



Expanding paradigms for cervical cancer screening

*The impact of the Alliance for
Cervical Cancer Prevention*

January 2009
Updated August 2013

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Abstract

In 1999, visual inspection methods of cervical cancer screening had garnered some interest, but were not yet considered “proven” technologies. In the nine years following inauguration of the Alliance for Cervical Cancer Prevention (ACCP), its partners conducted studies comparing a number of screening techniques including cytology, visual inspection methods using acetic acid (VIA) or Lugol’s iodine (VILI), and a state-of-the-art human papillomavirus (HPV) DNA test in over 20 low-resource settings around the world. The studies also investigated the feasibility of combining screening and cryotherapy treatment into a screen-and-treat approach more convenient for patients and providers, and which significantly reduces dropout and improves compliance. ACCP’s contribution to the body of evidence is significant—of 100 peer-reviewed articles on visual inspection published between 2000 and 2008, 49% included ACCP contributions. Screening and treatment programs that began as ACCP study sites now are scaling up in many countries worldwide and international policy guidelines commonly refer to ACCP findings and quote ACCP recommendations.

Key points

- Prior to ACCP, alternatives to cytology (visual inspection and HPV DNA testing) were considered unproven. New screening paradigms using these methods are now being featured in training courses from the World Health Organization and many other groups.
- Since 2000, the evidence base on these alternatives has increased exponentially, with much of the data generated through the ACCP grant.
- Visual inspection methods now are viewed not only as appropriate for primary screening, but also for treatment triage for women screened with new HPV DNA tests.

As more global health leaders and international organizations urge health care providers to examine the evidence on alternatives to cytology, and as more providers learn about these alternatives, ACCP expects that new screening paradigms will be adopted, and adapted, for local situations. Because the technologies were developed with low-resource settings in mind, it is likely that cervical screening finally can find success in the places where it is most needed.

Now, in 2013, acknowledging the rapid uptake of VIA and cryotherapy in much of the developing world, the partners have agreed that by and large the ACCP research agenda has been accomplished and have decided to disband the partnership. That said, many of the partners continue working on cervical cancer prevention, often focusing their energy on providing technical assistance for screening and treatment program inauguration or expansion, and collaborating with partners in other coalitions.

Introduction

The world now has an extraordinary opportunity to significantly reduce the global burden of cervical cancer. New innovations have dramatically increased the world's attention to cervical cancer and opened the door to global action.

–Cervical Cancer Action coalition, 2008

Cervical cancer has been known for thousands of years, but only recently have physicians been cognizant of how to prevent and manage the disease. The earliest description appears circa 400 BCE when Hippocrates noted that cervical cancer was untreatable once diagnosed. In 1713, an Italian doctor named Bernardino Ramazzini, observing that nuns had a relatively low incidence of cervical cancer, wondered if it could be due to their celibate lifestyle. This question laid the groundwork for understanding of human papillomavirus (HPV) as a sexually transmitted disease. About 230 years later, in the early 1940s, Drs. Papanicolaou and Traut published a monograph on the “Diagnosis of uterine cancer by the vaginal smear” and beginning in the 1960s, precancer screening using cytology, or the “Pap smear,” became a routine procedure for sexually active women. The result has been an approximately 70% decrease in both the incidence and mortality of cervical cancer in the United States and other countries.

Cytology-based screening, however, has not proven to be as successful in low-resource settings of the developing world. Lack of trained pathologists and technicians and a shortage of laboratories have contributed to that failure, along with patient difficulty returning to clinics or hospitals three or more times for test results, diagnosis, and treatment. Furthermore, Pap smears can miss disease, especially in low-quality labs, so they must be repeated every few years to increase the odds of early detection. This only contributes to the logistical constraints associated with this screening option.

Acknowledging these challenges, in the 1980s and 1990s, a number of clinicians and researchers became interested in exploring simpler, visual methods of inspecting the cervix for precancerous lesions, including using magnification and/or swabbing the cervix with acetic acid (vinegar) or Lugol’s iodine. They felt that, if proven effective, such methods could be key to improving cervical cancer prevention in low-resource settings. These alternatives to Pap smear became a focus for systematic investigation by a group of five organizations, established as the Alliance for Cervical Cancer Prevention or ACCP (1999–2008), with support from the Bill & Melinda Gates Foundation. The ACCP partnership included EngenderHealth, the International Agency for Research on Cancer (IARC),

Timeline of the development of alternatives to Pap smear screening

- 1985** First World Health Organization (WHO) mention of “unaided visual inspection” of the cervix.
- 1990** Ficsor et al. recommend VIA for primary screening.¹
- 1992** WHO working group acknowledges limitations of cytology and suggests visual inspection as an option for triage (but not for primary screening).
- 1999** Weight of evidence begins to shift in favor of VIA and HPV testing for screening in low-resource settings, but field evaluation is needed. ACCP grant is approved.
- 2000–2007**
 - ACCP publishes 43 peer-reviewed articles, contributes to 16 more, and self-publishes more than 40 manuals, fact sheets, and other documents, including “Ten Key Findings and Recommendations” (2007).
 - 13 ACCP core countries scale up VIA-based screening services.
 - 47 additional countries benefit from ACCP technical assistance.
 - 50 additional countries request assistance.
- 2008** ACCP expands membership and updates mission.

Jhpiego, the Pan American Health Organization (PAHO), and PATH, each of which made significant, and complementary, contributions to the evidence base.

This paper documents these contributions as well as recent progress scaling up successful approaches in countries where they are needed most. To put the contributions of ACCP and its partners in perspective, the report also presents the state of knowledge about alternative screening strategies prior to the establishment of the partnership, as well as contributions of non-ACCP-affiliated researchers to the field.

Chapter 1

The state of knowledge regarding alternatives to conventional, cytology-based cervical cancer screening programs prior to the ACCP partnership

The ACCP effort built on momentum going back as far as 1985 when WHO stated that in situations where cytological screening was not possible and where the majority of cases presented at an advanced state of disease, using a visual test to detect disease at an earlier stage, when still curable, might have positive impact. WHO called this “downstaging” and envisioned that it could be achieved by mobilizing health workers at the primary level, who had access to the women in need.² That visual test involved neither magnification nor the application of acetic acid. It also was known as unaided visual inspection (UVI). A few key studies on the feasibility and utility of the approach were conducted in India in the late 1980s,³ though these were not published. Conclusions were that UVI could effectively identify the abnormal and precancerous cervix, but that evidence was lacking that downstaging would prove beneficial in reducing disease and death.⁴

The first *published* study of visual methods for cervical cancer management dates to 1982. It investigated whether use of visual inspection with acetic acid (VIA) for triage could replace colposcopy and reduce colposcopy dropouts. The results were positive, leading the authors to conclude that “colposcopic magnification is not essential in clinical practice for the identification of the cervix at risk.”⁵

The first publication on experiences with VIA as a *primary screening test* appeared eight years later, in 1990. The authors of that study concluded that “VIA can also [in addition to cytology] detect individuals at risk for cervical cancer.” As VIA was faster and less expensive than cytology, they recommended that it be performed routinely.¹ In 1992, a WHO working group convened to discuss existing data; its deliberations were published as cervical cancer screening managerial guidelines.⁴ The guidelines noted that many developing countries were not able to launch or maintain effective, cytology-based programs. Downstaging by primary care workers was mentioned as a possible option—for treatment triage however, not for screening—as UVI was considered “unproven” for screening purposes. While the Ficsor et al. study was published before the 1992 WHO working group meeting, the group did not feel that the evidence on VIA was substantial enough to warrant serious consideration at that time.

The World Bank added to the global dialogue on cervical cancer by supporting a 1993 study showing that cervical cancer screening (defined as screening women every five years, with standard follow-up care for identified cases) could be a cost-effective intervention, associated with a disability-adjusted life year of US\$100. In contrast, the cost for treatment/palliative care for cervical cancer in the absence of precancer screening and treatment was estimated at \$2,600.⁶ This provided the rationale for the Bank to commission PATH to prepare a situational analysis of cervical cancer control efforts in 25 developing countries. That report concluded, among other points, that programs must be “aimed at raising women’s awareness of this problem, coupled with simple, inexpensive methods to diagnose and treat early cervical lesions before they become invasive.”⁷

Around the same time, in 1994, Jhpiego held a workshop in which future ACCP partners PATH and EngenderHealth (then the Association for Voluntary Surgical Contraception) participated. Speakers presented on how the addition of acetic acid to the cervix (VIA) improved the sensitivity of UVI. Visual inspection aided by magnification (VIAM), in the form of a low-powered (2X) device, also was being

evaluated as a potentially useful adjunct to cytology.⁸ Participants made recommendations for how best to design a rigorous test-accuracy study in low-resource settings that would add weight to the growing evidence supporting a role for VIA and other technologies as primary screening tests.⁹ A number of studies with this or a similar objective were initiated in the following years, including by future ACCP partners.

Cervical cancer screening needs also were of interest to organizations in Europe. In 1994, the European Research Organization on Genital Infection and Neoplasia (EUROGIN) organized a consensus conference on cervical cancer screening during their 2nd International Congress on Papillomavirus in Human Pathology. Two years later, enough new information and ideas had been generated, including on Pap smear alternatives, that another EUROGIN conference was convened to update the 1994 recommendations and deliberations. For example, regarding VIA, by 1996 seven studies had been conducted, of which six had been published,^{1;5;10-14} and another four or more—some including HPV testing—were ongoing.¹⁵⁻²² The main presentation on VIA at the conference noted the test's easy technique, low cost, high sensitivity, and immediate availability of results, making "VIA an attractive screening test."²³ The authors concluded, however, that the test was still "experimental" and its performance still needed to be established in well-conducted studies. Addressing this conclusion, another contributor noted that "the cytological approach to preventing invasive cancer was accepted and introduced without any formal evaluation of its effectiveness by means of a randomized trial."²⁴ The cytology research gap was recognized later, and filled, by ACCP.

In 1997, United States Agency for International Development (USAID) was exploring how to expand its reproductive health portfolio to address the 1994 Cairo International Conference on Population and Development program of action. In response, a small group (the Cervical Cancer Consultative Group) was invited to jointly assess cervical cancer research and programming needs and to make recommendations. The group prioritized technical questions about cervical cancer appropriate for clinical or operations research and policy or cost analysis.²⁵ An important reference document for the group's discussion was the PATH publication, *Planning Appropriate Cervical Cancer Prevention Programs, which* summarized scientific information to date as well as considerations for program design including cost considerations.²⁶

To begin to better engage stakeholders in high risk areas, in 1998, an East and Southern Africa Regional meeting on the Prevention and Control of Cervical Cancer was held in Nairobi, Kenya. Participants from 15 African countries met with technical experts to share information and to reach a consensus on future cervical cancer action for the region.²⁷ Findings were presented from ongoing studies in Zimbabwe and South Africa (supported by Jhpiego and EngenderHealth, respectively) suggesting VIA as a viable alternative to cytology for the region.

In January 1999, a consensus conference was held in Tunisia of the International Network on Control of Gynaecological Cancers during which participants reviewed the state of the art on screening for cervical cancer and considered "promising new developments," including VIA and linking screening directly with treatment. This would later be termed "see-and-treat." Results of studies in India, Zimbabwe, and South Africa—not available for discussion at the 1996 EUROGIN conference—were presented at this event. The performance and usefulness of VIA, speculoscopy, cervicography, and HPV testing as primary tests for developing countries were all reviewed. However, among these, only VIA and HPV testing were considered viable options for low-resource settings. Participants further agreed that

evaluation of these methods for wide-scale application needed to be carried out via demonstration projects or randomized controlled trials.²⁸ The road for future ACCP research and evaluation efforts was thereby clearly paved.

The results of the Zimbabwe study comparing VIA and cytology presented in Tunisia were published in the *Lancet* later that year.²⁹ In the accompanying commentary, the authors stated that “VIA represents a proven, simple means of identifying women with cervical intraepithelial neoplasia in undeveloped health facilities.” Of note is their use of the term “proven” compared to previous WHO documents stating that, despite promising evidence in support of alternatives to cytology, including VIA, the only proven method of reducing cervical cancer incidence and death was cytology.⁴ This raised the important issue of what constitutes “proof” and how much evidence is sufficient. ACCP was seen as a critical mechanism for systematically addressing this and other important questions.

Chapter 2

Contributions of ACCP to the evidence base

ACCP was established to achieve four specific key objectives, in collaboration with developing-country partners:

- Assess innovative approaches to screening and treatment.
- Improve service delivery systems.
- Ensure that community perspectives and needs were incorporated into program design.
- Heighten awareness of cervical cancer and effective prevention strategies.

As described in Chapter 1, prior to the establishment of ACCP, all five partner organizations were involved to different degrees in efforts to identify, advocate for, and/or test practical, feasible strategies to strengthen cervical cancer control programs in developing countries. The 1999 Bill & Melinda Gates Foundation grant to create ACCP energized the efforts of the partners and fostered synergies that did not previously exist.

The ACCP partners embraced the challenge of producing sufficient evidence for alternative screening approaches by supporting research and demonstration projects addressing the questions listed at right. A summary of key ACCP project findings is provided in the following pages. For ACCP's summary of its key findings and recommendations, see page 11.

In addition to generating new data and disseminating those results at meetings and in journals, ACCP also was prolific in producing over 40 fact sheets, manuals, articles, and white papers over the course of its nine-year history.

How accurately can alternative screening tests detect precancer or cancer under field conditions common in low-resource developing countries?

This question was addressed through support to a number of cross-sectional studies comparing the accuracy of VIA and cytology (and HPV testing in some cases), including a large, multi-center study covering 11 sites in six countries (India, Congo, Mali, Niger, Guinea, and Burkina Faso). The latter provided screening to 56,900 women aged 25–64, of whom 82% were in the age range 30–49. The large sample size and the fact that the study covered a number of different countries using the same protocol strengthened the ability to generalize those results (in addition to greatly adding to the pool of evidence on test accuracy and freedom from verification bias in low-resource settings). All studies yielded evidence in support of VIA as a testing alternative (and of HPV testing where incorporated). The main conclusion of the six-country study was that VIA and visual inspection with Lugol's iodine (VILI) are suitable alternate screening tests to cytology for detecting cervical dysplasia in low-resource settings.³⁰

Key research questions addressed by ACCP, 1999–2008

- How accurately can alternative screening tests detect precancer or cancer under field conditions common in low-resource, developing countries?
- To what extent does adjunctive testing improve test performance, especially concerning VIA specificity?
- How effective, affordable, and cost-effective is the “see-and-treat” approach using VIA compared to the multiple-visit, conventional cytology-based approach and other secondary prevention strategies?
- How well do alternative secondary prevention approaches “work” (i.e., are acceptable, feasible, reliable, and safe) in low-resource settings?

Meta-analyses are an important analytic tool for pooling data across studies to improve precision, to yield average estimates across time and space, and to assess internal study validity. Having supported a large multi-center study, ACCP decided to also commission a meta-analysis (including that study and two other datasets) to provide “higher level evidence” in the pursuit of proof regarding screening effectiveness.³¹ That analysis yielded many useful results and important confirmatory conclusions including:

- The use of VIAM did not improve the accuracy of a visual interpretation.
- Accuracy of both VILI and VIA was as good as or better than the Pap smear and that Pap smear, among all tests, showed the lowest sensitivity.
- Variability in test characteristics between settings and over time might reflect reduced test reproducibility, underscoring the need for strong training approaches and continuous supervision. The low variability of HVP test results suggested high test reproducibility.

A finding that was not consistent with many previously published results from other settings was a low observed sensitivity of HPV DNA testing.³¹

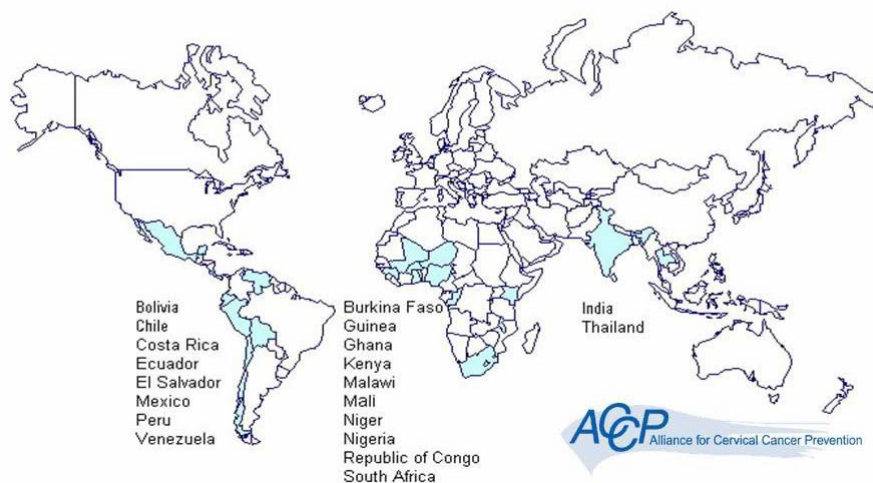
To what extent does adjunctive testing improve test performance, especially concerning VIA specificity?

The value of triage and adjunctive testing was assessed by analyzing the joint (net) effect of parallel versus sequential testing using the 1997 Zimbabwe dataset on 2000 women screened concomitantly with four tests. The study, involving computer simulation, assessed specifically whether testing with VIA could be improved through the addition of HPV testing. As is the nature of adjunctive testing, sequential testing improved overall specificity, yielding fewer false positives, but at the cost of reduced sensitivity and additional false negatives.³² The implications of this to overall program effectiveness were not evident, but future cost-effectiveness analysis would provide useful insights into this question (see below).

How effective, affordable, and cost-effective is the see-and-treat approach using VIA compared to the multiple visit conventional cytology-based approach and other secondary prevention strategies?

In light of the expressed need for hard data on program effectiveness, a number of Alliance partners set up multi-year projects involving rigorous protocols to yield valid effectiveness measures. Given the natural history of disease, the projects committed to long follow-up evaluation periods with the ability to

ACCP project areas



provide intermittent proxy measures. One ongoing study aims to provide concrete measures of the efficacy, effectiveness, and cost-effectiveness of a single round of screening by VIA, cervical cytology, or HPV testing on cervical cancer incidence and mortality. Women aged 30–59 years, living in 497 villages in Osmanabad district, India, were grouped into 52 clusters, randomized to a single round of screening with either VIA (n=34,289), cytology (n=32,263), HPV testing (n=34,383), or to a control group (n=30,378), and received no screening but were informed about existing facilities for early detection and prevention of cervical cancer. This large study is powered to detect a 50% reduction in cumulative mortality from cervical cancer within 15 years of enrollment.

Interim analysis has revealed an equal ability to accurately detect CIN2/3 among VIA, cytology, and HPV and significantly greater detection of CIN1 in the VIA arm.³³ Also, between 2000 and 2006, more than 40% of the cancers were diagnosed in Stage I in the intervention groups as compared to only 27% in the control group. This is an impressive finding, as in most developing countries with no functioning programs, almost all cancers present too late for treatment at Stage III+. Incidence and mortality from this truncated time period show lower rates for all arms compared to the control, the lowest rates being in the HPV testing arm (Table 1).

Table 1. Interim fatality rate results from the Osmanabad, India study

Study group	Total cases	Deaths	Fatality rate
Control	74	29	39.2%
VIA	143	40	28.0%
Cytology	139	38	27.3%
HPV testing	114	19	16.7%
Total	470	126	

The impact of a single round of screening with only VIA on cervical cancer incidence and mortality was investigated in a cluster randomized clinical trial in south India of approximately 80,000 women aged 30–59 years, randomized either to VIA screening by a nurse or to the control group. Study findings were reported earlier than anticipated, 7 versus 10 years, because the effect was greater than anticipated. The investigators found a 25% reduction in cervical cancer incidence and a 35% reduction in mortality associated with the VIA screening (and treatment) arm compared with the control group. They concluded that this study provided proof of its effectiveness in reducing incidence and death due to this disease.³⁴ In fact, this was the first randomized trial of its kind to definitely show the effectiveness of any secondary cervical cancer prevention intervention, including cytology, on subsequent disease and death.

Another randomized clinical trial involving 6,555 women was set up in South Africa to determine the efficacy and safety of a screen-and-treat approach for cervical cancer prevention. Women were screened using HPV and VIA and then subsequently randomized to one of three groups: cryotherapy treatment based on the HPV result, cryotherapy based on the VIA result, and delayed treatment. At 6 and 12 months, the prevalence of cervical intraepithelial neoplasia (CIN) 2 was significantly lower in the two screen-and-treat groups

(especially the HPV test group) than in the delayed treatment group. Specifically, by 12 months, CIN 2+ had been diagnosed among 1.4% (95% CI: 0.87–1.97) of women in the HPV arm, 2.9% (95% CI: 2.12–3.69) in the VIA arm and 5.4% (95% CI: 4.31–6.50) in the delayed evaluation group. No adverse treatment results were identified and the authors concluded that both screen-and-treat approaches are safe and effectively reduce disease occurrence.³⁵



ACCP partners present the “10 Key Findings and Recommendations” at a Washington, DC dissemination event in 2008

A mathematical model developed previously for South Africa was adapted for a five-country analysis, commissioned by ACCP, involving datasets from a number of core countries. Primary data were combined with findings from the literature to parameterize computer-based models, calibrated to age-specific cancer incidence and mortality rates in India, Kenya, Peru, South Africa, and Thailand. Analyses revealed that the most cost-effective strategies were those requiring the fewest visits, which were associated with higher rates of treatment (lower dropout). Screening women once in their lifetime, at age 35, with a one- or two-visit approach involving VIA or HPV testing, reduced the lifetime risk of cancer 25–36%, at a cost of less than \$500 per life-years saved. Although approaches involving single- or two-visit HPV testing were most effective, under model assumptions including high HPV sensitivity, a screen-and-treat approach with VIA was the most cost-effective given the low costs associated with the test and low assumed levels of dropout between testing and treatment.³⁶

How well do alternative secondary prevention approaches “work” (i.e., are acceptable, feasible, reliable, and safe) in low-resource settings?

Studies addressing the questions above sought to provide scientifically valid measures of efficacy, effectiveness, and cost-effectiveness associated with alternatives to Pap smear. However, the controlled conditions required for validity are not usually found under routine clinical operations. Demonstration projects, by design, usually do not measure the long-term clinical outcomes and objectives of secondary prevention (i.e., reduction in the incidence of and deaths due to cervical cancer). They do, however, provide a rich source of “grounded” information on how programs actually do (or do not) succeed in the field. To provide this additional evidence, ACCP demonstration projects were set up in El Salvador, Ghana, Kenya, Peru, South Africa, Suriname, and Thailand. The projects differed in design, according

to the needs and policies of the respective countries. Some involved the offer of immediate treatment post-screening while others involved referral or triage for additional testing as the basis for management decisions. However, all incorporated visual tests (particularly VIA) as one screening alternative and cryotherapy as an outpatient treatment modality. All aimed to serve as models for strengthening cervical cancer control efforts—and the basis for future expansion—locally, nationally, or regionally. As will be shown in Chapter 3, by and large this goal was achieved.

The assessments conducted, approaches tested, insights gained, materials produced, policies reformed, and commitments sealed cannot be adequately described in a short summary document. The lessons learned by individual partners and collectively by the Alliance are described in the many publications produced by ACCP, including *Planning and Implementing Cervical Cancer Prevention and Control Programs: A Manual for Managers* (available online at www.alliance-cxca.org and at www.rho.org),³⁷ which provides a roadmap for taking action to strengthen cervical cancer prevention in low-resource settings, based on ACCP's many country experiences. ACCP's ten most important findings and recommendations are summarized below.

ACCP 10 key findings and recommendations for effective cervical cancer screening and treatment (2007)

1. Every woman has the right to cervical screening at least once in her lifetime. In low-resource settings, the optimal age for screening to achieve the greatest public health impact is between 30 and 40 years old.
2. Although cytology-based screening programs using Pap smears have been shown to be effective in the United States and other developed countries, it is difficult to sustain high-quality cytology programs. Therefore, in situations where health care resources are scarce, resources should be directed toward cost-effective strategies that are more affordable and for which can be assured.
3. Studies have shown that the most efficient and effective strategy for secondary prevention of cervical cancer in low-resource settings is to screen using either HPV-DNA testing or VIA, then treat precancerous lesions using cryotherapy (freezing). This is optimally achieved in a single visit (currently possible with VIA plus cryotherapy) and can be carried out by competent physicians and non-physicians, including nurses and midwives.
4. The use of HPV DNA testing followed by cryotherapy results in greater reduction of cervical cancer precursors than the use of other screening and treatment approaches.
5. Cryotherapy, when conducted by competent providers, is safe and results in cure rates of 85 percent or greater.
6. Studies suggest that cryotherapy is protective against the future development of cervical disease among women with current HPV infection. Because of this, and due to the low morbidity of cryotherapy, the occasional treatment of screen-positive women without confirmed cervical disease is acceptable.
7. Unless there is a suspicion of invasive cervical cancer, the routine use of an intermediate diagnostic step (such as colposcopy) between screening and treatment is generally not efficient and may result in reduced programmatic success and increased cost.
8. Women, their partners, communities, and civic organizations must be engaged in planning and implementing services, in partnership with the health sector.
9. For maximum impact, programs require effective training, supervision, and continuous quality improvement mechanisms.
10. Additional work is needed to develop rapid, user-friendly, low-cost HPV tests and to improve cryotherapy equipment.

Chapter 3

Scale-up in ACCP countries and impact beyond the ACCP partnership

As a direct result of ACCP efforts, cervical cancer prevention programs have been launched or substantially strengthened in many countries with different cervical cancer control program histories, health infrastructures, cultural and professional traditions, and decision-making structures. However, all share the burden of unnecessary deaths and suffering due to cervical cancer and low screening and treatment rates. This chapter describes the extent to which ACCP efforts have been sustained, expanded, or scaled up locally or nationally in “core project” countries (i.e., where large-scale clinical trials or demonstration projects were supported). It also documents ACCP’s broader impact, within different regions and at the global level.

Core country scale-up

In all 13 ACCP core countries (Thailand, India, South Africa, Kenya, Ghana, Peru, El Salvador, Suriname, Congo, Mali, Niger, Guinea, and Burkina Faso), cervical cancer prevention activities—initially supported through the Alliance—are ongoing. Importantly, the public sector is now providing at least some funding support. Programs in Asia have experienced the largest scale-up, reflecting the ability of those countries to invest in health interventions, including cervical cancer screening, with the promise of future cost-savings. While potential savings are the same or potentially higher for core project countries in sub-Saharan Africa, severe resource constraints (including in some areas in South Africa) limit their ability to invest in anything but interventions providing immediate payoffs. Consequently, cervical cancer prevention efforts, while sustained, continue on a more modest scale and still require external input to achieve sustainable momentum.

Examples of how ACCP efforts have expanded in core countries follow:

Thailand

- ACCP-supported demonstration project experiences have resulted in health policy change and in an expanded single visit VIA-based screening and treatment (or referral) program.
- With continuing but reduced ACCP support, complemented by gradually increasing government funding, the screen-and-treat approach has since been extended to 17 of the 75 provinces in the country.
- Ministry of Health (MOH) policy now states that all eligible women should be screened with either a Pap smear *or* VIA and the National Health Insurance has approved VIA screening as an allowable/reimbursable health care cost.

Programmatic legacy of ACCP

- Scale up of VIA- and HPV test-based screening programs in all 13 core ACCP countries
- Assistance to another 47 countries, including major population centers Bangladesh, China and Indonesia
- WHO regional and national meetings now focus on VIA and HPV testing. ACCP publications frequently are cited.
- Influential professional associations such as ACOG and FIGO include alternatives to Pap in their meetings and publications.
- Cervical cancer prevention is on the World Bank’s list of suggested health interventions.
- The civil society Cervical Cancer Action coalition promotes alternatives to Pap in meetings and publications aimed at developing country programs.

- Local health officials see the screen-and-treat approach as a desired, cost-effective alternative to the long-term costs associated with undiagnosed and treated cervical cancer (for which they now are financially responsible).
- In addition to country expansion, Thailand has been an active regional advocate, providing both leadership and a model program for neighboring countries to adapt to local circumstances.

India

- A national task force on cervical cancer prevention met in December 2005 and reviewed the evidence from ACCP-supported studies from India and other countries. It recommended that VIA screening be initiated in 50 of the 610 districts countrywide. The government was also sufficiently convinced of the value of VIA-based screening to invest its own resources in these programs—granting each district 3 million rupees (US\$660,000) to sustain screening over the succeeding five years.
- Trivandrum District of Kerala state has become a major focal point for screening, and VIA services now are widely available there. Since this expansion, the district has experienced a measurable drop in cervical cancer rates, due in part to active case finding (precancer and early cancer) associated with visual-based screening. Gujarat state also has become a regional center, promoting VIA and VILI on its own by adapting ACCP-partner training materials.

South Africa

- Based on the Western Cape Province experience (an ACCP core site), cervical cancer prevention is now included as a key health indicator in the province's 2010 health plan and district managers are required to report on these activities as part of their performance evaluations.
- Core project successes have convinced government officials to expand to other areas of the country.
- The South African Department of Health endorsed ACCP-developed training manuals and intends to use them in its national roll-out program.
- To date, a screen-and-treat initiative has been started in at least one other province in Northwestern South Africa involving US President's Emergency Plan for AIDS Relief (PEPFAR) funding.*

Kenya

- Based on experience gained through ACCP, the Kenya MOH made a long-term commitment to cervical cancer prevention using alternative approaches, evidenced by their development of national guidelines and a five-year national plan of action.
- USAID and PEPFAR are currently funding a VIA and VILI initiative in several areas.
- A committed cadre of trained project clinicians skilled to provide VIA and VILI screening services continue to be available to assist MOH officials to teach other health workers and ensure continuation and expansion of services.

* As resource-appropriate cervical cancer prevention strategies were globally gaining visibility, PEPFAR began receiving developing-country proposals incorporating cervical cancer interventions (e.g., Tanzania, Kenya, Mozambique, Guyana, Ethiopia, South Africa, Lesotho, and Zambia). To respond to this, a technical group (to which Jhpiego was invited to participate) was developed to deliberate and decide upon whether cervical cancer interventions had a role/place in PEPFAR programs. The group decided they did and a number of country cervical cancer prevention proposals have been approved for PEPFAR funding (e.g., in South Africa, as described above, in Guyana as a stand-alone effort, and in Tanzania as part of a larger reproductive health program).

Ghana

- The three ACCP project sites (two in Accra and one in a semi-rural area outside Accra) continue to provide screening, integrated into broader reproductive health services. The MOH seeks to expand these services using government funding.
- Although cervical cancer screening using a screen-and-treat approach has not yet been adopted into Ghana's national policy, national service delivery guidelines have been modified to include screen-and-treat with VIA and cryotherapy, setting the stage for future policy revision.

IARC's multi-center study African sites

- Studies in Congo, Mali, Niger, Guinea, and Burkina Faso, supported as part of IARC's multi-center trial, provided an opportunity to organize cervical cancer prevention services where such services did not previously exist. They also provided a focal point for training in cervical cancer prevention.
- The service delivery models tested in ACCP countries all have been sustained, albeit at different levels of effectiveness.
- While the majority of project funding at the start came from ACCP, there was always a matching contribution, including from the WHO Regional Office for Africa (AFRO).
- WHO/AFRO is encouraging country governments in the region to add a budget line for VIA-based screening services, with the understanding that funding from WHO/AFRO will be provided to support training costs.
- In Guinea, the study helped catalyze major public health investment for cervical screening by the national government and the project investigator continues to be very active. Services have been expanded to the north through the country's network of public health centers with government support and some funding from United Nations Population Fund (UNFPA), USAID, and an Italian Catholic relief organization. The Government of Guinea has added a budget line item for these services and supports the training center in Conakry. The center is functioning well and provides courses for regional and national participants.
- In the Congo, the program is active and service uptake has been impressive. To accommodate this, training has been expanded from a single center in Brazzaville to second center in Pointe Noire.
- In Mali, sites continue to provide services and training is expanding.
- In Niger, subsequent to the study there was a thrust to introduce Pap smears instead of VIA, but this did not prove successful. That distraction led to a lull in cervical cancer prevention activity, but a recent effort will reinvigorate the program in many districts over the next 18 months.

Peru

- Based on experience with the ACCP TATI project (acronym for the Spanish term, *tamizaje y tratamiento inmediato*), the MOH is now developing a national cervical cancer program designed to improve access for follow-up care (a key challenge in the Peruvian context). PAHO, a technical partner in TATI, continues to collaborate closely with the Ministry, as does PATH through its HPV vaccine project.
- Local officials incorporated the use of VIA followed by immediate cryotherapy into routine services for the entire health region where the ACCP project took place (San Martín). Local governments also are scaling up efforts in three other rural regions.

- The information system established by the project continues to provide critical information to evaluate the effects of secondary prevention efforts. The quality of ongoing VIA and cryotherapy services continue to be monitored by trained TATI staff.
- Importantly, to expand screening coverage, health promoters from the department continue to support the campaign to recruit women for screening, using promotional materials developed through TATI.
- The National Cancer Institute continues to provide VIA, cryotherapy, and loop electrosurgical excision procedure (LEEP) training for providers from Peru and other countries. It soon will upgrade its facilities and services to become a center for excellence in training on alternatives to cytology and will foster creation of similar national-level training centers in neighboring countries.

El Salvador

- The results of the El Salvador demonstration project encouraged the MOH to examine the feasibility of incorporating VIA as a complementary screening method into routine health services.
- Government policies now allow VIA screening and cryotherapy treatment.
- The MOH is disseminating new national screening guidelines and is providing training to public-sector personnel based on new educational materials which were tested as part of the ACCP project.

Suriname

- The MOH is using project results to inform the development of a national cervical cancer prevention program, paying special attention to the Hinterlands area where the study took place.

ACCP impact in non-core countries and in the regions

In addition to the scaled-up initiatives ongoing in the ACCP core countries, the Alliance's reach has extended to many other nations in Asia, Latin America, sub-Saharan Africa, and Eastern Europe. Illustrative examples of these efforts are provided below:

Asia

- In 2005, 144 participants from 25 countries attended an ACCP-supported regional conference in Bangkok, Thailand. Subsequent to the conference, several countries expressed an interest in and commitment to improving their cervical cancer prevention programs, including the Philippines and Indonesia.

Philippines

- ACCP partner Jhpiego was able to leverage funding from GlaxoSmithKline/Singapore for a demonstration project using a screen-and-treat approach at three pilot sites in Luzon and the Visayas. Five operational screen-and-treat sites now exist that have collectively screened over 3500 women since March 2007. Two of these service sites in Manila and Cebu are designated as national and regional resource centers, respectively. Through this and other training support, the country now has enough training experience and human resources to conduct all its own trainings.
- The Department of Health has updated their National Policy and Guidelines on Cervical Cancer Prevention and Control to link VIA screening with treatment using cryotherapy.
- PhilHealth Insurance currently covers provision of VIA and is considering also covering outpatient cryotherapy treatment.

Indonesia

- Through Jhpiego advocacy, funding was obtained from the Ford Foundation to support a cervical cancer prevention initiative. The MOH is using these funds to support a pilot VIA-based demonstration project in five provinces on the islands of Java and Sumatra.
- National cervical cancer prevention policy and guidelines now incorporate VIA and cryotherapy and the screen-and-treat approach.

China

- In part due to ACCP advocacy and technical assistance, cervical cancer prevention programs have been established in at least one site in each of 42 Chinese provinces. The Chinese government has contributed funding to implement these demonstration projects and plans to extend VIA throughout all provinces.
- The China Cancer Research Foundation has translated an ACCP curriculum, including over 400 teaching slides into Chinese, and will be making it available in print, in electronic format on CD, and on the Foundation's website.
- Additional information about Chinese leadership in this area is included in Chapter 4.

Bangladesh

- With support from the government, ACCP partner IARC trained trainers for a VIA-based cervical cancer prevention program which now operates in 31 districts, with the expectation of eventually covering 64 districts.
- UNFPA is now funding program implementation.

Sub-Saharan Africa

Malawi

- Between 2000 and 2005, the MOH of Malawi received assistance from Jhpiego to establish an organized cervical cancer screening service.
- VIA and cryotherapy were included as part of the national cancer policy and the national strategy on cervical cancer prevention control. Additionally, service delivery guidelines were revised to include a screen-and-treat approach, and screen-and-treat services have been introduced into primary health centers across three regions of the country. Collectively, they have screened over 17,000 women and treated about 1,700 precancer lesions.
- Over the next five years, the government plans to scale up access to VIA-based cervical cancer prevention services, including for HIV-positive women, in an additional 120 clinics.

Tanzania, Angola, and Mozambique

- ACCP funds through IARC supported cross-sectional studies involving around 15,000 women in Tanzania and Angola to provide additional evidence on the comparative accuracy of the various tests in the African context.
- Tanzania post-study scale-up has been particularly impressive. The government is fully engaged, having invested almost US\$1 million of its own funding for cervical cancer prevention.
- Services are ongoing in seven districts, with expansion being planned for four more.

- In Mozambique, the program is now government-run, supported by government funds, and training is ongoing in Luanda and two other areas.

Latin America and the Caribbean

- The ACCP project in Peru serves as a model for other countries in the region, and PAHO advocacy based on these results has been successful in revitalizing public health interest and actions throughout Latin America and the Caribbean to improve cervical cancer prevention programs.
- In May 2008, 21 countries of the Americas declared their commitment to improved cervical cancer screening programs. At this PAHO-organized meeting, several countries presented their successful programs of VIA and HPV testing.
- PAHO sub-regional workshops for senior health authorities from 33 countries in the region, and meetings with MOH officials and senior health authorities from over 20 countries, has further contributed to influencing their national public health agendas.
- The Bolivian MOH tested and is now using VIA as an alternative screening method in very low-resource areas.
- The Haitian Ministry of Women’s Affairs has taken the leadership in supporting uptake of viable prevention options including a pilot VIA project. UNFPA has expressed interest in supporting the project.
- Other Latin American countries that have invited ACCP partners to initiate or strengthen their VIA-based cervical cancer prevention efforts include Guyana, which has won a PEPFAR grant, and Guatemala, where ACCP materials from Peru were used as part of a collaborative partnership between a California-based health agency and a local women’s health project. In Guatemala, the MOH supports VIA-based screening efforts in two departments.

Eastern Europe

- In 2004, PATH and the Open Society Institute co-sponsored a meeting in Albania of 28 nongovernmental and health ministry representatives from 13 countries. The event culminated in a regional commitment to adopting visual screening methods for preventing cervical cancer. Country action plans were developed supporting policy change and the development of an ongoing network of reproductive health professionals committed to establishing and improving cervical cancer prevention services in the region.

Table 2 below lists the 47 countries that have received direct technical assistance from ACCP partners. Table 3 lists 50 countries that have requested assistance from ACCP partners, but whose requests have not been fulfilled due to lack of resources.

Table 2. Countries that have received direct technical assistance from ACCP

Latin America and the Caribbean		Asia/Pacific	Africa	Eastern Europe	Middle East
Anguilla	Guyana	Bangladesh	Congo-Brazzaville	Bulgaria	Turkey
Antigua	Mexico	Nepal	Guinea-Bissau	Romania	
Argentina	Montserrat	South Korea	Kenya	Ukraine	
Bahamas	Nevis	Sri Lanka	Madagascar		
Bermuda	Sao Tome	Vanuatu	Mali		
Belize	St. Kitts	Vietnam	Mauritius		
Bolivia	St. Lucia		Mozambique		
Brazil	St. Vincent and the Grenadines		Niger		
Cape Verde	Tobago		Nigeria		
Costa Rica	Trinidad		Tanzania		
Dominica	Uruguay		Uganda		
Grenada			Zambia		
Guatemala					

Table 3. Countries that have requested new or additional assistance from ACCP

Latin America and the Caribbean	Asia		Africa		Eastern Europe
Argentina	Bangladesh	Thailand	Burkina Faso	Sudan	Ukraine
Brazil	Bhutan	Vietnam	Cote d'Ivoire	Tanzania	
Chile	Cambodia	Singapore	Eritrea	Uganda	
Columbia	China		Ethiopia	Zambia	
El Salvador	India		Kenya		
Guatemala	Indonesia		Lesotho		
Guyana	Korea		Madagascar		
Guyana	Malaysia		Mali		
Haiti	Mongolia		Morocco		
Honduras	Myanmar		Mozambique		
Mexico	Nepal		Niger		
Nicaragua	Pakistan		Nigeria		
Peru	Sri Lanka		Rwanda		
Suriname	Taiwan		South Africa		

ACCP impact at the global level

World Health Organization

While WHO globally was not an ACCP member, interested staff at the Geneva headquarters have been in close touch with ACCP partners throughout the course of the program and have routinely incorporated ACCP lessons into their strategic thinking and publications.

WHO's mandate to address cervical cancer is backed by several World Health Assembly resolutions. Attention to the problem has increased over the past decade, as a result of increased requests for assistance by member states, in part because of ACCP advocacy and evolution of the evidence base for alternative screening approaches. In 2006, both the Department of Reproductive Health and Research and the Department of Chronic Diseases and Health Promotion published a *Comprehensive cervical cancer control* guide, developed following consultations with a wide array of stakeholders. ACCP's

contribution to the consultation process was substantial and the guide discusses VIA followed by cryotherapy as an alternative prevention strategy suitable for low-resource countries.³⁸

To help provide additional evidence on the effectiveness of such programs, WHO's Department of Reproductive Health and Research invited proposals and is helping six countries in sub-Saharan Africa (Madagascar, Malawi, Nigeria, Tanzania, Uganda, and Zambia) to launch small-scale VIA-based secondary prevention programs. In these pilot efforts, VIA followed by cryotherapy is the main prevention strategy, complemented by the introduction of a monitoring system as the basis for data driven program decision-making. Funding to support country programs comes from various sources, including multilateral donors operating in the countries. The goal is for these programs to evolve in a sustainable way, incorporating all key elements of a program.

Other WHO offices also have contributed to the global momentum to reduce cervical cancer as a public health problem. For example, WHO/AFRO provides financial support directly to governments for training in cervical cancer prevention and is a strong advocate to countries to include line items in their budgets for cervical cancer prevention services. By the end of this year, all WHO regional offices will have organized consultative meetings with member countries relating to cervical cancer prevention. In most regions, much of the meeting content focuses on alternatives to cytology, as well as discussions about future introduction of HPV vaccine into a comprehensive control program. WHO country offices also have been sponsoring national seminars on the topic.

American College of Obstetricians and Gynecologists, the International Federation of Gynecology and Obstetrics, and other medical associations

In 2004, an American College of Obstetricians and Gynecologists (ACOG) ad hoc international working group on cervical cancer, formed of medical opinion leaders representing a number of obstetrics and gynecology associations, was convened to discuss the state of and challenges to cervical cancer prevention in low-resource settings, along with promising new innovations. These and future discussions, to which ACCP contributed in a substantial way, resulted in the development of a joint policy statement on cervical cancer prevention in low-resource settings. Among other key points, the statement recognized the value of VIA linked to immediate cryotherapy (or referral), indicating it appeared to be a viable option for reducing the incidence of cervical cancer in settings where services are limited and where other approaches are considered impractical or too expensive.³⁹

The International Federation of Gynecology and Obstetrics (FIGO) also has been a close partner of ACCP, inviting presentations of ACCP findings at its meetings and collaborating with ACCP on two special supplements to its *International Journal of Gynecology and Obstetrics*.⁴⁰

World Bank

In 2001, ACCP supported a presentation by the Harvard Policy Institute to the World Bank on the findings of a policy analysis of cervical cancer screening strategies in low-resource settings, including the cost-effectiveness of alternative strategies. This was in response to the Bank's continued interest in cervical cancer as an important public health problem, with implications for poverty reduction and economic development. Continuing dialogue with ACCP has paid off as cervical cancer prevention is now listed as one of the Bank's suggested health interventions.⁴¹ Additionally, the World Bank is supporting a project in Tamil Nadu which incorporates VIA.

International Atomic Energy Agency Programme of Action for Cancer Therapy

The Programme of Action for Cancer Therapy (PACT) was created by the International Atomic Energy Agency (IAEA), based in Vienna, Austria. PACT is developing multidisciplinary cancer capacity building projects called PACT Model Demonstration Sites in Albania, Nicaragua, Sri Lanka, Tanzania, Vietnam, and the Republic of Yemen. While VIA is not a specific focus of PACT itself, in its advocacy and coordinating role, PACT is soliciting funding and proposals to strengthen screening and early detection in its Model Demonstration Sites. Where VIA has a foothold or is particularly applicable due to constraints with cytology, this initiative provides a well-supported opportunity for VIA to be used to reduce the burden of disease in that country. IAEA/PACT has recently joined ACCP, along with new partners UICC and Partners in Health (PIH).

International Network for Cancer Treatment and Research

The International Network for Cancer Treatment and Research in Brussels, Belgium is dedicated to helping build developing country capacity for cancer research. To this end, they have worked collaboratively with ACCP member IARC over the past decade, funding a cervical cancer screening and treatment project in Nepal as well as a mobile cervical cancer screening clinic in Tanzania.

Chapter 4

Contributions to the evidence base from other organizations

ACCP partners and their close colleagues are not the only organizations interested in alternatives to cytology. As noted previously, interest in low-cost visualization techniques for detecting cervical lesions gained momentum in the 1980s, initially in developed-country settings as an adjunct to cytology to improve detection rates or as an alternative to colposcopy for confirming the presence of disease. Megevand et al.'s 1996 publication provided the first peer-reviewed assessment of VIA's performance in a low-resource/developing-country setting.¹⁰ However, other researchers in South Africa, aware of the failing of cytology-based programs in many parts of the country, were also investigating aspects of this and other alternative tests, beginning around the same time. Similarly, across the globe in India, several groups of researchers began to seriously investigate alternatives to cytology. Many of the above investigators continue to contribute to the published literature on alternative cervical cancer tests and prevention approaches.

Expansion of the evidence base

- From 2000 to mid-2008, 100 peer-reviewed manuscripts were published on visual inspection.
- 49% described ACCP work or included contributions from ACCP partners.
- Important research has been done by non-ACCP groups in Argentina, Brazil, and China in particular.

After Ottaviano's 1982⁵ reference to visual inspection with acetic acid wash, 16 other articles appear in the literature in 1999 describing experiences with or opinions regarding this test, referred to variously as direct visual inspection, cervicoscopy, acetic acid test, or VIA. In addition, two articles describing experiences with the Schiller's (iodine) test, most recently referred to as VILI, were published in the same Polish journal (in 1967 and in 1971). Between 1980 and 1999, however, published *developing-world* VIA experience existed only for three countries—all in some way associated with future ACCP partners: India (supported by IARC), Zimbabwe (supported by Jhpiego), and South Africa (involving a number of parties including the University of Cape Town, supported in part by EngenderHealth).

A Pubmed search for papers appearing since 2000 yielded 100 articles incorporating some description of visual inspection methods for cervical cancer prevention. In addition to the 74 publications describing country-specific experiences, another 26 articles involved meta-analyses, qualitative summaries, and descriptions of the testing and screening process in support of visual alternatives (VIA, VIAM, and VILI) to cytology-based programs.

While other groups and authors are represented among these papers, it is clear that the work of ACCP has dominated the published literature on this topic during this time period. Specifically, of the total 100 manuscripts, 42 were contributed by ACCP member "extended teams" (i.e., representatives of the five member organizations plus country counterparts), reflecting experiences from the 13 "core" field project countries supported through ACCP (Thailand, Ghana, South Africa, India, Peru, Kenya, Congo/Brazzaville, Niger, Mali, Burkina Faso, Guinea, El Salvador, Suriname). The magnitude of this corpus can be attributed not only to the productivity of ACCP and the peer-reviewed high-level quality of their work but also to the Alliance's strategic decision to populate a wide range of published journals, representing a variety of stakeholder audiences (physicians, nursing and midwifery practitioners, program staff, policymakers, researchers, etc.). See Table 4 (page 24) for a partial list of these targeted journals. Of the remaining 58 articles, while not co-authored by ACCP extended team partners, seven of

the papers received some kind of contribution from an ACCP extended team member. A number of studies and groups representing the latter stand out as solidly contributing to the VIA evidence base and expansion of VIA use worldwide. These include groups investigating alternatives to cytology-based methods in three large countries (China, India, and Brazil) that, in sheer numbers of women at risk, contribute substantially to the burden of global disease.

China

Foremost among those publishing on experiences with VIA is the team that conducted a study—published in 2001—comparing various screening tests, including VIA, in Shanxi, China.⁴² The group's initial interest was HPV DNA testing as an alternative to cytology, but as results from VIA studies were being presented in professional meetings and publications on VIA began to appear in the peer-reviewed literature, the value of assessing VIA in this large study setting as yet another alternative, became more compelling. This study was of high quality and benefited both from a lack of verification bias and minimal misclassification of the gold standard due to a strong design (including four-quadrant biopsy sampling for all women, test-negative and test-positive alike). In addition to work by some ACCP partners on these same two methodological challenges, this group helped “set the bar” in terms of epidemiological design features required to produce valid, field-based test-accuracy studies.*

Since then, those involved in the Shanxi study have contributed substantially to professional presentations and the published literature on alternative cervical cancer prevention strategies, including VIA. Most importantly, this group's effort has led to large-scale program implementation in China, currently rolling out in collaboration with ACCP partners IARC and PATH. The group has been key to development of a new, lower-cost HPV test called careHPV™ (manufactured by QIAGEN) which was evaluated in Shanxi, where 2,500 rural women were screened using vaginal and cervical samples. Study results showed that the sensitivity of the test is much better than VIA and approaches that of the commercial Hybrid Capture II test (upon which careHPV™ is based). CareHPV™ will be produced in China and commercialized in 2009.

Brazil

As indicated in Table 4, several articles have been published over the past decade describing experiences in Brazil with alternatives to cytology. The group based in Fortaleza was not a recipient of ACCP support but the principal investigator previously was a Jhpiego board member, and in that capacity during the late 1990s, was involved in the organizational decision to focus on cervical cancer prevention including alternative screening and treatment approaches. A number of other publications from Brazil derive from the Latin American Screening Study (LAMS) project, a European Union-funded initiative.

The Latin American Screening (LAMS) Study

The LAMS project involved eight research groups from three European Union countries (Italy, Finland, and Slovenia) and two Latin American countries (Brazil and Argentina). The project focused on establishing the magnitude of cervical cancer and its precursors in different populations and testing the performance of alternative screening tests including VIA (referred to in their project as “aided visual

* The importance of such design features has been described at length in the published literature but such journals often target a different audience and key conclusions are not necessarily appreciated by clinicians involved in field-based studies, nor those requested to under the peer review. The same issue arises regarding valid analytic techniques and underlying assumptions of statistical tests used.

inspection”). The long-term objective of the multi-year initiative was to provide the evidence base in support of an organized cervical cancer prevention program in those two countries.

India

In the late 1980s, investigators in India researched “downstaging” using visual inspection without acetic acid (referred to in some publications as unaided visual inspection or UVI) as an alternative to cytology. This effort was supported in part by WHO/IARC, reflecting their long-term commitment to reducing the burden of this world health problem. Over the next few decades, other groups in India began to explore cytology alternatives including HPV testing and visual-based tests. Their experiences are reflected in the large number of publications from this country. For many groups not involved in IARC’s core research projects, IARC contributed in other ways to their efforts (e.g., through training and different funding mechanisms). For other groups, ACCP member affiliation was more indirect, and in a few sites, the initiative had no clear ACCP-member association. Given the comprehensive advocacy strategy of ACCP, including website development and online availability of training materials, it is difficult to draw a clear line between ACCP’s reach and independent efforts. Regardless, investigators in India have demonstrated a strong commitment and contribution to the search for prevention strategies that can be applied in low-resource, in particular rural, settings.

Table 4. Peer-reviewed articles between 2000–2008 describing country experiences with visual screening methods

Country	Number of articles	Core project country	Core project site	ACCP funded	ACCP member extended team co-authored	ACCP involvement (direct or indirect)	If not involved, relationship with ACCP member
IARC India and 5 African countries: Congo-Brazzaville, Mali, Niger, Guinea, and Burkina Faso	3	Y	Y	Y	Y	Y	NA
Cost-effectiveness: Kenya, Peru, Thailand, India, and South Africa	1	Y	Y	Y	Y	Y	NA
Latin America and the Caribbean							
Peru	2	Y	Y/N	Y/N	Y/N	Y	NA
Honduras	1	N	N	N	N	?	?
Brazil	6	N	N	N	N	N (5) Y (1)	N (3) Y (2)
LAMS Brazil and Argentina	2	N	N (2)	N (2)	N (2)	N (2)	N (2)
Guatemala	1	N	N	N	N	N	?
Costa Rica	1	N	N	N	N	N	?
Mexico	1	N	N	?	Y	Y	NA
Nicaragua	1	N	N	N	N	N	Y
Asia							
Thailand	7	Y	Y(5) N (2)	Y (5) N (2)	Y (5) N (2)	Y (7)	NA
India	21	Y	Y (14) N (7)	Y (14) N (7)	Y (15) N (6)	Y (17) N (4)	?
China	4	N	N (4)	N (4)	N (4)	Y (1) N (3)	Y (3)
Pakistan	1	N	N	N	N	N	?
Mongolia	1	N	N	N	N	?	
Philippines	1	N	N	N	N	N	?
Africa							
South Africa	7	Y	Y (5) N (2)	Y (4) N (3)	Y (5) N (2)	Y (5) N (2)	N (2)
Ghana	1	Y	Y	Y	Y	Y	NA
Kenya	1	Y	N	N	N	N	Y
Nigeria	1	N	N	N	N	N	?
Zambia	1	N	N	N	N	N	?
Congo/DR	1	N	N	N	N	?	?
Zimbabwe	3	N	N (3)	Y (2) N (1)	Y (2) N (1)	Y (2) N (1)	Y
Cameroon	1	N	N	N	N	N	Y
Burkina Faso	1	Y	N	N	N	Y	NA
Middle East							
Egypt	3	N	N (3)	N (3)	N (3)	N (3)	N (3)
Iran	2	N	N (2)	N (2)	N (2)	N (2)	N (2)
TOTAL	76				32 ACCP co-authored	39 ACCP involvement	

Conclusion

The investment made when creating ACCP in 1999 has had a profound impact on the global vision for improved cervical cancer screening and treatment. Evidence in support of alternatives to cytology has grown exponentially over the past decade, with much of the research implemented as part of the ACCP agenda. Novel, less-resource-intensive screening paradigms which were judged “not yet proven” when ACCP began, now are being scaled up in many countries and a significant number are continuations of ACCP pilot programs. Regional training centers in Asia, Africa, and Latin America produce more qualified providers each year. And WHO-sponsored workshops worldwide provide a forum for program managers to discuss not *whether* they will introduce cervical cancer screening programs that include VIA, cryotherapy, and HPV testing; but *how and how soon* they will do so. ACCP partners often serve as speakers at those meetings and ACCP resource materials are common handouts and references.

Key points

- Prior to ACCP, alternatives to cytology (visual inspection and HPV DNA testing) were considered unproven. Now new screening paradigms using these methods are being featured in training courses from WHO and many other groups.
- Since 2000 the evidence base on these alternatives has increased exponentially, with much of the data generated through the ACCP grant.
- Visual inspection methods now are viewed not only as appropriate for primary screening, but also for treatment triage for women screened with new HPV DNA tests.

In the nine years following inauguration of the project, the ACCP partners conducted studies comparing a number of screening techniques including cytology, VIA, or VILI, and a state-of-the-art HPV test. The tests were evaluated in over 20 low-resource settings around the world.

VIA and HPV DNA testing have proven to be of special interest. ACCP found that VIA compares well to cytology in terms of sensitivity for disease detection, yet presents enormous advantages because it requires fewer specialized personnel and less infrastructure, training, and equipment. Cervical cancer screening using VIA can be offered in remote, less equipped clinics, thereby reaching more women. Another important advantage is that VIA provides immediate results, making it possible to screen-and-treat women during the same visit. Immediate treatment means that women do not have to make an extra visit to the health center; this reduces the number of women who are lost to treatment because they cannot return for one reason or another. Data suggest that a new, low-cost HPV test specifically designed for low-resource settings has much better performance than either cytology or VIA for primary screening and it can be coupled effectively with VIA for treatment triage. In the ACCP studies, these new screening methods have been successfully paired with cryotherapy, a relatively simple, inexpensive, and safe method of freezing affected cervical tissue. Cryotherapy can be done immediately following VIA or later at a convenient referral site. Studies have shown that cryotherapy can be effectively and safely performed by trained nurses or midwives in addition to physicians and gynecologists.

While other groups and authors have contributed to the overall experience with alternatives to Pap smear, it is clear that the work of ACCP dominated published literature on this topic, at least through 2009. Specifically, of the total 100 articles published since 2000, 42 were contributed by ACCP member “extended teams” and a further 7 received some kind of contribution (direct or indirect) from an ACCP member. This is due to the productivity of ACCP, the peer-reviewed high-level quality

of their work, and to their strategy of populating a wide range of published journals, representing a variety of stakeholder audiences.

As the body of evidence on the safety and impact of screen-and-treat and see-and-treat approaches has accumulated, many countries expressed interest in such strategies, and requests for assistance exceeded the ability of technical agencies to respond. Countries like Ghana, Malawi, Thailand, and the Philippines have implemented successful, large-scale, VIA-based programs, but more education and training are necessary if such programs are to expand globally. As more global health leaders and international organizations urge health care providers to examine the evidence on alternatives to cytology, and as more providers learn about these alternatives, ACCP expects that the new paradigms will be adopted, and adapted, for local situations. Because the technologies were developed with low- resource settings in mind, it is likely that cervical screening finally can find success in the places where it is most needed.

ACCP was aware of the challenges in maintaining this momentum and the obstacles limiting increased use of the new tools and acceptance of the new paradigms. In order to move the agenda forward more effectively, in 2008 the original five partners of the ACCP welcomed three new partners—IAEA, UICC, and PIH.

Now, in 2013, acknowledging the rapid uptake of VIA and cryotherapy in much of the developing world, the partners have agreed that by and large the ACCP research agenda has been accomplished and have decided to officially disband the partnership. That said, many of the partners continue working on cervical cancer prevention, often focusing their energy on providing technical assistance for screening and treatment program inauguration or expansion, and collaborating with partners in other coalitions.

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