

# ADVANCING CERVICAL CANCER PREVENTION IN INDIA

## Insights from Research and Programs

Suneeta Krishnan, Emily Madsen, Deborah Porterfield, Beena Varghese

October 2013





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## Health, Nutrition and Population (HNP) Discussion Paper

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# Health, Nutrition, and Population Discussion Paper

## Advancing Cervical Cancer Prevention in India: Insights from Research and Programs

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**Abstract:** Cervical cancer is the leading cause of cancer mortality in India, accounting for 17 percent of all cancer deaths among women age 30 to 69 years. At current incidence rates, the World Health Organization (WHO) estimates that the annual burden of new cases in India will increase to nearly 225,000 by 2025.

Despite the considerable burden of cervical cancer morbidity and mortality in India, there are few large-scale, organized cervical cancer prevention programs in the country. We reviewed the research literature and conducted interviews with individuals engaged in research and public health program implementation to identify important elements of cervical cancer prevention efforts in India and implementation issues that merit further investigation.

Although primary prevention through HPV vaccination has been endorsed by WHO, under certain conditions, in low- and middle-income countries (LMICs), its cost, partial efficacy and safety have been intensely debated in India. Further research and advocacy efforts are needed to determine the optimal strategies for its introduction and sustained use in the country. However, there is considerable research and programmatic evidence in support of secondary prevention of cervical cancer through screening and treatment. Regardless of screening approach, research and prevention programs have underscored the importance of ensuring strong linkages between screening, diagnosis, and treatment services for program and cost effectiveness. Available evidence also emphasizes that programs that are “women-centered,” or actively respond to women’s concerns and constraints are likely to be the most successful. In conclusion, research and prevention program experiences provide a strong rationale for investments in cervical cancer prevention in India.

**Keywords:** India, cervical cancer, HPV vaccination, screening, treatment

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## ACRONYMS

AIS	Adenocarcinoma In Situ
ANM	Auxiliary Nurse Midwife
CATCH	Community Access to Cervical Health
CIN	Cervical Intraepithelial Neoplasia
CIN2+	Cervical Intraepithelial Neoplasia Grade 2 or worse
CIN3+	Cervical Intraepithelial Neoplasia Grade 3 or worse
DNA	Deoxyribonucleic Acid
GAVI	Global Alliance for Vaccines and Immunization
HPV	Human Papillomavirus
IARC	International Agency for Research on Cancer
IEC	Information, Education, and Communication
LEEP	Loop Electrosurgical Excision Procedure
LMIC	Low and Middle Income Country
M&E	Monitoring and Evaluation
NCD	Non Communicable disease
Pap	Papanicolaou
PATH	Program for Appropriate Technology in Health
RCT	Randomized Controlled Trial
TNHSP	Tamil Nadu Health Systems Project
VI	Visual Inspection
VIA	Visual Inspection with Acetic Acid
VILI	Visual Inspection with Lugol's Iodine
WHO	World Health Organization

## GLOSSARY OF TERMS

AIS	Adenocarcinoma in situ. The recognized precursor to invasive cervical adenocarcinoma; it involves changes in the glandular epithelium of the uterine cervix.
CIN	Cervical intraepithelial neoplasia. A continuum of precancerous changes of the squamous cells on the surface of the cervix. Screening aims to detect, monitor, and treat a subset of these early changes to prevent progression to invasive cervical cancer. Changes are classified in terms of extent of tissue involvement and abnormality of cells as CIN1, CIN2, or CIN3, with CIN3 being the most severe.
Colposcopy	A diagnostic procedure that involves the use of an illuminated magnification tool (colposcope) to examine the cervix and distinguish between normal and precancerous and cancerous lesions. The procedure is also used to take directed biopsies for further pathological examination, and typically follows an abnormal screening test.
Cryotherapy	A procedure that uses an extremely cold instrument or liquid to freeze and eliminate precancerous lesions on the cervix when treatment is indicated. Cryotherapy comprises the “treatment” in screen-and-treat programs.
Endocervical curettage	A procedure in which the mucous membrane of the endocervical canal (the passage between the cervix and uterus) is scraped using a spoon-shaped instrument called a curette. The tissue sample is examined in a pathology laboratory for evidence of abnormal cells. This procedure is performed during colposcopy and typically follows an abnormal screening test.
HPV	A sexually transmitted DNA virus that causes genital warts and cancers of the penis, anus, and uterine cervix. Two HPV types (16 and 18) account for most cases of cervical cancer globally.
Intent-to-treat analysis	Analysis of data from a randomized controlled trial that includes data from all participants who have been randomized regardless of whether they adhered to the study protocol or withdrew from the study.
LEEP	A treatment to remove precancerous lesions (CIN) from the cervix through the use of a wire loop with an electric current that cuts away the layer of abnormal cells.
Per-protocol analysis	Analysis of data from a randomized controlled trial that is restricted to participants who adhered to study procedures (for example, those who received all three doses of a vaccine).
Sensitivity	A measure of test performance — the ability of a test to correctly identify persons with the condition of interest. It is the proportion of persons with a disease or condition that have a positive screening test.
Specificity	A measure of test performance — the ability of a test to correctly identify persons without the condition of interest. It is the proportion of persons without a disease or condition that have a negative screening test.

# EXECUTIVE SUMMARY

## BACKGROUND

This discussion paper reviews research findings and summarizes insights from pilot programs on cervical cancer prevention in India to inform future cervical cancer control efforts in the country.

In 2008, a quarter of the global incidence and mortality caused by cervical cancer was in India alone. Cervical cancer is the most common cancer among Indian women above 15 years of age: 38 percent of cases occur among women age 15 to 49. The majority of cases are diagnosed at advanced stages of the disease. Consequently, it is not surprising that cervical cancer is also the leading cause of cancer mortality among women in India, accounting for 17 percent of all cancer deaths among women age 30 to 69. Notably, between 1980 and 2010, despite considerable advances in cervical cancer prevention and treatment as well as improvements in India's health care infrastructure, little progress was made in reducing cervical cancer mortality. While in 1980 there were 37 women dying for every 100 new cases of cervical cancer, in 2010, the number of deaths had marginally declined to 32 for every 100 new cases.

Considerable research on cervical cancer screening, including large-scale randomized controlled trials, has been conducted in India. These studies have demonstrated that screening approaches such as visual inspection of the cervix using acetic acid or Lugol's iodine, the Papanicolaou (Pap) smear, and testing for human papillomavirus (HPV) are effective in promoting detection of the disease at earlier stages and reducing incidence and mortality. Despite the existence of these tools to promote early detection and treatment, few large-scale screening and treatment programs have been implemented in the country.

In 2011, India's national government launched a program to address chronic and noncommunicable diseases, including screening and treatment of cervical cancer. In parallel, several state governments are pilot-testing alternative noncommunicable disease prevention strategies. 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, highlight the various challenges to effective implementation of cervical cancer prevention efforts, and offer recommendations to strengthen programmatic and policy responses.

## METHODS

This paper is based on a review of English language peer-reviewed publications, gray literature, and interviews with individuals involved in the design and implementation of cervical cancer prevention programs in India.

Search engines including ISI Web of Knowledge, PubMed, and Google Scholar were employed to identify peer-reviewed articles published between 1990 and 2013. Search terms included cervical cancer, screening, early detection, HPV, and visual inspection, along with key words such as India and low- and middle-income countries. The gray literature was identified using

keyword search terms in Google’s search engine, reviewing references of published papers, and searching relevant organizations’ websites that contain document repositories.

In-depth interviews were conducted with individuals involved in the development and implementation of cervical cancer prevention programs, including public health officials engaged in state-level cancer prevention efforts, cancer experts at regional cancer centers, and individuals engaged in nongovernmental cervical cancer prevention initiatives in the southern states of Tamil Nadu, Kerala, and Karnataka. These interviews focused on ascertaining the factors that shaped decisions on program design, challenges faced in implementation, and potential strategies to overcome those challenges.

## RESEARCH EVIDENCE

### Primary Prevention: HPV Vaccination

HPV strains are easily transmitted; thus, a high proportion of sexually active individuals will become infected over their lifetime. Although the majority of infections are cleared by the immune system and have no health implications, a minority persist and can lead to genital warts and cervical cancer.

Currently, there are two widely marketed vaccines — the bivalent vaccine (Cervarix®), which targets HPV types 16 and 18, and the quadrivalent vaccine (GARDASIL®), which targets types 6, 11, 16, and 18. HPV types 16 and 18 cause 70 percent of cervical cancers worldwide, while types 6 and 11 are responsible for the majority of genital warts. Available data indicate that the vaccines are safe and effective, with reports of only mild, brief reactions at the site of injection.

The guidance note, *Comprehensive Cervical Cancer Prevention and Control*, published by the World Health Organization (WHO) in 2013, recommends that population-based HPV vaccination programs target girls age 9 to 13, before the initiation of sexual activity. Girls and their families will still need to be educated about the importance of screening for cervical cancer since the vaccines do not target all oncogenic HPV types and because the duration of protection and the need for boosters are still unknown.

WHO has recommended the inclusion of HPV vaccination in national immunization programs under the following conditions: relatively high prevalence of cervical cancer, effective delivery strategies to enable high coverage of the target population, sustainable financing and evidence of cost effectiveness, resources to engage in appropriate communication campaigns, and monitoring and evaluation mechanisms.

Resource-constrained countries need subsidies to afford the HPV vaccine. The vaccine’s current market price is approximately US\$40 per dose in India. In 2013 the GAVI Alliance announced that it would offer to eligible countries — those with a gross national income per capita below or equal to US\$1,520, based on World Bank data — the HPV vaccine at US\$4.50 per dose. Eligible countries (of which there are currently 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.

Besides cost, there are a number of other challenges to large-scale HPV vaccination. Strategies are required to identify and reach the primary target group of preadolescent and adolescent girls in low- and middle-income countries where large numbers of girls drop out of school in early adolescence. In addition, effective ways are needed to communicate fairly complex information about the vaccines, including the focus on adolescent girls, the partial efficacy of the vaccines because they target only select oncogenic HPV types, and the need for cervical cancer screening in adulthood due to the unknown duration of the vaccines' protection and the vaccines' partial efficacy. Continued research is needed to identify cheaper vaccines, and to better understand currently available vaccines in terms of duration of protection, coadministration with other vaccines, less complex dosage schedules, and cross-protection against other HPV types. Programs that offer HPV vaccination will require education and counseling components to assist parents and girls make an informed decision.

HPV vaccines are currently available in India through the private sector. Promoting HPV vaccination through the public health system has been an intensely debated issue in the mainstream press as well as in academic journals that centers on issues of cost, partial efficacy of the vaccine, and vaccine safety. Further research and advocacy efforts are needed to determine the optimal strategies for introducing the HPV vaccine in India. Given the costs, public provisioning will be essential to ensure equitable access and adequate coverage. However, evidence also suggests that cervical cancer screening and treatment will continue to be needed by women who are ineligible to receive the vaccines as well as by those who are vaccinated, as the duration of protection of the vaccines is unknown.

### **Secondary Prevention: Screening for Cervical Cancer**

Over the past decade, at least two randomized controlled trials and eleven cross-sectional studies have been conducted in India to evaluate the accuracy and effectiveness of cervical cancer screening. Cervical cancer prevention researchers and advocates have argued that the standard approach in high-income countries, namely cytology-based screening, is difficult to establish in low- and middle-income countries where laboratory infrastructure, trained personnel such as cytotechnicians and pathologists, and continuous quality assurance processes are largely unavailable. Consequently, research has focused on evaluating screening approaches requiring less training and fewer clinic visits and using existing (or minimal additional) human resources.

Specifically, studies have compared the specificity and sensitivity of visual inspection (VI)-based approaches (visual inspection of the cervix with acetic acid [VIA] or with Lugol's iodine [VILI]) with the Pap smear as well as with HPV DNA testing. These approaches have been implemented by health care providers, who vary across studies in their qualifications and extent of experience and training in cervical cancer screening.

Studies in India suggest that VIA and VILI have comparable sensitivity and specificity to cytology and HPV DNA test-based screening. An advantage of VI-based approaches is the immediate availability of screening test results, which provides an opportunity to conduct a biopsy or offer treatment during the same visit (the "screen and treat" approach) and reduces the likelihood of failure to follow up. That said, there is risk of overtreatment in this context, given that the specificity of VI-based approaches is lower than that of the Pap smear or of HPV DNA

testing. Although there is no clear evidence of harm resulting from overtreatment, some researchers contend that using the screen-and-treat approach entails risks that may become apparent only with longer follow-up.

Overall, achieving high levels of screening participation and adherence to diagnostic and treatment recommendations — without which it is difficult to justify screening — has been a challenge even in the context of well-resourced studies in India. Studies that have been successful in recruitment and retention have focused on interpersonal communication through face-to-face and group meetings with women, husbands, and family members; have offered personal invitations to eligible women and provided appointments and screening cards; and have involved local government health workers and community leaders to motivate women to participate in screening.

Reasons for refusal to undergo screening have included lack of symptoms indicating a health problem; fear of the tests/pelvic examination, a cancer diagnosis, and community gossip and perception; household responsibilities; family problems and illnesses; and refusal of husbands or other relatives to grant permission. Long waiting times and the presence of male doctors are additional barriers. Facilitators of and barriers to patient adherence to diagnostic and treatment recommendations were generally similar to those for screening.

The impact of screening on morbidity and mortality is contingent on achieving relatively high screening coverage as well as ensuring that screen-positive women receive appropriate diagnostic and treatment services. Treatment of precancerous cervical lesions can prevent progression to invasive cancer, reducing subsequent morbidity and mortality, and treatment of invasive cancer can prolong women's lives. The few studies that have engaged in longer-term follow-up of participants to estimate the impact of different cervical cancer screening approaches on morbidity and mortality in India have found that VIA-based screening leads to significant declines in cervical cancer mortality within a decade of the start of intervention. It is important to note that these declines have been observed in studies that have invested heavily in the follow-up and treatment of women who screened positive.

Cost-effectiveness analyses of screening approaches in India have produced varied results. In one study, which used data from a randomized controlled trial comparing VIA, cytology, and HPV DNA testing, VIA was found to be the least expensive option at US\$3.92 per woman eligible for screening, followed by cytology at US\$6.61. VIA detected 7.5 CIN2/3+ cases per 1,000 eligible women and cost US\$522 per case detected (compared with no screening), whereas cytology was 26 percent more expensive (US\$659 per case detected) and detected more cases (10 cases per 1,000). HPV DNA testing was nearly twice as expensive as cytology and was less effective than cytology in detecting CIN2/3+.

Another modeling study reported that a single lifetime screening using a one-visit VIA strategy (that is, a screen-and-treat strategy) was the least costly compared with cytology and HPV DNA testing at US\$10/year of life saved. However, it is unclear whether the strategy of combining screening and treatment of women with positive screening results in one visit at a primary-level facility is in fact feasible in a program context. A third modeling study concluded that screening

adult women two to three times per lifetime in addition to preadolescent vaccination was cost effective.

In summary, evidence suggests that VI-based screening can reduce cervical cancer incidence and mortality and be cost effective in India. Research has underscored the fact that impact and cost effectiveness are contingent on ensuring strong linkages between screening and treatment, a key challenge facing cervical cancer prevention efforts in India.

### **PROGRAMMATIC EXPERIENCES**

Few examples exist of large-scale cervical cancer screening programs in India. However, two such initiatives have been implemented in the state of Tamil Nadu. One is a statewide program by the World Bank–supported Tamil Nadu Health Systems Project (TNHSP) and the other is a citywide program of the Chennai Corporation. Both programs offer cervical cancer prevention services as part of a broader package of services addressing chronic conditions such as diabetes and hypertension, and offer screening services at the primary health care level.

The two programs demonstrate 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, human and financial resources, and community buy-in and involvement. The TNHSP experience underscores the importance of establishing linkages between different levels of the health care system to facilitate diagnostic confirmation and treatment provision. In fact, despite high screening coverage (about 70 percent), program performance in terms of patient follow-up was not as optimal. Only about half the screen-positive women underwent diagnostic investigations, and a mere 13 percent of women needing treatment received it through the program.

Due to limitations in program monitoring and evaluation plans and systems, few conclusions can be drawn about the impact of the TNHSP and Chennai Corporation programs. That said, project documents and interviews revealed a number of lessons that can guide the scale-up and replication of these cervical cancer prevention approaches; these are summarized below.

### **RECOMMENDATIONS FOR STRENGTHENING CERVICAL CANCER PREVENTION IN INDIA**

Research and programs in India have demonstrated that cervical cancer prevention initiatives have the potential to significantly reduce morbidity and mortality. To date, both research and program efforts have faced challenges to achieving high levels of screening coverage and adherence to diagnostic and treatment recommendations. Further work is needed to better understand the kinds of messages and communication methods that will promote utilization of prevention services and the kinds of strategies that may be needed to strengthen referral mechanisms.

Although many questions are yet to be answered, our review of research and programmatic experiences revealed several important aspects of successful cervical cancer prevention efforts in India and has led to the following recommendations for the country.

### **Leadership and Governance**

- Advocate for greater political commitment and administrative leadership to ensure adequate and sustained resource allocation, sufficient human resources and health care infrastructure, development of health information systems for program monitoring and evaluation, and expansion of access to health services.
- Enhance health system capacities to deliver services, including relevant policies, infrastructure, and skilled human resources.
- Use a multisectoral approach to raise awareness.
- Enhance health care access among vulnerable women (for example, those who are older, less educated, or from poor or marginalized households).

### **Community Mobilization**

- Sensitize and train local health care workers to raise awareness of cervical cancer screening and treatment.
- Engage local leaders such as members of local government, village health and sanitation committees, and women's self-help groups to mobilize support.
- Develop messages that are appropriate to the local context and target audience and that address known reasons for poor uptake of cervical cancer screening and treatment services. These reasons may include fear of cancer, misconceptions about cancer, and fear of screening tests and instruments/tools used.
- Disseminate information through reliable channels.

### **Comprehensive and Cost-Effective Service Delivery**

- Program design should be “women-centered,” that is, respond to women's concerns and constraints.
- Use a combination of primary and secondary prevention strategies that balance performance and practical considerations. Implementation research can inform these decisions.
- Ensure strong linkages within and between different levels of the health care system to ensure timely follow-up and referrals.
- Establish a quality assurance plan that defines standards at different levels of care and describes how quality reviews and improvements are conducted and by whom.
- Use prospective evaluation to provide feedback on program quality and progress and enable program improvements.

## PART I – INTRODUCTION

Cervical cancer is a major public health challenge in India. In 2008, a quarter of the global incidence and mortality caused by cervical cancer was in India alone (GLOBOCAN 2012). Despite the considerable burden, there are few organized cervical cancer screening programs in the country. The majority of women are diagnosed at advanced stages of disease, with poor prognosis (Jayant, Rao et al. 1995).

Nevertheless, considerable research on cervical cancer screening, including large-scale randomized controlled trials (RCTs), has been conducted in India. These studies have demonstrated that screening approaches such as visual inspection of the cervix using acetic acid or Lugol's iodine, the Papanicolaou (Pap) smear, and testing for human papillomavirus (HPV) are effective in promoting detection of the disease at earlier stages and in reducing incidence and mortality (Sankaranarayanan, Esmly et al. 2007, Sankaranarayanan, Nene et al. 2009, Gravitt, Paul et al. 2010). Programmatic experiences in Tamil Nadu and elsewhere have shown that provision of cervical cancer screening and treatment services is feasible. Globally, vaccination against HPV is emerging as a cornerstone of cervical cancer prevention efforts, and experiences in India indicate that vaccine delivery is feasible (Jacob 2010).

In this paper, we argue that sufficient evidence exists to justify the implementation of comprehensive cervical cancer prevention in India, including organized screening efforts as well as HPV vaccination although questions remain about the most acceptable, affordable, and cost-effective approaches. Drawing on published literature and interviews with cervical cancer prevention program staff, we describe what is known about implementing HPV vaccination as well as cervical cancer screening and treatment in India. We use this evidence to highlight the various challenges to effective implementation of cervical cancer prevention efforts, and offer recommendations for strengthening programmatic and policy responses.

### BACKGROUND: CERVICAL CANCER IN INDIA

Cervical cancer is the most common cancer among Indian women age 15 or older. According to estimates produced by the Institute for Health Metrics and Evaluation, approximately 1 in 53 Indian women will develop cervical cancer during her lifetime compared with 1 in 100 in developed regions of the world (Institute for Health Metrics and Evaluation 2011). In 2010, there were nearly 74,000 new cases of cervical cancer in India, 38 percent of cases among women in the reproductive age (15 to 49 years) (Institute for Health Metrics and Evaluation 2011). The *Cancer Atlas of India* suggests that the southern states of Tamil Nadu and Karnataka are high-incidence zones, with age-adjusted rates above national figures (Nandakumar, Gupta et al. 2005). Although these differences may be due to greater access to care and to higher levels of diagnosis and reporting of cases in the south, the prevalence of HPV and other sexually transmitted diseases such as HIV has also been found to be greater in these southern states. The relatively higher occurrence of cervical cancer in this region is consistent with the higher prevalence of HPV (Nandakumar, Gupta et al. 2005). According to the World Health Organization (WHO), in the absence of systematic prevention or screening efforts, the annual burden of new cases in

India will increase to nearly 225,000 by 2025 (WHO/ICO Information Centre on HPV and Cervical Cancer (HPV Information Centre) 2010).

The majority (70 percent) of Indian women diagnosed with cervical cancer have stage III or IV disease (Nandakumar, Anantha et al. 1995) and consequently poor prognoses. Fewer than a third of women diagnosed with stage III cervical cancer survived the first five years after their diagnosis; the five-year survival rate drops to nearly 6 percent (Nandakumar, Anantha et al. 1995).

Consequently, it is not surprising that cervical cancer is also the leading cause of cancer mortality among women in India, accounting for 17 percent of all cancer deaths among women age 30 to 69 (Dikshit, Gupta et al. 2012). Notably, between 1980 and 2010, despite considerable advances in cervical cancer prevention and treatment as well as improvements in India's health care infrastructure, little progress was made in reducing cervical cancer mortality. While in 1980, 37 women were dying for every 100 new cases of cervical cancer, in 2010 the rate had marginally declined to 32, which is similar to other South Asian countries (Institute for Health Metrics and Evaluation 2011). The age-standardized cervical cancer mortality rate in the southern state of Karnataka was 16.5 per 100,000 women, compared with 35.7 per 100,000 in Tamil Nadu, 11.1 per 100,000 in Kerala, and 16.0 per 100,000 nationally in 2010 (Dikshit, Gupta et al. 2012).

Globally and in India, two HPV types — 16 and 18 (Sowjanya, Jain et al. 2005, Singh, Datta et al. 2009) account for the majority of cervical cancers. The prevalence of HPV among Indian women with normal cytology is about 8 percent (WHO/ICO Information Centre on HPV and Cervical Cancer (HPV Information Centre) 2010). Additional cofactors that enhance the risk of cervical cancer if HPV infection exists, include young age at sexual debut and high parity, both of which are common among Indian women because of early marriage and social norms that support high fertility (Farooqui and Zodpey 2012).

Further, data suggest that incidence and mortality are higher among women from disadvantaged socioeconomic backgrounds and those living in rural areas (Kukure and Yeole 2006, Swaminathan, Selvakumaran et al. 2009, Swaminathan, Selvakumaran et al. 2009, Dikshit, Gupta et al. 2012). A 2006 study at the Regional Cancer Center in Thiruvananthapuram found that the odds of presentation with stage III or IV cervical cancer were twice as high among women who had only primary or no education (compared with women with secondary or higher levels of schooling) and among those who were widowed or divorced (compared with women who were married) (Kaku, Mathew et al. 2008). Lack of awareness, delayed health care seeking and diagnosis; limited access to treatment are also thought to underlie these discrepancies. For example, a study in rural Barshi, Maharashtra State, found that educating women about symptoms of cervical cancer and motivating symptomatic women to seek medical care led to a significant (13 percent) increase in the proportion of cases detected at early stages; similar increases were not observed in the control area (Jayant, Rao et al. 1995).

Health care in India is largely privately financed (69 percent of total health expenditure is private). Only a very small proportion of the population is covered by social or private health

insurance (Engelgau, Karan et al. 2012). The bulk of private expenditure on health — 86 percent — is out of pocket. According to the World Bank’s data for 2008–12, out-of-pocket payments for health amount to about US\$36 per capita (The World Bank 2013). Out-of-pocket expenses primarily include the costs of medicines, diagnostic tests, and medical appliances, and largely derive from personal income and savings (Engelgau, Karan et al. 2012). Consequently, the financial burden of treatment of cervical cancer and other chronic diseases on households is considerable.

A recent analysis of data for over 200,000 households across India revealed that the odds of incurring catastrophic expenditures (out-of-pocket spending greater than 40 percent of a household’s ability to pay) were nearly 170 percent higher among individuals with a noncommunicable disease (NCD) or an injury than among those with a communicable disease (Engelgau, Karan et al. 2012). The same authors also found that men and women with cancer reported higher expenditures and utilization of inpatient care and a greater likelihood of incurring catastrophic expenditures and household impoverishment than those with other NCDs such as cardiovascular disease (Mahal, Karan et al. 2010).

Approximately 60 percent of in-patient care for NCDs was provided in the private sector; and on average, out-of-pocket expenses at private facilities are higher than at public facilities, indicating the important role of public facilities in addressing the financial risks associated with NCD care (Mahal, Karan et al. 2010). Yet out-of-pocket expenses for a single hospital stay in a public facility due to cancer can still amount to nearly half of per capita income.

Insurance schemes such as the national Rashtriya Swasthya Bhima Yojana and Karnataka State’s Vajpayee Arogyasri Scheme provide financial protection against high medical expenses (including cancer surgery and related treatment) for households below the poverty line. But these schemes primarily cover tertiary-level diagnostic and treatment services, and do not address prevention services such as cervical cancer screening and treatment of precancerous lesions.

In summary, cervical cancer is an important cause of premature death and disability among women in India. In 2008, it is estimated that 466 disability-adjusted life years per 100,000 population were lost due to the disease — constituting about 25 percent of total number of years of life lost among women due to cancer (Soerjomataram, Lortet-Tieulent et al. 2012). Because it primarily affects women during their most productive years when they are also caregivers, cervical cancer has adverse social and economic impacts on families and communities. As suggested by studies of the economic impact of NCDs in India, diagnosis of advanced cervical cancer is also likely to have a catastrophic economic impact on households (Mahal, Karan et al. 2010, Saksena, Xu et al. 2011).

In contrast to the United States and other high-income countries that include cervical cancer screening as a part of routine primary care, no organized screening programs are in place in India (Vallikad 2006). Primary prevention through HPV vaccination is an important strategy that has been endorsed by WHO in settings where it is programmatically feasible, financially sustainable, and cost effective (World Health Organization 2009). For many low- and middle-income countries (LMICs), secondary prevention through screening remains the most affordable and

feasible option. Considerable research has examined the feasibility and performance of screening tests such as cytology, visual inspection of the cervix, and HPV DNA testing in these settings, including in India, and several LMICs have initiated screening programs (Sankaranarayanan 2012).

## **PART II – METHODS**

This paper is based on a review of English-language peer-reviewed publications, gray literature (including unpublished program reports, white papers, and conference presentations), and interviews with individuals involved in the design and implementation of cervical cancer prevention programs in India. Literature published between 1990 and 2013 was identified using ISI Web of Knowledge, PubMed, and Google Scholar. Search terms included cervical cancer, screening, early detection, HPV, and visual inspection, along with key words such as India and low- and middle-income countries. The gray literature was identified using keyword search terms in Google’s search engine, reviewing references of published papers, and searching relevant organizations’ websites that contain document repositories.

In-depth interviews were conducted with nine individuals involved in the development and implementation of cervical cancer prevention programs, including public health officials in state-level cancer prevention efforts, cancer experts at regional cancer centers, and individuals engaged in nongovernmental cervical cancer prevention initiatives in the southern states of Tamil Nadu, Kerala, and Karnataka. These interviews focused on ascertaining the factors that shaped decisions on program design, challenges faced in implementation, and potential strategies to overcome those challenges.

## **PART III – RESEARCH EVIDENCE**

We identified 44 peer-reviewed articles on cervical cancer prevention in India published within the time frame of interest. Articles were categorized in terms of those addressing primary prevention of cervical cancer through HPV vaccination and those addressing secondary prevention through screening, early detection, and treatment. Below we discuss the evidence in support of primary and secondary prevention approaches.

### **PRIMARY PREVENTION: HPV VACCINATION**

#### **HPV Vaccines**

HPV strains are easily transmitted; a high proportion of sexually active individuals will become infected over their lifetime. Although the majority of infections are cleared by the immune system and have no health implications, a minority persist and can lead to genital warts and cancers, including cervical cancer.

Currently, there are two widely marketed vaccines — the bivalent vaccine (Cervarix®), which targets HPV types 16 and 18; and the quadrivalent vaccine (GARDASIL®), which targets types 6, 11, 16, and 18 (World Health Organization 2009). HPV types 16 and 18 cause 70 percent of cervical cancers worldwide, while types 6 and 11 are responsible for the majority of genital warts

(World Health Organization 2013). The vaccines contain virus-like particles prepared using recombinant technology, and are administered as three doses over a six-month period.

Studies have shown that both the bivalent and quadrivalent vaccines are effective in generating an immune response against the targeted types after three doses in females (World Health Organization 2009, Mariani and Venuti 2010). Clinical efficacy studies typically use precancerous lesions (cervical intraepithelial neoplasia grade 2 or 3 [CIN2/3]) or adenocarcinoma in situ (AIS) as surrogate endpoints since the use of invasive cervical cancer is ethically unacceptable. They have found that both vaccines have >90 percent efficacy in preventing CIN2, CIN3, and AIS among women who have not had previous HPV-16 or HIV-18 infections (World Health Organization 2009). Recently published results from a randomized, double-blind trial of the bivalent vaccine reinforce earlier findings on vaccine efficacy: the overall efficacy of the bivalent vaccine against CIN3 and AIS (the immediate precursors to invasive cancer, and offering the strongest evidence) was 100 percent among women who had no evidence of oncogenic HPV types at baseline (Lehtinen, Paavonen et al. 2012). Consistent with earlier studies, efficacy was found to be substantially lower (46 percent) among women who were sexually active and likely to have been exposed to HPV.

Recent data from Australia indicate that the national HPV vaccination program, which uses the quadrivalent vaccine, is associated with a substantial (93 percent) fall in the incidence of genital warts among women under 21 years in 2011, four years after the introduction of the vaccine (Ali, Donovan et al. 2013). Another analysis noted a significant decrease in the incidence of high-grade cervical abnormalities in girls younger than 18 years within three years of the HPV vaccination program in Australia (Brotherton, Fridman et al. 2012). These emerging findings from high-income countries lend further support to the efficacy of the vaccine.

WHO's most recent guidance on cervical cancer prevention recommends that population-based HPV vaccination programs target girls age 9 to 13, before the initiation of sexual activity (World Health Organization 2013). Girls and their families will still need to be educated about the importance of screening for cervical cancer since the vaccines do not target all oncogenic HPV types and because the duration of protection and the need for boosters are still unknown (World Health Organization 2009). Thus, it is critical to combine vaccination with cervical cancer screening.

WHO has not recommended HPV vaccination for boys based on cost-effectiveness analyses, indicating that resources should aim for high coverage among girls. However, the quadrivalent vaccine has been licensed for use in males to prevent HPV-related external genital lesions (World Health Organization 2009). A per-protocol analysis of data from a randomized, double-blind trial revealed 90 percent efficacy for lesions related to HPV 6, 11, 16, or 18 among males who received all three doses and were negative for relevant HPV types at enrollment; efficacy was lower (65.5 percent) in intent-to-treat analysis (Giuliano, Palefsky et al. 2011).

In Australia, a significant decline was observed in the proportion of young men diagnosed with genital lesions in the postvaccination period. The authors attributed the observed declines to herd immunity — indirect protection resulting from decreased transmission of HPV in communities

where young women have been vaccinated (Ali, Donovan et al. 2013). Although these observations further support the WHO recommendation to focus vaccination efforts on girls, research is needed to explore differences in vaccine acceptability in LMIC settings, when the vaccine is offered only to girls as opposed to when it is offered to both girls and boys.

Available data indicate that the vaccines are safe. Only mild, brief reactions at the site of injection have been reported (World Health Organization 2009). However, longer-term follow-up of vaccine recipients and introduction of the vaccines in diverse populations are needed to confirm their safety. WHO does not recommend vaccinating women who are pregnant and individuals who have had allergic reactions to a previous dose of the vaccine or a vaccine component. Vaccination may also be postponed for individuals with a severe acute illness. Although studies on the safety and efficacy of coadministration of HPV vaccines with other vaccines are ongoing, available data suggest that they can be coadministered as long as different syringes and injection sites are used. Coadministration may enhance the potential for integrating HPV vaccines into national immunization programs (World Health Organization 2009). Contraindications and precautions for HPV vaccinations will have to be monitored in a population-based vaccination program.

Given the challenges of establishing organized screening programs and ensuring follow-up of screen-positive women in LMICs and of the availability of safe and efficacious HPV vaccines, WHO has recommended the inclusion of HPV vaccination in national immunization programs in settings where several conditions are met. These conditions include a relatively high prevalence of cervical cancer; assurance of sustainable financing and evidence of cost effectiveness; availability of effective delivery strategies to enable high coverage of the target population; resources to engage in appropriate communication campaigns; and mechanisms for postvaccination monitoring and program evaluation (World Health Organization 2009, Mattheji, Pollock et al. 2012, World Health Organization 2013).

India is in a position to meet these criteria although demonstration projects are needed to identify the most acceptable and cost-effective mechanisms for vaccine delivery. One mathematical modeling study informed by empirical data from India assessed the cost effectiveness of HPV vaccination and cervical cancer screening strategies and found that vaccination can reduce the lifetime risk of cervical cancer by 35 to 80 percent. Results indicated that, assuming 70 percent coverage, preadolescent vaccination for HPV types 16 and 18 alone can reduce lifetime cervical cancer risk by 44 percent, and is more effective than screening alone — regardless of screening test, screening frequency, and target age group (Diaz, Kim et al. 2008). In addition, the combination of preadolescent vaccination and screening of adult women proved to be more effective than either strategy alone. Specifically, a program that combined preadolescent vaccination and screening after age 30 (by Pap smear three times in a lifetime or by HPV DNA test twice in a lifetime — both at 70 percent coverage) could reduce lifetime cancer risk by 56 to 63 percent. This combined strategy was cost effective according to WHO benchmarks for developing countries if the vaccine was estimated to cost about US\$2 per dose or less.

Resource-constrained countries need subsidies to afford the HPV vaccine. The market price of the vaccine is currently approximately US\$40 in India. Partnerships with pharmaceutical

companies that produce the vaccine have supported its introduction in some LMICs, including Bhutan and Rwanda (Adams 2012, Binagwaho, Wagner et al. 2012). In 2013 the GAVI Alliance announced that it would offer to eligible countries (those with a gross national income per capita below or equal to US\$1,520, based on World Bank data) the HPV vaccine at US\$4.50 per dose (GAVI Alliance 2031). Eligible countries (of which there are currently 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. Eight countries — primarily in Sub-Saharan Africa — are slated to begin nationwide or demonstration projects with GAVI support in 2013. By 2020 GAVI aims to provide support to enable 30 million girls worldwide to receive the HPV vaccine.

Even with GAVI subsidies, HPV vaccination costs are relatively high. WHO estimates that delivering three doses of the HPV vaccine can cost approximately US\$7.20 per girl *in addition to* the cost of the vaccine (World Health Organization 2013); thus even at the subsidized price currently available through GAVI, the total cost of vaccination per girl will be about US\$20.70 (for three doses of the vaccine). Lower-middle-income countries such as India, which is on the borderline of GAVI eligibility, and upper-middle-income countries such as Thailand, which are not GAVI-eligible, will likely need to examine alternative avenues for financing HPV vaccination.

Besides cost, there are a number of other challenges to large-scale HPV vaccination. Strategies must be identified to reach the primary target group of preadolescent and adolescent girls in LMICs where large numbers of girls drop out of school in early adolescence. In addition, effective ways are needed to communicate fairly complex information about the vaccines, including the focus on adolescent girls, the partial efficacy of the vaccines because they target only select oncogenic HPV types, and the need for cervical cancer screening in adulthood due to the unknown duration of the vaccines' protection and due to the vaccines' partial efficacy. Continued research is needed to identify cheaper vaccines, and to better understand currently available vaccines in terms of duration of protection, coadministration with other vaccines, less complex dosage schedules, and cross-protection against other HPV types (Tsu Unknown). Finally, programs that offer HPV vaccination will need education and counseling components to assist parents and girls make informed decisions.

### **Indian Vaccine Experience**

HPV vaccines are available in India through the private sector. There has been limited research on HPV vaccine delivery and acceptability through the public sector. In 2007–08, the international nongovernmental organization, Program for Appropriate Technology in Health (PATH) with the National AIDS Research Institute (NARI) conducted formative qualitative research to understand sociocultural, health systems, and policy issues associated with HPV vaccine introduction in India. The goal of this study was to lay the foundation for a demonstration project to identify acceptable, affordable, and effective strategies for HPV vaccine rollout in India (PATH, Jacob 2010).

The formative research conducted by PATH and NARI identified three mechanisms for vaccine delivery: the existing national immunization program, adolescent health or cancer control services, and school- and community-focused campaigns. The study also highlighted several

requirements for successful introduction of the HPV vaccine in India, including the need for a communication strategy focused on raising community awareness of cervical cancer and addressing concerns over vaccine efficacy, safety, and potential impacts on fertility; engagement with community gatekeepers, such as local leaders and health workers to promote community acceptance and involvement; and advocacy to build broad-based political support for cervical cancer prevention.

Although the study identified several mechanisms that could facilitate vaccine introduction, such as including the vaccine in the established national immunization program or packaging it with adolescent health services, it also revealed systems-level challenges such as inadequate staffing of health centers, questionable ability of existing health staff to absorb the additional workload, and lack of coordination between government programs and departments that may need to be involved (Jacob 2010). Other research in southern India found that although parents held positive attitudes about vaccination, they did not support vaccinating preadolescent girls and felt that vaccination against HPV was more appropriate once girls had attained puberty (Madhivanan, Krupp et al. 2009). Concerns over cost and vaccine side effects were identified as additional barriers to acceptance.

Promoting HPV vaccination through the public health system has been a highly debated issue in the mainstream press as well as in academic journals (Dabade, Abhiyan et al. 2010, Kang 2010, Mudur 2010, Ramanathan and Varghese 2010, Rathod 2011, Srinivasan 2011, Mattheji, Pollock et al. 2012, Mudur 2012, Tsu 2012). Debates have centered on many of the issues identified in studies on vaccine acceptability such as sociocultural factors, cost, and postvaccination monitoring systems. Controversy over HPV vaccination came to a fore in 2009 after the launch of a demonstration project led by PATH with the Indian Council of Medical Research, Department of Health Research, the national Ministry of Health, and the state governments of Andhra Pradesh and Gujarat (Dabade, Abhiyan et al. 2010, Jacob 2010). A number of women's health activists and researchers questioned the Indian government's decision to conduct the project in light of the limited data on vaccine safety and efficacy, the relatively high cost of the vaccine, and its questionable cost effectiveness. In a letter to the minister of health published in the *Indian Journal of Medical Ethics*, the authors argued that the government should focus on promoting awareness of cervical cancer and ensuring access to comprehensive reproductive and sexual health services, including cervical cancer screening and treatment (Dabade, Abhiyan et al. 2010). Others have challenged investments in HPV vaccination by disputing the data on India's cervical cancer burden, arguing that national incidence is in fact on the decline (Mattheji, Pollock et al. 2012).

The controversy escalated after reports of the deaths of four adolescent girls involved in the demonstration project (Srinivasan 2011). The project was suspended in April 2010 by the government, and an enquiry was launched. The enquiry concluded that the deaths were unrelated to the vaccine (PATH), but highlighted a number of ethical violations, including the manner in which informed consent was obtained (Srinivasan 2011). The enquiry panel did not assign responsibility for those violations to any individual or institution.

The experience of this demonstration project and its fallout raise several issues for consideration in future efforts to promote HPV vaccination. First, they highlight the need for a system to monitor, report, and respond to adverse events after the introduction of a new vaccine for a defined period. The deaths of the adolescent girls do not appear to have been identified by the study team in a timely manner. Formative research in Andhra Pradesh and Gujarat had found that although guidelines were available for postimmunization adverse event management, they were typically not followed (Jacob 2010) — underscoring the need for greater emphasis on postimmunization monitoring systems in future vaccine introduction efforts.

Second, they emphasize the importance of a robust communication strategy to set the stage for and run parallel to future initiatives. Press and academic journal articles varied widely in their understanding of the project with some calling it a “trial” and PATH insisting that it was an observational study. There are also widely differing interpretations of the global data on the safety of HPV vaccines among various Indian stakeholders. Exploration of more effective means of communicating and disseminating the evidence on HPV vaccine safety and efficacy is warranted.

Third, the experience and fallout raise the issue of building research capacity and investing in mechanisms to ensure the ethical implementation of research and program pilots. Moreover, the focus of HPV vaccination efforts on adolescent girls and the links to sexual and reproductive health necessitate heightened attention to the process of community engagement and informed consent.

Available data indicate that HPV vaccination is a highly promising cervical cancer prevention strategy. In the Indian context, research and advocacy efforts are needed to determine the optimal methods for introducing it. Given the costs, public provisioning will be essential to ensure equitable access and adequate coverage. However, as noted, cervical cancer screening and treatment will continue to be needed by women who are ineligible to receive the vaccines as well as those who are vaccinated, since duration of protection of the vaccines is unknown.

## **SECONDARY PREVENTION: SCREENING FOR CERVICAL CANCER**

Over the past decade, at least two RCTs and eleven cross-sectional studies have been conducted in India to evaluate the accuracy and effectiveness of cervical cancer screening (Basu, Sankaranarayanan et al. 2003, Sankaranarayanan 2004, Sankaranarayanan 2004, Sankaranarayanan, Shastri et al. 2004, Sodhani, upta et al. 2006, Bhatla, Mukhopadhyay et al. 2007, Bhatla, Gulati et al. 2009, Gravitt, Paul et al. 2010, Bhatla, Puri et al. 2012, Deodhar, Sankaranarayanan et al. 2012, Ghosh, Gandhi et al. 2012, Shastri, Mitra et al. 2013). Cervical cancer prevention researchers and advocates have argued that the standard approach in high-income countries, namely cytology-based screening, is difficult to establish in LMICs where laboratory infrastructure; trained personnel, such as cytotechnicians and pathologists; and continuous quality assurance processes are largely unavailable (Saxena, Sauvaget et al. 2012). Consequently, research has focused on evaluating screening approaches requiring less training and fewer clinic visits and using existing (or minimal additional) human resources (table 1).

Specifically, studies have compared the specificity and sensitivity of visual inspection (VI)-based approaches (visual inspection of the cervix with acetic acid [VIA] or Lugol's iodine [VILI]) with the Pap smear as well as with HPV DNA testing. These approaches have been implemented by health care providers who differ across studies in their qualifications and extent of experience and training in cervical cancer screening (table 2). For example, projects in Dindigul, Tamil Nadu (May 2000 to April 2003) and Osmanabad, Maharashtra (October 1999 to November 2003) trained auxiliary nurse midwives (ANMs) or other female health workers to implement screening. Notably, nearly all studies set aside a substantial amount of time (two or three weeks) for training to ensure high-quality implementation.

### **Accuracy of Screening Tests**

Salient findings from Indian studies on the performance of cervical cancer screening tests are summarized in table 3. The majority of these studies were cross-sectional in design and involved either community- or hospital-based samples (Basu, Sankaranarayanan et al. 2003, Sankaranarayanan 2004, Sankaranarayanan 2004, Sankaranarayanan, Shastri et al. 2004, Sodhani, upta et al. 2006, Bhatla, Mukhopadhyay et al. 2007, Bhatla, Gulati et al. 2009, Gravitt, Paul et al. 2010, Bhatla, Puri et al. 2012, Deodhar, Sankaranarayanan et al. 2012, Ghosh, Gandhi et al. 2012). Two studies were RCTs (Sankaranarayanan 2004, Sankaranarayanan 2005, Sankaranarayanan, Esmey et al. 2007, Sankaranarayanan, Nene et al. 2009). To determine test sensitivity and specificity, most of these studies performed colposcopy for all participants and biopsy of abnormalities if indicated; in some studies the colposcopist was blinded to the initial screening test results (Bhatla, Mukhopadhyay et al. 2007, Bhatla, Puri et al. 2012, Deodhar, Sankaranarayanan et al. 2012). A few studies increased the rigor with which the disease status of participants was determined by conducting endocervical curettage or diagnostic loop electrosurgical excision procedure (LEEP) when the colposcopy was unsatisfactory or inconclusive (Bhatla, Mukhopadhyay et al. 2007, Deodhar, Sankaranarayanan et al. 2012). Of note, several observational studies (usually in academic centers) included women with gynecological complaints, which likely affected disease prevalence and may have also affected test performance (Sodhani, upta et al. 2006, Bhatla, Mukhopadhyay et al. 2007, Bhatla, Puri et al. 2012).

Overall, research in India suggests that VIA and VILI have comparable sensitivity and specificity to cytology and HPV DNA test-based screening (see table 3). Studies have found sensitivity to detect cervical intraepithelial neoplasia grade 2 or worse (CIN2+) to be similar for VIA (range 64.5 to 89.5 percent) and VILI (range 64.5 to 100 percent) compared with the Pap smear (range 52.6 to 62.3 percent). Research has also found test specificity of VIA (76.4 to 84.2 percent) to be lower than that of VILI (85.4 to 93.4 percent) and HPV testing (80.7 to 81.3 percent) and cytology testing to have the highest specificity (76.1 to 99.1 percent) (Basu, Sankaranarayanan et al. 2003, Sankaranarayanan 2004, Sankaranarayanan 2004, Sankaranarayanan 2004, Sankaranarayanan, Shastri et al. 2004, Sodhani, upta et al. 2006, Bhatla, Mukhopadhyay et al. 2007, Bhatla, Gulati et al. 2009, Gravitt, Paul et al. 2010, Bhatla, Puri et al. 2012, Deodhar, Sankaranarayanan et al. 2012, Ghosh, Gandhi et al. 2012).

One Indian study — Community Access to Cervical Health (CATCH), January 2005 to July 2007 in Andhra Pradesh — reported divergent test performance results. CATCH compared VIA,

HPV testing, and cytology and observed far lower estimates for sensitivity of VIA (CIN2+ 26.3 percent and CIN3+ 36.4 percent) than other Indian studies (Gravitt, Paul et al. 2010). The authors concluded that VIA is a highly subjective test and not robust enough to be substituted for other screening techniques, even with rigorous training of experienced providers. Additional analyses suggested that the study findings may have been due to interrater variability, VIA reactivity in the presence of inflammation due to unknown causes, or the inclusion of women over 50 years of age (for whom VIA is not recommended) (Vedantham, Silver et al. 2010).

In fact, studies have indicated that VI-based approaches have lower test sensitivity when used among older women because of the migration of the transformation zone into the endocervical canal (Sankaranarayanan, Esmey et al. 2007, Sankaranarayanan, Nessa et al. 2012). For example, in an RCT in Tamil Nadu, VIA screenings were not as accurate among older women: test positivity rates decreased from 12 to 14 percent for women between 30 to 34 years to less than 5 percent for women older than 45 years (Sankaranarayanan, Esmey et al. 2007). Thus screening strategies may need to differ depending on the age group of the target population of interest.

An advantage of VI-based approaches is that the immediate availability of screening test results provides the opportunity to conduct a biopsy or offer treatment at the same visit (“screen and treat”), reducing the likelihood of loss to follow-up. That said, there is risk of overtreatment in this context given that the specificity of VI-based approaches is lower than that of the Pap smear or HPV DNA testing. For example, Deodhar et al. (Deodhar, Sankaranarayanan et al. 2012) found that only 8 percent of women testing positive on VIA screening had CIN2 or CIN3 lesions, suggesting that if a screen and treat strategy were used, a large proportion of screen-positive women (90 percent) would receive unnecessary treatment. The extent of overtreatment would increase further if women with suspected low-grade lesions were also provided treatment rather than if only women with suspected high-grade lesions were treated immediately (Sankaranarayanan 2012). Although there is no clear evidence of harm arising from overtreatment (Chamot, Kristensen et al. 2010, Sankaranarayanan 2012), some researchers contend that the screen-and-treat approach entails risks that may become apparent only with longer follow-up (Szarewski 2007).

### **Screening Coverage and Treatment Linkages**

Achieving high levels of screening participation and adherence to diagnostic and treatment recommendations — without which it is difficult to justify screening — has been a challenge even in the context of well-resourced studies in India.

#### *Screening Uptake*

Several community-based studies in India determined the size of the population eligible for screening, and tracked participation and retention rates. They either enumerated all eligible women in the target communities (Sankaranarayanan 2004, Sankaranarayanan 2005, Bhatla, Gulati et al. 2009) or used census lists to determine the number eligible (Gravitt, Paul et al. 2010).

Studies that have been successful in recruitment and retention such as those in Dindigul district in Tamil Nadu (Sankaranarayanan 2004) and Osmanabad in Maharashtra (Sankaranarayanan

2005) focused on interpersonal communication through face-to-face and group meetings with women, husbands, and family members. In addition, they offered personal invitations to eligible women and provided appointments and screening cards (table 4). Researchers also involved local government health workers and community leaders to motivate women to participate in screening (Sankaranarayanan 2004, Sankaranarayanan 2005, Bhatla, Gulati et al. 2009).

For example, in Dindigul, community and government leaders in each *panchayat* ([local government](#)) and primary health center staff (medical officers and community health workers) encouraged women to participate. Accessibility was enhanced by offering screening services at local primary health centers, municipal offices, schools, women's club buildings, and in private houses on a scheduled basis (Sankaranarayanan 2004). The study screened 63 percent of eligible women.

A similar approach of house-to-house outreach and public announcements combined with screening services at temporary village-level clinics was followed in a study in north India. This study reported a similar participation rate of 59 percent (Bhatla, Gulati et al. 2009).

The Osmanabad trial had among the highest participation rates of community-based studies, with 80 percent of recruited women enrolling in the study. The high participation rate was attributed to community education, village-level clinics (held at primary health centers, municipal offices, and schools), provision of transportation to the central clinic for diagnosis and treatment, high-quality services, and cooperation from local governmental authorities (Sankaranarayanan 2005). Nene et al. (Nene, Jayant et al. 2007) noted that there was a high degree of community involvement with local leaders assisting in community presentations and husbands participating in educational activities, resulting in increased family understanding and acceptance of screening and treatment. Analyses indicated that women who underwent screening were more educated, married, younger (30 to 39 years), had used contraception, and had one or more children. Interestingly, after controlling for sociodemographic factors, the type of screening test was not a significant predictor of screening uptake or treatment adherence (Nene, Jayant et al. 2007). Similarly, Sankaranarayanan et al. (Sankaranarayanan, Rajkumar et al. 2003) found that women were more likely to participate in the Dindigul RCT if they were younger, educated, married, multiparous, lower income, and sterilized.

The importance of community education and mobilization is further underscored by the CATCH study, which despite using a two-phased approach, faced a range of challenges in promoting screening uptake (Gravitt, Paul et al. 2010). In phase I, the study used community liaisons and project health counselors to provide information on cervical cancer prevention in selected villages. In phase II, health supervisors and counselors were employed to make house-to-house visits. Eligible participants who agreed to participate were picked up at an appointed time and taken to a private tertiary care hospital for free screening. Despite these efforts, community acceptance of the cervical cancer screening and treatment program was a major barrier. CATCH had among the lowest participation rates of published studies in India: nearly three in five eligible women (59.4 percent) refused to undergo screening. Reasons for refusal included lack of symptoms indicating a health problem as well as a fear of the tests, the pelvic examination, a cancer diagnosis, and community gossip and perceptions.

Similar reasons for screening refusal were reported by Basu et al. (Basu 2006) in their study in Kolkata. In addition, they found that some women who were willing to undergo screening were unable to attend the clinic because of household responsibilities, family problems and illnesses, or 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), long waiting times, and the presence of male doctors.

### *Diagnostic and Treatment Linkages*

Facilitators of and barriers to patient adherence to diagnostic and treatment recommendations were generally similar to those for screening. Notably, failure to follow-up did not consistently vary by location of diagnostic and treatment service provision. In the Dindigul study, diagnostic confirmation and treatment of precancerous lesions were provided by trained nurses at primary health centers or community locations during the screening visit using a screen-and-treat approach. In the case of precancerous lesions requiring LEEP or cold knife conization or in the case of invasive cancers, referrals were made to a tertiary center (Sankaranarayanan 2004). In the Osmanabad and CATCH studies, doctors performed diagnosis and treatment at a central (tertiary-level) hospital (Sankaranarayanan 2005, Gravitt, Paul et al. 2010).

In the Osmanabad trial, which offered transportation to a central clinic, emphasized high-quality service provision, and received community support, 85 percent of those requiring diagnosis and treatment adhered to study procedures (Sankaranarayanan 2005). Slightly lower figures (diagnostic and treatment completion in 80 percent of CIN2–3 and 75 percent of invasive cancer cases) were reported in the Dindigul study (Sankaranarayanan 2004). The latter study also noted high failure to follow-up if women did not choose to be treated at the first or screening visit: 53 percent of women who decided to first consult with their husband and other family members did not return for treatment. The CATCH study reported the lowest acceptance of diagnostic and treatment procedures, with 34 percent of women refusing colposcopy and biopsy after a positive screening test (Gravitt, Paul et al. 2010).

Factors associated with adherence to diagnostic and treatment recommendations in the Dindigul and Osmanabad studies included being married, being younger, having lower parity, having higher educational levels, and having higher-grade precancerous lesions or invasive cancer (Sankaranarayanan, Rajkumar et al. 2003, Nene, Jayant et al. 2007). The relative role of factors such as cancer stigma and accessibility to services, as well as family support in shaping diagnostic and treatment adherence needs to be further explored.

In summary, available evidence emphasizes the need for education messages and strategies that respond to women's concerns and fears about cervical cancer screening, diagnosis, and treatment. Studies also indicate that screening services should be provided at the community-level, travel and waiting times should be minimized, and local leaders and health workers who have a rapport and standing with community members (as opposed to project-appointed staff alone) should help promote cervical cancer prevention. There is limited information on factors that facilitate or pose barriers to adherence to diagnostic and treatment recommendations. Further

research is needed to examine the role of similar factors such as treatment-related fears, cancer stigma, and financial costs in the retention and follow-up of screen-positive women.

### **Quality of Service Provision**

Quality of cervical cancer–related service provision in India will influence screening coverage, treatment adherence, and program outcomes and impact. To date, the quality of cervical cancer screening has been assessed primarily by researchers for validity and reliability of the screening tests. Although studies have found it feasible to train frontline health workers such as ANMs and staff nurses to implement VI-based screening and treatment of precancerous lesions using cryotherapy, concerns have been raised about the quality and consistency of service provision (Blumenthal, Lauterbach et al. 2005, Sankaranarayanan 2005). For example, in the Osmanabad study, ANMs received three weeks of training on cervical sample collection, VIA, and cryotherapy. Yet, the researchers found that there was poor concordance on VIA results between the master trainer and the nurses, leading to two rounds of refresher training (Sankaranarayanan 2005).

Several quality assurance methods have been employed to ensure that primary screening is accurately performed. Intensive training (ranging from five days to three weeks) to implement standardized screening protocols (for example, screening protocols of the International Agency for Research on Cancer), often followed by refresher courses, has been employed in several research efforts (for example, (Sankaranarayanan 2005, Bhatla, Gulati et al. 2009) and table 5). Verification of a sample of screening results by a different health care provider or by the same provider using a different screening test or through colposcopy and biopsy is another method (Basu, Sankaranarayanan et al. 2003, Bhatla, Mukhopadhyay et al. 2007, Deodhar, Sankaranarayanan et al. 2012).

Prescreening and postscreening procedures including informed consent and postscreening counseling, as well as tracking patient follow-up and retention in treatment are additional aspects of screening quality. In fact, uptake of diagnostic and treatment services should be monitored as an aspect of the quality of screening programs — an issue that has emerged as a challenge in program settings in India (discussed in a later section). Few research articles provide details on how implementation quality was monitored. For example, it is unclear whether studies used electronic or paper-based health information systems to monitor participant retention and follow-up, and whether any specific actions were taken to minimize loss to follow-up. Identifying best practices in quality assurance methods should be a future priority.

### **Impact of Screening on Morbidity and Mortality**

The impact of screening on morbidity and mortality is contingent on ensuring that screen-positive women receive appropriate diagnostic and treatment services. Treatment of precancerous cervical lesions can prevent progression to invasive cancer, reducing subsequent morbidity and mortality, and treatment of invasive cancer can prolong women’s lives. However, only a few studies have engaged in longer-term follow-up of participants to estimate the impact of different cervical cancer screening approaches on morbidity and mortality in India (Sankaranarayanan, Esmay et al. 2007, Sankaranarayanan, Nene et al. 2009, Shastri, Mitra et al. 2013).

In an RCT in Dindigul, a single round of VIA-based screening led to a 25 percent reduction in the incidence of cervical cancer and a 35 percent reduction in mortality over seven years of follow-up (Sankaranarayanan, Esmay et al. 2007). A statistically significant reduction in incidence was observed among younger women (age 30 to 39). This reduction was achieved with a screening coverage of 64 percent in the intervention arm and with high levels of treatment uptake (65 to 80 percent) facilitated by provision of colposcopy, directed biopsy, and cryotherapy (when appropriate) at the screening visit. Similar results were recently reported by a trial involving over 150,000 women in urban Mumbai, Maharashtra (Shastri, Mitra et al. 2013). Women in the intervention arm were offered four rounds of cancer education and VIA-based screening at two-year intervals while those in the control arm were offered cancer education at the time of recruitment. All participants were followed for an additional four years. At the end of 12 years of study implementation, a 31 percent reduction in cervical cancer mortality was observed. This trial also reported high screening coverage (89 percent) and adherence to diagnostic and treatment recommendations (79 and 86 percent, respectively).

Analyses of data from a third RCT in rural Osmanabad, Maharashtra, revealed that screening using VIA or cytology did not significantly reduce incidence of advanced cancers or cervical cancer mortality whereas a single round of HPV testing did lead to reductions compared with an unscreened control group (Sankaranarayanan, Nene et al. 2009). Screening uptake and treatment adherence did not differ between the study arms. However, questions have been raised about whether differences in diagnostic and treatment procedures across study arms may explain the observed mortality-related outcomes (Austin and Zhao 2009).

Overall, data from India indicate that VIA — when offered under the controlled conditions of a trial with systems for following-up screen-positive women 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.

### **Cost Effectiveness of Screening**

Cost-effectiveness analyses of screening approaches in India have produced varied results. For example, Legood et al. (Legood, Gray et al. 2005) used data collected in the Osmanabad RCT comparing VIA, cytology, and HPV DNA testing to estimate the costs of setting up and running a screening program covering 497 villages and 131,178 women. In addition, using case detection rates as their primary outcome measure, the authors compared the cost effectiveness of the three screening approaches. Notably, the study found that program implementation costs (over and beyond the costs of screening and diagnosis), including of the health information system to monitor recruitment and follow-up rates, were important to capture and were as high as one-fifth of the total costs in the VIA arm. The analysis found VIA to be the least expensive option at US\$3.92 per woman eligible for screening, followed by cytology at US\$6.61. VIA detected 7.5 CIN2/3+ cases per 1,000 eligible women and cost US\$522 per case detected (compared with no screening), whereas cytology was 26 percent more expensive (\$659 per case detected) and detected more cases (10 cases per 1,000). HPV DNA testing was nearly twice as expensive as cytology and was less effective than cytology in detecting CIN2/3+. This analysis is limited by

the fact that treatment costs and longer-term benefits in terms of life years saved were not considered. Moreover, these estimates have been derived in the context of a study, and therefore may not accurately reflect costs that arise in a programmatic setting.

Goldie et al. (Goldie, Gaffikin et al. 2005) used computer-based models, combining primary and secondary data to examine the cost effectiveness of various screening approaches in five LMICs, including India. They found that clinical outcomes and cost effectiveness were improved by strategies that ensured strong linkages between screening and treatment (by reducing the number of visits or improving follow-up) and that required less laboratory infrastructure than cytology-based approaches. Strategies that targeted women in their mid-30s were the most cost effective (compared with those that screened women below 30 years or over 45 years). The India-specific analysis showed that a single lifetime screening using a one-visit VIA strategy (that is, a screen-and-treat strategy) was the least costly compared with cytology and HPV DNA testing at US\$10/year of life saved. However, it is unclear whether the strategy of combining screening and treatment of women with positive screening results in one visit at a primary-level facility is feasible in a program context.

A third modeling study compared the cost effectiveness of HPV vaccination with different screening strategies (HPV DNA testing, cytology, and VIA) (Diaz, Kim et al. 2008). The results showed that combining preadolescent HPV vaccination and screening women age 30 years or older three times during their lifetime (with 70 percent coverage for both strategies) yielded a 56 to 63 percent reduction in cancer incidence. The cost effectiveness of screening strategies was influenced by test cost and performance, ability to be delivered in one or two visits, and failure to follow-up; whereas cost effectiveness of vaccination depended on vaccine cost, efficacy, coverage, and duration of protection. The authors concluded that the analysis provided strong support for preadolescent vaccination as well as for screening adult women two to three times per lifetime.

### **Ethical Issues in Screening Trials**

RCTs of cervical cancer screening strategies in India have prompted debates over research ethics. Two large RCTs, one in Mumbai, Maharashtra ( $n = 151,538$ ) and the other in rural Osmanabad, Maharashtra ( $n = 131,746$ ), have involved placebo control groups and used cervical cancer mortality as end points (Sankaranarayanan, Nene et al. 2009, Mitra, Mishra et al. 2010). Given the strong evidence in support of the effectiveness of cytology-based screening in reducing cervical cancer incidence and mortality in high-income countries, researchers have questioned the ethical acceptability of trials that compare women who are offered screening with those who are not (Suba, Donnelly et al. 2007, Austin and Zhao 2009, Rathod 2011). Critiques have also noted that nonmortality endpoints (such as incidence of CIN2+) have been used in other LMIC trials, raising the need for additional justification for using mortality as the main outcome in these studies (Rathod 2011). The trial investigators responded by noting that unscreened participants received the standard of care available to them in India (Sankaranarayanan, Nene et al. 2011).

Issues have arisen over the implementation of informed consent procedures in some studies. In the Osmanabad study, questions were raised about how the informed consent process addressed

the potential risks and benefits of participation: Whether and how women’s comprehension of the information was assessed, and whether women were aware of their risk status (Rathod 2011). A second cervical cancer screening study in Mumbai, funded by the US National Institutes of Health, was also investigated by the US government’s Office for Human Research Protections (OHRP) over protection of human subjects. OHRP found that the informed consent process inadequately educated individuals about screening and treatment options (Office for Human Research Protections 2012).

These debates and findings suggest the need for careful consideration of ethical issues in the design and implementation of cervical cancer–prevention research and programs. Researchers and program planners should identify acceptable standards of care based on the available evidence. Using comparative effectiveness approaches may be more appropriate when evaluating screening and treatment strategies for LMICs. Furthermore, attention must be paid to the content, quality, and modes of communication of cervical cancer prevention options — as these are likely to have implications for quality of care as well as for program impact.

## **PART IV – PROGRAMMATIC EXPERIENCES**

Few examples exist of large-scale cervical cancer screening programs in India. However, two such initiatives have been implemented in Tamil Nadu. One is a statewide program by the World Bank–supported Tamil Nadu Health Systems Project (TNHSP) and the other is a citywide program of the Chennai Corporation. Both programs have offered cervical cancer prevention services as part of a broader package of services addressing chronic conditions, including diabetes and hypertension, and screening services at the primary health care level. Below we describe the experiences and outcomes of these projects based on a review of program reports and interviews with experts and project teams.

### **TAMIL NADU HEALTH SYSTEMS PROJECT**

In 2007, Tamil Nadu launched a pilot cervical cancer screening program in two predominantly rural districts, Theni and Thanjavur, as part of a broader effort to address NCDs, including cardiovascular disease and women’s cancers (Tamil Nadu Health Systems Project undated). The goals of the cervical cancer prevention component included raising community awareness regarding cervical cancer, promoting early detection through the routine offer of VIA/VILI-based screening to 30 to 60-year-old women seeking public health services, and offering appropriate referrals and treatment (table 6). The Tamil Nadu government decided to pursue the pilot program because of the growing burden of NCDs, the importance of raising awareness of prevention, and the availability of effective screening-and-treatment approaches.

With leadership in the state health department, administrative support from the government of Tamil Nadu, and political backing, the pilot program was relatively well resourced and systematically planned and implemented. The NCD program was staffed by a team including public health physicians who were tasked with implementation coordination and oversight; nurses who were trained to provide NCD prevention services, including VIA/VILI; and data management personnel. Consultations were held with leading experts in NCD screening,

diagnosis, and treatment to finalize program procedures and protocols. A detailed capacity-building process was developed to train and equip staff to implement the program. In addition, an external monitoring and evaluation (M&E) and cost analysis of the program was commissioned.

Between 2007 and 2010, the program screened nearly 500,000 women, or about 74 percent of the eligible population (Tamil Nadu Health Systems Project undated). However, VIA/VILI positivity was lower than reported in the literature: 5.4 percent in Thanjavur and 2.6 percent in Theni compared with around 15 to 20 percent in Indian studies (Sankaranarayanan 2004, Sankaranarayanan, Nessa et al. 2012, Tamil Nadu Health Systems Project undated). Follow-up rates were also relatively low: only about half of screen-positive women underwent 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 — a mere 13 percent of women needing treatment received it through the program (Tamil Nadu Health Systems Project undated).

A number of implementation challenges are likely to have led to these outcomes (table 7). Efforts to mobilize women to undergo screening were constrained by the lack of an information, education, and communication (IEC) plan; limited evidence to guide the development of messages; and inconsistent and poor quality outreach, which was initially carried out by contractual workers hired by nongovernmental organizations (NGOs). The program subsequently hired a communications agency to develop an IEC plan, including messages and strategies to raise awareness at health facilities and in communities. However, administrative issues prevented the deployment of the plan within the pilot implementation period. The effectiveness of the multipronged IEC strategy that was developed remains to be evaluated.

The pilot project was also constrained by a number of human resource–related factors. Human resource shortages led to the use of newly hired project staff nurses to implement the NCD prevention program for provision of routine health care services. Poor motivation among existing health department staff to support the program because they had to assume additional NCD screening, diagnosis, and treatment responsibilities; frequent changes in personnel at the local, district, and state levels because of transfers and attrition; and lack of adherence to program protocols also affected the level and consistency of implementation.

These challenges were further compounded by infrastructural and logistical issues such as lack of availability of drugs (for example, drugs to treat reproductive tract infections) and reagents, infrastructural deficiencies (for example, lack of electricity), and equipment problems. In addition, because screening was promoted at the primary care level while diagnostic confirmation and treatment were offered at the secondary and tertiary levels of care (where related infrastructure and human resources were already available), coordination of referrals between the levels was necessary. However, inaccurate and inconsistent documentation and reporting hampered follow-up of patients and program monitoring, preventing timely responses to program deficiencies.

The results of the TNHSP pilot program highlight common limitations of cervical cancer prevention in LMIC settings — namely, weak linkages between primary and higher levels of care and limited capacity to engage in patient follow-up due to factors such as human resource constraints and lack of systems to facilitate identification and monitoring of cases for follow-up (Basu, Nessa et al. 2010, Mwanahamuntu M.H., Sahasrabuddhe et al. 2011, Moon, Silva-Matos et al. 2012).

Recognition of these challenges has led to a range of responses in the design of the statewide scale-up of the program (see table 7), including the introduction of an electronic health information system, with patient records accessible at different levels of the health care system. Discussions with staff and experts associated with the program suggest that links within the health care system and patient follow-up remain challenges in the scale-up. The lack of a culture of coordination and of mechanisms to facilitate communication appears to be a persistent barrier.

Experiences in countries such as Zambia (Mwanahamuntu M.H., Sahasrabuddhe et al. 2011) and El Salvador (Agurto, Sandoval et al. 2006) demonstrate 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. It remains to be seen whether TNHSP can significantly improve program performance based on the lessons learned from its pilot and the responses integrated. It is also unclear whether the M&E systems and procedures put in place will enable a rigorous analysis of the outcomes and impact of the scale-up. However, it is clear that the TNHSP NCD program scale-up has the potential to yield important insights on large-scale cervical cancer prevention programming in India.

### **CHENNAI CORPORATION**

The Chennai Corporation launched a similar VIA-based cervical cancer screening program in 2008 (One World Foundation India 2010). This program is notable for the way in which cervical cancer prevention was promoted. The Corporation provided screening services as part of a comprehensive “Well Woman Checkup” to motivate women to seek preventive health services and to reduce the stigma associated with cervical cancer screening by promoting a positive health message. Nurses educated women about healthy lifestyles and behaviors as well as the benefits of early detection and treatment of chronic diseases such as cervical and breast cancers, usually in small groups at the urban health post (One World Foundation India 2010). Trained physicians then conducted a clinical examination and screening tests, and when appropriate, offered treatment. Although asymptomatic women were initially reluctant to be screened, this changed over time because of the positive experiences of women who sought the service (Lakhani 2010). (TNHSP is using a similar positive health message combined with a comprehensive health examination. The approaches used by the Chennai Corporation and TNHSP seem promising, but as their effectiveness has not been evaluated, it is hard to draw conclusions.)

The Chennai program was initially pilot-tested in two urban health posts. Both VIA and cytology were conducted and the results were compared. The pilot revealed that, compared with cytology-based screening, VIA was faster to conduct, easier to read, more appropriate for low-resource settings because personnel such as cytotechnicians and pathologists were not needed at the

screening stage, and generally preferred by gynecologists (Lakhani 2010). The program was then scaled up across 93 health posts. About 500 multipurpose health workers and over 100 medical officers were trained to educate and mobilize women and to implement screening and treatment. Training was integrated into the curricula for urban health workers, and screening and treatment services were provided as part of the existing platform of women's reproductive and sexual health care. The health post infrastructure was upgraded to ensure the availability of a room with running water and an examination table in addition to other equipment and supplies.

Initially, the staff were resistant to taking on additional tasks, but communication and engagement with health worker associations has promoted their acceptance of the program. The Chennai program has had strong leadership at the municipal level and has also received considerable political support, including services being inaugurated by the mayor and state government ministers. In addition to political and bureaucratic leadership, the program was sustained through specially earmarked program funds in the municipal budget and an overall strategy of integration of the program into the existing urban health care system (Lakhani 2010, One World Foundation India 2010).

Both the TNHSP and Chennai Corporation programs demonstrate the feasibility and acceptability of introducing cervical cancer prevention into the Indian public health system — when adequate and consistent political and administrative support, human and financial resources, and community buy-in and involvement exist. However, due to limitations in program M&E plans and systems, few conclusions can be drawn about the outcomes and impacts of these efforts. Project documents and interviews suggest a few lessons to guide the scale-up and replication of cervical cancer prevention programs, underscoring the need for greater attention to documentation and M&E, and timely data analysis and reporting.

## **PART V – RECOMMENDATIONS TO STRENGTHEN CERVICAL CANCER PREVENTION IN INDIA**

The availability of primary and secondary prevention approaches has accelerated global efforts to prevent and control cervical cancer. Research and prevention and treatment programs in India have demonstrated that such initiatives have the potential to succeed. Formative research has identified factors that can influence the feasibility, acceptability, and effectiveness of HPV vaccination. Research and programs have also shown that secondary prevention through cervical cancer screening by frontline health workers, coupled with access to diagnostic and treatment services is feasible and can be effective.

Specifically, studies in India have shown that VI-based screening approaches can achieve comparable sensitivity and specificity to cytology-based screening, can be implemented by existing (or minimal additional) frontline health workers such as nurses, and can reduce cervical cancer incidence and mortality. However, research has also found that VI-based screening approaches still require substantial investment in capacity-building in terms of training and ongoing supervision, raising the question of whether these methods remain cost effective when implemented at scale. As cervical cancer prevention advocacy gains momentum in India and new programs are launched, there is an opportunity to engage in implementation research and robust

program evaluations to identify strategies that have the greatest impact and are cost effective in the Indian context.

Regardless of the screening approach used, the global and Indian evidence underscores the importance of ensuring strong linkages between screening, diagnosis, and treatment services for program and cost effectiveness. To date, both research and program efforts have faced challenges to achieving high levels of screening coverage and adherence to diagnostic and treatment recommendations. Further work is needed to understand what kinds of messages and communication methods can promote the utilization of prevention services and what kinds of strategies including incentives may be needed to strengthen referral mechanisms.

Although many questions are yet to be answered, our review of research and programmatic experiences revealed several important aspects of successful cervical cancer prevention efforts in India and has led to the following recommendations for the country.

## **LEADERSHIP AND GOVERNANCE**

### **Political and Administrative Leadership and Support**

As demonstrated by the TNHSP and Chennai Corporation programs, political commitment and administrative leadership to ensure adequate and sustained resource allocation, sufficient human resources and health care infrastructure, development of health information systems for program M&E, and expanded access to health services are essential (Sankaranarayanan, Nessa et al. 2012). Greater advocacy efforts are required in India to raise awareness of the need for cervical cancer prevention and to promote an understanding of the scientific evidence in support of comprehensive prevention efforts. Efforts should focus on educating the media, parliamentarians, and political leaders — in addition to engaging community leaders and women’s health advocates.

In addition to political support and leadership for advancing cervical cancer prevention, the TNHSP experience has highlighted the need for stable program leadership at the state and district levels. Field visits and interviews revealed that program implementation was boosted by the presence of “empowered” champions within the health system — individuals who have vision, authority, and resources to ensure public health action.

### **Health Systems Response**

In addition to building leadership and support for actions to reduce the burden of cervical cancer, health systems capacities to deliver services including relevant policies, infrastructure, and skilled human resources need to be enhanced. The feasibility, effectiveness, and sustainability of cervical cancer prevention programs may be improved through integration with existing health programs, such as those addressing reproductive and child health or NCDs such as diabetes, rather than as stand-alone initiatives (Mwanahamuntu M.H., Sahasrabudde et al. 2011). Moreover, improvements made to the health system to address cervical cancer prevention can also help advance other related health care priorities, such as promotion of adolescent health and prevention and treatment of cancers and other chronic diseases.

Both the TNHSP and Chennai Corporation programs integrated cervical cancer prevention into a broader initiative focused on NCDs, with screening taking place at the primary health care level. At that level, the NCD initiative has benefited from health systems strengthening (infrastructure upgrades, community outreach), which was previously undertaken with the goal of reducing maternal, neonatal, and child mortality.

### **Partnerships with Government Departments and Programs**

Given the challenges faced in mobilizing women to seek screening and treatment services, a multisectoral approach to raising awareness of cervical cancer prevention may be needed. In the scale-up of TNHSP, the health department is working with the Departments of Education, Rural Development, and others to disseminate information on NCD prevention, including the benefits of early detection and treatment at schools and workplaces and among women’s self-help groups. This approach is not without challenges — relevant government departments need to “buy-in” to the importance of the program, funds need to be available to support activities across departments, and effective mechanisms for coordination need to be available. Documentation and analysis of the process and outcomes of a multisectoral approach for community mobilization are also necessary.

### **Equitable Access**

Enhancing health care access among vulnerable women (for example, those who are older, less educated, or belong to poor or marginalized households) will promote equity and increase program effectiveness. Research has suggested that women who are older and have fewer socioeconomic resources are less likely to undergo screening and hence, have poorer outcomes. Cervical cancer prevention program–participation rates should be monitored by various vulnerability factors such as poverty and caste affiliation to determine which groups of women may be underserved and the reasons for that. Based on these findings, strategies to promote more equitable access such as transportation assistance and financial support may be tested.

## **COMMUNITY MOBILIZATION**

Although more research is needed to identify effective community mobilization strategies, the following lessons have been learned from research and program experiences.

### **Sensitization and Training of Health Care Workers**

Health care workers such as ANMs and accredited social health activists who live in the community and have a rapport with women and their families are best positioned to introduce cervical cancer prevention efforts. ANMs have also been trained to implement VI-based screening. However, these frontline health workers are already tasked with a range of responsibilities related to maternal, neonatal, and child health as well as other national- and state-level health initiatives. Moreover, while ANMs are employed by the public health system, accredited social health activists receive performance-based compensation. Appropriate methods of financial compensation for cervical cancer prevention work also need to be identified.

### **Engagement of Local Leaders**

Engagement of local leaders such as members of local government, village health and sanitation committees, and women's self-help groups has been consistently used in cervical cancer screening research and programs in India. Although not systematically evaluated, this engagement has been found to be important for promoting women's participation.

### **Prevention Messaging**

Research and program experiences have highlighted limited awareness of cervical cancer prevention, including the benefits of early detection; fear of cancer, screening tests, and instruments used; cancer stigma; and misconceptions about cancer as barriers to program uptake. Messaging to promote cancer prevention awareness should address these barriers. The Chennai program (and evidence from Zambia (Mwanahamuntu M.H., Sahasrabuddhe et al. 2011)) suggest that framing cervical cancer screening in terms of a wellness strategy may be effective. However, there is a dearth of evidence on the effectiveness of cervical cancer prevention messages, and future programs would benefit from further research on this issue.

Cervical cancer prevention efforts in India have delivered information through community meetings, door-to-door visits, and advertisements at health facilities. Programs have also used print and other media. However, it is unclear which of these communication channels is most effective in terms of reach and cost—another area that should be investigated.

## **COMPREHENSIVE AND COST-EFFECTIVE SERVICE DELIVERY**

### **Women-Centered Program Design**

Experiences in India have revealed that program design in terms of where services are delivered (for example, at the community-level through camps, at primary health centers), by whom, and how (for example, with or without transportation and financial support) all have an influence on program success. Programs that are “women-centered,” that is, those that actively respond to women's concerns and constraints are likely to be the most successful. Program planners can use formative assessments to understand women's perspectives on cervical cancer prevention as part of the design process.

### **Feasible and Effective Prevention Approach**

Over the longer term, the combination of primary and secondary cervical cancer prevention approaches may become the global norm. In the present context, the optimal approach will depend on a mix of factors including acceptability and availability of resources (funds, infrastructure, and health care personnel). Data suggest that secondary prevention using VI-based methods can significantly reduce cervical cancer morbidity and mortality in India (Shastri, Mitra et al. 2013). Moreover, as noted by Deodhar et al. (Deodhar, Sankaranarayanan et al. 2012), initiation of VI-based screening programs can strengthen health systems capacities over time and facilitate implementation of more sensitive and objective tests in the future, such as those using HPV DNA detection.

Implementation research can help identify which strategies are most effective in program — as opposed to research — settings. For example, it is worthwhile exploring the feasibility and effectiveness of a single visit screen-and-treat approach, especially given the challenges of ensuring patient follow-up (Sankaranarayanan 2012). A second option worth examining is whether using HPV DNA testing to triage women who screen positive by visual inspection can improve the accuracy of screening results and reduce overtreatment (and the use of treatment resources).

### **Referral Linkages**

Programs should ensure that diagnostic and treatment services are delivered in a timely fashion. Although research has indicated that the screen-and-treat approach is feasible in the Indian setting, results also suggest that there may be substantial overtreatment associated with this strategy. However, the TNHSP model of promoting screening at the primary health care level with diagnostic confirmation and treatment at the secondary and tertiary levels will require substantial improvements in referral linkages to ensure program effectiveness. Identifying mechanisms to improve these linkages to facilitate the continuum of cancer care (screening, detection, diagnosis, treatment, and survivorship) should be a focus of future work.

In El Salvador, a continuous quality improvement methodology involving multiple cycles of plan-do-study-act were used to strengthen linkages between steps in the cancer care continuum (Agurto, Sandoval et al. 2006). Specifically, referral linkages were strengthened by enhancing teamwork and coordination among health care workers, improving record-keeping, increasing the links between the community and health services through trained outreach workers, and establishing a quality control group that supported implementation of quality improvements.

In India, the introduction of health insurance schemes, the prominent role of the private health care system, and the growing availability of information and communications technologies (including telemedicine) offer opportunities for drawing on global experiences and creating innovative local solutions to the challenge of ensuring referral mechanisms.

### **Quality Assurance**

It is essential to establish a quality assurance plan that defines standards at different levels of care and that describes how quality reviews and improvements are conducted, and by whom (Basu, Nessa et al. 2010).

Ensuring efficient and uninterrupted procurement processes and distribution and maintenance of equipment, commodities, and supplies is integral to quality assurance. TNHSP has a set-aside budget for its NCD program, instituted centralized procurement, and identified and trained staff to manage the process.

Adequate training and supervision of staff are essential. Training duration has varied across studies and programs in India. The key lesson learned is that intensive, standardized training for an adequate amount of time (at least five days based on the TNHSP experience) supplemented with refreshers is needed. The Osmanabad trial, which conducted three weeks of training followed by two brief refreshers over four years, found that the proportion testing positive in the

VIA arm declined over time, suggesting that intensive standardized training and close supervision may have reduced the number of false positives (Sankaranarayanan 2005).

Additional quality assurance tools include regularly scheduled reviews of cases and clinical practices (for example, using telemedicine as in Zambia (Mwanahamuntu M.H., Sahasrabudde et al. 2011)), clinic observations, exit surveys, and community interviews.

### **Program Evaluation**

Program evaluations can provide feedback on program quality and progress, and can enable program improvements. They can also yield data on outcomes and on impact of screening and treatment efforts, generating evidence for scale-up of such efforts (Basu, Nessa et al. 2010).

## **CONCLUSION**

Much has been learned about cervical cancer prevention in India. Research and program experiences support the feasibility and acceptability of cervical cancer screening and treatment. In two large-scale RCTs, VI-based screening (coupled with diagnostic confirmation and treatment) resulted in significant reductions in cervical cancer morbidity and mortality. Given that a quarter of the global burden of cervical cancer is in India, there is no better time to translate research findings into practice. In Tamil Nadu, TNHSP has pilot-tested and is now scaling-up cervical cancer prevention across the state. Numerous insights from the Tamil Nadu experience can guide the design and implementation of similar programs across India. That said, these efforts can be greatly strengthened by the simultaneous conduct of implementation research to identify prevention approaches that have the greatest impact and are the most cost effective in the Indian context.

**Table 1. Overview of Primary Screening Tools for Cervical Cancer**

<b>Screening Test</b>	<b>Strengths</b>	<b>Limitations</b>
Visual inspection with acetic acid (VIA): <i>Acetic acid is applied to the cervix to identify precancerous and cancerous lesions. Process is often aided by a magnification tool.</i>	<ul style="list-style-type: none"> <li>• Requires less training (5–10 days) than other methods</li> <li>• Cheaper than cytology/HPV testing</li> <li>• Immediate results</li> <li>• Potential for immediate treatment (“screen and treat”)</li> </ul>	<ul style="list-style-type: none"> <li>• Variable (low to moderate) sensitivity and specificity for CIN2+</li> <li>• Possibility of overtreatment</li> <li>• Acetic acid must be prepared directly before screening</li> <li>• Inappropriate for older women (&gt;50 years) because of change in cervix position</li> </ul>
Visual inspection with Lugol’s iodine (VILI): <i>Lugol’s iodine is applied to the cervix to identify precancerous and cancerous lesions. Process is often aided by a magnification tool.</i>	<ul style="list-style-type: none"> <li>• Requires less training (5–10 days) than other methods</li> <li>• Cheaper than cytology/HPV testing</li> <li>• Immediate results</li> <li>• Potential for immediate treatment (“screen and treat”)</li> <li>• Has a 1-month shelf life</li> </ul>	<ul style="list-style-type: none"> <li>• Variable (low to moderate) sensitivity and specificity for CIN2+</li> <li>• Possibility of overtreatment</li> </ul>
Cytology (Papanicolaou smear): <i>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.</i>	<ul style="list-style-type: none"> <li>• High specificity for CIN2+</li> </ul>	<ul style="list-style-type: none"> <li>• Relatively low sensitivity</li> <li>• Requires laboratory and specialized technicians</li> <li>• Lag in test results can contribute to failure to follow up and can delay treatment</li> </ul>
Human papillomavirus (HPV) DNA test: <i>Sample of cells taken from the cervix by a provider or the woman herself. Sample is sent to laboratory for analysis by trained technicians.</i>	<ul style="list-style-type: none"> <li>• High specificity and sensitivity for HPV infection</li> <li>• Requires minimal training</li> <li>• Woman can self-collect sample</li> </ul>	<ul style="list-style-type: none"> <li>• Has to be followed by a test for dysplasia</li> <li>• Requires laboratory and trained technicians</li> <li>• Lag in test results can contribute to failure to follow up and can delay treatment</li> </ul>

*Source:* Adapted from (World Health Organization 2002, Denny, Quinn et al. 2006).

*Note:* CIN2+ = Cervical intraepithelial neoplasia grade 2 or higher.

**Table 2. Health Care Workers Trained to Perform Cervical Cancer Screening and Treatment in Studies in India**

<b>Study (location)</b>	<b>Personnel trained (qualifications)</b>	<b>Screening-and-treatment approach</b>	<b>Duration of training (curriculum)</b>	<b>Frequency of retraining</b>
Sankaranarayanan et al. 2004 (Dindigul, Tamil Nadu)(Sankaranarayanan 2004)	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	-	-
	Surgeons	Training on cold knife conization	-	-
	Pathologists, laboratory technicians	Retraining on biopsy specimen processing and reporting	-	-
Sankaranarayan et al. 2004 (Mumbai, Maharashtra; Jaipur, Rajasthan; Kolkata, West Bengal; Thiruvananthapuram, Kerala) (Sankaranarayanan 2004)	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 day (IARC)	1–2 days with unspecified frequency
	Physicians (gynecologists and nongynecologists)	Training on colposcopy, cryotherapy, LEEP	15 day (IARC)	1 day every 4–6 months
	Pathologists, laboratory technicians	Retraining on biopsy specimen processing and reporting	1 day refresher	-
Sankaranarayan et al. 2005 (Osmanabad, Maharashtra) (Sankaranarayanan 2005)	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	2 weeks	Refresher after

Study (location)	Personnel trained (qualifications)	Screening-and-treatment approach	Duration of training (curriculum)	Frequency of retraining
	Laboratory technicians	reporting Training on processing and reporting cytology slides, biopsy, HPV test	(TMC) 3 months (TMC)	9 months Refresher after 9 months
Bhatla et al. 2009 (Faridabad district, Haryana) (Bhatla, Gulati et al. 2009)	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) (Deodhar, Sankaranarayanan et al. 2012)	Nurses	Retraining on VIA, cell sampling for cytology and HPV, cryotherapy	- (IARC)	Every 6 months after retraining
	Physicians (colposcopists)	Retraining on colposcopy, cryotherapy, and LEEP	- (IARC)	Every 6 months after retraining
	Physicians (pathologists)	Retraining on cytology, biopsy reporting	- (IARC)	Every 6 months after retraining
	Cytotechnicians	Retraining on processing and reporting cytology slides, biopsy	- (IARC)	Every 6 months after retraining
Gravitt et al. 2010 (Medchal Mandal, Andhra Pradesh) (Gravitt, Paul et al. 2010)	Physicians (gynecologists)	VIA, VILI, HPV DNA, colposcopy	-	-

*Source: (Sankaranarayanan 2004, Sankaranarayanan 2004, Sankaranarayanan 2005, Bhatla, Gulati et al. 2009, Gravitt, Paul et al. 2010, Deodhar, Sankaranarayanan et al. 2012)*

*Notes:* IARC = International Agency for Research on Cancer; LEEP = loop electrosurgical excision procedure; TMC = Tata Memorial Center, Mumbai; VIA = visual inspection with acetic acid; VILI = visual inspection with Lugol's iodine.

**Table 3. Summary of Indian Studies on Accuracy of Cervical Cancer Screening Tests**

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 (%)
Visual inspection with acetic acid (VIA)	Andhra Pradesh (Gravitt, Paul et al. 2010)	Population-based <i>N</i> = 2,331, Age: 25+	Cross-sectional	26.3, 6.4;	36.4, 6.5	-	-	-
	Solapur district (Deodhar, Sankaranarayanan et al. 2012)	Population-based <i>N</i> = 5,519 Age: 30–49	Cross-sectional	64.5, 84.2	-	-	-	-
	Dindigul district (Sankaranarayanan 2004)	Population-based <i>N</i> = 80,269 Age: 30–59	RCT	-	-	-	-	71.1, no specificity
	IARC multicenter (Sankaranarayanan 2004)	Population-based <i>N</i> = 104,061 Age: 26–65	Cross-sectional	-	-	-	76.8, 85.5 79.3, 85.5	-
	Lok Nayak Hospital, New Delhi (Ghosh, Gandhi et al.	Opportunistic <i>N</i> = 350 Age: 25–39	Cross-sectional	-	-	89.47, 91.23	-	-

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 (%)
				2012)				
	Kolkata (Basu, Sankaranarayanan et al. 2003)	Population-based <i>N</i> = 5,881 Age: 30–64	Cross-sectional	55.7, 82.1	-	-	-	-
		Opportunistic <i>N</i> = 100 Age: 30+	Cross-sectional	-	-	100.0, 53.3	-	-
	New Delhi, Gyne OPD (Bhatla, Mukhopadhyay et al. 2007)	Opportunistic <i>N</i> = 472 Age: 20–60	Cross-sectional	86.7, 90.7	-	-	-	-
		Population-based <i>N</i> = 3000 Age: 25–59	Cross-sectional	No sensitivity, 86.1	-	-	-	-
	New Delhi, Women's Clinic (Sodhani, Gupta et al. 2006)	Opportunistic <i>N</i> = 548 Age: 30+	Cross-sectional	82.5, 66.9	-	-	-	-
	Faridabad district (Bhatla, Gulati et al. 2009)	Population-based <i>N</i> = 18,675	Cross-sectional	60.3, 86.8 VIA with magnification	-	-	-	-

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 (%)
		Age: 25–65		: 64.2, 86.8				
	New Delhi, Gyne OPD (Bhatla, Puri et al. 2012)	Opportunistic <i>N</i> = 20,053 Age: 25–65	Cross-sectional	54.4–78.7, 88.6–90.9	-	-	-	-
	Mumbai, Kolkata (comparison with magnification) (Sankaranarayan, Shastri et al. 2004)							
	Kolkata, Mumbai, Trivandrum (Sankaranarayan 2004)							
Visual inspection with Lugol's iodine (VILI)	Solapur district (Deodhar, Sankaranarayan et al. 2012)	Population-based <i>N</i> = 5,519 Age: 30–49	Cross-sectional	64.5, 85.5	-	-	-	-

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 (%)
	IARC multicenter (Sankaranarayan 2004)	Population-based <i>N</i> = 104,061 Age: 26–65	Cross-sectional	-	-	-	91.7, 85.4; 92.2, 85.5	-
	Lok Nayak Hospital, New Delhi (Ghosh, Gandhi et al. 2012)	Opportunistic <i>N</i> = 3 50 Age: 25–39	Cross-sectional	-	-	100.00, 93.35	-	-
	Faridabad district (Bhatla, Gulati et al. 2009)	Population-based <i>N</i> = 3000 Age: 25–59	Cross-sectional	84.7	-	-	-	-
	Kolkata, Mumbai, Trivandrum (Sankaranarayan 2004)	Opportunistic <i>N</i> = 20,053 Age: 25–65	Cross-sectional	76.2–76.9 86.3–89.3	-	-	-	-
Cytology (Pap smear)	Andhra Pradesh (Gravitt, Paul)	Population-based <i>N</i> = 2,331,	Cross-sectional	63.2, 76.2	81.8, 76.1	-	-	-

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 (%)
	et al. 2010)	Age: 25+						
	Solapur district (Deodhar, Sankaranarayanan et al. 2012)	Population-based N = 5,519 Age: 30–49	Cross-sectional	67.7, 95.4	-	-	-	-
	Lok Nayak Hospital, New Delhi (Ghosh, Gandhi et al. 2012)	Opportunistic N = 350 Age: 25–39	Cross-sectional	-	-	52.6, 99.1	-	-
	Kolkata (Basu, Sankaranarayanan et al. 2003)	Population-based N = 5,881 Age: 30–64	Cross-sectional	29.5, 92.3	-	-	-	-
		Opportunistic N = 100 Age: 30+	Cross-sectional	-	-	89.7, 98.9	-	-
	New Delhi, Gyne OPD (Bhatla, Mukhopadhyay et al. 2007)	Opportunistic N = 472 Age: 20–60	Cross-sectional	91.4, 86.6	-	-	-	-

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 (%)
	New Delhi, Women's Clinic (Sodhani, upta et al. 2006)	Population-based N = 3000 Age: 25–59	Cross-sectional	No sensitivity, 94.8 (ASCUS) 97.2 (LSIL)	-	-	-	-
	Faridabad district (Bhatla, Gulati et al. 2009)	Opportunistic N = 548 Age: 30+	Cross-sectional	77.5, 86.8 (ASCUS) 71.8, 94.4 (LSIL)	-	-	-	-
	New Delhi, Gyne OPD (Bhatla, Puri et al. 2012)	Opportunistic N = 20,053 Age: 25–65	Cross-sectional	36.6–72.3 (ASCUS), 87.2–98.6 (LSIL)	-	-	-	-
	Kolkata, Mumbai, Trivandrum (Sankaranarayan 2004)							
HPV DNA test	Andhra Pradesh(Gravitt, Paul et al.	Population-based N = 2,331,	Cross-sectional	84.2, 81.3	100.00, 80.72	-	-	-

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 (%)
	2010)	Age: 25+						
		Opportunistic N = 100 Age: 30+	Cross-sectional	-	-	85.7, 50.0	-	-
	New Delhi, Gyne OPD (Bhatla, Mukhopadhyay et al. 2007)	Opportunistic N = 472 Age: 20–60	Cross-sectional	97.1, 84.2	-	-	-	-
	New Delhi, Women's Clinic(Sodhani, upta et al. 2006)	Opportunistic N = 548 30+	Cross-sectional	Provider: 90.0, 91.5 Self: 80.0, 88.1	-	-	-	-
	New Delhi, Gyne OPD (Bhatla, Puri et al. 2012)	Opportunistic N = 20,053 Age: 25–65	Cross-sectional	Sensitivity: 45.7–80.9, Specificity: 91.7–94.6	-	-	-	-
	Kolkata, Mumbai, Trivandrum (Sankaranarayanan 2004)							

*Source:(Basu, Sankaranarayanan et al. 2003, Sankaranarayanan 2004, Sankaranarayanan 2004, Sankaranarayanan 2004, Sankaranarayanan, Chatterji et al. 2004, Sodhani, upta et al. 2006, Bhatla, Mukhopadhyay et al. 2007, Bhatla, Gulati et al. 2009, Gravitt, Paul et al. 2010, Bhatla, Puri et al. 2012, Deodhar, Sankaranarayanan et al. 2012, Ghosh, Gandhi et al. 2012)*

*Notes:* ASCUS = atypical cells of undetermined significance; CIN2+ = cervical intraepithelial neoplasia grade 2 or higher; CIN3+ = cervical intraepithelial neoplasia grade 3 or higher; HSIL = high-grade squamous intraepithelial lesion; HSIL+ = high-grade squamous intraepithelial lesion or greater;LSIL=low-grade squamous intraepithelial lesion; OPD=outpatient department.

**Table 4. Strategies Used to Promote Screening in India**

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- Mobilization efforts led by local health workers (medical officers, community health workers) who are known and respected in the community.
  - Involvement of community leaders (for example, *panchayat* [village government], women’s group members).
  - Use of advertisement 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:* (Sankaranarayanan 2004, Bradley 2006, Nene, Jayant et al. 2007, Bhatla, Gulati et al. 2009, Tamil Nadu Health Systems Project Undated).

**Table 5. Quality Assurance Methods**

<b>Task</b>	<b>Personnel</b>	<b>Methods of quality assurance</b>
Community mobilization	Health workers, PHC nurses/staff, study staff, local resource persons	<ul style="list-style-type: none"> <li>• None</li> </ul>
Informed consent	Female health workers	<ul style="list-style-type: none"> <li>• Training of staff (Sankaranarayanan 2004, Bhatla, Gulati et al. 2009, Deodhar, Sankaranarayanan et al. 2012)</li> </ul>
Training	Health workers (ANMs, nurses), technicians, doctors	<ul style="list-style-type: none"> <li>• Training and periodic refresher training (Sankaranarayanan 2005)</li> </ul>
Screening implementation	Community health workers, gynecologists, nurses	<ul style="list-style-type: none"> <li>• Comparison of different primary screening modalities implemented by different health workers who are blind to results of other tests (Basu, Sankaranarayanan et al. 2003) or by same health worker (Deodhar, Sankaranarayanan et al. 2012)</li> <li>• Colposcopy/biopsy conducted by a gynecologist blind to the results of the primary screening test (Bhatla, Mukhopadhyay et al. 2007)</li> </ul>
Diagnostic confirmation	Physicians and laboratory technicians	<ul style="list-style-type: none"> <li>• Quality control checks by master trainers/ experts (Sankaranarayanan 2005)</li> <li>• Review of a random sample of slides by master trainers/experts (Sankaranarayanan 2005)</li> </ul>
Counseling	Physicians (Gravitt, Paul et al. 2010), nurses (Sankaranarayanan, Esmey et al. 2007)	<ul style="list-style-type: none"> <li>• None</li> </ul>
Treatment	Physicians	<ul style="list-style-type: none"> <li>• Receipt of second opinion</li> <li>• Quarterly review of treatment outcomes (TNHSP)</li> </ul>
Data collection	Staff nurses, statisticians	<ul style="list-style-type: none"> <li>• Establishment of health information system</li> <li>• Training, queries, and monitoring by statistical assistants and district-level managers (TNHSP)</li> </ul>

*Source: (Basu, Sankaranarayanan et al. 2003, Sankaranarayanan 2004, Sankaranarayanan 2005, Bhatla, Mukhopadhyay et al. 2007, Bhatla, Gulati et al. 2009, Deodhar, Sankaranarayanan et al. 2012)*

**Table 6. Tamil Nadu Health Systems Project by Level of Care**

<b>Level</b>	<b>Services provided</b>	<b>Method</b>	<b>Health institutions</b>	<b>Staff (in pilot)</b>	<b>Staff (in scale-up)</b>
Primary	Screening	VIA/VILI  (with magnification)	Primary health centers  Government hospitals  Government medical college & 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 college & hospitals	Obstetrician gynecologists (specifically trained for the task)	Same
Tertiary	Treatment	Dependent on severity	Government medical college & hospitals	Specialists	Same
District/region	Monitoring and evaluation	n.a.	n.a.	Cancer control officers	Statistical assistants  Regional medical officers  Regional consultants

*Source:* Tamil Nadu Health Systems Project.

*Note:* n.a. = not applicable.

**Table 7. Lessons Learned from the Tamil Nadu Health Systems Project**

Challenges during pilot implementation	Actions to address challenges during scale-up
<i>Community mobilization</i>	
<ul style="list-style-type: none"> <li>• Lack of strategic mobilization plan that detailed formative research, staff/community involvement, methods, and levels of outreach, which adversely affected screening coverage</li> <li>• Difficulty building awareness and buy-in to screening program in rural areas</li> </ul>	<ul style="list-style-type: none"> <li>• Agency hired to conduct formative research and develop IEC strategy and materials</li> <li>• Use of multipronged strategy (television, radio, print)</li> <li>• Awareness created at four levels: clinical, school, community, and workplace</li> <li>• Advertisements targeted at all eligible women and men</li> </ul>
<i>Project staffing/training</i>	
<ul style="list-style-type: none"> <li>• Task shifting — medical officers initially charged with screening, but tasks eventually fell to nurses and even counselors</li> <li>• Role creep — nurses engaged in provision of routine services rather than those related to noncommunicable diseases (NCDs)</li> <li>• Village-level “volunteers” (contractual workers given honorarium) ineffective in mobilizing women and doing follow-up</li> <li>• Staff turnover at all levels of care</li> <li>• Subjective nature of screening tests make quality assurance difficult and leads to large number of false positives</li> </ul>	<ul style="list-style-type: none"> <li>• Appointment of staff nurses specifically for NCDs</li> <li>• NCD training for all nurses to keep services running in absence of NCD staff nurse</li> <li>• Reliance on village health nurses (health department staff) to mobilize women and support follow-up</li> <li>• Regular payment of salaries and building staff relationships</li> <li>• Expanded training program with adequate exposure to positive and negative cases</li> <li>• Periodic refresher trainings</li> </ul>
<i>Procurement/maintenance</i>	
<ul style="list-style-type: none"> <li>• Lack of regular supply of drugs/reagents</li> <li>• Malfunctioning equipment</li> </ul>	<ul style="list-style-type: none"> <li>• Separate budget created and approved for purchases</li> <li>• Central procurement by NCD coordinating site to ensure timely supply of drugs and other consumables</li> <li>• Ensure staff trained on stocking equipment and monitoring orders</li> <li>• System to monitor and maintain equipment</li> </ul>

Challenges during pilot implementation	Actions to address challenges during scale-up
<i>Protocols and guidelines</i>	
<ul style="list-style-type: none"> <li>• Nonadherence to protocols</li> <li>• Reluctance by staff to document and report service provision</li> <li>• Inability to meet targeted screening goals</li> </ul>	<ul style="list-style-type: none"> <li>• Simplification and refinement of protocols and reduced number of conditions requiring referrals</li> <li>• Staff supported to estimate case load based on local conditions and to monitor actual case load</li> </ul>
<i>Data collection</i>	
<ul style="list-style-type: none"> <li>• Poor data quality</li> <li>• Lack of analysis/corrections of reports at district level</li> <li>• Incorrect information provided by patients (e.g., addresses)</li> </ul>	<ul style="list-style-type: none"> <li>• NCD staff nurse responsible for data entry</li> <li>• Dedicated statistical assistant to monitor data quality and compilation</li> <li>• Routine reporting of data through monthly videoconferences</li> </ul>
<i>Access to treatment</i>	
<ul style="list-style-type: none"> <li>• Few centers equipped to do colposcopy and biopsy</li> <li>• Poor follow-up of patients needing diagnostic and treatment services; small proportion (13%) of women obtained treatment</li> <li>• Weak linkages between different health system levels</li> </ul>	<ul style="list-style-type: none"> <li>• Village health nurses responsible for following up patients and facilitating links to tertiary-level services</li> <li>• Coordination with state health insurance scheme for cashless tertiary-care services for individuals belonging to households below the poverty line.</li> <li>• Improved tracking of cases through the health information system</li> </ul>

*Source:* Tamil Nadu Health Systems Project, personal communication.

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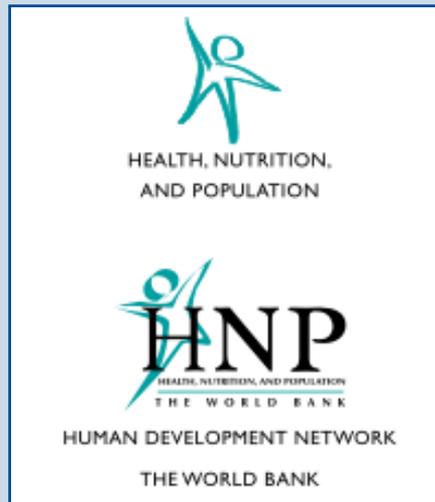
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