Safety, Acceptability, and Feasibility of Community-based careHPV for Cervical Cancer Prevention in Rural Thailand

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PART I: A REVIEW OF THE LITERATURE

While frequently repeated cytology screening has led to an 80% decline in cervical cancer mortality in the developed world, cervical cancer remains an important public health problem among women in developing countries. About 88% of cervical cancer deaths occur in low- and middle-income countries. It has been estimated that only 5% of women in developing countries have been screened for cervical dysplasia in the past 5 years compared with over 75% from developed countries. Until recently, cervical cancer was the number one cause of cancer death in women throughout the developing world.

In this paper, I will argue for the need for low-resource cervical cancer screening technologies in the developing world in general and in Thailand in particular, so that we can more effectively prevent cervical cancer morbidity and mortality in low-resource settings. More specifically, I will make the case that a study assessing the safety, acceptability and feasibility of a new community-based low-resource screening technology called careHPV is an essential next step in ultimately determining whether low-resource approaches can substantively decrease cervical cancer incidence and mortality in Thailand and beyond.

In the first part of this paper, I will discuss the natural history of cervical cancer. I will then detail the difference in prevention strategies in the developed versus developing world, followed by a discussion of screening technologies that have been developed to prevent cervical cancer in low-resource settings. In the second part of this paper, I will provide an overview of Thailand’s public health system and infrastructure. I will then specifically discuss Thailand’s cervical cancer burden, ending with an explanation of how studying the safety, acceptability and feasibility of careHPV is most logical in this setting.

I. CERVICAL CANCER PREVENTION IN LOW RESOURCE SETTINGS

Natural History of Cervical Cancer

The vast majority (99.7%) of cervical cancer cases worldwide are associated with infection of one or more types of human papillomavirus (HPV), which is sexually transmitted. High-risk strains of the HPV virus first enters the cells covering the cervix and then slowly cause cellular changes that can result in cancer. Although women generally are infected with HPV in their teens, twenties, or thirties, invasive cancer may not develop for as long as 10-20 years after infection. The progression moves from mild dysplasia (cervical intraepithelial neoplasia, i.e. CIN 1), where only a few cervical cells are abnormal, to moderate dysplasia (CIN 2), where the abnormal cells involve about ½ of the thickness of the surface lining of the cervix, to carcinoma-in-situ (CIN 3), where the entire thickness of cells is disordered, but the abnormal cells have not spread below

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*a In the last several years, a theory has developed that CIN 1 and CIN 2-3 are actually different diseases. The theory suggests that CIN 1 is caused by the non-oncogenic virus subtypes (e.g. 6,11) and never progresses to cancer. CIN2-3, in contrast, are caused by the high risk subtypes (e.g. 16, 18, etc) and can cause cancer.*
the cervix. About 10-20 years after the onset of this progression, invasive cancer, where the cells have invaded the tissue underlying the surface, may develop. This slow progression from precancer (CIN I, II, and III) to invasive cancer explains why cervical cancer is considered the most preventable of all cancers. Cervical cancer, moreover, can be prevented by using relatively inexpensive screening methods to detect and then treat abnormal cervical tissue before its progression to invasive disease\(^3\). Yet despite this fact, the disease is responsible for more deaths than all other STDs combined, with the recent exception of HIV/AIDS.\(^4\) The WHO projects that without urgent action, deaths due to cervical cancer worldwide are projected to rise by as much as 25% in the next 10 years.\(^5\)

**Cervical Cancer Prevention: Developed vs. Developing World**

It is widely agreed upon that screening with cytology (the Papanicolaou of “Pap” smear) fulfills the criteria of an effective screening program, which includes cost effectiveness, reduction of incidence of a disease and reduction of morbidity and mortality from a disease\(^6\). A Pap smear is a microscopic examination of cells scraped from the opening of the cervix. To perform a Pap smear, a doctor or other health care provider performs a pelvic exam and uses a small brush or spatula to collect cells from the cervix. The cells are smeared on a glass slide (called a traditional Pap smear) or added to a preservative fluid (called liquid-based, thin layer testing) and sent to a lab for microscopic examination. Lab technicians look for dysplastic cervical cells (i.e. CIN 1, 2 and 3). Results take an average of 2 weeks to obtain. Women with abnormal results must return for follow-up and further testing with colposcopy and directed biopsy. If dysplasia is confirmed, precancerous lesions can be removed with electrocoagulation, cryotherapy, laser ablation or local surgery—essentially preventing progression from dysplasia to cancer. Cytology has been used in numerous countries since the 1950s, and, as stated above, is thought to be primarily responsible for an 80% decline in cervical cancer incidence and mortality in much of the developed world.

In the United States, (as of March 15, 2012), the US Preventative Task Force (USPTF) recommends cytology-based screening for women beginning at age 21 and screening at least every 3 years until the age of 65 (if the woman has had normal recent Pap smears) for cervical cancer prevention.\(^7\) Similarly the European Union recommends cervical cytology, beginning between the ages of 20-30 with screening continued at 3-5 year intervals until the age of 60 or 65, once a woman has had three or more consecutive (recent) previous normal cytology results\(^8\). Many developed nations, including the US, also supplement these recommendations with HPV testing, if available, for women 30 and older. This year, the USPTF has for the first time formally included HPV testing in its recommendations “as an alternative for women aged 30 to 65 who want to be screened less frequently” (every 5 years)\(^7\), though thoughts about the best programmatic use for HPV testing are still evolving\(^9\).

Taking into consideration the needs of developing countries—where it has been much more difficult to achieve such frequency of cytology-based screening— the WHO cervical cancer screening recommendations are as follows\(^5\):
• New programs should start by screening women aged 30 years or more, and include younger women only when the higher-risk group has been covered. Existing organized programs should not include women less than 25 years of age in their target populations.

• If a woman can be screened only once in her lifetime, the best age is between 35 and 45 years.

• For women over 50 years, a five-year screening interval is appropriate. In the age group of 25-49 years a three-year interval can be considered if resources are available.

• Screening is not necessary for women over 65 years, provided the last two previous smears were negative.

• Annual screening is not recommended.

Even with the potential for a much more limited screening frequency recommended by the WHO, cytology-based screening programs have largely failed in low-resource settings for infrastructural, economical, and social/political reasons. Infrastructurally, cytology-based programs need highly trained personnel, well-equipped laboratories, ability to transport specimens, and an effective system for following up patients, rare or scarce commodities in many countries. Economically, the demands of other competing health needs often result in a lack of resources or political will to make cervical cancer screening a priority, especially since existing health care services tend to focus on curative, rather than preventative health care. Social and political conditions in low resource settings often impede cervical cancer screening programs as well. Reliable and affordable modes of communication and transportation are often lacking, leaving women unable to travel to a screening site for an initial or follow-up visit. Moreover, women in poor countries may be illiterate or may use a local dialect that differs from the national language, making it more challenging to educate and inform them of prevention services. Vaccines that prevent or treat HPV are under development and, ultimately, may be the answer to this important public health problem. However, large-scale vaccine implementation is still several years away in the countries that need it the most. This dilemma has led to the investigation of screening tests that use fewer resources and offer rapid results.

Low Resource Screening Technologies

**Visual Inspection: Overview**

Among cervical cancer screening tests, visual inspection has proven to be a promising candidate for screening in low-resource settings as it fulfills the basic criteria
of a satisfactory screening test (accurate, reproducible, inexpensive, easy to perform and easy to follow-up, acceptable and safe\textsuperscript{11}), and has demonstrated effectiveness in reducing incidence of and mortality from cervical cancer\textsuperscript{12}. Like the Pap smear, visual inspection also involves a pelvic examination of women, but unlike cytology-based screenings, results are retrieved on the spot; there is no need to send specimens to a lab to be read by a technician. Visual inspection can be performed with acetic acid (VIA) or Lugol’s iodine (VILI). When vinegar is applied to abnormal cervical tissue in the transformation zone near the squamo-columnar junction (SCJ), it temporarily turns white, allowing the provider to make an immediate assessment of a positive (normal) or negative (abnormal) result with the naked eye. If iodine is applied to the cervix, precancerous and cancerous lesions appear well-defined, thick, and mustard in color, while squamous epithelium stains brown or black and columnar epithelium retains its normal pink color.\textsuperscript{5}

Visual inspection testing is inexpensive, simple, and can be provided at all levels of the healthcare system by nurses and midwives. Another key advantage of visual inspection is that the results are immediately available. This means that management decisions, especially whether to offer outpatient treatment if the cervix is found to be abnormal, can be made during a woman’s initial visit, a significant benefit in countries where health care facilities are not easily accessible.\textsuperscript{13}

**VIA**

Use of VIA screening followed by treatment reduces the rate of cervical cancer compared with no screening. This was best illustrated in the only randomized trial to address the use of this test in a low resource setting. Clinics serving over 80,000 women aged 30-59 in India were assigned to either VIA screening or cervical cancer health education\textsuperscript{12}. Women with positive screening tests were further evaluated with colposcopy and directed biopsy, and those with CIN were treated with cryotherapy or excision. At seven-year follow-up, women in the screening group versus the health education group showed a significant decrease in age-standardized rates of cervical cancer incidence (75 versus 99 per 100,000-person years) and mortality (40 versus 57 per 100,000 person-years).

Though the India study described above did not determine VIA’s sensitivity or specificity, the sensitivity and specificity of VIA in developing countries for detection of CIN or cervical cancer has been evaluated in multiple observational studies\textsuperscript{14-21}. A meta-analysis of 11 studies with over 58,000 women aged 25-64 in India and Africa reported a VIA sensitivity and specificity of 79 and 85\% respectively for detecting of CIN2 or CIN2+\textsuperscript{22}.

**VILI**

VILI is more sensitive than VIA, but equally specific\textsuperscript{23}. In the meta-analysis of 11 studies described above, women were evaluated with both VIA and VILI in 10 of the studies. For detection of CIN 2+ the sensitivity and specificity for VILI was 91 and 85\% respectively. No randomized trials have been preformed using specifically VILI to assess cervical cancer incidence, but VILI is procedurally identical to VIA and there is
no reason to believe it would not decrease rates of cervical cancer equally or more than VIA did in India. However, Lugol’s iodine is hard to find or create from scratch, and is 4x more expensive than using acetic acid.

Despite these promising study results, screening by visual inspection has a number of disadvantages. The tests are relatively subjective, as providers must interpret what they see on the cervix, causing variation in test interpretation. Moreover, a long period (>2 weeks) of provider training is crucial to be able to perform visual inspection and additional workshops to maintain skills are also necessary, thus decreasing the cost-effectiveness of the approach.\(^2\) Furthermore, the SCJ is often not visible in older women (especially post-menopausal) because the junction tends to recede into the cervical canal and can be hard to visualize. Therefore, for women over 50—a non-trivial high-risk group, visual inspection is not routinely advised as a screening method.\(^2\)

**HPV Testing**

Because of these VIA disadvantages, experts in the field have been waiting for improvements of the technology that the WHO predicts will be the “gold standard” in cervical cancer screening in low-resource settings: HPV DNA testing. HPV testing is more objective and reproducible than visual inspection and does not depend on the visibility of the SCJ of the cervix. It is less demanding in terms of training and quality assurance.

Today, HPV DNA testing is used almost exclusively in the developed world in combination with cervical cytology. Developed countries use the Hybrid Capture II test (HC2, Qiagen, Gaithersburg, MD) to screen for HPV, an expensive test that costs approximately $50 to $100 per woman. A randomized trial of 131,746 women aged 30-59 years in rural India assessed the effectiveness of HC2-based HPV DNA testing in the developing world, comparing a single lifetime screening with one of three screening modalities (HPV testing using HC2, cervical cytology, or VIA) with the standard care (control group). At 8-year follow-up, women who received HPV testing versus standard care had a 50% reduction in stage II or higher cervical cancer and cervical cancer mortality rates were also reduced by half compared to control. These results were superior to VIA or cytology, which showed no significant reductions in the number of advanced cancer or deaths compared to control.

While these results are promising for HPV DNA testing, the overarching drawback has been that the HPV DNA technology has been 1) too expensive for routine use in developing countries and 2) marred by a lengthy turnaround time, precluding the retrieval of results in a single-visit.\(^1\)

In an attempt to address these issues, the pharmaceutical company Qiagen, in partnership with the global health nonprofit PATH, has developed careHPV, an HPV DNA test that reportedly could cost less than US$5 per kit, could theoretically be administered in a static or mobile clinic with no refrigeration, and can get results (for batches of either 24, 48, or 96 samples) in approximately 2.5 hours. The careHPV test can detect 14 high-risk types of carcinogenic HPV and the swab can be performed by a
health provider (cervical swab) or by the woman herself (vaginal self-swab). This test is not yet commercially available.

In an effort to determine the most practical and beneficial way this new technology could be implemented into current cervical cancer prevention programs, Trope et al. conducted a study on stakeholder attitudes toward careHPV-focused screening programs in Roi- et Province, Thailand. The results indicated that overall, participants supported an innovative screening protocol in which women would be screened in their homes and villages using the vaginal-swab version of the careHPV test and only those who screened positive for HPV would be then examined with VIA. HPV-positive women would then be treated on the basis of their VIA results thereafter. For the rest of this paper, this protocol is referred to as the “community-based careHPV protocol.”

Since these results were published, additional studies using cost modeling techniques have shown that the careHPV test is both potentially cost-effective and, if women are tested 3 times in life, more clinically effective than traditional cytology because it allows a closer link between screening and treatment. In October 2008, Lancet Oncology published results from a clinical study conducted primarily in rural areas of China. The study is the first of two studies to date that have evaluated the careHPV test’s sensitivity and specificity. Through a cross-sectional study of 2,388 women aged 20-54, the study demonstrated that the careHPV Test had a 90% clinical sensitivity for identifying CIN 2+ — a higher sensitivity than either VIA or Pap testing. Moreover, the study showed that vaginal specimens (though slightly less sensitive than cervical specimens) are an effective way to utilize the careHPV DNA test. Further enhancing the potential feasibility of careHPV, a recent Lancet study conducted in rural Mexico found that HPV testing detected approximately 4.2 times more invasive cancers than did cytology and found that even home-testing with vaginal samples was more sensitive than cytology-based screening.

Though the careHPV test is not being formally incorporated as part of any cervical cancer screening program in the world to date, it has become increasingly clear that the test has great promise. In particular, the community-based careHPV protocol described above has the potential to overcome many of the challenges seen with cytology-based screening programs. First, use of this protocol would require fewer highly trained personnel than cytology-based programs, given that the careHPV test would be administered by the woman herself and follow-up examination would be done with VIA, and only on the small subset of HPV-positive women. There would be no need to transport specimens, or wait for follow-up, as results would be retrieved in a single day. Moreover, the community-based careHPV protocol could greatly reduce the resources needed for cervical cancer screening, as it would be used as an inexpensive tool to exclude a large majority of the population (i.e. those HPV negative) from further assessment, instead focusing resources on the relatively few women who are HPV positive. Such efficient use of resources may be critical in many developing regions.

II. CERVICAL CANCER PREVENTION IN THE CONTEXT OF THAILAND
Thailand Public Health System Overview

Thailand’s public health system is renowned for its many successes. The Thai government regards health as “the state of physical, mental, social and spiritual well being that is interrelated holistically,” and Thailand’s equity-based health system is oriented to the improvement of health rather than concentrating solely on treatment of disease. Moreover, the country’s charters address the need to reach neglected and marginalized groups. The steering committee on National Health Development has defined the desirable image of the Thai health system as follows:

A proactive health system that emphasizes health promotion of the people, in parallel with a satisfactory health insurance system, so that the people will have access to health care that is solicitous and of good quality when necessary; whereas all sectors of society at all levels have potential and participate in the creation and management of the health system according to the sufficiency economy philosophy, through learning and utilization of Thai and international wisdom in a well-informed manner, so as to make Thai society survive in a self-reliance and healthy manner in the global society that is interconnected and extensively influential to each other.

Similarly, the 10th National Health Development Plan focuses on “the mobilization of resources from the entire society for promoting health” and strives to advance health consciousness in all sectors of society.

These are not just words or declarations to the Thai Ministry of Public Health, as evidenced by the many remarkable successes of the Thai Public Health program. Family planning is one great example. Thailand is widely credited for proving that developing countries can attain replacement level fertility rapidly, and without coercion. Thailand officially launched its Population Policy in 1971, as a partnership between the government and an NGO called the Population and Community Development Association (PDA). Since the launch of the population policy, the Total Fertility Rate (TFR) in Thailand has declined from 6 in 1970 to replacement level today, use of contraceptives among married couples has increased from 15 to 70%, and the population growth rate has been cut by more than half. It took the United States 58 years to transition from a TFR of 6 to a TFR of 3.5. Thailand accomplished the same in just 12 years.

Thailand’s rapid success in achieving the Millennium Development Goals is another great example of the high efficiency and effectiveness of Thailand’s public health program. In September 2000, Thailand was among 189 countries that pledged support to the Millennium Development Goals (MDGs) that placed priority on human development and on narrowing development gaps among countries. By 2009, Thailand had achieved the majority of the MDGs well in advance of the global timeframe of 2015, and is currently making strides in new, ambitious targets that go well beyond the original development goals.

Thailand’s Health Care Infrastructure
Thailand’s public health system works so well in part because of its structure. The core agency in the Thai public health system is the Ministry of Public Health (MoPH). Comprised of the central administration in Bangkok and local provincial administrations, it is the principal organization responsible for the promotion, support, control and coordination of all physical and mental health activities, the provision of health services nationwide, and the overall well-being of Thai people.

For the last half-century, the ministry has gradually become more integrated, with health services largely expanded at the provincial level. Between 1977 and 1987, district primary hospitals and subdistrict primary health centers were established in each district and subdistrict nationwide. Since 2000, there has been a strong push towards a more decentralized health system, increasing the flexibility and power of provincial level health facilities. Currently, the structures of all MoPH agencies have been designed to cover all geographical areas at all levels and to provide curative, promotive, preventive and rehabilitative care in an integrated manner.

The central administration of the Ministry of Public Health in Bangkok is composed of ten agencies that oversee Public Health of the nation. Two of these— the Department of Medical Services (DOMS) and the Department of Health (DOH), described below, are integral for planning and maintaining the cervical cancer screening program in Thailand. The provincial administration, under the provincial governor, oversees the local health system in each province. Provincial health facilities include:

- **Provincial level hospitals** that provide mainly secondary (and minimal tertiary) care,
- **District level community hospitals** that provide primary and also limited secondary care,
- **Subdistrict level health centers** that provide primary care and
- **Village level health posts** that are often the closest primary care facilities for villagers. Each provincial hospital is headed by a provincial health director who is responsible for the staff and health services in his hospital. Each district hospital has a district medical director in charge, responsible for the staff and health services in his district hospital. Districts are divided into 5 to 10 subdistricts. These subdistricts each have one primary health center responsible for 5 to 10 villages. Every village has 10 to 20 health workers working at health posts serving between 100 and 200 dwellings (each dwelling is generally home to a large family). Every health center is staffed by community health officers (a health worker, a midwife and a technical nurse). There is one district health officer responsible for these smaller primary health centers.

The provincial health officer, working in the Provincial Public Health Office, oversees all the hospitals and health centers and is responsible for public health policy in his province. The Provincial Public Health Office in each province directly reports to the provincial governor.

Health insurance in Thailand comes in three forms and nearly 100% of Thai people are covered by at least one plan. The first type—Health Insurance for All—is free and governed by the National Health Security Office. All Thai people are automatically registered to this plan and are then excluded if they are additionally registered for either of the other two insurance plans. The second type—Civil Servant Medical Benefit Scheme—is governed by the Comptroller General’s Department of the Ministry of...
Finance and is provided to all government employees. The final coverage—Social Security Scheme and Workmen’s Compensation Scheme—is governed by the Social Security Office and is provided to people in employment sectors such as industries, private enterprises, NGOs and some selected government offices. This system ensures that all (or more realistically, nearly all) Thai citizens are covered by at least one type of health insurance.31

With an excellent healthcare infrastructure, a dedicated team of health personnel and a universal healthcare scheme, Thailand is a model for healthcare for poorer countries worldwide. As renowned OB-GYN Dr. Khunying Kobchitt Limpaphayom, Professor Emeritus at Chulalongkorn Medical School said, “if your health program cannot work in Thailand, it will not work anywhere in the developing world.”

**Thailand and Cervical Cancer**

Despite Thailand’s strong initiatives in disease prevention and health promotion and its exemplary progress in healthcare in the last decades, approximately 6,000 Thai women die from cervical cancer annually and the number is increasing36. Cervical cancer is the second most common cause of cancer incidence and mortality in Thai females1. By comparison, breast cancer has a higher incidence than cervical cancer (20.2% of female cancer versus 16.0% respectively), but has a lower mortality rate (12.7% versus 14.9% respectively). Liver cancer is the leading cause of female cancer death in Thailand, accounting for 19.4% of cancer death.1

The age-standardized cervical cancer incidence ratio in Thailand is very high, at 20.9 per 100,000 women-years*. The burden is unlikely to decrease without improved prevention strategies, as 40% of Thailand’s women are between 30-60 years, and 25% of the population is under the age of 15.36

With full knowledge of the potential for an increased cervical cancer burden in the years ahead, in 2005 the Department of Medical Service (DOMS) and the Thai National Cancer Institute (TNCI) intensified their strategy to decrease cervical cancer incidence in Thai women by attempting to expand coverage of the Pap smear as a screening test and implementing follow-up by colposcopy for abnormal results. This expansion strategy has been implemented in all 76 provinces of Thailand.37

The use of the Pap smear as a screening technology is not new; it has been used as a cervical cancer screening method in Thailand for 4 decades. Yet, as seen elsewhere in the developing world, the Pap smear has thus far proved too logistically challenging to have any substantial health impact in Thailand38. Thailand’s Pap smear implementation challenges are multifactorial. There have been reports of large-scale mismatches between slides and names of clients, long-term delays in delivering test results, and significant losses to follow-up. There is also a reported lack of public awareness and knowledge about cervical cancer, as well as a widespread negative perception of screening tests that involve genital organs.38 Finally, and perhaps most significantly, there is a lack of health care infrastructure for effective Pap smear implementation, even since the 2005 policy has been in effect. There are only about 150 cytoscreeners and 400 pathologists able to analyze Pap smear slides in Thailand37. To get 80% coverage of women between 30 and 60 years every year, as the DOMS policy
dictates, 12 million pap tests would have to be done annually. Even if coverage was reduced to 80% every 5 years, 2.4 million pap test slides would have to be read annually, well beyond the ability of the existing facilities and staff. Moreover, were it even possible to read all these slides, current incidence rates show that there would be approximately 24,000 abnormal Pap smear results needing colposcopy and further treatment each year. According to compliance statistics, 40% of these women who get abnormal results would not go to their follow-up colposcopic examination. With only 150 colposcopists (most in Bangkok), there would be little capacity to screen all abnormal women even with such a low follow-up rate. Evidently, a more feasible and financially sustainable approach is needed.

Fully aware of these challenges, common to the developing world, the international nonprofit Jhpiego, in collaboration with the Thai Ministry of Public Health, chose to pilot a “single-visit” cervical cancer prevention approach (combining VIA and cryotherapy) in Thailand. The target population was between 30 and 45 years of age. Roi-et Province—a Northeastern province with a population of approximately 1.2 million—was selected because it is mostly rural, its cervical cancer prevention services had not been successful there in the past, and its proximity to Khon Kaen province where a health facility—Khon Kaen University Medical Center, exists to adequately treat referral cases. In 2000, the single-visit approach was piloted to four districts within Roi Et Province, and soon expanded to the whole province. In just 6 years, Roi-et improved coverage from 4.7% in 2000 to the highest coverage in Thailand with over 60% screened.

Because the VIA/cryotherapy program is only 11 years old in Roi-et and much younger elsewhere in Thailand, there have been no studies as of yet looking at cervical cancer mortality as an outcome variable. However, Chumworathayi, Blumenthal et al. (2010) looked at the effect of introducing VIA and cryotherapy on cervical cancer incidence rates in Roi Et Province between 1997 and 2006, comparing rates with two nearby provinces. The study found an apparent increase in cervical cancer incidence rates in Roi Et as compared to the other two provinces in the same period of time. The authors attribute the increase in incidence to an increase in cervical cancer case detection rates due to the expansion of screening coverage. This assumption is consistent with the literature; a finding of increased incidence is fairly typical for a study that increases screening coverage. The authors predict that as screening with VIA/cryotherapy continues, the incidence of disease will eventually fall. They recommend that a follow-up study should be done in the next 5 years to determine if incidence and mortality from cervical cancer decreases in Roi Et due to the VIA/cryotherapy program, as expected.

Due to the successful increase in screening coverage in Roi-et, the Thai Nursing Council has, with the approval of the Thai Medical council, formally promoted the practice of VIA and cryotherapy by registered nurses. The VIA program falls under the jurisdiction of the Department of Health (DOH) within the central administration of the Ministry of Public Health. From 2002 to the present, the Ministry has implemented a dual-track cervical cancer screening program, which combines VIA (for those between 30-45 years and a visible SCJ) in conjunction with cryotherapy in a single visit and a
Pap smear policy (for the other groups of women)\textsuperscript{36}. The DOH finances VIA technology, while the DOMS finances Pap smears. It has taken a notoriously long time to scale-up the VIA and cryotherapy program to other provinces in Thailand\textsuperscript{38}. Currently, 16 provinces use the dual-tract system (VIA and Pap smear), while the rest remain exclusively Pap smear based. The current overall goal is to have >80% of women between 30 and 60 screened for cervical cancer at least every five years-- a formidable challenge.\textsuperscript{39}

**Why study careHPV safety, acceptability, and feasibility in Thailand?**

In this paper, I have described the major inequities in cervical cancer screening prevention in the developed and developing world, arguing that cytology-based programs are not well-suited for low-resource settings. I have detailed the different low-resource technologies that have been researched for use in the developing world, describing the large body of research that has elucidated the pros and cons of visual inspection and the newer research showing both clinical promise in careHPV and patient acceptability in a method that combines vaginal-swab careHPV with VIA.

Despite indications that the careHPV DNA test is clinically acceptable using the vaginal self-swab, and despite a potential community-based careHPV protocol through which this test can be implemented in low-resource settings, no studies have been published assessing the safety, acceptability, and feasibility of a patient-administered vaginal-swab followed by immediate visual confirmation and treatment, especially when the entire rubric takes place at the community level. Moreover, no one has assessed the technology in the way that it was first envisioned; as a point-of-care screening test that would be both portable and offer real-time results.

Thailand is the ideal location to assess the careHPV test in this manner. As described above, Thailand’s challenges in cervical cancer prevention are comparable to those of other developing nations despite Thailand’s excellent public health advances and relatively well-organized health infrastructure. Moreover, all but 16 provinces in the country still use exclusively cytology-based screening, and implementing the dual-track VIA/ cytology protocol has been notoriously slow to scale-up. The careHPV can be an cheap and effective way to scale up screening, by markedly reducing the number of women who would need individual examination with VIA or Pap smear, and by rapidly increasing the programmatic capacity for screening in a single day.

If the community-based careHPV protocol is not deemed safe, acceptable or feasible in a developing country’s health system as organized and successful as Thailand’s, it may need several modifications in order to be successful elsewhere in the developing world. If the protocol is, however, shown to be successful in this setting, it could dramatically help Thailand achieve its goal of screening > 80% of women between 30 and 60 for cervical cancer every five years. Moreover, it could stand as a promising model protocol for cervical cancer prevention throughout the developing world.
PART II: SAFETY, ACCEPTABILITY AND FEASIBILITY OF COMMUNITY-BASED CAREHPV PREVENTION IN RURAL THAILAND

I. BACKGROUND
Cervical cancer is an important public health problem among adult women in developing countries. While Pap smears have decreased the incidence of cervical cancer in the developed world by 80% by catching precancerous lesions early, such cytology-based cervical cancer-screening programs have largely failed in the developing country context. This is in part because of an impoverished health care infrastructure, too few trained and skilled professionals, uninformed women who get lost to follow-up and a lengthy turn-around time. These realities have resulted in the investigation of preventive approaches that use fewer resources and offer rapid results.

Among these approaches, visual inspection with acetic acid (VIA) has proven to be a promising candidate for screening in low-resource settings as it fulfills the basic criteria of a satisfactory screening test (accurate, reproducible, inexpensive, easy to perform and easy to follow-up, acceptable and safe) and has demonstrated effectiveness in reducing incidence of and mortality from cervical cancer. VIA works by a simple principle: when vinegar is applied to abnormal cervical tissue in the transformation zone near the squamo-columnar junction (SCJ), it temporarily turns white, allowing the provider to make an immediate assessment of a positive (abnormal) or negative (normal) result with the naked eye. Yet there are important disadvantages to VIA. VIA testing can be subjective, it does not yield a definitive ‘diagnosis.’ In addition, a long period (~2 weeks) of provider training (as well as periodic refresher retraining) is necessary to be able to perform VIA, reducing the cost-effectiveness of the approach.

As an alternative, HPV DNA testing has been seen as a potential programmatic enhancement to VIA in cervical cancer prevention protocols. The overarching drawback of HPV testing has been that the HPV DNA technology has been both too expensive for routine use in developing countries and has a lengthy turnaround time, precluding the retrieval of results in a single-visit. In an attempt to address these issues, the pharmaceutical company Qiagen, in partnership with the global health nonprofit Path, has developed the careHPV machine. The careHPV machine is an HPV DNA test that could cost less than US$5 per kit, could theoretically be administered with no refrigeration in a static or mobile clinic, and yields results (for batches of either 24, 48, or 96 samples) in approximately 2.5 hours. The careHPV test can detect 14 high-risk types of carcinogenic HPV. The swab can be performed by a health provider (cervical swab) or by the woman herself (vaginal self-swab).

The careHPV test has performed well in early research. Studies using cost modeling techniques have shown that the careHPV test is both potentially cost-effective and, if women receive three lifetime tests, more clinically effective than traditional cytology because of the linkage between testing and treatment through a reduced number of visits. Qiao et al., 2008 also published results from a clinical study conducted in rural...
China, which demonstrated that the careHPV test had a 90.0% and 81.4% clinical sensitivity for identifying moderate or severe cervical disease (CIN 2+) when using cervical swabs or self-swabs respectively. The study concluded that self-swab (vaginal) specimens could be an effective way to utilize the careHPV DNA test. A recent study from rural Mexico took vaginal-testing out of the laboratory and found that sampling at home with the vaginal swab was more sensitive than routine local cervical cytology, further enhancing the potential feasibility of careHPV.

Despite these promising results, the careHPV test has not yet been formally incorporated into a cervical cancer prevention program to date, and the best use of the careHPV test in prevention protocols is still under investigation. In an effort to contribute data to this ongoing question on the most effective way to incorporate careHPV technology into current cervical cancer prevention programs, Trope et al., 2009 conducted a study concerning stakeholder attitudes toward careHPV-focused screening programs in Roi-et Province, Thailand. The results indicated that, overall, participants supported a protocol in which women would be screened in their homes and villages using the self-swab version of the careHPV test. Only those who screened positive for HPV would be further triaged with VIA screening. In other words, participants envisioned the careHPV test as a potentially inexpensive tool to exclude a large majority of the population (i.e. those HPV negative) from needing further assessment, instead focusing resources on the relatively few women who had a positive careHPV result.

Despite experimental evidence that the careHPV DNA test is clinically acceptable using the vaginal self-swab, and despite an acceptable method by which this test can be implemented in low-resource settings, no studies have been published assessing the safety, acceptability, and feasibility of a patient-administered vaginal-swab followed by immediate visual confirmation and treatment, especially when administered at the community level. Moreover, the technology has not yet been assessed in the way that it was first envisioned; as a point-of-care screening test that would be both portable and offer real-time results.

II. OUR STUDY
From July to August 2011, we piloted an itinerant, point-of-care protocol in Roi-et Province, Thailand—a rural province in the Northeastern part of the country. Specifically, we spent 14 days over an unusually hot 3-week period testing the safety, acceptability and feasibility of this unique self-swab, community-based protocol. Our study team included a careHPV technician and three VIA providers. Only one of the three VIA providers participated on each study day.

\[b\]These results were using a 0.5 relative light unit (RLU) threshold for a positive test. Qiao et al. found that the sensitivity was 84% for cervical specimens and 73% for vaginal specimens when using a 1 RLU threshold, which is the threshold of the careHPV machine used in this study.
On each day of the study, we transported the careHPV unit to a different local community health center in the region. Women, who were often waiting for us to arrive at the health center, would first be briefed on the study and asked to give informed consent. The study was approved by the Institutional Review Boards of the University of California at Berkeley and the Thailand Ministry of Public Health. Women were included if they were between 25-60 years of age and had sexual intercourse in the past. Women were excluded if they had a history of cervical cancer, had a total hysterectomy, were currently pregnant, or had been screened for cervical cancer in the last 5 years. Women were compensated US$3 for their travel time to the study site, but received no other form of compensation for study participation.

Women were orally instructed as a group regarding how to perform the self-sample. They were also given written instructions. Women then took the self-samples to private areas (bathrooms, examination rooms etc.), collected specimens, and returned them to the technician. After returning their sample, women were instructed to return at a designated time for results, approximately 3 hours after they had submitted their sample. It is important to note that each day, several women would present for screening after the study briefing had been given to the larger group. We briefed these latecomers as they came in and gave them self-swab kits to collect specimens, which delayed the start-time for the machine. Also noteworthy was the fact that the program was undertaken in a rice-farming region. The majority of women would come in from the fields, swab themselves, submit the specimen and then go back to work while waiting for the results.

Once all the samples were returned, the technician would run the machine. Samples took approximately 3 hours to process, after which women returned for results. Those who were HPV negative were told to be screened again in 5 years. This is consistent with current Thai policy on negative screening results as well as the results of Sankaranarayanan et al.’s 2007 and Lancet papers, which looked at the effect of VIA- and HPV- based screening on cervical cancer incidence and mortality, respectively, in India. The women who were positive were offered VIA. VIA-positive women were referred to the hospital for cryotherapy. After receiving their results and VIA (if HPV-positive), women were given an exit survey to complete. Surveys were completed themselves, with the exception of illiterate women, who had the surveys read to them and filled out by study staff. The exit survey formed basis for acceptability and some feasibility indicators. Analysis of program throughput (times required to obtain specimens, run the tests and provide results) formed the basis for the remaining feasibility parameters. Safety was assessed through adverse event reports.

III. RESULTS
Overall, during this two-week period, we screened an average of 31 women per day, for a total of 431 women. In all, we went to 14 out of the 18 intended districts in Roi-et Province. However, on day 14, the careHPV unit stopped working (there was an error
message when it came time to give us results) and was not reparable for the last few days of the study.

**a. Safety of the Protocol**
There were no adverse events or problem visits.

**b. Acceptability of the careHPV-based protocol**

*Patient:*
Patients found the protocol to be overwhelmingly acceptable (Table 1). 90.5% would take a self-swab again (6.5% responded that they did not want to take the self-swab again, 3.0% did not respond), 95.5% would recommend the test to a friend (0.8% would not, 3.8% did not respond), and 87.5% preferred to screen for cervical cancer near home (3.0% prefer to screen in the hospital, 8.0% did not care either way and 1.5% did not respond). With respect to how a specimen was obtained, 71.3% preferred to screen for cervical cancer with a self-swab while 9.8% preferred the physician to administer the swab, (16.0% did not care either way and 3.0% did not respond). Finally, 79.0% thought that administering the self-swab was “easy” (2.3% thought it was difficult, 8.0% were neutral and 10.8% did not respond).

<table>
<thead>
<tr>
<th>Would You Take Self-Swab Again?</th>
<th>YES n= 362 (90.5%)*</th>
<th>NO n= 26 (6.5%)</th>
<th>x</th>
<th>NO RESPONSE n= 12 (3.0%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Would You Recommend the Test to a Friend?</td>
<td>YES n=382 (95.5%)</td>
<td>NO n=3 (0.8%)</td>
<td>x</td>
<td>NO RESPONSE n=15 (3.8%)</td>
</tr>
<tr>
<td>Would you Prefer to Screen Near Home or at the Hospital?</td>
<td>NEAR HOME n=350 (87.5%)</td>
<td>HOSPITAL n=12 (3.0%)</td>
<td>DO NOT CARE n=32 (8.0%)</td>
<td>NO RESPONSE n=6 (1.5%)</td>
</tr>
<tr>
<td>Would you Prefer to Screen with a Self-swab or a Clinician-swab?</td>
<td>SELF-SWAB n=285 (71.3%)</td>
<td>CLINICIAN-SWAB n=39 (9.8%)</td>
<td>DO NOT CARE n=64 (16.0%)</td>
<td>NO RESPONSE n=12 (3.0%)</td>
</tr>
<tr>
<td>How Easy or Difficult was it for you to Take the Swab Yourself (Scale of 1-5)?</td>
<td>EASY n=316 (79.0%)</td>
<td>NEUTRAL n=32 (8.0%)</td>
<td>DIFFICULT n=9 (2.3%)</td>
<td>NO RESPONSE n=43 (10.8%)</td>
</tr>
</tbody>
</table>

*denominator is 400 for all results

**Table 1. Summary of Patient Acceptability Results**

*Provider:*
There were three VIA providers who were part of the study staff. We administered an exit survey to these 3 providers at the end of the study. The nurses were of mixed opinion regarding the acceptability of the protocol. Their concerns included whether or not women were taking the self-swabs “correctly” and whether the machine was reliable in low-resource settings.

However, all three providers were enthusiastic about the potential coverage expansion that a self-swab-based screening program could provide.
c. Feasibility of the careHPV protocol

Training:
There were two training experiences in this project. First, the first author (LT) visited Qiagen’s offices in Gaithersburg, Maryland, USA to be trained on the careHPV machine with the goal of learning to run the assays herself, and to train the technician who would run the assays in Thailand. It took 4 days for LT to gain the necessary skills to assemble the unit when in Thailand and to feel competent to train the local technician.

Upon arriving in Thailand, LT then trained a local technician in Roi-et. The study technician assigned to the project was a nurse’s assistant with no previous pipetting, hybrid-capture, or PCR experience. She spoke limited English but understood English relatively well. She was highly motivated to run the machine successfully, and even brought the plates home to practice pipetting with water. Ultimately, the training of the local study technician took 2.5 days. The technician made no significant technical mistakes throughout the project period.

Patient Perspective:
From the women’s perspective, this screening protocol was remarkably feasible (Table 2). 99.8% of the eligible women agreed to be tested. Consistent with their desire to be screened locally, women required an average of 12.9 minutes to travel to the health center. Most women arrived by motorbike, car or walking.

The program took very little of a woman’s time. Prior to receiving a swab, group counseling took place during which women were briefed on the study objectives, the procedure was demonstrated, and women were informed of the risks and potential benefits. Women were free to come as early or as late as they wanted up until the point at which the run for that morning’s batch of tests was initiated. Thus, depending on when a given woman arrived for briefing and returned for results, it could take as little as 3.2 hours from arrival to the health center to receiving results (for women who were last to arrive to get samples, but first to arrive for results) or as long as 5.3 hours (for those who were first to arrive for samples but last to arrive for results). However, the total amount of time an HPV-negative woman would actually spend at the center as part of the program (i.e. not including the time she went home or back to work while the test was being run) was about 32 minutes from screening to HPV results. Similarly, the total amount of time an HPV-positive woman would spend at the center as part of the program was about 46 minutes from screening to VIA results.

Only 21 women did not return for same-day follow-up; 94.8% of the women obtained their results on the same day. Of the 21 that did not return on the same day 100% returned to the health center within one week to hear that they were HPV negative (none of the women who did not return same-day were positive).

Study Staff Perspective:
From the perspective of the project staff, the screening protocol was feasible overall, but had room for improvement (Table 2). From the time the project staff arrived at the health center to the time they left, a screening day took on average 5 hours, 32 minutes. This included:

- the time required to transport the equipment and unload the van
- setting up the equipment for the day’s screening
- providing instruction and screening kits to the women
- running the batch of tests
- providing results and organizing VIA for those who were HPV+
- dismantling the equipment and putting it back into the van for transport

Importantly, the size of the equipment and the need to transfer it safely required daily transport with a van. Adequate surface space was needed in the clinic as well as access to a reliable power supply.

**Success of mobile specimens**
We intended to compare the field-obtained, mobile results to results obtained with a static careHPV machine housed in the laboratory under stable, climate-controlled conditions. We did this for the first 131 samples and got 100% correspondence, but did not test the remaining samples because the careHPV machine became inoperable.

**Machine failure:**
As mentioned above, on Day 14 of testing, the careHPV machine gave us an “error” message and could no longer provide results, resulting in the cancellation of our visits to the last 4 study sites. Although a number of attempts were made to “resuscitate” the unit, it remained inoperable.

**IV. DISCUSSION**
This study, which is the first project reporting completely field-based, mobile use of the careHPV technology, aimed to assess the safety, acceptability and feasibility of field-based primary HPV testing in a low-resource setting.

In sum, we found no adverse events or problem visits. Both patients and providers found the protocol overwhelming acceptable, though providers were concerned about the reliability of the machine and whether or not women were retrieving the self-swabs correctly. Before the machine failure, the protocol was remarkably feasible. Training of the technician was expeditious and screening with the careHPV test was efficient and convenient for women and, importantly, could be completed in a single day. However, there was a 3-hour period of “downtime” for the providers, during which they had no responsibilities in terms of the protocol. Of course, the machine failure on day 14 put into question the reliability of such technology in comparable conditions.
Still, our results show that there were many strengths to this careHPV-based program, including:

- **Training was expeditious.** Unlike VIA training, training the technician took only 2.5 days. It is possible that such rapid training may not be replicable everywhere, but it does demonstrate that, given the right conditions and trainees, relatively little time is required for training.

- **Still a same-day visit approach.** Women were screened and received results in as little as 3.2 hours. VIA was provided immediately to those who were positive. Eligible VIA-positive women were referred for cryotherapy, but cryotherapy could even be added to the van and brought to each site in future protocols.

- **Potential for scale-up.** It would take approximately two days to get 31 women screened with just 1 VIA provider in a VIA-exclusive program. Moreover, in such a program, all the women would have to be positioned on an examination table, have a speculum inserted and submit to the VIA exam. Using careHPV only those that were HPV positive would require a gynecological exam. This protocol gave women results in as little as 3.2 hours. Moreover, the machine can test up to 90 women at once. Thus, a careHPV-based program could be much easier to scale-up than an exclusively VIA-based program.

- **Opportunity for additional services.** There was a 3-hour “hole” while the machine was running where VIA providers had nothing to do in terms of the program. This is a potential opportunity for the VIA providers to provide other health services (immunizations, Voluntary Counseling and Testing for HIV, family planning etc.).

- **Convenient for women.** Screening was essentially *brought to women* in their communities. Women only spent between 30-50 minutes of their total time with the program from screening to results. Given that cervical cancer rates tend to be high in more rural populations, being able to offer screening in a community-based settings is likely an important component of a successful program.

Challenges include:

- **“Buy-in” from Providers.** A possible problem with “buy-in” from providers is a sense that a self-swab may not be sufficient for accurate results. Programmatically oriented trainings will need to transmit to study staff the accuracy of the self-swab in achieving sufficient sensitivity to ensure confidence in the screening method by stakeholders.

- **Unlikely to use careHPV testing as only screening tool in prevention protocol.** One issue facing incorporation of HPV tests as a primary screening tool is that HPV tests have been shown to have relatively low specificity. Therefore, if treatment for precancerous lesions were based on HPV testing
alone, the result could lead to significant overtreatment, leading to both potential complications for women from unnecessary treatment and adding needless costs to the health care system. Furthermore, treatment for precancerous lesions, which is an integral part of any prevention program, must be preceded by an assessment of the cervix to determine whether a lesion too large for cryotherapy or a suspected cancer is present. In order to triage in this fashion it has been suggested that another screening approach, visual inspection with acetic acid (VIA), be used in concert with careHPV as a mechanism whereby patients with no visible lesions or lesions too large for immediate treatment or suspected cancer could be observed or referred for care, respectively. VIA has itself been shown to be useful for screening in low-resource settings, and has demonstrated effectiveness in reducing incidence of and mortality from cervical cancer\textsuperscript{3}. Theoretically, cervical cancer screening protocols in low-resource settings could combine the careHPV and VIA screening tests in order to optimize care.

- **Reduced sensitivity of self-swab approach.** This study did not assess test performance, but some studies have reported decreased sensitivity for detecting $\geq$ CIN 2 with the self-swab as compared to clinician-obtained specimens\textsuperscript{8, 9}. However, as discussed above, self-swab exams both increase acceptability by avoiding speculum exams for most women and have the potential for scaling-up screening coverage. These benefits would likely offset the decrease in sensitivity found in self-swab specimens.

- **Machine failure.** Though the cause for this machine-failure could not be determined in Thailand, the machine was returned to the US and carefully inspected. Qiagen ran several tests on the machine, which again functioned normally in the US setting. After reviewing all the components of the machine, the best estimate as to the cause of failure was that it could be related to current fluctuations in Thailand and the sensitivity of the various digital components to either changes in voltage or intermittent surges. In light of these experiences, we now recommend that, unless a specific issue can be identified, a Uninterrupted Currency/Power Supply (UPS) device should be used to prevent this from happening in similar settings and be included in the “package” of equipment required when careHPV is to be used in a setting of questionable power supplies. As mentioned above, during the week the machine failed, it was unusually hot in Roi-et. We therefore cannot rule out high temperature as potentially interfering with the machine’s function, though all reagents were retested in Maryland after the study termination and were successful in providing results. The team at Qiagen felt as though the high temperature hypothesis was less likely than the current fluctuation hypothesis. There is a possibility that the high temperature may have caused the power company to regulate power during this high-demand weather, leading to a “brown out” which would reduce voltage to all users on the grid. Perhaps such a reduction in voltage may have affected the sensitive digital components of the careHPV machine. Obviously, a machine that is designed for
low-resource settings needs to withstand the conditions in these settings. Hopefully, it appears we can solve the machine technical issues with a UPS, voltage regulator and/or surge protector.

Major next steps include testing the durability of the careHPV machine with the addition of a UPS device. In addition, more studies are needed to confirm that self-swab careHPV specimens are sufficiently sensitive to be used as a primary screening tool. The results of such studies should be presented to providers to ensure confidence in the screening method.

Overall, this assessment suggests that a cervical cancer prevention program based on self-swab HPV testing using an itinerant, mobile, community-based approach could be programmatically safe, acceptable, feasible, and effective in low-resource settings.
REFERENCES


6. WHO Programme on Cancer Control: Cervical Cancer Screening in Developing Countries: A Report of a WHO Consultation, 2002


