pdf. Accessed October 14,2013.

57. Bradley J, Coffey P, Arrossi S et al. Women's perspectives on cervical screening and treatment in developing countries: Experiences with new technologies and service delivery strategies. Women Health 2006;43:103–121.

58. Nene B, Jayant K, Arrossi S et al. Determinants of womens participation in cervical cancer screening trial, Maharashtra, India Bull World Health Org 2007;85:264–272.