# ASSESSING THE CLINICAL VALIDITY AND COST-EFFECTIVENESS OF HUMAN PAPILLOMAVIRUS TESTING USING SELF-COLLECTED SPECIMENS FOR CERVICAL CANCER SCREENING IN KENYA

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## ABSTRACT

Jessica Yasmine Islam: Assessing the clinical validity and cost-effectiveness of human papillomavirus testing using self-collected specimens for cervical cancer screening in Kenya
(Under the direction of Jennifer S. Smith)

Invasive cervical cancer (ICC) is the leading cause of cancer-related deaths among women in sub-Saharan Africa (SSA). Through the implementation of organized cytology-based screening programs, high-income countries have reduced ICC incidence and mortality by 80%. However, challenges remain in screening program implementation and coverage in SSA due to relatively weak healthcare infrastructure, poorly equipped health facilities, and limited skilled healthcare providers. In Kenya, the estimated screening coverage is only 3.5% among women aged 25 - 64years, compared to the global coverage of 40%. To improve access and effectiveness of cervical cancer prevention programs in low-resource settings, screening methods that are cost-effective, simple to implement, and incorporate effective linkage to treatment are needed.

From 2013 to 2018, a total of 399 female sex workers participated in this cross-sectional study. Participants provided two self-collected specimens: one stored dry(sc-DRY) using a Viba brush (Rovers), and one stored wet (sc-WET) with Aptima media (Hologic) using an Evalyn brush (Rovers). Two physician-collected specimens for HPV mRNA testing (APTIMA) and conventional cytology were collected. We estimated test characteristics for each hr-HPV screening method using conventional cytology as the gold standard. We also examined participant preference for sc-DRY and sc-WET.

HR-HPV mRNA positivity was higher in sc-WET (36.8%) than sc-DRY samples (31.8%). Prevalence of ≥HSIL was 6.9% (n = 27). Sensitivity of hr-HPV mRNA testing for detecting ≥HSIL was similar in sc-WET (85%, 95% CI: 66-96), and sc-DRY specimens (78%, 95% CI: 58-91). Specificity was 65% (95% CI: 61-71) in sc-WET and 70%, (95% CI: 65-75) in sc-DRY specimens. Women preferred sc-DRY specimen collection (46%) compared to sc-WET (31%). However, more women preferred

physician-collection (64%) than self-collection (36%), which should be further evaluated. Sc-DRY specimens appeared to perform similarly to sc-WET for the detection of ≥HSIL.

To evaluate cost-effectiveness of cervical cancer screening delivery using self-collection, we assessed the outcomes, costs, and cost-effectiveness of four cervical cancer screening scenarios in Kenya, each using community health campaign (CHC) based HPV self-screening: (1) followed by VIA to assess appropriateness of cryotherapy ("HPV & Treat"), with standard linkage to treatment and (2) "HPV & Treat" with enhanced linkage to treatment; and (3) followed by VIA screening for triage to treatment ("HPV+VIA & Treat"), with standard linkage to treatment and (4) "HPV+VIA & Treat" with enhanced linkage to treatment.

Compared to "HPV+VIA & treat," we found that "HPV & Treat" led to better health outcomes, as measured in DALYs and was more cost-effective due to fewer missed cases of CIN2+ eligible for treatment. More specifically, we found that compared to no screening, HPV& Treat with enhanced linkage to treatment was the most cost-effective option at $5492.62 I$/DALY averted. Deterministic sensitivity analyses showed that the proportion of women successfully linked to treatment significantly impacted the cost-effectiveness of "HPV& treat" options. Future studies to assess programmatic costs from the perspective of the Kenyan Ministry of Health to inform national scale-up of CHCs are needed.

*To my ancestors who came before me, particularly the strong women who paved the way for my success.*

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## LIST OF ABBREVIATIONS

| | |
|---|---|
| ASCUS | Atypical squamous cells of unknown significance |
| CHC | Community-based health campaign |
| CIN | Cervical intraepithelial neoplasia |
| DALY | Disability-adjusted life year |
| DNA | Deoxyribonucleic acid |
| FSW | Female sex workers |
| LSIL | Low-grade squamous intraepithelial lesions |
| HSIL | High-grade squamous intraepithelial lesions |
| HPV | Human papillomavirus |
| HIV | Human immunodeficiency virus |
| ICC | Invasive cervical cancer |
| ICER | Incremental cost-effectiveness ratios |
| LMIC | Low- and middle-income countries |
| mRNA | Messenger ribonucleic acid |
| PCR | Polymerase chain reaction |
| SSA | Sub-Saharan Africa |
| SCJ | Squamous-columnar junction |
| STI | Sexually transmitted infections |
| VIA | Visual inspective with acetic acid |
| VILI | Visual inspective with Lugol's iodine |
| WHO | World Health Organization |

# CHAPTER 1. SPECIFIC AIMS

Specific Aim 1:

To compare the clinical validity of hr-HPV mRNA detection assays to detect high-grade cervical lesions or more severe (≥HSIL) as the clinical endpoint for self-collected vaginal specimens ("wet self" versus "dry self"), compared to hr-HPV mRNA detection of physician-collected cervical specimens; and to VIA.

Hypothesis: There will be similar clinical validity for CIN2+ detection of wet versus dry self-collected tests for ≥HSIL. HPV mRNA tests will have a higher clinical sensitivity than VIA and conventional cytology for ≥HSIL detection.

Each study participant provided self-collected cervical specimens ("wet self" and "dry self") and underwent pelvic speculum exam for physician-collection of HPV samples, VIA, and cytology. We will compare the prevalence of detected abnormal results of each screening test and assess agreement using kappa statistic. We calculated the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) to detect ≥HSIL for (i) self-collected dry HPV mRNA; (ii) self-collected wet HPV mRNA; (iii) physician-collected hr-HPV RNA; and (iv) VIA.

Specific Aim 2:

To assess the health impact and incremental cost-effectiveness of the following four screening strategies each using community health campaigns for self-collected HPV testing: (1) followed by VIA to assess appropriateness of cryotherapy ("HPV & Treat") with *standard* linkage to treatment; (2) "HPV & Treat" with *enhanced* linkage to treatment; (3) followed by VIA screening for triage ("HPV+VIA & Treat") with *standard* linkage to treatment; and (4) "HPV+VIA & Treat" followed by VIA screening for triage with *enhanced* linkage to treatment.

*Hypothesis:* Community-based HPV self-screening using the "HPV & Treat" strategy with enhanced linkage to treatment will lead to the most substantial reduction in disability-adjusted life years at the lowest cost, relative to the next less expensive or effective alternative.

We compared the screening strategies to the standard of care in Kenya, which is no screening due to low screening coverage. We modeled population health outcomes (disability-adjusted life years [DALYs]) for each relevant arm and used these estimates to calculate incremental cost-effectiveness ratios (ICERs), expressed in International dollars per DALY averted.

## CHAPTER 2. BACKGROUND AND SIGNIFICANCE

### Human Papillomavirus and Cervical Cancer

Persistent infection with high-risk human papillomavirus (hr-HPV) is the necessary cause of cervical cancer(1) and its precursor lesions (cervical intraepithelial neoplasia or CIN). Globally, HPV infection is the most common sexually transmitted infection. Based on a pooled meta-analysis of 194 studies conducted worldwide using polymerase chain reaction (PCR) for HPV detection among women with normal cervical cytology, the global prevalence of HPV is around 11-12%(2). There is considerable variation in HPV prevalence by global region: the highest prevalence of HPV was measured in sub-Saharan Africa (24%) and Eastern Europe (21%)(3). Particularly high prevalence of HPV was observed in Eastern Africa, where prevalence exceeds 30%.

The prevalence of HPV infection includes a mix of both incident and persistent infections that may have accumulated due to poor clearance among the population(4, 5). While the majority (90%) of new HPV infections at any age point regress or clear in 6-18 months(6), persistent infection of high-risk HPV (hr-HPV) types result in progression to high-grade CIN. High-grade CIN is characterized by abnormal cell growth on the surface of the cervix, or the epithelial tissue (intraepithelial), and is categorized into three stages: low-grade neoplasia or CIN1, high-grade neoplasia CIN2, and CIN3, which is also known as stage 0 cervical carcinoma in situ(7). The probability of clearance of HPV depends on the duration of infection, i.e., the longer the period of infection, the less likely the infection will clear(8). Established risk factors for persistent HPV infection include immunodeficiency and infection with high-risk HPV DNA-types (9).

Currently, more than 200 types of HPV have been identified, of which 40 can spread through direct sexual contact through vaginal, anal, and oral sex(10). Sexually transmitted HPV types are categorized as either low-risk HPV, which can lead to genital skin warts, or high-risk HPV, which can

cause cancer. The International Agency for Research on Cancer (IARC) first classified two types of HPV, HPV 16 and HPV 18, as cervical carcinogens or hr-HPV in 1995(11). Subsequently, IARC expanded the group of cervical carcinogens in 2005 to include the following 11 types: HPV 31, HPV 33, HPV 35, HPV 39, HPV 45, HPV 51, HPV 52, HPV 56, HPV 58, HPV 59 and HPV 66. Worldwide, HPV 16 and HPV 18 DNA types are the most common HPV-types identified in cervical cancer cases, with a combined prevalence of ~70%(12).

In sub-Saharan Africa (SSA), HPV prevalence among women with normal cytology varies by country and ranges from 3.2% to 47.9% with higher prevalence among HIV positive women (13). Similar to global estimates, the most common HPV type identified in invasive cervical cancer cases is HPV 16 and ranges from 38.5% to 81.8% prevalence among sub-Saharan African women (13). In Kenya, HPV prevalence among women with normal cytology attending a family planning clinic was 40.3%(14).

Cervical Cancer Screening

Globally, cervical cancer is the most widely screened cancer in both high- and middle-income countries(15). Successfully integrated population-based cervical cytology screening programs through regular Papanicolaou (Pap) smear testing have reduced cervical cancer incidence and mortality by 80% in developed countries in the past seven decades, including North America, Australia, and New Zealand (16). Early detection by screening is effective to prevent cervical cancer due to cancer's long preclinical detection phase consisting of slowly progressing precancerous or precursor lesions such as CIN2 and CIN3. The precursor lesions may progress to invasive cervical cancer over 1 to 4 decades(17). With quality assurance and trained providers, cervical cancer screening tests can identify women with high-grade lesions before the development of invasive cancer.

While the application of cervical cytology has led to dramatic decreases in cervical cancer incidence and mortality in developed countries, low- and middle-income countries (LMICs) have not seen similar success due to difficulty in establishing and maintaining effective cervical cytology programs. Cytology programs require developed healthcare infrastructure with significant resources, including

trained cytology technicians and cytopathologists. Consequently, unavailability of healthcare providers and low awareness and cost of available preventive services has led to low uptake of Pap smear screening, despite the availability of opportunistic screening(18). For example, in Kenya in 2001-2002, only 3.2% of women were estimated to have undergone cytology-based screening in the past three years (19), compared to 40% globally. Additionally, following a positive cytology test, women are required to follow-up for treatment, which requires resources and skilled personnel that are mostly lacking in developing countries. Further barriers to cytology-based screening programs include the need for referral to urban or distant health facilities for screening and treatment, and the long waiting times for cytology results(20).

In addition to logistical barriers of cytology-based screening programs, limitations in cytology testing exist. Pap smear interpretation is inconsistent across providers and cytopathologists(21, 22). The ASCUS-LSIL Triage Study (ALTS), a randomized control trial (RCT) conducted in the US on the management and interpretation of cytology test results found that quality control reviewer interpretation of low-grade squamous intraepithelial lesion (LSIL) concurred with the original interpretation in 68% of cases, and in 47% of high-grade squamous intraepithelial lesion (HSIL) cases(22). Additionally, Pap smears have low sensitivity for detecting CIN 2+(range 20-35%), i.e., Pap smears frequently miss cases of CIN2+(23).

To meet the needs of developing countries, direct naked-eye visualization of the cervix after application of acetic acid or Lugol's Iodine, also known as VIA or VILI respectively, has been widely used and evaluated as a screening strategy in a low resource setting. This test requires few resources and is simple to implement. VIA provides immediate results and can be used towards the successful implementation of the "see and treat" strategy recommended for low-resource settings by the World Health Organization (WHO). The single-visit "see and treat" strategy leads to immediate treatment with cryotherapy or thermocoagulation LEEP to women who have screened positive without clinical evidence of cancer. Visual inspection methods are more sensitive but less specific than Pap smears(24, 25). A randomized controlled trial conducted in India demonstrated that VIA is an effective method to prevent

cervical cancer-related morbidity and mortality in LMICs(26), however, there is wide variability in the literature of reported sensitivity and specificity of visual inspection methods(25, 27-29). The low specificity of visual inspection methods may lead to overtreatment, which is of significant concern in resource-limited settings due to constrained treatment availability and resource allocation(29).

The latest development in cervical cancer screening has been the advent of molecular testing for HPV DNA detection. Molecular HPV testing provides an objective and highly reproducible test result(30). Advantages of hr-HPV testing as a primary screening tool include, it can be tested by high through-put laboratory processing with built-in quality control measures, can be used to triage women at higher risk for developing cervical cancer, and provides a dichotomous, easy to interpret result for providers(31, 32). Moreover, the clinical sensitivity of hr-HPV testing for the detection of CIN2+ is about 90-95%, which is higher than conventional cytology and may lead to earlier diagnosis and lower incidence of high-grade cervical neoplasia(33-35). However, hr-HPV DNA has a lower specificity (30.6%) (36) than cytology tests (60-95%) (37) for the detection of high-grade cervical neoplasia as the majority of HPV infections are transient and will not lead to high-grade lesions. The low specificity of hr-HPV for the detection of high-grade lesions may lead to unnecessary follow-up, psychosocial distress, and overtreatment(36, 38-41). Alternative screening methods to alleviate the concerns of overtreatment and higher test specificity to avoid unnecessary referral or treatment are necessary for optimal programming in resource-limited settings.

High-risk HPV mRNA

An alternative to HPV DNA testing is to test for hr-HPV mRNA (messenger RNA or mRNA) for the detection of HPV. HPV infection occurs in the epithelium and specifically targets keratinocytes. The virus cannot replicate on its own and relies heavily on the cellular division and stratification of the epithelium starting from the basal layer upwards towards the suprabasal layers(42). The HPV uses the cellular division process to replicate and produce new viruses allowing for viral genome amplification to occur. The E6 and E7 oncoproteins play crucial roles in this process and enable the virus to maintain cell

proliferation targeting diverse cellular pathways involved in the cell cycle. During this process, while the HPV infection may be transient, there is low expression of E6/E7 to maintain viral replication(43). Through persistent infection of HPV, the viral DNA becomes randomly integrated into the host genome. Once the virus has integrated, the expression of E6 and E7 oncoproteins become deregulated, leading to cell immortalization and the promotion of irregular cell growth by inactivating the tumor suppressor protein p53 protein(42). Overexpression of E6 and E7 are strictly required for the development of cervical cancer. As such, testing for HPV mRNA may improve specificity for high-grade lesions detection compared with HPV DNA as it may be able to distinguish between transient and persistent HPV infections or those that may progress to invasive disease(43).

Currently, there are two commercial assays available to detect E6/E7 mRNA: PreTect® (BioMerieux) and APTIMA® (GenProbe). These two assays detect different sets of hr-HPV; PreTect can only detect 5 types, including HPV 16, 18, 31, 33, and 45, while APTIMA® can detect 14 types of hr-HPV (HPV 16, 18, 31, 33, 39, 45, 41, 52, 56, 58, 69, 66, 68). Several studies to assess the detection and role of HPV mRNA in cervical neoplasia development have been conducted(44-48). These studies suggest that mRNA assays and testing methods could be a more powerful screening tool than HPV DNA testing for prediction of the risk of progression of CIN2+ to invasive disease due to its high specificity. In a meta-analysis conducted to summarize studies conducted to evaluate HPV mRNA against HPV DNA testing for detection of CIN2+, sensitivity of HPV mRNA testing for CIN2+ detection depended on the assay used; for the PreTect assay, sensitivity ranged from 0.41 to 0.86, but was higher for APTIMA and ranged from 0.90 to 0.95(43). Specificity also varied based on the assay used and ranged from 0.63 to 0.97 and from 0.42 to 0.61 when the PreTect or the APTIMA assay were used, respectively. Variability in assay performance may be attributable to types of hr-HPV detected. Due to the high degree of heterogeneity across studies included in the review, the authors were unable to pool the data and concluded that mRNA tests have diagnostic relevance, but additional studies are needed to make conclusions on the clinical utility of HPV mRNA testing.

Few studies to compare self- to physician-collected sampling of HPV mRNA testing have been conducted (49-55) (Table 2.1), although several have been done to assess self-collected samples for HPV DNA detection(56). Studies to evaluate HPV mRNA testing through self-collection vary widely in outcome used as the gold standard to calculate sensitivity and specificity of mRNA testing methods.

Self-Collection for Cervical Cancer Screening

A significant benefit of HPV molecular testing is that self-collected specimens can be used to test for the presence of HPV. Studies that have evaluated the validity of HPV DNA tests to detect high-grade cervical disease have shown that the sensitivity of self-collected samples for CIN2+ detection is high [76% (95% CI: 69-82)], but lower than provider-collected [91% (95% CI: 87-94)] samples (Table 2.1) (57-61). Using self-collected methods for hr-HPV detection has been suggested as one way to increase cervical cancer screening coverage in low-resource settings(31). Self-sampling may remove known barriers to clinic-based testing such as cost, fear of speculum examination conducted by a health provider, cultural and religious barriers, and feelings of embarrassment and inconvenience. (62), In Kenya, perceived barriers of cervical cancer screening among health care providers include staffing shortages, lack of adequately trained staff, female patient discomfort with male providers, wait time of patients, and patient's fear of pain caused by the speculum exam(63). Additionally, self-sampling for HPV testing is highly acceptable among women and patients frequently report preference for self-collection over physician-collection due to factors such as ease and privacy(64).

Dry versus Wet HPV DNA Collection

Numerous studies have been conducted with a diversity of individual self-sampling devices; however, little attention has been given to the direct comparison of different self-sampling devices. There are a wide variety of self-collection methods available such as swabs, brushes, tampons, pads and cervicovaginal lavages. The majority of devices used to self-collect cervical or vaginal samples for HPV

detection are placed in a liquid transport medium at the time of collection. Impractical and higher cost aspects of liquid transport may hinder the widespread use of self-collection methods; mainly as self-collection methods are particularly useful for hard-to-reach women to alleviate costs associated with screening. A dry swab, without the need for liquid transport medium, could potentially offer advantages in terms of collection, cost, and shipment. Additionally, dry storage of self-collected samples could reduce the potential for spillage and leakage during collection and transit of samples stored in liquid transport solutions.

Prior studies have evaluated the use and feasibility of dry transport of vaginal or cervical samples for STD testing, and these demonstrated good agreement between dry and wet collection and transportation methods for detecting sexually transmitted infections, including *Neisseria gonorrhea* and *Chlamydia trachomatis(65).* Shipped samples have the potential for loss of HPV DNA through degradation(66, 67), and degradation may occur more frequently in samples transported in a dry state (Feng 2010). Prior studies conducted to assess self-collected dry vs. wet stored samples of HPV DNA have been conducted(68-80) (Table 2.2). These studies have generally identified good agreement based on kappa statistics between the two dry and wet stored samples. These results indicate that dry storage and transport of HPV DNA samples is a feasible option. However, prior studies have not evaluated or compared dry storage of HPV mRNA samples to wet self-collected samples. HPV mRNA is less stable than HPV DNA, and the potential for degradation is higher(81). As such, for implementation of HPV mRNA testing suitable for low-resource settings, evaluation of dry versus wet HPV mRNA self-collected samples is crucial.

Cost-Effectiveness of Cervical Cancer Screening in Low- Resource Settings

To optimize cervical cancer screening delivery, cost-effectiveness analyses are needed to provide a systematic approach to evaluate potential alternatives while considering both cost and health outcomes associated with each evaluated strategy. In light of inadequate screening coverage and unavailability of adequate screening services globally, studies to assess the cost-effectiveness of different cervical cancer

screening methods in low- and middle-income countries have been conducted(82). Cervical cancer screening technologies that have been evaluated include cytology, VIA, provider-collected HPV DNA testing and self-collected HPV DNA testing(82). A recent systematic review of cervical cancer screening in LMICs found that cytology is the least efficient screening method to implement in low-resource countries, as it was dominated by HPV testing or VIA in nine of the thirteen studies that evaluated cytology(82). However, self-collection for HPV DNA testing was found to be the most cost-effective when it yielded high population coverage over other screening methods (83). High-population coverage of HPV self-screening methods is key to achieving successful cervical cancer prevention programs in LMICs.

Community health campaigns (CHCs) are a viable strategy to deliver preventive services in LMICs. CHCs occur over a short duration and can provide preventive services to a high volume of people leading to high-population coverage. When repeated intermittently, CHCs have been successfully utilized to improve uptake of several preventive health services including, malaria prevention(83), hypertension and diabetes prevention(84), mental health services(85), and tuberculosis screening(86). Community-based approaches to cervical cancer screening have been found to improve cancer screening coverage, particularly among those groups known as “hard-to-reach” populations. When cervical cancer screening options are limited to clinic-based screening, low screening coverage is mainly attributable to the high proportion of women who do not visit government clinics due to reasons such as time, cost, travel barriers, and cultural factors(87). Effective community-based interventions are sustainable and can overcome known barriers to screening when tailored to the needs of the target population(88). Periodic, short-term community-based approaches to screening, mainly using self-collection screening methods, can alleviate barriers identified in Kenya, including the need for an initial pelvic exam and discomfort of patients with providers. In fact, a pilot conducted in Kenya of a community-based approach to cervical cancer screening found that the campaign had high-attendance, a high screening uptake (>95%), and was accepted by providers(89).

A crucial aspect of successful community-based cervical cancer screening is to assure that appropriate follow-up is available to women who screen-positive with successful linkage to treatment. Additionally, an advantage of community-based screening versus a clinic-based screening model is that only women who screen-positive for HPV will need to access treatment for follow-up which reduces the burden on the health care facilities and optimizes resource allocation for treatment of cervical cancer neoplasia. Although not previously tested in cervical cancer screening strategies, alternative methods to enhance linkage to treatment and improved follow-up have been evaluated in other reproductive health campaigns in Kenya such as text messaging, vouchers, and mobile treatment units(90-92). Assessing the effectiveness and associated costs of community-approved strategies to link HPV-positive screened women to treatment will be vital in identifying a cost-effective cervical cancer screening strategy.

Limited studies have evaluated the cost-effectiveness of community-based cervical cancer screening, and none have been conducted in Kenya. In Uganda, a cost-effectiveness analysis to assess home-based HPV self-collection in comparison to VIA found that HPV self-collection screening followed by immediate treatment (screen-and-treat strategy) was the most cost-effective cervical cancer screening strategy. Home-based HPV self-collected reduced the lifetime absolute risk of cervical cancer from 4.2% to 3.5% with an ICER of $130 per year of life saved when performed once per lifetime(93).

**Table 2.1:** Summary of Studies Conducted to Evaluate HPV mRNA detection in self- versus physician-collected samples using various disease endpoints

| | | | | | | | Self-Collection | | Physician-Collection | |
|---|---|---|---|---|---|---|---|---|---|---|
| Author (year) | Country | N | Median/ Mean Age | Population | Outcome/ Gold standard | Sample Device | Sensitivity | Specificity | Sensitivity | Specificity |
| Asciutto (2018) | Sweden | 209 | 30 (20-68) | Women attending colposcopy clinic | ≥HSIL | Swab | 86% (75-93) | 48% (38-58) | 100% (95-100) | 49% (39-59) |
| Adamson (2015) | South Africa | 325 | 42 (35-48) | HIV positive women at colposcopy clinic | Clinician-sampled HPV mRNA | Tampon | 77% (69-85) | 78% (72-84) | - | - |
| Chernesky (2014) | Canada | 30 | 39 | Women attending colposcopy clinic | CIN 2+ | Brush | 87% (70-95) | 60% (56-64) | 80% (63-91) | 68% (64-72) |
| Nieves (2013) | Mexico | 2049 | 39 (30-50) | Population-based | ≥CIN 3 | Brush | 63% (35-85) | 93% (92-94) | 100% (78-100) | 94% (92-95) |
| Ting (2013) | Kenya | 344 | 28 (18-49) | Female sex workers, high-risk | ≥HSIL | Brush | 79% (55-95) | 75% (70-79) | 86% (62-98) | 73% (68-79) |

**Table 2.2:** Comparison of sensitivity and specificity of high-risk HPV DNA testing of wet versus dry collected specimens

| Reference | Country | N | Mean/Median Age | Test Type | Collection Device | Outcome/Gold Standard Used | Sensitivity | Specificity |
|---|---|---|---|---|---|---|---|---|
| Haguenoer (2014) | France | 722 | 30-65 | Dry-Self collection | Swab | Physician-collected | 89% (83-93) | 93% (90-95) |
| | | | | Wet-Self Collection | Swab | | 87% (81-92) | 91% (88-93) |
| | | | | Wet-physician Collection | Brush | | | |
| Catarino (2015) | Geneva | 130 | 42 (34-50) | Dry-self collection | FTA cartridge | ≥LSIL | 64% (45-78) | 39% (30-49) |
| | | | | Dry-self collection | Swab | | 85% (67-94) | 28% (20-38) |
| | | | | Wet-physician collected | Swab | | 77% (58-89) | 38% (29-48) |
| Darlin (2013) | Sweden | 121 | 34 (18-65) | Dry Self-collected | Swab | ≥HSIL | 81% (67-95) | 49% (37-60) |
| | | | | Physician-collected | Brush | | 90% (80-100) | 53% (42-65) |
| Jentschke (2016) | Germany | 136 | 36 (17-78) | Dry-self collection | Brush | CIN2+ | 90% (81-98) | 67% (57-77) |
| | | | | Dry-self collection | Qvintip | | 84% (73-84) | 69% (59-79) |
| | | | | Physician-collection | Broom | | 90% (81-98) | 64% (54-74) |
| van Baars (2012) | Netherlands | 134 | 40 (21-66) | Dry-self collection | Brush | CIN 2+ | 81.50% | 54.20% |
| | | | | Physician-collected | Brush | | 88.90% | 55.10% |
| Khan (2014) | London | 495 | 20-69 | Dry-Self collection | Tampon | CIN2+ | 76% (65-85) | 61% (56-66) |
| | | | | Wet-physician collection | Brush | | 92% (83-97) | 46% (41-51) |

## CHAPTER 3. METHODS

Specific Aim 1

Study Population and Sample Collection Procedures

The Mombasa Cohort is an open cohort study of female sex workers (FSWs) in Mombasa, Kenya, and approved by the Kenyatta National Hospital-University of Nairobi Ethics Review Committee (94, 95). Participants of The Mombasa Cohort were recruited between February 1993 and December 2012. Procedures for recruitment remained consistent throughout the enrollment period. Outreach meetings were conducted at bars around the Mombasa District one to two times each month. Additional meetings were coordinated through peer leaders who helped to identify venues and notify colleagues of sessions. During these informational sessions, outreach staff provided a talk on a health topic requested by the women of the community. Interested women were given a referral card and asked to visit the clinic site, located in the Ganjoni Municipal Communicable Disease Control Center. The Ganjoni Clinic has been a primary venue for FSW sexually transmitted infection (STI) testing and treatment in Mombasa for over 25 years. The criterion for inclusion into the cohort included: 1. Women over the age of 18 years; 2. Residing in the Mombasa area; 3. Self-identifying as exchanging sex for payment in cash or in-kind and 4. Able to provide informed consent.

For this specific study, eligible women were invited to participate at the visit when they were scheduled to have specimen collection for *Trichomonas vaginalis, chlamydia trachomatis,* and *Neisseria gonorrhea* nucleic acid amplification testing (NAAT), based on their study timeline and enrollment date. Specimen collection for STI testing occurred periodically every three months. As such, enrollment into this validation study started in 2012 and ended in 2018. At this visit, they were provided with appropriate counseling on cervical cancer screening, which included information on potential risks and benefits, specific screening procedures they will undergo (experimental and non-experimental), risk and benefits

associated with these diagnosis procedures, options for treatment of confirmed high-grade pre-cancerous lesions or more severe, as well as the risks and benefits of early treatment. Interested women were asked to provide written informed consent, and their comprehension was assessed using a comprehension checklist. For this cross-sectional ancillary study, procedures were integrated into ongoing follow-up procedures for the Mombasa cohort, including the collection of standardized interview data (demographic, medical, obstetrical, sexual risk behavior), physical examination including a pelvic speculum examination, and laboratory diagnosis of STIs including HIV-1. We utilized convenience sampling to recruit 400 women over the age of 18 years. The exclusion criteria for this study included: 1. Women under the age of 18 years; 2. were currently pregnant; 3. Currently menstruating; 3. Have a previous history of hysterectomy or cervical conization; and 4. Women who have previously enrolled in a cervical cancer screening study.

Specimen Collection for Self-Collected HPV mRNA Samples

After providing written consent, participants were directed to a private area where they self-collected genital specimens using provided cytobrushes. Genital specimen self-collection was performed according to verbal instructions complemented with pictorial illustrations. Generally, participants were required to squat and insert the cytobrush as far up into the vaginal vault as possible, rotating it 3-5 times then withdrawing. One cytobrush (Evalyn® brush) was placed whole in its provided carrier for dry-storage to be tested for hr-HPV mRNA ("dry test"). The participants removed the tip of the second cytobrush (Rovers® Viba brush) and placed it into a plastic cryovial containing 1 ml of APTIMA GenProbe® liquid transport media tested for hr-HPV mRNA ("wet test"). After self-collection, participants detached the brush head of the cytobrush and deposited into the cryovial containing the APTIMA media. The APTIMA media is called PreservCyt™ Solution and is a methanol-based buffered preservative solution composed of methanol and water. The first 200 women were asked to perform self-collection using the Evalyn® brush first followed by the Rovers® Viba brush. The next 200 women performed self-collection using the Rovers® Viba brush first followed by the Evalyn® brush. The

participants then returned the dry cytobrushes in their carriers and the vial with the tip of the Viba cytobrush to a study nurse who affixed labels with the participant's unique identification number.

### Specimen Collection for Physician-Collected HPV mRNA Samples

Participants then continued with regular Mombasa Cohort procedures, including a pelvic speculum examination with collection of vaginal and cervical specimens for diagnosis of STIs by study physicians. All clinicians in this study were trained and experienced in genital examination and specimen collection. After collection of genital samples per protocol for the Mombasa Cohort, the study physician collected a cervical specimen using a third cytobrush (GenProbe® brush). Sample collection was performed by inserting it into the cervical canal and rotating 3-5 times, withdrawing, and then rotating around the full circumference of the transformation zone. Unlike self-collected samples, clinician specimens were collected from the endocervix. The tip of this cytobrush was removed and also placed in a plastic vial containing PreservCyt™ Solution liquid transport media. The Evalyn® brushes were transported at room temperature to the research laboratory for hr-HPV mRNA testing. The tips of the other two cytobrushes (Rovers® Viba and GenProbe® brushes) were transported in liquid transport media to the research laboratory similarly for HPV mRNA testing. All specimens were archived and collected for external quality assurance (EQC) purposes as well as potential future testing.

### Visual Inspection with Acetic Acid (VIA)

The study physician performed VIA on eligible participants. Participants were eligible for this procedure if the study physician was able to visualize a well-demarcated transformation zone and no part of the squamous-columnar junction (SCJ) within the cervical canal. If there was some bleeding due to the previous specimen collections, the study physician swabbed this away and waited for bleeding to stop before performing VIA. VIA was performed by blotting the cervix with a cotton-tipped swab soaked in dilute 3-5% acetic acid and inspecting after one minute. VIA was considered positive if inspection of the

cervical epithelium on the transformation zone after a minute revealed raised, thickened and well-delineated areas of whitening.

### Specimen Collection for Cytology Assessment

Cytology assessment was performed using a Pap smear that was prepared using a wooden Ayre's spatula rotated firmly around the full circumference of the transformation zone then lightly and evenly smeared across the surface of a glass slide labeled with the participant's unique identification number and date of collection. An additional specimen was collected using an endocervical brush inserted about 2cm into the cervical canal, rotated 180º, and pulled straight out to ensure adequate sample collection from the cervix. The additional specimen was then smeared onto the same, labeled glass slide. Smears were immediately fixed using a commercial alcohol fixative provided in the collection kit and sent to the University of Nairobi, Nairobi, Kenya.

### Laboratory Procedures and HPV Testing

Trained technologists at the research laboratory at Coast Provincial General Hospital (CPGH) carried out hr-HPV mRNA testing. Laboratory personnel was blinded to the results of the other screening tests. Self-sampled and physician-sampled genital specimens were tested for hr-HPV mRNA using the GenProbe APTIMA HPV Assay® which detects mRNA encoding the E6/E7 proteins from 14 high-risk HPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68). Specimen processing comprises three main steps: Target capture, target amplification by Transcription-Mediated Amplification (TMA), and amplicon detection by the Hybridization Protection Assay (HPA).

Briefly, cell specimens in the assay solution are lysed, releasing mRNA. The target HPV mRNA was captured by an oligonucleotide, which contains sequences complementary to specific regions of the target HPV mRNA. The captured oligonucleotide-target complex then hybridized with another oligonucleotide, which was attached to magnetic particles, resulting in a micro-particle containing the captured target HPV mRNA bound to it. This micro-particle was pulled to the side of the tube by magnets

and washed. The target HPV mRNA was then amplified by TMA. With the use of complementary probes with chemiluminescent labels, HPA detected the resulting amplicon. The light emitted from RNA-DNA hybrids was measured by a luminometer and reported as Relative Light Units (RLU). This process was automated on GenProbe's Panther® platform, per the manufacturer's instructions.

Statistical Methods and Analytic Approach

The primary analyses of this Aim entailed the direct comparison of self-collected wet- versus dry-HPV mRNA testing for the detection of high-grade squamous intraepithelial lesions (HSIL) and above. We calculated the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) to detect HSIL or above for (i) self-collected dry HPV mRNA and (ii)self-collected wet HPV mRNA. We calculated differences in sensitivity and specificity between HPV testing types using Wald-like confidence intervals(96). We evaluated preferences for HPV testing collection devices stratified by age and HIV status. We presented demographic variables of participants and prevalence of HPV by screening method stratified by HIV status.

Specific Aim 2

We estimated the incremental cost-effectiveness of the following strategies each using CHCs based HPV self-screening: (1) followed by VIA to assess appropriateness of cryotherapy ("HPV & Treat") with *standard* linkage to treatment, and (2) "HPV & Treat" with *enhanced* linkage to treatment; and (3) followed by VIA screening for triage to treatment ("HPV+VIA & Treat") with *standard* linkage to treatment; and (4) "HPV+VIA & Treat" with *enhanced* linkage to treatment.

We developed a decision tree to estimate the impact of HPV screening and linkage to treatment in a hypothetical cohort of 1000 women aged 25-65 years of age in Migori County, in Kenya. The model explicitly portrays the paths from disease status, HPV infection, detection of HPV infection, the risks of clinical progression and disease characteristics, and outcomes with and without treatment. Base case values for the model were taken from the literature and include local epidemiology of HPV prevalence

and cervical cancer, the clinical course of HPV and cervical cancer, and the effectiveness of treatment with cryotherapy or LEEP. Programmatic assumptions were based on the delivery model, screening uptake, and treatment uptake of a clustered-randomized control trial conducted in Migori County, Kenya described below. We used cost data collected from the micro-costing analysis of screening and treatment associated costs measured through a clustered randomized control trial (RCT). Finally, we calculated incremental cost-effectiveness ratios defined as the cost (discounted per women cost) divided by the health benefit (discounted DALYs or disability-adjusted life years) of a screening strategy compared with the next most costly screening strategy, after eliminating strategies that were dominated (defined as either more costly or less effective).

Study Design Overview

Data for this cost-effectiveness analysis were collected from a 2-phase cluster-randomized trial in 12 communities in western Kenya to evaluate an implementation strategy for a cervical cancer prevention protocol consistent with recommendations by the WHO and the Kenya Ministry of Health. Between January and November 2016, phase 1 of a cluster-randomized trial was carried out in 12 communities in Migori County, Kenya, to compare cervical cancer screening delivery strategies for hr-HPV testing offered using self-collected samples among women aged 25–65 years in CHCs versus government health facilities. Nyanza province is a low socioeconomic status area where about two-thirds of the population live in less than $1 per day and has the highest prevalence of HIV in Kenya at about 15%(97). The study target population were residents of included rural communities, women aged 25-65 years with an intact cervix and uterus. For this trial, a community was defined as follows: clusters of villages or sublocations within a defined administrative boundary with a total population between 5000 to 9500.

Before the RCT was started, potential communities for inclusion were defined through a variety of strategies. Study communities were characterized using a combination of census data, health facility information, mapping, and prospective demographic data. To be eligible for this trial, communities had to have the following characteristics: (1) At least two government health facilities with capacity to provide

HPV testing; (2) Support from community leaders for the community outreach and community health campaigns; (3) Accessibility to health centers through a maintained transportation route; and (4) Sufficient distance from other potential study sites to limit contamination between arms. Communities were excluded if: (1) community was located in an urban area and (2) communities participating in a cluster-randomized trial of HIV testing through community-health campaigns.

Communities of approximately 5000 to 9500 people in Migori which fit the above criteria were identified. Community size was estimated in two ways: (1) using 2009 Kenyan census data, including population growth estimates for 2015; and (2) population catchment areas as defined by the local health facilities assigned to cover these communities. The size of the target population of 25-65 years in each community was estimated in two ways: (1) a proportion of the estimated total population calculated using demographic data from an ongoing cluster-randomized trial; and (2) direct estimates of the number of eligible women by community health volunteers (CHVs) assigned to the health facilities in the study communities. Direct estimates of the number of eligible women were based on door-to-door enumeration completed by a prior large-scale community randomized trial in western Kenya(98). Final communities were randomized to either intervention using 1:1 allocation sequence generated by Stata/11 MP.

## Study Procedures

### Phase 1

The overall objective of Phase 1 of this trial was to assess the efficacy of clinic-based versus community-based HPV testing by comparing outcomes from communities randomized to clinic-based screening (control) to communities randomized to community-based screening using HPV testing (intervention) (Figure 1). During phase 1 of this trial, six communities were randomly assigned to community-based screening using HPV self-collected testing through a community health campaign. Community health-campaigns followed a 6-week timeline which consisted of outreach and mobilization (2-weeks), screening implementation in communities (2-weeks), and notification and standard referral to treatment (2-weeks). Before the community health campaign, a team of mobilizers from the community

met with community leaders and used posters, leaflets, and radio advertising to describe the dates and activities of the community health campaigns to encourage participation. The CHC moved from multiple sites over the two weeks, with approximately four days at each location, to reach the entire community. Health workers provided additional instructions about self-collection and collected a mobile number before dispensing the HPV kit. Women who did not have a mobile number were given instructions to go to the health facility closest to their homes to obtain their HPV results. Standard referral to treatment strategies included home visits, text messages, and phone calls. Women went to a private room in the CHC tent to self-collect the specimen and returned the collection kit to a health worker before leaving. A prior costing analysis conducted using Phase 1 data from this trial found the cost per woman screened through clinic-based screening was higher than that of CHC-based screening(97) and was therefore not in the scope of this dissertation.

All women who tested positive for hr-HPV DNA were referred for treatment with cryotherapy. Pretreatment pelvic exam and VIA were conducted to determine whether a woman was eligible for cryo based on lesion appearance and lesion size. Women who had lesions too large, abnormal cervical anatomy, or any suspicion of invasive cervical disease were offered LEEP.

Phase 2

The objective phase 2 of this trial was to assess the efficacy of standard referral to treatment compared to the community-driven enhanced linkage strategy. Community-health campaigns with enhanced linkage to treatment were carried out in an additional six communities. Recruitment and enrollment for Phase 2 took place before undergoing cervical cancer screening at the community health campaigns. Study activities in the enhanced intervention communities paralleled the activities described in Phase 1, with a few modifications. All six communities offered community-based HPV testing with the enhanced linkage strategy developed in partnership with the community. Community-based screening with enhanced linkage to treatment strategies included reminder text messages with updated messaging only sent to women who did not appear for their recommended treatment within three months after

receiving their positive test results and holding community health campaigns in locations within proximity to clinics where treatment is available (decentralization of treatment center). Additionally, during Phase 2, women who did not avail screening through the CHC were targeted for home-based screening described as a "mop-up" intervention.

Costs

The health care costing evaluations were completed using a societal perspective and included costs to both the health care system and the patients. Costs to the health care system for cervical cancer screening through CHCs included: (1) outreach and mobilization, (2) community-based screening procedures, (3) notification and standard referral to both intervention and control communities, (4) notification and enhanced referral to treatment in intervention communities, and (5) costs of treatment. Activities costed from the patients' perspective involved calculating productivity cost by placing a wage-based value on an ill worker's absenteeism, which was captured through the treatment information sheet.

Data were collected on personnel time and associated costs to provide outreach and mobilization, community-based screening, notification and standard referral for treatment, notification and enhanced linkage to treatment, and treatment in each of the participating communities. Information on the other resources required, such as recurrent goods and services, equipment, and administrative support needed to deliver the screening program activities were also collected. Costing included: 1) personnel; 2) recurring supplies and services; 3) capital goods and equipment, and 4) facility space. A uniform cost data collection protocol was used to quantify the resources and costs of the intervention in each of the study sites (CHCs, laboratories, and district hospitals). Data were obtained through administrative records review and interviews with administrative staff, finance staff, human resources staff and study staff, supplemented by "time and motion" studies as described below.

A "time and motion" (T&M) analysis was conducted in addition to the collection of personnel time and cost data obtained via micro-costing workbooks(99). The T&M component involved structured self-documentation of provider activities throughout the workday, for a limited period, in the health

facilities and the CHCs during screening and treatment, to verify the time staff members devoted to specific activities.

The micro-costing approach emphasizes resources (inputs) used for service delivery and includes the value of all supplies needed for services even if not paid for by the project. Thus, the full value of donated or subsidized inputs was assigned. For example, for facility costs, if facility space was not rented, the rental rate was estimated based on the average rental price of a similar facility in the market. Research costs were identified in the costing exercise but were excluded from the final cost calculations. The micro-costing workbook has an allocations section, which reflects the portion of each item's time in use that is devoted to research. However, the objective of the costing evaluation was to determine the incremental cost and cost-effectiveness of the intervention as it would be implemented on a routine basis.

Costs in local units (Kenyan Shillings or KSH) were inflated to 2018 KSH. Next, we converted KSH costs to International Dollars (I$) using purchasing power parity (ppp) exchange rates(100). A ppp exchange rate is the number of units of a country's currency required to buy the same amount of goods and services as one U.S. Dollar would buy in the United States(100, 101). An International Dollar, therefore, is a hypothetical currency that is used to translate and compare costs of one country to the other using a common reference point, the US dollar.

Analytic Approach

The DALY is a societal measure of overall disease burden, expressed as the number of years lost due to poor health, disability, or premature death. DALYs accumulated due to a specific health condition are calculated as the sum of measures of life expectancy and adjusted quality of life due to disease or disability. Specifically, it is the sum of years of life lost (YLL) due to premature mortality in the population and years lived with a disability (YLD) for people living with the health condition or its consequences. Below is the formula:

$$DALY = YLL + YLD$$

$Here, \quad YLL = N * L$

N = number of deaths

L = standard life expectancy at the age of death in years

$$YLD = P * DW$$

P = number of prevalent cases

DW = disability weight

A disability weight, which is used to calculate YLD, is a factor that reflects the severity of disease or disability on a scale from 0 (perfect health) to 1 (equivalent to death). We used the decision-tree model to calculate the incremental cost-effectiveness ratio (ICER), defined as the incremental cost per DALY averted when comparing cervical cancer screening strategies. We calculated ICERs compared to the current standard, which is no organized available screening, using baseline data of screening availability.

The incremental cost-effectiveness ratio is calculated as follows

$$ICER = \frac{C_1 - C_0}{E_1 - E_0}$$

$C_1$ = cost in intervention group

$C_0$ = cost in standard care group

$E_1$ = Effect in intervention group

$E_0$ = Effect in standard care group

We carried out one-way and probabilistic (multivariable) sensitivity analyses to assess the robustness of the assumptions of the model(102). During probabilistic sensitivity analysis, each input parameter is simultaneously varied across a given range of values from the parameter's defined distribution. With each 'draw,' a new incremental cost and DALYs averted is calculated, as compared with the referent scenario (next least costly). The resulting point estimates were presented as ICER planes, representing the ICERs of 10,000 draws executed through Monte Carlo simulation.

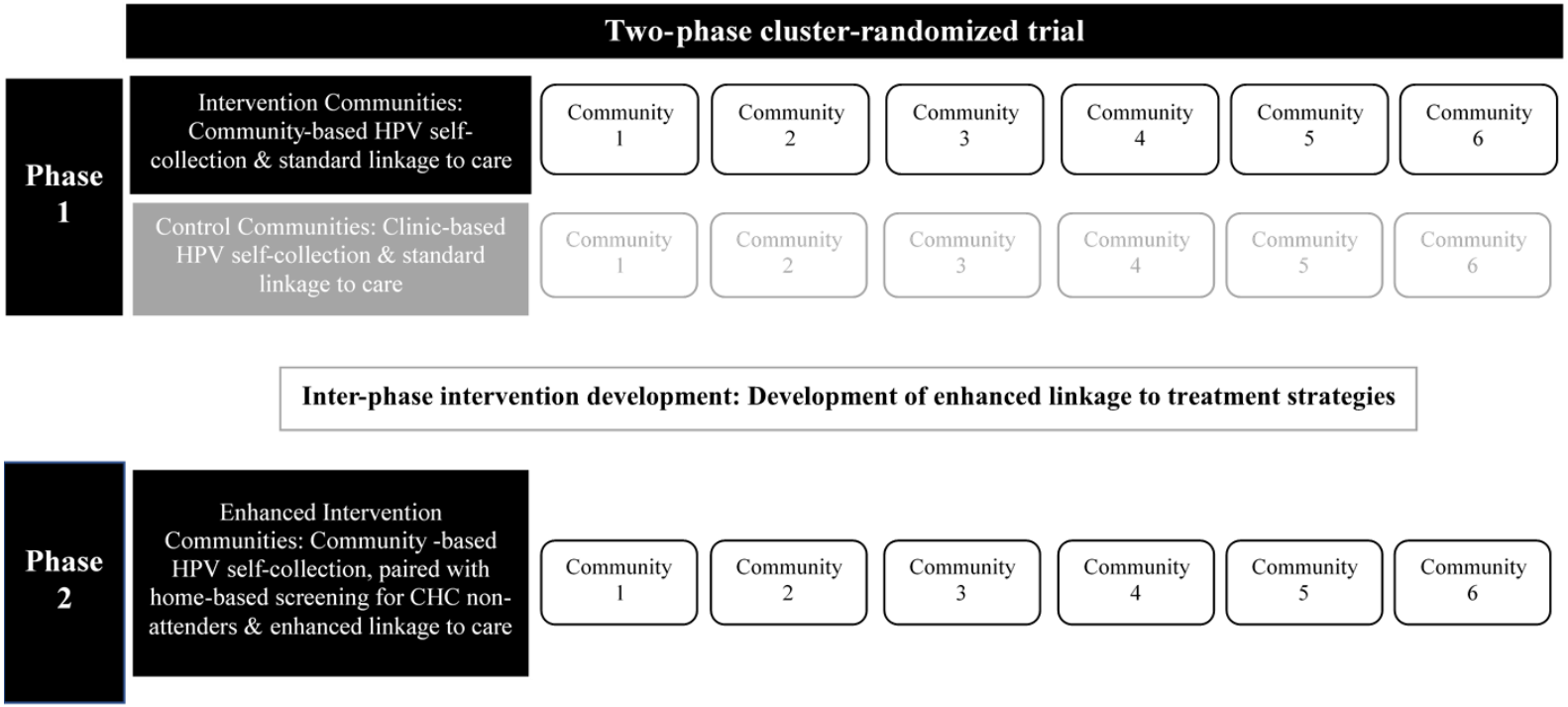


**Figure 3.1:** Summary schematic of the cluster-randomized control trial conducted in Migori County, Kenya to assess alternative methods of cervical cancer screening delivery through community health campaigns. Data from this trial were used to inform programmatic assumptions and costs of cervical cancer screening delivery models included in the cost-effectiveness analysis described for Aim 2

## CHAPTER 4. HIGH-RISK HUMAN PAPILLOMAVIRUS mRNA TESTING OF WET- AND DRY- SELF-COLLECTED SPECIMENS FOR CERVICAL LESION DETECTION AMONG HIGH-RISK WOMEN IN KENYA

Overview

High-risk HPV (hr-HPV) mRNA testing may improve cervical cancer screening. HR-HPV mRNA testing using self-collected specimens stored in liquid media (stored wet) has comparable performance to physician-collection. HR-HPV mRNA with self-collected specimens stored dry could enhance the feasibility of specimen collection and storage; however, its performance is unknown. We compared the performance of hr-HPV mRNA testing with dry-and wet-stored self-collected specimens for detecting ≥HSIL.

From 2013 to 2018, a total of 399 female sex workers participated in this cross-sectional study. Participants provided two self-collected specimens: one stored dry(sc-DRY) using a Viba brush (Rovers), and one stored wet (sc-WET) with Aptima media (Hologic) using an Evalyn brush (Rovers). Two physician-collected specimens were collected for HPV mRNA testing (APTIMA) and conventional cytology. We estimated test characteristics for each hr-HPV screening method using conventional cytology as the gold standard. We also examined participant preference for sc-DRY and sc-WET.

HR-HPV mRNA positivity was higher in sc-WET (36.8%) than sc-DRY samples (31.8%). Prevalence of ≥HSIL was 6.9% (n = 27). Sensitivity of hr-HPV mRNA testing for detecting ≥HSIL was similar in sc-WET (85%, 95% CI: 66-96), and sc-DRY specimens (78%, 95% CI: 58-91). Specificity was 65% (95% CI: 61-71) in sc-WET and 70%, (95% CI: 65-75) in sc-DRY specimens. Women preferred sc-DRY specimen collection (46%) compared to sc-WET (31%). However, more women preferred physician-collection (64%) than self-collection (36%).

Sc-DRY specimens appeared to perform similarly to sc-WET for the detection of ≥HSIL. However, women's preference for either type of self-collection method was lower than physician-collection.

Background

Invasive cervical cancer is caused by persistent infection with high-risk human papillomavirus (hr-HPV) (1). Although highly preventable through early detection and treatment of cervical precancerous lesions(103), cervical cancer remains the fourth most common cause of cancer-related morbidity and mortality among women worldwide(104). In high-resource countries, the successful implementation of cytology-based, or Papanicolaou (Pap) smear, screening has reduced cervical cancer incidence and mortality by about 80% (105, 106). However, there are several barriers to the implementation of cytology-based programs in low- and middle- income countries (LMICs), including limited healthcare infrastructure, reduced access to clinicians to conduct pelvic examinations, and fewer trained cytopathologists (107). Consequently, the burden of cervical cancer disproportionately impacts both never and under-screened women in LMICs, where nearly ~90% of the deaths attributable to cervical cancer occur(104, 108). In Kenya, where the estimated population-based screening coverage is estimated to be 13%(109), cervical cancer is the leading cause of cancer-related mortality among women(104).

The development of molecular-based laboratory assays to detect hr-HPV has recently changed the approach to cervical cancer screening(110-112). Evidence from randomized controlled trials shows that primary hr-HPV screening is more effective than cytology for the detection of high-grade precancerous lesions, with higher sensitivity and less frequent intervals required between screenings(110, 113, 114). Molecular hr-HPV testing has been associated with lower mortality attributable to cervical cancer(115, 116) and offers the opportunity to implement cervical cancer screening programs using self-collected sampling by women themselves(33, 117). Following World Health Organization recommendations(103), LMICs are implementing molecular HPV testing as a primary screening tool(19).

Self-collection of cervicovaginal specimens for cervical cancer screening is a clinically valid method for hr-HPV testing, with the potential to circumvent barriers to clinic-based screening(21, 59, 118-120). Additionally, sensitivity for the detection of high-grade cervical lesions using self-collected samples is equivalent to physician-collected samples(121). However, hr-HPV DNA testing does have limitations. For example, in populations and geographical areas where hr-HPV prevalence is high, providing HPV DNA testing may have notably low specificity for high-grade cervical lesions detection, [two] resulting in unnecessary follow-up procedures, and overburdening of referral clinics for treatment(54).

One potential strategy to improve the specificity of cervical cancer screening is to test for hr-HPV mRNA of the oncogenic proteins E6 and E7, which may accurately predict progression to invasive disease(43). Few prior studies have evaluated the validity of using self-collected samples for HPV mRNA testing(49, 54, 122). These available data evaluating self-collection for HPV mRNA testing have been generated using samples stored in liquid transport media, which requires refrigeration and is relatively more costly than dry self-collection(72).

The feasibility of self-collected sampling for hr-HPV testing with dry swabs transported stored at room temperature might facilitate more efficient screening strategies in LMICs. To date, there is a lack of data on the performance of self-collection using brushes stored dry (sc-DRY) compared to self-collected samples stored wet in transport media (sc-WET) to evaluate the clinical validity for high-grade cervical lesion detection. We present here results comparing the performance of APTIMA hr-HPV mRNA (Hologic Corporation, San Diego, CA) testing using sc-DRY and sc-WET specimens for the detection of cytological high-grade cervical lesions or more severe (≥ HSIL) among female sex workers (FSWs) in Mombasa, Kenya. We also evaluated participants' preferences for HPV sampling methods.

## Methods

### Study Population

From August 2013 to April 2018, FSWs participating in a longitudinal cohort study of women at high risk of acquiring STIs and HIV in Mombasa, Kenya were invited to participate in this cross-sectional cervical cancer screening study. Study clinical procedures, including self- and physician-collection of

genital samples for HPV mRNA testing, were performed at the Ganjoni Health Centre in Mombasa. The Ganjoni Health Centre has been a primary research site for the Mombasa Cohort(123) and venue for STI testing and treatment among at-risk and HIV-positive women in Mombasa for over 25 years.

Study procedures were integrated into the ongoing follow-up procedures for the Mombasa Cohort, as previously described(94, 95). Briefly, the Mombasa Cohort is an open cohort study of FSWs established in 1993 to provide high-quality care to at-risk women and supports research efforts of HIV prevention, treatment, and care. For participant recruitment, outreach meetings were conducted at popular sex work venues one to two times each month. During these meetings, outreach staff provided counseling on a health topic requested by the women of the community and general information describing the clinic. Interested women were provided with a referral card and invited to visit the Ganjoni Health Centre.

The criterion for inclusion into the Mombasa Cohort included: 1. Women aged 18 years and above; 2. Residing in the Mombasa area; 3. Self-identifying as exchanging sex for payment in cash or in-kind and 4. Able to provide informed consent. Eligible women were invited to participate in this cervical cancer screening study during the visit for specimen collection for Chlamydia trachomatis and Neisseria gonorrhea testing. We used convenience sampling to enroll women who agreed to participate from among those who were eligible and carried out enrollment to ensure half of participants were HIV-positive. Women were excluded from this study if they were currently pregnant or had a history of hysterectomy or treatment for cervical precancer. Participating women were counseled on the risks and benefits of cervical cancer screening, and administered a questionnaire to collect socio-demographic, reproductive, and sexual behavior data.

## Sample Collection

Each woman was directed to a private room at the clinic to perform self-collection of genital specimens. A study nurse provided verbal instructions and pictorial diagrams with detailed instructions on self-collection were available in the private room. Participants were instructed to squat and insert a cytobrush up into the vaginal vault, rotating it 3-5 times, and then withdrawing. Each woman performed

self-collection using two different specimen brushes: (1) the Evalyn cytobrush (Rovers®, Netherlands) for dry self-collection (sc-DRY) and (2) the Viba cytobrush (Rovers®, Netherlands) for wet self-collection (sc-WET), which included a plastic cryovial containing 1 ml of Aptima liquid transport media (Hologic®, USA). To minimize potential bias from the order of specimen collection, women assigned odd study numbers self-collected using the Evalyn brush first, while those with even study numbers self-collected using the Viba cytobrush first.

After self-collection, a study clinician performed a speculum-assisted pelvic examination to collect cervical specimens for hr-HPV mRNA testing. Physician-collection of cervical specimens from the endocervix was performed using a cervical specimen collection brush (Hologic®, USA). Similar to the Viba brush (for sc-WET), physician-collected specimens were stored in Aptima media. After specimen collection, the clinician performed visual inspection with acetic acid (VIA) and a conventional Pap smear for cytology assessment. All study clinicians had extensive training and experience in genital examination and specimen collection as part of the procedures in the Mombasa Cohort. Following the clinical examinations, women participated in a structured interview using a standardized questionnaire to assess their experiences undergoing self- and physician-collection.

Conventional cytological smears were evaluated at the University of Nairobi and classified according to the 2001 Bethesda System. Two cytopathologists, who were blinded to HPV mRNA and VIA screening results, independently read all cytological smears. For discrepant cases, the final diagnosis was made after a consensus of the two reviewing cytopathologists. Positive screening results included any or a combination of the following: i. Positive HPV mRNA; ii. Abnormal cytology [ASCUS or greater (ASCUS+)] and iii. Abnormal VIA. All participants with a positive screening result were scheduled for a colposcopy examination with biopsy collection or endocervical curettage (ECC) for histological assessment. Women with histological cervical intraepithelial neoplasia stage two or above were referred to standard care and treatment at the Kenyatta National Hospital. All biopsy specimens were archived for external quality control and future testing.

HPV mRNA Lab Testing

The physician- and both self-collected samples were transported to the research laboratory at the Coast Provincial General Hospital (CPGH) for hr-HPV mRNA testing. Self-sampled and physician-sampled genital specimens were tested for hr-HPV using the Hologic Corporation APTIMA HPV Assay® which detects mRNA encoding the E6/E7 proteins from 14 high-risk HPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68). Specimen processing comprises three main steps including, target capture, target amplification by Transcription-Mediated Amplification (TMA), and amplicon detection by the Hybridization Protection Assay (HPA) carried out according to the manufacturer's instructions. This process was automated using Hologic's Panther® platform by trained technologists.

Statistical Analyses

Of 400 FSWs, one woman was missing hr-HPV mRNA testing results and excluded from analyses, resulting in a final sample of 399. Sociodemographic and sexual behavioral characteristics were assessed for all women and stratified by HIV-status using univariate analyses. Pairwise comparisons using McNemar's test was conducted to assess differences in hr-HPV mRNA prevalence in sc-DRY and sc-WET sample specimens and in sc-WET versus physician-collection, which is included in the Appendix. Two-by-two tables were constructed to calculate sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for the detection of ≥HSIL with 95% confidence intervals. Differences in sensitivity, specificity and predictive values of screening tests were assessed using a Wald-type test with confidence intervals. We calculated prevalence differences with 95% confidence intervals to assess potential differences in preference of self-collection devices by age (<40 years and ≥40 years).

Sensitivity analyses were conducted to estimate PPV and NPV values of sc-DRY and sc-WET specimens for varying ≥HSIL prevalence to address concerns regarding the generalizability and transportability of findings. Currently, the World Health Organization (WHO) recommends cervical cancer screening to start as soon as a woman has tested positive for HIV, regardless of age(103).

Therefore, we present results stratified overall, and by HIV status. All statistical analyses were performed using SAS® 9.4.

## Results

### Participant Characteristics

Overall, the median age of women was 39 years (range 19-66) (Table 4.1). The prevalence of hr-HPV mRNA appeared similar in physician- (34.4%), sc-WET (36.8%), and sc-DRY (31.8%) samples. Most women had 8 or fewer years of education (57%), and reported being divorced or widowed (62%). A higher proportion of women reported using either no contraception (35%) or condoms only (21%) during sexual acts.

For all three individual HPV-mRNA screening tests, the prevalence of hr-HPV mRNA was higher among HIV-positive women compared to HIV-negative (sc-WET: PD 0.15, 95%CI: 0.06-0.24; sc-DRY: PD 0.14, 95% CI: 0.04-0.23; physician: PD 0.19, 95% CI: 0.10-0.28). The prevalence of abnormal cytology (≥ASCUS) was 26.6% and was also higher among HIV-positive women (30.8%) than HIV-negative women (22.8%) (PD: 0.06, 95% CI: 0.01-0.11).

### Concordance of hr-HPV mRNA detection between self-collected samples

Overall, approximately one-third of women tested positive for hr-HPV mRNA using the self-collected sampling stored wet (n=147, 36.8%) or stored dry (n=127; 31.8%). A quarter of women (97/387) were positive for hr-HPV mRNA with both sc-WET and sc-DRY samples, 12% (47/387) were hr-HPV mRNA positive using the sc-WET sample but not the sc-DRY sample, 6.9% (27/387) were positive for hr-HPV mRNA using the sc-DRY but not the sc-WET sample, and 55.8% (216/387) were negative for hr-HPV mRNA using both the sc-DRY and sc-WET samples (Table 4.2). Using the McNemar's test for paired samples, hr-HPV mRNA positivity was higher in sc-WET samples compared sc-DRY ($p = 0.02$). High risk-HPV mRNA concordance was determined between sc-WET and sc-DRY

samples, stratified by cytology diagnosis. Twelve participants did not have cytology diagnoses available and were excluded from the stratification analyses.

Performance of screening methods for the detection of ≥HSIL

The overall sensitivity of hr-HPV mRNA for ≥HSIL of sc-WET [85% (95% CI: 66-96)] and sc-DRY [78% (95% CI: 58-91)] were comparable (Difference: -0.07, Wald 95% CI: -0.21 to 0.07) (Table 4.3). Physician-collected samples for hr-HPV mRNA testing showed a similar sensitivity for ≥HSIL detection [93% (95% CI: 76-99] as sc-WET (Difference: -0.07, Wald 95% CI: -0.19 to 0.09) and sc-DRY (Difference: 0.15, Wald 95% CI: -0.02 to 0.32). Overall, the specificity of hr-HPV mRNA for ≥HSIL detection was similar when comparing sc-WET to physician-collection (Difference: -0.03, 95% CI: -0.08 to 0.01). However, specificity was lower for sc-WET [66% (61-71)] than sc-DRY [71% (66-76)] (Difference: -0.05, 95%CI: -0.10 to -0.00). The specificity of VIA for ≥HSIL was 56% (95% CI: 51-62).

The positive predictive value was 16% (95% CI: 10-23) for sc-WET and 17 (95% CI: 11-25) % for sc-DRY. The physician-collection positive predictive value was 19% (95% CI: 12-26). Sensitivity analyses showed that for all three tests as the prevalence of ≥HSIL increases to 20%, the PPV increases to about ~40% and the NPV only decreases slightly (Table 4.6).

Of the 27 women with ≥HSIL 25 underwent colposcopy-directed biopsy as two women were lost to follow-up. Seventeen had histological ≥CIN2, and eight were considered disease negative (four CIN1 and four normal histology). Of the 17 ≥CIN2 cases, all were positive for hr-HPV mRNA based on the physician-collected samples. However, four women were negative for hr-HPV mRNA based on the dry-stored self-collected test, and one was negative for hr-HPV mRNA based on the wet-stored self-collected test. The specimen which was negative for hr-HPV mRNA based on the sc-WET test was also negative for hr-HPV mRNA based on the sc-DRY test.

Acceptability of self-collection methods

Overall, 144 (36%) of women reported preferring self-collection compared to physician-collection (Table 4.5). Preference for self-collection did not appear to vary by age (<40 years: 39%; ≥40 years: 32%; PD: 0.07, 95% CI: -0.03 to 0.16) or HIV status (HIV-positive: 44%; HIV-negative: 56%; PD: -0.07, 95% CI: -0.16 to 0.03). Women more frequently reported to prefer self-collection stored dry (46%) compared to storage in media (31%). Most women agreed that the Evalyn brush (used for dry storage) was comfortable to insert (88%), and came with instructions easy to understand (95%). About half of participants were concerned that the use of the Evalyn brush for self-collection might lead to pain (45%) and about 60% were concerned about properly using the Evalyn brush. Similar patterns were observed for the Viba brush (used for wet storage).

Discussion

To our knowledge, this is the first study to compare hr-HPV mRNA testing on self-collected wet- and dry-stored specimens to detect ≥HSIL. Among 399 FSWs in Kenya, high-risk HPV mRNA testing using self-collected samples stored wet and dry demonstrated similar sensitivity for ≥HSIL detection, although the specificity of dry-stored samples appeared higher. High-risk HPV mRNA positivity was similar in self-collected wet (36%) compared to physician-collected (34%), however, was lower in self-collected dry brushes (32%). Although we found high sensitivity and specificity of hr-HPV mRNA testing using self-collected samples for the detection of ≥HSIL, our cohort of Kenyan FSWs preferred physician-collection of cervical samples over self-collection methods for cervical cancer screening.

Our results demonstrate that compared to wet-stored specimens, dry-stored specimens have similar test characteristics the detection of high-grade cervical lesions, indicating that dry-stored samples are a viable option for home-based cervical cancer screening programs. Prior studies have directly compared HPV DNA testing using self-collected specimens stored dry- and wet-stored, comparable sensitivities were found for the detection of CIN 2+(71, 74, 77), and ≥HSIL(70). Sensitivity estimates of HPV DNA testing on dry-stored samples to detect high-grade cervical neoplasia or more severe was

similar to our study and ranged from 76% to 90%(70, 71, 74, 77). However, specificity for high-grade cervical neoplasia in prior studies of HPV DNA testing in dry versus wet stored samples was low for both self-collection methods(70, 71, 74, 77). Our results support prior studies that show high-risk HPV mRNA testing has improved specificity for high-grade cervical neoplasia compared to HPV DNA testing(124).

The prevalence of hr-HPV mRNA based on self-collection specimens in our study was similar to other hr-HPV mRNA studies conducted in sub-Saharan Africa among high-risk groups. In a South African study of 325 HIV-infected women, the prevalence of hr-HPV mRNA based on self-collected samples was 43.5%(54), which is similar to the prevalence we found in HIV-positive women (44.6%, sc-WET and 38.9%, sc-DRY). Among a cohort of 344 female sex workers in Nairobi, of which 25% were HIV positive, the prevalence of hr-HPV mRNA was 30%(49). Given that HPV DNA is typically detected at higher prevalence proportions than HPV mRNA within various populations studied(125-127), our study population has a notably high prevalence of hr-HPV infection.

The high prevalence of hr-HPV underscores the need for more specific tests to reduce the potential for unnecessary referral and overtreatment in a resource-constrained setting. With a high NPV, high-risk HPV mRNA testing can effectively identify women at higher risk of developing high-grade by detecting oncogenic proteins E6 and E7. A low-cost method such as dry-stored self-collection for HPV mRNA testing has the potential to improve test specificity to identify those at the highest risk of developing invasive disease. Our study provides support for the potential integration of dry-stored hr-HPV testing as a cervical cancer screening tool in areas with high prevalence of hr-HPV, such as sub-Saharan Africa

Among female sex workers in Kenya, we found that physician-collection was more frequently preferred than either self-collection method. These findings are inconsistent with prior studies that found that women generally reported preference of self-collection over physician-collected sampling for cervical cancer screening(64). A recent meta-analysis found that of 12,610 women, 59% (95% CI: 48%-69%) reported preference for self-sampling compared to physician-collection(64). However, there was wide variability across individual studies (22% to 95% of respondents). In our study, women frequently

reported feeling concerned about hurting themselves when inserting the self-collection brush into their vaginal canal and also, expressed concerns about their ability to properly carry out self-collection. Our findings are similar to the results of a study conducted in Cameroon, which showed that while women found self-collection more comfortable, a higher proportion preferred physician-collection (62% vs. 29%) as they were concerned about the reliability of results(128). Indeed, factors facilitating uptake of HPV self-collection among women in Kenya include confidence in the ability to complete HPV self-sampling, proximity to screening sites, and feelings of privacy and comfort conducting the HPV self-sampling(129). Future research should address barriers to self-collection uptake to inform the implementation of cervical cancer screening programs in sub-Saharan Africa.

Our study approach has several advantages. First, this validation study was nested within an ongoing prospective study with established follow-up procedures, including HIV-positive women—a population at notably high-risk of cervical cancer. Secondly, conventional cervical cytology slides were independently read by two cytopathologists to improve the accuracy of cytological diagnoses. Third, screening collection methods were performed sequentially on the same day, allowing for direct comparison of the samples collected. Additionally, we randomized each participant to either first complete self-collection for the dry-or wet-stored sample to ensure the order of procedures did not affect our results. Finally, we present novel data on the preference of self-collection for cervical cancer screening as few prior studies in sub-Saharan Africa have evaluated the acceptability of different collection methods for hr-HPV molecular testing in this region. Among study limitations, women participating in the Mombasa Cohort volunteer for research visits with regular HIV and STI screening; as such, our findings may not be generalizable to all women eligible for cervical cancer screening in LMICs. Our small sample size limited our ability to compare the agreement (using the $\kappa$ statistic) between sc-DRY and sc-WET in women with <HSIL compared with those with ≥HSIL. The interpretation of our analyses is limited due to few HSIL cases, although comparable to prior cervical cancer screening studies conducted in sub-Saharan Africa(49). Further research is needed to assess the use of dry-stored specimens HPV mRNA testing to detect high-grade cervical lesions in large cohorts to confirm our study findings.

In conclusion, using dry-stored specimens appears to be a viable option for hr-HPV mRNA testing due to the similar sensitivity and specificity of wet -stored self-collected hr-HPV testing for ≥HSIL detection. The possibility of using dry-stored self-collected samples without the need of storage media would improve the utility of self-collection for hr-HPV testing. Utilizing dry stored methods could reduce the costs needed for the storage and transport of samples. Limited resources may then be focused on follow-up and treatment services for women who screen positive for hr-HPV, which would be ideal for resource-constrained settings. Additional research to address preferences and any barriers to self-collection is crucial.

**Table 4.1:** Sociodemographic and Sexual Behavioral Characteristics of 399 Female Sex Workers in Mombasa, Kenya, 2013 -2018

| | Overall (n = 399) | | HIV - Positive (n = 193) | | HIV - Negative (n = 206) | |
|---|---|---|---|---|---|---|
| | n | Median or % | n | Median or % | n | Median or % |
| Characteristic | | | | | | |
| Age, years (range) | | 39 (19-66) | | 42 (21-62) | | 34 (19-66) |
| HPV (physician-collected) | | | | | | |
| Negative | 262 | 65.7 | 108 | 55.9 | 154 | 74.8 |
| Positive | 137 | 34.3 | 85 | 44.0 | 52 | 25.2 |
| HPV (self-collected, stored wet) | | | | | | |
| Negative | 252 | 63.2 | 107 | 55.4 | 145 | 70.4 |
| Positive | 147 | 36.8 | 86 | 44.6 | 61 | 29.6 |
| HPV (self-collected, stored dry) | | | | | | |
| Negative | 272 | 68.2 | 118 | 61.1 | 154 | 74.8 |
| Positive | 127 | 31.8 | 75 | 38.9 | 52 | 25.2 |
| Cervical cytology* | | | | | | |
| Normal | 284 | 73.4 | 128 | 69.2 | 156 | 77.2 |
| ASCUS | 56 | 14.5 | 26 | 14.1 | 30 | 14.9 |
| LSIL | 20 | 5.2 | 12 | 6.5 | 8 | 4.0 |
| ≥ HSIL | 27 | 6.9 | 19 | 10.3 | 8 | 4.0 |
| Sexually transmitted infections† | | | | | | |
| Chlamydia | 11 | 2.8 | 2 | 1.0 | 9 | 4.4 |
| Gonorrhea | 10 | 2.5 | 4 | 2.1 | 6 | 2.9 |
| *Trichomonas vaginalis* | 17 | 4.3 | 13 | 6.7 | 4 | 1.9 |
| Education | | | | | | |
| ≤ 8 years | 228 | 57.1 | 121 | 62.7 | 107 | 51.9 |
| > 8 - 12 years | 130 | 32.6 | 59 | 30.6 | 71 | 34.5 |
| ≥13 years | 41 | 10.3 | 13 | 6.7 | 28 | 13.6 |
| Marital status† | | | | | | |
| Never Married | 136 | 34.9 | 48 | 24.7 | 89 | 43.2 |
| Currently Married | 7 | 1.8 | 3 | 1.6 | 4 | 1.9 |
| Divorced/Widowed | 247 | 63.3 | 140 | 72.2 | 107 | 51.9 |

| | | | | | | |
|---|---|---|---|---|---|---|
| Number of pregnancies (range) | | 2 (0 - 10) | | 2 (0 - 10) | | 2 (0 - 8) |
| Number of live births (range) ‡ | | 2 (0 - 7) | | 2 (0 - 7) | | 2 (0 - 7) |
| Age at sexual debut, years (range) ‡ | | 17 (9-29) | | 17 (11-25) | | 17 (9 - 29) |
| Type of contraception currently used | | | | | | |
| None | 138 | 34.6 | 78 | 40.4 | 60 | 29.1 |
| Condoms only | 83 | 20.8 | 34 | 17.6 | 49 | 23.8 |
| Oral contraceptive pill | 35 | 8.8 | 15 | 7.8 | 20 | 9.7 |
| Depo Provera | 85 | 21.3 | 43 | 22.3 | 42 | 20.4 |
| IUD/Tubal ligation/Norplant | 58 | 14.5 | 23 | 11.9 | 35 | 17.0 |
| Frequency of vaginal intercourse during the past week (range) ‡ | | 2 (0 - 60) | | 1 (0 - 30) | | 3 (0 - 60) |
| Frequency of vaginal intercourse with condom during the past week (range) ‡ | | 1 (0 - 56) | | 1 (0 - 30) | | 2 (0 - 56) |
| Number of sexual partners in the last working week (range) ‡ | | 1 (0 - 60) | | 1 (0-30) | | 2 (0 - 60) |
| Number of new sexual partners in the last month (range) ‡ | | 0 (0 - 40) | | 0 (0 - 40) | | 1 (0 - 40) |
| Charge per transaction (KSh) (range) § | | 400 (10 - 10,000) | | 275 (10 - 4000) | | 500 (10 - 10,000) |
| Tobacco use (≥ 1 cigarette per day) § | 68 | 17.0 | 28 | 14.5 | 40 | 19.4 |
| Alcohol use (≥ 1 drink per week) § | 317 | 79.5 | 148 | 76.7 | 169 | 82.0 |

Abbreviations: AHPV - APTIMA hrHPV mRNA; Hologic/ San Diego, CA; ASCUS - Atypical squamous cells of undetermined significance; KSh - Kenyan Shilling

* Numbers do not add up to 399 due to missing cytology or inadequate sample (Overall n = 11; HIV Positive n = 8; HIV Negative n = 4)

† Samples for STI testing were collected by the study physician and are laboratory confirmed using APTIMA

‡ Numbers do not add up to 399 due to missing values: marital status (n = 9); number of live births (n = 6); sexual debut (n = 9); frequency of vaginal intercourse (n = 11); frequency of vaginal intercourse with condoms (n = 13); sexual partners in the last week (n = 11); new sexual partners (n = 13);

§ Collected at enrollment into parent Mombasa Cohort study

**Table 4.2:** HPV mRNA detection agreement of self-collected samples stored wet (sc-WET) and stored dry (sc-DRY) samples, stratified by cytology diagnosis (n = 387)

| | Total sc-WET+ | Total sc-DRY+ | sc-WET + sc-DRY + | sc-WET + sc-DRY - | sc-WET - sc-DRY + | sc-WET - sc-DRY - | P* |
|---|---|---|---|---|---|---|---|
| Overall | 147 | 127 | 97 | 47 | 27 | 216 | 0.03 |
| NILM (n = 284) | 90 | 75 | 52 | 38 | 23 | 171 | 0.07 |
| ASCUS (n = 56) | 23 | 21 | 19 | 4 | 2 | 31 | 0.69 |
| LSIL (n = 20) | 8 | 7 | 6 | 2 | 1 | 11 | 1.00 |
| HSIL (n = 27) | 23 | 21 | 20 | 3 | 1 | 3 | 0.62 |
| Missing cytology (n = 11) | 3 | 9 | 3 | 0 | 0 | 9 | - |

Abbreviations: sc-WET+: Positive for self-collected sample stored wet in preservation media; sc-WET- : Negative for self-collected sample stored dry; sc-DRY+ : Positive for self-collected sample stored dry; sc-DRY- : Negative for self-collected sample stored dry; NILM: negative for intraepithelial lesions and malignancy; ASCUS: atypical squamous cells of undetermined significance; LSIL: low-grade squamous intraepithelial lesions; HSIL: high-grade squamous intraepithelial lesions; CI: confidence intervals

* Determined using McNemar's test

**Table 4.3:** HPV mRNA detection agreement of self-collected wet- (sc-WET) and physician collected samples (PC) stratified by cytology diagnosis (n = 387)

| | Total sc-WET+ | Total PC+ | sc-WET + PC + | sc-WET + PC - | sc-WET - PC + | sc-WET - PC - | *P** |
|---|---|---|---|---|---|---|---|
| Overall | 147 | 137 | 106 | 41 | 31 | 221 | 0.24 |
| NILM (n = 284) | 90 | 81 | 58 | 32 | 23 | 171 | 0.22 |
| ASCUS (n = 56) | 23 | 23 | 18 | 5 | 5 | 28 | 1.00 |
| LSIL (n = 20) | 8 | 6 | 5 | 3 | 1 | 11 | 0.32 |
| HSIL (n = 27) | 23 | 25 | 23 | 0 | 2 | 2 | 0.16 |
| Missing cytology (n = 11) | 3 | 2 | 2 | 1 | 1 | 9 | - |

Abbreviations: sc-WET+: Positive for self-collected sample stored wet; sc-WET- : Negative for self-collected sample stored dry; PC+ : Positive for physician-collected samples (stored wet); PC- : Negative for physician-collected samples (stored wet); NILM: negative for intraepithelial lesions and malignancy; ASCUS: atypical squamous cells of undetermined significance; LSIL: low-grade squamous intraepithelial lesions; HSIL: high-grade squamous intraepithelial lesions; CI: confidence intervals

* Determined using McNemar's test

**Table 4.4:** Performance of HPV Testing of Physician-Collected, Wet Self-Collected, and Dry Self-Collected Specimens, and Visual Inspection with Acetic Acid (VIA) for the detection of cytological high-grade cervical lesions in 387 female sex workers in Mombasa, Kenya (2013-2018)

| | | Overall (n = 387) | HIV Positive (n = 185) | HIV Negative (n = 202) |
|---|---|---|---|---|
| | ≥HSIL Prevalence | 6.9% (n=27) | 10.3% (n=19) | 4.0% (n=8) |
| Collection Method | Sensitivity / Specificity for ≥ HSIL | | | |
| Physician-Collected | | | | |
| | Sensitivity of HPV (95% CI) | 93% (76-99) | 95% (74-100) | 88% (47-100) |
| | Specificity of HPV (95% CI) | 69% (64-74) | 61% (53-68) | 77% (70-83) |
| | Positive Predictive Value (95% CI) | 19% (12-26) | 22% (13-32) | 14% (6-26) |
| | Negative Predictive Value (95% CI) | 99% (97-100) | 99% (95-100) | 99% (96-100) |
| Self-Collected stored Wet | | | | |
| | Sensitivity of HPV (95% CI) | 85% (66-96) | 84% (60-97) | 88% (47-100) |
| | Specificity of HPV (95% CI) | 66% (61-71) | 60% (52-67) | 72% (65-78) |
| | Positive Predictive Value (95% CI) | 16% (10-23) | 19% (11-29) | 12% (5-22) |
| | Negative Predictive Value (95% CI) | 98% (96-100) | 97% (92-99) | 99% (96-100) |
| Self-Collected stored Dry | | | | |
| | Sensitivity of HPV (95% CI) | 78% (56-91) | 74% (49-91) | 88% (47-100) |
| | Specificity of HPV (95% CI) | 71% (66 - 76) | 65% (57-72) | 77% (70-83) |
| | Positive Predictive Value (95% CI) | 17% (11-25) | 19% (11-31) | 14% (6-26) |
| | Negative Predictive Value (95% CI) | 98% (95-99) | 96% (90-99) | 99% (96-100) |
| VIA | | | | |
| | Sensitivity of VIA (95% CI) | 82% (62-94) | 79% (54-93) | 88% (47-100) |
| | Specificity of VIA (95% CI) | 56% (51- 62) | 61% (53-68) | 53% (45-60) |
| | Positive Predictive Value (95% CI) | 12% (8-18) | 19% (11-29) | 7% (3-14) |
| | Negative Predictive Value (95% CI) | 98% (94-99) | 96% (90-99) | 99% (95-100) |

Abbreviations: CI: confidence intervals; HIV: human immunodeficiency virus; HSIL: high-grade squamous intraepithelial lesions; VIA: visual inspection with acetic acid

**Table 4.5:** HPV sampling preference of dry (Evalyn Brush) and wet (Viba Brush) HPV mRNA self-collection among females sex workers in Mombasa, Kenya (n = 399)

| | | Age Group | | |
|---|---|---|---|---|
| | Overall (n = 399) | < 40 years (n = 214) | ≥ 40 years (n = 185) | PD (95% CI) |
| HPV sample collection method preference | | | | |
| Physician-collection | 255 (63.9) | 130 (60.8) | 125 (67.6) | Ref. |
| Self-collection | 144 (36.1) | 84 (39.3) | 60 (32.4) | 0.07 (-0.03 to 0.16) |
| Type of self-collection brush preference | | | | |
| No preference | 91 (22.8) | 34 (15.9) | 57 (30.8) | Ref. |
| Evalyn brush (self-collection stored dry) | 184 (46.1) | 108 (50.5) | 76 (41.1) | 0.18 (0.08 to 0.29) |
| Viba brush (self-collection stored wet in media) | 124 (31.1) | 72 (58.1) | 52 (28.1) | 0.20 (0.07 to 0.33) |
| Was the Evalyn brush comfortable to insert? | | | | |
| Agree | 354 (88.7) | 193 (90.2) | 161 (87.0) | Ref. |
| Neither agree or disagree | 1 (0.3) | 0 (0.0) | 1 (0.5) | - |
| Disagree | 44 (11.0) | 21 (9.8) | 23 (12.4) | -0.03 (-0.09 to 0.03) |
| Were the instructions for self-collection using the Evalyn brush easy to understand? | | | | |
| Agree | 377 (94.5) | 201 (93.9) | 176 (95.1) | Ref. |
| Neither agree or disagree | 1 (0.3) | 1 (0.5) | 0 (0.0) | - |
| Disagree | 21 (5.3) | 12 (5.6) | 9 (4.9) | 0.01 (-0.04 to 0.05) |
| Were you concerned about hurting yourself using the Evalyn brush? | | | | |
| Agree | 181 (45.4) | 99 (46.3) | 82 (44.3) | Ref. |
| Neither agree or disagree | 0 (0.0) | 0 (0.0) | 0 (0.0) | - |
| Disagree | 218 (54.6) | 115 (53.7) | 103 (55.7) | -0.02 (-0.12 to 0.08) |
| Were you concerned about using the Evalyn brush properly? | | | | |
| Agree | 236 (59.2) | 133 (62.2) | 103 (55.7) | Ref. |
| Neither agree or disagree | 5 (1.3) | 3 (1.4) | 2 (1.1) | - |
| Disagree | 158 (39.6) | 78 (36.5) | 80 (43.2) | -0.06 (-0.16 to 0.03) |
| Was the Viba brush comfortable to insert? | | | | |
| Agree | 313 (78.5) | 162 (75.7) | 151 (81.6) | Ref. |
| Neither agree or disagree | 2 (0.5) | 1 (0.5) | 1 (0.5) | - |
| Disagree | 84 (21.1) | 51 (23.8) | 33 (17.8) | 0.06 (-0.02 to 0.14) |

| | | | | |
|---|---|---|---|---|
| Were the instructions for self-collection using the Viba brush easy to understand? | | | | |
| Agree | 367 (92.0) | 198 (92.5) | 169 (91.4) | Ref. |
| Neither agree or disagree | 1 (0.3) | 0 (0.0) | 1 (0.5) | - |
| Disagree | 31 (7.8) | 16 (7.5) | 15 (8.1) | -0.01 (-0.06 to 0.05) |
| Were you concerned about hurting yourself using the Viba brush? | | | | |
| Agree | 218 (54.6) | 124 (57.9) | 94 (50.8) | Ref. |
| Neither agree or disagree | 4 (1.0) | 2 (0.9) | 2 (1.1) | - |
| Disagree | 177 (44.4) | 88 (41.1) | 89 (48.1) | -0.07 (-0.17 to 0.03) |
| Were you concerned about using the Viba brush properly? | | | | |
| Agree | 252 (63.2) | 146 (68.2) | 106 (57.3) | Ref. |
| Neither agree or disagree | 9 (2.3) | 5 (2.3) | 4 (2.2) | - |
| Disagree | 138 (34.6) | 63 (29.4) | 75 (40.5) | -0.11 (-0.20 to -0.01) |

Abbreviations: HPV, human papillomavirus; PD, prevalence difference; CI, confidence intervals; Ref, reference

**Table 4.6:** Sensitivity Analyses to Calculate PPV and NPV for varying prevalence of ≥HSIL

| HPV Test Type | Prevalence of ≥HSIL (Gold Standard) | Positive Predictive Value (PPV) | | | Negative Predictive Value (NPV) | | |
|---|---|---|---|---|---|---|---|
| | | (%) | Confidence Interval | | (%) | Confidence Interval | |
| Self-Collected stored Dry | | | | | | | |
| | 5.0 | 12.5 | 9.9 | 15.6 | 98.4 | 96.8 | 99.2 |
| | 7.5 | 18.1 | 14.5 | 22.2 | 97.5 | 95.1 | 98.8 |
| | 10.0 | 23.2 | 18.9 | 28.1 | 96.7 | 93.4 | 98.3 |
| | 12.5 | 28.0 | 23.1 | 33.5 | 95.7 | 91.7 | 97.9 |
| | 15.0 | 32.4 | 27.0 | 38.3 | 94.8 | 90.0 | 97.4 |
| | 17.5 | 36.6 | 30.8 | 42.8 | 93.8 | 88.2 | 96.9 |
| | 20.0 | 40.5 | 34.4 | 46.8 | 92.8 | 86.3 | 96.3 |
| Self-Collected stored Wet | | | | | | | |
| | 5.0 | 11.8 | 9.7 | 14.2 | 98.8 | 97.2 | 99.5 |
| | 7.5 | 17.0 | 14.2 | 20.3 | 98.2 | 95.7 | 99.3 |
| | 10.0 | 22.0 | 18.5 | 25.9 | 97.6 | 94.2 | 99.0 |
| | 12.5 | 26.6 | 22.6 | 31.0 | 96.9 | 92.7 | 98.7 |
| | 15.0 | 30.9 | 26.5 | 35.7 | 96.2 | 91.1 | 98.4 |
| | 17.5 | 35.0 | 30.3 | 40.0 | 95.5 | 89.5 | 98.1 |
| | 20.0 | 38.8 | 33.8 | 44.0 | 94.7 | 87.9 | 97.8 |
| Physician-Collected | | | | | | | |
| | 5.0 | 13.8 | 11.7 | 16.2 | 99.4 | 97.9 | 99.9 |
| | 7.5 | 19.7 | 16.9 | 22.9 | 99.1 | 96.8 | 99.8 |
| | 10.0 | 25.2 | 21.8 | 28.9 | 98.8 | 95.7 | 99.7 |
| | 12.5 | 30.2 | 26.4 | 34.3 | 98.5 | 94.5 | 99.6 |
| | 15.0 | 34.8 | 30.7 | 39.2 | 98.2 | 93.3 | 99.5 |
| | 17.5 | 39.1 | 34.7 | 43.7 | 97.8 | 92.1 | 99.4 |
| | 20.0 | 43.1 | 38.5 | 47.8 | 97.4 | 90.8 | 99.3 |

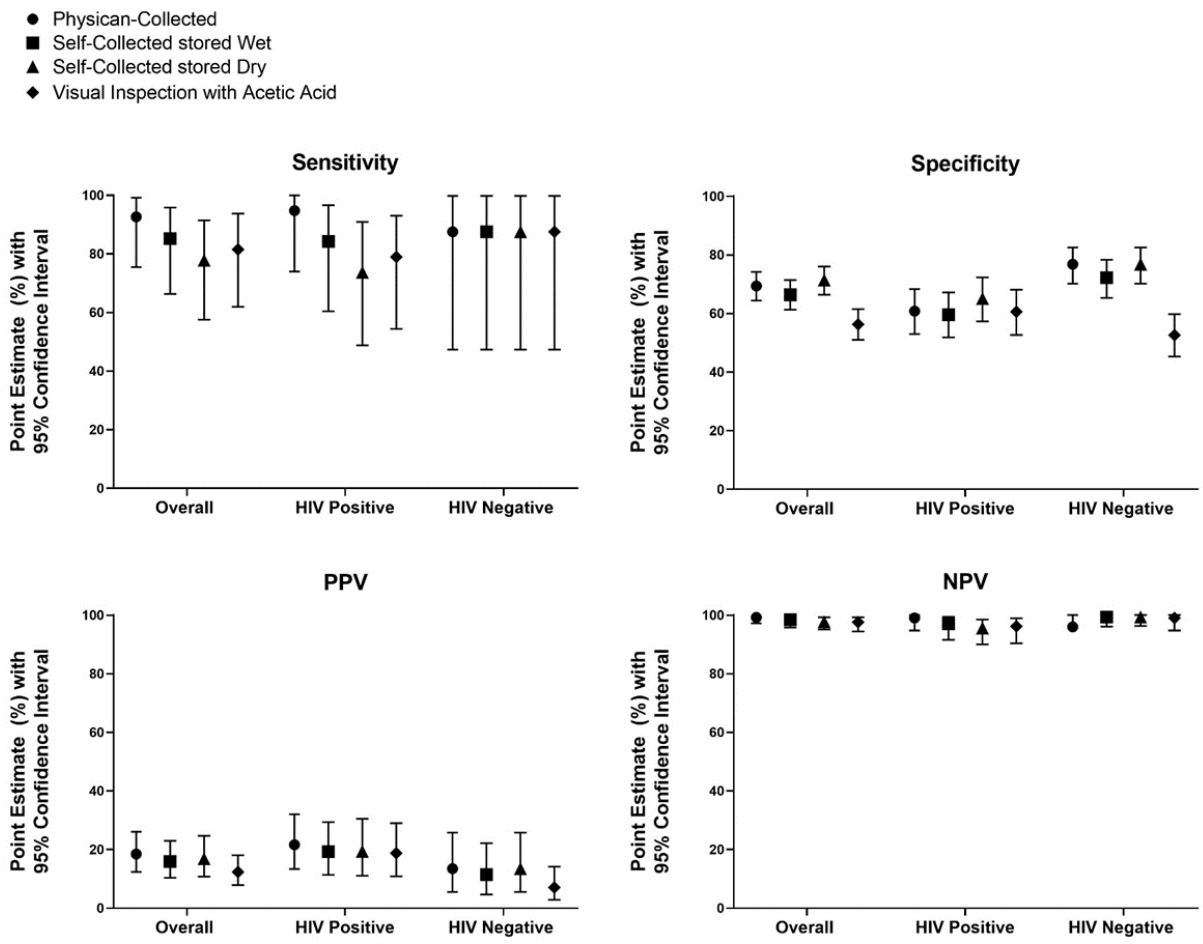


**Figure 4.1:** Performance of HPV Testing of Physician-Collected, Wet Self-Collected, Dry Self-Collected and Visual Inspection with Acetic Acid Specimens for the detection of cytological high-grade cervical lesions in 387 female sex workers in Mombasa, Kenya (2013-2018)

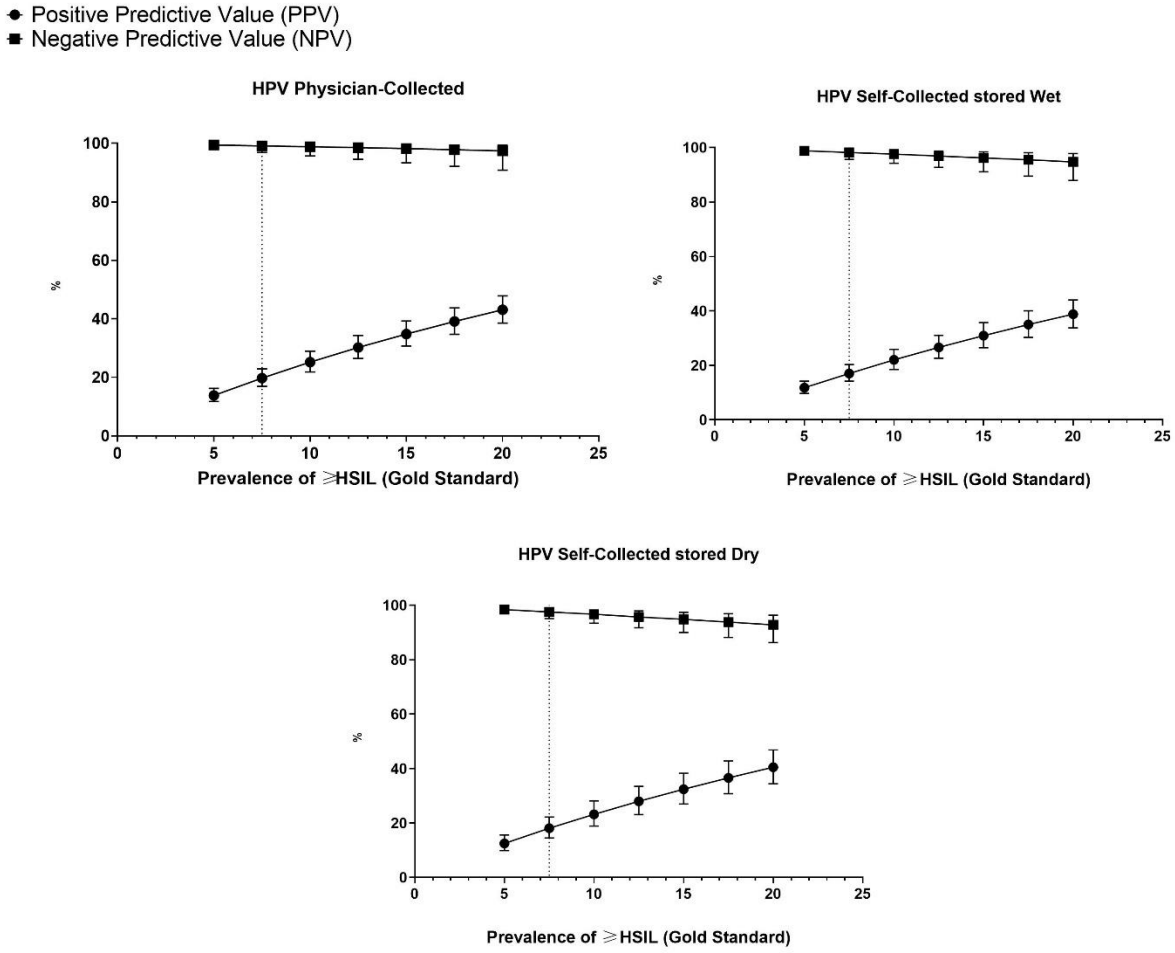


**Figure 4.2:** Summary graph of sensitivity analyses conducted for HPV mRNA testing using physician-collected, self-collected stored wet, and self-collected stored dry samples for the detection of ≥HSIL

# CHAPTER 5. COST-EFFECTIVENESS OF COMMUNITY HEALTH CAMPAIGN STRATEGIES TO DELIVER SELF-COLLECTED HUMAN PAPILLOMAVIRUS-BASED TESTING FOR CERVICAL CANCER SCREENING IN KENYA

## Overview

Cervical cancer (CC) is the leading cause of cancer-related deaths among women in Kenya, with national CC screening coverage as low as 13% due to barriers to access and uptake. Using community health campaigns to deliver CC screening services is a potential solution to low uptake when paired with adequate access to treatment following a positive screening result. While HPV-based self-screening is known to be a cost-effective approach in low-resource settings, options for linkage to treatment after a woman has screened positive have not been evaluated. Data are needed to inform policymakers in Kenya on the cost-effectiveness of CC screening using different models of follow-up and linkage to treatment.

The objective of this study was to evaluate the health outcomes (measured in disability-adjusted life years or DALYs), costs, and cost-effectiveness of four cervical cancer screening scenarios in Kenya, each using community health campaign (CHC) based HPV self-screening: (1) followed by VIA to assess appropriateness of cryotherapy ("HPV & Treat"), with *standard* linkage to treatment; (2) "HPV & Treat" with *enhanced* linkage to treatment; (3) followed by VIA screening for triage to treatment ("HPV+VIA & Treat"), with *standard* linkage to treatment; and (4) "HPV+VIA & Treat" with *enhanced* linkage to treatment. We modeled the screening delivery strategies and linkage to treatment methods based on a clustered randomized control trial carried out in Kenya.

We created a decision tree model in Excel to estimate program and health care costs, outcomes, disability-adjusted life years (DALYs), and cost-effectiveness (net cost per DALY averted) for each screening scenario, over a 6-year time horizon for women aged 25-64 years. We used published literature to estimate test performance, and short- and long-term clinical outcomes. Cost data were collected during

a two-phase clustered-randomized trial of the scenarios conducted in Migori County, Kenya. Deterministic and probabilistic sensitivity analyses were conducted.

Compared to strategies that used "HPV+VIA & Treat", "HPV & Treat" strategies led to better health outcomes, as measured in DALYs and were more cost-effective due to fewer missed cases of CIN2+ eligible for treatment. More specifically, we found that compared to no screening, "HPV & Treat" with enhanced linkage to treatment was the most cost-effective option at $5,492.62 I$/DALY averted. Deterministic sensitivity analyses showed that the cost of screening and disability weights associated with screening most impacted the cost-effectiveness of "HPV & Treat" options.

CHCs using HPV-based self-collection followed by "HPV & Treat" with enhanced linkage to treatment appears to be a cost-effective option for Kenya. Future studies to assess national programmatic costs from the perspective of the Kenyan Ministry of Health to inform scale-up of CHCs are needed.

## Background

Cervical cancer is the leading cause of cancer-related deaths among women in sub-Saharan Africa, including Kenya (104). Although national estimates are unavailable, using data from the Nairobi Cancer Registry, 65% of women with cervical cancer die within one year of diagnosis in Kenya (130). Cervical cancer is highly preventable through screening, early detection, and treatment of cervical precursor lesions (103). Routine screening with Papanicolaou (Pap) smear testing has reduced cervical cancer incidence and mortality by at least 80% in high-income countries, such as the United States (105, 106). However, the implementation of Pap-based programs in low-resource settings has not been feasible due to systemic national barriers, including few trained personnel or available clinics, particularly in rural areas, and limited healthcare budgets and infrastructure (107). In Kenya, where current screening efforts are limited to opportunistic screening with Pap testing or visual inspection with acetic acid (VIA), cervical cancer screening program coverage among women aged 30-49 years is only 13.8% nationwide and below 11% in rural areas, compared to the global coverage of 40%(131). To improve access to

cervical cancer prevention in low-resource settings, screening delivery methods that are cost-effective, simple to implement, and remove the need for pelvic speculum examination are needed.

The World Health Organization recommends the use of VIA or testing for high-risk HPV (hr-HPV) DNA, the necessary cause of cervical cancer, in low-resource countries (1, 132). Although VIA requires few resources, there is wide variability in the reported sensitivity and specificity of VIA for the detection of cervical neoplasia based on the setting, target population, and provider training (25, 27-29). Low sensitivity and specificity of VIA for the detection of cervical neoplasia may lead to missed cases if high-quality VIA testing cannot be assured(133). On the other hand, molecular hr-HPV DNA testing provides an effective, objective, and highly reproducible test result (30). Most importantly, molecular hr-HPV DNA testing can be reliably conducted using self-collected samples(56, 121). Self-collection for hr-HPV testing has the potential to increase the number of women screened by addressing frequently cited barriers to screening (62), including clinic accessibility, clinic-based staffing shortages, patient's fear of pain caused from the speculum exam, and costs (63). Self-collected HPV testing has been shown to be cost-effective compared to VIA and cytology in low-resource settings when it yields population coverage gains over other screening methods (82).

To effectively deliver hr-HPV DNA testing through self-collection in Kenya, high-population coverage of hr-HPV self-screening methods is needed with effective linkage to treatment once a woman screens positive for hr-HPV DNA. Community health campaigns (CHCs) are a viable and effective strategy to deliver cervical cancer screening in low-resource settings. CHCs occur over a short duration and can provide preventive services to a high volume of people. Community-based approaches to cervical cancer screening have been found to improve cancer screening coverage, particularly among those groups known as "hard-to-reach" populations(87). In addition to adequate coverage as an advantage, CHCs provide an opportunity to link women who test hr-HPV-positive to treatment. Although not previously tested in cervical cancer screening strategies, alternative methods to improve linkage to treatment and follow-up have been evaluated in other reproductive health campaigns in Kenya such as text messaging, vouchers, and mobile treatment units (90-92). Assessing the effectiveness and associated costs of

community-based strategies to link hr-HPV positive women to treatment is crucial to identifying a screening strategy that will effectively reduce the burden of cervical neoplasia and subsequent invasive disease.

To our knowledge, no prior studies have evaluated the cost-effectiveness of community health campaigns for cervical cancer screening delivery in Kenya or assessed alternative methods for linkage to treatment once a woman has screened positive for HPV. As governments and policymakers consider how to utilize national resources and achieve the most significant health impact, information on costs and cost-effectiveness of cervical cancer screening delivery models is crucial to inform decision-making. Our objective was to assess the relative cost-effectiveness of four different scenarios each utilizing community health campaigns to deliver cervical cancer screening through self-collection for hr-HPV testing with alternative triage approaches for linkage to treatment in Kenya. We modeled the screening delivery strategies and linkage to treatment methods based on a clustered randomized control trial carried out in Kenya.

## Methods

### Overview

We estimated the total costs, health outcomes measured in disability-adjusted life years (DALYs), and incremental cost-effectiveness of four strategies to deliver HPV-based cervical cancer screening using community health campaigns for a hypothetical cohort of 1000 women aged 25-65 years in Kenya. We constructed a decision-tree analytic model using Excel™ 2016 (Microsoft Corp, Redmond, WA, USA) to compare the following four strategies over a 6-year time horizon, each using community health campaign (CHC) based HPV self-screening: (1) followed by VIA to assess appropriateness of cryotherapy ("HPV & Treat"), with *standard* linkage to treatment; (2) "HPV & Treat" with *enhanced* linkage to treatment; (3) followed by VIA screening for triage to treatment ("HPV+VIA & Treat"), with *standard* linkage to treatment; and (4) "HPV+VIA & Treat" with *enhanced* linkage to treatment. A simplified version of this model is portrayed in Figure 5.1. Additionally, we compared these four strategies to the standard of care

for cervical cancer screening in Kenya, which we assumed to be no screening due to low coverage in the population. The model was informed by screening and treatment uptake, follow-up, linkage to treatment strategies, and micro-costing data from a cluster-randomized control trial conducted in rural Migori County, Kenya. The primary outcome measure was the incremental cost-effectiveness ratio (ICER), defined as the incremental 2018 International Dollars (I$) per disability-adjusted life-year averted. Cost-effectiveness was defined according to the WHO guidelines as an ICER $\leq$ 3 times the per capita gross domestic product (GDP). According to The World Bank, Kenya has an overall per capita GDP of 3461.4 I$. (134). In keeping with guidelines on cost-effectiveness analyses, we discounted all costs and DALYs at a rate of 3% to account for time preferences(100) and evaluated costs from a societal perspective.

Programmatic Assumptions and Screening Strategies

Programmatic assumptions and screening strategies for this decision tree model were based on the health care delivery models implemented in a two-phase cluster-randomized control trial conducted to compare HPV-based cervical cancer screening in community-health campaigns using alternative methods for linkage to treatment following an HPV-positive test result. During Phase 1 of this trial, which occurred from January to November 2016, CHC-based screening delivery took place in six randomly-selected communities for two weeks. Phase 1 also included clinic-based screening delivery; however, a prior costing evaluation found the cost per woman screened using clinic-based screening was much higher than CHC-based screening and thus was not included in this cost-effectiveness analysis(97).

During the CHCs, there were three stages of workflow: outreach, screening, and notification. For outreach, members of the CHC team carried out stakeholder meetings, information sessions, door-to-door mobilization, announcements using public-address systems and posters. During the screening stage, the entire CHC team traveled to different areas of the CHC community every morning to set up tents. Each woman who visited the tent went through a sequence of screening activities: registration, group education, informed consent, and self-collection of screening specimens using the careHPV test kit. After two weeks

of screening, the CHC team moved into the notification of results and standard referral, which also lasted two weeks.

During Phase 1, women were notified of their results and, if HPV positive, referred to treatment using “standard linkage” using text messages, phone calls, and home visits conducted by community health volunteers. Along with their test results, HPV-positive women were provided with instructions on appropriate follow-up as recommended by the Kenya Ministry of Health Guidelines(19). HPV-positive women in all communities received a standard referral to one treatment site located in Migori County Hospital for evaluation for treatment with cryotherapy, which was offered by a team of trained nurses. A pretreatment pelvic examination and VIA were performed to determine if a woman was eligible for cryotherapy. Women with lesions too large for cryotherapy or any suspicion of micro-invasive disease were offered Loop Electrosurgical Excision Procedure (LEEP); otherwise, all women were provided cryotherapy based on their positive HPV result (i.e. “HPV & Treat”)(103).

Phase 2 of this trial occurred from February to October 2018 in another six rural communities. Similar to Phase 1, the implementation of the CHCs during phase 2 included three stages, outreach, screening, and notification of results with enhanced referral to treatment (i.e., enhanced linkage to treatment). There are two critical differences in the screening delivery model between Phase 1 and Phase 2: (1) During Phase 2, women in the target age range who did not attend the CHCs for screening (46.4% of the target population) were offered home-based screening in November 2018, (2) “enhanced linkage” to treatment strategies were implemented. Enhanced linkage to treatment methods included reminder text messages with updated messaging only sent to women who did not appear for their recommended treatment within three months after receiving their positive test results and holding community health campaigns in locations within close proximity to clinics where treatment is available (decentralization of treatment center). During Phase 2, women were referred for treatment at a clinic in proximity to their respective communities; there were four treatment centers available, including the Migori County Hospital. Treatment procedures during phase 2 paralleled that of phase 1 described above.

For our decision tree model, we also compared the "HPV & Treat" strategy implemented in the trial to an alternative form of treatment triage. Currently, the Kenyan Ministry of Health Guidelines for cervical cancer screening recommends alternative types of "screen-and-treat" triage approaches following a positive HPV-test, where women are either referred to treatment based on the results of VIA screening and HPV-test ("HPV+VIA & Treat"), or based solely on the results of an HPV-test alone ("HPV & Treat") (19, 103) (Figure 5.2). Using the "HPV+VIA & Treat" strategy, following a positive HPV test women are referred to VIA and if the VIA screening result is positive, women are referred to cryotherapy or LEEP, or colposcopy and biopsy if cancer is suspected. However, if the VIA result is negative, there is no follow-up or treatment. There is concern that HPV testing followed by VIA triage can compromise the sensitivity of the original test (HPV screening) and may miss some precancer among HPV-positive women. However, this may be a cost-saving strategy as not all women are treated.

Model Structure and Health Inputs

We carried out an in-depth literature review to identify the relevant probabilities of paths from true disease status, hr-HPV infection to detection (by clinical presentation or screening), the risks of clinical progression from cervical neoplasia to invasive cervical cancer, and potential outcomes with or without treatment as summarized in Table 5.1. Preference was given to data from sub-Saharan Africa and East Africa, but for outcomes with no such evidence available we prioritized utilizing data from longitudinal studies of the natural history of HPV in a low-resource country setting or meta-analyses. Disagreement over study eligibility, base-case estimates, transition probabilities, and disability weights was resolved by consensus among all authors, including clinical experts.

Our model followed a hypothetical cohort of 1000 women aged 25-65 years starting with true disease status; women either had cervical intraepithelial neoplasia stage 2 and above (CIN2+) or were <CIN2 (i.e., disease negative). The probability of CIN2+ was 6.9% as reported by a meta-analysis with estimates from East Africa(135). We assumed that 100% of women with CIN2+ were positive for hr-HPV DNA(136). Women with <CIN2 were either hr-HPV positive or hr-HPV negative based on the local

epidemiology of HPV infection(2). We utilized sensitivity and specificity estimates of self-collected HPV DNA testing (using careHPV) and VIA for the detection of CIN2+ from a multicountry evaluation of cervical cancer screening methods(137). Following screening, women either underwent cryotherapy or LEEP based on the size of their lesion or were lost to follow-up. As local data were unavailable, the probability of long-term outcomes (persistent or newly developed CIN2+ and cervical cancer) for women who were lost to follow-up or did not attend screening campaigns were estimated based on the risk estimates used to develop the latest American Society for Colposcopy and Cervical Pathology (ASCCP) cervical cancer screening and management guidelines(138).

Among women who received treatment, we assumed the probability of LEEP referral was 12% based on a prior cluster-randomized trial of cervical cancer screening in India. The RCT from India provided estimates for cryotherapy use (i.e., LEEP referral) based on multiple screening tests including VIA, which is relevant to our model of health care delivery (139). We accounted for the probability of potential complications following both cryotherapy or LEEP. Using data from a meta-analysis, we calculated the probability of minor complications, defined as minor bleeding, following cryotherapy (0.14%) and LEEP (1.55%)(140). Additionally, we calculated the probability of major complications following cryotherapy (0.34%), which was defined as major bleeding. The probability of major complications following LEEP was 2.14% and included the following potential complications: major bleeding, major infection, pelvic inflammatory disease, and damage to organs. Major complications following cryotherapy were limited to major bleeding as it was the most common and the remaining conditions were very rare (<0.05%). Following treatment with either cryotherapy or LEEP, the cure rate (i.e. probability of treatment effectiveness) of each treatment was obtained from a meta-analysis to compare LEEP versus cryotherapy in the treatment of CIN (141). We specifically utilized estimates from a study conducted in Zimbabwe included in the meta-analysis; the cure rate of CIN2+ at 12 months following cryotherapy was 88.3% and following LEEP was 96.4%(142).

Additionally, among women with <CIN2 the probability of CIN2+ after 12 months was 95.2% following cryotherapy and 96.4% following LEEP(141). Women with recurrent CIN2+ or newly

developed CIN2+ within the time horizon (true disease status negative at baseline) either received treatment with LEEP during follow-up, as recommended by the WHO(143) or were lost to follow-up (70%). Among women who were lost to follow-up, the probability of developing cervical cancer within six years was 0.3%(144). We estimated the proportion of women with cervical cancer who will access treatment was 35.5% based on a prior study conducted in Kenya(145). The probability of survival following a cervical cancer diagnosis was 15.9% based on a study conducted in Uganda, a similar low-resource setting. We assumed the risk at six-years of cervical cancer was 0% among women who's true disease status was disease negative (<CIN2) at the start of the decision model(146).

Prior reports have shown that accounting for the potential small loss in quality of life following screening to calculate DALYs for HPV screening produces substantially different results(147, 148). Therefore, we calculated DALYs incurred both excluding and including disability weights for screening-related health states. In the absence of disability weights for cervical cancer screening, we utilized the complement of utility values generated from international studies and previous health economic models(147-149), as has been done in prior cost-effectiveness analyses(150-152) (Table 5.1). To account for DALYs incurred for complications following treatment, we utilized the major (>1 L blood lost) and minor (<1 L blood lost) bleeding disability weights available in the 2017 Global Burden of Disease (GBD) study(153). Additionally, for major complications following LEEP, we utilized the generalized disability weights from the 2013 GBD for abdominopelvic problems with varying levels of severity (mild, moderate, and severe) depending on time since the complication occurred. Disability weights for cervical cancer-related outcomes used to calculate DALYs incurred throughout this model were taken from the 2017 GBD (153). We assumed the baseline disability weight value of normal health to be 0.0. Estimates for the duration of reductions in quality of life were mainly based on expert opinion and prior literature.

Cost Parameters

Cost inputs included in this analysis were mainly collected through the micro-costing efforts carried out during both Phase 1 and Phase 2 of the cluster-randomized control trial conducted in Migori

County, Kenya (Table 5.2). Details regarding the micro-costing procedures have been previously published(97, 99). Direct costs were estimated from the health system perspective, and included costs of labor or wage rates of staff and health care providers were based on market wages and salaries. Research-related costs were omitted from program cost estimates.

Capital goods cost estimation was based on total costs from expenditure records. Capital goods were defined as tangible assets such as the vehicle for transportation, tents for CHCs, and the careHPV test system, which is a rapid test for HPV DNA for use in low-resource settings (Qiagen, Gaithersburg, Maryland). Costs of CHC personnel were based on established salaries and time spent at each CHC by phase: outreach, screening, and notification and referral. Since all stages of the CHCs lasted for two weeks, the personnel cost for a phase was the personnel's salary for two weeks. Expenditure records, interviews, time and motion logs, market rates, direct counts made by the costing lead, salary records and estimations based on the Ministry of Health's data for facility costs were the sources of primary data used to measure the costs of each intervention activity and phase. The cost data were collected manually and electronically recorded into Excel workbooks. The cost items were classified under five input types: recurrent goods, services, personnel, capital goods, and facility overhead. The cost of each input and the number of units were converted into the total economic cost. A time and motion study was carried out to quantify the average time spent by each patient during the screening process (99) by direct and systematic observation during the CHCs. Time measures collected were total visit time, time spent during the screening process, and wait time between each stage of cervical cancer screening. To obtain these data, research assistants recorded the amount of time spent on all activities involved with screening from the patient's arrival to the end of the visit, using activity forms.

Treatment-related costs were also micro-costed from the health system perspective. Personnel costs were estimated based on each provider's monthly salary, taken from the salary records, and the amount of time spent providing treatment. We estimated facility costs by multiplying the proportion of space at the government health clinic dedicated to cryotherapy treatment with the Ministry of Health clinic facilities construction rates. Recurrent goods refer to items consumed within one year. These

included nitrous oxide gas, cryo-tips, sanitary towels, and gloves. Services include expenditure on intervention-related intangible items such as consultant fees, IT support, utilities, vehicle maintenance, and other day-to-day recurring expenses. Costs for recurrent goods and services were estimated from expenditure records. Interviews were conducted with staff to verify the list of recurrent items and services, number of units used, and allocation of items.

Costs for LEEP treatment, major and minor complications, cancer treatment and associated time costs to women were not micro-costed and were taken from a previously conducted cost-effectiveness analysis conducted in several countries including Kenya(154). These costs were published in 2000 International Dollar, which we converted to 2000 Kenyan Shillings (KSH). Micro-costed cost data were collected in local units, which was 2016 Kenyan Shillings (KSH) during Phase 1 and 2018 KSH during Phase 2. Using the historical Kenyan Consumer Price Index (CPI) taken from the Kenya National Bureau of Statistics, we inflated all costs to 2018 KSH. Next, we converted 2018 KSH to both 2018 US$ using direct exchange rates and 2018 International dollars (I$) using purchasing power parity (PPP) exchange rates(101) to compare cost estimates utilizing either approach. We utilized The World Bank's PPP conversion factor for private consumption, which was 50.25 I$ as of 2018(155). To convert local currency units (KSH) to US$ and international dollars, we divided the local currency unit by the respective exchange rate.

### Cost-Effectiveness and Sensitivity Analyses

Baseline values summarized in Table 5.1 were used for the base-case analysis. The ICER, our primary outcome measure, was defined as the incremental cost measured in I$ per DALY averted when comparing intervention strategies. We also calculated the ICER compared to the current standard which is no organized available screening. To calculate ICERs, we conducted sequential comparisons rank-ordered by the total cost(156). We used the extended dominance principle, where a program is not surpassed by any single alternative but by a mixed strategy of two other alternatives, to further identify the most cost-effective strategy compared to no screening(157). We defined the cost-effectiveness willingness to pay

threshold as three-times the per capita GDP of Kenya using Purchasing Power Parity or PPP, which was $10,384.2 International Dollars(155).

Deterministic (one-way univariate) and probabilistic sensitivity analyses were performed to assess the robustness of the assumptions in the decision model using Crystal Ball (Oracle, Redwood Shores, CA). In general, we used ranges that represent values reported in the scientific literature. One-way sensitivity analyses were performed for parameters identified as significant drivers of the ICER for each strategy. Distribution of probabilities was based on observed ranges reported in the primary literature (Table 5.1). Where range data were lacking or unavailable, assumption ranges were generally set to 0.5 (min) and 1.5 (max) times the base case value.

To assess a range of possible outcome values and assess the confidence in our ICER outcome, we performed probabilistic sensitivity analysis using Monte Carlo simulations. Each model parameter was assigned a distribution based on the range of values observed in the literature, and all parameters were varied simultaneously with 10,000 iterations of possible input values, generating an equal number of possible cost and quality outputs. Cost variables were modeled using a gamma distribution, which restricts values to be nonnegative and can represent the usually right-skewed nature of cost data(102, 158). Probabilities were modeled with a beta distribution, which restricts probabilities between 0 and 1. The beta distribution is generally described by the number of times a given event occurred ($\alpha$) and the number of times the event did not occur ($\beta$). Disability weights were modeled with a triangular distribution describing the expected maximum, minimum, and modal value.

## Results

### Health Outcomes

In the base case scenario of 1000 women in rural Kenya while accounting for DALYs incurred due to screening, “HPV+VIA & Treat” with standard linkage to treatment offered minor improvements compared to no screening intervention, amounting to 1.16 DALYs averted (Table 5.4). Using “HPV & Treat” with standard linkage led to an improvement in health outcomes with 4.16 DALYs averted compared to “HPV+VIA & Treat” with standard linkage. HPV+VIA & enhanced linkage to treatment led

to the smallest improvement in health compared to the "HPV & Treat" strategy with standard linkage (0.91 DALYs averted per 1000 women). The most substantial improvement was provided by the HPV& Treat with enhanced linkage strategy with 6.28 DALYs averted compared to "HPV+VIA & Treat" with enhanced linkage.

Using the extended dominance principle(157), which is defined as using the set of all possible strategies that dominate a strategy in both higher effectiveness and less cost, we excluded the strategies that involved HPV+VIA. In this scenario, compared to no screening, HPV& Treat with standard linkage averted 5.32 DALYs. Additionally, although more expensive, compared to "HPV & Treat" with standard linkage, enhanced linkage averted an additional 7.19 DALYs. When compared to no screening, "HPV & Treat" with enhanced linkage led to the largest reduction in DALYs (12.50).

We observed substantial differences in health outcomes (DALYs averted) when we excluded DALYs incurred due to screening. Using the extended dominance principle when we examined only "HPV & Treat" strategies, we observed a reduction in 15.38 DALYs when "HPV & Treat" with standard linkage is compared to no screening. Using "HPV & Treat" with enhanced linkage averted an additional 10.13 DALYs, compared with no screening. Again, when compared to no screening, "HPV & Treat" with enhanced linkage led to a large reduction in DALYs at 25.50.

Incremental Cost-Effectiveness

The base case ICERs of our interventions are: $28,131/DALY averted for the "HPV+VIA & Treat" with standard linkage to treatment compared to no intervention, $287/DALY averted for HPV& Treat compared to "HPV+VIA & Treat" both with standard linkage to treatment, $29,593/DALY averted for "HPV+VIA & Treat" with enhanced linkage compared to "HPV & Treat" with standard linkage to treatment, and $1284/DALY averted for HPV& Treat compared to "HPV+VIA & Treat" both with enhanced linkage to treatment. The ICERs for both "HPV & Treat" strategies met the willingness to pay threshold of "very cost-effective" which is equal to the per capita GDP of Kenya (I$3461.4)(155).

Under extended dominance, we excluded the strategies that involved "HPV+VIA & Treat". The result was $6343/DALY averted for "HPV & Treat" strategy with standard linkage compared to no screening, and $4,864/DALY averted for HPV& Treat with enhanced linkage compared to standard linkage. Compared to no screening, the ICER for "HPV& Treat" with enhanced linkage was $5,492/DALY averted. All three comparisons met the willingness to pay threshold of "cost-effective," which is equal to 3 times the per capita GDP of Kenya (I$10,384.20)(155). When we compared each strategy to no screening, "HPV & Treat" with enhanced linkage was the most cost-effective ($5493/DALY averted).

When we excluded DALYs incurred due to screening, we observed substantial differences in ICERs for all comparisons, particularly those that include HPV+VIA screening. Compared to no screening, "HPV+VIA & Treat" with standard linkage to treatment demonstrated an ICER of $2688/DALY averted, which would be categorized as "very cost-effective" at the willingness to pay threshold of I$ 3461.4/DALY averted in sharp contrast to the ICER when DALYs incurred due to screening are included ($28,131/DALY).

Sensitivity Analyses

In one-way sensitivity analyses, we estimated the potential range of ICERs for the strategies comparing all strategies evaluated and remaining strategies after extended dominance. Table 5.4 summarizes the results from the most influential input parameters and compares the following strategies: "HPV+VIA & Treat" with standard linkage compared with no screening, "HPV & Treat" with standard linkage compared with "HPV+VIA & Treat" with standard linkage, "HPV+VIA & Treat" with enhanced linkage compared with "HPV & Treat" with standard linkage; and finally "HPV & Treat" with enhanced linkage compared with "HPV+VIA & Treat" with enhanced linkage. Overall, sensitivity analyses showed that the model was most sensitive to changes in disability weights for all three screening-related health states. Additionally, the proportion of women who presented for treatment using standard or enhanced

referral both affected the ICERs considerably; a higher proportion of women successfully linked to treatment led to more favorable ICERs.

Table 5.5 summarizes the results of the one-way sensitivity analyses evaluating the following "HPV & Treat" screening comparisons: standard linkage compared with no screening, enhanced linkage compared with standard linkage, and enhanced linkage compared with no screening. Here, the most influential parameters were the proportion of HPV-positive women that present for treatment using either standard or enhanced linkage to treatment methods; and the disability for testing HPV positive.

Probabilistic sensitivity analyses or PSA was performed using Monte Carlo simulation by 10,000 iterations; demonstrated an overall robust model, where each input parameter is simultaneously varied across a given range of values from the parameter's defined distribution. When evaluating only "HPV & Treat" strategies (Figure 5.3), we find that compared to no screening, "HPV & Treat" with standard linkage to treatment was cost-effective (with an ICER below the 3 times willingness to pay threshold of I$10,384.2/DALY averted) in 32% of the iterations. About 13% of the simulations were dominated (in which standard linkage to treatment was both more costly and less effective than no screening). When comparing enhanced linkage to treatment to standard linkage, 67% of iterations were below the willingness to pay threshold and considered cost-effective (three times the GDP). The remaining iterations showed enhanced linkage to be more effective, however, more costly and above the willingness to pay threshold. Finally, when comparing enhanced linkage to treatment to no screening, 67% of iterations were cost-effective (Figure 5.4).

## Discussion

To our knowledge, this is the first study to evaluate the cost-effectiveness of cervical cancer screening delivery through community health campaigns to women in Kenya. We found that utilizing "HPV & Treat" as a strategy to recommend women for treatment led to better health outcomes and was more cost-effective, compared to "HPV+VIA & Treat" due to fewer missed cases of CIN2+ eligible for treatment. More specifically, we found that compared to no screening, "HPV& Treat" with enhanced

linkage to treatment was the most cost-effective option at $5492.62 I$/DALY averted. Finally, we found that excluding potential DALYs incurred due to screening highly affected the cost-effectiveness of cervical cancer screening scenarios modeled. When screening-related DALYs were excluded, "HPV & Treat" paired with screening delivery models used with standard linkage to treatment and enhanced linkage to treatment met the WHO definition of "very cost-effective" when compared to no screening.

In resource-constrained settings, the World Health Organization recommends implementing VIA as a triage strategy to refer women to treatment. The Kenyan Ministry of Health has adopted the recommendation and included it in their guidelines for screening and treatment of cervical neoplasia. Although utilizing VIA screening in conjunction with HPV-testing leads to lower overall costs compared to "HPV & Treat" methods, the overall cost-effectiveness is lower due to poorer health outcomes or fewer DALYs averted. This finding is similar to a recent cost-effectiveness analysis conducted in Uganda to compare home-based HPV self-collection delivered through community campaigns to VIA (159). Similar to our results, they found that HPV testing is more effective without VIA triage before cryotherapy(159). Our findings demonstrate that the sensitivity of VIA (i.e. ability of the test to correctly identify cases) highly impacts the cost-effectiveness of utilizing VIA triage before cryotherapy compared to HPV-testing alone. Our base-case analysis assumed the sensitivity of VIA for the detection of CIN2+ was 74%, which was based on the results from Uganda of a multicountry evaluation of several cervical cancer screening methods including careHPV, VIA, and cytology(137). Prior studies have evaluated the sensitivity of VIA as a triage test, and have shown considerable variability in the point estimate ranging from 25% to 81.9%(28, 29, 160). Variability in VIA test performance is highly dependent on setting, provider training, and severity of disease. As such, our results suggest that implementing an "HPV & Treat" strategy may be most suitable for low-resource settings. However, before implementation, policymakers must consider the added workload this strategy may place on the health care sector as all HPV-positive would be recommended for cryotherapy, or LEEP depending on the size of cervical lesions.

Prior studies have evaluated the cost-effectiveness of self-collected HPV testing in low-resource settings, demonstrating that HPV-based self-collection can be cost-effective compared to alternative

screening methods if it leads to substantial gains in population coverage(82). For example, a prior cost-effectiveness analysis conducted in Uganda demonstrated that decreasing HPV test sensitivity by 20% using self-collection instead of physician-collection could be offset by a 20% improvement in screening coverage(161). Our results suggest that the proportion of women who are successfully linked to treatment may have a higher impact on cost-effectiveness than screening uptake and coverage. In one-way sensitivity analyses of "HPV & Treat" strategies, we observed that the ICERs comparing both standard and enhanced linkage treatment strategies were dominated when compared to no screening (i.e. more costly and less effective than no screening). As "HPV & Treat" with enhanced linkage to treatment was the most cost-effective strategy compared to no screening, future programs may consider employing enhanced linkage strategies utilized by the cluster-randomized trial. Decentralization of treatment availability provided women with the opportunity to avail treatment in proximity to their community where the campaigns took place. Additionally, targeting women who did not appear for their recommended treatment within three months after receiving their positive test results with reminder text messages and updated messaging

To our knowledge, our study is the first to apply disutility of cervical cancer screening-related health states to a cost-effectiveness analysis in a low-resource setting. This is due to the unavailability of health state utility or disability weight data from low-resource countries. We utilized data collected from women in high-resource countries, namely Australia(149) and the U.S(162). Prior studies have shown there is a small loss of quality of life following cervical cancer screening. The loss in quality of life is comprised of the time needed to attend screening, and any anxiety caused by waiting for the result(163). Larger losses in quality of life are known to occur following treatment with cryotherapy and LEEP, which have also not been accounted for in prior economic models in low-resource settings. Despite the reduction in effectiveness (DALYs averted) after including DALYs incurred due to screening, "HPV & Treat" cervical cancer screening delivery models were still cost-effective at three-time the Kenyan GDP willingness-to-pay threshold. Future efforts to collect utility data using a cohort of women from low-resource countries should be prioritized.

There are several limitations to take into consideration when interpreting the results of this analysis. First, the cost-effectiveness results are sensitive to several model inputs that were not collected from women in Kenya or similar low-resource settings. Although we conducted several sensitivity analyses to examine a wide range of potential values of inputs, our base case results may be limited. Second, we utilized the trial data for base-case values of key assumptions and costs to carry out the cost-effectiveness analysis, which may limit the scope of this cost-effectiveness analysis. It is unclear how real-world human resource constraints might affect the cost-effectiveness of different screening strategies. Although Migori County is a rural area, the cost-effectiveness of our modeled strategies may be limited in areas where clinics may be further away or with fewer resources for treatment. For DALYs incurred due to screening-related health states, we calculated disability weights using health utilities derived from women in developed countries. The transferability of health disutility from high-resource to resource-constrained settings is poorly understood and may not be suitable for our setting. Finally, we utilized a decision-tree framework to model the progression of disease from hr-HPV infection to invasive disease and as such, we're unable to account for dynamic effects of factors such as age, sexual behavior, and disease recurrence or regression. While this model is useful for the prediction of programmatic costs and health impact, it does not account for ongoing HPV transmission. Additionally, our time horizon was limited to 6-years due to availability of long-term outcome data, which may have led to an underestimate in the benefit of cervical cancer screening as we are missing deaths that may occur downstream.

Despite these limitations, our analysis shows that using “HPV & Treat” with enhanced linkage to treatment is a cost-effective approach compared to no screening. The programmatic assumptions and health care delivery models is based on trial data rather than hypothetical assumptions, which is a significant strength of our approach. Additionally, we were able to leverage micro-costing data collected during the trial which ensures all necessary components of the program were included in our overall cost estimates.

In conclusion, we found that using community health campaign delivered “HPV & Treat” strategies were more cost-effective than including VIA triage before cryotherapy due to the high false-

negative rate of VIA. Implementing strategies to ensure women are linked to treatment is crucial to effective cervical cancer screening programming. Although highly preventable, cervical cancer continues to be the leading cause of cancer-related mortality among women in Kenya. Our analysis demonstrates there are cost-effective options to prevent deaths due to cervical cancer. Future cost-effectiveness analyses that include national programmatic costs from the perspective of the Kenyan Ministry of Health are warranted. National integration of cervical cancer screening using community health campaigns, with an emphasis on increasing the number of women successfully linked to treatment following a positive HPV test should be considered.

**Table 5.1:** Base case values and ranges of variables used in decision tree analysis

| Variable | Base case value | Range | Reference |
|---|---|---|---|
| Disease Progression Characteristics | | | |
| Prevalence of HPV infection in women with no cervical abnormalities in East Africa | 0.336 | 0.30-0.37 | Bruni et al. |
| Prevalence of high-risk HPV infection in women with CIN2+ | 1.000 | - | Bosch et al. |
| Prevalence of cervical abnormalities (CIN2+) among women in East Africa | 0.070 | 0.02-0.15 | Fokom-Domgue et al |
| Five-year risk of CIN2+ with cervical abnormalities and hr-HPV positive at baseline | 0.750 | 0.74-0.77 | Demarco et al |
| Five-year risk of CIN2+ with no cervical abnormalities and hr-HPV positive at baseline | 0.090 | 0.09-0.10 | Demarco et al |
| Five-year risk of cervical cancer with cervical abnormalities and hr-HPV positive at baseline | 0.060 | 0.05-0.07 | Demarco et al |
| Persistent hr-HPV infection after six years | 0.150 | 0.8-0.23 | Rodriguez et al |
| Cervical lesions ineligible for cryotherapy, LEEP referral | 0.120 | 0.00-0.30 | Sankaranayam et al |
| Probability of LEEP referral with <CIN2 | 0.050 | 0.00-0.10 | Campos et al, Expert opinion |
| Test Characteristics | | | |
| Self-collection for HPV DNA testing (careHPV) | | | |
| Sensitivity for detecting CIN2+ | 0.770 | 0.67-0.85 | Jeronimo et al |
| Specificity for detecting CIN2+ | 0.820 | 0.81-0.83 | Jeronimo et al |
| Visual Inspection with Acetic Acid | | | |
| Sensitivity for detecting CIN2+ | 0.740 | 0.63-0.82 | Jeronimo et al |
| Specificity for detecting CIN2+ | 0.670 | 0.65-0.68 | Jeronimo et al |
| Complication Rates Following Treatment | | | |
| Minor complications following cryotherapy | 0.001 | 0.001-0.002 | Santesso et al |
| Major complications following cryotherapy | 0.003 | 0.002-0.005 | Santesso et al |
| Minor complications following LEEP | 0.016 | 0.014-0.017 | Santesso et al |
| Major complications following LEEP | 0.021 | 0.018-0.025 | Santesso et al |
| Potential Outcomes Following Treatment | | | |
| One-year cure rate of CIN2+ following cryotherapy | 0.880 | 0.82 - 0.93 | D'Alessandro et al, Chirenje et al |

| | | | |
|---|---|---|---|
| One-year cure rate of CIN2+ following LEEP | 0.960 | 0.92-0.99 | D'Alessandro et al, Chirenje et al |
| One-year cure rate of ≤CIN1 following cryotherapy | 0.950 | 0.87-0.99 | D'Alessandro et al, Singh et al |
| One-year cure rate of ≤CIN1 following LEEP | 0.960 | 0.87-1.00 | D'Alessandro et al, Singh et al |
| One-year probability of CIN2+ following cryotherapy after false positive HPV test | 0.000 | - | Campos et al, Assumption based on expert's experience in Kenya |
| Six-year cumulative risk of CIN2+ following LEEP for CIN2+ at baseline | 0.060 | 0.03-0.11 | Kreimer et al |
| Six-year cumulative risk of CIN2+ following LEEP for <CIN2 at baseline | 0.020 | 0.01-0.04 | Kreimer et al |
| Six-year cumulative risk of cervical cancer following treatment for neoplasia | 0.003 | 0.00-0.02 | Kreimer et al |
| Five-year survival due to cervical cancer | 0.159 | 0.10-0.22 | Gondos et al |
| Coverage and Loss to Follow-Up | | | |
| HPV screening campaign uptake (Phase 1)* | 0.595 | 0.30-0.89 | Kenya trial data |
| HPV screening campaign uptake (Phase 2) | 0.769 | 0.38-1.00 | Kenya trial data |
| HPV-positive women presents for treatment (Phase 1) * | 0.357 | 0.18-0.54 | Kenya trial data |
| HPV-positive women presents for treatment (Phase 2) | 0.459 | 0.23-0.69 | Kenya trial data |
| Lost-to-follow-up after referral for LEEP treatment | 0.700 | 0.35-1.00 | Kenya trial data |
| Proportion of women with invasive cervical cancer who access treatment | 0.350 | 0.00-0.50 | Kenya trial data |
| Disability Weights (Duration) | | | |
| Experience of being screened (1 year) | 0.003 | 0.000-0.005 | Simonella et al, Simms et al |
| HPV-positive test result (1 year) | 0.027 | 0.000-0.050 | Simonella et al, Simms et al |
| False positive screening test (1 year) | 0.030 | 0.000-0.050 | Mandleblatt et al |
| Treatment for pre-cancerous lesions (1 year) | 0.030 | 0.000-0.005 | Simonella et al, Simms et al |
| Major bleeding (> 1 L blood lost) (4 weeks) | 0.324 | 0.220-0.442 | GBD 2017 |
| Minor bleeding (<1 L blood lost) (4 weeks) | 0.114 | 0.078-0.159 | GBD 2017 |
| Abdominopelvic problem, mild (1 year)‡ | 0.011 | 0.005-0.021 | GBD 2013 |
| Abdominopelvic problem, moderate (1 year)§ | 0.114 | 0.078-0.442 | GBD 2013 |
| Abdominopelvic problem, severe (8 weeks)‖ | 0.324 | 0.219-0.442 | GBD 2013 |
| Controlled phase of cervical cancer (1 year) | 0.049 | 0.072-0.031 | GBD 2017 |
| Metastatic phase of cervical cancer (1 year) | 0.451 | 0.600-0.307 | GBD 2017 |
| Diagnosis and primary therapy phase of cervical cancer (1 year) | 0.288 | 0.399-0.193 | GBD 2017 |

| | | | |
|---|---|---|---|
| Terminal phase: with medication (1 year) | 0.540 | 0.687-0.377 | GBD 2017 |
| Terminal phase: without medication (1 year) | 0.569 | 0.727-0.389 | GBD 2017 |
| Death due to cervical cancer (1 year) | 1.000 | - | GBD 2017 |

Abbreviations: HPV, human papillomavirus; CIN2+, cervical intraepithelial neoplasia stage 2 and above; LEEP, loop electrical excision procedure; GBD, Global Burden of Disease Study

*During Phase 1, CHC only screening and standard linkage to treatment efforts were implemented.

†During Phase 2, CHC non-attenders were offered home-based self-testing and enhanced linkage to treatment efforts were implemented .

‡Mild is described as having some pain in the belly area that may cause nausea but does not interfere with daily activities.

§ Moderate is described as having pain in the belly area that causes nausea and interferes with strenuous activities.

|| Severe is described as having severe pain in the belly area that causes causea and interferes with daily activities

**Table 5.2:** Cost Inputs for decision-tree model to evaluate cervical cancer screening strategies delivered by community health campaigns in Kenya

| Per-Procedure Costs | Per-client cost (rounded) | | | | | | Per-client time cost (rounded) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Kenyan Shillings (KSH) | | | International Dollar 2018* | | | Kenyan Shillings (KSH) | | | International Dollar 2018 | | |
| | Base Case | Range Min | Max | Base Case | Range Min | Max | Base Case | Range Min | Max | Base Case | Range Min | Max |
| CHC-based self-screening, standard linkage (Phase 1)‡ | 2,624 | 1,312 | 3,936 | $52 | $26 | $78 | 22 | 11 | 34 | $0.5 | $0.2 | $0.7 |
| CHC-based self-screening, enhanced linkage (Phase 2)§ | 3,613 | 1,806 | 5,419 | $72 | $36 | $108 | 17 | 9 | 26 | $0.3 | $0.2 | $0.5 |
| Cryotherapy treatment, standard Linkage (Phase 1)‡ | 1,826 | 913 | 2,738 | $36 | $18 | $55 | 1 | 0.6 | 2 | $0.02 | $0.01 | $0.03 |
| Cryotherapy treatment, enhanced Linkage (Phase 2)§ | 5,059 | 2,529 | 7,588 | $101 | $50 | $151 | 14 | 7 | 21 | $0.3 | $0.1 | $0.4 |
| LEEP treatment‖ | 12,736 | 6,368 | 19,105 | $253 | $127 | $380 | 57 | 28 | 85 | $1.1 | $0.6 | $1.7 |
| Minor complications due to treatment‖ | 361 | 180 | 541 | $7 | $4 | $11 | 57 | 28 | 85 | $1.1 | $0.6 | $1.7 |
| Major complications due to treatment‖ | 4,329 | 2,164 | 6,493 | $86 | $43 | $129 | 566 | 283 | 849 | $11 | $6 | $17 |
| Cancer treatment‖ | 79,229 | 39,614 | 118,843 | $1,577 | $788 | $2,365 | 1,980 | 990 | 2,970 | $39 | $20 | $59 |

Abbreviations: CHC: Community health campaign

*Converted from Kenyan Shillings to International $ using purchasing power parity factor (Source: The World Bank; 50.25 KSH/I$)

‡During Phase 1, CHC only screening and standard linkage to treatment efforts were implemented.

§During Phase 2, CHC non-attenders were offered home-based self-testing and enhanced linkage to treatment efforts were implemented.

‖Cost estimate from Goldie 2005 for Kenya

**Table 5.3:** Base case cost-effectiveness results of 4 strategies for cervical cancer screening delivery models using community health campaigns in Kenya (6-year time horizon and 1000 women)

| Screening Strategy | Total Costs (International $) | DALYs incurred | ▲Cost (International $) | DALYs averted | ICER (International $ per DALY averted) |
|---|---|---|---|---|---|
| No Screening | $2,077 | 118.91 | | | |
| HPV + VIA & Treat; Standard linkage* | $34,602 | 117.76 | $32,521 | 1.16 | $28,131 |
| "HPV & Treat"; Standard linkage* | $35,798 | 113.60 | $1,195 | 4.16 | $287 |
| HPV + VIA & Treat; Enhanced linkage† | $62,689 | 112.69 | $26,891 | 0.91 | $29,593 |
| "HPV & Treat", Enhanced linkage† | $70,752 | 106.41 | $8,063 | 6.28 | $1,284 |
| Using extended dominance‡: | | | | | |
| No Screening | $2,077 | 118.91 | | | |
| "HPV & Treat"; Standard linkage* | $35,798 | 113.60 | $33,721 | 5.32 | $6,343 |
| "HPV & Treat", Enhanced linkage† | $70,752 | 106.41 | $34,955 | 7.19 | $4,864 |
| No Screening | $2,077 | 118.91 | | | |
| "HPV & Treat", Enhanced linkage† | $70,752 | 106.41 | $68,676 | 12.50 | $5,493 |
| Excluding DALYs incurred due to screening | | | | | |
| | Total Costs (International $) | DALYs incurred | ▲Cost (International $) | DALYs averted | ICER (International $ per DALY averted) |
| No Screening | $2,077 | 118.91 | | | |
| HPV + VIA & Treat; Standard linkage* | $34,602 | 106.81 | $32,521 | 12.10 | $2,688 |
| "HPV & Treat"; Standard linkage* | $35,798 | 103.54 | $1,195 | 3.28 | $365 |
| HPV + VIA & Treat; Enhanced linkage† | $62,689 | 98.81 | $26,891 | 4.73 | $5,683 |
| "HPV & Treat", Enhanced linkage† | $70,752 | 93.41 | $8,063 | 5.40 | $1,494 |
| Using extended dominance‡: | | | | | |
| No Screening | $2,077 | 118.91 | | | |
| "HPV & Treat"; Standard linkage* | $35,798 | 103.54 | $33,721 | 15.38 | $2,193 |
| "HPV & Treat", Enhanced linkage† | $70,752 | 93.41 | $34,955 | 10.13 | $3,451 |
| No Screening | $2,077 | 118.91 | | | |
| "HPV & Treat", Enhanced linkage† | $70,752 | 93.41 | $68,676 | 25.50 | $2,693 |

Abbreviations: HPV, human papillomavirus; VIA, visual inspection with acetic acid; DALY, disability adjusted life-year
*During Phase 1, CHC only screening and standard linkage to treatment efforts
†During Phase 2, CHC non-attenders were offered home-based testing and enhanced linkage to treatment efforts
‡Defined as the set of all possible mixed strategies that dominates a single strategy in both higher effectiveness and less cost

**Table 5.4:** One-way sensitivity analyses comparing alternative cervical cancer screening strategies

| Parameter | Input | | ICER: I$/DALY averted | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | "HPV+VIA" with STD. vs. No Screen | | HPV & STD. vs. "HPV+VIA" STD | | "HPV+VIA" & ENH. vs. HPV & STD. | | HPV & ENH vs. "HPV+VIA" & ENH | |
| | Low | High | Low | High | Low | High | Low | High | Low | High |
| Sensitivity of VIA for the detection of CIN2+ | 0.63 | 0.82 | D | $12,114 | $203 | $447 | D | $7,829 | $881 | $2,123 |
| Specificity of VIA for the detection of CIN2+ | 0.65 | 0.68 | $32,621 | $23,718 | $264 | $312 | $39,723 | $23,503 | $1,206 | $1,368 |
| HPV screening campaign uptake (Phase 1)* | 0.30 | 0.89 | $28,124 | $28,134 | $289 | $287 | $12,304 | D | $1,285 | $1,284 |
| HPV screening campaign uptake (Phase 2)† | 0.38 | 1.00 | $28,131 | $28,131 | $287 | $287 | $1,757 | $16,266 | $1,338 | $1,272 |
| HPV positive women presents for treatment (Phase 1)* | 0.18 | 0.54 | D | $4,285 | $280 | $446 | $3,367 | D | $1,298 | $1,270 |
| HPV positive women presents for treatment (Phase 2)† | 0.23 | 0.69 | $28,131 | $28,131 | $287 | $287 | D | $2,547 | $801 | $1,533 |
| LTFU to visit central site (LEEP) | 0.35 | 1.00 | $18,939 | $48,878 | $367 | $205 | $23,747 | $37,368 | $1,340 | $1,233 |
| DW for experience of being screened | 0.00 | 0.005 | $11,158 | D | $287 | $287 | $18,897 | $47,538 | $1,284 | $1,284 |
| DW for testing HPV positive | 0.00 | 0.05 | $5,603 | D | $204 | $446 | $39,367 | $24,324 | $965 | $1,807 |
| DW for false positive screening test | 0.00 | 0.05 | $5,714 | D | $756 | $203 | $6,053 | D | $2,431 | $977 |
| DW for treatment for precancerous lesion | 0.00 | 0.05 | $15,624 | $62,752 | $215 | $373 | $204,260 | $18,620 | $934 | $1,732 |
| Cost of CHC-based screening during standard linkage phase (Phase 1)* | $26 | $78 | $14,699 | $41,567 | $287 | $287 | $46,685 | $12,499 | $1,284 | $1,284 |
| Cost of CHC-based screening during enhanced linkage phase (Phase 2)† | $36 | $108 | $28,131 | $28,131 | $287 | $288 | D | $60,019 | $1,284 | $1,284 |
| Cost of cryotherapy treatment during standard linkage phase (Phase 1)* | $18 | $54 | $27,643 | $28,619 | $69 | $505 | $31,213 | $27,975 | $1,284 | $1,284 |
| Cost of cryotherapy treatment during enhanced linkage phase (Phase 2)† | $50 | $151 | $28,131 | $28,131 | $287 | $287 | $26,736 | $32,451 | $619 | $1,950 |

Abbreviations: D, dominated; HPV, human papillomavirus; VIA, visual inspection with acetic acid; DALY: disability adjusted life year; ICER: Incremental cost-effectiveness ratio; CIN2+, cervical intraepithelial neoplasia stage 2 and above; LEEP, loop electrical excision procedure; DW, disability weight

Strategies in order of appearance: HPV+VIA, STD = HPV+VIA screening & treat with standard linkage to treatment; NS = No screening; HPV, STD = HPV screening & treat with standard linkage to treatment; HPV +VIA, ENH = HPV+ VIA screening & treat with enhanced linkage to treatment; HPV, ENH = HPV screening with enhanced linkage to treatment

*During Phase 1, standard linkage to treatment efforts were implemented.

†During Phase 2, CHC non-attenders were offered home-based testing and enhanced linkage to treatment efforts were implemented

**Table 5.5:** One-way sensitivity analyses comparing remaining alternative cervical cancer screening strategies using extended dominance

| Parameter | Input | | ICER: I$/DALY averted | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | HPV STD VS. NS | | HPV, ENH VS. HPV, STD | | HPV+ENH VS. NS | |
| | Low | High | Low | High | Low | High | Low | High |
| HPV screening campaign uptake (Phase 1)* | 0.30 | 0.89 | $6,343 | $6,343 | $5,261 | $4,007 | $5,493 | $5,493 |
| HPV screening campaign uptake (Phase 2)† | 0.38 | 1.00 | $6,343 | $6,343 | $5,080 | $5,080 | $5,493 | $5,493 |
| HPV positive women presents for treatment (Phase 1)* | 0.18 | 0.54 | D | $2,696 | $2,495 | D | $5,523 | $5,457 |
| HPV positive women presents for treatment (Phase 2)† | 0.23 | 0.69 | $6,343 | $6,343 | D | $2,124 | D | $3,012 |
| LTFU to visit central site (LEEP) | 0.35 | 1.00 | $5,688 | $7,072 | $4,617 | $5,104 | $5,090 | $5,909 |
| DW for experience of being screened | 0.00 | 0.005 | $4,766 | $8,138 | $4,539 | $5,107 | $4,648 | $6,250 |
| DW for testing HPV positive | 0.00 | 0.05 | $2,892 | D | $3,866 | $6,278 | $3,317 | $12,841 |
| DW for false positive screening test | 0.00 | 0.05 | $4,636 | $8,406 | $4,505 | $5,136 | $4,568 | $6,349 |
| DW for treatment for precancerous lesion | 0.00 | 0.05 | $4,419 | $9,063 | $3,988 | $5,731 | $4,189 | $6,993 |
| Cost of CHC-based screening during standard linkage (Phase 1)* | $26 | $78 | $3,421 | $9,265 | $7,025 | $2,702 | $5,493 | $5,493 |
| Cost of CHC-based screening during enhanced linkage (Phase 2)† | $36 | $108 | $6,343 | $6,343 | $1,017 | $8,711 | $3,282 | $7,704 |
| Cost of cryotherapy treatment during standard linkage (Phase 1)* | $18 | $54 | $6,066 | $6,620 | $5,068 | $4,659 | $5,493 | $5,493 |
| Cost of cryotherapy treatment during enhanced linkage (Phase 2)† | $50 | $151 | $6,343 | $6,343 | $3,921 | $5,806 | $4,951 | $6,034 |

Abbreviations: HPV, human papillomavirus; VIA, visual inspection with acetic acid; DALY: disability adjusted life year; ICER: Incremental cost-effectiveness ratio; CIN2+, cervical intraepithelial neoplasia stage 2 and above; LEEP, loop electrical excision procedure; DW, disability weight

Strategies in order of appearance: NS = No screening; HPV, STD = HPV screening & treat with standard linkage to treatment; HPV, ENH = HPV screening with enhanced linkage to treatment

*During Phase 1, standard linkage to treatment efforts were implemented.

†During Phase 2, CHC non-attenders were offered home-based testing and enhanced linkage to treatment efforts were implemented

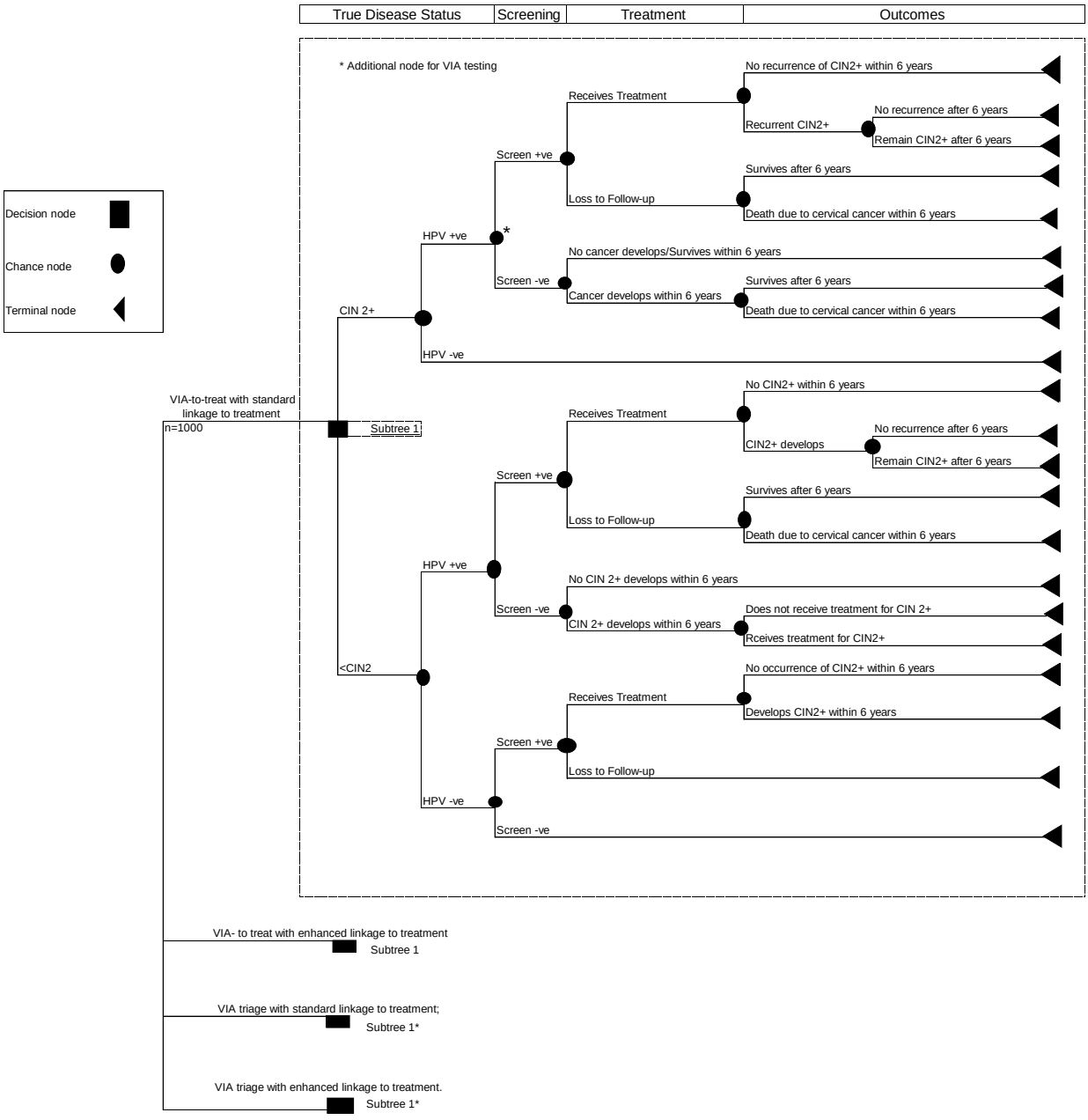


**Figure 5.1:** Simplified version of decision tree model used for cost-effectiveness analysis to evaluate cervical cancer screening strategies delivered through community health campaigns in Kenya

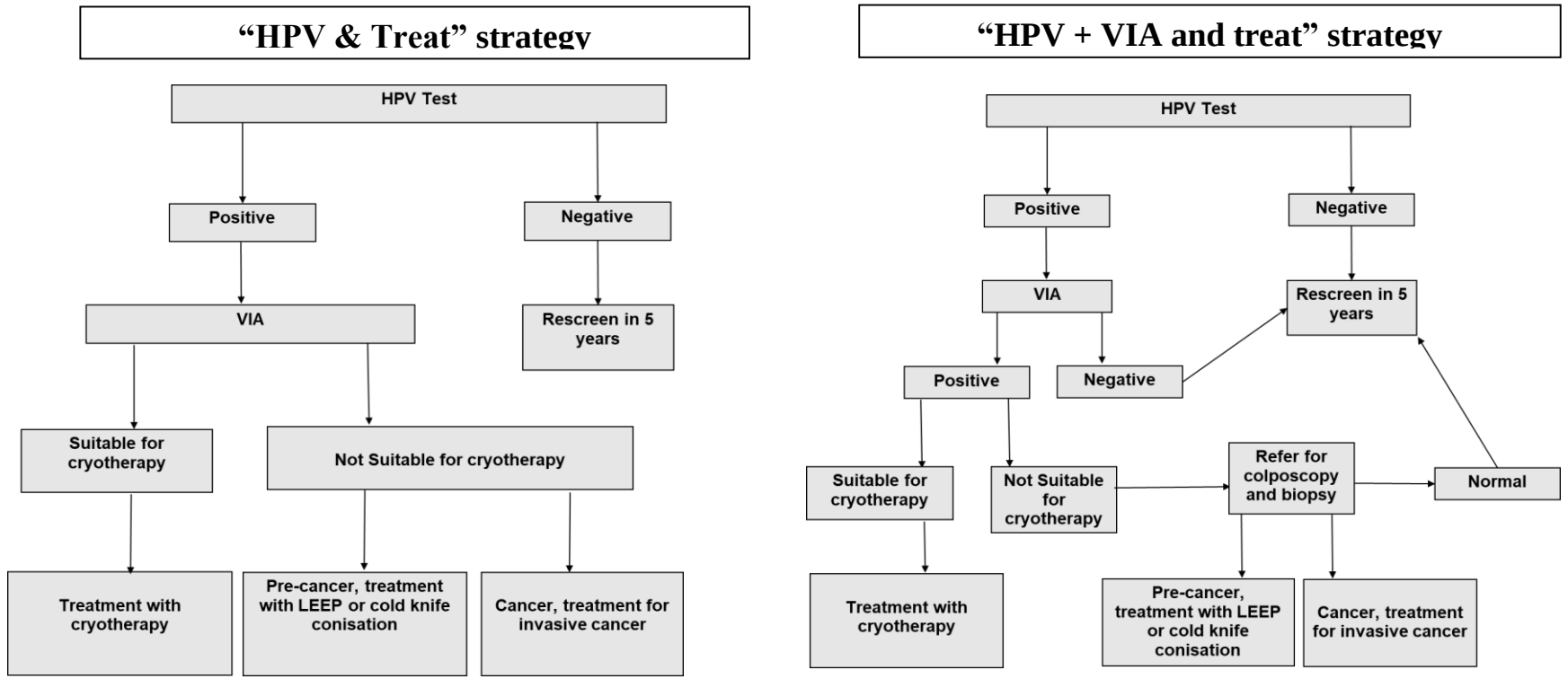


**Figure 5.2:** Strategies implemented in cervical cancer screening scenarios to evaluate cost-effectiveness of community health campaigns in Kenya. The "HPV & Treat" strategy was implemented in the clustered-randomized trial. In this strategy, all HPV-positive women will receive treatment; the VIA is used to evaluate appropriateness for treatment with cryotherapy. The HPV + VIA and treat strategy is recommended by the World Health Organization and has been adopted by the Kenyan Ministry of Health as part of their guidelines for treatment and prevention of cervical neoplasia. We applied this strategy to our health care delivery models utilized in the trail to assess the appropriateness of this recommendation. Using "HPV+VIA & Treat", HPV-positive women undergo VIA as a screening procedure. Women who are found to be disease negative based on the VIA test, will not be referred to treatment.

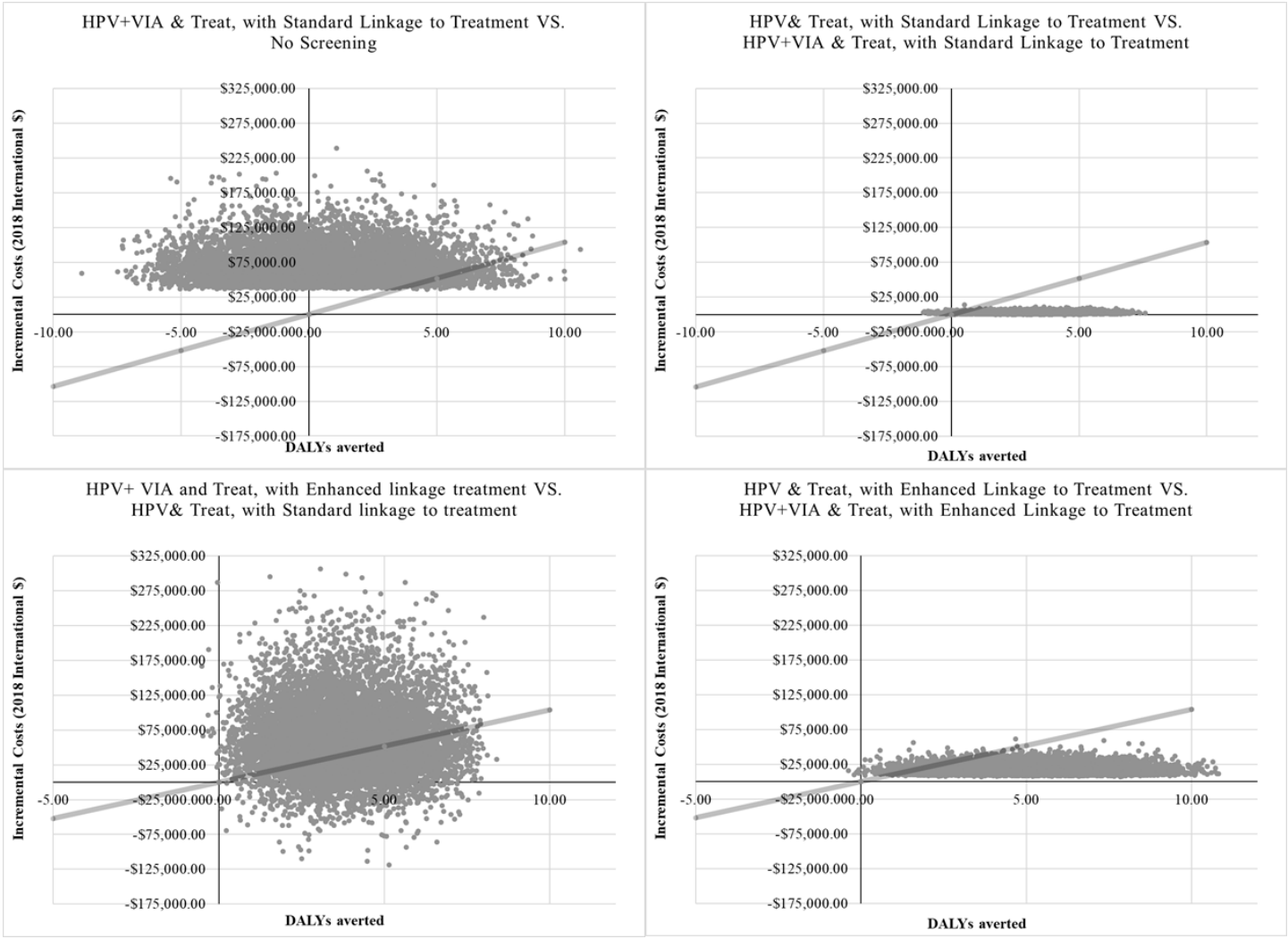


**Figure 5.3:** Probabilistic sensitivity analysis of incremental cost-effectiveness of all base-case scenarios shown in a scatter plot. Each point estimate represents one iteration (total 10,000) of incremental cost and incremental effectiveness measured by DALYs averted, based on the range of parameter distributions. The sold line represents the willingness-to-pay threshold of I$ 10,384/DALY averted, or 3 times the per capita GDP (PPP) of Kenya. Any points to the left of the solid line represents an incremental cost-effectiveness ratio (ICER) above the willingness-to-pay threshold.

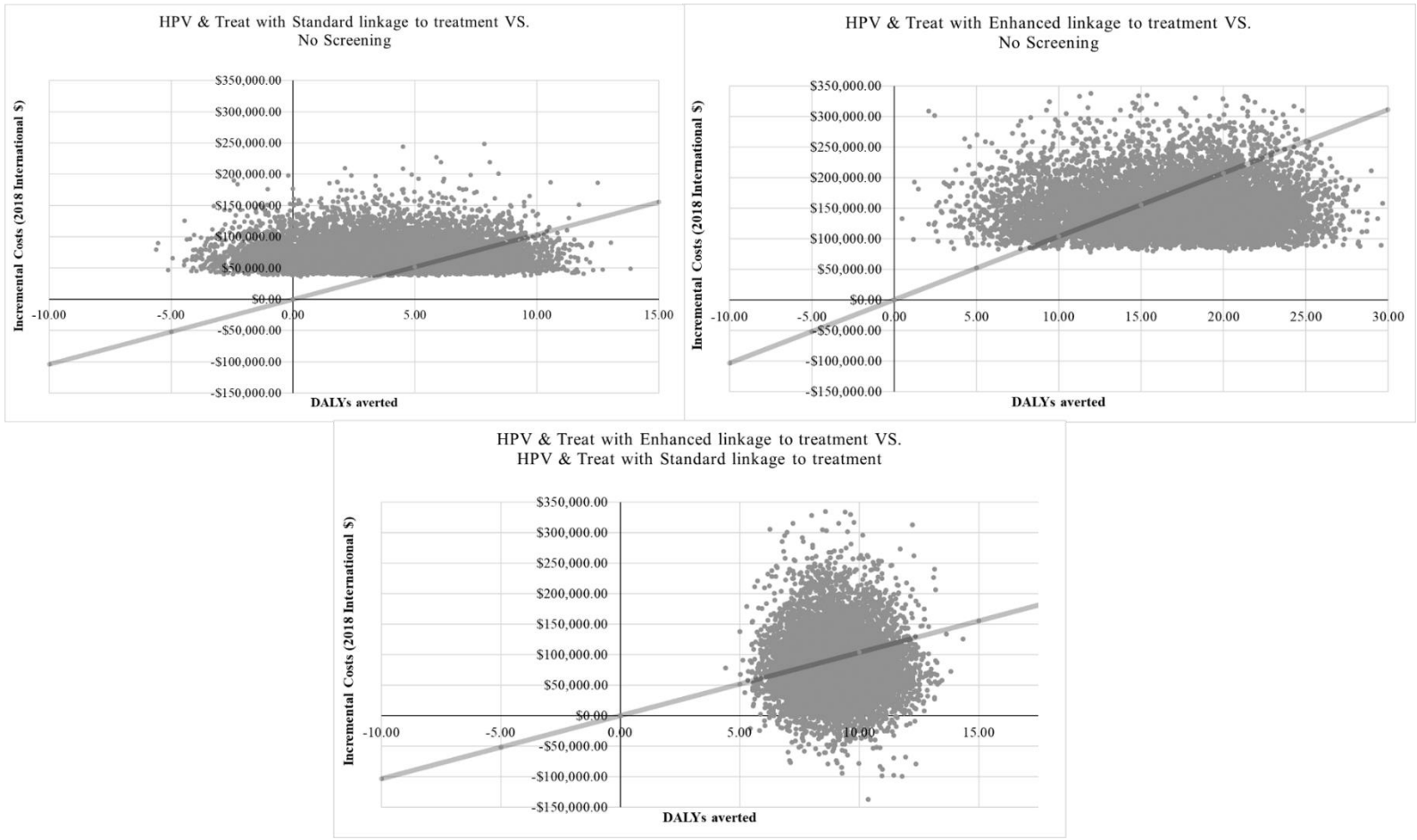


Figure 5.4 Probabilistic sensitivity analysis of incremental cost-effectiveness of "HPV & Treat" strategies. Each point estimate represents one iteration (total 10,000) of incremental cost and incremental effectiveness measured by DALYs averted, based on the range of parameter distributions. The sold line represents the willingness-to-pay threshold of I$ 10,384/DALY averted, or 3 times the per capita GDP (PPP) of Kenya. Any points to the left of the solid line represents an incremental cost-effectiveness ratio (ICER) above the willingness-to-pay threshold.

# CHAPTER 6: CONCLUSIONS

## Summary of Findings

The sensitivity and specificity of HPV testing using dry-stored self-collected specimens for the detection of ≥HSIL were similar to wet-storage of specimens. Although the prevalence of HSIL was low in our study and our estimates were imprecise, they nevertheless suggest that using dry-stored self-collected specimens may provide a simple, private and convenient self-test which can help increase access to screening in low-resource regions. However, FSWs preferred physician-collection HPV testing compared to self-collection. FSWs indicated they were concerned that using the brush to self-collect may cause pain and about their ability to properly use the brush for self-collection. Additional research to address preferences and any barriers to self-collection is crucial.

To deliver HPV-testing using self-collection methods in a low resource setting such as Kenya, community health campaigns are a viable option with appropriate linkage to treatment of HPV-positive women. Utilizing "HPV & Treat" strategies, where VIA is used to determine the appropriateness of cryotherapy treatment, and all HPV-positive women are treated, is more cost-effective than "HPV+VIA & Treat" strategies when the VIA test is used as a triage method to treatment. This is due to the high false-negative rate (i.e. low sensitivity) of VIA, the implications of which are more evident in a high-burden area such as Kenya.

Compared to no screening, "HPV & Treat" with enhanced linkage to treatment appeared to be the most cost-effective at I$ 5492.62/DALY averted, which is below the willingness-to-pay threshold of three times Kenya's per capita GDP ($10. 384.2/DALY averted). Similarly, "HPV & Treat" with standard linkage to treatment was also considered cost-effective when compared to no screening intervention (I$ 6342.86/DALY averted). The proportion of HPV-positive women who were successfully linked to treatment had the most substantial impact on ICERs comparing "HPV & Treat" strategies. Future efforts

to improve linkage to treatment in existing cervical cancer screening programs or those to be developed in Kenya should prioritize successful methods to link women to treatment. In this trial, successful strategies included the decentralization of treatment centers, so women were able to obtain treatment in closer proximity to the community the CHC they attended occurred and follow-up with women who did not receive treatment within three months of test result notification through text message.

Probabilistic sensitivity analyses or PSA was performed using Monte Carlo simulation by 10,000 iterations; demonstrated an overall robust model, where each input parameter is simultaneously varied across a given range of values from the parameter's defined distribution. When comparing enhanced linkage to treatment to standard linkage, 67% of iterations were below the willingness to pay threshold and considered cost-effective. The remaining iterations showed enhanced linkage to be more effective, however, more costly and above the willingness to pay threshold. Finally, when comparing enhanced linkage to treatment to no screening, 67% of iterations were cost-effective.

Public Health Significance

Testing self-collected specimens for detection of high-risk HPV infection can reduce the proportion of women who would require a pelvic speculum examination at a health facility for cervical cancer screening. Self-collection of cervicovaginal samples using "dry test" self-collection methods could potentially provide a scalable, and easy to implement method to improve screening uptake and coverage in resource-limited areas.

We observed low positive predictive values for HPV testing using sc-WET (16%), sc-DRY (17%), and physician-collection (19%). Positive predictive value is defined as the probability that subjects with a positive screening test truly have disease; it is similar to sensitivity excluding the denominator which is now all women who screened rather than all women who have disease. Although similar to prior studies conducted to evaluate HPV mRNA testing(49, 50, 52), the low PPV is concerning as it may lead to unnecessary treatment of many women if implemented in an "HPV & Treat" scenario. More specific biomarkers for the detection of CIN2+ may be needed, particularly in areas where screening is readily

available. However, in areas where women may screen only once in their lifetime, the low PPV may not be as much of concern due to a woman's lifetime risk of hr-HPV infection and persistence. In low-resource settings, the potential benefits of using a screen and treat strategy based on a test with low specificity may outweigh the harms of overtreatment(122).

Acceptance and preference of self-collection will be critical to successful implementation of HPV-based community health campaigns. We found that women preferred physician-collection due to concerns regarding pain and their ability to correctly collect the sample. Indeed, a recent qualitative study of women in Kenya and their experience with self-collection showed that facilitators of screening included, confidence in their ability to complete HPV self-sampling and comfort conducting the HPV self-sampling(129). Women in this qualitative study were provided with in-depth educational interventions and were then asked to carry out self-collection before carrying participating in the focus group interview. Findings from this study and our analysis indicate that potentially with experience and motivational instruction, women in Kenya may be willing to self-collect cervical samples, although further research is warranted.

A vital aspect of a successful cervical cancer screening program is linkage to treatment for screen-positive women. We demonstrated that implementing enhanced linkage to treatment methods led to more DALYs averted and improved incremental cost per DALY averted. The World Health Organization recommends use of VIA following an HPV-positive result ("HPV+VIA & Treat"), however, we found that this strategy is not cost-effective compared to "HPV & Treat," where VIA is used only to evaluate appropriateness of cryotherapy. The results of this dissertation may inform Kenyan national policies for the implementation of cervical cancer screening programs. Improved screening accessibility paired with linkage to treatment will increase coverage of screening programs could reduce morbidity and mortality due to ICC, particularly in low-resource, high incidence countries such as Kenya.

Limitations

There are several limitations to consider when interpreting our findings. Although similar to prior studies conducted in sub-Saharan Africa(49), the prevalence of ≥HSIL cases was low (6.9%) in our study

of FSWs. The low prevalence of our gold standard and outcome may limit the interpretation of our findings. Cervical histology data collected through biopsy was unavailable for almost half of included FSWs, and as such, we utilized a screening test (cytology) as our outcome, which may limit the accuracy of our results as histological-based CIN is a better marker of disease than cytology. Since this study will be performed among a population of high-risk women, generalizability of the results to the general population may be limited. However, these results may be applicable to low-risk populations given that the comparative performance between each screening option will still be valid. We were unable to conduct genotyping of hr-HPV type as APTIMA does not differentiate between hrHPV types. Finally, the survey used to assess preference of self-collection methods versus physician-collection was a quantitative survey using a Likert scale ranging from 1 to 5. Although the research assistants provided in-depth instructions on participation

For our cost-effectiveness analysis, all strategies considered here assume that women only receive one screening per lifetime and does not take into account the effect of interval-based screening. However, the WHO recommends a once-in-a-lifetime screening approach for women living in developing countries(103). Our cost-effectiveness results are sensitive to several model inputs that were not collected from women in Kenya or similar low-resource settings. Although we conducted several sensitivity analyses to examine a wide range of potential values of inputs, our base case results may be limited.

Although Migori County is a rural area, the cost-effectiveness of our modeled strategies may be limited in areas where clinics may be further away or with fewer resources for treatment. Additionally, women were notified of their results frequently using mobile phones, and when a woman did not use a mobile phone, community health volunteers conducted home-visits to inform women of their results in person. In more remote areas, where fewer women may have mobile phones, cost of home visits by community health volunteers may diminish the cost-effectiveness of modeled strategies. Finally, we utilized a decision-tree framework to model the progression of disease from hr-HPV infection to invasive disease, and as such, we were unable to account for dynamic effects of factors such as age, sexual

behavior, and disease recurrence or regression. While this model is useful for the prediction of programmatic costs and health impact, it does not account for ongoing HPV transmission.

Future Research Directions

Although we found that test characteristics of sc-DRY were similar to sc-WET for detection of high-grade, future research studies among larger cohorts of women in a low-resource setting are warranted to confirm our findings. Additionally, further data comparing self-collection methods for hr-HPV mRNA testing to physician-collection are needed, particularly in low-resource settings.

Health utility evaluations of cervical cancer screening-related health states among women in low-resource settings are needed. Using methods such as standard gamble to assess the utility of hypothetical scenarios related to cervical cancer screening among women in Kenya or a similar setting will be beneficial towards more accurately assessing the cost-effectiveness of cervical cancer screening.

Lastly, future cost-effectiveness analyses may be conducted utilizing the hr-HPV mRNA test characteristics calculated in Aim 1 of this dissertation. The improved specificity of HPV mRNA testing compared to HPV DNA test may lead to enhanced effectiveness, and more DALYs averted. Micro-costing data on screening using HPV mRNA are not currently available, and would also need to be collected to carry out such a cost-effectiveness analysis.

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