Cervical Cancer in Low-Income Settings: Costs, Cost-Effectiveness, and Budget Impact of Integrating Screening and Treatment into Existing Health Systems in East Africa

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Abstract

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Cervical cancer is one of the most frequently occurring cancers among women in sub-Saharan Africa (SSA). While preventable if detected early, many women experience challenges accessing life-saving screening and treatment due to health systems inefficiencies, costs, perceptions of screening, and time required to seek care. Integration of cervical cancer screening into existing public health programs, such as screening women as they enter the health system for HIV treatment or bring their children to obtain routine immunizations, may increase screening coverage rates at low marginal costs. This dissertation aimed to evaluate the potential costs, cost-effectiveness, and budget impact of integrating cervical cancer screening into a routine childhood immunization clinic in Uganda and an HIV-treatment facility in Kenya. First, using primary facility-level data, a model-based analysis was conducted to estimate the individual level-costs of treatment for pre-cancerous lesions, cervical cancer, and cervical cancer palliative care in Kenya. Second, a Markov model was developed to assess the potential cost-effectiveness of integrating screening programs into an HIV treatment clinic in Kenya and a routine childhood immunization clinic in Uganda. Third, a budget impact model estimated the size of the target population and potential uptake of screening, as well as the impact on the current health system, of each integration strategy. Study findings indicate that integrating cervical cancer screening into existing health systems in East Africa is likely to be cost-saving or cost-effective in terms of cost-per life year saved, compared to current strategies of non-integrated screening. These findings provide decision-makers in Kenya, Uganda, and other similar LMICs with information on the costs and cost-effectiveness of innovative methods for increasing access to life-saving cervical cancer screening and treatment interventions.

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DEDICATION

This dissertation is dedicated to my family, who has been my cheering section, and my husband, who is my spirit bond.

Chapter 1. INTRODUCTION

Cervical cancer is one of the most frequently occurring cancers among women in sub-Saharan Africa (SSA).[1] While cervical cancer is preventable if detected early, many women experience challenges accessing life-saving screening and treatment due to health systems inefficiencies, costs, patients' perceptions of screening, and the time required to seek care.[2–5] Estimates of cervical cancer screening coverage rates in SSA remain low, between 2.6%-4.0%.[5,6] Improving prevention and early detection of cervical cancer through expanded access to screening is and will continue to be a high priority in low-income countries since cancer treatment is prohibitively expensive for most women and their families.[7–9]

To increase the number of women receiving screening, the World Health Organization has promoted the implementation of programs that (1) reduce patient time required for screening and treatment and (2) leverage existing infrastructure to deliver screening.[10–12] One option is a same-day see-and-treat strategy, which combines visual inspection with acetic acid (VIA) screening and treatment of pre-cancerous lesions into a single visit.[13–15] This safe and effective screening method may reduce patient time, opportunity costs, and loss to follow-up associated with standard methods.[13,14,16,17] Another option is the integration of cervical cancer screening into existing public health programs, such as screening women as they enter the health system for HIV treatment or bring their children to obtain routine immunizations, which may increase screening coverage rates at low marginal costs.[18–23] Economic evaluations of these and other innovative cervical cancer screening and treatment strategies may guide policymakers on which delivery services achieve the best value for the scarce resources available to invest in cervical cancer prevention and treatment. Additionally, economic analyses may be useful in identifying which integrated settings (e.g., HIV clinics, routine immunization clinics, etc.) might be most appropriate for a specific country and population.

The research objectives of this dissertation aimed to address the gaps identified in the literature related to costs, cost-effectiveness and budget impact of integrated cervical cancer screening services. First, a comprehensive assessment was performed to estimate the individual-level costs of treatment for pre-cancerous lesions, cervical cancer, and cervical cancer palliative care among HIV-positive women in Kenya. Second, the potential cost-effectiveness and budget impact of a same-day see-and-treat strategy integrated into HIV-care in Kenya was assessed. Finally, the potential cost-effectiveness and budget impact of integrating VIA screening into a routine childhood immunization program in Uganda was evaluated.

Chapter 2. ESTIMATING THE COSTS OF HIV CLINIC INTEGRATED VERSUS NON-INTEGRATED TREATMENT OF PRE-CANCEROUS LESIONS AND COSTS OF CERVICAL CANCER IN KENYA.

2.1 INTRODUCTION

Cervical cancer remains the leading cause of cancer deaths among women in Sub-Saharan Africa (SSA) with an age-standardized mortality rate ranging from 43.3 to 69.8 per 100,000 women [24]. A high prevalence of cervical cancer is common in developing countries where more than 85% of the global burden of cervical cancer occurs [25]. This significant burden adds to challenges of economic development and limited healthcare infrastructure. Although largely preventable through screening and/or vaccination against human papillomavirus (HPV), many women in low-income settings arrive at the health facility with pre-cancerous lesions or cervical cancer, requiring time-intensive and invasive treatments that are often prohibitively expensive for women and families [26,27]. The urgency to increase prevention, early detection, and treatment of cervical cancer is particularly high in countries with high rates of human immunodeficiency virus (HIV), since HIV is associated with both higher risk for infection with HPV and faster cervical cancer progression [28]. Women in Kenya, for example, experience an age-standardized cervical cancer mortality rate of 21.8 per 100,000 women and an incidence rate of 40.1 per 100,000 women. Adding to this public health burden, a meta-analysis recently estimated that 64% of Kenyan women with HIV are co-infected with HPV [29]. However, only 3.5% of women aged 25-64 in Kenya have ever received screening for cervical cancer [30]. There are many challenges to increasing screening rates, including the time and financial burden required of women to attend a health facility for screening, results and treatment [31].

To address these issues, health systems in SSA have begun to integrate cervical cancer screening and treatment into existing health programs [20–23,32]. Integrated services leverage the fact that women are already attending a healthcare facility and provide the option to add cervical cancer screening and/or treatment during the same visit. Integration has gained support from global organizations, such as Pink Ribbon Red Ribbon which works to simultaneously address HIV and cervical cancer in SSA [33,34]. Other examples include studies investigating health and economic outcomes of integrating screening into routine childhood immunization clinics in Uganda and family planning clinics in Malawi [35,36]. HIV treatment centers are of particular interest for service integration since they are pervasive in SSA due to concentrated efforts to curb the proliferation of HIV in high prevalence regions, and women living with HIV have a higher incidence of cervical cancer. In Kenya alone, approximately 1.5 million people were living with HIV, including 830,000 adult women (>15 years) [37]. In 2015, it was estimated that 59% of individuals living with HIV –and nearly 68% of adult women with HIV– were on anti-retroviral therapy (ART) for treatment, which commonly requires monthly clinic visits for ART prescription renewals [37]. Offering screening and treatment to women as they enter the health system for routine HIV care and ART renewal may increase screening coverage and treatment, and may do so at a low societal marginal cost [23].

Clinical effectiveness should drive adoption and uptake of appropriate treatment strategies for pre-cancerous lesions and cervical cancer. However, cost analyses are an essential yet often missing component of healthcare planning that can bolster current health policy work by providing an understanding of resource requirements for health service delivery. Prior to scale up of services, up-to-date information about costs of treatment for pre-cancerous lesions and cervical cancer in both integrated and standalone treatment settings should be considered [38]. This is particularly true in resource-constrained settings where health care budgets are limited and the external funding environment is uncertain [38]. In Kenya, existing estimates of cervical cancer treatment costs are out of date with most recent estimates from 2005 using data from 2000 [39]. Additionally, most estimates in the literature do not include costs of palliation, often the only treatment option available to women who arrive at the clinic with late-stage cancer. Finally, to our knowledge, no studies have assessed marginal costs of integrating treatment for pre-cancerous lesions into routine HIV-care in Kenya. As such, the goal of this study was to assess societal costs of treatments along the cervical cancer care continuum—integrated and non-integrated treatment for pre-cancerous lesions; early- and advanced-stage cervical cancer treatment; and palliative care—at two health facilities in Nairobi, Kenya.

2.2 Materials and Methods

We conducted a micro-costing study in 2014 at Coptic Hope Center for Infectious Diseases (CHC) and Kenyatta National Hospital (KNH), Nairobi, Kenya, to estimate the marginal societal costs of integrating cervical cancer screening and treatment for pre-cancerous lesions into clinics serving HIV-positive women [40]. Costs of treatment for cervical cancer and cervical cancer palliative care at KNH were also evaluated. Costs of screening have been reported previously [40]. CHC is a PEPFAR-funded HIV treatment center providing healthcare at no charge to HIV-positive individuals, including ART and prophylaxis [41]. CHC also offers preventive services, including cervical cancer screening and treatment. KNH is a public, tertiary care center providing preventive and urgent care for individuals across Kenya. KNH has a reproductive health unit actively offering cervical cancer screening and treatment for pre-cancerous lesions and cancer. It also includes a Palliative Care Center that is volunteer-based and serves patients seeking hospice for late stage diseases including cervical cancer.

To collect cost data, interviews were conducted with 54 patients receiving treatment for pre-cancerous lesions and cervical cancer at CHC and KNH during the study period (July 1 to October 31, 2014). Additionally, 23 care providers, lab personnel, and administrative staff participated in interviews, which elicited information about typical care patterns, resource use, and costs associated with treatment methods. Patients were referred by providers to the study team and invited to participate. Snowball sampling was used to identify providers that performed treatment for pre-cancerous lesions and cervical cancer, as well as employees involved in accounting, operations, and supplies management [42]. Personnel within laboratories contracted by CHC and KNH were also interviewed. All individuals provided informed consent prior to participation. Ethics approval was received from Institutional Review Boards at KNH and University of Washington.

Cost estimates included direct medical (e.g., supplies), direct non-medical (e.g., patient transportation) and indirect costs (e.g., patient time) from the recommended societal perspective [43] for pre-cancerous lesions, cervical cancer, and cervical cancer palliative care. Components of care included clinician consultations; colposcopy-guided biopsy; cryotherapy;

LEEP; adverse and serious adverse events associated with precancerous lesions and cancer; treatment strategies for local, regional and distant invasive cancer; palliative care; and follow-up visits. Resources used in treatment were identified based on clinic activities related to detection of and treatment for pre-cancerous lesions at CHC and KNH and cervical cancer at KNH, as informed by interviews. (Figure 2.1) For the costing analysis, the base case model assumed that treatment was non-integrated: patients were assumed to return to the health care facility on separate days for each required visit of treatment (i.e., treatment visit, followed by a subsequent visit to obtain test results).

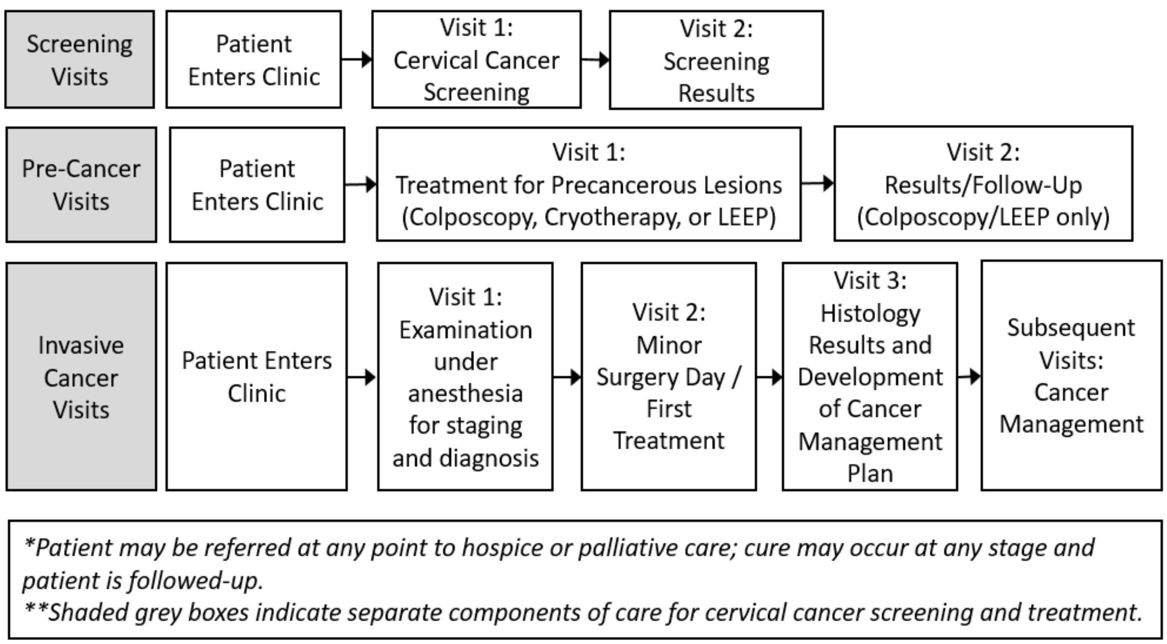


Figure 2.1. Visit sequence for cervical cancer screening and treatment under base case (non-integrated) costing assumptions

For individuals receiving treatment of cervical pre-cancerous lesions via colposcopy, cryotherapy, or LEEP, two additional scenarios were evaluated to assess costs of integrating treatment into HIV-care centers: 1) A *fully integrated* scenario in which each required clinical component of treatment for pre-cancerous lesions was assumed to be conducted on the same day as an HIV-treatment visit (i.e., Visit 1: HIV-related visit + treatment of pre-cancerous lesions; Visit 2: HIV-related visit + treatment results/follow-up); and 2) a *semi-integrated scenario* in which only procedures performed on the first treatment visit were conducted on the same day as an HIV treatment visit, while procedures scheduled for subsequent follow-up were completed in additional visits to the health center independent of their HIV treatment schedule. Colposcopy-guided biopsy and LEEP were each modeled to require two visits for treatment procedure and results/follow-up, whereas cryotherapy was modeled to require a single visit for the treatment procedure only. Often, colposcopy is conducted as a precursor to LEEP; however, these were modeled separately to calculate independent costs of each.

Of the two study sites, cancer care is only provided at KNH and is not expected to be integrated into HIV care. All cancer treatment costs were collected from KNH and are therefore non-integrated. Patients with cervical cancer generally receive some combination of hysterectomy, radiotherapy, chemotherapy, and palliative care, depending on stage and individual characteristics. For the model, three round-trip visits to KNH were assumed for cancer patients, including: Visit 1—Examination under anesthesia for staging and diagnosis; Visit 2—Minor theater day/first treatment; Visit 3—One return visit for histology report and development of management plan. An adverse event was defined to be an event where a patient required one outpatient visit with a clinician whereas a serious adverse event was defined to be an event where a patient required a one-night stay in the hospital. One round trip to the health facility was assumed for adverse events.

Base-case cervical cancer costs estimates reflect standard treatment regimens identified through interviews and clinical recommendations by the International Federation of Gynecology and Obstetrics (FIGO) [44]. Local invasive cancer treatment at KNH typically included costs of: consultation, radical or simple hysterectomy, and pain-relief medications (e.g., morphine). Regional invasive cancer treatment included costs of: consultation, radical hysterectomy, 28 sessions of radiotherapy, 3 sessions of chemotherapy, and pain-relief medications. Finally, distant invasive cancer treatment comprised costs of: consultation, 28 sessions of radiotherapy, 3 sessions of chemotherapy, and pain-relief medications. Since many cancer patients attend follow-up visits, costs for one follow-up visit were also included for each type of cancer treatment. Similar to reported literature, the follow-up visit was estimated to cost the same as a standard colposcopy visit [39]. Palliative care visits were assumed to take 60 minutes and included costs of: consultation, family therapy, wound dressing, renewal of prescriptions, and rehydration.

Direct medical costs included medical expenditures required to provide treatment, such as patient out-of-pocket expenditures, medical supplies, personnel costs, and laboratory costs. Personnel costs were calculated based on salaries, estimated time spent with patients, and staff training. Supplies, equipment and laboratory costs were based on administrative and financial reports. Laboratory costs included equipment, personnel, quality control, and processing time. Direct non-medical costs included expenses incurred while seeking care not due to treatment. These included patients’ transportation to and from the facility, patient upkeep (e.g., meals during care), and overhead costs (e.g., rent, utilities, and insurance). For integrated cost estimates, overhead costs were allocated over the total annual number of patients attending the facility to obtain an integrated overhead cost per procedure. In contrast, for all non-integrated estimates, overhead costs were allocated over the annual number of patients receiving each specific cervical cancer-related procedure to obtain a non-integrated cost per procedure. Finally, indirect costs were derived from patient interviews and comprised resources used due to treatment but not directly associated with healthcare services. These included economic costs of lost productivity due to missed work, amount of time spent waiting in the facility, and costs of hiring caregivers for children and elderly relatives.

Mean cost estimates from study data were used for the base case and scenario analyses. To evaluate potential cost drivers, we conducted one-way sensitivity analyses where each parameter was varied individually using high and low values equivalent to +/- 20% of base case estimates. A Monte Carlo simulation was performed over 10,000 iterations for each cost model parameter to establish 95% credible ranges around mean base case cost estimates using a normal distribution for all inputs. Scenario analyses were also conducted to evaluate potential variation in treatment costs based on different treatment strategies, as identified by FIGO.

All costs were collected in 2014 Kenyan Shillings and converted to U.S. dollars using official World Bank exchange rates [45]. Costs obtained from literature were inflated or deflated to 2014 U.S. dollars using annual Consumer Price Indices for appropriate years [46].

2.3 Results

Interviews were conducted with 23 administrative, clinical and laboratory staff, as well as 54 women attending CHC and KNH for treatment of precancerous lesions and cervical cancer. Patients who participated in the study had a mean age of 41 and a daily wage of $6.

Two-thirds had completed at least secondary school. The vast majority of patients (93%) commuted to the health facility by bus, with the average trip taking 2.8 hours one-way. Nearly 70% missed an average of eight hours of work to attend the facility. (

Table 2.1)

Table 2.1. Characteristics of Patients Attending CHC and KNH for Treatment of Pre-Cancerous Lesions and Cervical Cancer (N=54)

Mean Age	41 years
Education Level	
% Less than primary school (<8 years)	11%
% Primary school (8 years)	22%
% Secondary school or vocational training (8-12 years)	56%
% University or higher (>12 years)	11%
Average Daily Wage, 2014 USD (24 hour)	$6.14
Average Travel Time to Facility (One-Way)	2.83 hours
Mode of Transportation to Facility	
Walk	1.85%
Bus	92.59%
Car	3.70%
Other	1.86%
Missed Work to Attend Facility	
Patients who Missed Work	69%
Average Amount of Work Missed (among those who missed)	8.05 hours

Under the base case assumptions of a non-integrated scenario, per-procedure costs for treating pre-cancerous lesions were $177 for colposcopy, $67 for cryotherapy, and $121 for LEEP. Integrated per-procedure costs were lower for colposcopy, cryotherapy, and LEEP in both the semi-integration and in the full-integration scenarios. In the semi-integrated scenario, colposcopy was $153, cryotherapy was $67, and LEEP was $79, representing respective cost reductions of 14%, 0%, and 35% compared to non-integrated treatment. (Figure 2.2)

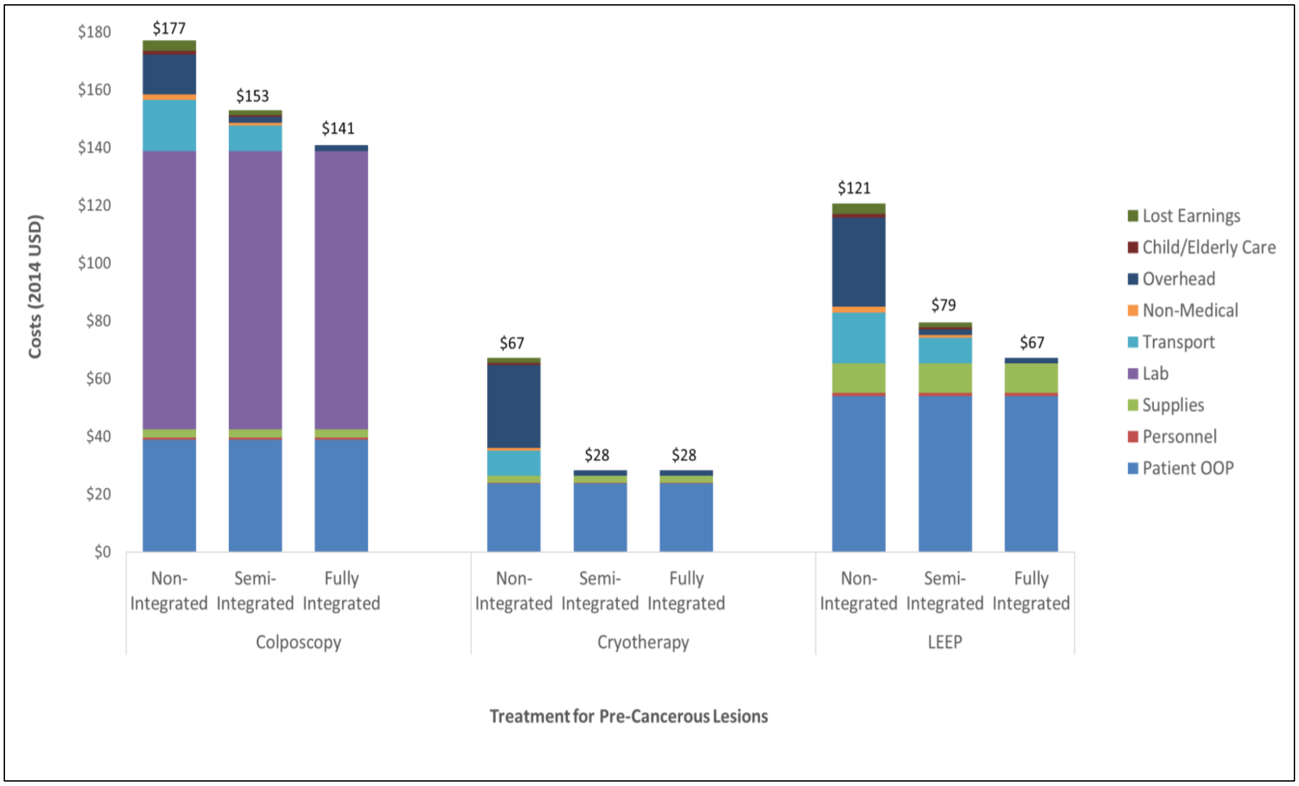


Figure 2.2. Comparison of Integrated vs. Non-Integrated Costs of Treatment for Pre-Cancerous Lesions by Care Component

In the fully-integrated scenario, colposcopy cost was $141, cryotherapy cost was $28, and LEEP cost was $67, representing respective cost reductions of 20%, 58% and 45% compared to non-integrated treatment. Costs for pre-cancerous lesions under each scenario are provided in Table 2.2. Treatment of adverse and serious adverse events cost $195 and $966, respectively. A full course of treatment was $1,130 for local invasive cancer, $6,440 for regional invasive cancer, and $5,100 for distant invasive cancer under the base case assumptions.

Table 2.2. Estimated Costs for Treatment of Pre-Cancerous Lesions Integrated into HIV Care (2014 USD)

	Colposcopy			Cryotherapy			LEEP		
Costs	**Non-Integrated (95% CI)**	**Semi-Integrated (95% CI)**	**Fully Integrated (95% CI)**	**Non-Integrated (95% CI)**	**Semi-Integrated (95% CI)**	**Fully Integrated (95% CI)**	**Non-Integrated (95% CI)**	**Semi-Integrated (95% CI)**	**Fully Integrated (95% CI)**
Direct Medical									
Patient Out-of-Pocket Costs	38.87 (31.16, 46.69)	38.87 (31.04, 46.65)	38.93 (31.26, 46.83)	23.76 (19.10, 28.57)	23.83 (19.06, 28.64)	23.80 (19.10, 28.61)	53.96 (43.13, 64.96)	54.03 (43.36, 64.94)	54.01 (42.80, 64.76)
Personnel	0.64 (0.51, 0.76)	0.64 (0.51, 0.76)	0.64 (0.51, 0.76)	0.18 (0.15, 0.22)	0.18 (0.15, 0.22)	0.18 (0.15, 0.22)	1.08 (0.86, 1.29)	1.08 (0.86, 1.29)	1.08 (0.87, 1.29)
Supplies	2.87 (2.30, 3.45)	2.87 (2.31, 3.45)	2.88 (2.31, 3.45)	2.30 (1.85, 2.74)	2.30 (1.84, 2.77)	2.31 (1.85, 2.76)	10.19 (8.10, 12.21)	10.18 (8.17, 12.20)	10.19 (8.13, 12.22)
Lab	96.50 (77.24, 115.62)	96.33 (76.67, 115.87)	96.15 (76.57, 115.22)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)
Direct Non-Medical									
Patient Transport	17.60 (12.78, 22.35)	8.77 (3.85, 13.44)	0.00 (0.00, 4.98)	8.79 (7.04, 10.54)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	17.60 (14.14, 21.11)	8.77 (7.04, 10.59)	0.00 (0.00, 0.00)
Non-Medical Expenses while Receiving Care (e.g. meals, etc.)	2.01 (0.00, 6.80)	0.96 (0.00, 5.60)	0.00 (0.00, 0.00)	0.99 (0.79, 1.19)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	1.98 (1.58, 2.39)	0.99 (0.79, 1.19)	0.00 (0.00, 0.00)
Overhead	13.76 (9.03, 18.48)	1.94 (0.00, 6.68)	1.94 (0.00, 6.70)	28.69 (22.99, 34.42)	1.94 (1.55, 2.33)	1.94 (1.55, 2.33)	30.86 (24.77, 36.87)	1.94 (1.56, 2.34)	1.94 (1.55, 2.34)
Indirect									
Child/Elderly Care	1.42 (0.00, 6.23)	0.70 (0.00, 5.45)	0.00 (0.00, 0.00)	0.71 (0.57, 0.85)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	1.42 (1.14, 1.70)	0.71 (0.57, 0.85)	0.00 (0.00, 0.00)
Loss of Earnings from Missed Work	3.47 (0.00, 8.35)	1.72 (0.00, 6.50)	0.00 (0.00, 0.00)	1.72 (1.37, 2.06)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	3.44 (2.75, 4.12)	1.72 (1.37, 2.06)	0.00 (0.00, 0.00)
Total	**176.95 (172.23, 181.67)**	**153.01 (148.23, 157.77)**	**140.75 (135.91, 145.53)**	**67.11 (53.75, 80.82)**	**28.25 (22.59, 33.95)**	**28.19 (22.41, 33.69)**	**120.58 (96.92, 145.34)**	**79.24 (63.32, 95.06)**	**67.17 (53.83, 80.55)**

One day of facility-based palliative care was estimated to cost $58. Figure 2.3 demonstrates the distribution of cost parameters as a percent of total costs for each treatment option and Table 2.3 demonstrates the costs for cancer treatment.

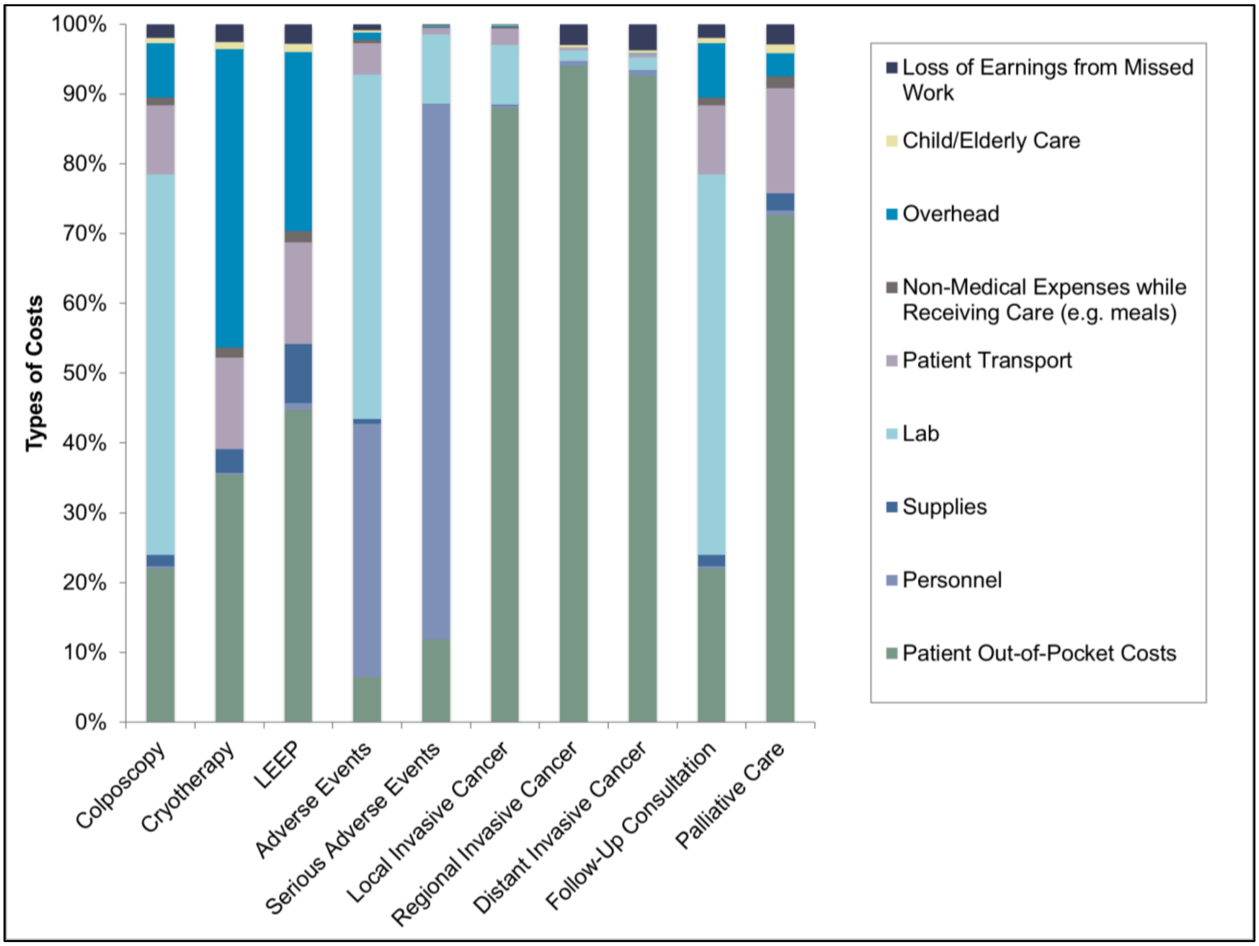


Figure 2.3. Distribution of Cost Parameters as Percent of Total Costs for Treatment Options

Table 2.3. Estimated Costs of Treatment for Cervical Cancer in Nairobi, Kenya (2014 USD)

Costs	Adverse Events (95% CI)	Serious Adverse Events (95% CI)	Local Invasive Cancer (95% CI)	Regional Invasive Cancer (95% CI)	Distant Invasive Cancer (95% CI)	Follow-Up Visit (95% CI)	Palliative Care (95% CI)
Direct Medical							
Patient Out-of-Pocket Costs	12.75 (10.13, 15.36)	114.78 (91.73, 137.79)	992.36 (793.42, 1189.83)	6048.57 (4855.21, 7251.94)	4714.65 (3768.21, 5655.03)	38.83 (31.05, 46.56)	42.28 (33.86, 50.60)
Personnel	70.60 (56.27, 84.97)	738.35 (594.12, 886.26)	5.13 (4.09, 6.14)	42.42 (33.82, 51.11)	37.30 (29.83, 44.72)	0.64 (0.51, 0.76)	0.39 (0.32, 0.47)
Supplies	1.43 (1.14, 1.72)	1.43 (1.14, 1.72)	1.43 (1.14, 1.71)	1.43 (1.14, 1.71)	1.43 (1.15, 1.72)	2.87 (2.30, 3.44)	1.43 (1.14, 1.72)
Lab	96.19 (76.95, 115.21)	96.30 (76.93, 115.47)	96.45 (77.13, 115.42)	96.29 (76.97, 115.48)	96.19 (77.06, 115.53)	96.43 (77.10, 115.81)	0.00 (0.00, 0.00)
Direct Non-Medical							
Patient Transport	8.79 (7.03, 10.59)	8.79 (7.06, 10.52)	26.34 (21.02, 31.61)	26.41 (21.25, 31.71)	26.33 (21.07, 31.55)	8.80 (7.06, 10.54)	8.79 (7.04, 10.56)
Non-Medical Expenses while Receiving Care	0.99 (0.79, 1.19)	0.99 (0.79, 1.20)	2.97 (2.37, 3.57)	0.99 (0.79, 1.19)	0.99 (0.80, 1.20)	0.99 (0.80, 1.19)	0.99 (0.80, 1.19)
Overhead	1.94 (1.56, 2.33)	1.94 (1.56, 2.33)	1.94 (1.55, 2.32)	1.94 (1.55, 2.33)	1.94 (1.55, 2.33)	1.94 (1.55, 2.33)	1.94 (1.55, 2.33)
Indirect							
Child/Elderly Care	0.71 (0.57, 0.85)	0.71 (0.57, 0.85)	0.71 (0.57, 0.85)	22.69 (18.01, 27.27)	22.68 (18.16, 27.21)	0.71 (0.56, 0.85)	0.71 (0.57, 0.85)
Loss of Earnings from Missed Work	1.72 (1.37, 2.07)	1.72 (1.38, 2.07)	1.72 (1.37, 2.07)	191.78 (154.17, 230.84)	191.97 (152.87, 230.34)	1.72 (1.38, 2.06)	1.72 (1.38, 2.06)
Total	**195.40 (156.01, 234.69)**	**967.17 (775.82, 1157.92)**	**1130.63 (903.56, 1356.64)**	**6448.88 (5148.58, 7725.87)**	**5104.44 (4084.68, 6118.97)**	**152.98 (121.84, 183.45)**	**58.36 (46.81, 69.99)**

Based on the one-way sensitivity analysis, the largest drivers of non-integrated procedure costs were patient out-of-pocket costs, laboratory costs, overhead costs, and costs of patient transportation. Personnel were a main cost driver for the treatment of adverse and serious adverse events. Facility overhead, supplies, personnel, and patient transportation became less influential on results in the semi-integrated and fully-integrated scenarios for colposcopy, cryotherapy and LEEP. For example, overhead costs for colposcopy, cryotherapy and LEEP in the non-integrated scenario were $14, $29, and $31, respectively. However, when overhead costs were allocated across all patients in the health facility under integrated assumptions, these costs were reduced to approximately $2 per visit for each treatment strategy. Similarly, in a non-integrated scenario, patient transportation costs were $18 for two round-trip visits for colposcopy and LEEP, and $9 for one round-trip visit for cryotherapy. In contrast, in a fully-integrated scenario, $0 in marginal transportation costs were expected for all treatment methods.

When evaluating costs of different stage-based cancer treatment strategies to reflect variation in care (Appendix Tables 1 and 2), costs of treatment for local invasive cancer ranged from $1,130 for treatment with simple hysterectomy to $4,363 for treatment with radiotherapy only when surgery was contraindicated to $5,239 for treatment with simple hysterectomy followed by radiotherapy. Treatment for regional invasive cancer ranged from $4,362 for treatment with radiotherapy only, to $5,100 for chemotherapy and radiotherapy combined, to $6,440 for radical hysterectomy, chemotherapy and radiotherapy. Finally, treatment strategies for distant invasive cancer ranged from $5,100 for chemotherapy and radiotherapy to $5,127 for chemotherapy, radiotherapy, plus a day of facility-based palliative care. Adding palliative care to any treatment scenarios would add $58 per day.

2.4 Discussion

Our study evaluated costs of integrating treatment for pre-cancerous lesions into an HIV-treatment center in Kenya and demonstrated that, from a societal perspective, integrated care can provide substantial cost savings—on the order of 58% in the case of cryotherapy, 45% in the case of LEEP, and 20% in the case of colposcopy. Furthermore, the convenience of same day treatment is likely to increase uptake in the population and thereby provide greater aggregate savings. Additionally, our findings provide cost estimates of treatment for pre-cancerous lesions and cervical cancer treatment, including facility-based palliative care in Kenya

At CHC, visual inspection with acetic acid has been used as part of a same-day screen-and-treat strategy with cryotherapy [29]. Integrating cryotherapy to treat pre-cancerous lesions on the same day as screening would result in marginal direct medical costs of approximately $28. Similarly, researchers at KNH studied the potential use of a two-visit screen-and-treat process with Papanicolaou smear ("Pap") on the first visit followed by a second visit at which both colposcopy biopsy and LEEP –usually provided in two separate visits– were performed to treat pre-cancerous lesions [15]. Investigators found that a two-visit process resulted in similar detection of disease (84%) while reducing the average time between abnormal Pap smear results and LEEP treatment by approximately 77 days [15]. Based on the cost estimates presented here, a two-visit Pap followed by colposcopy plus LEEP would cost slightly over $200 in direct medical costs, but would save approximately $38 per treatment per visit in non-medical and indirect medical expenses when compared to a standard 3-visit strategy (Pap, colposcopy, and LEEP). Similarly, economic savings from integrated services compared to non-integrated services would primarily come from lower marginal costs of patient transportation and overhead that would be reduced by achieving efficiencies of scope through provision of cervical cancer related care on the same day as HIV treatment visits. Overlap in required supplies for HIV care and treatment of pre-cancerous lesions, such as specula and standard clinical sterilization supplies, would support integrating services at low marginal costs. Importantly, costs should be combined with effectiveness data to adequately assess the value achieved due to integration.

Cost and cost-effectiveness estimates of integrated health services have been identified as important research gaps in global health [38]. However, few cost estimates for integrated treatment of pre-cancerous lesions are available in the literature. To our knowledge, this is the first study to assess costs of treatment for pre-cancerous lesions integrated into HIV care in Kenya. A recent evaluation of the costs and cost-effectiveness of integrating cervical cancer screening into care for HIV-positive women in South Africa estimated a lower cost per procedure for colposcopy ($69-$76; range: $52-$95 [inflated from 2013 to 2014 U.S. dollars for comparison]) than our findings from Kenya ($141; range: $136-$146).[48] Cost differences between our findings and South African estimates presented in the literature were primarily due to lower estimated laboratory costs and exclusion of direct non-medical and indirect costs through a provider perspective in the South Africa study. In contrast, Kenya costs were estimated from the societal perspective to include opportunity costs of patients' time [48].

Similarly, few estimates of cervical cancer treatment costs are available for comparison in Sub-Saharan Africa. To our knowledge, most recent published costs of cervical cancer treatment in Kenya are based on estimates published in 2005 using data from 2000 nearly 20 years ago [39]. These estimates ranged from $1,901 for treatment for local invasive cancer with radical or simple hysterectomy to $2,414 for treatment with radiotherapy for regional and distant invasive cancer (converted from 2000 International dollars to 2014 USD for comparison)[39]. Similar estimates were derived for Tanzania using average direct medical cost data from 2002-2011 with cervical cancer treatment costs ranging from $1,770-$3,049 USD (converted from 2013 to 2014 USD for comparison), depending on stage. Our estimates ranged from $1,130-$6,449 for cancer treatment and reflected combined use of hysterectomy, radiotherapy, chemotherapy and palliative care in the cost calculations – identified through clinical and administrative interviews as standard KNH practice at the time of the study. However, combined use of therapies may have contributed to higher cost estimates than those published from 2005 (Kenya) and 2013 (Tanzania) [18, 23], in addition to variable inclusion of non-medical and indirect costs.

The high costs of treating invasive cancer, relatively low-cost of treatment for pre-cancerous lesions, and high cervical cancer mortality rates in Kenya and SSA suggest an imperative for improving coverage of preventive strategies. Recent guidelines and initiatives put forth by key stakeholders, such as the World Health Organization, Pink Ribbon Red Ribbon, and the Bill & Melinda Gates Foundation, have contributed to growing global interest in better understanding potential health and economic outcomes of cervical cancer detection and treatment, particularly when integrated into existing health services such as care for HIV, routine childhood immunization clinics, or family planning services [19,33,35,50]. Given uncertainty in funding sustainability for cervical cancer care through multi-lateral donor programs such as the U.S. President's Emergency Plan for AIDS Relief (PEPFAR) [51], integration of screening and treatment with programs that continue to be funded (e.g., HIV treatment) could increase coverage rates at low marginal cost.

Recent recommendations by the *Disease Control Priorities, 3rd Edition* (DCP3) of interventions for improved cancer control in LMICs included cervical cancer screening, early diagnosis and treatment of cervical cancer, and palliative care –particularly opioid availability– as potentially cost-effective methods for reducing the global burden of cancers [52]. The DCP3 analysis suggests that adding palliative care to public health cancer prevention would add \$0.05-\$0.06 in marginal costs per capita to a public health cancer prevention strategy in LMICs, although this was not limited to a specific country or focused on cervical cancer or cancer patients receiving palliation [52]. One country-based study in South Africa identified general hospital-based palliative care to cost \$123 per visit (inflated from 2007 to 2014 USD) from a provider perspective, compared to our societal estimate of \$58 in Kenya for a facility-based cervical cancer palliation visit [53]. The South African estimate is likely higher due to inclusion of more capital costs, such as buildings, vehicles, facilities, and general hospital equipment, which were not included in the Kenya estimate [32].

This study has several limitations. Cost estimates derived through this study reflect standard practices in an urban setting and may not generalize to costs in rural areas. Additionally, while primary health care services in Kenya are partially subsidized through national and private insurance, patients shoulder out-of-pocket costs for consultation fees and services. Particularly for specialized cancer services, patients bear the brunt of service costs. In practice, the amount that patients pay may cover some facility costs, such as supplies and overhead. However, due to limitations with data availability and lack of explicit assumptions about proportional patient cost sharing, we chose to model a conservative estimate that includes the full patient out-of-pocket costs, in addition to supplementary facility costs. Furthermore, our study did not evaluate the potential burden of integration on the health system. For example, integrating screening into an HIV treatment center may require additional, and often limited, facility space and staff. Our study assumed that these resources would be shared with the addition of screening; however, we did not model the financial impact of displacing current services or the additional costs of expanding facility space or hiring new staff. Future studies should evaluate the potential impact of integrated screening on facility capacity.

Cancer treatment costs were based on the most commonly reported treatment regimen at a public tertiary hospital at the time of the study. However, on-the-ground treatment decisions may vary based on individual patient characteristics and preferences, health facility resources available, supply chain challenges, and other factors. A range of treatment regimens were assessed via scenario analyses. Furthermore, while the study examined costs and resource use for facility-based palliative care, it did not assess the costs of home- or institution-based palliative care, which many patients may prefer to in-hospital end-of-life care. Also, facility-based palliative care may not be readily available to patients seeking treatment for cervical cancer. At KNH, for example, palliative care providers work as volunteers on top of their other duties. Therefore, palliative care costs may vary based on availability of services, average wages of the personnel volunteering, and consistent operation of the palliative care center. In general, better data on the value of palliative care is needed. Future studies might evaluate and compare potential health benefits of palliative care when consistently available, training curriculum for palliative care provision, comparisons of palliative care staffing models (e.g., volunteer vs. paid staff, task-shifting, community health worker models, etc.), and home-based palliative care.

Results from this cost analysis provide valuable and relevant information that could be combined with effectiveness data in integrated and non-integrated settings to evaluate the potential cost-effectiveness and budget impact of local and national cervical cancer treatment programs. Our findings can also be used to support decision-making and research related to HPV vaccination and other modes for preventing and treating cervical cancer in Kenya and other similar low- and middle-income countries. The cost estimates presented here can support decision-making among ministries of health, health facilities, and other stakeholders focused on leveraging HIV-treatment resources to improve treatment of pre-cancerous lesions and cervical cancer through application in cost-effectiveness and budget impact models comparing potential screening and treatment strategies. Cost of treatment estimates can also support investment decisions and research related to HPV vaccination and other programs designed to prevent and treat cervical cancer.

2.5 Conclusions

Integrating treatment of pre-cancerous lesions into HIV care is estimated to achieve between a 20% and 58% reduction in costs from a societal perspective. Cost savings are expected to be derived primarily through reduction in per-patient non-medical costs such as overhead and indirect costs such as patient time spent seeking care. These societal cost estimates can be applied in cervical cancer-related economic evaluations in Kenya and similar urban settings in other low-income countries.

Chapter 3. POTENTIAL COST-EFFECTIVENESS AND BUDGET IMPACT OF INTEGRATING CERVICAL CANCER SCREENING INTO A ROUTINE CHILDHOOD IMMUNIZATION PROGRAM IN UGANDA

3.1 INTRODUCTION

More than 85% of the global burden of cervical cancer occurs in developing countries. While cervical cancer is preventable if detected early through screening, many women in low-resource settings experience challenges accessing life-saving screening and treatment due to health systems inefficiencies, costs, patients' perceptions of screening, and the time required to seek care.[2–5] The highest incidence rates for cervical cancer occur in sub-Saharan Africa, yet screening coverage rates for the region are low. In Uganda, the age-standardized incidence rate of cervical cancer is 44.4 per 100,000 women resulting in nearly 2,300 deaths annually.[1] Recent prevention efforts to scale up HPV vaccination efforts among Ugandan girls ages 10-14 years old have been largely viewed as successful, with vaccination coverage >90%. However, cervical cancer screening among older girls not yet vaccinated and women older than the target vaccination age remains low, between 2-4%.[8,54] For these groups of women, improving prevention and early detection of cervical cancer through expanded access to screening is and will continue to be a high priority in Uganda and other low-income countries.[7–9]

To increase the number of women receiving screening, the World Health Organization has promoted the implementation of programs that (1) reduce time required for patients to seek screening and treatment and (2) leverage existing infrastructure to deliver screening.[10–12] One strategy is to offer screening to women as they enter the health system for other clinical needs, such as bringing their children in to obtain routine immunizations, which may increase screening coverage rates at low marginal costs.[18–23]

In Uganda, routine childhood immunization clinics are part of a national campaign, the Uganda National Expanded Program on Immunisation, to ensure that all children receive full vaccination against 11 target diseases.[55] Given that immunization is a national priority and that women tend to be the main caregiver of children in Uganda, routine immunization clinics may present an opportunity to simultaneously increase vaccination coverage among children and cervical cancer screening coverage among women while leveraging existing infrastructure and shared clinical resources.

To evaluate this potential, a pilot study was conducted in 2014 to assess the feasibility, acceptability, costs, and effectiveness of integrating VIA screening into a routine childhood immunization program in rural central Uganda.[56] During the pilot, 625 eligible women were offered screening as they entered the health facility with their children.[56] In this setting, screening was found to be highly acceptable (91% agreed to screening), and it was feasible to train nurses to provide VIA screening.[56] Women who refused screening reported fears of learning they had cancer and lack of time.[56] Effectiveness data was limited by a small sample size of women with positive test results; however, in other screening trials in Uganda, VIA had a sensitivity of 22-74% and a specificity of over 85%.[57] Data on direct medical costs and patient time were also collected as part of the pilot study. The 2014 pilot study was the first study to investigate the potential acceptability and costs of integrating cervical cancer screening into a childhood immunization clinic in SSA.[56]

Integration of cervical cancer screening into currently existing routine childhood immunization clinics in Uganda may yield positive benefits associated with prevention and detection of disease at low marginal costs. However, evidence about potential costs and health outcomes for integrated programs are limited. Economic evaluations of these and other innovative cervical cancer screening and treatment strategies may guide policymakers on which delivery methods achieve the best value for the scarce resources available to invest in life-saving cervical cancer prevention and treatment. As such, this study evaluated the potential cost-effectiveness and budget impact of integrating cervical cancer screening using visual inspection with acetic acid (VIA) into a routine immunization clinic in Uganda.

3.2 Methods

3.2.1 *Cost-Effectiveness Analysis*

A cost-effectiveness analysis (CEA) was conducted using a combined decision-tree and Markov model to compare the potential costs and health outcomes of integrated screening programs to non-integrated programs for a cohort of women entering the clinic. (Figure 3.1) The analysis assumed a once-per-lifetime screening strategy.

Through the decision tree, women were simulated to either receive VIA screening in a RCIC integrated setting or in a non-integrated setting. For the proportion of women who received screening, test performance (sensitivity and specificity) was applied based on reported results in each setting. The decision tree accounts for background prevalence of disease (Normal, HPV/CIN1, CIN2, CIN3, and cervical cancer). Combined with sensitivity and specificity data, this allowed for the effect of true positives, false positives, true negatives, and false negatives to be accounted for in the model.

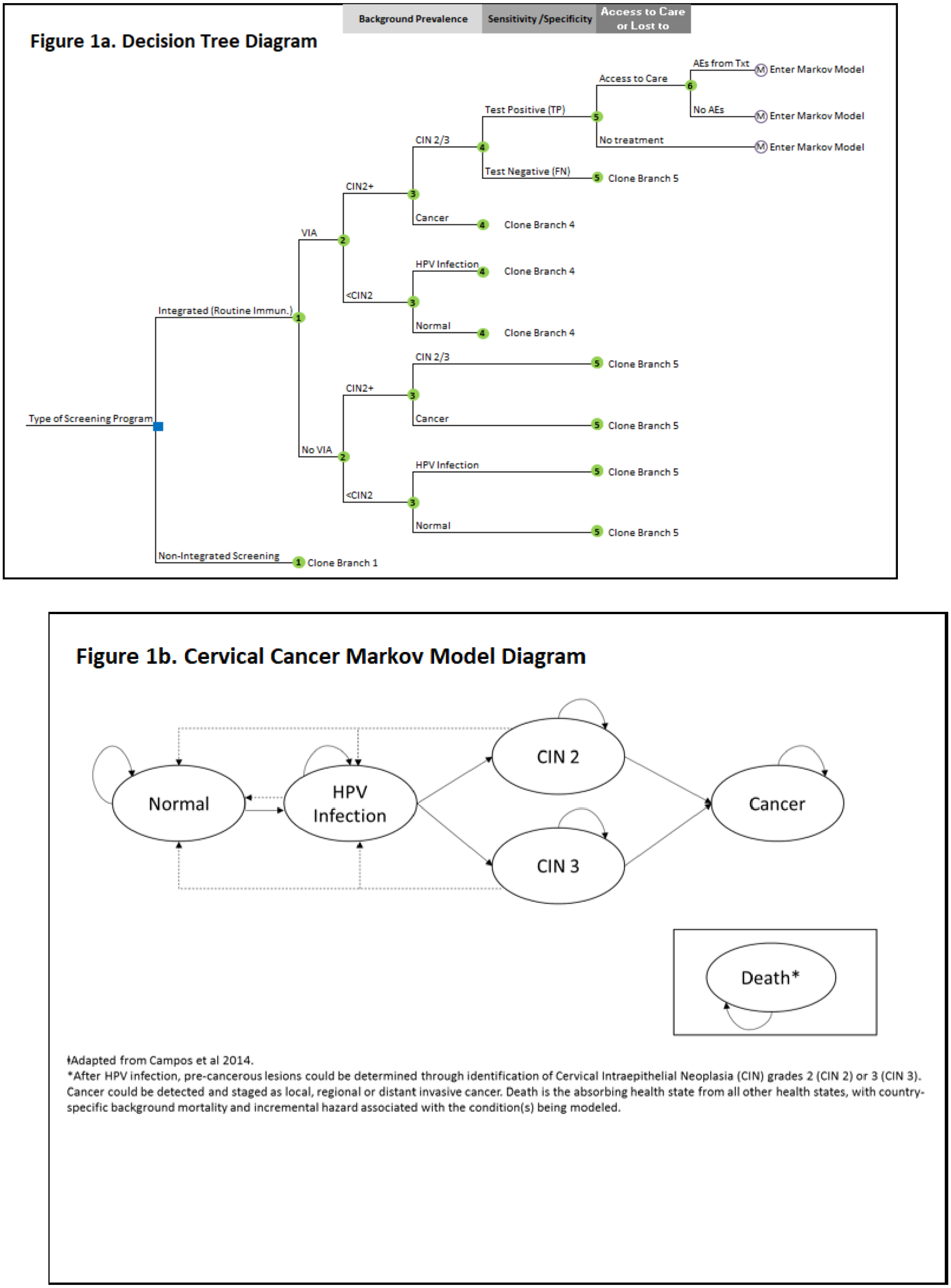


Figure 3.1. Economic model diagrams comparing integrated to non-integrated screening

Several assumptions were made for the base case and scenario analyses for both arms of the cost-effectiveness study. (Table 3.1) Cost and outcomes parameters are presented in Table 3.2. All women who were identified as positive for disease (i.e., true positives and false positives) were assumed to be referred to treatment. For treatment of CIN 2/3 precancerous lesions, 80% of women were assumed to be referred to cryotherapy. The 20% of women expected to be ineligible for cryotherapy were assumed to be referred to colposcopy biopsy + loop electrosurgical excision procedure (LEEP).[58] Cervical cancer was expected to be treated based on stage, with 20% of women experiencing local invasive, 40% regional invasive, and 40% distant invasive cancer.[59] A proportion of women were assumed to be lost to follow-up at each phase in the care process (15%-50%), following the reported experience in the literature; the rest were assumed to receive treatment.[57,60,61] Of those receiving treatment, less than 1% were assumed to experience an adverse event (defined as an event requiring an outpatient visit) or serious adverse event (defined as an event requiring an inpatient visit with one overnight hospital stay). (Table 3.2)

Finally, treatment effectiveness estimates were only applied to the proportion of women receiving treatment. Conditional probabilities were calculated to identify the proportion of women to end in each branch of the decision tree. Treatment effectiveness was then applied to the branches where women received treatment to determine the proportion of women who became cured or in remission after treatment and those who were not. Costs of each branch were also calculated to estimate the costs associated with screening and treatment in the integrated and non-integrated setting. At the end of the decision tree, women proportionally entered into the appropriate health state in the natural history model.

Table 3.1. Base Case, Scenario, and Threshold Analysis Assumptions by Evaluation Arm

	Base Case Analysis *Integrated Arm*	 *Non-Integrated Arm*	**Primary Scenario Analysis** *Integrated Arm*	 *Non-Integrated Arm*	**Threshold Analysis** *Varied over threshold?*
Model Perspective	Limited Societal		Limited Societal		N/A
Time Horizon	100 years		100 years		N/A
Analysis Level	Following pilot study at regional level (Luwero) and National		Pilot Study and National		N/A
Mean age at screening	Mean age of screening at RCIC in integration pilot study in Uganda[35]	Mean age of screening from non-integrated study in Uganda[57]	Same screening age		Varied to encompass all reproductive ages (15-49) at time of screening, both simultaneously and separately for each arm
Screening Coverage (cost denominator)	Number of women screened during pilot study	National Coverage Rate x Reproductive Aged Women	Pilot study coverage rate	National Coverage Rate x Reproductive Aged Women	Varied 0-100%
VIA Test Sensitivity	Pilot Study Sensitivity	Non-Integrated Sensitivity[57]	Same sensitivity of VIA		Varied 0-100%
Demand generation and staff training	Screening promotion, patient recruitment costs, and staff training were assumed to be equivalent across both arms.		Screening promotion, patient recruitment costs, and staff training were assumed to be equivalent across both arms.		None
Staff time					None
Screening Nurse	15 minutes	15 minutes	15 minutes	15 minutes	
Health Educator	15 minutes	Not included	15 minutes	Not included	
Patient Follow-Up	15 minutes	15 minutes	15 minutes	15 minutes	
Supply costs	Shared supply costs were calculated for items used in both RCIC and screening settings over the total number of outpatient visits; screening-specific supplies accumulated 100% of costs over total number of screening visits.	100% of costs were attributed to the screening program; per patient cost was calculated over total number of screening visits.	Same as base case	Same as base case	None
Marginal Round Trip Visits to Clinic for Screening	None	1	None	1	None
Time spent waiting for screening	90 minutes	90 minutes	90 minutes	90 minutes	Integrated arm varied over 0-100% increase in wait time compared to non-integrated arm.

Table 3.2. Input parameters for base case and one-way sensitivity analysis

Table 3.2a Screening and treatment parameters for base case and one-way sensitivity analysis			
Screening Assumptions	**Base Case**	**One-way SA range**	**Reference**
Demographics			
Cervical Cancer Incidence	0.00044	(0.0004-0.0005)	[1]
Integrated Screening			
Mean age at screening	27	(21-32)	[56]
Receive Screening	0.914	(0.4840-1.0000)	[56]
VIA Sensitivity	0.5	(0.4000-0.6000)	[Study data on file]
VIA Specificity	0.977	(0.7816-1.0000)	[Study data on file]
Non-Integrated Screening Outcomes			
Mean age at screening	37	(29-44)	[57,62]
Receive Screening	0.048	(0.0040-0.1400)	[6,63]
VIA Sensitivity	0.736	(0.6300-0.8240)	[57]
VIA Specificity	0.666	(0.6490-0.6830)	[57]
Referral to Advanced Care			
For Detected CIN2+:			
% Referred to cryotherapy	0.8	(0.6400-0.9600)	[58]
% Referred to Colposcopy + LEEP (ineligible for cryotherapy)	0.2	(0.1600-0.2400)	[58]
Loss to Follow-Up after Screening			
% LTFU: Screening to Cryotherapy	0.15	(0.1200-0.1800)	[57]
% LTFU: Screening to Colposcopy Biopsy	0.34	(0.2720-0.4080)	[60]
% LTFU: Colposcopy Biopsy to LEEP	0.15	(0.1200-0.1800)	[61]
% LTFU: Colposcopy to Treatment	0.5	(0.4000-0.6000)	[57]
Treatment Effectiveness			
Cryotherapy	0.92	(0.6600-0.9000)	[58]
Colposcopy + LEEP	0.96	(0.7680-1.1520)	[58]
Treated cancer cure probability (monthly)	0.1500	(0.1200-0.1800)	[39]

Table 2b. Cost parameters for base case and one-way sensitivity analysis

Cost Parameters	Base Case Estimate (OWSA Range)		References
	Integrated	*Non-Integrated*	
Direct Medical Costs per Screen			
Demand generation	$4.71 ($4-$6)	$4.71 ($4-$6)	Study data on file
Training costs	$0.62 ($0-$1)	$0.62 ($0-$1)	Study data on file
Clinic staff	$0.27 ($0-$0)	$0.18 ($0-$0)	Study data on file
Supplies	$0.50 ($0-$1)	$0.53 ($0-$1)	Study data on file
Non-Medical Costs per Screen			
Transportation	$0.0	$10.93 ($9-$13)	Calculation
# marginal round trip visits for VIA	$0.0	$1.0	Assumption
Average Cost (round trip)	$10.93 ($9-$13)	$10.93 ($9-$13)	[58]
Indirect Costs per Screen			
Loss of earnings from missed work	$3.55 ($3-$4)	$3.38 ($3-$4)	Calculation
Time spent seeking care for screening (minutes)	45 (36-54)	30 (24-36)	Study data on file; [58]
Wait time in medical center (minutes)	90 (72-108)	90 (72-108)	Study data on file; [58]
Transportation time (minutes, round trip)	180 (144-216)	180 (144-216)	Study data on file; [58]
Add-on cost for receiving positive results	$0.17 ($0.14-$0.20)	$0.17 ($0.14-$0.20)	Calculation
Add-on time for receiving positive results (minutes)	15 (12-18)	15 (12-18)	[58]
Sum of Integrated Screening Costs	$9.65 ($8-$12)	$20.35 ($16-$24)	Calculation
Costs of Treatment for Pre-Cancerous Lesions			
Colposcopy Biopsy	$15.78 ($13-$19)		[58]
Cryotherapy	$5.50 ($4-$7)		[58]
LEEP	$89.55 ($72-$107)		[58]
Costs of Cancer Treatment			
Local Invasive	$947.48 ($904-$1,357)		[58]
Regional Invasive	$1,254.78 ($5,149-$7,726)		[58]
Distant Invasive	$1,254.78 ($4,085,-$6,119)		[58]
Other Costs of CxCa Related Care			
Adverse Events	$195.40 ($156-$235)		[64]
% AEs requiring outpatient visit	0.045 (0.04-0.05)		[65]
Serious Adverse Events	$967.17 ($776-$1158)		[64]
% SAEs requiring inpatient visit	0.0075 (0.01-0.01)		[65]
Female hours of work per week	40		[66]
Female Hourly Wage (2016 USD)	$0.68		[66]

Table 2c. Disease transition probabilities for base case and one-way sensitivity analysis

Transition Probabilities (monthly)	**Base Case**	**One-way sensitivity analysis range**	**Reference**
Background Prevalence			
Normal	0.8506	(0.6805-1.0000)	[57]
HPV Infection	0.1217	(0.0974-0.1461)	[57]
12-14 years	0.4150	(0.3320-0.4980)	[67]
15-19 years	0.2050	(0.1640-0.2460)	[67]
20-24 years	0.2050	(0.1640-0.2460)	[67]
25-29 years	0.1150	(0.0920-0.1380)	[67]
30-34 years	0.1200	(0.0960-0.1440)	[67]
35-39 years	0.0700	(0.0560-0.0840)	[67]
40-44 years	0.0900	(0.0720-0.1080)	[67]
45-49 years	0.0400	(0.0320-0.0480)	[67]
50-54 years	0.0530	(0.0424-0.0636)	[67]
55-59 years	0.0650	(0.0520-0.0780)	[67]
60-64 years	0.1300	(0.1040-0.1560)	[67]
65-69 years	0.1000	(0.0800-0.1200)	[67]
CIN1	0.0000	(0.0000-0.0000)	[57]
15-19 years	0.0670	(0.0536-0.0804)	[67]
20-24 years	0.0700	(0.0536-0.0804)	[67]
25-29 years	0.0610	(0.0560-0.0840)	[67]
30-34 years	0.0640	(0.0488-0.0732)	[67]
35-39 years	0.0620	(0.0512-0.0768)	[67]
40-44 years	0.0550	(0.0496-0.0744)	[67]
45-49 years	0.0660	(0.0440-0.0660)	[67]
50-54 years	0.0920	(0.0528-0.0792)	[67]
55-59 years	0.0660	(0.0736-0.1104)	[67]
60-64 years	0.0970	(0.0776-0.1164)	[67]
65-69 years	0.0630	(0.0504-0.0756)	[67]
CIN 2	0.0197	(0.0158-0.0236)	[57]
25-29 years	0.0090	(0.0072-0.0108)	[67]
30-34 years	0.0096	(0.0077-0.0115)	[67]
35-39 years	0.0104	(0.0083-0.0125)	[67]
CIN 3	0.0060	(0.0048-0.0072)	[57]
25-29 years	0.0090	(0.0072-0.0108)	[67]
30-34 years	0.0096	(0.0077-0.0115)	[67]
35-39 years	0.0104	(0.0083-0.0125)	[67]

Cancer	0.0019	(0.0015-0.0023)	[57]
20-24 years	0.0000	(0.0000-0.0000)	[67]
25-29 years	0.0001	(0.0001-0.0001)	[67]
30-34 years	0.0003	(0.0002-0.0003)	[67]
35-39 years	0.0005	(0.0004-0.0006)	[67]
40-44 years	0.0008	(0.0006-0.0009)	[67]
45-49 years	0.0011	(0.0009-0.0013)	[67]
50-54 years	0.0013	(0.0010-0.0015)	[67]
55-59 years	0.0015	(0.0012-0.0018)	[67]
60-64 years	0.0014	(0.0011-0.0017)	[67]
65-69 years	0.0012	(0.0009-0.0014)	[67]
70-74 years	0.0015	(0.0012-0.0018)	[67]
75-79 years	0.0012	(0.0009-0.0014)	[67]
% of Cancer in Local Cancer[b]	0.2000	(0.1600-0.2400)	[68]
% of Cancer in Regional Cancer[b]	0.4000	(0.3200-0.4800)	[68]
% of Cancer in Distant Cancer[b]	0.4000	(0.3200-0.4800)	[68]
Undetected cancer identification via symptoms (monthly)			
Local Cancer	0.0174	(0.0139-0.0209)	[69]
Regional Cancer	0.0735	(0.0588-0.0882)	[69]
Distant Cancer	0.1746	(0.1397-0.2095)	[69]
Transition Probabilities (monthly)			
Normal Remain	0.9950	(0.7960-1.0000)	1-Progression from Normal to HPV
Normal to HPV Infection[a]	0.0051	(0.0040-0.0061)	[67]
HPV Regress to Normal	0.0305	(0.0244-0.0366)	[67]
HPV Remain	0.9355	(0.7484-1.0000)	1-Regress to Normal
HPV to CIN 2	0.0170	(-0.0026-0.0366)	[70]
HPV to CIN 3	0.0170	(0.0136-0.0204)	[70]
CIN 2 Regresses[c]	0.0087	(0.0070-0.0104)	[69]
CIN 2 Regress to HPV Infection	0.0044	(0.0035-0.0052)	[69]
CIN 2 Regress to Normal	0.0044	(0.0035-0.0052)	[69]
Progression CIN 2 to Local Cancer[d]	0.0031	(0.0024-0.0037)	[67]
CIN 2 Remain	0.9883	(0.7906-1.0000)	Calculated from CIN 2 progression and regression.
CIN 3 Regresses[c]	0.0044	(0.0035-0.0052)	[69]
CIN 3 Regress to HPV Infection	0.0022	(0.0017-0.0026)	[69]
CIN 3 Regress to Normal	0.0022	(0.0017-0.0026)	[69]
Progression CIN 3 to Local Cancer[d]	0.0031	(0.0024-0.0037)	[67]

CIN 3 Remain	0.9926	(0.7941-1.0000)	Calculated from CIN 3 progression and regression.
Local Cancer to Regional Cancer	0.0200	(0.0160-0.0240)	[67,69]
Local Invasive Cancer Mortality	0.0059	(0.0047-0.0071)	[71]
Local Cancer Remain	0.9741	(0.7793-1.0000)	Calculated from local invasive progression.
Regional Cancer to Distant Cancer	0.0250	(0.0200-0.0300)	[69]
Regional Cancer to Death	0.0151	(0.0121-0.0182)	[71]
Regional Cancer Remain	0.9599	(0.7679-1.0000)	Calculated from regional invasive progression.
Distant Cancer to Death	0.1746	(0.1397-0.2095)	[71]
Distant Cancer Remain	0.8254	(0.6603-0.9905)	Calculated from distant invasive progression.
Treated cancer cure probability (monthly)	0.1500	(0.1200-0.1800)	[39]
Background Mortality			
Age-Standardized Mortality Rate (Females)	0.000272		[1]

a: Incorporated the average of the baseline value ranges presented for HPV 16, 18, and other types of HPV presented in [67].
b: Local cancer defined as Stage IA1; regional cancer defined as Stage IB2, IIA2, IIIA or IIIB; distant cancer defined as Stage IVA or IVB.
c: Assumed that among individuals with CIN 2 or CIN 3 that regress, 50% regress to normal and 50% regress to HPV Infection, based assumptions from original data source. [69]
d: Assumed that invasive cancer always starts at the local stage. [67]

Table 2d. Coverage estimates for budget impact model base case and one-way sensitivity analysis

Budget Impact Model Parameters	**Base Case**	**One-way sensitivity analysis range**	**Reference**
Demographics			
Total population, Uganda (female)	20,854,313		[72]
Reproductive Aged Women, 15-49 (% of total female population)	0.45		[72]
Reproductive Aged Women in Luweero Catchment Area	9,405		[35]
Luwero HCIV Annual Outpatient Attendances	27,710	(22,168-33,252)	[73]
Expected population growth (annual %, 2016)	0.033		[72]
% of children fully vaccinated	0.52	(0.23-0.94)	[74]
Estimated full course of vaccine coverage among total female population[a]	0.026	(0.0100-0.0460)	[75]
Ages 10-14	0.954	(0.3700-1.0000)	[75]
Ages 15-19	0.949	(0.0000-1.0000)	[75]
Ages 20-29	0	(0.0000-0.0000)	[75]
Estimated one dose vaccination coverage among total female population[a]	0.006	(0.0030-0.0090)	[75]
Ages 10-14	0.776	(0.0470-1.0000)	[75]
Ages 15-19	0.969	(0.0000-1.0000)	[75]
Ages 20-29	0	(0.0000-0.0000)	[75]
HPV full course vaccine efficacy (OR)	0.7	(0.0000-1.0000)	[75]
HPV one course vaccine efficacy (OR)	0.7	(0.0000-1.0000)	[75]

a: Estimates were identified from report of coverage in East Africa region. [75]

For the cohort of women in the integrated arm, base case cost and screening outcomes data parameters were derived from primary data collected during the pilot study conducted at Luwero Health Center IV (“LHC-IV”) between July 2014 to May 2015.[35] LHC-IV is a rural clinic in the Central Region of Uganda that provides primary care to over 40,000 individuals, including nearly 10,000 women of reproductive age, and hosts a routine childhood immunization program.[76] During the study, 625 women eligible for the study brought children into the clinic for routine immunization and were offered screening while in the waiting area.[56] In total, 571 (91%) of women agreed to the screening.[76] Those who agreed received screening via visual inspection with acetic acid in the clinic.[76] Any women with identified cervical abnormalities, lesions or cervical cancer were referred to an outside facility for treatment and follow-up care. Women were excluded from participation if they were pregnant, diagnosed with cervical cancer, menstruating at time of recruitment, or had given birth in the 6 weeks prior to attending the clinic.[76]

For the non-integrated arm, base case estimates were derived from published estimates of VIA screening in the general population in Uganda.[57,58] The mean age of women in the integrated setting was 26 years old compared to 37 years old in the non-integrated setting. Screening coverage was 91% among women attending the routine childhood immunization clinic, compared to 4% coverage among the general population.[6, 7, 26] Finally, test sensitivity was approximately 50% in the integrated setting (study data on file) compared to 74% in the non-integrated setting.[57] Health outcomes, disease progression and other transition probabilities, treatment effectiveness and lost to follow-up data were obtained from the literature. (Table 3.2)

Direct medical and direct non-medical costs of VIA screening in an integrated setting were derived from primary data collected at LHC-IV during the study period. Indirect costs for the study were based on previous estimates of patient and provider time associated with screening and other service provision in Uganda.[71] Costs of screening in a non-integrated setting were derived from the literature. Costs of treating precancerous lesions with cryotherapy, colposcopy biopsy, LEEP and cervical cancer were derived from the literature.

The base case CEA was conducted from the limited societal perspective and included all direct medical (e.g. supplies, staff), direct non-medical (e.g., meals) and indirect (e.g., patient time) costs associated with screening in each setting. A secondary analysis was conducted at the clinic-level that included only direct medical and direct non-medical costs specific to the facility. The CEA was conducted using month-long cycles over a patients' lifetime horizon to allow for all future effects in terms of costs and health consequences of the population cohort to be included in the model.[78] Mean age of women screened in each setting was used in conjunction with published country-specific life tables to estimate survival and calculate mortality rates.[79] A discount rate of 3% was applied for both costs and consequences. Half-cycle correction was not applied to the Markov Model given the large number of cycles and short length of cycle times.[80]

Results were reported as cost per cancer case avoided, cost per life-year (LY) saved, and as an incremental cost-effectiveness ratio (ICER). The ICER is a ratio of the difference in costs of integrated and non-integrated care and the difference in consequences of integrated and non-integrated care. All costs were reported in 2016 U.S. dollars, and conversions were made using official World Bank exchange rates.[81] Costs were inflated to 2016 U.S. dollars using annual Consumer Price Indices for appropriate years.[46]

Model uncertainty was assessed using one-way and probabilistic sensitivity analyses (PSA). The one-way sensitivity analysis was used to identify outcomes and costs that were highly influential in the model. Results are presented here as tornado diagrams. For the PSA, a Monte Carlo simulation was used to estimate the joint parameter uncertainty and robustness of the model. The simulation was run 10,000 times to obtain a random distribution and 95% credible range around each deterministic value in the model. Outcomes parameters were assigned a beta distribution and costs were assigned a gamma distribution for the simulation. Results from the simulation are plotted on the cost-effectiveness plane to illustrate the range of economic value that could be achieved through integrated screening services. For the purposes of this analysis, an integrated approach to screening was considered cost-effective over non-integrated screening if the cost per LY saved was less than 3 x Uganda’s gross domestic product per capita (GDP) and highly cost-effective if less than 1 x GDP per capita (2016 GDP per capita: $615; 3xGDP: $1846). A threshold analysis was conducted to project the cost-effectiveness over different willingness to pay ranges. These results were presented using a cost-effectiveness acceptability curve, which illustrates the probability that integrated screening is cost-effective at various willingness to pay thresholds.

Subsequent scenario and threshold analyses were calculated to evaluate how various assumptions about the health system and access to screening may impact the model’s outcomes. First, integrating health services may increase patient wait times in the clinic due to overburden of the health system. To evaluate the potential impact of new clinical bottlenecks and health systems' inefficiencies on program costs and benefits, a threshold analysis was conducted varying wait times for patients in the integrated setting. Second, women in the integrated arm were younger and had higher screening coverage than women in the non-integrated arm, on average. Threshold analyses were conducted evaluating the impact of varying these parameters in both groups. A full scenario analysis was conducted when assuming that women in both arms were the same age at screening.

Finally, preliminary data analysis of the routine childhood immunization study showed that, while screening offered in an RIC setting was highly acceptable (>90%), the number of women receiving both VIA and a confirmatory Pap smear test was too low to use reliably to establish a reliable estimate of VIA sensitivity in the integrated setting. However, conducting a new research study to obtain the necessary statistical power to evaluate effectiveness would require additional funding, resources, training, and personnel, which can be challenging in a low-resource setting like rural Uganda. As such, a threshold analysis was done to assess how various ranges of test sensitivity might impact the value (e.g., cost per LY saved) of integrating screening into immunization clinics in Uganda.

3.2.2 *Budget Impact Analysis*

A recent publication on the standard for reporting results of cost-effectiveness analyses in low-resource settings encourage the simultaneous evaluation of an intervention's potential impact on the payer's short-term fiscal budget.[82] In many low-income countries like Uganda, CEA findings may indicate that an intervention would be more cost-effective than the alternative studied. However, the reality of severe resource-constraints means that not all cost-effective interventions will be implemented, nor are they necessarily affordable given the

MOH's other potential investments. To address concerns of affordability, a budget impact analysis (BIA) was conducted to evaluate the feasibility and sustainability of scaling up integrating cervical cancer screening into rural immunization clinics in Uganda. This assessment evaluated the potential impact on the health plan budget from the perspective of the local health facility and Ugandan MOH (i.e., national health budget).

The BIA was developed to project outcomes over a one- to five-year time horizon, following methods described by the ISPOR Task Force on Principles of Good Practice for Budget Impact Analysis.[83] Secondary analyses were conducted over a 10-year horizon to project the potential impact of increased HPV vaccination coverage on the value of screening. Following the ISPOR BIA framework, the model predicted the current (non-integrated) and new (integrated) environments of cervical cancer screening and treatment, including the total eligible population, population with precancerous lesions or cervical cancer, target treatment population (i.e., women most at risk for cervical cancer), resource utilization, and costs of illness.[83] Cervical cancer prevention strategies, including HPV vaccination, were modeled to include current and projected coverage rates over time based on current and future predicted utilization.

The current cervical cancer prevention environment for the budget impact evaluation included: screening in a non-integrated setting only; HPV vaccination only (for those <26 years old); screening in a non-integrated setting + HPV vaccination; no screening or HPV vaccination. The new environment with introduction of screening integration included: screening in a non-integrated setting only; screening in an integrated setting only (as a substitution for non-integrated screening); HPV vaccination only; screening in an integrated setting + HPV vaccination; screening in a non-integrated setting + HPV vaccination; no screening or HPV vaccination.

Demographic data from the literature was used to estimate the current and projected eligible population for integration into routine immunization clinics in Uganda. An estimated 5.2 million women would be eligible for cervical cancer screening based on the current recommended screening ages put forth by the Ugandan MOH (26-49 years old). Based on current population and fertility rates, we estimated that 2.65 million are mothers of 0-36-month-old children recommended to receive routine immunizations. We do not have records of the number of women entering the routine facility; thus, country-level vaccination rates were used as a proxy for the percentage of women entering the clinic with their children. Recent estimates indicate that 55% of children 0-36 months are fully vaccinated.[74] Among those only partially vaccinated, vaccine coverage rates range from 23% (DPT vaccine) to 94% (BCG vaccine), depending on the vaccination.[74] The BIA assessed results assuming this same range of screening coverage in a scaled-up RIC program: 55% (range 23-94%) vaccination coverage multiplied by the number of women eligible for screening with children in the target age range for immunizations.

Women who already have pre-cancerous lesions or cervical cancer were excluded from the budget impact analysis. Additionally, girls who received the HPV vaccine and were expected to age into the recommended screening age range during the BIA timeframe were excluded from the future eligible population. Costs of the current and new intervention mix, including condition-related costs of cervical cancer outcomes and potential resource use were derived from the CEA model. In contrast to the CEA, BIA costs were not discounted.[83,84] To estimate the budget impact from the perspective of the Ugandan MOH, total costs were multiplied by the total eligible population and also by the proportion of the eligible population expected to use each type of screening/vaccination method or combination of methods. Indirect costs were not included in the BIA. Uncertainty were evaluated through best-case and worst-case analyses, where all parameters were simultaneously varied to their high and low estimates, respectively.

3.3 Results

3.3.1 *Baseline Economic Evaluation*

Over base case assumptions, offering VIA screening to women entering routine immunization clinics was projected to result in longer life expectancy by 4.1 years and cost $2,370 more than the alternative of non-integrated screening annually. This resulted in an incremental cost-effectiveness ratio of $579 per LY saved from the modified societal perspective. When compared to the presumed willingness to pay threshold based on GDP per capita, integrating VIA screening into routine immunization clinics would be considered a potentially highly cost-effective strategy in Uganda compared to non-integrated screening. In the base case analysis, no significant differences were found based on the perspective of the analysis. (Table 3.3)

Table 3.3. Estimated lifetime costs, cancer cases prevented, life expectancy results for base case and sensitivity analysis

Scenario	Strategy	Lifetime Costs			Life expectancy
		Societal Perspective	Clinic Perspective	Expected Cancer Cases	(years from screening)
Base case Observed age at screening and test sensitivity	Integrated Screening	$7,913 ($3,927, $11,835)	$7,910 ($3,945, $11,817)	7.4 (3.65, 11.01)	21.1 (18.5,23,9)
	Non-Integrated Screening	$5,543 ($2,450, $8,522)	$5,542 ($2,452, $8,500)	5.2 (2.29,7.95)	17.0 (13.8, 20.4)
Sensitivity Analysis					
Same age at screening	Integrated Screening	$5,496 ($1,839, $9,023)	$5,494 ($1,836, $9,020)	5.1 (1.71, 8.41)	17.1 (12.5, 21.7)
	Non-Integrated Screening	$5,543 ($2,397, $8,531)	$5,542 ($2,398, $8,533)	5.2 (2.24, 7.96)	17.1 (13.8, 20.4)
Same age at screening and same test sensitivity	Integrated Screening	$5,460 ($1,812, $8,981)	$5,457 ($1,873, $8,984)	5.1 (1.69, 8.36)	17.1 (12.5, 21.8)
	Non-Integrated Screening	$5,543 ($2,397, $8,570)	$5,542 ($2,440, $8,548)	5.2 (2.24, 7.99)	17.1 (13.8, 20.4)

3.3.2 *Cancer Prevention*

Non-integrated screening was expected to prevent 2.19 more cervical cancer cases in the base case. However, when age at screening and/or VIA sensitivity were held constant across evaluation arms, integrated screening was projected to prevent more cancer cases (0.08 more cases with constant age and test sensitivity; 0.01 more cases with constant age).

3.3.3 *Sensitivity and Uncertainty Analysis (CEA)*

One-way sensitivity analysis indicated that mean age at screening appeared to impact the results, with the most influential parameters being the expected age-based monthly health state transition probabilities and age-based disease rates. (Figure 3.2) When age at screening – and, therefore, age-based background rates and transition probabilities – was held constant at 37 years old (the mean age of screening for women in non-integrated screening based on literature estimates) between the integrated and non-integrated arm, results changed significantly. In this scenario from the societal perspective, integrated screening was the dominant strategy. It was projected to yield 0.01 more discounted LYs, prevent 0.05 more cancer cases, and cost $46 less annually compared to non-integrated screening. When only program costs were included, incremental costs for integrated screening were $48 less than non-integrated screening. When both age and VIA test sensitivity were assumed to be the same across arms, integrated screening remained the dominant strategy from both the limited societal and program perspectives with incremental cost savings of $83, 0.02 more LYs gained, and 0.08 more cancer cases prevented compared to non-integrated screening.

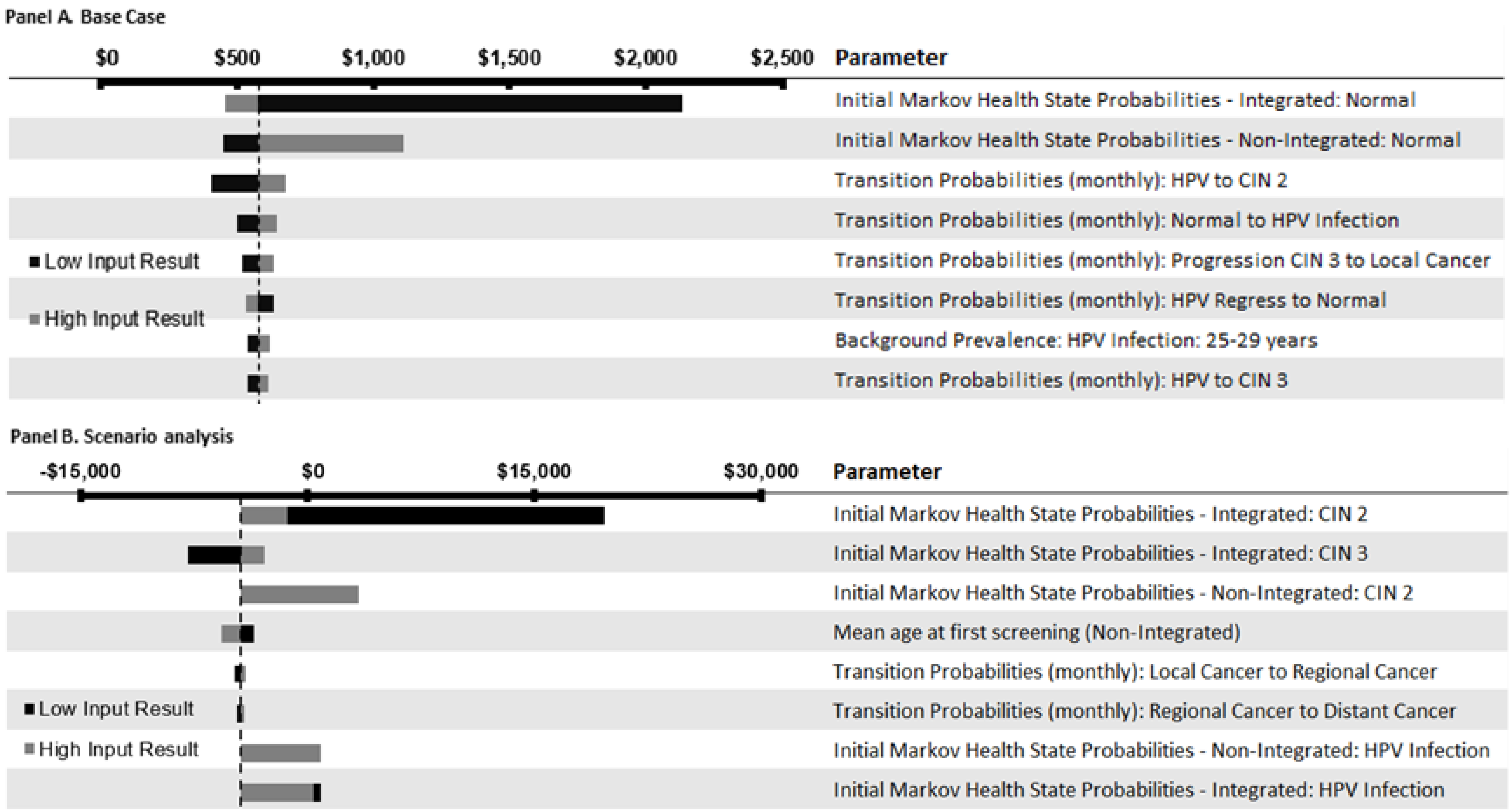


Figure 3.2. One-way sensitivity analysis of parameters influencing the projected cost-effectiveness of integrating cervical cancer screening into routine childhood immunization clinics (base case and primary scenario analyses).

However, uncertainty analyses suggested that, in all scenarios, integrated screening could range from a potentially cost-effective initiative to a strategy that is cost-saving but results in shorter life expectancy and few cancer cases detected compared to the non-integrated screening. ICER results from the societal-level evaluation of joint parameter uncertainty indicated that integrated screening could range from being $429 less costly with a reduction of 0.001 LYs to potentially cost-effective with an ICER of $463 per LY saved compared to the alternative. (Figure 3.3) From the program perspective, the estimated cost per-LY saved remained the same; however, joint parameter uncertainty was wider indicating that integrated screening could range from the dominant strategy to $633 per LY saved.

Panel

Panel

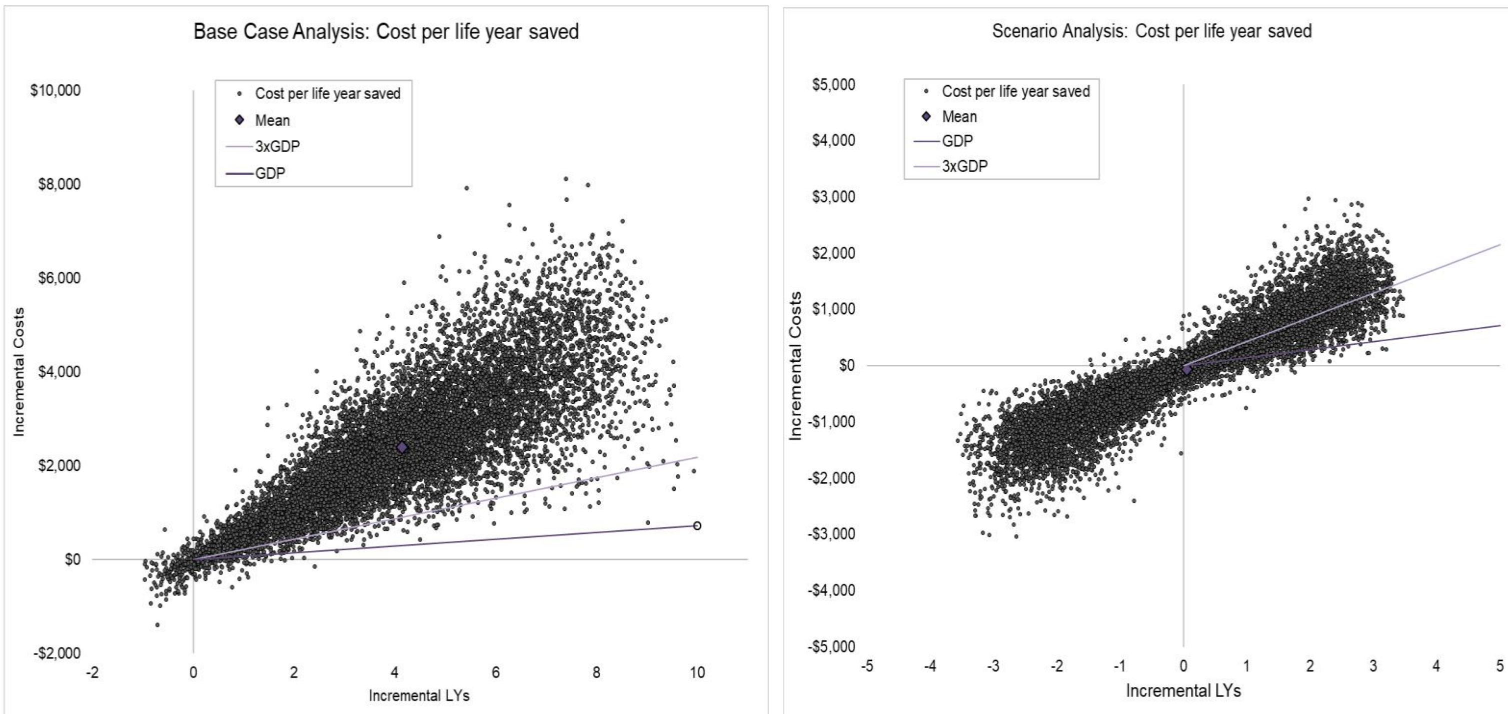


Figure 3.3. Probabilistic sensitivity analysis results for base case and primary scenario analyses.

3.3.4 *Threshold Analysis*

Threshold analysis evaluating various ages at screening in both the integrated and non-integrated settings suggested that integrated screening is potentially more cost-effective than non-integrated screening at any age when compared to a willingness to pay threshold of 3xGDP. This was particularly true when women in the integrated screening setting were simulated to be older than women attending general clinics for screening. ICERs ranged from $14 per LY saved when integrated screening age was 30 years vs. non-integrated screening age of 29 years to $1,388 per LY saved when integrated screening age was 20 years vs. non-integrated screening age of 19 years. When women's ages in each program were assumed the same for both interventions, the incremental cost per LY saved for screening in an integrated vs. non-integrated settings ranged from $600 at an assumed mean screening age of 20 years old to $1170 at an assumed mean screening age of 49 years old. Varying integrated uptake and wait times to evaluate potential health systems challenges imposed by an integrated program had no significant impact on expected costs or health outcomes. As expected, improved VIA test sensitivity yielded slightly lower costs and better health outcomes. At 80% sensitivity, for example, life expectancy after screening was projected to increase by 0.01 years, with 0.04 fewer cancer cases, and $10 fewer costs compared to base case sensitivity resulting in an expected ICER of $567 per LY saved.

3.3.5 *Probabilistic Sensitivity Analysis*

In the base case scenario from both the limited societal and program perspectives, integrating screening into routine immunization clinics appears to be potentially cost-effective

98% of the time when the payer is willing to pay at least 3xGDP ($1,845) per LY saved. However, when age at screening and/or VIA test sensitivity are held constant at non-integrated values, the probability that integrated screening is cost-effective decreases to approximately 51-52%, regardless of perspective. (Figure 3.4)

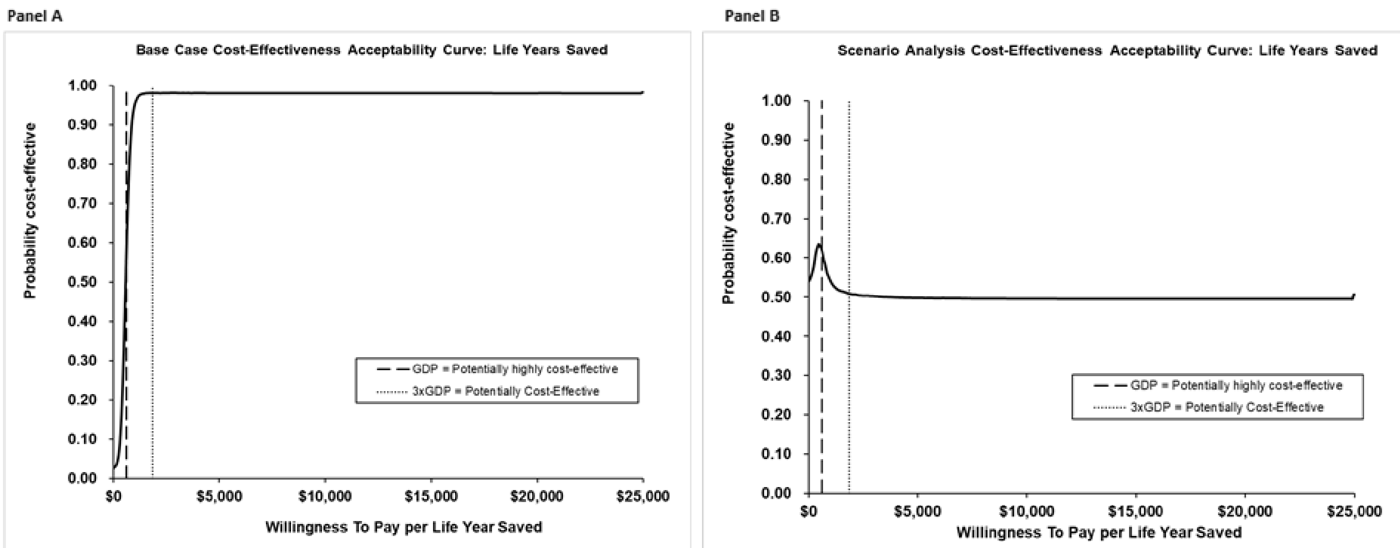


Figure 3.4. Cost-effectiveness acceptability curves for the base case and primary scenario analysis.

3.3.6 *Budget Impact Analysis*

Results from the budget impact analysis estimated the expected cost to the Ugandan MOH cervical cancer prevention and treatment with and without screening integration into RCICs over a 10-year time horizon across the population of women in the recommended screening ages of 25-49 years old. At baseline, there were 5,177,670 women of recommended screening age in Uganda. (Figure 3.5)

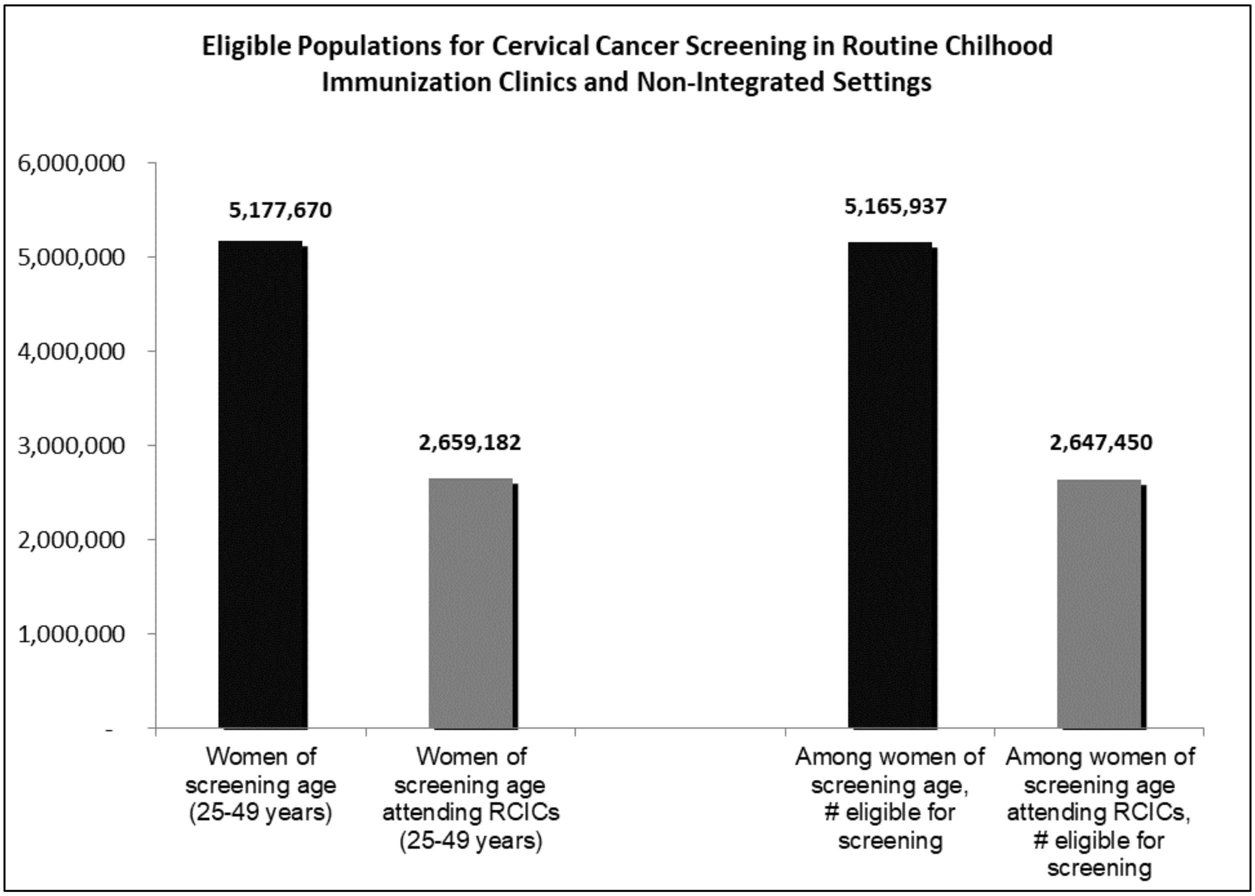


Figure 3.5. Eligible populations for cervical cancer screening in integrated and non-integrated settings to be included in budget impact analysis.

Of those, 2,659,182 were identified as likely to attend an RCIC to bring their 0-36 month old child in for routine immunizations. Among these women, 11,732 were expected to already have identified neoplasia through screening or symptom detection; these women were excluded from the eligible population. At baseline, no women were expected to be vaccinated, 4.8% were expected to receive screening through non-integrated strategies, and 95% were expected to receive no screening. With the addition of integrated screening over the following 10 years, it was projected that 0-32% were vaccinated, 3-5% received screening in non-integrated settings, 47% received screening in an integrated setting, and 18-48% remained unscreened annually. (Figure 3.6)

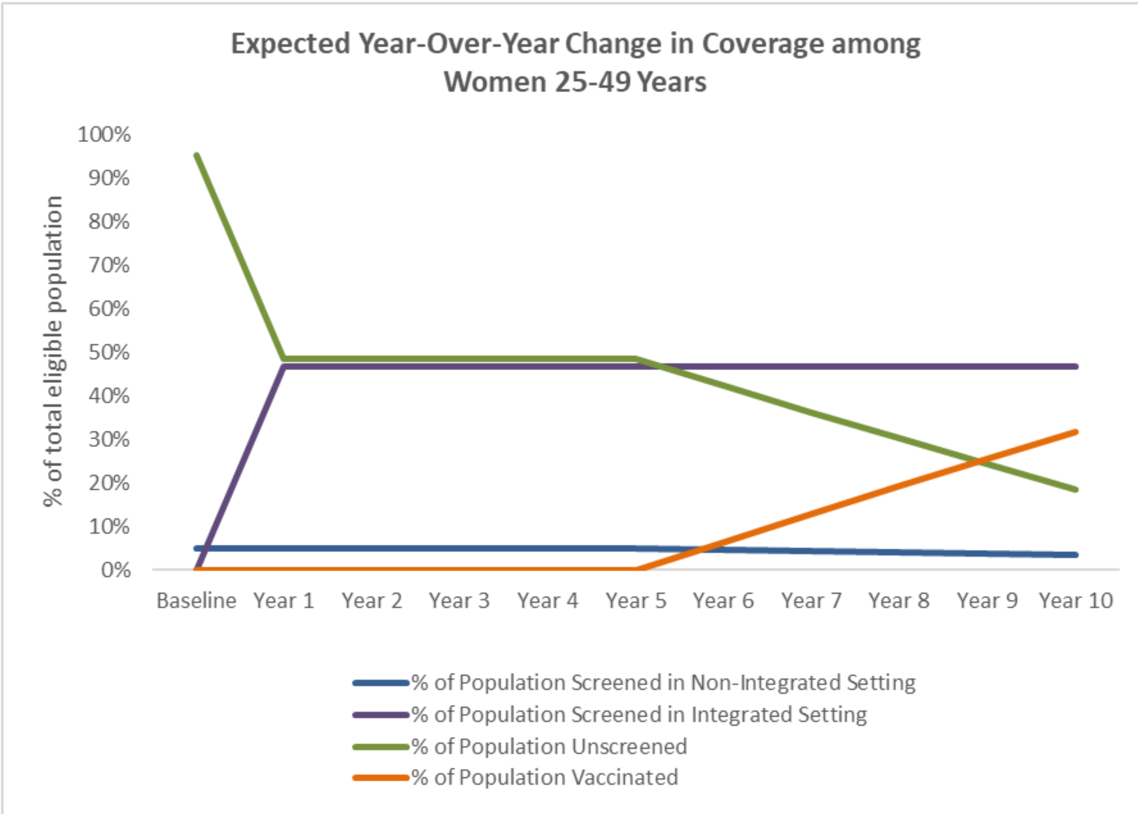


Figure 3.6. Expected Year-Over-Year Change in Coverage Among Women 25-49 Years Old when Integrated Strategies are Included

In the current state with HPV vaccination and non-integrated screening, the MOH could expect to spend an average of $4.49 million annually combined on vaccination, screening and treatment in years 1-5. In this model with current coverage rates projected with population growth, 6% of women who have received partial protection through the vaccine begin to enter the recommended screening age bracket in years 6-10. Once those vaccinated age into the recommended screening brackets, the model projects average annual expenditures of $6.98 million on vaccination, screening and treatment. When integrated screening is introduced, expected average expenditures are $12.19 million in years 1-5 and $24.4 million in years 6-10 for vaccination, screening and treatment. (Table 3.4)

Table 3.4. Budget impact estimates of expected annual coverage and costs of cervical cancer prevention with integrated screening

	Women Previously Vaccinated against HPV				**Women in Non-Integrated Settings**				**Women in Integrated Settings**				**Women Not Receiving Screening**		**All Women 25-49 Years Old (N=5,177,670)**		
	Expected Coverage†	Vaccine Costs	Treatment Costs	Total Costs	Expected Coverageǂ	Screening Costs	Treatment Costs	Total Costs	Expected Coverageǂ	Screening Costs	Treatment Costs	Total Costs	%	Total Costs	Total	Total # Covered§	Total Costs
Baseline	0%	$0.0M	$0.0M	$0.0M	5%	$1.5M	$0.2M	$1.8M	0%	$0.0M	$0.0M	$0.0M	95%	$2.6M	100%	0.2M	$4.4M
Year 1	0%	$0.0M	$0.0M	$0.0M	5%	$1.6M	$0.0M	$1.6M	47%	$15.3M	$0.0M	$15.3M	48%	$1.4M	100%	2.8M	$18.2M
Year 2	0%	$0.0M	$0.0M	$0.0M	5%	$1.6M	$0.0M	$1.7M	47%	$15.8M	$0.0M	$15.8M	48%	$1.4M	100%	2.8M	$18.8M
Year 3	0%	$0.0M	$0.0M	$0.0M	5%	$1.7M	$0.0M	$1.7M	47%	$16.3M	$0.1M	$16.3M	48%	$1.5M	100%	2.9M	$19.5M
Year 4	0%	$0.0M	$0.0M	$0.0M	5%	$1.8M	$0.0M	$1.8M	47%	$16.8M	$0.1M	$16.9M	48%	$1.5M	100%	3.0M	$20.2M
Year 5	0%	$0.0M	$0.0M	$0.0M	5%	$1.8M	$0.0M	$1.8M	47%	$17.4M	$0.2M	$17.6M	48%	$1.6M	100%	3.1M	$21.0M
Year 6	6%	$0.9M	$0.1M	$1.0M	4%	$1.8M	$0.0M	$1.8M	47%	$17.9M	$0.3M	$18.3M	42%	$1.3M	100%	3.6M	$22.4M
Year 7	13%	$2.0M	$0.1M	$2.1M	4%	$1.7M	$0.0M	$1.7M	47%	$18.5M	$0.5M	$19.0M	36%	$1.1M	100%	4.1M	$23.9M
Year 8	19%	$3.0M	$0.2M	$3.2M	4%	$1.6M	$0.0M	$1.7M	47%	$19.1M	$0.6M	$19.7M	30%	$0.9M	100%	4.7M	$25.5M
Year 9	25%	$4.2M	$0.3M	$4.4M	4%	$1.5M	$0.0M	$1.6M	47%	$19.8M	$0.7M	$20.5M	24%	$0.7M	100%	5.3M	$27.2M
Year 10	32%	$5.3M	$0.4M	$5.7M	3%	$1.5M	$0.0M	$1.5M	47%	$20.4M	$0.8M	$21.2M	18%	$0.5M	100%	5.8M	$28.9M

†Coverage refers to those vaccinated with at least one-dose of HPV vaccine; ǂCoverage refers to those who have been screened for cervical cancer at least once per lifetime;
§Total number covered refers to the total number of women of recommended screening age that have received at least one-dose of HPV vaccine or have been screened for cervical cancer at least once per lifetime.
HPV: Human papillomavirus.

The budget impact model projected that offering integrated screening would result in an average of 2.67 million more women receiving screening or partial protection from the HPV vaccine and an average cost increase of 14.94 million annually in the first 5 year compared to a scenario with non-integrated screening only. After vaccinated women age into the recommended screening age in years 6-10, the model projected that 3.14 million more women would be covered via screening or vaccination with incremental costs of $17.59 million when integrated screening is included. (Figure 3.7)

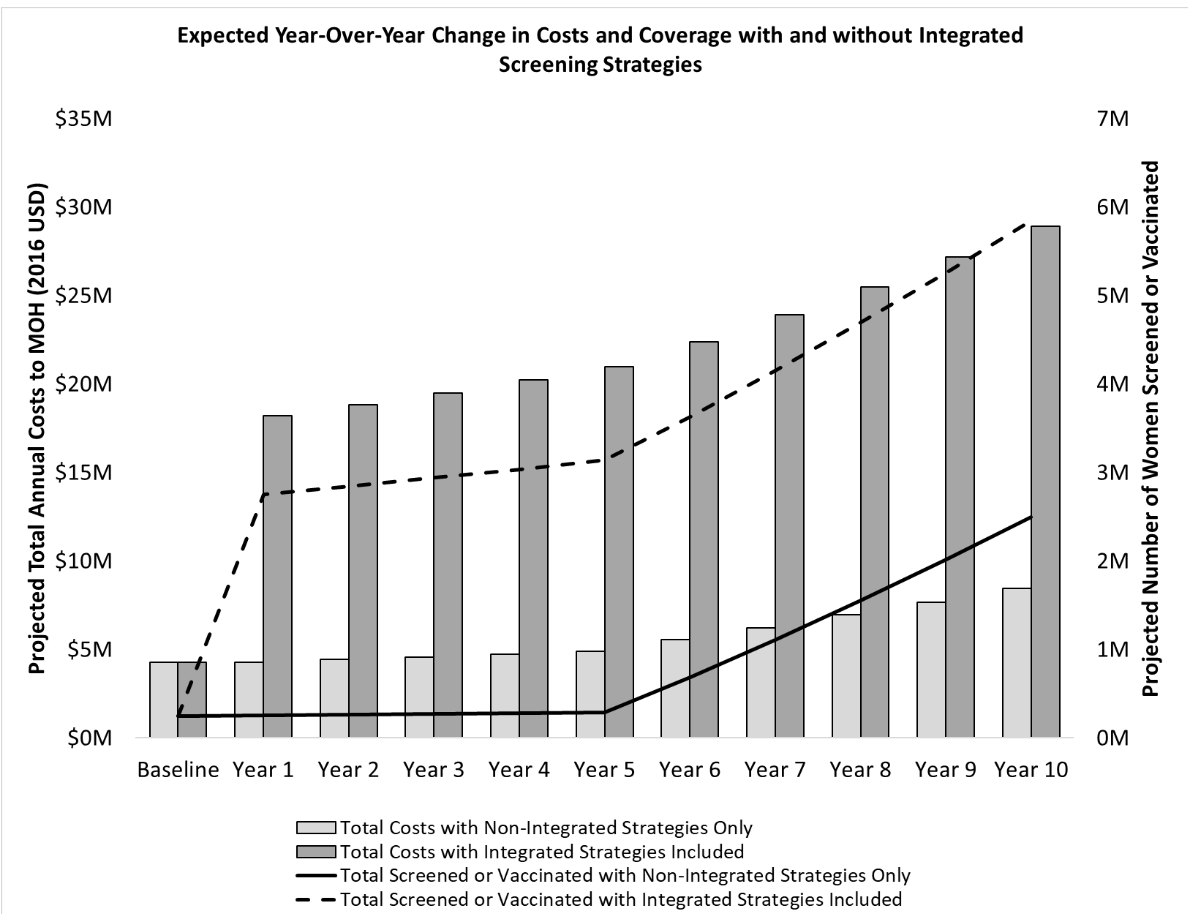


Figure 3.7 Expected year-over-year change in projected costs to Ministry of Health budget and national cervical cancer prevention coverage among women 25-49 years old with and without screening integrated into routine childhood immunization clinics in Uganda.

3.3.7 *Univariate Sensitivity Analysis (BIA)*

One-way sensitivity analyses suggest that parameters used to identify the eligible population for integrated screening were the largest drivers of projected budget impact. This includes the expected proportion of children receiving vaccinations – and therefore, the estimated number of women entering the routine childhood immunization clinic offered and receiving screening – and the proportion of women of reproductive age with living children. Expected HPV vaccine coverage and costs were also influential on model results. (Figure 3.8)

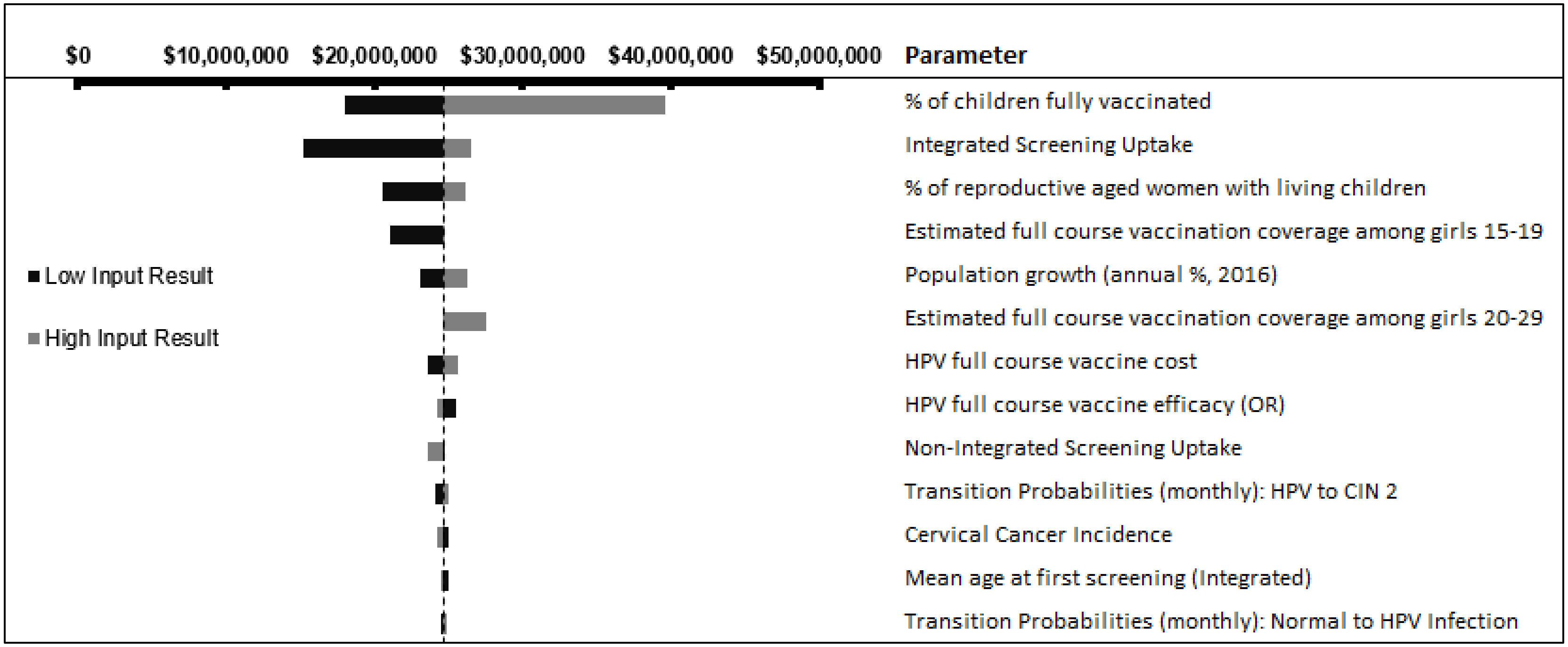


Figure 3.8. One-way sensitivity analysis evaluating influential parameters in budget impact analysis outcomes

3.4 DISCUSSION

This study evaluated the potential health, economic and budget impact of offering once-per-lifetime cervical cancer screening with VIA to women at routine childhood immunization clinics as they enter the facility with their children in Uganda. The analysis was conducted from both a limited societal perspective where indirect costs of patients' time were included and a program perspective where only direct medical costs to the facility were included. To the authors' knowledge, this is the first study to evaluate the potential impact of integrating cervical cancer screening into routine childhood immunization clinics in a low-income country.

The analysis suggests that integrating screening into routine childhood immunization clinics would be a cost-effective strategy compared to the current state of non-integrated screening options from any perspective. Scenario analyses indicated that this finding was consistent across varying assumptions of age, screening uptake, test sensitivity and patient wait times. While the ICER remained relatively constant across assumptions, uncertainty analysis demonstrated that integrated screening was projected to range from being a cost-saving strategy that yielded slightly poorer health outcomes to a highly cost-effective strategy. Offering screening to women when they are already engaging with the health system at RCICs was expected to improve screening coverage by nearly 50% among women of recommended screening ages (25-49 years); this increased coverage would lead to average annual cost increases of $13.9 to $19.3 million for the Ugandan MOH compared to non-integrated screening strategies.

Recent studies evaluating the cost-effectiveness of integrating cervical cancer screening into existing health programs in SSA, such as HIV treatment clinics and family planning centers, have found that integrated strategies may lead increased disease detection and treatment for low marginal costs.[48,85,86] A pilot study of integrating screening into RCICs in Uganda found that patient acceptability for screening in this setting is high.[87] The high acceptability combined with potentially low costs associated with integration identified through the analysis presented here suggests that RCICs may be another venue for health officials to consider for increasing screening coverage and disease detection in Uganda and other similar low-income countries in SSA. Research suggests that integrating screening with family planning services may improve uptake of both contraception and screening simultaneously.[86] Integrating screening into childhood immunization clinics may lead to a simultaneous increase in screening as predicted through the budget impact model and increased childhood immunization coverage. Future studies should evaluate the joint outcomes and costs associated with both health services.

This study addresses several gaps in the literature. First, while studies on cost-effectiveness of cervical cancer screening in Uganda have been conducted previously,[59,88] little data is available on costs of integrating screening into existing clinical and public health programming.[38] Integration of screening into other existing services is currently promoted by the WHO and other influential policy organizations; however, there is a paucity of evidence demonstrating which service lines provide the most appropriate venue for supporting an integrated service approach. The cost-effectiveness results provide information on the potential societal level impact (in terms of costs and health outcomes) of integrated approaches to increase the coverage rate by reaching women of child-bearing age at a place where they are already engaging with the health system.

Additionally, there has been a recent call for more studies assessing the impact that a health intervention might have on a national health budget since a potentially cost-effective strategy may not be affordable to implement given other competing health spending priorities.[82] The budget impact results offered here provide directional guidance to decision makers (e.g., ministries of health and clinic administrators) in SSA to help them better understand the magnitude of financial and personnel resources that would be needed to offer integrated screening services in RCICs. Given the resource constraints that limit health expenditures in low-income countries, future budget impact analyses should be conducted to complement cost-effectiveness evaluations of integrated and non-integrated screening strategies to assess affordability considerations in addition cost per health outcome.

There are several limitations to this study. First, some of the cost data here were collected to compare incremental costs of VIA to other screening strategies, rather than other delivery settings (e.g. non-integrated care). To address this, varying assumptions were made to account for expected differences between integrated and non-integrated screening settings. Screening cost data were also supplemented with estimates of costs for advanced procedures reported in the literature; most of these data points were derived from referral centers where these of high cost and resource intensive treatments are generally performed. The effectiveness data for VIA may be limited by the low number of women that received VIA and screened positive. The impact of the uncertainty of this variable were addressed through a threshold analysis, and found to change the outcomes modestly.

In addition, the Markov model is memory-less and does not allow for disease history to influence likelihood of health state transitions. Given that health state transition probabilities were identified as influential parameters in the model, future studies with additional health states or a microsimulation model may be warranted to better evaluate how results might change when disease history is able to be accounted for. Finally, there may be benefits or drawbacks to integration that were difficult to capture in an economic model. For example, integration may lead to more training and increase overall standards of care. Alternatively, integration of screening may impact clinic workflow with disruptions to patient care. To address this, a threshold analysis was conducted to evaluate potential increase of wait times for patients in the integrated setting with no significant resulting impact on costs or outcomes. While wait times were assessed, potential attrition because of increased wait times was not (i.e., women leaving without screening). If integrated screening is expected to disrupt patient flow, potential attrition should be evaluated in the future. In the RCIC setting, women were offered screening while waiting for their children's health visit, so disruption was expected to be minimal.

For the budget impact, it was assumed that the eligible population for RCIC-based screening would mirror childhood vaccination rates in Uganda. This may or may not be true in practice, which could limit the budget guidance provided by this study. Additionally, information on the proportion of women 15-26 who are currently vaccinated against HPV and not at risk for cervical cancer was not available for Uganda. Therefore, we may be overestimating the number of women who could benefit from integrated screening. Finally, a ten-year time horizon will likely not be enough to capture offsets in treatment averted due to early cervical cancer detection. Thus, estimates here likely provide a conservative estimate of cost offset and a higher estimate of budget impact.

The study findings may also be limited in generalizability. On average, 54% of Ugandan children are fully immunized, but vaccination rates for certain diseases (e.g., BCG vaccination for tuberculosis) range from 23-90%.[89] Research suggests that women with higher education (>primary) are more likely to fully immunize their children compared to mothers with lower levels of education.[89] Only 9% of women in rural areas of Uganda achieve education beyond the primary level,[74] which might limit the reach of screening programs integrated into routine immunization programs in this setting. Additionally, the WHO recommends starting cervical cancer screening among women at age 25, with priority given to women aged 30-49 years old.[90] Mean maternal age at first birth in Uganda is approximately 19 years old; thus, integrating screening into childhood immunization programs could result in screening mothers who are younger than the WHO-recommended screening age, yielding fewer cancer cases prevented for additional costs.[74] This may be reflected in the study findings: in the base case, integrated screening participants were younger, on average, by 9 years than their non-integrated screening counterparts. In this case, non-integrated screening was projected to prevent 2.19 more cancer cases annually than integrated screening. However, in the scenarios where age was held constant across strategies at an older mean age (37 years old), integrated screening was project to prevent more cancer cases.

3.5 Conclusions

This study found that integration of cervical cancer screening into currently existing routine childhood immunization clinics may yield positive benefits associated with prevention and detection of disease for low marginal costs. However, the expected age distribution of women entering the screening facility should be considered, in addition to the expected health expenditures and affordability in the context of other health investment priorities at the national level.

Chapter 4. POTENTIAL COST-EFFECTIVENESS AND BUDGET IMPACT OF INTEGRATING A SAME-DAY SCREEN-AND-TREAT PROGRAM FOR CERVICAL CANCER INTO AN HIV CLINIC IN NAIROBI, KENYA

4.1 Introduction

Over the past 20 years, there has been an increasingly urgent call to address the growing burden of cervical cancer among women in Sub-Saharan Africa (SSA) where cancer incidence is disproportionately high, particularly in high HIV-prevalence regions.[91] For most women in SSA, cancer treatment is prohibitively expensive, making prevention and detection of early disease a high priority for countries and governments through national human papillomavirus vaccination and cervical cancer screening efforts. While HPV vaccination efforts in many SSA countries, including Kenya, have been successful in achieving high (>90%) coverage rates among girls 10-19, the preventive benefits of vaccination will not be born out until the generation of girls currently receiving the first wave of HPV vaccination age into the recommended screening age group.[75] Until then, a multipronged approach that includes improving currently low screening coverage rates should be continued with targeted efforts in high-risk populations, particularly women who are co-infected with HIV and at risk for accelerated incidence and progression of cervical lesions and cancer.[91]

In Kenya, cervical cancer is the leading cause of cancer death with an age-standardized incidence and mortality rate of 40.1 and 21.8 per 100,000, respectively.[1] In addition to high rates of cervical cancer, HIV remains a significant problem for women in Kenya. Prevalence of

HIV was 6.9% among women nationally in 2012 with estimates as high as 16.1% in certain regions; the majority of this burden is among women of reproductive age.[92] Among those aware of their HIV status, 71% receive antiretroviral treatment (ART).[92] Unfortunately, women infected with HIV are 4-5 times more likely to develop cervical cancer and experience more aggressive progression of cervical cancer compared to HIV-negative women.[28] The WHO recommends that all HIV+ women receive cervical cancer screening as soon as possible after testing positive for HIV, with Kenyan national guidelines recommending screening for women 18-65 years old.[90,93]

Offering screening to women with HIV as they enter the health system for routine HIV care may increase screening coverage rates at low marginal costs among a population particularly vulnerable to disease.[23] Integration of cervical cancer screening and other preventive health services has gained support from global organizations, such as Pink Ribbon Red Ribbon which works to simultaneously address HIV and cervical cancer in SSA.[33,34] A recent cost-effectiveness model projected that integrating VIA into an HIV-treatment center in Kenya would yield the greatest cost savings and the greatest increase in life expectancy compared to other screening methods, and noted that cost-effectiveness of cervical cancer screening methods may vary by CD4 count.[85]

Integrating screening strategies into HIV can potentially reduce loss to follow-up between a positive screen and referral to treatment, since many women return to the HIV-treatment center monthly for recurring antiretroviral therapy and could be offered treatment on a subsequent visit. However, the World Health Organization (WHO) estimates that nearly 25% of women with HIV only attend an HIV-clinic once, which could limit the potential benefit of integrated screening strategies.[14] Therefore, prioritizing strategies that allow for women to receive screening and treatment in the same visit may increase the number of women with positive screens that actually receive treatment and prevent disease progression. However, prior to investing resources into screen-and-treat strategies across HIV clinics in Kenya, the potential effectiveness and cost-effectiveness should be evaluated using data specific to this unique patient population and treatment setting.

The most common screen-and-treat strategy includes screening with Visual Inspection with Acetic Acid and Lugol's Iodine (VIA/VILI) combined with cryotherapy treatment for positive screens. Although not currently widespread, careHPV can also be combined with cryotherapy for a same-day strategy, contingent on the lab running the test on the same day and women's availability to wait for the laboratory process to be completed. Additionally, there is potential for screening to be combined with colposcopy and LEEP as a same-day strategy. In an HIV-treatment setting in Nairobi, Kenya, VIA/VILI was found to have a sensitivity of 63% and specificity of 66%; HPV testing (HC2) has a sensitivity of 84% and a specificity of 56%.[47] Another study found that HC2 and careHPV have excellent testing agreement (Kappa = 0.88) among HIV-positive women in SSA, suggesting that careHPV can be used as a suitable substitute for HC2 in this setting.[94] CareHPV is a lower-cost, rugged HPV DNA test with a high sensitivity of 93% and specificity of 58%.

For treatment of pre-cancerous lesions, LEEP is generally recommended as a safe method for use among HIV-positive women and has a cure rate of over 85% in some SSA settings.[95–98] However, costs and resource constraints may limit the availability of LEEP in low- and middle-income settings; thus, the WHO supports use of cryotherapy as a sufficient alternative that is cheaper and requires less training.[9] While the literature on cryotherapy effectiveness in HIV-positive women is limited, evidence to date suggests that it is a safe and effective method for treating precancerous lesions in this population with a cure rate of more than 70%.[99–101] Furthermore, cryotherapy use among HIV-positive women does not increase cervical shedding of HIV-1, which is associated with increased risk of infectivity and transmission to others.[102] Notably, however, one study of HIV-positive women in Western Kenya found that screen-and-treat with cryotherapy may under-detect invasive cancer cases due to lack of histopathology sampling.[96]

Prior to promoting same-day screen-and-treat methods in HIV clinics on a wide scale, impact of integration on the marginal costs and health outcomes achieved in an integrated setting should be considered. Economic analyses may shed light on the potential value created through screening integration.

4.2 Methods

This study evaluated the potential cost-effectiveness and budget impact of integrating a same-day screen-and-treat program into HIV-care in Nairobi, Kenya. The study estimated the costs and health outcomes in terms of cancer cases averted and life years gained through an integrated same-day screen-and-treat program compared to a non-integrated setting among women living with HIV.

4.2.1 *Cost-Effectiveness Analysis*

An Excel-based decision tree and Markov model was developed to compare the costs and health outcomes of integrating screening into an HIV treatment clinic compared to non-integrated screening for a cohort of patients. (Figure 1)

Figure 1a. Decision Tree Diagram

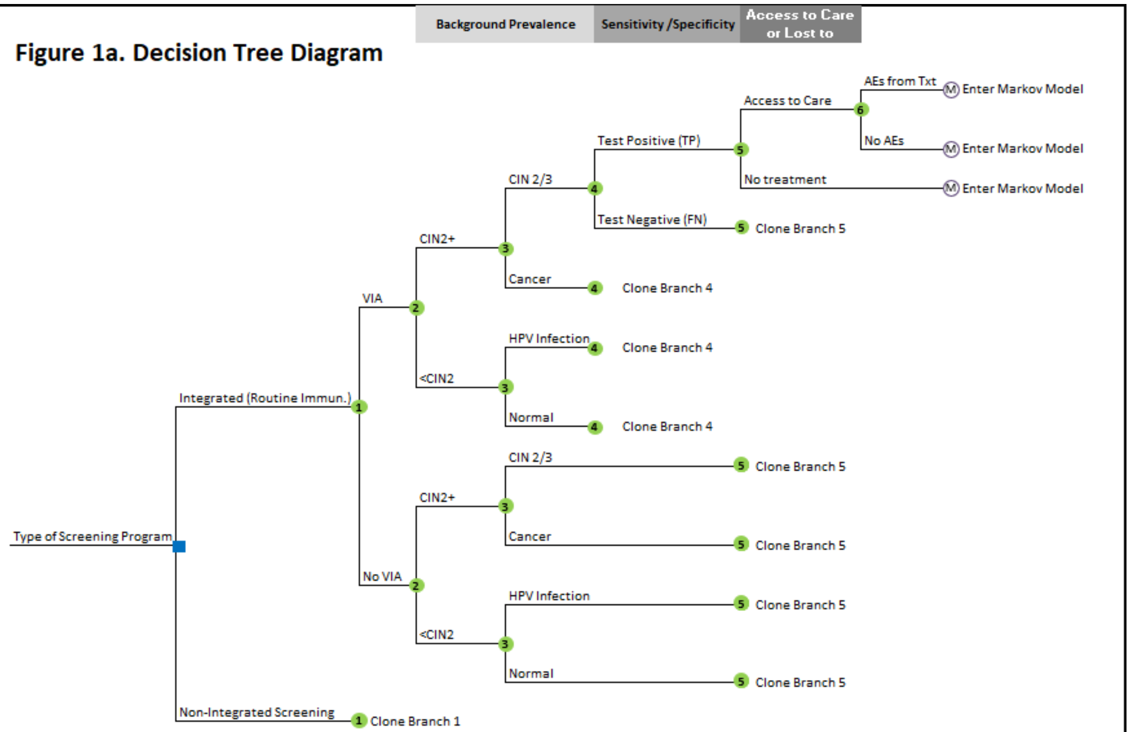
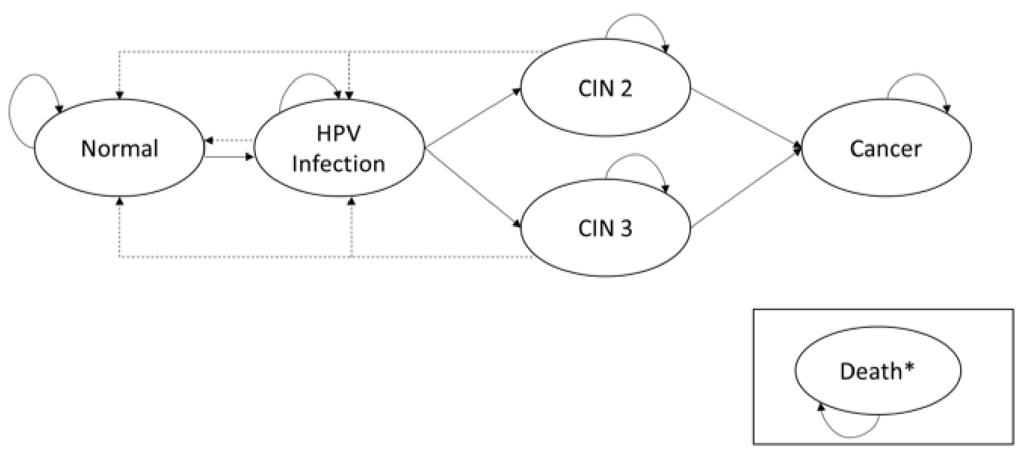


Figure 1b. Cervical Cancer Markov Model Diagram



ǂAdapted from Campos et al 2014.
*After HPV infection, pre-cancerous lesions could be determined through identification of Cervical Intraepithelial Neoplasia (CIN) grades 2 (CIN 2) or 3 (CIN 3). Cancer could be detected and staged as local, regional or distant invasive cancer. Death is the absorbing health state from all other health states, with country-specific background mortality and incremental hazard associated with the condition(s) being modeled.

Figure 4.1. Economic Model Diagrams Comparing Integrated to Non-Integrated Screening.

The study compared women with HIV receiving same-day screen and treat (VIA+cryotherapy, VIA+LEEP, careHPV+cryotherapy, careHPV+LEEP) to (1) HIV-clinic patients receiving VIA or careHPV screening and treatment (cryotherapy or LEEP) on separate days, and (2) women who receive screening and treatment in a non-integrated setting. Women who accepted screening and tested positive for disease (whether a true or false positive), were modeled to accept treatment on the same day following uptake estimates in the literature. Women were modeled to receive screening with VIA and careHPV in equal frequency. Those with test positive results were assumed to receive cryotherapy if eligible (80% and LEEP if determined clinically ineligible for cryotherapy (20%). (Table 4.1)

Table 4.1. Model parameters for demographics, test performance, costs and disease outcomes

Table 1a. Demographic and Screen and Treat Parameters			
Screening Assumptions	**Base Case**	**Sensitivity Range**	**Reference**
Demographics			
Cervical Cancer Incidence, HIV+	0.00120	(0.0008, 0.0016)	[86]
Test Performance			
VIA Sensitivity	0.61	(0.49, 0.73)	[64]
VIA Specificity	0.63	(0.5, 0.76)	[64]
CareHPV Sensitivity	0.933	(0.838, 0.982)	[103]
CareHPV Specificity	0.579	(0.545, 0.982)	[103]
Integrated Screening			
Mean age at screening	38	(18, 65)	[64]
Receive Screening	0.723	(0.12, 0.87)	[40]
Receive Same-Day Screen-and-Treat	0.9125	(0.86, 0.965)	[104]
Non-Integrated Screening Outcomes			
Mean age at screening	38	(25, 49)	[64]
Receive Screening	0.035	(0.004, 0.202)	[105]
Receive Same-Day Screen-and-Treat	0.70	(0.56, 0.84)	[106]
Referral to Advanced Care			
For Detected CIN2+:			
% Referred to cryotherapy	0.8	(0.64, 0.96)	[61]
% Referred to Colposcopy + LEEP (cryo ineligible)	0.2	(0.16, 0.24)	[61]
Loss to Follow-Up after Screening in HIV Clinic			
% LTFU from HIV Center (no subsequent visits)	0.238	(0.233, 0.243)	[107]
%LTFU: Same Day	0.00	(0.00,0.00)	Assumption
% LTFU: Screening to Treatment if Refused Same-Day Treatment	0.27	(0.216, 0.324)	[108]
Loss to Follow-Up after Screening in Non-Integrated			
% LTFU: Screening to Cryotherapy	0.279	(0.2232, 0.3348)	[101]
% LTFU: Screening to Colposcopy Biopsy	0.279	(0.2232, 0.3348)	[101]
% LTFU: Colposcopy Biopsy to LEEP	0.493	(0.3944, 0.5916)	[101]
% LTFU: Referral to cancer treatment	0.596	(0.4768, 0.7152)	[101]
Treatment Effectiveness			
Cryotherapy	0.92	(0.66, 0.9)	[64]
Colposcopy + LEEP	0.96	(0.768, 1.152)	[64]
Treated cancer cure probability (monthly)	0.1500	(0.12, 0.18)	[39]

Table 1b. Cost Parameters

Costs per Procedure	**Integrated Screening**	**Non-Integrated Screening**	**Reference**
VIA/VILI			
Direct Medical Costs	$1.04	$1.39	[40]
Direct Non-Medical Costs	$1.97	$14.01	[40]
Indirect Costs	$0.44	$2.48	[40]
CareHPV			
Direct Medical Costs	$8.83	$9.15	[40]
Direct Non-Medical Costs	$8.83	$18.83	[40]
Indirect Costs	$8.83	$4.98	[40]
Cryotherapy			
Direct Medical Costs	$26.65	$26.60	Data on file
Direct Non-Medical Costs	$1.97	$39.00	Data on file
Indirect Costs	$1.97	$2.46	Data on file
Colposcopy			
Direct Medical Costs	$140.52	$140.80	Data on file
Direct Non-Medical Costs	$1.97	$33.83	Data on file
Indirect Costs	$1.97	$4.96	Data on file
LEEP			
Direct Medical Costs	$11.43	$66.13	Data on file
Direct Non-Medical Costs	$1.97	$51.14	Data on file
Indirect Costs	$1.97	$4.93	Data on file
Cancer Treatment			
Local Cancer Treatment	$1,144.65	$1,144.65	Data on file
Regional Cancer Treatment	$6,521.40	$6,521.40	Data on file
Distant Cancer Treatment	$5,163.86	$5,163.86	Data on file

Table 1c. Budget Impact Analysis Input Parameters

Budget Impact Model Parameters	Base Case	One-way sensitivity analysis range	Reference
Total population, Kenya (female)	24,376,019		[109]
Number of women 18-65 living with HIV	738,369		[109]
% of individuals on antiretroviral therapy	71%		[109]
Expected population growth (annual %, 2016)	2.6%		[109]
Estimated full course of vaccine coverage among total female population	0.026	(0.0100-0.0460)	[75]
Ages 10-14	0.954	(0.3700-1.0000)	[75]
Ages 15-19	0.949	(0.0000-1.0000)	[75]
Ages 20-29	0	(0.0000-0.0000)	[75]
Estimated one dose vaccination coverage amove total female population	0.006	(0.0030-0.0090)	[75]
Ages 10-14	0.788	(0.0470-1.0000)	[75]
Ages 15-19	0.969	(0.0000-1.0000)	[75]
Ages 20-29	0	(0.0000-0.0000)	[75]
HPV full course vaccine efficacy (OR)	0.7	(0.0000-1.0000)	[75]
HPV one course vaccine efficacy (OR)	0.7	(0.0000-1.0000)	[75]
Proportion of women screened with VIA	90%	(0.72-1.00)	Assumption
Proportion of women screened with careHPV	10%		Assumption

In both integrated and non-integrated settings, all women assigned to the same-day screen-and-treat arms were assumed to receive screening and treatment during a single visit. A proportion of women screened were assumed to refuse same day treatment. In the integrated setting, nearly 25% of women were assumed to be completely lost to follow-up, reflecting estimates of the proportion of women who attend an HIV-clinic once but never return for follow-up HIV care.[110] The remaining three-quarters were modeled to be offered screening at their next HIV-treatment visit, incurring no additional marginal costs for the second visit. A portion of womzen were assumed to refuse screening at the next visit and the remaining were modeled to receive screening. In the non-integrated arm, women who refused treatment on the same day of screening were assumed to be lost-to-follow-up or access care at a future visit at rates observed in the literature. Those who returned would incur full costs of the visit, including non-medical and indirect costs.

After modeling the screening and treatment pathways, the cohort was then simulated to progress through the Markov model following the natural history of disease for cervical cancer.[69] The Markov model health states included (1) normal health; (2) HPV infection and low-grade squamous lesions, defined as cervical intraepithelial neoplasia (CIN) 1; (3) high-grade squamous lesions, defined as CIN 2 or CIN 3; (4) locally invasive cancer; (5) regional invasive cancer; (6) distant invasive cancer; and (7) death.[69] Monthly transition cycles were applied to reflect the current transition estimates available in the literature.[67,69,70] After entering the Markov model from the decision tree, women were modeled to either stay in their initial health state or move between health states over time. Evidence of CIN 1-3 on the cervical surface indicates existence of cell abnormalities and/or pre-cancerous lesions, and can be treated or progress into cervical cancer.[69] Similarly, cervical cancer can be treated or it can progress to a later stage or death.[69] The death health state was considered to be an absorbent state, capturing all-cause and disease-specific mortality. (**Error! Reference source not found.**)

Table 4.2. Disease transition probabilities for base case and one-way sensitivity analysis

Transition Probabilities (monthly)	Base Case	One-way sensitivity analysis range	Reference
Background Prevalence			
Normal	0.317	(0.6805-1.0000)	[111]
HPV Infection/CIN1	0.395	(0.0974-0.1461)	[111]
CIN 2	0.140	(0.0158-0.0236)	[111]
CIN 3	0.100	(0.0048-0.0072)	[111]
Cancer	0.048	(0.0015-0.0023)	[111]
% of Cancer in Local Cancer[b]	0.2000	(0.1600-0.2400)	[111]
% of Cancer in Regional Cancer[b]	0.4000	(0.3200-0.4800)	[111]
% of Cancer in Distant Cancer[b]	0.4000	(0.3200-0.4800)	[111]
Undetected cancer identification via symptoms (monthly)			
Local Cancer	0.0174	(0.0139-0.0209)	[69]
Regional Cancer	0.0735	(0.0588-0.0882)	[69]
Distant Cancer	0.1746	(0.1397-0.2095)	[69]
Transition Probabilities (monthly)			
Normal Remain	0.9950	(0.7960-1.0000)	1-Progression from Normal to HPV
Normal to HPV Infection[a]	0.0051	(0.0040-0.0061)	[67]
HPV Regress to Normal	0.0305	(0.0244-0.0366)	[67]
HPV Remain	0.9355	(0.7484-1.0000)	1-Regress to Normal
HPV to CIN 2	0.0170	(-0.0026-0.0366)	[70]
HPV to CIN 3	0.0170	(0.0136-0.0204)	[70]
CIN 2 Regresses[c]	0.0087	(0.0070-0.0104)	[69]
CIN 2 Regress to HPV Infection	0.0044	(0.0035-0.0052)	[69]
CIN 2 Regress to Normal	0.0044	(0.0035-0.0052)	[69]
Progression CIN 2 to Local Cancer[d]	0.0031	(0.0024-0.0037)	[67]
CIN 2 Remain	0.9883	(0.7906-1.0000)	Calculated from CIN 2 progression and regression.
CIN 3 Regresses[c]	0.0044	(0.0035-0.0052)	[69]
CIN 3 Regress to HPV Infection	0.0022	(0.0017-0.0026)	[69]
CIN 3 Regress to Normal	0.0022	(0.0017-0.0026)	[69]
Progression CIN 3 to Local Cancer[d]	0.0031	(0.0024-0.0037)	[67]
CIN 3 Remain	0.9926	(0.7941-1.0000)	Calculated from CIN 3 progression and regression.
Local Cancer to Regional Cancer	0.0200	(0.0160-0.0240)	[67,69]
Local Invasive Cancer Mortality	0.0059	(0.0047-0.0071)	[71]
Local Cancer Remain	0.9741	(0.7793-1.0000)	Calculated from local invasive progression.
Regional Cancer to Distant Cancer	0.0250	(0.0200-0.0300)	[69]

Regional Cancer to Death	0.0151	(0.0121-0.0182)	[71]
Regional Cancer Remain	0.9599	(0.7679-1.0000)	Calculated from regional invasive progression.
Distant Cancer to Death	0.1746	(0.1397-0.2095)	[71]
Distant Cancer Remain	0.8254	(0.6603-0.9905)	Calculated from distant invasive progression.
Treated cancer cure probability (monthly)	0.1500	(0.1200-0.1800)	[39]
Background Mortality			
Age-Standardized Mortality Rate (Females)	0.000272		[1]

The cost-effectiveness analysis (CEA) was conducted from the societal perspective (base case) and clinic perspective. The societal-level analysis included all direct medical (e.g., supplies, staff), non-medical (e.g., meals) and indirect (e.g., patient time) costs associated with integrating screening into an existing HIV or routine immunization clinic, while the clinic-level analysis included only direct medical costs specific to the facility. Cost data was based on a micro-costing study conducted at Coptic Hope Center and Kenyatta National Hospital in Kenya in 2014, published previously.[64,112] The study collected primary data through a time-and-motion study as well as interviews with administrative, clinical, and laboratory staff to estimate direct medical (e.g., supplies), non-medical (e.g., overhead), and indirect (e.g. patient time) costs. Integrated and non-integrated costs were calculated for screening methods (VIA, Pap smear, HC2 and careHPV testing), as well as treatment of pre-cancerous lesions and cervical cancer.[64,112] Outcomes data (e.g., sensitivity and specificity of screening, health outcomes, etc.) were derived from the literature.[17,99,113] Where Kenya-specific estimates were unavailable, we relied on data from similar countries with published data on screening among HIV-positive women. All costs were inflated to 2016 USD using consumer price indices.[46]

The CEA was conducted over a patients' lifetime horizon to allow for all future effects, in terms of costs and consequences, of the population cohort to be included in the model.[78] A mean age of screening among women with HIV (asge 38) was applied in conjunction with published country-specific life tables to estimate survival and calculate mortality rates in the Markov model.[79] A discount rate of 3% was applied for both costs and consequences, which is consistent with the current literature and economic evaluation guidelines.[78] The model was developed to assess cost per cancer case avoided, cost per life year saved, and the Incremental Cost Effectiveness Ratio (ICER), which is a ratio of incremental costs to incremental health outcomes among the integrated vs. non-integrated care setting.

We assessed uncertainty in the model using a univariate sensitivity analysis to identify influential model parameters. A probabilistic sensitivity analysis was conducted in which all parameters were jointly varied and run 10,000 times through a Monte Carlo simulation to evaluate model robustness. Outcomes parameters were assigned beta or normal distributions, as appropriate, and costs were assigned a gamma distribution for the simulation.[114] We also conducted a number of threshold analyses to evaluate how various assumptions about the health system and access to screening and treatment may impact the results, including a range of patient ages at screening, screening uptake, LTFU estimates for treatment of CIN2/3, and patient wait times.

4.2.2 *Budget Impact Analysis*

A budget impact analysis (BIA) was conducted to evaluate the feasibility and sustainability of scaling up integrated cervical cancer screening into HIV-treatment centers in Kenya. The BIA projected the potential financial impact of integrated screening compared to status quo from the perspective of the Kenyan MOH (i.e., national health budget), following guidelines put forth by the ISPOR Task Force on Principles of Good Practice for Budget Impact Analysis.[83] We estimated the budget impact over a one-year to 10-year time horizon, with results presented for each year. We modeled the current cervical cancer prevention environment without integrated screening, as well as a “new” environment where cervical cancer screening and treatment are integrated into HIV-treatment centers. The current environment included screening in a non-integrated setting only, as well as cohorts of girls receiving vaccination against HPV (for those <26 years old) and no-screening options. The new environment included: screening in a non-integrated setting only; screening in an integrated setting, as a substitution for non-integrated screening; HPV vaccination; and no-screening options.

We estimated the eligible population size for each integration program and used demographic data from the literature to calculate the eligible population for integration into HIV-treatment centers in Kenya. Women who had been previously vaccinated against HPV or had detected CIN2/3 or cervical cancer were excluded from the population. We applied current rates of expected Kenyan population growth (3%) and screening uptake in non-integrated (3.5%) and integrated (72%) strategies to estimate the mix of treatment strategies in the current and future environments.

BIA costs were undiscounted and derived from the CEA. [83,84] To estimate the budget impact for the Kenyan and Kenyan Ministries of Health, we multiplied each cost by the total eligible population and also by the proportion of the eligible population expected to use each type of screening/vaccination method or combination of methods. Uncertainty was evaluated through a one-way sensitivity analysis to identify drivers of financial projections.

4.3 Results

4.3.1 *Baseline Economic Evaluation*

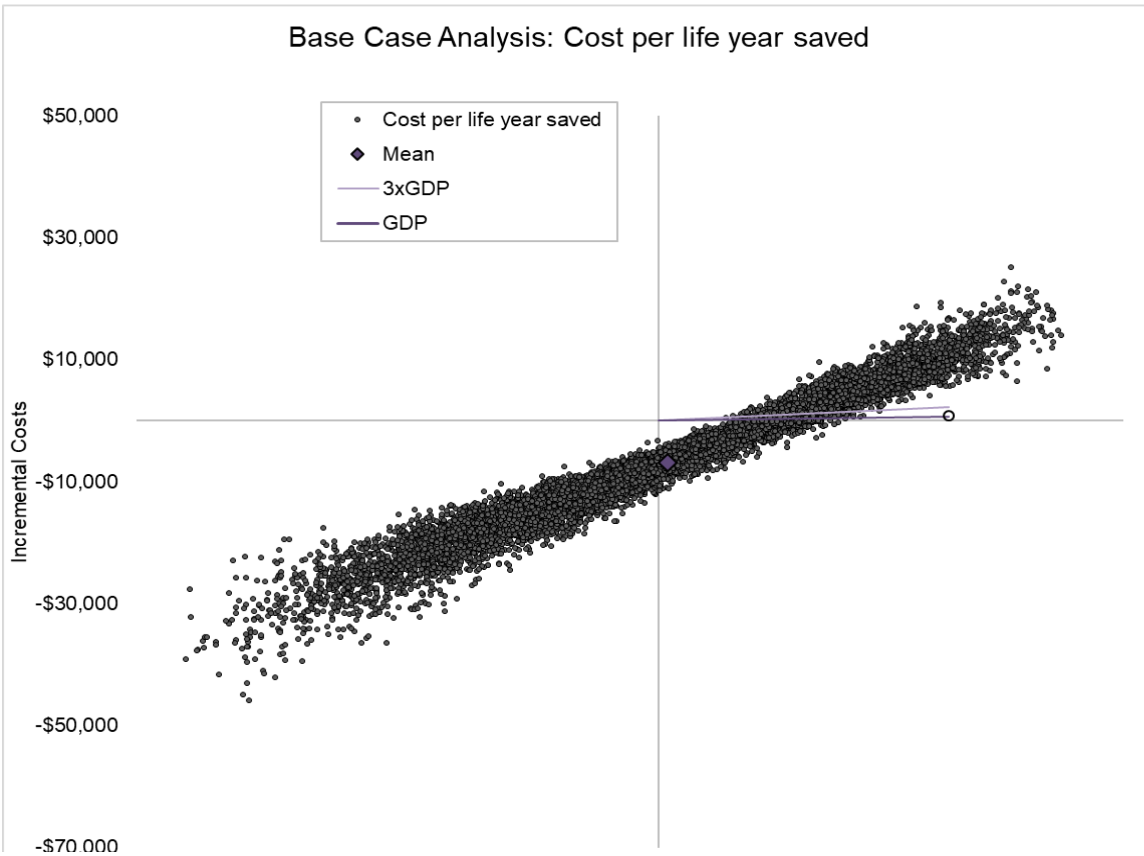
In the base case from the societal perspective, offering screening and treatment to HIV-positive women in an integrated setting resulted in both longer life expectancy (17.5 years vs. 17.0 years) and cost $6,551 less than a non-integrated program making it the dominant strategy. (Table 4.3) No differences were found by analysis perspective. In addition, integrated screening and treatment was expected to prevent 2.1 more cervical cancer cases in the base case compared to non-integrated screening and treatment. This was projected to range from prevention of 4.2 fewer cases to 8.6 more cases than non-integrated screening and treatment.

Table 4.3. Estimated lifetime costs, cancer cases prevented, and life expectancy results for base cases and sensitivity analysis

Strategy	Lifetime Costs		Expected Cancer Cases	Life expectancy (years from screening)
	Societal Perspective	Clinic Perspective		
Integrated Screening	$31,130	$31,130	9.3	17.5
Non-Integrated Screening	$37,681	$37,681	11.3	17.0

4.3.2 *Probabilistic and Univariate Sensitivity Analysis (CEA)*

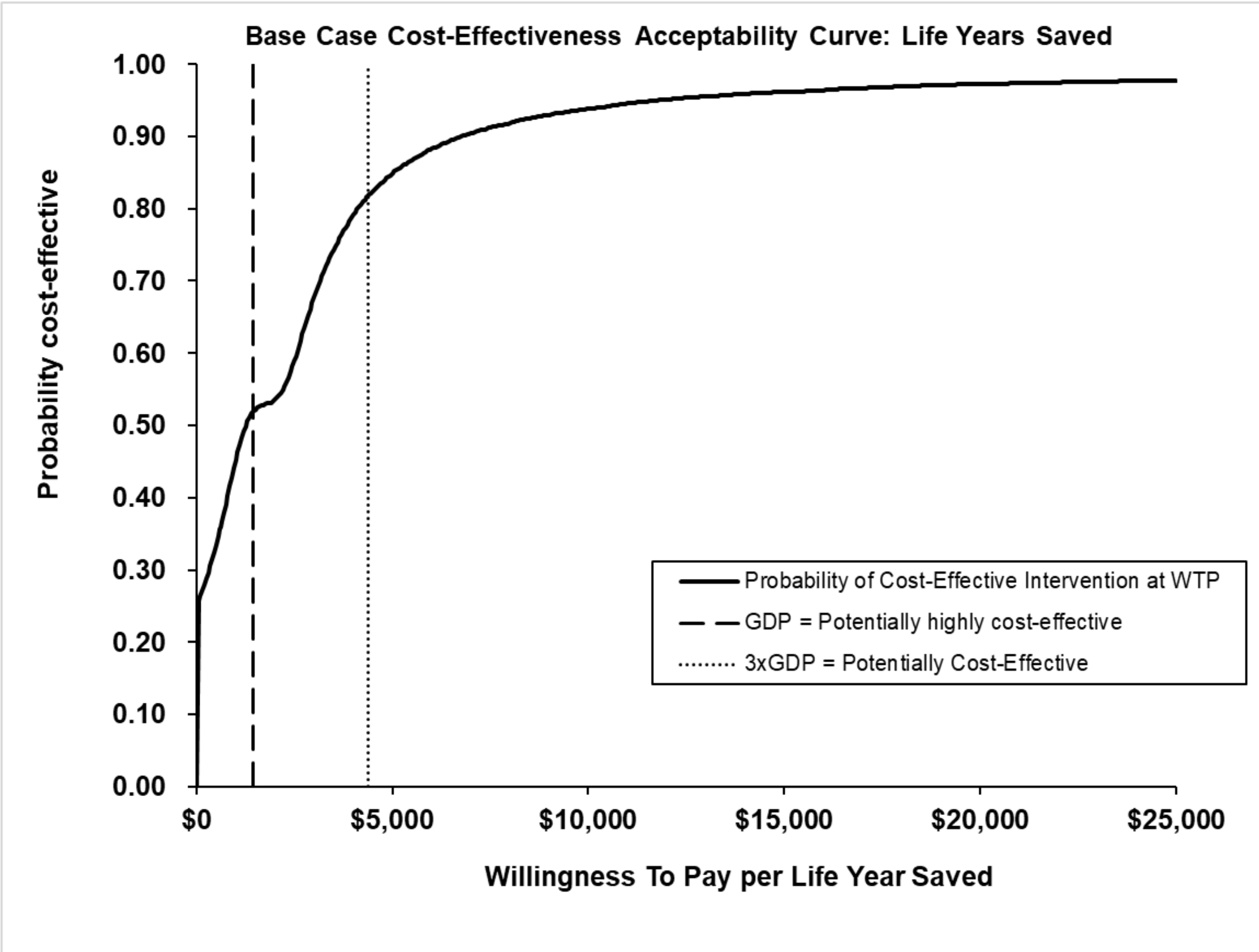
Probabilistic uncertainty analysis of the projections estimated that base case results could vary widely. (Figure 4.2)



The density plot shows the ICER output from the probabilistic sensitivity analysis for the base case analysis. A cloud of results in the Southeast quadrant indicates a more effective new treatment with lower cost. A cloud in the Northwest quadrant indicates a more costly and less effective new treatment. A cloud in the Northeast quadrant indicates a more expensive and effective new treatment. A cloud in the Southwest quadrant is less costly but also less effective. The line depicting 3xGDP indicates the probability that integrated care would be potentially cost-effective assuming a willingness to pay of 3xGDP in Kenya compared to the alternative of a non-integrated program. The line depicting GDP indicates the probability that integrated care would be potentially highly cost-effective assuming a willingness to pay equal to the GDP in Kenya compared to the alternative of non-integrated screening.

Figure 4.2. Probabilistic sensitivity analysis results for base case analysis

Cost and health outcomes could range from being cost saving by $27,830 yet shorter life expectancy by 10.9 years with an integrated program compared to a non-integrated program to costing $14,058 more but leading to longer life expectancy by 11.5 years. The latter would result in an ICER of $1,227 per life year saved, indicating that screen-and-treat integration into HIV treatment centers would be considered a highly cost-effective strategy compared to a willingness to pay threshold based on Kenyan GDP of $1,455. Integrating same-day screen and treat into HIV treatment centers appears to be more cost-effective than non-integrated settings 82% of the time when the payer is willing to pay at least 3xGDP ($4,366) per LY saved. (Figure 4.3)



This plot describes the probability that integrated screen-and-treat is cost-effective compared to the comparator at a variety of acceptability ratios (represented on the horizontal axis). Note that this plot only describes the uncertainty of the model's prediction of the cost-effectiveness of Integrated Screening.

Figure 4.3. Cost-effectiveness acceptability curve for base case analysis.

One-way sensitivity analysis indicated that patient out-of-pocket costs for regional cancer, mean age at screening and cancer progression and mortality. (Figure 4.4) When age at screening was held constant at the average screen age of 38 years in both settings, results appeared to be most impacted by patient out-of-pocket costs for regional and local cancer and cancer progression and mortality. However, main results did not change.

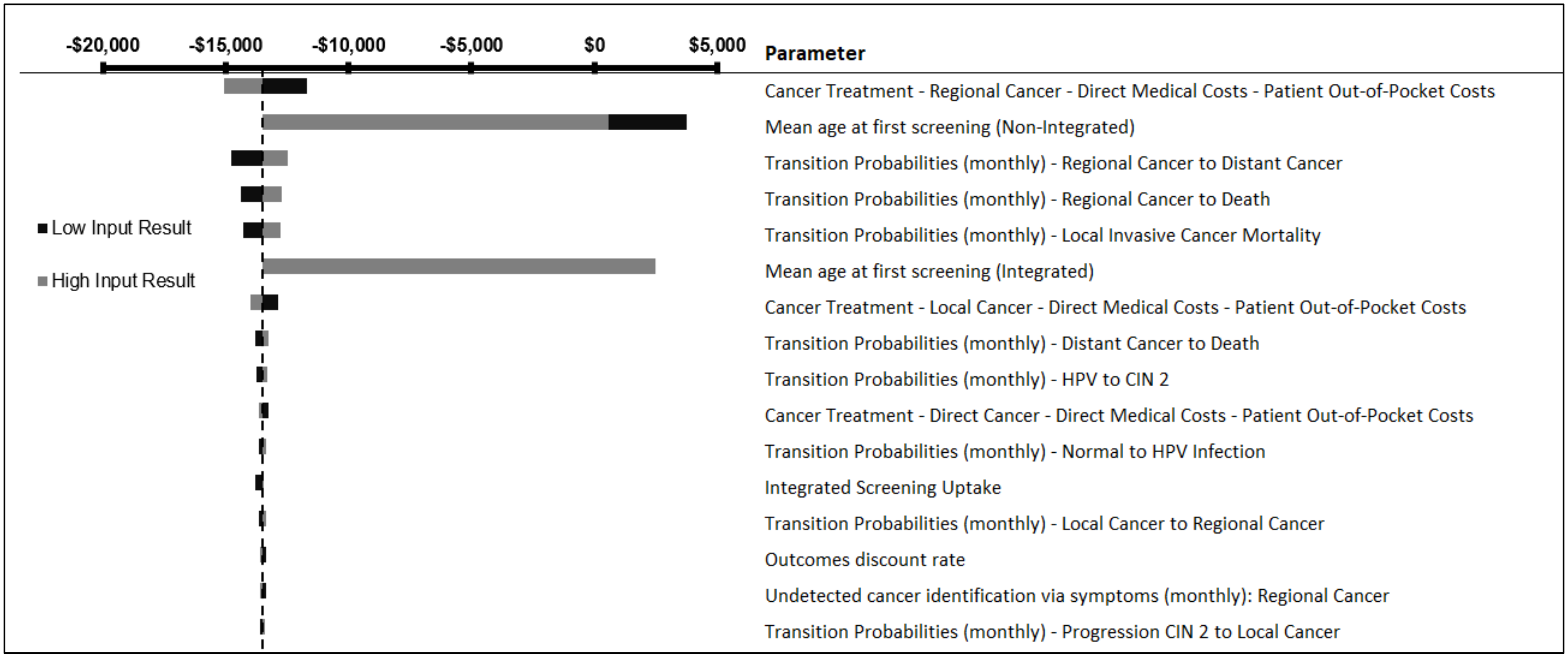


Figure 4.4. One-way sensitivity analysis of parameters influencing the projected cost-effectiveness of integrating same-day screen-and-treat into HIV-treatment clinics.

4.3.3 *Threshold Analysis*

Results were robust to changes of screening acceptance rates, VIA test sensitivity, lost-to-follow-up and increased wait times in the integrated setting. However, results varied when age at first screening among women in the HIV-treatment center was analyzed across the range of recommended screening ages (18-65 years). Integrated screening with screen-and-treat remained the dominant strategy when women in the HIV-treatment center were 30-39 years old and was projected to be a potentially highly cost-effective strategy compared to non-integrated screen-and-treat among women 18-29 years with an ICER range of $99-$1,031 per life year saved. When the mean age of screening in non-integrated settings was held fixed at 35 and the integrated age was 40+ years, non-integrated screening and treatment resulted in cost-savings ranging from $8,100-$26,000 but shorter life expectancy ranging from 0.36-11 years.

4.3.4 *Budget Impact Analysis*

The budget impact analysis projected the financial costs to the Kenyan MOH associated with integrating a same day screen-and-treat program into HIV treatment clinics over 10-year time horizon among HIV-positive women ages 18-65 years. At baseline, there were 738,369 women living with HIV of recommended screening age in Kenya, of whom 524,242 were identified as likely to attend a HIV treatment clinic based on national estimates of ART coverage. Among these women, approximately 1% were excluded from the eligible population based on previously identified neoplasia through screening or symptom detection. An additional 6,015 women were expected to have been vaccinated against HPV, comprised entirely of 18-19 year olds and were excluded. This resulted in 725,499 eligible to be screened in non-integrated settings, of whom

519,375 would be likely to engage with an HIV-treatment center and therefore be eligible for integrated screening.

We estimate that the Kenyan MOH could expect to spend an average of $1.9 million annually or a total of $22.7 million on vaccination, screening and treatment among this population over the next 10 years if current rates of screening and vaccination coverage hold. Under the modeled environment that includes integrated screen-and-treat, the MOH could expect to spend an average of $14.9 million annually or $186.2 million total over 10 years. (Table 4.4) The additional investment associated with integrated screen-and-treat strategies would lead to an estimated 4.3 million more HIV-positive women receiving cervical cancer prevention over 10 years. Figure 4.5 illustrates the expected year-over-year change in projected costs and coverage among women 18-65 living with HIV with and without integrated screening.

Table 4.4. Results from budget impact analysis estimating expected annual coverage and costs of cervical cancer prevention with the introduction of integrated screening

	Women Previously Vaccinated against HPV				**Women in Non-Integrated Settings**				**Women in Integrated Settings**				**Women Not Receiving Screening**		**All Women 18-65 Years Old (N=738,369)**		
	Expected Coverage†	Vaccine Costs	Treatment Costs	Total Costs	Expected Coverageǂ	Screening Costs	Treatment Costs	Total Costs	Expected Coverageǂ	Screening Costs	Treatment Costs	Total Costs	%	Total Costs	Total	Total # Covered§	Total Costs
Baseline	1%	$14,130	$440	$14,571	3%	$0.05M	$1.07M	$1.12M	0%	$0.0M	$0.0M	$0.0M	96%	$0.2M	100%	0.0M	$1.3M
Year 1	1%	$22,208	$692	$22,900	3%	$0.06M	$0.07M	$0.13M	51%	$0.7M	$0.7M	$1.4M	44%	$0.1M	100%	0.4M	$1.6M
Year 2	2%	$30,076	$937	$31,013	3%	$0.06M	$0.29M	$0.34M	51%	$0.7M	$2.1M	$2.8M	44%	$0.1M	100%	0.4M	$3.3M
Year 3	2%	$38,035	$1,185	$39,220	3%	$0.06M	$0.67M	$0.73M	51%	$0.7M	$4.9M	$5.6M	44%	$0.1M	100%	0.4M	$6.5M
Year 4	2%	$46,078	$1,436	$47,514	3%	$0.06M	$1.17M	$1.23M	51%	$0.8M	$8.7M	$9.5M	43%	$0.1M	100%	0.5M	$10.8M
Year 5	3%	$54,191	$1,688	$55,879	3%	$0.06M	$1.71M	$1.77M	51%	$0.8M	$13.1M	$13.9M	43%	$0.1M	100%	0.5M	$15.8M
Year 6	3%	$62,352	$1,943	$64,294	3%	$0.06M	$2.22M	$2.28M	51%	$0.8M	$17.7M	$18.5M	43%	$0.1M	100%	0.5M	$20.9M
Year 7	3%	$70,537	$2,198	$72,734	3%	$0.06M	$2.65M	$2.72M	51%	$0.8M	$22.1M	$22.9M	42%	$0.1M	100%	0.5M	$25.8M
Year 8	4%	$78,719	$2,453	$81,171	3%	$0.07M	$2.97M	$3.04M	51%	$0.8M	$26.0M	$26.9M	42%	$0.1M	100%	0.5M	$30.1M
Year 9	4%	$86,868	$2,707	$89,575	3%	$0.07M	$3.20M	$3.27M	51%	$0.9M	$29.4M	$30.2M	42%	$0.1M	100%	0.5M	$33.7M
Year 10	4%	$95,103	$2,963	$98,066	3%	$0.07M	$3.35M	$3.42M	51%	$0.9M	$32.0M	$32.9M	42%	$0.1M	100%	0.6M	$36.5M

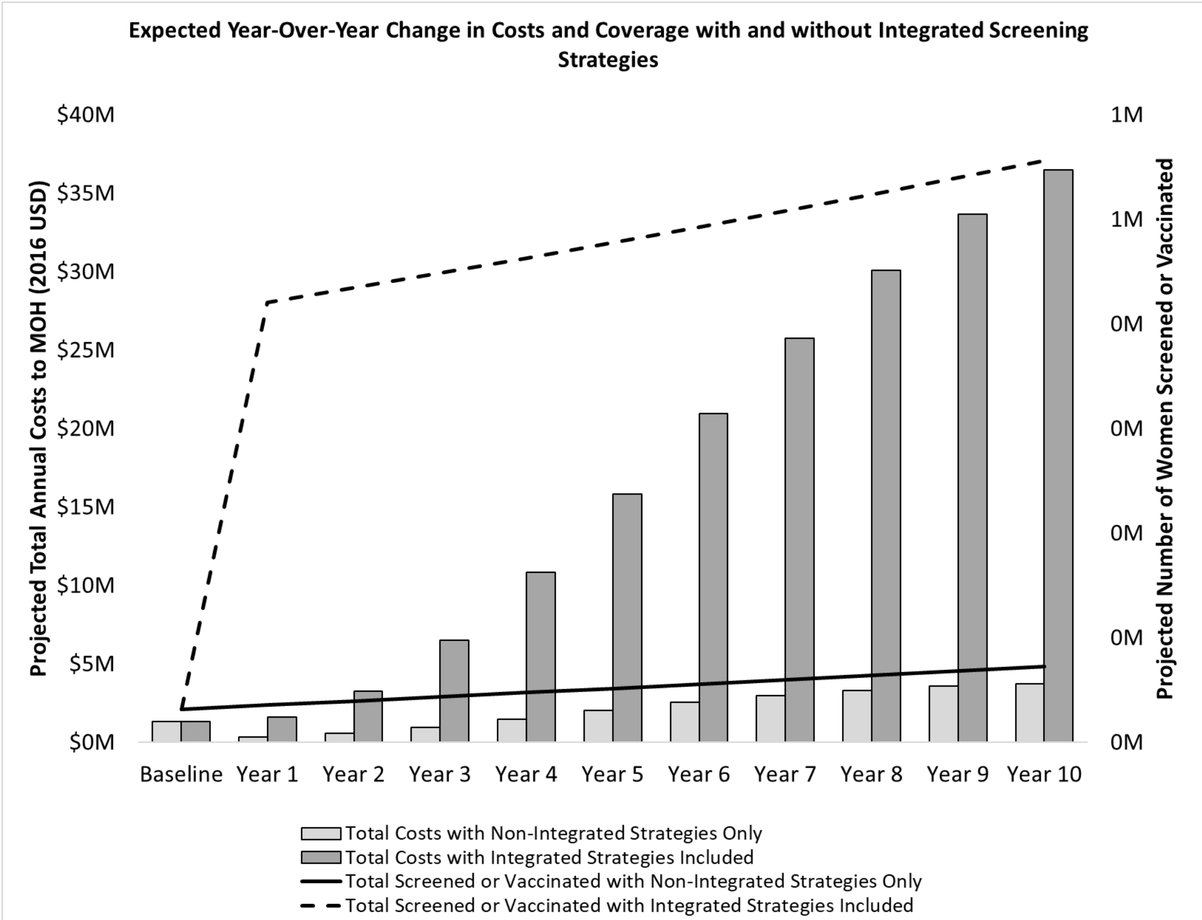


Figure 4.5. Expected year-over-year change in projected costs to Ministry of Health budget and national cervical cancer prevention among women 18-65 living with HIV with and without screening integrated into HIV-treatment centers in Kenya

4.3.5 *Univariate Sensitivity Analysis (BIA)*

One-way sensitivity analyses suggest VIA sensitivity, non-integrated screening uptake and HIV prevalence, and projected population growth were the biggest drivers of outcomes. The proportion of women screened with VIA vs. careHPV was also influential on model results. (Figure 4.6)

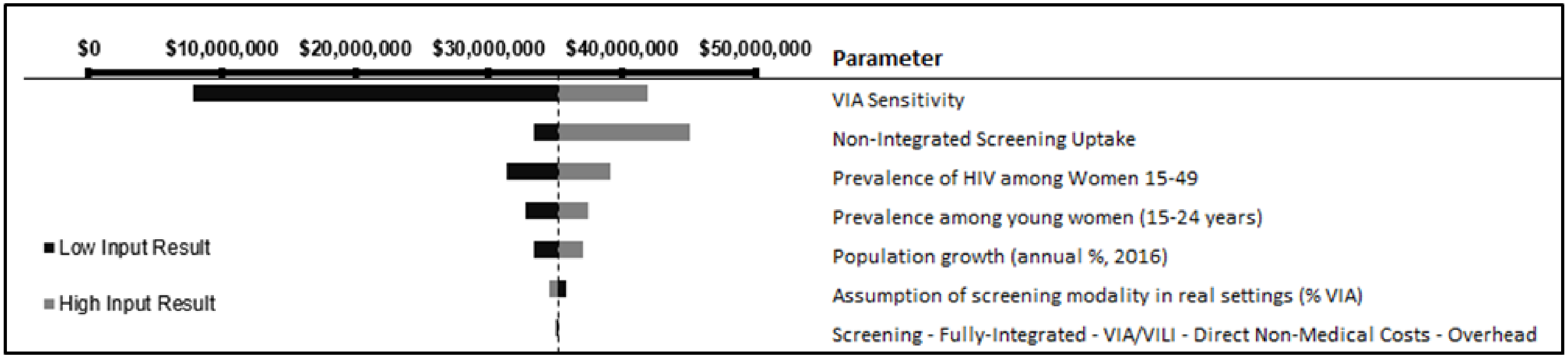


Figure 4.6. One-way sensitivity analysis evaluating influential parameters in budget impact analysis outcomes

4.4 Discussion

This study assessed the potential cost-effectiveness and budget impact associated with offering same-day screen-and-treat strategies for cervical cancer prevention to women living with HIV who attend HIV-treatment clinics for care in Kenya. The analyses were conducted assuming once-per-lifetime screening from a limited societal and program perspective and projected over a lifetime horizon. The study found that integrating same-day cervical cancer screen-and treat strategies into currently existing HIV-treatment centers is likely to be less expensive and improve health outcomes among HIV-positive women compared to non-integrated strategies from any perspective. These findings were consistent across varying assumptions about loss to follow-up from screening to treatment, screening acceptance rates, test sensitivity, and patient wait times. Age at screening appeared to impact the model results, indicating that targeting HIV-positive women 18-39 years old would provide most value for health dollars invested.

Integrating screen-and treat strategies may detect early cervical abnormalities and prevent more cases of cervical cancer for lower marginal costs due to economies of scope and scale, which may be attractive to Kenya and other, similar lower-income countries with very limited funding for healthcare investments.[50] However, these countries may also lack the infrastructure and financing to train staff at HIV-treatment facilities to provide these services.[3,115] Based on our analysis, offering screening and same-day treatment to women in the HIV-treatment setting was projected to improve screening and treatment coverage by over 50% among women 18-65 and add approximately $14 million to the national health budget annually. As the number of girls vaccinated age into the recommended screening age, the potential investment required to prevent and treat cervical cancer in the long-term may decline. In the interim, continued focus on innovative ways to improve screening and treatment at low marginal costs remains of key importance. Our cost-effectiveness findings suggest that integrated care would prevent more cases of advanced stage disease and early mortality compared to non-integrated provision of the same services. Reduced costs associated with increased disease detection could offset marginal costs of adding screening into other service lines by leveraging existing overhead, supplies, staff and other resources.

Importantly, the budget impact analysis was conducted from the perspective of the national health budget. However, in countries with high HIV prevalence like Kenya, PEPFAR and other bilateral funding organizations finance the majority of HIV treatment and related services. For example, in Kenya, 2015 PEPFAR spending on HIV-related services totaled $485 million. Combined with other international funding sources, this represents 70% of the total expenditures on HIV and AIDS interventions in Kenya.[116] If PEPFAR were to assume responsibility for financing cervical cancer screening and treatment for women living with HIV attending HIV treatment centers, we estimate that it could expect to spend approximately $715,000 annually for screening or $14 million annually for both screening and treatment.

There were some limitations to our analysis. First, the cost data used was derived from a micro-costing study that included a small sample size (N=148).[40] In addition, the Markov model is memory-less and does not allow for disease history to influence likelihood of health state transitions. Finally, there may be benefits or drawbacks to integration that may be difficult to capture in a model. For example, integration may lead to more training and increase overall standards of care.[86] Alternatively, integration of screening may negatively impact clinic workflow and cause disruptions in patient care.[86] Additionally, health systems inefficiencies, such as staff no-shows and gas stocks outs may impact both the potential costs and outcomes of integrated systems.

Diverting healthcare resources toward integrated screening programs may present opportunity costs associated with the forgone option to invest these resources on strengthening infrastructure, repairing machines, ensuring cryotherapy gas is refilled, and hiring on-call nurses to fill in for staff who are absent from work.[36] As such, infrastructure investments could potentially create more positive societal value than an integrated system. While we did not assess the costs associated with health systems inefficiencies, we did evaluate the potential impact of these inefficiencies on patient wait times. However, this appeared to have little impact on model outcomes given the relatively small cost associate with wait times. However, future research could estimate the costs and outcomes of integrating screening compared to health systems infrastructure investments. Furthermore, local variation in priority setting, existence of screening guidelines, and international partnerships focused on reducing the burden of cervical cancer could limit the generalizability of our findings. Cultural perceptions and acceptance of cervical cancer prevention may vary in different geographic regions of Kenya and SSA. For example, there is wide variation in the reported proportions of women who participated in studies across Kenya that had ever heard of cervical cancer (15-91%).[2,4,117–119]

However, this study offers several learnings for improving the prevention of cervical cancer in an important sub-group of women who are particularly susceptible to HPV and rapid cervical cancer progression. The global community has called for further evidence on the potential impact of service integration on technical and allocative efficiency in healthcare through evaluations of costs and cost-effectiveness of these services for a range of resource use scenarios.[50] In general, however, the potential value and budget impact of integrating screening into HIV-treatment clinics and other settings have not been rigorously studied in SSA.[38] While integration of screening into other existing services is currently promoted by the WHO and other influential policy organizations, there remains a paucity of evidence demonstrating which service lines provide the most appropriate venue for supporting an integrated service approach. The cost-effectiveness results presented here provide information on the potential societal-level impact of an integrated approach to increase the coverage rate by reaching HIV-positive women where they are already engaging with the health system and further reduce potential loss to follow-up through same-day screen and treat strategies. The budget impact analysis estimated the total number of women eligible to participate in integrated screening, as well as the population-level costs associated with screening and treatment. These estimates can provide national decision makers with the projected impact on their capacity and budget.

The findings from this study may provide critical guidance to policymakers on which delivery methods achieve the best value for the scarce resources available to invest in cervical cancer prevention and treatment. The budget impact component of this study addresses affordability by extrapolating expected costs and outcomes to estimate the likely impact of scaling up innovative screening and treatment programs on local and national health care budgets.

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APPENDIX A

Appendix Table 1. Varying Assumptions for Staff and Patient Time Required for Components of Cervical Cancer Treatment

	Time Required
Radiotherapy: (28 sessions total for full course)	Low: 15 minutes per session Average: 37.5 minutes High: 60 minutes
Chemotherapy: (3 sessions total for full course)	Low: 30 minutes per session Average: 2 hours per session High: 4 hours per session
Palliative Care Care (one facility-based visit)	Low: 48 minutes per session Average: 1 hour per session High: 1.5 hours per session

Appendix Table 2. Scenario Analyses Evaluated for Alternative Cervical Cancer Treatment Strategies

Scenario	**Severity**	**Stage**	**Treatment Option**	**Cost**
Base Case	Local Invasive	IA1; IA2; IB1; IIA1	Radical Hysterectomy/Surgery	$1130.06
	Regional Invasive	IB2; IIA2; IIIA; IIIB	Radical Hysterectomy + Chemo + Radiotherapy	$6,440.29
	Distant Invasive	IVA; IVB	Chemo + Radiotherapy	$5,099.80
Scenario 1	Local Invasive	IA1; IA2; IB1; IIA1	Simple Hysterectomy/Surgery	$1130.06
	Regional Invasive	IB2; IIA2; IIIA; IIIB	Radical Hysterectomy + Chemo + Radiotherapy	$6,440.29
	Distant Invasive	IVA; IVB	Chemo + Radiotherapy + Palliative Care	$5,127.12
Scenario 2	Local Invasive	IA1; IA2; IB1; IIA1	Simple Hysterectomy/Surgery	$1130.06
	Regional Invasive	IB2; IIA2; IIIA; IIIB	Chemo + Radiotherapy	$5,099.80
	Distant Invasive	IVA; IVB	Chemo + Radiotherapy	$5,099.80
Scenario 3	Local Invasive	IA1; IA2; IB1; IIA1	Simple Hysterectomy/Surgery	$1130.06
	Regional Invasive	IB2; IIA2; IIIA; IIIB	Chemo + Radiotherapy	$6,440.29
	Distant Invasive	IVA; IVB	Chemo + Radiotherapy + Palliative Care	$5,127.12
Scenario 4	Local Invasive	IA1; IA2; IB1; IIA1	Radiotherapy (Contraindicated for Surgery)	$4,362.53
	Regional Invasive	IB2; IIA2; IIIA; IIIB	Radical Hysterectomy + Chemo + Radiotherapy	$6,440.29
	Distant Invasive	IVA; IVB	Chemo + Radiotherapy	$5,099.80
Scenario 5	Local Invasive	IA1; IA2; IB1; IIA1	Radiotherapy (Contraindicated for Surgery)	$4,362.53
	Regional Invasive	IB2; IIA2; IIIA; IIIB	Radical Hysterectomy + Chemo + Radiotherapy	$6,440.29
	Distant Invasive	IVA; IVB	Chemo + Radiotherapy + Palliative Care	$5,127.12
Scenario 6	Local Invasive	IA1; IA2; IB1; IIA1	Radiotherapy (Contraindicated for Surgery)	$4,362.53
	Regional Invasive	IB2; IIA2; IIIA; IIIB	Chemo + Radiotherapy	$5,099.80
	Distant Invasive	IVA; IVB	Chemo + Radiotherapy	$5,099.80
Scenario 7	Local Invasive	IA1; IA2; IB1; IIA1	Radiotherapy (Contraindicated for Surgery)	$4,362.53

	Regional Invasive	IB2; IIA2; IIIA; IIIB	Chemo + Radiotherapy	$5,099.80
	Distant Invasive	IVA; IVB	Chemo + Radiotherapy + Palliative Care	$5,127.12
Scenario 8	Local Invasive	IA2; IB1; IIA1	Simple Hysterectomy + Radiotherapy	$5,238.55
	Regional Invasive	IB2; IIA2; IIIA; IIIB	Radical Hysterectomy + Chemo + Radiotherapy	$5,975.82
	Distant Invasive	IVA; IVB	Chemo + Radiotherapy	$5,099.80
Scenario 9	Local Invasive	IA2; IB1; IIA1	Simple Hysterectomy + Radiotherapy	$5,238.55
	Regional Invasive	IB2; IIA2; IIIA; IIIB	Radical Hysterectomy + Chemo + Radiotherapy	$6,440.29
	Distant Invasive	IVA; IVB	Chemo + Radiotherapy + Palliative Care (single visit)	$5,127.12
Scenario 10	Local Invasive	IA2; IB1; IIA1	Simple Hysterectomy + Radiotherapy	$5,238.55
	Regional Invasive	IB2; IIA2; IIIA; IIIB	Chemo + Radiotherapy	$5,099.80
	Distant Invasive	IVA; IVB	Chemo + Radiotherapy	$5,099.80
Scenario 11	Local Invasive	IA2; IB1; IIA1	Simple Hysterectomy + Radiotherapy	$5,238.55
	Regional Invasive	IB2; IIA2; IIIA; IIIB	Chemo + Radiotherapy	$5,099.80
	Distant Invasive	IVA; IVB	Chemo + Radiotherapy + Palliative Care (single visit)	$5,127.12
Scenario 12	Local Invasive	IA2; IB1; IIA1	Simple Hysterectomy	$1130.06
	Regional Invasive	IB2; IIA2; IIIA; IIIB	Radiotherapy	$4,362.53
	Distant Invasive	IVA; IVB	Palliative Care (single visit)	$58.36
Scenario 13	Local Invasive	IA2; IB1; IIA1	Palliative Care (single visit)	$58.36
	Regional Invasive	IB2; IIA2; IIIA; IIIB	Palliative Care (single visit)	$58.36
	Distant Invasive	IVA; IVB	Palliative Care (single visit)	$58.36

VITA

Elisabeth Vodicka received her Masters in Healthcare Administration from the University of Washington (Department of Health Services) directly prior to pursuing her PhD in the School of Pharmacy. Elisabeth's research focuses on the evaluation of programs, policies, and technologies that aim to improve access to care and strengthen health systems in low-resource settings, with particularly focus on economic and social impact. Domestically, Elisabeth has explored issues related to patient reported outcomes, contraception coverage, and health information technology. Globally, she has assessed health care delivery systems related to women's health and chronic disease management. Prior to graduate school, Elisabeth worked for eight years in non-profit development and public health research.