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Cervical Cancer Elimination in Low-and-middle-income countries: The Role of Cost and Empowerment in the Implementation of Human Papillomavirus Self-Sampling

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Abstract

Cervical Cancer Elimination in Low-and-middle-income countries: The Role of Cost and Empowerment in the Implementation of Human Papillomavirus Self-Sampling

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The World Health Organization (WHO) announced an ambitious call for global cervical cancer elimination within the next century. More than 80% of cervical cancers occur in low-and-middle-income countries (LMICs), where the age-standardized mortality rates are six-times higher than in high-income countries. The goal of this dissertation is to outline a roadmap toward cervical cancer elimination in LMICs and evaluate a community-based HPV self-sampling program in Peru via micro-costing and mixed-method study of empowerment. In the first aim, we conduct a scoping review to synthesize evidence-based primary and secondary prevention strategies for cervical cancer and highlight research gaps and priorities. We find that effective prevention methods

include HPV vaccination, screening using visual inspection and HPV testing and thermocoagulation, and discuss implementation challenges in LMICs. Aims 2 and 3 are nested within a community-based HPV self-sampling social entrepreneurship in Peru called the Hope Project, where volunteer women (Hope Ladies) from socioeconomically disadvantaged peri-urban area of Lima sell HPV self-sampling kits in their communities to increase cervical cancer screening coverage. In Aim 2, we conduct a micro-costing analysis from the program perspective to determine the unit costs of: (1) recruitment and training of Hope Ladies, (2) Hope Ladies distributing HPV self-sampling kits (*care*HPV), and (3) Hope Ladies linking screened women with appropriate follow-up care. We find that community-based HPV self-sampling appears to be a feasible way to improve cervical cancer screening in Peru. In Aim 3, we evaluate the Hope Ladies' individual and collective relational and financial empowerment after participating in the Hope Project. We use deductive content analysis and surveys informed by empowerment frameworks (e.g., Kabeer's conceptual model) to triangulate our qualitative and quantitative findings. We develop an implementation-science informed causal pathway for the Hope Project, where the Hope Ladies' financial/relational empowerment function as the mechanism of action for this intervention and articulate the pre-conditions necessary to increase the screening coverage. Finally, we conclude that cervical cancer elimination in LMICs would require intersectoral collaboration to increase access to and coverage of evidence-based strategies. We call for implementation, scale-up and economic and programmatic evaluation of community-based HPV self-sampling in LMICs.

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DEDICATION

For womxn.

Chapter 1. INTRODUCTION

Human papillomavirus (HPV) causes virtually all cervical cancer (1), which is a leading cause of cancer-related deaths among women in low- and middle-income countries (LMICs). More than 80% of cervical cancer cases occur in LMICs (2, 3), where the age-standardized cervical cancer mortality rates are six-times higher than in high-income countries (4). In addition to the higher burden, these disparities reflect limited infrastructure, healthcare access and resources in LMICs since cervical cancer is almost entirely preventable with current technologies (5, 6). Despite the World Health Organization (WHO)'s 2018 call for global cervical cancer elimination (7), efficacious interventions are not reaching those who need them most. Approximately 20% of women in LMICs have ever been screened compared to 60% in high-income countries (8), far from achieving the WHO's target of 70% twice-lifetime screening of women ages 35-45 and 90% treatment of cervical cancer and precancer by 2030 (9). Most LMICs lack the necessary, well-organized screening programs that markedly reduced cervical cancer incidence and mortality in high-income countries (10-12). Therefore, there is an urgent need to test, implement and invest in effective screening strategies for cervical cancer elimination in LMICs.

HPV testing can detect precancerous lesions with superior sensitivity compared to visual inspection with acetic acid (VIA) and traditional cytology, which are the most common standard of care in LMICs (13-15). HPV self-sampling has the potential of making HPV testing more accessible to women because women can collect their own cervical samples at home without having to visit a clinic for a pelvic exam for the initial part of the screening. HPV self-sampling has demonstrated the potential for increasing population uptake of cervical cancer screening (16), and is recommended by the WHO as an approach to increase screening uptake for women aged 30-60 years (17). HPV self-sampling has shown variable size and direction of effect in improving screening uptake, highlighting the importance of cost-effectiveness in local contexts, especially in LMICs, where the screening

coverage of effective algorithms is low (16, 18). In addition, a rigorous framework for implementation research has not been applied to provide guidance on the scale-up of HPV self-sampling. This dissertation attempts to fill these evidence gaps by moving beyond identifying barriers and facilitators to discovering actionable factors associated with successful implementation. Future scale-up will require an understanding of the factors that are critical to build a comprehensive implementation package for HPV self-sampling.

Implementation science is a scientific field that promotes systematic uptake of research findings and other evidence-based practices into routine practice (19). Figure 1.1 describes the types of research outcomes in implementation research. Using an implementation science framework, this dissertation first examines appropriate strategies for cervical cancer elimination in LMIC settings in Aim 1. Aims 2 and 3 closely evaluates a community-based HPV self-sampling social entrepreneurship in Peru called the Hope Project. Aim 2 enumerates the costs associated with HPV self-sampling, which is a critical component of determining feasibility and adoption (20). Aim 3 evaluates the relational and financial empowerment of the social entrepreneurs who offer HPV self-sampling kits in their communities in the Hope Project.

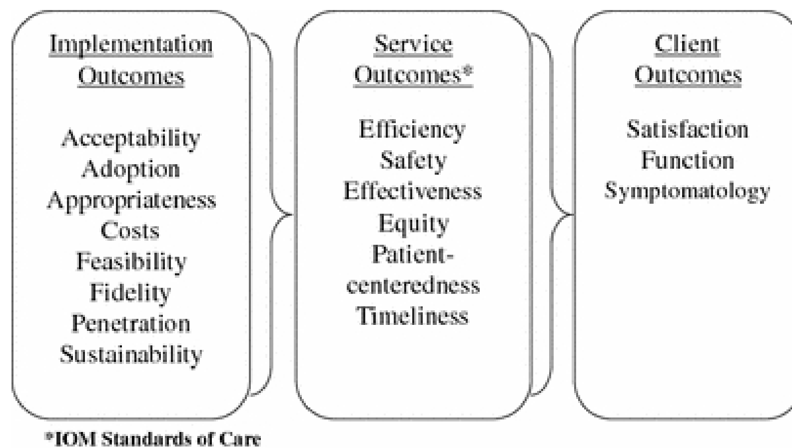

Figure 1.1 Types of outcomes in implementation research (20)

This dissertation contributes to (1) synthesizing of the current state of science as it relates to cervical cancer elimination; (2) establishing the necessary baseline for future economic evaluations for HPV self-sampling in Peru and other LMIC settings; and (3) providing a theory-informed implementation guidance for the scale-up of HPV self-sampling using the social entrepreneurship model. The cross-cultural context of the Hope Project will also add value for other HPV self-sampling programs who aspire to adapt implementation science methods in similar settings for community engagement. Our hope is that our findings will be applicable to numerous low resource contexts and serve as a valuable case study for other HPV self-sampling programs, ultimately closing the disparity between the high and low resource settings.

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- Northwest Public Health Training Center

The funding agencies did not affect the identification, design, conduct, and reporting of the dissertation research. We declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Chapter 2. A FRAMEWORK FOR CERVICAL CANCER ELIMINATION IN LOW-AND-MIDDLE-INCOME COUNTRIES: A SCOPING REVIEW AND ROADMAP FOR INTERVENTIONS AND RESEARCH PRIORITIES

2.1 ABSTRACT

Background: The WHO announced an ambitious call for cervical cancer elimination worldwide. With existing prevention and treatment modalities, cervical cancer elimination is now within reach for high-income countries. Despite limited financing and capacity constraints in LMICs, prevention and control efforts can be supported through integrated services and new technologies. We conducted this scoping review to outline a roadmap toward cervical cancer elimination in LMICs and highlight evidence-based interventions and research priorities to accelerate cervical cancer elimination.

Methods: We reviewed and synthesized literature from 2010-2020 on primary and secondary cervical cancer prevention strategies. In addition, we conducted expert interviews with gynecologic and infectious disease providers, researchers, and LMIC health officials. Using these data, we developed a logic model to summarize the current state of science and to identify evidence gaps and priority research questions for each prevention strategy.

Results: The logic model for cervical cancer elimination maps needs for improved collaboration between policy makers, production and supply, healthcare systems, providers, health workers, and communities. The model articulates responsibilities for stakeholders and visualizes processes to increase access to and coverage of prevention methods. We discuss the challenges of contextual factors and highlight innovation needs. Effective prevention methods include HPV vaccination, screening using visual inspection and HPV testing, and thermocoagulation. However, vaccine coverage remains low in LMICs. New strategies, including single-dose vaccination could enhance impact. Loss to

follow-up and treatment delays could be addressed by improved same-day screen-and-treat technologies.

Conclusion: We provide a practical framework to guide cervical cancer elimination in LMICs. The scoping review highlights existing and innovative strategies, unmet needs, and collaborations required to achieve elimination across implementation contexts.

Abstract presented at the International Cancer Screening Network in Rotterdam, Netherlands, June 3-5, 2019. Shin MB, Liu G, Mugo N, Garcia P, Rao D, Wasserheit J, Barnabas RV. A Framework for Cervical Cancer Elimination: Gaps in evidence and next steps.

2.2 INTRODUCTION

Globally, there are more than half a million new cervical cancer cases and more than a quarter-million cervical cancer-related deaths each year (21). Due to effective screening and treatment of precancerous lesions and cancer, high-income countries have seen marked decreases in cervical cancer incidence and mortality in recent decades (10, 11, 22). High coverage of human papillomavirus (HPV) vaccination has also contributed to declines in HPV prevalence and cervical lesions in countries with established national vaccination programs (23). Given the success of effective interventions for prevention and treatment, the WHO issued a call in 2018 to eliminate cervical cancer as a public health problem globally, defined as an incidence rate less than 4 per 100,000 women-years (24). To achieve this goal, the WHO proposes an intermediate 90-70-90 target (also known as "triple-intervention"), which aims to vaccinate 90% of girls by age 15, screen 70% of women with a high-performance test by ages 35 and 45, and treat 90% of women with cervical disease (24). Australia is projected to achieve elimination by 2050, and other high-income countries are following close behind (25).

However, the timeline for cervical cancer elimination is significantly longer in LMICs (26). This longer timeline is due in part to the current higher burden of disease. More than 80% of cervical cancer cases occur in LMICs (27), where age-standardized cervical cancer mortality rates are at least six-fold higher than in high-income countries (4). These disparities reflect low access to prevention, screening and treatment due to limited infrastructure, technical expertise, and resources (4). Of the 118 million women who received the HPV vaccine by 2016, only 1.4 million (1%) lived in LMICs (28). Implementation of successful screening programs in LMICs has been challenged by the lack of equipment and personnel to initiate and maintain the screening program, the financial and logistical burden of multiple visits, high rates of loss-to-follow-up, and lack of resource allocation for specialized training (29).

The science, technology, and implementation of cervical cancer prevention and treatment are changing rapidly, with effective and scalable strategies on the horizon. A recent modeling analysis of 78 LMICs demonstrated the importance of successful implementation and scale-up by predicting that the triple-intervention would reduce cervical cancer mortality of women ages 30-69 years by 33.9% (24.4-37.9 per 100,000 women) by 2030 and almost 99% by 2120 (30). The purpose of this scoping review is to 1) synthesize the evidence on the effectiveness of available and emerging cervical cancer elimination strategies, 2) provide a mechanism for visualizing how primary, and secondary prevention methods work together using a logic model framework, and 3) highlight gaps in evidence in primary and secondary prevention, and propose research priorities to address these gaps and accelerate progress toward elimination in particular for LMICs.

2.3 METHODS

Our team conducted a scoping review of the literature on primary and secondary, cervical cancer prevention strategies using methods adapted from Arksey and O'Malley (31). Scoping review is a method used to "map" the relevant literature when the field of interest is broad. It differs from a traditional systematic review in that it includes study designs other than randomized trials or other systematic reviews. We chose this method because the topic of cervical cancer elimination in low-resource settings is one that is complex and the science is still nascent in some aspects (e.g., one-dose HPV vaccine regimen), yet critically important. Our review focuses on primary and secondary prevention to deliver a more in-depth summary on these strategies. The areas of expertise in cervical cancer prevention on our team include: infectious disease specialists (RB, JW, PG, LE), obstetrics gynecologists (LE, LP, NM), LMIC practitioners (PG, NM), epidemiologists (GL, DR), modeling specialists (GL, DR, CB), a gynecologic oncologist (LP), and a nurse (MS). The Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) Checklist is available in Table 2.1 (32). The scoping review process is described in detail in Table 2.2.

Table 2.1 Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) Checklist (32)

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
TITLE			
Title	1	Identify the report as a scoping review.	16
ABSTRACT			
Structured summary	2	Provide a structured summary that includes (as applicable): background, objectives, eligibility criteria, sources of evidence, charting methods, results, and conclusions that relate to the review questions and objectives.	16-17
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known. Explain why the review questions/objectives lend themselves to a scoping review approach.	18-19
Objectives	4	Provide an explicit statement of the questions and objectives being addressed with reference to their key elements (e.g., population or participants, concepts, and context) or other relevant key elements used to conceptualize the review questions and/or objectives.	19
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists; state if and where it can be accessed (e.g., a Web address); and if available, provide registration information, including the registration number.	N/A
Eligibility criteria	6	Specify characteristics of the sources of evidence used as eligibility criteria (e.g., years considered, language, and publication status), and provide a rationale.	Table 2.2
Information sources*	7	Describe all information sources in the search (e.g., databases with dates of coverage and contact with authors to identify additional sources), as well as the date the most recent search was executed.	Table 2.2
Search	8	Present the full electronic search strategy for at least 1 database, including any limits used, such that it could be repeated.	Supplementary Table 2.1
Selection of sources of evidence†	9	State the process for selecting sources of evidence (i.e., screening and eligibility) included in the scoping review.	22-23, Table 2.2
Data charting process‡	10	Describe the methods of charting data from the included sources of evidence (e.g., calibrated forms or forms that have been tested by the team before their use, and whether data charting was done independently or in duplicate) and any processes for obtaining and confirming data from investigators.	22-23, Table 2.2
Data items	11	List and define all variables for which data were sought and any assumptions and simplifications made.	22-23, Supplementary Table 2.2

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	REPORTED ON PAGE #
Critical appraisal of individual sources of evidence§	12	If done, provide a rationale for conducting a critical appraisal of included sources of evidence; describe the methods used and how this information was used in any data synthesis (if appropriate).	N/A
Synthesis of results	13	Describe the methods of handling and summarizing the data that were charted.	N/A
RESULTS			
Selection of sources of evidence	14	Give numbers of sources of evidence screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally using a flow diagram.	N/A
Characteristics of sources of evidence	15	For each source of evidence, present characteristics for which data were charted and provide the citations.	Supplementary Table 2.2
Critical appraisal within sources of evidence	16	If done, present data on critical appraisal of included sources of evidence (see item 12).	N/A
Results of individual sources of evidence	17	For each included source of evidence, present the relevant data that were charted that relate to the review questions and objectives.	24-47
Synthesis of results	18	Summarize and/or present the charting results as they relate to the review questions and objectives.	24-47
DISCUSSION			
Summary of evidence	19	Summarize the main results (including an overview of concepts, themes, and types of evidence available), link to the review questions and objectives, and consider the relevance to key groups.	48-51, Table 2.9
Limitations	20	Discuss the limitations of the scoping review process.	51
Conclusions	21	Provide a general interpretation of the results with respect to the review questions and objectives, as well as potential implications and/or next steps.	52
FUNDING			
Funding	22	Describe sources of funding for the included sources of evidence, as well as sources of funding for the scoping review. Describe the role of the funders of the scoping review.	15

Table 2.2 Scoping review framework and description of methods

Arksey and O'Malley framework stage	
1. Identifying the research question	• What do we already know? • What are the gaps in evidence? • What are the relevant innovations? • What are the most pressing questions we need to answer to scale-up cervical cancer elimination strategies?
2. Identifying relevant studies	• Search sources: PubMed, Scopus, reference lists, and governmental and nonprofit organizational websites • Inclusion criteria: o Programmatic interventions identified by the WHO life course model (33) o English language published between 2010 and 2020 o Peer-reviewed studies and conference abstracts that examined efficacy, effectiveness, sensitivity, and/or specificity of existing and emerging strategies to prevent HPV infection and detect or treat cervical pre-cancers and cervical cancer o Interventional studies that address innovations and implementation gaps
3. Study selection	• Systematic reviews, meta-analysis and randomized controlled trials were prioritized for each intervention. When these were not available, we selected longitudinal and prospective cohort studies with relative risks or odds ratios that address HPV acquisition, progression to precancer and treatment of cancer. Individual cross-sectional studies were reviewed only if sufficient data from the above types of studies were not available.
4. Charting the data	Two authors (MS and GL) screened the search results for relevant articles and independently extracted data relevant to the key questions. The last update of the search was conducted in August 2020, and the following data was extracted using Microsoft Excel sheet. (see supplementary materials): • Primary prevention: author, year, study design, location, population, exposure, unit of exposure, comparison, comparison number of doses, outcomes, sample size, key findings • Secondary prevention: author, year, intervention, study design, location, population, intervention, comparison, outcomes, clinical endpoint, key findings
5. Collating, summarizing, and reporting the results	As specified by Arksey and O'Malley, a narrative literature review method was used, in which data synthesis and interpretation of the findings were conducted simultaneously, in an iterative manner with the research team. In addition to the narrative synthesis, we followed the Centers for Disease Control and Prevention's Program Evaluation Framework to organize the evidence on the available and emerging strategies for cervical cancer elimination into a logic model (34)

We chose to review articles published starting year 2010, because while HPV vaccine was introduced to the world in 2006, it was not until 2010 that it become incorporated into the national

immunization program in LMICs settings, starting with Bhutan in 2010 and Rwanda in 2011 (35). We used WHO's "Life-course approach to cervical cancer interventions" as a guide to organize our review (36). We defined primary prevention as the prevention of HPV infection (e.g., vaccine administration, condom use, etc) and secondary prevention as the detection and treatment of precancerous cervical lesions.

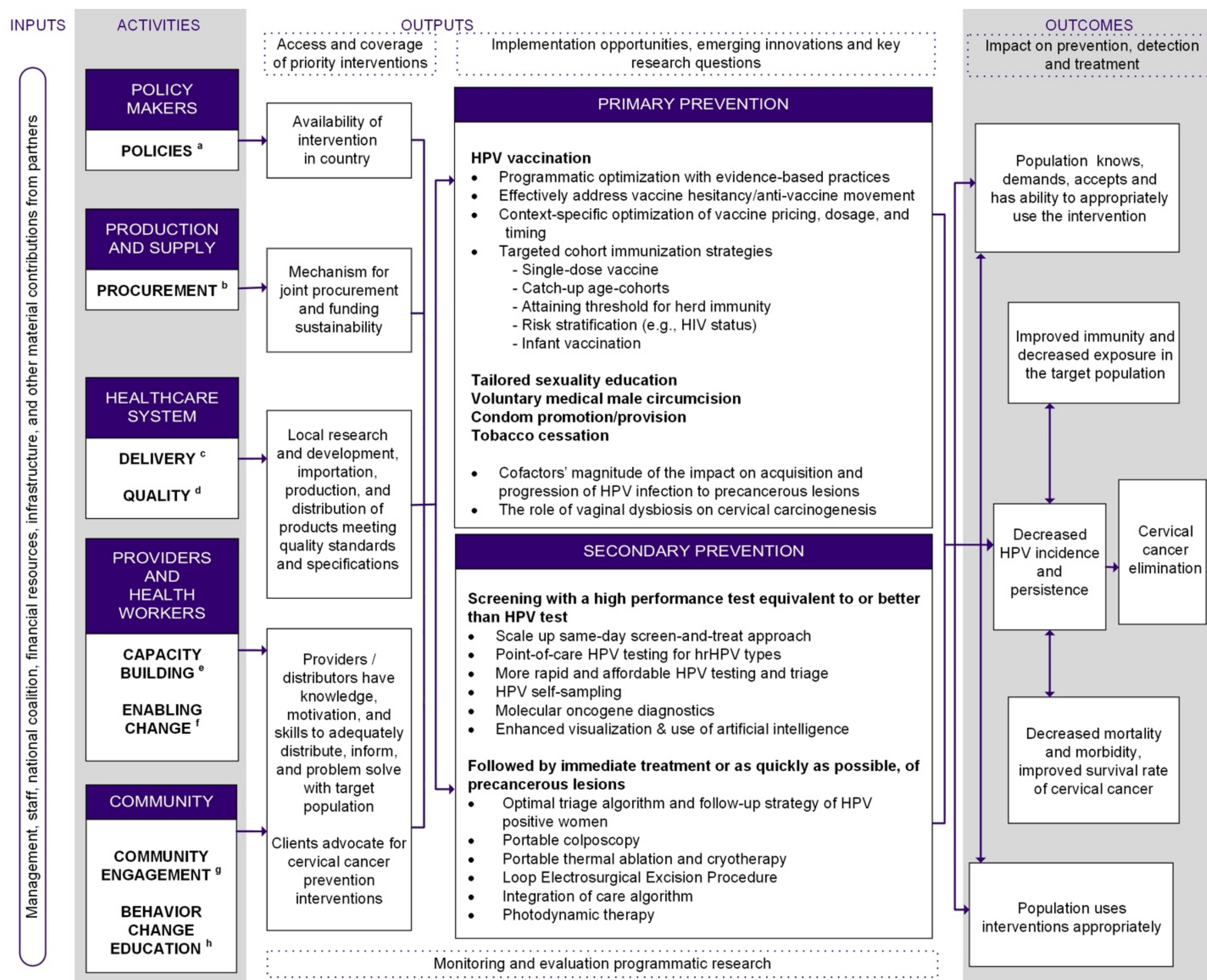
Two authors (MS and GL) screened the search results for relevant articles and extracted data independently. All authors provided feedback on study selection, data extraction, and synthesis, which informed further search and interpretation of the findings. Our search for primary prevention strategies focused on the effect of HPV vaccination, voluntary medical male circumcision (VMMC), tobacco cessation, condom use (33), and vaginal dysbiosis. While vaginal dysbiosis is not commonly mentioned as a risk factor for cervical cancer, we decided to include it in our review because there is relatively strong and consistent evidence that the vaginal microbiota play a role in cervical cancer pathology (37-40).

We divided secondary prevention into screening and treatment strategies. For screening, we compared cytology, HPV tests, and visual inspection with acetic acid (VIA). As the WHO recommends screening with a high-performance test equivalent to or better than HPV testing, we reviewed implementation challenges of HPV testing in low-resource settings. For immediate treatment of precancerous lesions, we focused on cryotherapy, thermal ablation, and loop electrosurgical excision procedure (LEEP). We identified emerging screening and triage options in LMICs as HPV self-sampling, oncogenesis biomarkers, optical techniques such as portable colposcopes and automated visual evaluation, and therapeutic vaccines. We also dedicated a section to prevention of cervical cancer among women living with HIV to highlight the differences in HPV acquisition and progression in this population.

2.4 RESULTS

2.4.1 *Logic Model*

We developed a logic model from our review that summarizes and describes the process flow for cervical cancer elimination (Figure 2.1). Step one is marshaling crucial resources needed for sustainable cervical cancer elimination programs in LMICs: healthcare worker capacity, political commitment, funding, and infrastructure and material support from domestic and global partners ("Inputs") as explicitly captured in the WHO's "Global strategy towards eliminating cervical cancer as a public health problem"(33). To acquire these resources, key stakeholders must build capacity within their sectors and foster cross-sector collaborations ("Activities"). The intended impact of the program is organized into primary and secondary prevention nodes ("Outputs"). For each prevention strategy, we summarized what is known, the impact of the intervention, and innovations under development. All strategies lead to "Outcomes," which are the expected intermediate impacts on the path towards cervical cancer elimination. Synthesizing the efficacy of current interventions identified gaps in innovation in primary and secondary prevention, which are summarized in Figure 2.1.



(A) Policies: develop and implement policies, legislation regulations, and registrations.
(B) Procurement: develop and implement provision, production, procurement and training strategies.
(C) Delivery: develop and implement delivery system, strategy for management, training, and maintaining motivation among providers and distributors.
(D) Quality: develop and implement an external and internal quality control system.
(E) Capacity building: providers and health worker skills training, infrastructure and capacity building.
(F) Enabling change: cultivate dialogue to promote adoption of innovative technologies and approaches (e.g., task-shifting/sharing) to simplify care delivery and break conflicts of interest.
(G) Community engagement: demand promotion by empowering local stakeholders and advocacy.
(H) Behavior change education: develop and implement intervention strategy for information, education, and communication for behavior change.

Figure 2.1 Logic model for comprehensive, intersectoral cervical cancer prevention

2.4.2 *Primary Prevention*

2.4.2.1 Current State of Science

2.4.2.1.1 HPV Vaccines

HPV vaccines, which have the potential to prevent 90% of cervical cancer cases (41), are by far the most efficacious primary prevention modality. Among HPV-naïve adolescent girls and young women, the efficacy of available vaccines (bivalent, quadrivalent, and nonavalent) is >95% for preventing HPV infections and cervical lesions caused by vaccine-targeted HPV types (42-47). Since the median age of sexual initiation is 15-17 years in many populations (48), the WHO recommends vaccination programs to target 9-13 year-old girls (49). Mathematical modeling analyses from 73 LMICs found that routine vaccination at age 9 and multi-cohort vaccination of girls ages 10-14 reduced cervical cancer deaths by 30-40%, or 1.2-1.8 million, over the lifetime of the vaccinated cohorts in addition to the number of deaths averted with routine vaccination only (50). As of 2014, more than 90% of the 600 million females aged 10-19 around the world fell outside HPV vaccination programs with limited or no access to catch-up campaigns (51), and a comprehensive strategy is needed for cervical cancer elimination (36).

The economic landscape of HPV vaccines is quickly changing to promote access to the vaccines in LMICs and adoption of national HPV immunization programs. Just prior to the Global Vaccine Summit 2020, five manufacturers of HPV vaccines committed to increasing the supply in GAVI-supported countries (52). The proportion of LMICs with national programs is low (22 of the 78 LMICs versus 50 of the 57 high-income countries as of 2020) (53, 54), but increasing, since GAVI Alliance negotiated the price of the vaccine from $4.50 USD per dose for the poorest countries in 2013 (55). The cost-effectiveness of vaccination strategies is dependent on the vaccine price, which is likely to be significantly reduced as new vaccines being developed in India and

China increase HPV vaccine supply over the next ten years (56). Economic evaluations from modeling studies suggest that HPV vaccination of adolescent girls is cost-effective for most countries, especially low-income countries (57, 58) and when the vaccine price low enough for the country's income level (59).

2.4.2.1.2 Voluntary Medical Male Circumcision

VMMC for HIV-negative men has been shown to reduce penile HPV viral load of incident infections and the persistence of prevalent HPV infections, which likely reduces male-to-female HPV transmission (60, 61). Even when transmission occurs, female partners of circumcised men had lower HPV viral load (61). The incidence of high-risk HPV (hrHPV) infection was lower among women whose male partners received circumcision than those who did not (incidence rate ratio=0.77, 95% CI: 0.63–0.93) (62).

2.4.2.1.3 Other Cofactors

HPV incidence is inversely associated with the frequency of condom use (63). In a longitudinal study with eight months of follow-up, female college students who reported using condoms during all vaginal intercourse were 70% less likely to acquire a new infection than those who reported using condoms less than 5% of the time, after adjusting for the number of new partners and estimated number of previous partners of the male partner (64).

Current smokers were 1.6 times more likely to have prevalent hrHPV infection (95% CI: 1.2–2.1) and 1.4 times more likely to have newly detected hrHPV infection than never smokers (95% CI: 1.0 –1.9) (65). This increased risk may be explained by the lack of immune response after a natural infection among people who smoke, which lowers their defense against subsequent infection (65).

Vaginal dysbiosis, including but not limited to bacterial vaginosis, is positively correlated with prevalent HPV infection and cervical intraepithelial neoplasia (CIN) among women with and without HIV (38, 66-68). While vaginal dysbiosis increased risk of persistent HPV infection (69), high grade squamous intraepithelial lesions (HSIL) and cervical cancer (70), healthy cervicovaginal microbiome, dominated by multiple species of Lactobacillus bacteria, were associated with lower prevalence of hrHPV infection (71). There is a need to further investigate the complex relationship between the microbiome of the female reproductive tract, HPV and cervical carcinogenesis (72).

Table 2.3 summarizes the efficacies and effect of co-factors in prevention of HPV infection. The clinical endpoints and the intervention effect are not uniform; hence, the potential impact of different preventative strategies cannot be compared to each other.

Table 2.3 Summary of HPV vaccine efficacy and effect of co-factors on HPV-related clinical endpoints

Primary prevention method	**Endpoint**	**Effect (%)**	***Reference***
HPV vaccine*			
(HPV)-16/18 AS04-adjuvanted vaccine	CIN2-3 associated with HPV 16/18 (mean f/u: 34.9 months)	92.9 (96.1% CI: 79.9-98.3)	*(42)*
Quadrivalent vaccine (HPV 6, 11, 16, 18)	CIN 1-3 or adenocarcinoma in situ associated with HPV 6, 11, 16, 18 (mean f/u: 36 months)	100.0 (95% CI: 94.0-100.0)	*(44)*
	CIN 2 or 3, adenocarcinoma in situ, or cervical cancer related to HPV 16 or 18 (mean f/u: 36 months)	98.0 (95.89% CI: 86.0-100.0)	*(45)*
Nonavalent vaccine (HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58)	CIN 2 or 3, adenocarcinoma in situ, invasive cervical carcinoma, and vulvar disease related to HPV 31, 33, 45, 52, and 58 (up to 6 years)	97.4 (95% CI: 85.0–99.9)	*(46)*
	High-grade cervical, vulvar, or vaginal disease related to HPV-31, 33, 45, 52, and 58 (up to 54 months)	96.7 (95% CI: 80.9 to 99.8)	*(47)*

Voluntary medical male circumcision			
	HPV prevalence risk ratios among women partners 24 months after intervention	0.72 (95% CI: 0.60-0.85)	*(62)*
	Incidence rate ratio of hrHPV†	0.77 (95% CI: 0.63-0.93)	*(62)*
Tobacco use ‡			
	Odds ratio of hrHPV infection at baseline	1.60 (95% CI: 1.20–2.10)	*(65)*
	Odds ratio of CIN2-3 at baseline	1.80 (95% CI: 1.30–2.50)	*(65)*
	Risk ratio of incident hrHPV infection	1.40 (95% CI: 1.00–1.90)	*(65)*
	Risk ratio of incident CIN2-3	3.60 (95% CI: 1.50–8.60)	*(65)*
Condom use ¶			
	Percent reduction of incident genital HPV infection	70.0% (95% CI: 40.0-90.0)	*(64)*
Vaginal dysbiosis			
	Risk ratio of incident HPV infection	1.35 (95% CI: 1.18-1.50)	*(37)*
	Risk ratio of HPV persistence	1.14 (95% CI: 1.01-1.28)	*(37)*
	Risk ratio of high grade squamous intraepithelial lesion/squamous cell changes	2.01 (95% CI: 1.40-3.01)	*(37)*

* Indicates vaccine efficacy
† HPV 6, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68
‡ Comparing current smokers to never smokers
¶ Comparing condom use 100% of the time during 8 months among to those whose partners used condoms less than 5 percent of the time among women who had never had vaginal intercourse or had first had intercourse with one male partner within the previous three months of the study

2.4.2.2 Priority Research Questions for Primary Prevention Strategies

We prioritized implementation and scale-up of HPV vaccination in primary prevention opportunities, as it directly addresses the known causal agent of most cervical cancer (73). Several barriers specific to LMICs have been identified, such as costs associated with the vaccine and service delivery, political commitment, challenges specific to the target population of adolescent girls, and global vaccine shortage (54). In addition, the scale-up of HPV vaccination programs has faced challenges of vaccine hesitancy due to concerns about the safety and side effects of the vaccine and the belief that vaccination can lead to sexual promiscuity (74).

Successful implementation and scale-up of HPV vaccine programs depends on achieving and maintaining high rates of vaccine uptake (23), which require context-informed delivery strategies. Microplanning for HPV vaccine encompasses logistical considerations such as delivery of multi-dose vaccines, reaching out-of-school girls, and alignment with the school calendar, as well as careful navigation of complex sociopolitical settings where sensitization to reproductive health can be delicate (75). For example, Australia, which has one of the highest coverages in the world (70% of 12-17 year-old girls as at 2007 nationwide completely vaccinated with the 3-dose regimen), attributes its success to the publicly funded school-based HPV immunization program (76). High enrollment rate in schools serves as a key facilitator of high coverage, as 98.5% of girls aged 14 are enrolled in schools in Australia (76). In contrast, an estimated 18.6 million girls (23%) aged 6-11 years old are not enrolled in primary schools in sub-Saharan Africa (77). GAVI-eligible countries have proposed many strategies to locate hard-to-reach girls, such as enumeration by community health workers and mapping health facilities (75), but more research is needed to evaluate the currently existing programs and develop reproducible, validated interventions (78).

HPV vaccine introduction efforts must compete for limited financial and human resources, and therefore have faced more challenges than pneumococcal conjugate vaccine, rotavirus and inactivated polio vaccines which can be readily integrated into the existing infant immunization schedules. While low school attendance in some settings limits school-based routine vaccination, most LMICs have well-established infant immunization programs (79, 80). The competition for resources to scale-up HPV vaccine programs will likely worsen in LMICs due to the COVID-19 pandemic (81), as vaccine coverage is expected to decrease even in high-income countries (82), and prevention activities have been disrupted (83). Development of an HPV vaccine that can be safely administered to infants and maintain immunity into adulthood like the Hepatitis B vaccine

would bypass some of the current logistical and financial challenges and expand access and coverage.

Immune correlates of protection against HPV are poorly understood (84, 85), preventing optimization of vaccine dosing schedules, such as through multi-cohort vaccination or reduced-dosing strategies (86, 87). A better understanding of serological correlates of protection can help define vaccine dosage needed for protection (85). In particular, reduced-dose vaccination, both single-dose and extended interval dosing (at least 12 months between the first and the second dose) (86), would have significant programmatic implications and allow increased coverage of vaccination in settings with limited healthcare access, infrastructure, personnel, and financial resources (88, 89). Among women who did not complete the required number of HPV vaccine doses, one dose induced robust immune responses with comparable decreases in precancerous lesions compared to women who received multiple doses (90, 91). Clinical trials to evaluate single-dose HPV vaccine efficacy and the duration of protection are underway to inform decisions about adoption of a one-dose regimen (see NCT03675256, NCT03747770, NCT03728881 on ClinicalTrials.gov) (92).

For all scenarios of expanded HPV vaccine coverage, clear communication addressing vaccine hesitancy and increasing parents', caregivers', and adolescents' acceptance of an HPV vaccine are critical. For example, following media coverage of unconfirmed reports of adverse events in Japan, the Japanese Ministry of Health, Labour and Welfare suspended proactive recommendations for HPV vaccine in June 2013 (93, 94). The HPV vaccination rate among adolescents born in and after 2002 has dropped from about 70% in 2013 to 1% or less in 2019 (94). Upon the launch of a national HPV immunization program in 2012, Colombia had reached first dose coverage of 94.8% among the target population (girls aged 9-17) by 2014 (95). However,

crisis ensued in 2014, during which over 500 girls from a town called Carmen de Bolivar who had received the HPV vaccine months before reported adverse symptoms such as headache, shortness of breath, and fainting, which was covered widely by the media (96). Although epidemiologic evaluation found no association between the HPV vaccine and the adverse symptoms, public confidence in the vaccine decreased and led to discontinuation of school-based programs (95, 97). The 2016 national coverage rates fell to as low as 14% and 5% for the first and second dose, respectively (96). However, with the help of projects geared toward restoring confidence in HPV vaccination, such as a roundtable of stakeholders and experts including the Ministry of Health and universities, and a communication intervention targeting communities with the highest cervical cancer mortality rates, the first dose coverage rose to 34% in 2019 (95). Experiences in Japan and Colombia demonstrate the importance of community acceptance of the HPV vaccine for achieving and maintaining high coverage.

Table 2.4 Priority research questions for primary prevention strategies

1. Do voluntary male circumcision, condoms, smoking cessation, and treatment for bacterial vaginosis reduce persistent HPV infection, and to what extent?
2. How can monitoring and evaluation provide evidence to support best practices for HPV vaccination programs?
3. How can we address vaccine hesitancy and the anti-vaccination movement to increase HPV vaccine coverage?
4. What is the safety, efficacy, durability, and acceptability of an HPV vaccine administered in infancy?
5. What is the efficacy and durability of one-dose HPV vaccine in routine and catch-up vaccination?
6. How can we obtain LMIC context-specific estimates of the impact of prevention strategies and make them more reliable and approachable to policy makers?

2.4.3 *Secondary Prevention*

2.4.3.1 Current State of Science

2.4.3.1.1 Screening of Precancerous Lesions

The WHO's cervical cancer elimination targets are to screen 70% of women with a high-performance test by age 35, and again by age 45 (24). Self-reported lifetime prevalence of cervical cancer screening among women in 55 LMICs was only 43.6%, ranging widely from 0.3%-97.4% (98). A modeling analysis of LMICs predicted that one-lifetime screen could lead to elimination in 96% of LMICs by the end of the century, compared to elimination in 60% of LMICs with HPV vaccine only, and there are still generations of women who will not benefit from the vaccination (26).

Screening for cervical cancer is currently conducted by cytology (Papanicolaou/Pap smear screening), HPV DNA testing, or VIA. VIA is currently the predominant cervical cancer screening method in many LMICs due to its relatively low cost and ease of execution compared to cytology or HPV testing (99). VIA can facilitate same-day screen-and-treat algorithms that minimize loss-to-follow-up when coupled with treatment of detected lesions (100). However, the performance of VIA in detecting HSIL or CIN2-3 varies widely (Table 2.5), as the interpretation of the results is subjective (101). Quality assurance is another challenge, as the number of micro-invasive cancers that are undetected by the screen-and-treat method of VIA and cryotherapy is unknown (101). About 90% of VIA screen-positive women who are treated are unlikely to have pre-malignant cervical lesions, which raises concern for overtreatment (102-105).

Table 2.5 Summary of sensitivity and specificity of cervical cancer screening methods for detecting CIN2-3

Sensitivity (%, 95% CI)	**Specificity (%, 95% CI)**	***Reference***

Cytology		
65.9 (54.9-75.3)*	96.3 (94.7- 97.4)	*(106)*
75.5 (66.6-82.7)†	91.9 (88.4-94.3)	*(107)*
HPV DNA Testing		
88.1(81.4-92.7)	83.7 (74.9-89.8)	*(108)*
88.3 (73.1-95.5)	73.9 (50.7-88.7)	*(108)*
94 (89-97)	88 (84-92)	*(109)*
Visual Inspection with Acetic Acid		
79.2	84.7	*(110)*
82.4 (76.3-87.3)	87.4 (77.1-93.4)	*(104)*
78 (73–83)	88 (85–91)	*(111)*
69 (54–81)	87 (79–92)	*(111)*
Visual Inspection with Acetic Acid and Lugol's Iodine		
89	85	*(104)*
90 (85–94)	83 (79–86)	*(111)*

* Conventional Pap
† Liquid-based cytology
Endpoints are all CIN2-3, reference standard = colposcopy with or without biopsy

While cytology-based screening is used widely in high-income settings, it requires established healthcare infrastructure, repeat client visits to diagnose precancer, training of pathologists and clinicians, and a robust quality assurance program. Cytology-based screening also has lower sensitivity and specificity compared to HPV DNA testing (29). For these reasons, cytology screening is not recommended for scale-up of cervical cancer screening in LMICs (112).

The wide range of sensitivity and specificity of subjective tests such as cytology and VIA leads to variation in the number of women triaged to treatment. For example, the estimates of sensitivity of cervical cytology to detect CIN 2-3 in India, Nicaragua and, Uganda varied between 40.7-73.7% and 21.9-73.6 using VIA in one study (113). The variation in the number of women

triaged to treatment can have significant implications for the risk of overtreatment and already-overburdened health systems in low-resource settings.

HPV DNA testing has superior sensitivity compared to cytology and VIA in detecting CIN2-3 (Table 2.5) and has replaced cytology as a primary screen or is offered as a co-test (14, 114). The test has a high negative predictive value for detecting CIN2-3, which has the advantage of elongating the screening interval to five years for screened negative women compared to three years for cytology (24). However, it also has a low specificity and positive predictive value, which can lead to overtreatment especially among younger women (115).

Large-scale RCTs have demonstrated the efficacy of HPV testing in reducing cervical cancer incidence, and that HPV testing provides 60-70% greater protection against invasive cervical cancer than cytology (116). Despite also demonstrating cost-effectiveness compared to cytology in multiple settings (117-119), HPV testing has been difficult to scale-up in LMICs due to cost (29). However, recently there have been many successful demonstration projects and launch of national scale-up and adoption of HPV testing in Latin America using careHPV (120). Notably, the Ministry of Health of El Salvador has updated its guidelines to recommend HPV testing (121), Guatemala and Honduras are planning to use HPV testing for cervical cancer screening after demonstration projects (120), and Argentina and Mexico have been offering HPV testing in their public health systems for several years (122).

The WHO endorses self-sampled HPV tests as an additional approach to cervical cancer screening for individuals aged 30-60 years (123). In a meta-analysis, sensitivity or specificity for detecting CIN2-3 was not statistically different between self-sampled and clinician-sampled HPV tests based on polymerase chain reaction (PCR) assay (124). However, self-collected hrHPV assays based on signal amplification (careHPV) had lower sensitivity (pooled ratio: 0.85, 95% CI:

0.80-0.89) and lower specificity (pooled ratio: 0.96, 95% CI: 0.93-0.98) to exclude CIN2-3 compared to the clinician-collected samples. Both self-sampled and clinician-sampled HPV testing with a PCR assay have better sensitivity and can allow for longer screening intervals than cytology-based screening programs. Any potential loss in sensitivity is likely outweighed by increased screening uptake (125). For example, a 15-year cohort study in rural China found that while HPV testing with self-sampling was less sensitive than physician-sampling, they performed equally on screening efficiency and predicting cumulative cases, and were as sensitive as high-quality cytology in detecting cumulative CIN2-3 cases (126).

Self-sampling as an alternative method of screening can overcome barriers such as access to the health facility and fear associated with pelvic examination, opening new possibilities of reaching under-screened women (127). Acceptability of self-sampling has been reported across cultures and resource-settings (128-132). HPV self-sampling has the potential to make HPV testing more affordable and cost-effective by increasing screening coverage (18). One meta-analysis found women who were offered the option of self-sampling were twice as likely to participate in cervical cancer screening services than those who were offered cytology, VIA, or clinician-collected HPV testing (16). The difference was greater when the sampling kits were sent directly to women's' homes or offered door-to-door by a health worker (16). Self-sampling has been incorporated into the national screening guidelines in high income countries such as the Netherlands, Australia, and Finland (127). Among LMICs, self-sampling was successfully scaled-up in Jujuy province in Argentina (133). Additional research is needed on best practices for self-sampling follow up, such as community collection of specimens, delivery of results, and linkage to treatment.

2.4.3.1.2 Treatment of Precancerous Lesions

The international consensus is to treat CIN2-3/HSIL, except during pregnancy, by ablation or excision (134). Cryotherapy and thermal ablation (the latter also known as cold coagulation or thermocoagulation) are the two most commonly used ablative treatments, and LEEP and cold knife conization are commonly used excisional treatments. Meta-analyses that compared the efficacy of cryotherapy, thermal ablation, LEEP, and cold knife conization are summarized in Table 2.6.

Table 2.6 Summary of efficacy of LEEP, cold knife conization, cryotherapy, and thermal ablation

Method	Endpoint	Pooled cure proportions (%, 95% CI)	*Reference*
LEEP			
	CIN2-3 negative after 12 months	94.7 (96.3-93.1)	*(135)*
	HSIL negative after 12 months follow up	92.0 (N/A)	*(136)*
Cold Knife Conization			
	CIN2-3 negative after 12 months	98.6 (99.2-98.0)	*(137)*
Cryotherapy			
	CIN2-3 negative after 6 months in LMICs	82.6 (77.4–87.3)	*(138)*
	CIN2-3 negative at follow up (duration unspecified)	86.0 (83.0-89.0)	*(139)*
	CIN2-3 negative after 12 months	94.7 (96.1-93.2)	*(137)*
	HSIL negative after 12 months follow up	80.9 (N/A)	*(136)*
Thermal Ablation			
	CIN2-3 negative after 6+ months	91.6 (88.2-94.5)	*(138)*
	CIN2-3 negative after 6+ months (LMICs only)	82.4 (75.4-88.6)	*(138)*
	CIN2-3 negative after 4-6 months	93.6 (90.8- 96.0)	*(140)*

The cervical lesion must be small enough to be covered by the equipment and fully visible with no extension into the endocervix or onto the vaginal wall to be eligible for ablative therapy (134,

141). An estimated 50-80% of cervical lesions found during screening are eligible for ablative therapy (141). In meta-analyses, 81-95% of the women treated with cryotherapy were negative for CIN2-3 12 months after treatment (Table 2.6) (138, 142). Similarly, 82-94% of the women treated with thermal ablation were negative for CIN2-3 after treatment; however, the duration of post-treatment follow-up was shorter relative to studies on cryotherapy. In LMICs, the efficacy of cryotherapy and thermal ablation was 83% and 82%, respectively (137).

WHO has recommended thermal ablation for women who have histologically confirmed CIN2-3 or have screened positive in screen-and-treat strategies because of its advantages for implementation in LMICs (141). The traditional gas-based cryotherapy is difficult to implement because refrigerant gas, such as CO_2, is expensive and difficult to procure and transport (141). Thermal ablation devices can be battery-operated, are lightweight (2-5 kg), and have a shorter treatment time (141). The use of thermal ablation in low-resource settings has shown to be effective and acceptable (143). In Zambia, thermal ablation (44%), cryotherapy (48%), and LEEP (47%) achieved similar hrHPV clearance six months after treatment (144). It should be noted that up to 54% of the participants in each study arm were seropositive for HIV, and women living with HIV have a higher risk for treatment failure of precancerous lesions (144). The prevalence of treatment failure is unknown in this study, as no histological studies were performed prior to treatment. There are several ongoing and completed clinical trials on development and evaluation of the use of thermal ablation devices for LMIC settings (see NCT02956239, NCT03429582, NCT03510273 on ClinicalTrials.gov) (92).

LEEP is recommended for treating CIN2-3 if there is a medical contraindication for ablative therapy (134) or if the lesion extends into the endocervical canal (145). LEEP is often preferred over ablative techniques in high-resource settings because of its benefit of

histopathologic diagnosis (145). Two meta-analyses found that 92-95% of the women treated with LEEP and 99% of the women treated with cold knife conization were free of CIN2-3 or HSIL twelve months post-treatment (Table 2.6) (136, 137). CIN2-3 persistence (RR: 0.87, 95% CI: 0.76-0.99) and recurrence (RR: 0.91, 95% CI: 0.84-0.99) were lower with LEEP than with cryotherapy (136).

The complication rates differ by the treatment technique. The most common adverse events associated with treatment are bleeding and infection at the cervix, which occur in <5% of treated women (139, 140, 146-148). Relative to LEEP and cold knife conization, cryotherapy and thermal ablation are cheaper, safer, and simpler to use, which makes scale-up and task-shifting more feasible, particularly in LMICs (136, 137, 149). For example, it is easier to train nurses or lay health workers to perform cryotherapy than LEEP or cold knife conization, because of the lower risk of serious complications (142). In a meta-analysis, women who previously underwent cold knife conization had the highest risk of subsequent perinatal mortality (RR: 2.87, 95% CI: 1.42-5.81) and preterm delivery at less than 32-34 weeks (RR: 2.78, 95% CI: 1.72-4.51), compared to the women who did not receive this procedure (149). Thermal ablation was not included in the comparisons of complications.

2.4.3.2 Priority Research Questions for Secondary Prevention Strategies

2.4.3.2.1 Screening and Triaging Precancerous Lesions

2.4.3.2.1.1 HPV DNA-based Testing

Point-of-care cervical cancer screening tests that facilitate same-day treatment would minimize loss to follow-up and improve continuity of care. While careHPV meets some of the REASSURED criteria (real-time connectivity, ease of specimen collection, affordable, sensitive, specific, user-friendly, rapid, equipment-free, delivered) (150, 151), and has a point-of-care platform (152), it

requires batch testing (121), which enables same-day treatment only under special circumstances such as health campaigns, and the sensitivity is significantly lower with self-sampling (124). In addition, the final cost after implementation has not been consistently affordable. For example, per-test cost estimate was reported as US$42 in a pilot careHPV-based screening program in Myanmar, despite some economic analysis based in low-income countries estimated as low as $US5 (153). Although PCR-based point-of-care tests are currently available (e.g., GeneXpert [Cepheid, Sunnyvale, CA]) and graded pricing exists for LMICs, it is still cost-prohibitive and the required infrastructure is a barrier (154). Real-time PCR-based tests such as AmpFire, [Atila BioSystems, Inc., Mountain View, CA]) (155) and Q-POC (QuantuMDx [Newcastle upon Tyne, UK]) are being evaluated and developed, which will have important implications for scaling up self-sampling. More innovation is needed to make more point-of-care tests and tools affordable and widely available.

Clinician- and self-sampled first-void urine is also being evaluated as a viable biomarker for detecting cervical precancers (156). In an RCT among a Pacific Island population, HPV detection (using Roche Cobas 4800 system, Roche Molecular Systems, Inc) in self-collected urine demonstrated moderate agreement with clinician-collected cervical samples (Kappa=0.55, 95% CI: 0.43-0.66), with agreement for detection of hrHPV among women ages 40 and older being higher (Kappa=0.65, 95%CI: 0.46-0.85) than that of women ages 20-39 (Kappa=0.45, 95% CI: 0.25-0.64) (157). Formal evaluation of biomarker-based triage is needed in LMICs (158).

2.4.3.2.1.2 HPV-associated Oncogenesis Biomarkers

Strategies based on identifying biomarkers of HPV-associated oncogenesis are being developed to improve the precision of current screening methods and prevent the physical, psychological, and financial harms of overtreatment (159). Some examples of biomarkers include, but are not limited

to, p16^{ink4a} and E6/E7 oncoproteins (134, 159-161). Tests for E6/E7 oncoproteins present a promising option for triaging screened positive women given high positive predictive value and limited laboratory equipment (158). However, more than 60% of HPV positive women were also E6/E7 mRNA positive (162), which would present a challenge in identifying women with precancerous lesions. A systematic review of three types of HPV E6/E7 mRNA tests (Aptima, Quantivirus, and PreTect Proofer) found that while the tests have diagnostic relevance to detect CIN2-3, the higher specificity of some tests is due to the limited number of HPV types it detects (163). In a 10-year prospective cohort study in China, HPV methylation and co-testing with E6 oncoprotein showed superior area under curve values compared to cytology, viral load, and VIA (164). However, it also faces challenges of detecting only two HPV types.

2.4.3.2.1.3 Optical Techniques

Several optical techniques are in development, including spectroscopy and other imaging techniques (165). Such techniques have the potential to reduce the number of required visits and to save time and cost, which can be helpful especially where infrastructure for laboratories is sparse (165). For example, redesigned portable colposcopes have a high agreement with standard-of-care colposcopy for pathology (see NCT00602368 as an example) (92, 166-168). A smartphone-based colposcope can enhance VIA by taking digital images of the cervix and uploading them to an online repository for remote decision support (166). Additionally, automated visual evaluation of images with machine learning, trained using >60,000 images of the cervix from a Costa Rican tumor registry has shown greater accuracy than traditional VIA or cytology in detecting HSIL (169, 170). This algorithm can increase screening capacity and minimize subjectivity (171). Devices which could be inserted by the women herself for remote visualization of the cervix are also being developed and tested (172). However, a large (n=9406) ongoing study in Nigeria noted

that the squamocolumnar junction where cancers arise was not fully visible for almost 64.6% of women by age 49 using enhanced visual assessment (MobileODT, Israel) (173). Challenges of adequate visualization of the cervix have pertinent implications for both ablative treatments and visual screening or triage efforts (173).

2.4.3.2.2 Treating Precancerous Lesions

Identification of women with a precancerous lesion necessitates appropriate linkage to care and treatment to prevent cancer (174). While thermal ablation has been widely recommended and is being adopted in low-resource settings, further data is needed for it to be the new standard for treating patients with precancerous lesions (175).

To optimize screen-and-treat methods, portable treatment tools such as battery-operated cryotherapy instruments are under development (see NCT03084081) (92, 176). There are also new, portable, solar-powered (141), and battery-powered thermal ablation tools, which can be adapted to low-resource settings without stable electricity (see NCT02956239, NCT03429582) (92, 141, 176).

Photodynamic therapy has shown promising results in the treatment of CIN (177, 178). This novel technology uses photosensitizers to accumulate selectively in pathologic tissue and destroy tumor cells by inducing necrosis (177, 179). Such technology has the potential to be a tissue-preserving treatment alternative and minimize cost (178).

The development of therapeutic vaccines against hrHPV could help women who are already infected by stopping progression, triggering regression of lesions, and preventing recurrence of disease (180). Currently, there is no therapeutic HPV vaccine approved by the US Food and Drug Administration (181). While the use of therapeutic vaccines to treat invasive cervical cancer or other HPV-related cancers is beyond the scope of this review, many of the

completed and currently ongoing trials (see NCT02481414, NCT00054041, NCT01022346, NCT03870113 as examples, not a comprehensive list) use CIN and/or HSIL as the treatment target. Smalley Rumfield *et al.* recently conducted a review of peptide, protein, viral vector, bacterial vector, cell, DNA, and RNA-based therapeutic vaccines as well as multi-platform and combination therapies, which demonstrate diverse potential therapies that can be useful in LMIC settings, while presenting new and different challenges (181).

In summary, the priority for secondary prevention is the optimization and scale-up of single-visit screen-and-treat modalities. Self-sampling for HPV testing offers several advantages to optimize screening coverage. Subsequent molecular oncogenic evaluation has the potential to detect lesions that are most likely to progress to cancer while reducing overtreatment. Further development is needed to simplify the testing procedure and reduce costs. The feasibility of integrating cervical cancer screening into the existing healthcare system is being explored (182, 183). For example, delivery models that leverage established HIV care infrastructure, such as staff and coordination between the clinics, can screen-and-treat women for cervical cancer to maximize efficiency (184).

Table 2.7 Priority research questions for secondary prevention strategies

1. Is the scale-up of current point-of-care HPV tests and HPV self-sampling effective, feasible, and cost-effective, and how can delivery models adapt sustainably to incorporate them?
2. What is the most efficient and safe model of task-shifting for providing cervical cancer screening, cervical biopsy and treatment of pre-invasive disease?
3. What is the optimal triage algorithm and follow-up for hrHPV positive women and those without visible precancerous lesions when biopsy is unavailable?
4. Are there reliable biomarkers to predict persistent infection with hrHPV?
5. Would self-visualization of the cervix as a screening tool be feasible, reliable and acceptable?

6. What are the strategies for surveillance of HPV positive women with negative oncogenic biomarkers?

2.4.4 *Cervical Cancer Elimination Among Women Living with HIV*

2.4.4.1 Current State of Science

Compared to women without HIV, women living with HIV have at least two-fold higher HPV prevalence (185, 186), and experience greater persistence of HPV infection (187, 188), and more rapid progression of precancerous lesions to HPV-associated cancers (189-192). A meta-analysis showed an estimated 33,999 new cases of cervical cancer occurred among women living with HIV in 2018, corresponding to 5.8% of cases (193). In this study, women living with HIV had overall pooled relative risk of 6.07 (95% CI: 4.40-8.37) of developing cervical cancer compared to their counterparts without HIV. Women living with HIV are significantly more likely to have multiple hrHPV types detected in normal cytology, HSIL, and cervical cancer cells or tissue (194, 195). When markedly immune-suppressed (i.e., CD4+ cell count <200 cells/ul), the risk for cervical cancer is eight-fold higher in women living with HIV compared to HIV-negative women (196). The risk of cervical cancer among women living with HIV can be mitigated to some extent with sustained antiretroviral therapy (197, 198). In a population-level analysis in Botswana, women living with HIV on antiretroviral therapy had a lower prevalence of hrHPV than those not on antiretroviral therapy (RR: 0.83, 95% CI: 0.70-0.99) (198). However, in settings with low primary and secondary prevention coverage, cervical cancer incidence and mortality among women living with HIV are high even when antiretroviral therapy is available (199). This is thought to be due to prolonged survival of effectively treated women (198).

HPV vaccines elicit high seroconversion rates and type-specific antibody levels among adolescent girls and young women living with HIV (200-209). CD4+ cell count at vaccination is positively correlated with seroconversion and immune response (202, 205-207). Although

seropositivity and antibody levels decline more rapidly among vaccinated women living with HIV compared to vaccinated women without HIV, they are significantly higher compared to unvaccinated women living with HIV and naturally infected women without HIV (201, 204-206). However, as the correlate of protection against HPV is unknown, the relatively lower antibody level does not necessarily mean lower vaccine efficacy. The bivalent, quadrivalent, and nonavalent vaccines are safe for women living with HIV, as all three are virus-like particle-based vaccines (201, 210, 211).

The endpoints in most vaccine trials in HIV-positive populations are HPV seroconversion rates and immunogenicity. Studies using clinical endpoints (i.e., HPV infections and cervical abnormalities) as the outcome are still needed. The duration of protection in vaccinated adolescent girls and young women living with HIV is unknown. Extending the age of vaccination to include infants and older women could accelerate cervical cancer elimination in HIV-positive populations, although the efficiency and cost-effectiveness of such strategies depend on the prevalence of HPV infection at older ages and the duration of protection afforded by the vaccines. Context-specific modeling work would be valuable to evaluate these outcomes and inform the implementation of effective vaccination programs in settings with high HIV prevalence. In addition, the vaccine efficacy and durability of a reduced dose schedule (two or one doses) among adolescents and young adults living with HIV need to be determined. The OPTIMO Trial, which aims to see if fewer doses can be used for children/adolescents living with HIV, will begin soon (see NCT04265950) (92).

Prevention strategies such as VMMC can help prevent both HIV and reduce cases of cervical cancer. A modeling study of HIV prevention and HPV control in Tanzania showed that

VMMC will have lowered cervical cancer incidence and mortality rates by 28% and 26%, respectively (212).

The American Society for Clinical Oncology and the WHO recommend screening sexually active women living with HIV for HPV or cervical abnormalities as soon as they are diagnosed with HIV and rescreening within three years if they are HPV-negative and free of cervical lesions (134). In the United States, women living with HIV below age 30 are recommended to receive Pap screening within one year of onset of sexual activity regardless of the mode of HIV transmission and no later than age 21 (213). One study in the United States found that the risk of cervical cancer among regularly-screened women living with HIV was similar to HIV-negative women, highlighting the importance of screening in this population (213).

HIV presents challenges to accurate screening for women. There are more false-positive rates with VIA among women living with HIV than women without HIV (214, 215), likely due to the higher rates of cervical inflammation (216, 217). While HPV testing is an effective screening method among women living with HIV, it could lead to overestimates of cervical lesion prevalence and overtreatment (218).

Treatment failure and recurrence is more common among women living with HIV than in the general population (219). A meta-analysis found that treatment failure was twice as common among women living with HIV as among HIV-negative women (pooled OR: 2.7, 95%CI: 2.0–3.5) (219). Women living with HIV in Sweden were five times more likely to experience recurrence than HIV-negative women (Hazard Ratio: 5.0 [95% CI: 2.1-11.6]) (220). In a study Kenya, women living with HIV whose high-grade lesions were treated with cryotherapy experienced a significantly higher rate of recurrence than those treated with LEEP over 24 months (221). More

research is needed to determine the most appropriate treatment method for precancerous lesions in this population.

Cervical cancer prevention services can be integrated into existing health infrastructure as women already engage in health care throughout their lifetime (e.g., antenatal care, well-child visits, and family planning. Integration of cervical cancer screening with HIV care is acceptable to women living with HIV and feasible on a small scale, however, more data are needed to determine scalability and sustainability (183).

Table 2.8 Priority research questions for cervical cancer elimination among women living with HIV

1. What is the duration of protection in vaccinated adolescent girls and young women living with HIV? 2. What is the clinical efficacy of a reduced HPV vaccine dose (e.g., two-dose or single-dose) schedule in women living with HIV? 3. What are innovative ways of effectively integrating cervical cancer prevention and treatment into HIV care? 4. What is the most optimal treatment method of precancerous lesions among women living with HIV? 5. What are the optimal screening modalities and intervals for women living with HIV on antiretroviral therapy?

2.5 DISCUSSION

Global cervical cancer elimination is achievable with an increase in HPV vaccine uptake and coverage, implementation of screening and treatment strategies and emerging technologies, and development of innovative delivery approaches. Our scoping review and gap analysis designed a roadmap that prioritizes expanding HPV vaccination and collaborating with global organizations to allocate resources needed to eliminate cervical cancer. The focus of the concerted effort must

be 1) scaling up evidence-based interventions, including the application of implementation science and measurement of population-level impact, and 2) filling the gaps through research and harnessing emerging innovations that are simple, effective and affordable for all settings (Table 2.9)

Table 2.9 Innovative technologies and approaches that may be appropriate for comprehensive prevention packages

Priorities	**Recommended intervention**	**Rationale**
Primary prevention		
Increase access to and coverage of HPV vaccine by the sustainable implementation of HPV immunization programs	Reduce vaccination dosage	Evidence that single-dose is as protective as multi-dose regimen are emerging (187, 222, 223). Single-dose regimen can be as cost-effective as the two-dose regimen, if high coverage can be achieved in low-resource settings (224, 225).
Secondary prevention		
Maximize early detection of precancers and micro-invasive disease without the harms of overtreatment by increasing cervical cancer screening coverage with HPV testing and treatment starting at age 30 for at least 35 years for women without HIV	HPV testing, focusing on self-sampling	HPV DNA testing has superior sensitivity compared to cytology and VIA in detecting CIN2-3 (14, 15, 224). Self-sampling can overcome individual and structural level barriers to traditional screening methods (226, 227). It has demonstrated similar accuracy as clinician-collected samples (124, 228), and is accepted across cultures and resource-settings (229).
	Triage HPV positive women with enhanced visual assessment or a low-cost test for oncogenesis markers	The triage methods used in high-resource settings such as cytology, colposcopy, and HPV genotyping are not ideal for low-resource settings because of their need for multiple visits, equipment, and personnel (18, 29). Innovations such as a portable colposcope, enhanced visual assessment that utilizes mHealth and artificial intelligence, and low-cost rapid biomarker tests can accurately stratify women by the risk of progression to invasive cancer and make the process more efficient (158).
	Treat eligible precancerous lesions with thermal ablation	Thermal ablation has shown comparable efficacy to cryotherapy in treating ablation-eligible CIN2-3 in a shorter amount of time (138), and it is easier to implement in LMICs than cryotherapy because it does not need CO_2 (141) and devices are battery-operated and portable.

Lessons can be learned from the global response to HIV, which built the infrastructure that allowed for the scale-up of HIV prevention and treatment services. Since the global initiative to eliminate mother-to-child transmission of HIV was announced in 2011 (230), 80% of expecting mothers with HIV received antiretroviral therapy (ART) as part of their antenatal care (compared to 17% in 2010), and transmission dropped below 5% in several high HIV burden countries in sub-Saharan Africa (231). The Joint United Nations Programme on HIV/AIDS (UNAIDS) recommended a HIV prevention “package" that combines multiple types of interventions targeting HIV transmission and treatment at multiple levels to address the various interacting risk factors of HIV (230, 232). Similar strategies can be used to combine contextually appropriate cervical cancer prevention and treatment services. Scale-up of programs through community-based clinical trials may be more efficient and increase uptake of the interventions.

Following the framework of the logic model, key domestic and global stakeholders should work together to prioritize funding to procure vaccines and strengthen healthcare systems. Healthcare practitioners and communities should be engaged at every step of discussion and programmatic planning in order to build capacity and ensure successful implementation (233). Global advocacy and partnership are needed to continue the ongoing support for HPV vaccine coverage and increased access to low-cost screening and treatment tools. For both primary and secondary prevention strategies, access to and coverage of efficacious interventions over a woman’s lifetime must be prioritized. The current disparities in morbidity and mortality are likely to worsen as additional innovations emerge and are adopted more readily in high-resource than in low-resource settings.

While reviewing tertiary prevention strategies (e.g., treatment of invasive cervical cancer) is beyond the scope of this article, their importance in low-resource settings cannot be overlooked.

Screening implies the capacity and ethical responsibility for health agencies to make the treatment of cervical cancer available. The regions with the highest prevalence of cervical cancer have the lowest availability of skilled personnel and treatment facilities for diagnosis, surgery, chemotherapy and radiation (234, 235). The shortage of radiotherapy equipment and gynecological oncologists is a barrier to care for women with invasive cervical cancer in LMICs (235). Twenty-nine countries in Africa do not have a radiation unit (236). Gynecological oncologists are often limited to tertiary care hospitals, and women with invasive cancer have to travel long distances or wait for a long duration to access treatment (237). Moreover, an extreme shortage of clinical oncologists, defined as more than 1,000 incident cancers per clinical oncologist, was reported in 25 countries in Africa and two countries in Asia (237). These regions have some of the highest burden of cancer in the world (3). Decentralization of services, where a local expert at the primary care center is supervised and mentored by a specialist, can increase access to specialty care for women living in rural or remote areas (238). Such a model can also serve as a community-based hub for dissemination of vaccines and screening efforts such as HPV self-sampling, thereby increasing equitable access to cancer care at all levels of prevention.

The limitations of this review result from its narrative approach. Compared to systematic reviews or meta-analyses, narrative reviews are characterized by subjective study selection. In addition, due to the broad nature of the scoping review, we did not compile an exhaustive list of potentially relevant, innovative strategies and technologies. However, this paper provides an overview of the current landscape of science around cervical cancer elimination and guides the formulation of pertinent questions that deserve further exploration.

In conclusion, the effort to eliminate cervical cancer must focus on sustainable and continuous access to prevention strategies. Large scale demonstration projects have been

successfully implemented across resource settings for HPV vaccination and screen-and-treat using HPV testing and thermal ablation. Building on the lessons learned, we propose a demonstration project that combines the above-recommended strategies and provides a comprehensive cervical cancer prevention continuum to show that cervical cancer elimination can be achieved at the local level within LMICs. With a strong evidence base and effective implementation established, strategies can be scaled up more broadly. By strategically and skillfully putting the scientific advances to practice, global cervical cancer elimination can be achieved.

Chapter 3. COST OF COMMUNITY-BASED HPV SELF-SAMPLING IN PERU: A MICRO-COSTING STUDY

3.1 ABSTRACT

Background: Cost is an essential component of economic evaluations and a determinant of implementation feasibility of HPV self-sampling programs. Yet, reliable evidence that can be used in low-income and middle-income countries, where cervical cancer burden is highest, remains scarce. Here, we estimate the total and unit costs associated with the Hope Project, a community-based HPV self-sampling social entrepreneurship program in the peri-urban area of Lima, Peru.

Methods: We conducted a micro-costing analysis from the program perspective to determine the unit costs of: (1) recruitment and training of community leaders (known as Hope Ladies); (2) Hope Ladies distributing HPV self-sampling kits (named *care*HPV) in their communities; and (3) Hope Ladies linking screened women with appropriate follow-up care. A procedural manual was used to identify the program's activities. A structured questionnaire was administered, and in-depth interviews were conducted with three program administrators to estimate the resource use for each activity and time associated with intervention delivery. Laboratory materials (disposable and durable) and equipment were also costed. We obtained unit costs for each input previously identified from program budgets and expenditure reports from Nov 1, 2018, to March 30, 2020.

Results: The annual cost per community leader recruited and trained was $147.51 (2018 USD); cost per HPV self-sampling kit distributed was $45.39. The cost per HPV-positive woman identified was $378.14; and the cost per woman who received the intervention was $55.64. Personnel and laboratory costs represented 56.1% and 24.7% of programmatic costs, respectively. During the study period (Nov 1, 2018, to March 30, 2020), the program recruited and trained 62

Hope Ladies, who distributed 4882 HPV self-sampling kits to women in their communities. Of the screened women, 586 (12%) tested positive for HPV.

Conclusion: Community-based HPV self-sampling appears to be a feasible way to improve cervical cancer screening coverage. These findings can be used as the basis for economic evaluations, such as a cost-effectiveness analysis, or to model the scaling of the intervention.

Abstract presented at the Consortium of Universities for Global Health Conference virtually, March 12-14, 2021 and published in the Lancet Global Health. 2021;9:S12. Shin MB, Fiestas JL, Saldarriaga EM, Barnabas RV, Gimbel S, Garcia PJ. Cost of community-based human papillomavirus self-sampling in Peru: a micro-costing study.

3.2 INTRODUCTION

Cervical cancer is the fourth most common cause of cancer incidence and mortality in women worldwide, with an estimated 604,000 cases and 342,000 deaths in 2020 (21). Nearly 90% of the new cases and deaths occur in LMICs (239). To achieve the WHO's 2018 call for global cervical cancer elimination (7), high coverage cervical cancer screening of women in LMICs will be essential. Globally, approximately 20% of women in LMICs have ever been screened compared to 60% in high-income countries (8), far from achieving the WHO's target of 70% twice-lifetime screening of women ages 35-45 and 90% treatment of cervical cancer and precancer by 2030 (9).

In Peru, cervical cancer is the leading cause of cancer deaths in women aged 15-44 (240). The age-standardized incidence rate in Peru is 23.2 per 100,000 women per year, compared to the world average of 13.1 per 100,000 women (240). Although Peruvian women can receive a Pap test (also known as cytology) free of charge at public health hospitals (241), multiple barriers toward achieving high-quality cytology programs have been identified. These include an unequal regional concentration of lab facilities and clinics, inconsistency of procedures, women's ability to pay, distance, fear of the gynecological examination, and shame (242-245). According to the Peruvian Demographic and Family Health Survey from 2015 to 2017, only 52.4% of women aged over 30 reported having had a Pap test in the last two years (246).

The WHO recommends HPV self-sampling as an approach to increase screening uptake for women aged 30-60 years (17). HPV self-sampling is an alternative strategy that can overcome barriers to screening because additional providers, facilities, and visits are not required for the initial part of the screening. A meta-analysis of HPV self-sampling across resource settings, ethnicities and countries, found greater screening uptake among HPV self-sampling participants

than those who received Pap test, visual inspection with acetic acid (VIA), or clinician-collected HPV testing (16).

The Hope Project is a social entrepreneurship program that was initially started by the Universidad Peruana Cayetano Heredia in 2015 as a pilot project to address the barriers to screening with HPV self-sampling (247). The program offers HPV self-sampling kits (*care*HPV) to high-income women (commercial component) at a higher price point to create a sustainable platform to offer subsidized testing to women with fewer resources (social component). The commercial component targets women of higher socioeconomic status living in the metropolitan area of Lima, who can purchase the HPV self-sampling kits online for 150 Peruvian Soles (PEN), equivalent to 46 US Dollars (USD) in 2018. Each kit contains a cytobrush, a collection vial, and a simple instruction on how to self-sample (Figure 3.1). In the social component, the same kit is offered door to door for 10 PEN (~3 USD) by volunteer women (known as Hope Ladies) from socioeconomically disadvantaged communities, who are trained to promote cervical cancer screening through HPV self-sampling. The *care*HPV test was specifically developed to lower the cost of HPV testing in low-resource settings (248). During the program feasibility pilot, 59 women were trained to distribute self-sampling kits, and 2,090 community women participated in HPV self-sampling (249).

Figure 3.1 HPV self-sampling kits sold by the Hope Project

HPV self-sampling has shown variable size and direction of effect in improving screening uptake, highlighting the importance of cost-effectiveness in local contexts, especially in LMICs, where the screening coverage of effective algorithms is low (16). Cost is a critical component of determining feasibility and adoption (20), yet, economic evaluation of HPV self-sampling in LMICs is scarce (250). Micro-costing a real-world implementation scenario like the Hope Project can address the evidence gap and facilitate future economic evaluations such as budget impact and cost-effectiveness analysis and inform the scale-up and integration of HPV self-sampling into the public health system. Therefore, we conducted this study to estimate the total and unit costs associated with the social component of the Hope Project that can be used to project impact at larger scale.

3.3 Methods

3.3.1 *Study Setting*

The social component of the Hope Project was initiated in 2015 in a socioeconomically disadvantaged peri-urban area called Ventanilla district in the Callao region of Peru as a pilot to

evaluate feasibility and acceptability of HPV self-sampling promoted by women from the community. After a successful pilot (251), the program was officially implemented in two additional neighboring districts called “Mi Perú” and “Pachacútec” in November 2018 (Figure 3.2).

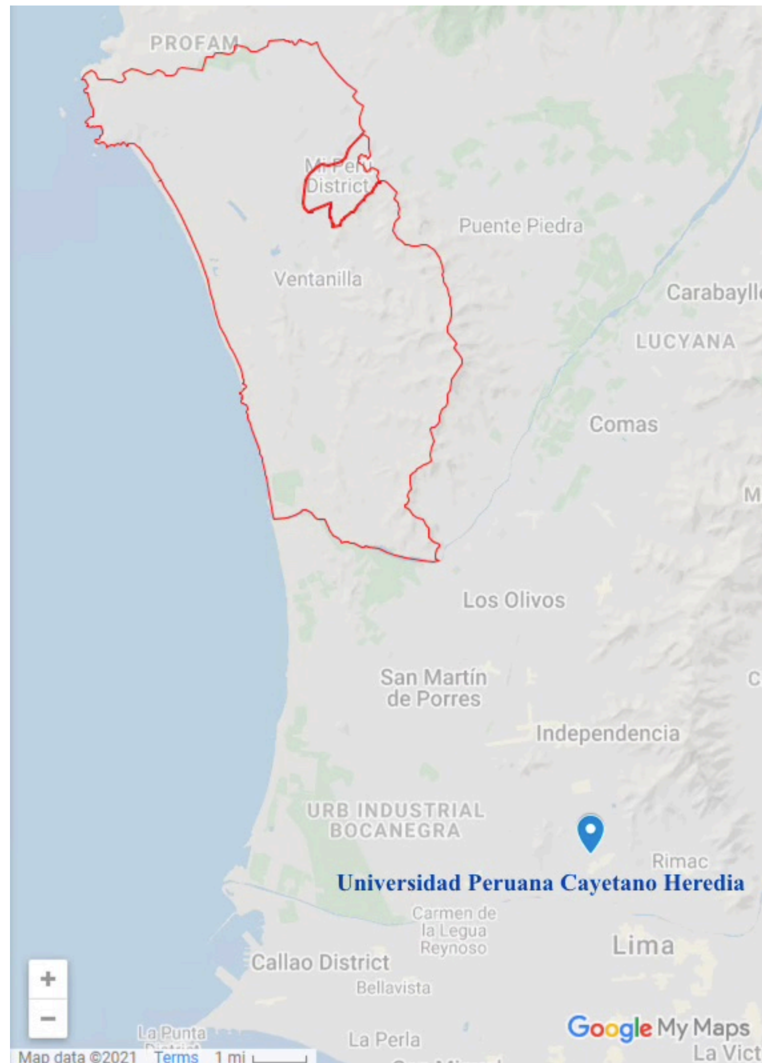


Figure 3.2 Map of the catchment area

In the Hope Project, the Hope Ladies raise awareness about cervical cancer, HPV self-sampling and guide women through the screening pathway in their communities. The screening pathway consists of detecting HPV infection by HPV testing, participants receiving their results via text messages, and follow-up of HPV-positive women in public health clinics (usually with VIA) to

detect precancerous or cancerous lesions (Figure 3.3). Participating women who do not have HPV infection are advised to follow up in five years, and HPV-positive women without lesions are advised to follow up in one year. The Hope Ladies promote HPV self-sampling and sell it to women in their communities door-to-door at a significantly subsidized price of 10 PEN (~3 USD). They make a small profit of 5 PEN (~1.50 USD) per HPV self-sampling kit distributed, which serves as an incentive for wide dissemination. The Hope Ladies pick up the samples from the participants and bring them to a central location, which are then transferred to the laboratory once a week. The test results are sent to women via short message service within one week of the testing and remain available on a secure website for their reference. The Hope Ladies counsel women through the full screening process by raising community awareness, promoting stigma reduction, distributing kits, counseling about the test results, and linking women to care with appropriate providers and public health clinics that provide follow-up and treatment as needed. The micro-costing protocol was approved by the University of Washington Human Subjects Division and the program administrators who participated in in-depth interviews provided oral informed consent.

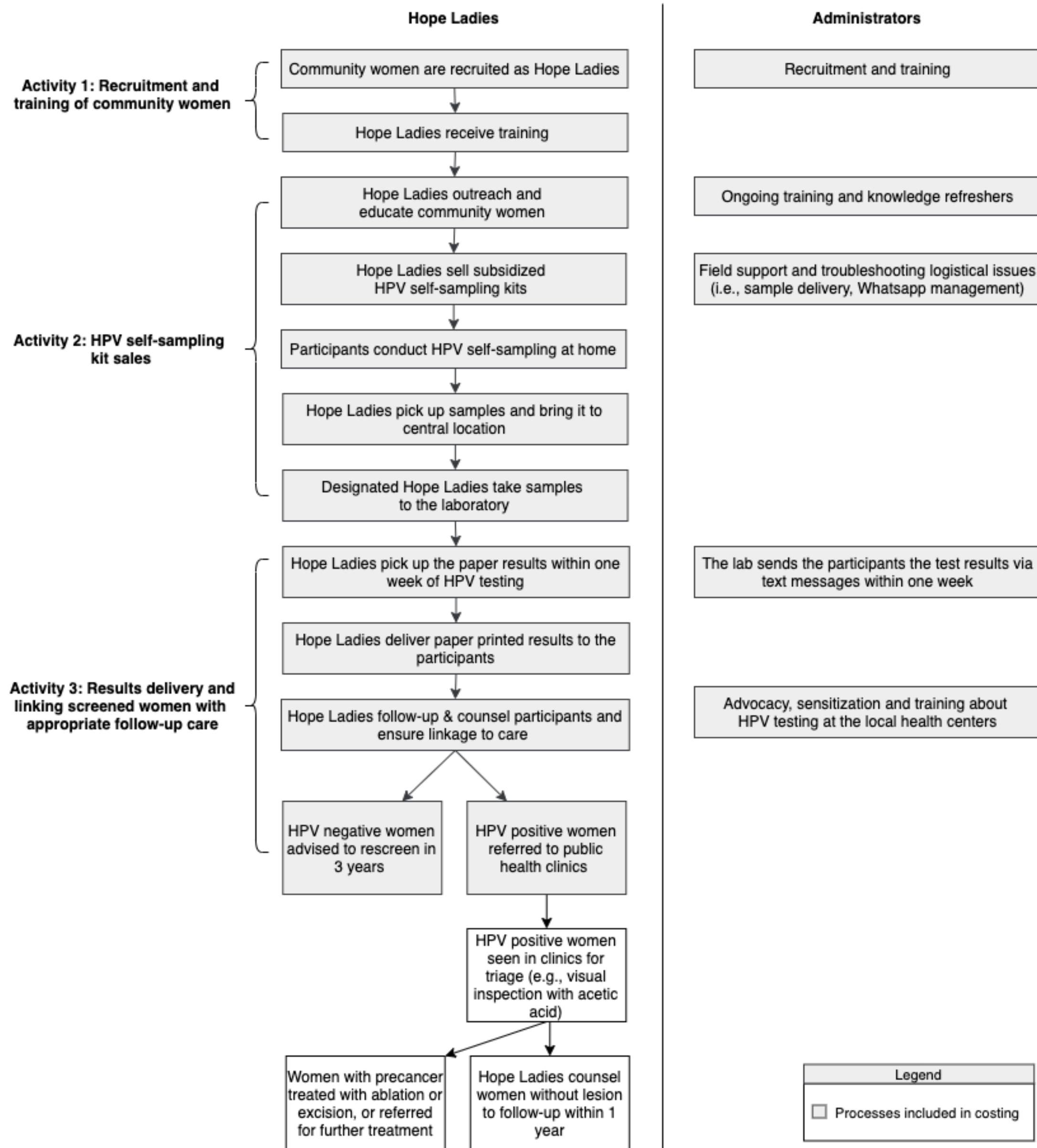


Figure 3.3 Hope Project screening pathway

3.3.2 *Costs*

We estimated the incremental economic cost of HPV self-sampling from the provider perspective, guided by the principles of the Global Health Cost Consortium Reference Case (252). The costing source was the Hope Project, which was the only provider considered for the analysis. We used

three forms of data: (1) program expense report, (2) in-depth interview with three program administrators, and (3) program procedural manual that described its activities and processes.

We considered three program activities: (1) recruitment and training of the Hope Ladies; (2) Hope Ladies offering HPV self-sampling kits (*care*HPV) in their communities; and (3) Hope Ladies linking screened women with appropriate follow-up care. Due to the COVID-19 pandemic, we conducted in-depth interviews with the three program administrators via Zoom instead of a time-and-motion study to enumerate the materials and time spent on each activity.

We categorized costs as either fixed or variable costs. Costs were considered fixed if the amount of the inputs used stayed constant regardless of the program output over one year. Variable costs were defined as those directly related to the program output. We estimated the financial cost (e.g., as implemented cost) and the economic cost for both fixed and variable costs. We followed the Global Health Costing Consortium's definition of financial costs, which were financial outlays for goods and services needed to carry out the Hope Project (252). Economic costs were defined as the full value of all resources utilized in performing the activities. The costing data was collected in local currency units (PEN). We applied Gross Domestic Product deflators to adjust all costs to 2018 and converted them to US Dollars using the 2018 average exchange rate (1 USD ~ 3.29 PEN) (253). We used Excel 2018 (Microsoft, Redmond, USA) for our analysis. The input category definitions and the Excel file used for the analysis are available in the supplementary material.

Fixed costs consisted of six mutually exclusive input categories: start-up (microplanning and training), supervision and administration, overhead, capital and personnel costs associated with microplanning, training, and supervision. The first kit sale was made by a Hope Lady in March 2019, hence, we considered the start-up period to be November 2018 to March 2019. The start-up and capital costs were annualized over the expected useful life of the goods, which were

assumed to be five years or less using 3% discount rate. We allocated costs associated with the building and the laboratory facilities based on the monthly budget projection for the following year. The personnel cost in the supervision and administration category was divided into two sub-categories: general administration, and advocacy and sensitization of HPV testing in local public health clinics. The input categories of overhead (e.g., buildings and utilities and laboratory facility) and capital (e.g., *care*HPV diagnostic machines) were shared with the program's commercial component. We assumed the cost incurred by the social sector to be 89.0% in these categories, which was the proportion of the total number of HPV self-sampling kits sold by the social component (n=4,882) compared to the commercial component (n=601).

Variable costs consisted of four mutually exclusive input categories: service delivery, laboratory costs, variable supplies, and personnel costs associated with service delivery. Service delivery referred to costs associated with activities related to HPV self-sampling kit sales, following up with the participants about their results, and helping HPV-positive women to attend their local public health clinics for triage. The laboratory costs included the material and service costs associated with HPV self-sampling kits, such as consumables, delivery services, packaging, and kit assays. We divided the cost incurred on the expense report by the number of goods purchased to calculate the financial unit cost of items for supplies and commodity costs.

The personnel costs of persons involved in both the program's social and commercial components were calculated based on the full-time equivalent (FTE) allocated to the social sector in the program's strategic plan, which is available in the supplementary materials. The opportunity costs associated with the Hope Ladies' time were measured based on the administrators' report of daily activities. We derived the Hope Ladies' time costs by using the minimum wage in Peru as of 2019, which was 930 PEN per month (930 PEN per month divided by 137 working hours per

month = 6.79 PEN per hour) (254). From the administrator reports during the interviews, we derived the financial and economic costs of the Hope Ladies' travel associated with kit sales and following up with participants who had the HPV test by assuming that one half of the community encounters with participants from January to March required public transportations due to the hot climate in this region during these months, and that one third of the community encounters required transportation during the rest of the year (April to December). The average trip costs associated with training, kit sales, and follow-up was calculated by taking an average between the Hope Ladies' hourly wage (for walking) and the estimated cost of the public transportation (5 PEN) from the Hope Ladies' houses.

We calculated the average unit costs by allocating fixed and variable costs to each activity and dividing by the program output measures: number of Hope Ladies recruited and trained, HPV self-sampling kits distributed and HPV-positive women identified, and the number of participants followed up with their results (HPV-positive and HPV-negative women), and HPV-positive women attending their local public health clinic for triage. Fixed costs that were allocated to the program in general (e.g., overhead, capital) were apportioned using the minutes of service producing the program output estimated by the program administrators. The program output was abstracted from the administrative records from November 1, 2018, to March 30, 2020. While the aggregate costs for each activity were assumed to be mutually exclusive of each other, the unit costs represent all costs incurred during activities leading up to the output, as described in Figure 3.3. For example, "cost per HPV self-sampling kit distributed" is the sum of the cost of training the Hope Ladies and HPV self-sampling kit distribution, divided by the number of kits sold. Likewise, the "cost per HPV-positive woman successfully linked to VIA" represents the sum of

the cost of training, kit distribution, and follow-up activities after the screening, divided by the number of HPV-positive women who attended their public clinics for VIA.

3.3.3 *Sensitivity analysis*

We explored the impact of HPV self-sampling kit price and screening volume on the total program cost in a two-way sensitivity analysis. We assumed that the number of Hope Ladies, HPV prevalence, and the proportion of HPV-positive women successfully linked to VIA stayed constant in the sensitivity analysis. In a systematic analysis of cost-effectiveness analyses of HPV self-sampling (250), the combined kit and testing cost (in 2017 USD) in LMICs varied from 9.24 USD (Uganda), 9.70 USD (India), 10.47 USD (China), 14.69 USD (Nicaragua), and 16.11 USD (Mexico) (255-257). As we knew that major uncertainty had been reported on the parameter of cost per kit in implementation settings (258), we varied the kit price of 5-50 USD in increments of 5 USD in our analysis. We used this equation:

$$T(v_2, y) = F + v_1 x + v_2 y + v_3 z \qquad (3.1)$$

where F represents the total fixed costs of the Hope Project, v_1 represents variable unit cost of recruiting and training of the Hope Ladies, x represents the number of Hope Ladies recruited and trained, v_2 represents variable unit cost of kit distribution, y represents the number of kits distributed (e.g., screening volume), v_3 represents variable unit cost of follow-up and linkage to care, and z represents the number of women followed up for appropriate treatment. For the sensitivity analysis only, the variable unit costs of the three activities were assumed to be mutually exclusive of one another, meaning that the variable unit cost of kit distribution did not include the cost of recruiting and training the Hope Ladies. The variable unit cost of the kit distribution included the consumable and disposable goods used to assemble the kits (e.g., chemical solvents and supplies), services (e.g., freight transport of supplies), and the kit components (e.g.,

cytobrushes, vials, and boxes). It also included the personnel and overhead costs associated with community outreach and kit distribution, such as the Hope Ladies' time and transportation costs spent on home visits, education, sample collection, and delivery. It did not include the testing machinery, the software platform for uploading the results, or the laboratory personnel salary, as these were accounted for as fixed costs.

We increased the screening volume by 2-5 times in our sensitivity analysis, corresponding to screening coverage of 4.1%, 8.1%, 12.2%, 16.2%, and 20.3% in our catchment area, respectively. The coverage was calculated based on the number of eligible women (n=120,523) in the Callao, Mí Peru, and Ventanilla districts ages 30-49 as reported in the 2017 Demographic Census Survey (259), assuming that women had not been screened previously with HPV testing in these districts. The reported screening coverage in Peru varies widely based on the region, study period, and how the coverage was defined (260). For example, based on data from 2005-2008, Barrionuevo-Rosas et al. found that 72.4% of the women in Callao aged 30 to 49 reported having a Pap smear in the last five years (261). As HPV testing is not available in the public health system in Peru, the Ministry of Health has set a goal of increasing the screening coverage to 60%, defined as the percentage of women ages 30-49 screened with HPV testing over 12 months (262).

3.4 Results

During the study period (November 2018 to March 2020), the program recruited and trained 62 Hope Ladies, who distributed 4,882 HPV self-sampling kits to women in their communities. Of the screened women, 586 (12.0%) tested positive for HPV, and of these, 365 (62.3%) were successfully linked to VIA in their public health clinic for triage. The total annualized program cost was 271,625.29 USD (Table 3.1).

Table 3.1 Total cost breakdown by input and activities (2018 USD)

Total and Unit Costs (2018 USD) (*calculated w/o personnel costs)	Hope Ladies recruitment and training (n=62)	HPV self-sampling kit distribution (n=4,882)	Follow-up (n=4,882)	Total annual cost
Variable				
Personnel (service delivery)	$0.00	$57,806.39	$18,355.09	$76,161.48
Service Delivery	$0.00	$2,406.42	$2,529.43	$4,935.86
Laboratory (e.g., consumables, delivery services, packaging, assays)	$0.00	$67,144.03	$0.00	$67,144.03
Variable supplies	$234.06	$0.00	$0.00	$234.06
Sub-total	**$234.06**	**$127,356.85**	**$20,884.52**	**$148,475.43**
Fixed				
Microplanning	$37.93	$964.29	$330.32	$1,332.54
Training	$623.86	$0.00	$0.00	$623.86
Supervision and administration	$583.57	$14,837.58	$5,082.70	$20,503.85
Personnel (e.g., microplanning, supervision and administration, training, laboratory)	$6,971.19	$51,614.79	$17,680.93	$76,266.91
Overhead (e.g., buildings and utilities)	$496.27	$12,618.06	$4,322.39	$17,436.72
Capital (e.g., *care*HPV diagnostic machines)	$198.83	$5,055.40	$1,731.75	$6,985.98
Sub-total	**$8,911.66**	**$85,090.12**	**$29,148.08**	**$123,149.86**
Total annual cost (variable + fixed)	**$9,145.72**	**$212,446.97**	**$50,032.60**	**$271,625.29**

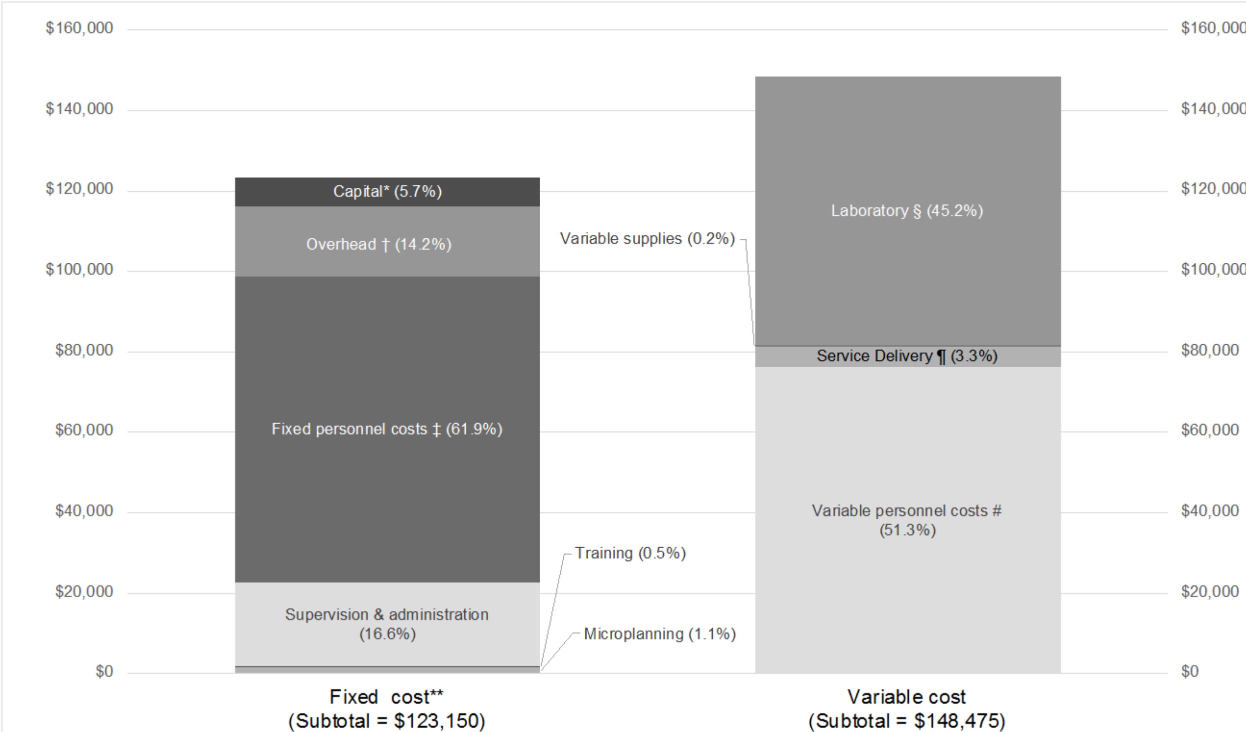
The average unit cost per Hope Lady recruited and trained was 147.51 USD, and cost per HPV self-sampling kit distributed was 45.39 USD. The cost per HPV-positive woman identified was 378.14 USD, the cost per woman successfully linked to VIA was 744.18 USD. The cost per woman who completed the screening pathway through the Hope Project was 55.64 USD (Table 3.2).

Table 3.2 Program output and unit cost per activity

	Output	Unit cost
Unit cost per Hope Lady recruited and trained	62	$147.51
Unit cost per HPV kit distributed	4,882	$45.39
Unit cost per HPV-positive women identified	586	$378.14

Unit cost per women follow up	4,882	$55.64
Unit cost per HPV-positive women linked to VIA	365	$744.18

Costs associated with personnel and laboratory kits (e.g., consumables, delivery services, packaging, assays) represented 56.1% and 24.7% of the total annual cost of the program, respectively (Figure 3.4). 171,307.48 USD (63.1%) was financial cost (as implemented), and the rest were opportunity costs. The program administrators' time dedicated to meeting with health providers in local health clinics to sensitize and advocate for HPV testing and appropriate follow-up of the tested women attributed 14.2% (10,806.38 USD) of the fixed personnel costs.

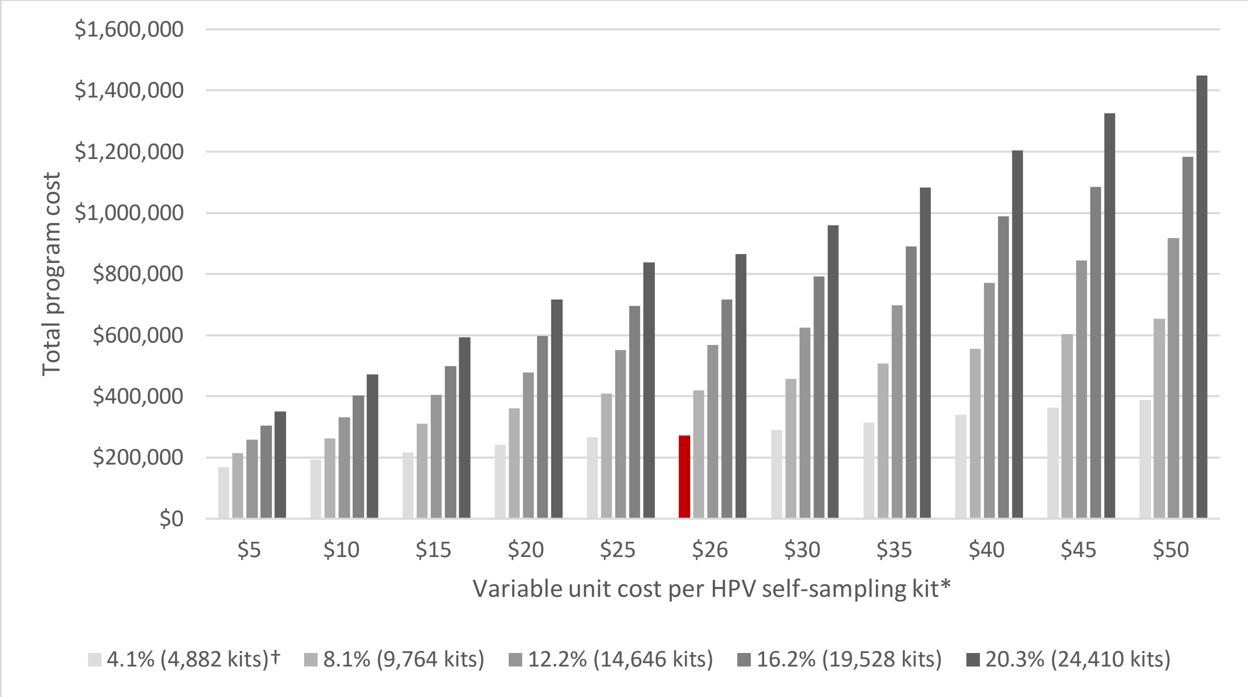


* Capital: *care*HPV diagnostic machines
† Overhead: buildings and utilities
‡ Fixed personnel costs: includes administrators' salary and Hope Ladies' opportunity costs associated with supervision & administration, microplanning & training, lab personnel
§ Laboratory: consumables, delivery services, packaging, assays
¶ Service delivery: activities related to HPV self-sampling kit distribution and results follow-up
# Variable personnel costs: includes administrators' salary and Hope Ladies' opportunity costs associated with HPV kit distribution & follow-up visit
** Proportions represent the percentage of the input in respective categories, either "Fixed" or "Variable"

Figure 3.4 Cost breakdown by input categories

From the interviews with program administrators about daily program activities, we estimated that 62 Hope Ladies collectively contributed 33,765 hours to the program during the study period (supplementary material). As an employee working 1.0 FTE (including holidays and leave) who works 137 working hours per month, each Hope Lady would have contributed about four months of labor. The opportunity cost of the labor (76,045.58 USD), which was adjusted for seasonal variance and calculated based on the 2019 Peruvian minimum wage (930 PEN per month, ~282.68 USD) consisted 75.8% of all opportunity costs incurred by the program. On average, each Hope Lady sold ~79 kits and incurred about 1,226.54 USD during the study period spanning one year of active kit sales (March 2019 to March 2020, excluding the start-up period). In contrast, they earned 393.70 PEN (~119.67 USD) of profit per person based on 5 PEN of profit per kit.

Our sensitivity analysis showed that if the non-cumulative variable cost per kit stayed at 26.09 USD, increasing the number of kits sold by 200% (e.g., 14,646 kits or 12.2% screening coverage) would yield the total program cost of 568,152 USD.



*Current coverage and total cost in red
† Coverage calculated based on number of eligible women (n=120,523) in the Callao, Mí Peru, and Ventanilla districts ages 30-49 reported in the 2017 Demographic Census Survey(259)

Figure 3.5 Two-way sensitivity analysis adjusting HPV self-sampling price per kit and screening coverage

3.5 DISCUSSION

We estimated the total and unit costs of a community-based HPV self-sampling program within social entrepreneurship in Ventanilla-Callao, Peru, from the provider perspective. We assumed that program itself was the sole provider and conducted a micro-costing study to estimate the costs associated with recruitment and training of Hope Ladies, HPV self-sampling kit distribution and follow-up with screened women. To our knowledge, this is the first study to estimate the detailed costs of community-based HPV self-sampling in Peru.

Many barriers to Pap tests have been documented in Peru, the only screening test studied nationwide (263). The barriers include environmental factors (244, 264), fear of gynecological exams, shortage of laboratories and cytopathologists (244), as well as insurance status (261). Those

who have been screened are often lost to follow-up and/or cannot access the necessary treatment due to prohibitive cost or geography (245). While the screening rates in coastal, urban regions tend to be higher than in the highlands, rainforest, or rural areas (265), women are still subjected to socio-demographic inequities (263). Education has been identified as a significant determinant of screening coverage among younger women living in urban areas (ages 18-29) (265), and among Pap test-eligible women (ages 30-59) in Peru (263). Among the 98 women who were surveyed after participating in our 2015 pilot, only two people had university-level education, and 85 (86.7%) had secondary education or less (247). In Ventanilla, Mi Perú, and Pachacútec, where the Hope Project operates, about 30% live in poverty, and one hospital and 13 community clinics serve the population of about 500,000 (266). In the region of Callao where these districts are located, only ten colposcopy instruments were found in public health clinics in 2017, along with one cryotherapy and loop electrosurgical excision procedure instruments to treat precancerous lesions for the entire district (262).

HPV self-sampling has demonstrated great potential to overcome these barriers in LMICs (267). A four-year demonstration project in Nicaragua, Guatemala, and Honduras demonstrated high acceptability towards HPV self-sampling among nearly a quarter million women and feasibility of screening (120). A large proportion (55.8% in Nicaragua and 30.0% in Guatemala) of women were screened for the first time, and the number of women screened increased substantially upon extending the option to self-sample in Honduras. In Peru, high levels of satisfaction with HPV self-sampling have been documented in the Jungle (37) and our 2015 pilot, where 74.2% of the users reported feeling at least satisfied with the program and 68.0% preferred the self-sampling to clinician-sampling (247).

In their systematic review on cost-effectiveness studies of HPV self-sampling, Malone *et al*. found that only five of the 16 studies included in their analysis were from LMICs, despite bearing the majority of the global burden of cervical cancer (250). The drivers of cost-effectiveness in LMICs varied, including screening attendance (268), the cost of HPV self-sampling materials and testing (269), and higher sensitivity to detect precancerous lesions (256). While further information is needed to demonstrate the cost-effectiveness of HPV self-sampling in Peru compared to other screening methods such as the Pap test, our analysis confirms that both the cost per kit and screening coverage would play important roles.

Our study also shows that women from the community can play an important role in improving screening uptake among other women, especially in socioeconomically disadvantaged areas where the screening coverage is already low. The 62 Hope Ladies in the current program were instrumental in raising awareness about cervical cancer, educating their peers about HPV self-sampling and how to perform it, and widely distributed 4,882 kits from March 2019 to March 2020. In a meta-analysis, women were 2.37 times (95% CI: 1.12-5.03) more likely to participate in cervical cancer screening when health workers offered HPV self-sampling door-to-door than under standard of care conditions (16). Another meta-analysis showed that self-sampling increased screening coverage among never- or under-screened populations (124). In this study, the door-to-door outreach method achieved pooled participation of 94.2% in the self-sampling arms compared to 53.3% in the control arms with practitioner-sampled Pap tests, HPV tests, or VIA. Notably, this study also found that assays based on single amplification HPV tests, such as *care*HPV in our study, had lower sensitivity but comparable specificity to clinician-collected HPV testing.

The Hope Ladies' ability to minimize loss to follow-up among HPV-positive women can greatly impact the cost-effectiveness of HPV self-sampling against Pap tests. As of August 2020,

the proportion of HPV-positive women successfully triaged in their public health clinics was 62.3% in our study, comparable to 58.8%-84.7% triaged in the demonstration project in Nicaragua, Honduras, and Guatemala (120). More women are expected to follow up once the clinics open again after the pandemic. The administrators reported that the Hope Ladies spend a significant amount of time counseling some of the screened-positive women who are reluctant to follow up for triage due to long queues and fear, and sometimes accompany the women to the local public health clinics for peer support. The administrators also described the challenges of educating the providers in the local clinics about HPV testing because it is not yet widely available in the public health system in Peru. In addition to the online platform where the screened women can access their test results at any time, the program began printing and delivering individual test results shortly after the kit sales because the local health clinics did not understand how to interpret the test results or how to appropriately triage HPV-positive women. Costs associated with such activities can be saved if HPV testing is widely endorsed by the public health system itself.

Our study has several limitations. First, all of our costing data came from the Hope Project, which is the sole provider of its services. This may limit the generalizability of our findings to other settings, especially when integrating the program components into a public health system. The COVID-19 pandemic imposed several challenges in conducting our study. We were unable to perform a time-and-motion study with independent observers. Using an alternate approach, we extrapolated the amount of time dedicated by the Hope Ladies from interviews with the program administrators conducted online instead of direct observation. We did not interview the Hope Ladies directly because they have limited technological resources (e.g., computer or smart-phones, internet, etc), and it was not feasible to interview them virtually. Additionally, our scope did not include costs incurred in the public health clinics (e.g., performing VIA to identify precancerous

lesions), as they were closed. Furthermore, we were unable to accurately estimate how many precancerous lesions were found among HPV-positive women because the monitoring and evaluation coordinators were unavailable due to the pandemic.

Despite the challenges, we found valuable information pertinent for the scale-up and sustainability of this model, especially in Peru. We captured the time and cost associated with the efforts of the Hope Ladies, including transportation. We also learned that the sales trend might vary by season. According to the administrators, the Hope Ladies reported that they were able to sell more self-sampling kits during the months that their children were attending schools (March-June, and August-November). Indeed, we observed a drop in kit sales in the months of July and another sharp decline in December. However, the sales did not precisely mirror the Peruvian academic calendar (supplementary material). As noted in the methods, we also accounted for variations in travel costs during the warmer months, which may have more significant cost implications in regions with less accessible geographical terrains and extreme climates.

In conclusion, community-based HPV self-sampling appears to be a feasible way to improve cervical cancer screening coverage and follow-up treatment of HPV-positive women in Peru. These findings can inform costing inputs for a model of HPV infection and cervical cancer, especially in Peru or other LMIC's, which can then be used as the basis for economic evaluations, such as cost-effectiveness analysis, or to model the scaling of the intervention.

Chapter 4. EVALUATION OF WOMEN'S EMPOWERMENT IN A COMMUNITY-BASED HPV SELF-SAMPLING SOCIAL ENTREPRENEURSHIP PROGRAM (HOPE PROJECT) IN PERU: MIXED-METHOD STUDY

4.1 ABSTRACT

Background: Understanding the women community leaders' sense of relational and financial empowerment in the social entrepreneurship context will be key to developing a sustainable pathway to scale-up community-based HPV self-sampling programs in low resource settings. The Hope Project, a social entrepreneurship (SE) near Lima, Peru, trains women leaders (Hope Ladies) to promote HPV self- sampling in their communities. This study aims to evaluate the Hope Ladies' own relational/financial empowerment after participating in the program.

Methods: The Hope Ladies participated in semi-structured in-depth interviews (n= 20) and nine question five-point Likert scale survey (n=7-14) that evaluated their relational/financial empowerment after participating in the social entrepreneurship. The interview and the survey questions were developed using validated empowerment frameworks, indicators, and theory, respectively: 1) Kabeer's conceptual framework, 2) International Center for Research on Women (ICRW), and 3) Relational Leadership Theory (RLT). Deductive content analysis was used to deductively evaluate the interviews with predetermined codes and categories of empowerment. Descriptive statistics were used to analyze the survey results.

Results: All reported experiencing empowerment in the SE. *Interviews:* The findings from the interviews were organized into 3 categories/10 sub-categories: 1) resources (balancing the roles between the household and working as a Hope Lady, camaraderie with other Hope Ladies, recognition from the community as a resource); 2) agency (improved ability to express themselves,

increased knowledge about reproductive health, ability to speak out against male-dominant culture); and 3) achievement (increased economic assets, improved ability to make financial decisions, widened social network and technology skills development). *Survey*: All indicated an increase in social contacts (100%), some reported increased unaccompanied visits to a healthcare provider (86%), confidence in discussing reproductive topics (100%), improved ability to make household decisions about money (57% pre-intevention vs 92% post-intervention).

Conclusion: The Hope Ladies' experience in this SE demonstrated the complex relationship between various domains of empowerment (e.g., relational/financial). More studies are needed to elucidate the relationship between empowerment and worker retention/performance to inform scale-up of HPV self-sampling SE's.

Abstract presented at the Association for Clinical and Translational Science Conference virtually, March 30-April 2, 2021 and published in the Journal of Clinical and Translational Science. 2021:1-2. Shin MB, Dotson ME, Valderrama M, Chiappe M, Barnabas RV, Asbjornsdottir K, et al. Evaluation of women's empowerment in a community-based HPV self-sampling social entrepreneurship in Peru: Mixed-method study.

4.2 INTRODUCTION

Social entrepreneurship is a highly theorized field of knowledge that has rapidly emerged in recent decades. The definitions of social entrepreneurship and the participants of this phenomenon vary widely across disciplines and perspectives (270). As such, there has been a proliferation of systematic reviews (271, 272), bibliometric studies (273-275), and other endeavors (276-278) to explore them and other efforts to set forth research direction and framework for the future (279-281). Here, we partake in a broad definition of social entrepreneurship as phenomenon (282) or organizations (271) that leverage economic activities or innovative business models with the mission of creating or implementing positive social change (283-287) rather than personal or shareholder wealth (288, 289). Social entrepreneurs are often characterized as "change agents" (290) who attempt to provide solutions for social and/or environmental problems, meet a social need (291), create social values (292), and bring a "pattern-breaking change" (293), while also ensuring their own survival and sustainability (294). The desired social change in health promotion usually entails improving public health, such as community-based malaria (295) and HIV/syphilis testing (296).

Social entrepreneurship activities in economically emerging countries have often taken the form of microfinance or microcredit programs designed to advance women's economic development (297). Women working in health-oriented social entrepreneurship programs seek to become financially self-sufficient by promoting health, rather than being dependent on or being employed by an organization (298). Women-driven social entrepreneurship programs have been shown to empower the entrepreneurs, not only economically, but by widening their social network in their communities, giving them technical skills with earning potential, and challenging the gender norm and their status in families and society (299). In her seminal work, Kabeer explains

women's empowerment as a process of changes, "by which those who have been denied the capacity for choice gain this capacity" that entails the inter-related, "indivisible" dimensions of resources (pre-conditions), agency (process), and achievements (outcomes) (300, 301). Kabeer emphasizes that women are embedded, active members within their society and hence, their empowerment, which is the "expansion in the capacity to make strategic and meaningful choices…actively challenge[s] the structures of inequality in their society", thereby creating social change in those societies where women lack equal power (301). Therefore, some scholars support the claims that the elements of empowerment are inherently and essentially embedded in the for-profit social entrepreneurship models (302-304).

The Hope Project is a social entrepreneurship initially started by the Universidad Peruana Cayetano Heredia in 2015 when a pilot evaluated the feasibility and acceptability of HPV self-sampling promoted by women from the community (247). After the successful pilot, the program officially began in November 2018 with two components: commercial and social. The commercial component offers HPV self-sampling kits (*care*HPV) online to high- and middle-income women in Peru for a higher price (150 Peruvian Soles [PEN], ~46 US Dollars [2018 USD]) to create a sustainable platform to offer subsidized testing to women with fewer resources in the social component. In the social component, which is currently located in Ventanilla, Callao (a coastal district in Peru), volunteer women (known as Hope Ladies) from the communities are trained to promote cervical cancer screening through HPV self-sampling and guide other women through the screening pathway (Figure 4.1). The Hope Ladies buy the HPV self-sampling kits for 5 PEN per kit (~1.50 USD [2018]) from the Hope Project and sell the kits in their communities at a significantly subsidized price of 10 PEN (~ 3 USD). The Hope Ladies sell the kits door-to-door by leveraging their social networks in their spare time, and they keep a small profit of the sales as

an incentive for wide dissemination. They provide education about cervical cancer prevention in the communities to sell the kits, instruct their clients on how to perform HPV self-sampling, and provide follow-up care as needed (e.g., encouraging HPV-positive women to go to their public health clinics for triage).

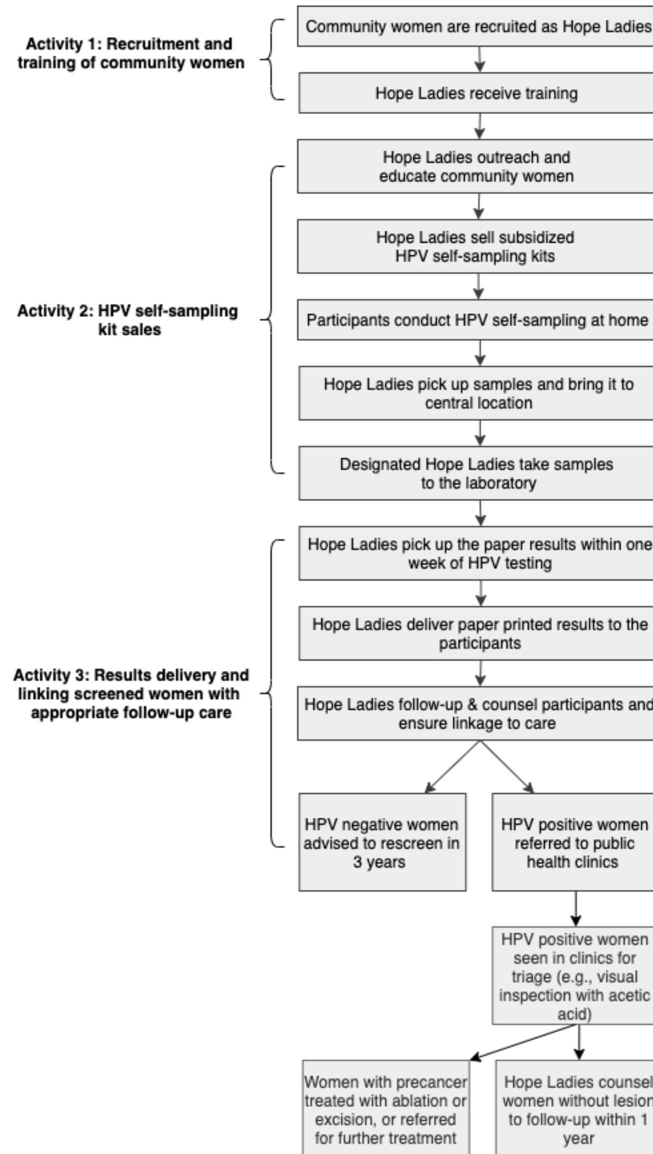


Figure 4.1 Activities within the Hope Project social entrepreneurship

Many residents of Ventanilla district (where the Hope Ladies live) are migrants from different regions of Peru who live there to work in the metropolitan area of Lima-Callao (305). Some parts

of the district, namely Nuevo Pachacútec, were established in early 2000 when the government resettled over 7,000 migrant families living in informal housing from another metropolitan area (306). Ventanilla was once known as an "extreme poverty zone" with limited water and sewage infrastructure, schools, and hospitals. While there are ongoing community development initiatives and progress has been made, many residents still face challenges of difficult living conditions (307).

The concept of women's empowerment has been explored as a mediator between social entrepreneurship and change (299), but not in the context of HPV self-sampling. Understanding the relationship between these concepts will be key to inform future program direction and to develop a scalable social entrepreneurship model to increase access to cervical cancer screening. Therefore, we undertook this study to 1) evaluate the Hope Ladies' relational and financial empowerment after participating in the social entrepreneurship, and 2) develop a causal pathway to illustrate if and how empowerment improves the effectiveness of the Hope Project intervention.

4.3 METHODS

We evaluated the Hope Ladies' experiences of empowerment using parallel mixed methods (308). Eligible participants were Hope Ladies who are all 18 years of age or older. The administrators invited the Hope Ladies through WhatsApp to participate in a survey and an individual in-depth interview. Each participant gave written informed consent in Spanish. Participant characteristics were gathered from the administrative data, which was provided by the Hope Project administrators. Percentages and medians were reported where applicable. The interview and survey were conducted in the participants' homes, without the presence of other family members or program administrators. The data was collected by at least two trained study personnel, one of

whom was fluent in Spanish. The study was approved by the International Review Boards of Duke University (#2020-0376) and University of Washington (STUDY00010676).

4.3.1 *Quantitative Methods*

For the quantitative portion, we used basic frequencies and proportions to analyze the results of the financial and relational empowerment surveys. The financial empowerment survey questions (n=5) were developed from International Center for Research on Women (ICRW)'s economic empowerment indicators (309). The ICRW's framework measures women's economic empowerment by tracking indicators such as control over assets, the agency in decision making, autonomy and mobility, self-confidence and self-efficacy, gender norms, and gender roles within the household. The relational empowerment survey questions (n=4) were developed from the Relational Leadership Theory, which shifts the attention away from individuals to the "collective action of interconnected individuals" (310). We used the Relational Leadership Theory to examine empowerment in the context of family, social networks, and communities, with the assumption that power is "developed and exercised through relationships" (311). Each survey instrument was designed to take 10 minutes, prepared in English and translated and reviewed by the study personnel, piloted by the Hope Project administrators, and amended according to their feedback before finalization (Appendix 4.1). All questions were based on a five-point Likert scale except for one question related to financial empowerment, which asked to describe the three biggest household expenditures. The surveys were administered orally in Spanish by study personnel. Quantitative data was analyzed through Excel 2018 (Microsoft, Redmond, WA, USA).

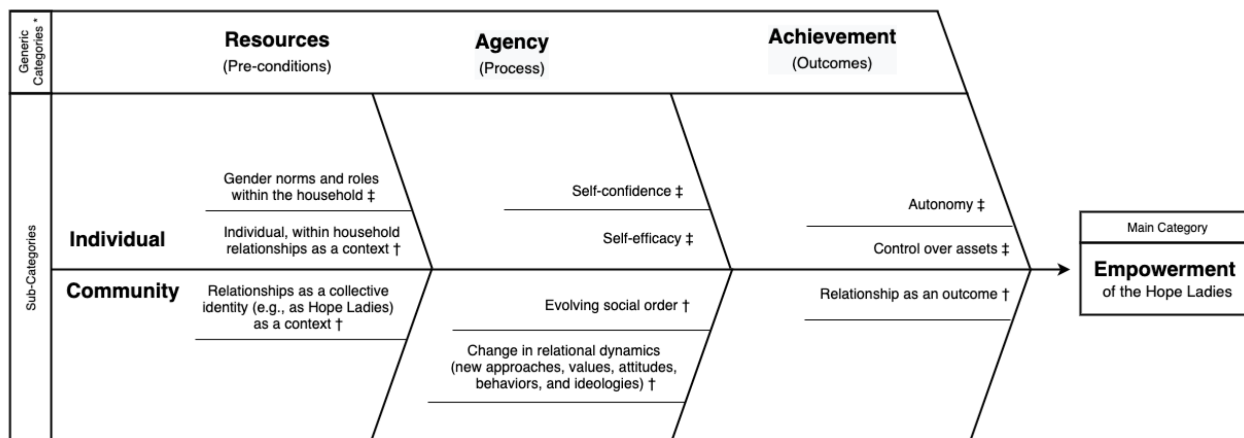
4.3.2 *Qualitative Methods*

We performed individual in-depth interviews, following the guide of fourteen questions developed using ICRW's economic empowerment indicators and the Relational Leadership Theory (Table 4.1).

Table 4.1 Questions from In-depth Interview Guide

1. Are you currently active as a Hope lady?
2. Please walk us through what a typical day looks like for your Hope Lady work.
3. How many women do you visit and test each day?
4. How many times do you have to interact with a woman in order for them to buy and take an HPV test?
5. Do you believe that the Hope program is vital to your community? If so, why or why not?
6. How much time have you been working as a Hope lady?
7. Why do you choose to educate your fellow female peers? (**RLT**)
8. Women's empowerment is defined as the process by which women acquire greater control over their own lives, the circumstances surrounding it, and the elements that are part of it, such as reproductive health.
    a. How has this program empowered you? In other words, how has it affected your access to health care and female education? **(ICRW, RLT**)
9. How does the Hope micro-business model help empower you in your everyday life or improved your earning opportunities? **(ICWR)**
10. What new skills have you learned since becoming a Hope lady, those being related to education, finances, and social? **(ICWR, RLT)**
11. What do you teach women when you interact with them and teach them about women's health? (**RLT**)
12. Would you describe your ability to balance your Hope Lady duties with your personal life as: 1) very easy, 2) easy, 3) difficult 4) very difficult **(RLT)**
13. Have you faced any setbacks that have kept you from your Hope Lady work? If so, what are they, and what brings your back to doing the Hope Lady work?
14. What would help you maintain your Hope Lady position?

Each interview was designed to take about 35 minutes and was transcribed verbatim in Spanish by an independent contractor fluent in Spanish and a resident of a nearby city. We conducted a structured deductive content analysis (312), using the categorized matrix organized in a fishbone diagram as depicted in Figure 4.2.



* Constructs from Kabeer's conceptual framework of empowerment
† Pre-determined codes about the Hope Ladies' relational empowerment, derived from Relational Leadership Theory
‡ Pre-determined codes about the Hope Ladies' economic empowerment, derived from International Center for Research on Women

Figure 4.2 Conceptual frameworks

Two authors (MS, LD) independently cleaned the data and organized the pre-determined codes from ICRW framework and relational leadership theory into the individual- and community-level sub-categories. Then, codes and constructs were mapped onto the generic categories of resource, agency, and achievements from Kabeer's conceptual model of empowerment, acknowledging that these constructs are not mutually exclusive but rather inter-related (300). We decided to use the three frameworks (e.g., ICWR, Relational Leadership Theory, and Kabeer's conceptual framework) because the science of defining and measuring women's empowerment is complex and evolving (313-316), and Kabeer's framework has been successfully used to analyze women's empowerment in social entrepreneurship in developing countries (301, 302). The two authors (MS and LD) met subsequently to iteratively discuss their individual findings from the qualitative data analysis and discuss discrepancies until reaching consensus. In addition, they discussed how the qualitative and quantitative data converged and diverged to triangulate their findings (317). Salient quotes were translated from Spanish to English by MS and verified by other bilingual authors. Qualitative analysis was performed using NVivo 12 (QRS International, Burlington, MA, USA).

4.3.3 *Development of Potential Causal Pathway*

To discover actionable determinants and move beyond identifying barriers and facilitators, we developed an implementation science-based causal pathway that can be used for hypothesis generation and testing in the future. Using the Agile Science-informed method specified by Lewis et al. and the findings of our surveys and interviews, we developed a pathway model for the Hope Project to increase HPV self-sampling kit sales (proximal outcome), thereby increasing cervical cancer screening coverage (distal outcome) (318).

We followed the definition of the mechanism of action by Lewis et al., which was "process or event through which the implementation strategy operates to affect desired implementation outcomes." The cognitive moderator was defined as individual-level perception or attitudes that increase or decrease the level of the influence of the Hope Project. In contrast, the organizational moderator was defined as community-level factors such as culture or widely held beliefs. We also defined pre-conditions, or factors necessary for an implementation mechanism to be activated and the proximal outcome to be realized, in the Hope Project.

4.4 RESULTS

Overall, 20 Hope Ladies participated in the individual in-depth interviews. The number of responses to the quantitative survey questions ranged from seven to fourteen due to unforeseen logistical challenges with limited time due to the COVID-19 pandemic and country lockdown. All were females between ages 32 and 64 (median: 45 years old) and had been involved with the Hope Project a median of 9 months (range 1 to 12 months) (Table 4.2). The participants had lived in the Ventanilla region for a median of 20 years (range 10 to 37 years) and 55% (n=11) were born in the coastal regions like Ventanilla. The participants had sold a median of 151 HPV self-sampling

kits, averaging profit of 25 to 254 PEN (~7.60 to 77.20 USD) per month (median: 82 PEN [24.90 USD]).

Table 4.2 Characteristics of the Hope Ladies

Characteristics		Median (Range)	N (%)
Age (years)		45 (32-64)	
Place of birth	Andean		7 (35)
	Coastal		11 (55)
	Amazon		1 (5)
Residence in the catchment area (years)		20 (10-37)	
Period of involvement with the Hope Project (months)		9 (1-12)	
Number of kits sold		151 (10-610)	
Average profit per month (2020 Nuevos Soles)*		82 (25-254)	

* Calculated by multiplying the total number of kits sold up to March 2020 by 5 Soles and dividing by total months of HPV self-sampling sales

The following presents findings organized in Kabeer's conceptual framework of empowerment, consisting of resources, agency, and achievement. The summary of deductive content analysis of the in-depth interviews is available in the supplementary material (Appendix 4.2) with salient quotes from the participants. The relational and financial empowerment survey result is available in Table 4.3. The survey data has been integrated with the qualitative data with illustrative quotes from the in-depth interviews.

Table 4.3 Relational and Financial Empowerment Survey Results

Relational Empowerment			
Question	**Number of Responses**	**Responses**	**N (%)**
Would you say that your number of social contacts within and outside the family has increased since the beginning of your Hope lady journey?	N=14	Totally disagree	0 (0)
		Disagree	0 (0)
		Agree	3 (21)
		Totally agree	11 (79)
Would you say that you have been able to help other women in moments of need since the beginning of your Hope lady journey?	N=14	Totally disagree	0 (0)
		Disagree	0 (0)
		Agree	5 (36)
		Totally agree	9 (64)

Would you say that you have been able to increase your unaccompanied visits to a health care provider to meet your personal needs since the beginning of your job as a Hope lady?	N=14	Totally disagree	0 (0)
		Disagree	2 (14)
		Agree	7 (50)
		Totally agree	5 (36)
Would you say that you have felt confident because of learning about your reproductive health and how to prevent certain diseases compared to starting your job Hope lady?	N=14	Totally disagree	0 (0)
		Disagree	0 (0)
		Agree	4 (29)
		Totally agree	10 (71)
Financial Empowerment			
Question	**Number of Responses**	**Responses**	**N (%)**
Currently, do you decide how to spend money in your household?	N=12	Always	11 (92)
		Sometimes	0 (0)
		Rarely	1 (8)
		Never	0 (0)
In the past before joining Hope project, did you decide how to spend money in your household?	N=7	Always	2 (29)
		Sometimes	2 (29)
		Rarely	2 (29)
		Never	1 (14)
Currently, are you allowed to comment on the purchase of large domestic assets in the household?	N=7	Always	4 (57)
		Sometimes	1 (14)
		Rarely	2 (29)
		Never	0 (0)
In the past before joining Hope project, were you allowed to comment on the purchase of large domestic assets in the household?	N=7	Always	4 (57)
		Sometimes	2 (29)
		Rarely	1 (14)
		Never	0 (0)
Currently, what are the top three expenses that you spend money on?	N=11	Food	9 (82)
		Education	4 (36)
		Healthcare	2 (18)
		Travel	2 (18)

4.4.1 *Resources*

Kabeer refers to resources (including those of economic, human, and social nature) as something that serves to "enhance the ability to exercise choice" (300). The pre-determined codes in this category were: 1) gender norms and roles within the household (ICWR); 2) relationships at the

individual-level either within the household or in healthcare settings (RLT); and 3) relationships at the community-level as the collective identity of Hope Ladies (RLT). The Hope Ladies described the challenge of managing their roles within the household and working as a Hope Lady. They also discussed the benefit of peer support within the Hope Project and being recognized as a resource for women's reproductive health in their communities. The following further describes and provides exemplars.

Maintaining roles within the household and working as a Hope Lady:

Majority of the Hope Ladies (n=15, 75%) mentioned during the interviews that it is difficult for them to manage their time to sell HPV self-sampling kits in their communities due to their various roles in their households, such as childrearing and caregiving. One stated, *"I have a baby. When she grows a little more, I don't think I will have any obstacles with the Hope Project,"* (P17, age 35), and another stated, *"I have my mother-in-law in my care. She needs me to take care of her...because she cannot get out of bed. I go [out to sell the kits], but with the thought, 'what if she suddenly falls out of bed,' or I do not know she will urinate on herself. Sometimes I wonder, 'Should I continue [to work as a Hope Lady] or not?' and sometimes I stop [selling the kits]. But my friends [other Hope Ladies] tell me, 'Don't stop, keep going for us.'"* (P3, age 33). Another stated, *"It's not easy, it's definitely not easy...it is a matter of organizing, it is a matter of habit, it is a matter of accustoming the family. It has its consequences, but it is possible to balance."* (P5, age 33). In contrast, others found it easy or manageable to organize their time. For example, one mentioned, *"It's not difficult for me [to manage my time] because the issue here is to organize ourselves. If we organize ourselves, everything works out for us."* (P2, age 45).

Hope Ladies as a resource for the communities: In the relational empowerment survey, all participants also responded "agree" (n=5, 36%) or "totally agree" (n=9, 64%) to the question,

"would you say that you have been able to help other women in moments of need since the beginning of your Hope Lady journey?" (Table 4.3). Half (n=10, 50%) of the Hope Ladies reported being recognized for their knowledge about cervical cancer in their communities and said, *"They [the community women] talk to me more because you know in the hospital, they [the doctors] will hardly talk to them like we [Hope Ladies] talk to them."* (P2, age 45).

The camaraderie with other Hope Ladies: Nearly half (n=9, 45%) of the Hope Ladies commented on enjoying the peer support with other Hope Ladies and stated collaborating with other colleagues helped sell their kits. One said, *"We would agree with other colleagues [Hope Ladies]…and we would go out in a group because it is less tedious [than] when you are alone."* (P10, age 64). Another person commented they look forward to the growth of the Hope Project, saying, *"we are working with the Cayetano [University], so that [the Hope Project] grows and we can amplify the good work."* (P19, age 54).

4.4.2 *Agency*

Kabeer defines agency as "the ability to define one's goal and act upon them" (300). The pre-determined codes in this category were: 1) individual-level self-confidence and self-efficacy (ICWR); and 2) evolving social order and change in relational dynamics (RLT). The Hope Ladies reported an increased sense of confidence and efficacy in themselves stemming from increased knowledge about reproductive health and improved communication ability and express themselves. They also discussed changes in behaviors, values, attitudes, and ideologies, such as advocating for their clients to make autonomous decisions about HPV self-sampling against male-dominant culture (*machismo*).

Improved self-confidence and ability to communicate and express thoughts: All participants agreed (n=4, 29%) or totally agreed (n=10, 71%) that they felt more confident than before working

as a Hope Lady because they learned about the female reproductive health system. One person mentioned, *"If it weren't for this [the Hope Project], I wouldn't even have taken the test,"* (P9). More than half (n=12, 60%) of the participants reported improved communication abilities to express themselves. One reported, "*It has helped me to have more confidence in words, that is, in being able to express myself with confidence what I am talking about.*" (P11, age 33). Another emphasized the importance of ongoing support and training by the Hope Project to her and said, "*I have lost the shame of communicating with people, because before I was not capable, when I started, I was very shy, but now I have enough skills. I have acquired that with [Hope Project] because of the training that they also give us. They support us in everything that we do, we also consult with them."* (P7, age 46).

Increased knowledge and self-efficacy: All the Hope Ladies said the increased knowledge and education about cervical cancer helped them to make informed decision-making for themselves, as well as other community women. 50% (n=7) agreed, 36% (n=5) totally agreed that they have been able to increase unaccompanied visits to a healthcare provider to meet their personal needs since the beginning of your job as a Hope Lady?" One stated, *"It has empowered me, and I have gained a lot of experience…It taught me to express myself, to reach the families who are the most in need, and I saw that there is a lot of need in the communities that I have visited, and others thank you and tell you, 'Thanks for coming! Thank you for remembering me!' And all that makes your self-esteem rise, and you have more desire to continue working, for them, for them more than anything."* (P16, age 47).

Advocating for women against male-dominant culture: Almost all (n=18, 90%) of the Hope Ladies mentioned male-dominant culture (*machismo*) in the households as a barrier to selling the HPV self-sampling kits, and they advocate for community women to make autonomous decisions

about their bodies by educating them and sometimes their husbands. Some (15%) Hope Ladies reported clients who buy the HPV self-sampling kits in secret, without informing their husbands. A quarter of participants (n=5, 25%) mentioned their clients shared that they sometimes experience domestic violence. One said, *"We are not talking about the test anymore; we talked and encountered different problems. We are like a heart doctor. They already believe us [heart] doctors, because they ask us different things. We try to do that, to be able to lift the woman so that they are not left saying, 'Oh, I'm going to ask my husband's permission!'"* (P5, age 33). One person reported, *"Women are well-trodden, sometimes it depends a lot…I say to them, 'Who is the one who is going to show their body [to the doctor]? Who is the one who is going to get sick? Your husband or you?'…There are cultural barriers…Because the liberation of women is also being imposed!"* (P10, age 64).

The Hope Ladies identified the Hope Project as a source of advocacy against the male-dominant culture, saying, *"We help them so that they can become aware that the decision is in themselves, and that we do not depend on anyone. We say, 'We have come alone, and we are going to leave alone, so each one is the owner of what to do and what decisions to make.' And that is what I have learned with Hope Project."* (P7, age 46). Another person said, *"The empowerment that [the Hope Project] brings to us, that other institutions cannot, is women's self-realization, their power to decide themselves, not to ask their partner."* (P6, age 48).

4.4.3 *Achievements*

Kabeer views achievement as the outcome of the resources and agency, particularly those "which draw attention to inequalities in the ability to make a choice" (300). The pre-determined codes in this category were: 1) control over assets (ICWR); 2) financial autonomy (ICWR); and 3)

relationship as an outcome (RLT). The Hope Ladies reported an increased sense of financial autonomy and expanded social network since joining the Hope Project.

<u>Increased economic assets</u>: All participants reported that the supplemental income from selling HPV self-sampling kits was economically helpful. One participant responded, *"Of course, it has helped me a lot…It helps me for my children's bus fares, which is daily for school."* (P2, age 45). Another stated, *"Yes, it helps [financially]. It is a job that helps you financially and that you are also helping other people, other women, I think it does help you financially."* (P20, age 51). Of the 11 participants who listed their top three household expenses, 9 (82%) answered food, 4 (36%) children's education, 2 (18%) healthcare, and 2 (18%) travel.

<u>Improved financial autonomy</u>: The majority of participants (11 of 12, 92%) reported that currently, they "always" decide on how to money in their household. In contrast, when asked the same question before starting the Hope project, only 29% (2 of 7) responded "always." In the individual interviews, the change in the ability to make financial decisions since working as a Hope Lady was more subtle. One participant who is a single-parent stated, *"I'm the one who works. I am a mother and father, I have a daughter, and I am the one who says how much money comes into my house and how much I am going to spend. I try to balance what is my priority."* (P16, age 47). Another stated, *"Although I don't [work], I have always tried to solve all the house expenses. [My husband] is the one who contributes."*

<u>Widened social network and gaining technology skills</u>: All participants responded either "agree" (n=3, 21%) or "totally agree" (n=11, 79%) that the number of social contacts within and outside the family has increased since working as a Hope Lady. One stated, *"They [the community women] comment on the program and they look for us, and they call us about this topic [of HPV*

self-sampling]. They call us, they leave our numbers, and other people who have never met call us, and you get to know more people." (P2, age 45).

In relation to the widened social network, technology skills development emerged as a significant achievement. Many mentioned they had no to limited experience with social media or cell phones prior to joining the Hope Project. One stated, *"I didn't know how to use [a touchscreen phone] at all. And when I joined the Hope Project, it was practically indispensable…[the administrators] themselves have taught me to use it, they have taught me to enter the page, to enter the data, all those things, so they have taught us all that there; I have also learned everything about technology with the Hope Project, because before I didn't even care to pick up a phone, but now I do."* (P7, age 46). Another stated, "*Social networks...the cell phone for me was nothing more like the phone that you go and answer, nothing at all! now I know, well, I chat everything*." (P5, age 33).

4.4.4 *Empowerment as the Mechanism of Action*

We developed a potential causal pathway model for the Hope Project based on the mixed-methods findings (Figure 4.3). Empowerment was evident as the predominant causal mechanism to increase HPV self-sampling kit sales and cervical cancer screening in the Hope Project. In this model, the implementation strategy of microfinancing and peer-education operate through the process of Hope Ladies' empowerment to achieve the proximal and distal outcomes. The individual and collective improvement of resources, agency, and achievement, necessary for the mechanism of empowerment to be activated. Perceived value of financial and relational incentive emerged as cognitive moderators, whereas logistical and sociocultural barriers to HPV self-sampling in the community, such as male-dominant culture, were organizational moderators. As the pre-condition

for the proximal outcome, the Hope Ladies must have the financial and logistical means of buying and selling HPV self-sampling kits for the sales to increase.

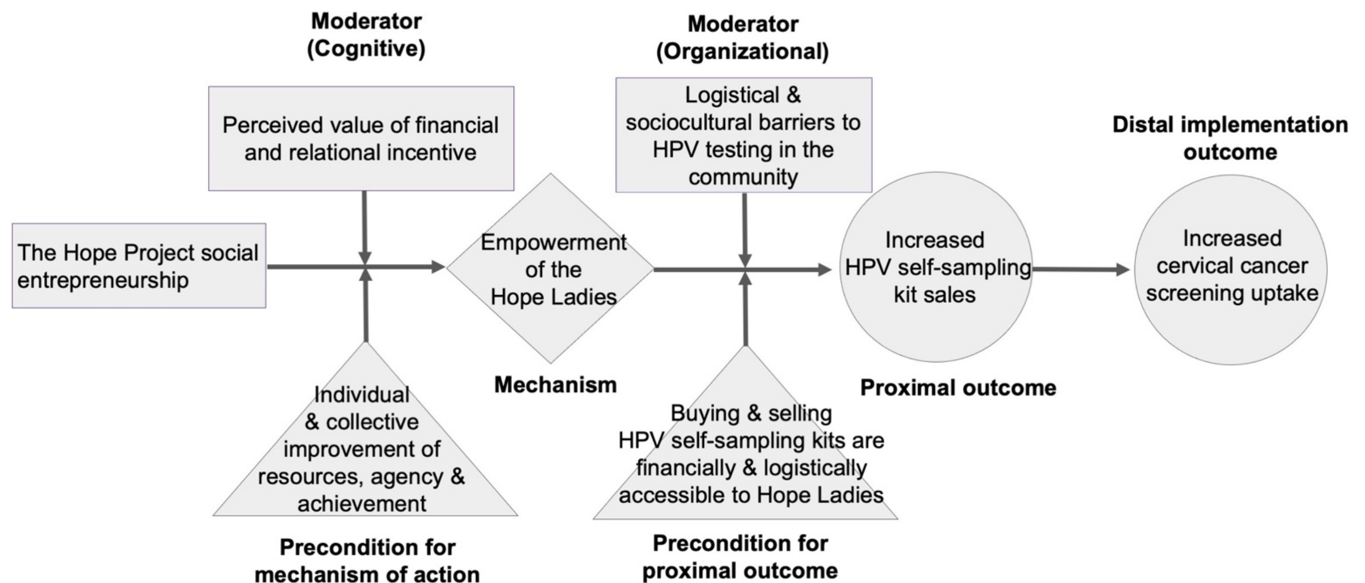


Figure 4.3 Empowerment as the mechanism of action for the Hope Project

4.5 DISCUSSION

We evaluated the relational and financial empowerment of women participating in social entrepreneurship called the Hope Project in Peru using surveys and in-depth interviews and created a pathway model to inform future program direction and scaling of this community-based HPV self-sampling intervention. We found that the Hope Ladies individually and collectively experienced meaningful improvement of resources, agency, and achievement in varying degrees and forms, which expanded their capacity to make strategic and meaningful choices in their households and communities. Using a pathway model, we demonstrated how HPV self-sampling kit sales are achieved *through* the empowerment of the Hope Ladies, which function as the mechanism of action for the Hope Project.

There is strong evidence linking women's economic empowerment to improved health outcomes for both women and their families. Benefits include uptake of family planning, improved nutrition, and reduced maternal and child mortality (309). The social entrepreneurship model has been used successfully to incentivize the uptake of health services and behavior change in the context of HIV (319, 320), syphilis (296), and malaria (295). Social entrepreneurship programs are uniquely positioned to empower women who are vulnerable to sexually transmitted infections such as HIV due to gender disparity in social structures and relationships, such as income inequality, violence, and educational opportunities (321, 322). For example, Haitian women who participated in a microfinance program were less likely to report partner infidelity and more likely to report condom use with their partners than those who did not participate in the program (323). A micro-grant intervention called the SHAZ! Project reported a significant improvement in economic security and decreased HIV risk factors such as transactional sex or gender-based violence among the adolescent female orphans in Zimbabwe (324).

As noted in Kabeer's conceptual model, resources, agency, and achievements were interrelated and indivisible for the empowerment of the Hope Ladies in our study. The Hope Ladies reported that improved resources in the form of supplemental income improved their ability to participate in financial and household decisions. The recognition of the Hope Ladies as a community resource for reproductive health widened their social network and gave them more social capital. Increased knowledge, self-confidence, and expanded social network empowered the Hope Ladies to see and advocate for the women in their communities by speaking out against the unequal power relations with their spouses, disparate access to healthcare, and fear of stigma in being diagnosed with cervical cancer.

As demonstrated in our causal pathway, the relational and economic empowerment of the Hope Ladies is necessary but not sufficient to produce the pre-conditions of financial and logistical means of buying and selling HPV self-sampling kits. For example, the empowerment of the Hope Ladies alone cannot protect their time against competing household priorities such as caring for another family member. Leveraging the social entrepreneurship structure and increasing their financial incentives would bolster their empowerment and protect the Hope Ladies' time to sell more kits which would modify the effects of the aforementioned contextual moderators.

Our study has several limitations. First, the sample size was small, and the Hope Ladies who chose to participate in the study may have been different from those who did not. In addition, the number of respondents varied widely among the survey questions because the data collection took place during the week Peru closed its borders due to the COVID-19 pandemic. These factors may negatively impact the generalizability of our findings. Secondly, the interviews took place in the participants' homes, which may have biased their responses due to privacy concerns. Although the interviewers were fluent in Spanish and the Hope Project administrators were not present during the interview, the presence of other study personnel may have contributed to social desirability bias. Despite the limitations, we rigorously evaluated the financial and relational empowerment of the Hope Ladies, using multiple well-established conceptual frameworks and mixed-methods.

In conclusion, the participants in the community-based HPV self-sampling social entrepreneurship experienced financial and relational empowerment in the program. More research is needed to test and demonstrate the association between the Hope Ladies' empowerment and cervical cancer screening uptake by community members to scale this intervention to a broader population.

Chapter 5. CONCLUSION

This dissertation drew on implementation science as a guiding framework to understand how to promote the systematic uptake of research findings as it relates to global cervical cancer elimination (19). The overall goals of this dissertation were to (1) synthesize the current state of science as it relates to cervical cancer elimination; (2) establish the necessary baseline for future economic evaluations for HPV self-sampling in Peru and other LMIC settings; and (3) provide a theory-informed implementation guidance for the scale-up of HPV self-sampling using the social entrepreneurship model. This dissertation used scoping review, micro-costing, and mixed-methods designs and analysis to achieve these aims, respectively. For each aim, we present a summary of the findings and the future research implications.

5.1 A Framework for Cervical Cancer Elimination in Low-and-Middle-Income Countries: A Scoping Review and Roadmap for Interventions and Research Priorities

Aim 1 considered how we can achieve cervical cancer elimination in LMICs through the WHO's 90-70-90 target (also known as "triple-intervention"), which aims to vaccinate 90% of girls by age 15, screen 70% of women with a high-performance test by ages 35 and 45, and treat 90% of women with cervical disease by 2030 (24). Applying the scoping review method to WHO's "Life-course approach to cervical cancer interventions" (36), we provided a high-level overview of the current state of science and priority research questions for primary and secondary prevention strategies. We organized our findings into a logic model that provides a visual guide for intersectoral collaboration and dedicated a section to cervical cancer elimination among women living with HIV who have greater prevalence and persistence of HPV infection and progression to HPV-

associated cancers. We concluded that global cervical cancer elimination will require multi-faceted approaches that focus on scaling up HPV vaccine uptake and screening and treatment strategies that are simple, effective and affordable. To this end, we proposed a "comprehensive prevention packages" that contain interventions such as reduced vaccination dosage approaches, screening with HPV self-sampling and other low-cost oncogenetic markers and treatment of precancerous lesions with thermal ablation that can be tailored to the contextual needs of the implementation settings. Moving forward, such packages can be used in a demonstration project to test effectiveness for cervical cancer elimination at the population-level.

5.2 Cost of Community-based HPV Self-sampling in Peru: A Micro-costing Study

Aim 2 evaluated a real-world implementation case of a community-based HPV self-sampling program called the Hope Project in Peru. Specifically, we applied micro-costing methods to determine the total and unit costs of the Hope Project to address the evidence gap of costing information from LMICs. We estimated the economic cost of three program activities from the provider perspective: 1) recruitment and training of the Hope Ladies (147.51 USD per Hope Lady); (2) Hope Ladies offering HPV self-sampling kits (*care*HPV) in their communities (45.39 USD per kit); and (3) Hope Ladies linking screened women with appropriate follow-up care (55.64 USD per woman who completed the screening pathway). The total annualized program cost was 271,625.29 USD. During the study period (November 2018 to March 2020), the program recruited and trained 62 Hope Ladies, who distributed 4,882 HPV self-sampling kits to women in their communities. Of the screened women, 586 (12.0%) tested positive for HPV, and of these, 365 (62.3%) were successfully linked to VIA in their public health clinic for triage. In our study, community-based HPV self-sampling demonstrated a great potential to improve screening

coverage and minimize loss to follow-up among HPV positive women. Our results can serve as input parameters for future economic modeling studies to compare the potential health gains or losses (e.g., quality-adjusted or disability-adjusted life-years) of HPV self-sampling to that of current intervention in Peru (e.g., cytology or VIA).

5.3 Evaluation of women's empowerment in a community-based HPV self-sampling social entrepreneurship program (Hope Project) in Peru: Mixed-method study

In Aim 3, we evaluated the financial and relational empowerment of the social entrepreneurs, Hope Ladies, after participating in the Hope Project. The Hope Ladies buy HPV self-sampling kits from the Hope Project and sell them in their communities door-to-door to increase cervical cancer screening coverage. They keep a small profit of 5 PEN (~1.50 USD) as an incentive for wider distribution. In a 9-question survey adapted from ICRW's economic empowerment indicators and RLT (309, 325), all Hope Ladies indicated an increase in social contacts (n=14/14, 100%) and confidence in discussing reproductive topics (n=14/14, 100%), most reported increased unaccompanied visits to a healthcare provider (n=12/14, 86%) and improved ability to make household decisions about money (n=3/7, 57% pre-intervention vs n=11/12, 92% post-intervention). The qualitative interviews were analyzed using Kabeer's conceptual framework of empowerment. The Hope Ladies discussed improvement in 1) resources (balancing the roles between the household and working as a Hope Lady, camaraderie with other Hope Ladies, recognition from the community as a resource); 2) agency (improved ability to express themselves, increased knowledge about reproductive health, ability to speak out against male-dominant culture); and 3) achievement (increased economic assets, improved ability to make financial decisions, widened social network and technology skills development). Additionally, we

developed a causal pathway to illustrate the relationship between empowerment and the effectiveness of the Hope Project. Our findings can be used for further hypothesis generation to elucidate relationship between empowerment and social entrepreneurs' performance and build a sustainable model of HPV self-sampling scale-up in low-resource settings.

5.4 Final Remarks

This dissertation has several limitations. Aim 1 used a narrative approach in scoping the literature, hence, was not a comprehensive, systematic review of the topic. For both Aims 2 and 3, the data source was limited to the Hope Project itself, which could limit the generalizability of its findings. However, this dissertation offers a unique interdisciplinary perspective that combines nursing, epidemiology, and economics, and sets the stage for continued collaboration between researchers and practitioners. Global cervical cancer elimination will require tailored and concerted efforts to leverage all the technologies and innovation available to us. We hope to carry forward our work to investigate other pertinent implementation outcomes such as sustainability of the social entrepreneurship model in cervical cancer screening and effectiveness of HPV self-sampling at the population level using economic evaluations.

5.5 SUPPLEMENTARY MATERIAL

Appendix 2.1 Search results

Prevention node	Prevention strategy	Database	Search strategy/keywords	Total number of studies retrieved	Date of retrieval	Number of studies included in the manuscript
Primary prevention	HPV vaccination	PubMed	((("Uterine Cervical Neoplasms"[Mesh]) AND (("2006/1/1"[Date - Publication] : "2019/1/25"[Date - Publication])) AND ((ffrft[Filter]) AND (meta-analysis[Filter] OR randomizedcontrolledtrial[Filter] OR systematicreview[Filter])) AND ((ffrft[Filter]) AND (meta-analysis[Filter] OR randomizedcontrolledtrial[Filter] OR systematicreview[Filter]))) AND ((ffrft[Filter]) AND (booksdocs[Filter] OR clinicaltrial[Filter] OR clinicaltrialphasei[Filter] OR clinicaltrialphaseii[Filter] OR clinicaltrialphaseiii[Filter] OR clinicaltrialphaseiv[Filter] OR controlledclinicaltrial[Filter] OR journalarticle[Filter] OR meta-analysis[Filter] OR multicenterstudy[Filter] OR observationalstudy[Filter] OR pragmaticclinicaltrial[Filter] OR randomizedcontrolledtrial[Filter] OR review[Filter] OR systematicreview[Filter]) AND (fft[Filter]) AND (english[Filter])) AND ((ffrft[Filter]) AND (booksdocs[Filter] OR clinicaltrial[Filter] OR clinicaltrialphasei[Filter] OR clinicaltrialphaseii[Filter] OR clinicaltrialphaseiii[Filter] OR clinicaltrialphaseiv[Filter] OR controlledclinicaltrial[Filter] OR journalarticle[Filter] OR meta-analysis[Filter] OR multicenterstudy[Filter] OR observationalstudy[Filter] OR pragmaticclinicaltrial[Filter] OR randomizedcontrolledtrial[Filter] OR review[Filter] OR systematicreview[Filter]) AND (fft[Filter]) AND (english[Filter]))) AND (hpv vaccine[MeSH Terms])	107	21-Jan-20	20
		Embase	('hpv'/exp OR hpv) AND vaccin* AND ('efficacy'/exp OR efficacy OR effectiveness OR 'sensitivity'/exp OR sensitivity OR 'specificity'/exp OR specificity) AND (('meta analysis'/de OR 'randomized controlled trial'/de OR 'systematic review'/de)) AND [2010-2020]/py	408	5-Jan-21	

	Tobacco cessation	PubMed	Search: (("Uterine Cervical Neoplasms"[Mesh]) AND (("2006/1/1"[Date - Publication] : "2019/1/25"[Date - Publication])) AND ((ffrft[Filter]) AND (meta-analysis[Filter] OR randomizedcontrolledtrial[Filter] OR systematicreview[Filter])) AND ((ffrft[Filter]) AND (meta-analysis[Filter] OR randomizedcontrolledtrial[Filter] OR systematicreview[Filter]))) AND (tobacco) Filters: Free full text, Full text, Books and Documents, Clinical Trial, Clinical Trial, Phase I, Clinical Trial, Phase II, Clinical Trial, Phase III, Clinical Trial, Phase IV, Controlled Clinical Trial, Journal Article, Meta-Analysis, Multicenter Study, Observational Study, Pragmatic Clinical Trial, Randomized Controlled Trial, Review, Systematic Review, English	8	21-Jan-20	1
		Embase	(cervical AND cancer) AND (tobacco AND cessation) OR (tobacco AND educat*) AND ('meta analysis'/de OR 'randomized controlled trial'/de OR 'systematic review'/de) AND ('article'/it OR 'conference abstract'/it OR 'conference paper'/it OR 'conference review'/it OR 'review'/it) AND ('efficacy'/exp OR efficacy OR effectiveness OR 'sensitivity'/exp OR sensitivity OR 'specificity'/exp OR specificity) AND [2010-2020]/py	3	5-Jan-21	
		Embase	(cervical AND cancer) AND ((tobacco AND cessation) OR (tobacco AND educat*)) AND ('efficacy'/exp OR efficacy OR effectiveness OR 'sensitivity'/exp OR sensitivity OR 'specificity'/exp OR specificity) AND [2010-2020]/py	19	5-Jan-21	
	Sexual education	PubMed	((("Uterine Cervical Neoplasms"[Mesh]) AND (("2006/1/1"[Date - Publication] : "2019/1/25"[Date - Publication])) AND ((ffrft[Filter]) AND (meta-analysis[Filter] OR randomizedcontrolledtrial[Filter] OR systematicreview[Filter])) AND ((ffrft[Filter]) AND (meta-analysis[Filter] OR randomizedcontrolledtrial[Filter] OR systematicreview[Filter]))) AND ((ffrft[Filter]) AND (booksdocs[Filter] OR clinicaltrial[Filter] OR clinicaltrialphasei[Filter] OR clinicaltrialphaseii[Filter] OR clinicaltrialphaseiii[Filter] OR clinicaltrialphaseiv[Filter] OR controlledclinicaltrial[Filter] OR journalarticle[Filter] OR meta-analysis[Filter] OR multicenterstudy[Filter] OR observationalstudy[Filter] OR pragmaticclinicaltrial[Filter] OR randomizedcontrolledtrial[Filter] OR review[Filter] OR systematicreview[Filter]) AND (fft[Filter]) AND (english[Filter])) AND ((ffrft[Filter]) AND (booksdocs[Filter] OR clinicaltrial[Filter] OR clinicaltrialphasei[Filter] OR clinicaltrialphaseii[Filter] OR clinicaltrialphaseiii[Filter] OR clinicaltrialphaseiv[Filter] OR controlledclinicaltrial[Filter] OR journalarticle[Filter] OR meta-analysis[Filter] OR multicenterstudy[Filter]	5	21-Jan-20	0

			OR observationalstudy[Filter] OR pragmaticclinicaltrial[Filter] OR randomizedcontrolledtrial[Filter] OR review[Filter] OR systematicreview[Filter]) AND (fft[Filter]) AND (english[Filter]))) AND (sex education)			
		Embase	(cervical AND cancer) AND (sex* AND education) AND ('meta analysis'/de OR 'randomized controlled trial'/de OR 'systematic review'/de) AND ('article'/it OR 'conference abstract'/it OR 'conference paper'/it OR 'conference review'/it OR 'review'/it) AND ('efficacy'/exp OR efficacy OR effectiveness OR 'sensitivity'/exp OR sensitivity OR 'specificity'/exp OR specificity) AND [2010-2020]/py	12	5-Jan-21	
		Embase	(cervical AND cancer) AND (sex* AND education) AND ('efficacy'/exp OR efficacy OR effectiveness OR 'sensitivity'/exp OR sensitivity OR 'specificity'/exp OR specificity) AND [2010-2020]/py	153	5-Jan-21	
	Condoms	PubMed	((("Uterine Cervical Neoplasms"[Mesh]) AND (("2006/1/1"[Date - Publication] : "2019/1/25"[Date - Publication])) AND ((ffrft[Filter]) AND (meta-analysis[Filter] OR randomizedcontrolledtrial[Filter] OR systematicreview[Filter])) AND ((ffrft[Filter]) AND (meta-analysis[Filter] OR randomizedcontrolledtrial[Filter] OR systematicreview[Filter]))) AND ((ffrft[Filter]) AND (booksdocs[Filter] OR clinicaltrial[Filter] OR clinicaltrialphasei[Filter] OR clinicaltrialphaseii[Filter] OR clinicaltrialphaseiii[Filter] OR clinicaltrialphaseiv[Filter] OR controlledclinicaltrial[Filter] OR journalarticle[Filter] OR meta-analysis[Filter] OR multicenterstudy[Filter] OR observationalstudy[Filter] OR pragmaticclinicaltrial[Filter] OR randomizedcontrolledtrial[Filter] OR review[Filter] OR systematicreview[Filter]) AND (fft[Filter]) AND (english[Filter])) AND ((ffrft[Filter]) AND (booksdocs[Filter] OR clinicaltrial[Filter] OR clinicaltrialphasei[Filter] OR clinicaltrialphaseii[Filter] OR clinicaltrialphaseiii[Filter] OR clinicaltrialphaseiv[Filter] OR controlledclinicaltrial[Filter] OR journalarticle[Filter] OR meta-analysis[Filter] OR multicenterstudy[Filter] OR observationalstudy[Filter] OR pragmaticclinicaltrial[Filter] OR randomizedcontrolledtrial[Filter] OR review[Filter] OR systematicreview[Filter]) AND (fft[Filter]) AND (english[Filter]))) AND (condom)	5	21-Jan-20	2

		Embase	(cervical AND cancer) AND (condom) AND ('meta analysis'/de OR 'randomized controlled trial'/de OR 'systematic review'/de) AND ('article'/it OR 'conference abstract'/it OR 'conference paper'/it OR 'conference review'/it OR 'review'/it) AND ('efficacy'/exp OR efficacy OR effectiveness OR 'sensitivity'/exp OR sensitivity OR 'specificity'/exp OR specificity) AND [2010-2020]/py	6	5-Jan-21	
		Embase	(cervical AND cancer) AND (condom) AND ('efficacy'/exp OR efficacy OR effectiveness OR 'sensitivity'/exp OR sensitivity OR 'specificity'/exp OR specificity) AND [2010-2020]/py	53	5-Jan-21	
	Voluntary medical male circumcision	PubMed	((("Uterine Cervical Neoplasms"[Mesh]) AND (("2006/1/1"[Date - Publication] : "2019/1/25"[Date - Publication])) AND ((ffrft[Filter]) AND (meta-analysis[Filter] OR randomizedcontrolledtrial[Filter] OR systematicreview[Filter])) AND ((ffrft[Filter]) AND (meta-analysis[Filter] OR randomizedcontrolledtrial[Filter] OR systematicreview[Filter]))) AND ((ffrft[Filter]) AND (booksdocs[Filter] OR clinicaltrial[Filter] OR clinicaltrialphasei[Filter] OR clinicaltrialphaseii[Filter] OR clinicaltrialphaseiii[Filter] OR clinicaltrialphaseiv[Filter] OR controlledclinicaltrial[Filter] OR journalarticle[Filter] OR meta-analysis[Filter] OR multicenterstudy[Filter] OR observationalstudy[Filter] OR pragmaticclinicaltrial[Filter] OR randomizedcontrolledtrial[Filter] OR review[Filter] OR systematicreview[Filter]) AND (fft[Filter]) AND (english[Filter])) AND ((ffrft[Filter]) AND (booksdocs[Filter] OR clinicaltrial[Filter] OR clinicaltrialphasei[Filter] OR clinicaltrialphaseii[Filter] OR clinicaltrialphaseiii[Filter] OR clinicaltrialphaseiv[Filter] OR controlledclinicaltrial[Filter] OR journalarticle[Filter] OR meta-analysis[Filter] OR multicenterstudy[Filter] OR observationalstudy[Filter] OR pragmaticclinicaltrial[Filter] OR randomizedcontrolledtrial[Filter] OR review[Filter] OR systematicreview[Filter]) AND (fft[Filter]) AND (english[Filter]))) AND (male circumcision)	2	21-Jan-20	3
		Embase	(cervical AND cancer) AND (male AND circumcision) AND ('meta analysis'/de OR 'randomized controlled trial'/de OR 'systematic review'/de) AND ('article'/it OR 'conference abstract'/it OR 'conference paper'/it OR 'conference review'/it OR 'review'/it) AND ('efficacy'/exp OR efficacy OR effectiveness OR 'sensitivity'/exp OR sensitivity OR 'specificity'/exp OR specificity) AND [2010-2020]/py	1	5-Jan-21	

		Embase	(cervical AND cancer) AND (male AND circumcision) AND ('efficacy'/exp OR efficacy OR effectiveness OR 'sensitivity'/exp OR sensitivity OR 'specificity'/exp OR specificity) AND [2010-2020]/py	10	5-Jan-21	
Secondary prevention	HPV test	PubMed	((("Uterine Cervical Neoplasms"[Mesh]) AND (("2006/1/1"[Date - Publication] : "2019/1/25"[Date - Publication])) AND ((ffrft[Filter]) AND (meta-analysis[Filter] OR randomizedcontrolledtrial[Filter] OR systematicreview[Filter])) AND ((ffrft[Filter]) AND (meta-analysis[Filter] OR randomizedcontrolledtrial[Filter] OR systematicreview[Filter]))) AND ((ffrft[Filter]) AND (booksdocs[Filter] OR clinicaltrial[Filter] OR clinicaltrialphasei[Filter] OR clinicaltrialphaseii[Filter] OR clinicaltrialphaseiii[Filter] OR clinicaltrialphaseiv[Filter] OR controlledclinicaltrial[Filter] OR journalarticle[Filter] OR meta-analysis[Filter] OR multicenterstudy[Filter] OR observationalstudy[Filter] OR pragmaticclinicaltrial[Filter] OR randomizedcontrolledtrial[Filter] OR review[Filter] OR systematicreview[Filter]) AND (fft[Filter]) AND (english[Filter])) AND ((ffrft[Filter]) AND (booksdocs[Filter] OR clinicaltrial[Filter] OR clinicaltrialphasei[Filter] OR clinicaltrialphaseii[Filter] OR clinicaltrialphaseiii[Filter] OR clinicaltrialphaseiv[Filter] OR controlledclinicaltrial[Filter] OR journalarticle[Filter] OR meta-analysis[Filter] OR multicenterstudy[Filter] OR observationalstudy[Filter] OR pragmaticclinicaltrial[Filter] OR randomizedcontrolledtrial[Filter] OR review[Filter] OR systematicreview[Filter]) AND (fft[Filter]) AND (english[Filter]))) AND (hpv test*)	185	21-Jan-20	18
		Embase	(cervical AND cancer) AND (hpv AND test*) AND ('meta analysis'/de OR 'randomized controlled trial'/de OR 'systematic review'/de) AND ('article'/it OR 'conference abstract'/it OR 'conference paper'/it OR 'conference review'/it OR 'review'/it) AND ('efficacy'/exp OR efficacy OR effectiveness OR 'sensitivity'/exp OR sensitivity OR 'specificity'/exp OR specificity) AND [2010-2020]/py	245	5-Jan-21	
	VIA	PubMed	((("Uterine Cervical Neoplasms"[Mesh]) AND (("2006/1/1"[Date - Publication] : "2019/1/25"[Date - Publication])) AND ((ffrft[Filter]) AND (meta-analysis[Filter] OR randomizedcontrolledtrial[Filter] OR systematicreview[Filter])) AND ((ffrft[Filter]) AND (meta-analysis[Filter] OR randomizedcontrolledtrial[Filter] OR systematicreview[Filter]))) AND ((ffrft[Filter]) AND (booksdocs[Filter] OR clinicaltrial[Filter] OR clinicaltrialphasei[Filter] OR clinicaltrialphaseii[Filter] OR clinicaltrialphaseiii[Filter] OR clinicaltrialphaseiv[Filter] OR controlledclinicaltrial[Filter] OR journalarticle[Filter] OR meta-	59	21-Jan-20	10

			analysis[Filter] OR multicenterstudy[Filter] OR observationalstudy[Filter] OR pragmaticclinicaltrial[Filter] OR randomizedcontrolledtrial[Filter] OR review[Filter] OR systematicreview[Filter]) AND (fft[Filter]) AND (english[Filter])) AND ((ffrft[Filter]) AND (booksdocs[Filter] OR clinicaltrial[Filter] OR clinicaltrialphasei[Filter] OR clinicaltrialphaseii[Filter] OR clinicaltrialphaseiii[Filter] OR clinicaltrialphaseiv[Filter] OR controlledclinicaltrial[Filter] OR journalarticle[Filter] OR meta-analysis[Filter] OR multicenterstudy[Filter] OR observationalstudy[Filter] OR pragmaticclinicaltrial[Filter] OR randomizedcontrolledtrial[Filter] OR review[Filter] OR systematicreview[Filter]) AND (fft[Filter]) AND (english[Filter]))) AND (visual inspection with acetic acid OR VIA)			
		Embase	(cervical AND cancer) AND (visual AND inspection AND with AND acetic AND acid OR via) AND ('meta analysis'/de OR 'randomized controlled trial'/de OR 'systematic review'/de) AND ('article'/it OR 'conference abstract'/it OR 'conference paper'/it OR 'conference review'/it OR 'review'/it) AND ('efficacy'/exp OR efficacy OR effectiveness OR 'sensitivity'/exp OR sensitivity OR 'specificity'/exp OR specificity) AND [2010-2020]/py	118	5-Jan-21	
	Cytology	PubMed	((("Uterine Cervical Neoplasms"[Mesh]) AND (("2006/1/1"[Date - Publication] : "2019/1/25"[Date - Publication])) AND ((ffrft[Filter]) AND (meta-analysis[Filter] OR randomizedcontrolledtrial[Filter] OR systematicreview[Filter])) AND ((ffrft[Filter]) AND (meta-analysis[Filter] OR randomizedcontrolledtrial[Filter] OR systematicreview[Filter]))) AND ((ffrft[Filter]) AND (booksdocs[Filter] OR clinicaltrial[Filter] OR clinicaltrialphasei[Filter] OR clinicaltrialphaseii[Filter] OR clinicaltrialphaseiii[Filter] OR clinicaltrialphaseiv[Filter] OR controlledclinicaltrial[Filter] OR journalarticle[Filter] OR meta-analysis[Filter] OR multicenterstudy[Filter] OR observationalstudy[Filter] OR pragmaticclinicaltrial[Filter] OR randomizedcontrolledtrial[Filter] OR review[Filter] OR systematicreview[Filter]) AND (fft[Filter]) AND (english[Filter])) AND ((ffrft[Filter]) AND (booksdocs[Filter] OR clinicaltrial[Filter] OR clinicaltrialphasei[Filter] OR clinicaltrialphaseii[Filter] OR clinicaltrialphaseiii[Filter] OR clinicaltrialphaseiv[Filter] OR controlledclinicaltrial[Filter] OR journalarticle[Filter] OR meta-analysis[Filter] OR multicenterstudy[Filter] OR observationalstudy[Filter] OR pragmaticclinicaltrial[Filter] OR randomizedcontrolledtrial[Filter] OR review[Filter] OR systematicreview[Filter]) AND (fft[Filter]) AND (english[Filter]))) AND (pap OR cytology)	301	21-Jan-20	3

		Embase	(cervical AND cancer) AND (cytology OR pap) AND ('meta analysis'/de OR 'randomized controlled trial'/de OR 'systematic review'/de) AND ('article'/it OR 'conference abstract'/it OR 'conference paper'/it OR 'conference review'/it OR 'review'/it) AND ('efficacy'/exp OR efficacy OR effectiveness OR 'sensitivity'/exp OR sensitivity OR 'specificity'/exp OR specificity) AND [2010-2020]/py	304	5-Jan-21	
	Thermal ablation	PubMed	((("Uterine Cervical Neoplasms"[Mesh]) AND (("2006/1/1"[Date - Publication] : "2019/1/25"[Date - Publication])) AND ((ffrft[Filter]) AND (meta-analysis[Filter] OR randomizedcontrolledtrial[Filter] OR systematicreview[Filter])) AND ((ffrft[Filter]) AND (meta-analysis[Filter] OR randomizedcontrolledtrial[Filter] OR systematicreview[Filter]))) AND ((ffrft[Filter]) AND (booksdocs[Filter] OR clinicaltrial[Filter] OR clinicaltrialphasei[Filter] OR clinicaltrialphaseii[Filter] OR clinicaltrialphaseiii[Filter] OR clinicaltrialphaseiv[Filter] OR controlledclinicaltrial[Filter] OR journalarticle[Filter] OR meta-analysis[Filter] OR multicenterstudy[Filter] OR observationalstudy[Filter] OR pragmaticclinicaltrial[Filter] OR randomizedcontrolledtrial[Filter] OR review[Filter] OR systematicreview[Filter]) AND (fft[Filter]) AND (english[Filter])) AND ((ffrft[Filter]) AND (booksdocs[Filter] OR clinicaltrial[Filter] OR clinicaltrialphasei[Filter] OR clinicaltrialphaseii[Filter] OR clinicaltrialphaseiii[Filter] OR clinicaltrialphaseiv[Filter] OR controlledclinicaltrial[Filter] OR journalarticle[Filter] OR meta-analysis[Filter] OR multicenterstudy[Filter] OR observationalstudy[Filter] OR pragmaticclinicaltrial[Filter] OR randomizedcontrolledtrial[Filter] OR review[Filter] OR systematicreview[Filter]) AND (fft[Filter]) AND (english[Filter]))) AND (thermal ablation OR thermocoagulation)	2	21-Jan-20	11
		Embase	(cervical AND cancer) AND (thermal AND ablation OR thermocoagulation) AND ('meta analysis'/de OR 'randomized controlled trial'/de OR 'systematic review'/de) AND ('article'/it OR 'conference abstract'/it OR 'conference paper'/it OR 'conference review'/it OR 'review'/it) AND ('efficacy' OR effectiveness) AND [2010-2020]/py	12	5-Jan-21	
	Cryotherapy	PubMed	((("Uterine Cervical Neoplasms"[Mesh]) AND (("2006/1/1"[Date - Publication] : "2019/1/25"[Date - Publication])) AND ((ffrft[Filter]) AND (meta-analysis[Filter] OR randomizedcontrolledtrial[Filter] OR systematicreview[Filter])) AND ((ffrft[Filter]) AND (meta-analysis[Filter] OR randomizedcontrolledtrial[Filter] OR systematicreview[Filter]))) AND ((ffrft[Filter]) AND (booksdocs[Filter] OR clinicaltrial[Filter] OR clinicaltrialphasei[Filter] OR clinicaltrialphaseii[Filter] OR	10	21-Jan-20	7

			clinicaltrialphaseiii[Filter] OR clinicaltrialphaseiv[Filter] OR controlledclinicaltrial[Filter] OR journalarticle[Filter] OR meta-analysis[Filter] OR multicenterstudy[Filter] OR observationalstudy[Filter] OR pragmaticclinicaltrial[Filter] OR randomizedcontrolledtrial[Filter] OR review[Filter] OR systematicreview[Filter]) AND (fft[Filter]) AND (english[Filter])) AND ((ffrft[Filter]) AND (booksdocs[Filter] OR clinicaltrial[Filter] OR clinicaltrialphasei[Filter] OR clinicaltrialphaseii[Filter] OR clinicaltrialphaseiii[Filter] OR clinicaltrialphaseiv[Filter] OR controlledclinicaltrial[Filter] OR journalarticle[Filter] OR meta-analysis[Filter] OR multicenterstudy[Filter] OR observationalstudy[Filter] OR pragmaticclinicaltrial[Filter] OR randomizedcontrolledtrial[Filter] OR review[Filter] OR systematicreview[Filter]) AND (fft[Filter]) AND (english[Filter]))) AND (cryotherapy)			
		Embase	(cervical AND cancer) AND (cryotherapy) AND ('meta analysis'/de OR 'randomized controlled trial'/de OR 'systematic review'/de) AND ('article'/it OR 'conference abstract'/it OR 'conference paper'/it OR 'conference review'/it OR 'review'/it) AND [2010-2020]/py	67	5-Jan-21	
	LEEP	PubMed	((("Uterine Cervical Neoplasms"[Mesh]) AND (("2006/1/1"[Date - Publication] : "2019/1/25"[Date - Publication])) AND ((ffrft[Filter]) AND (meta-analysis[Filter] OR randomizedcontrolledtrial[Filter] OR systematicreview[Filter])) AND ((ffrft[Filter]) AND (meta-analysis[Filter] OR randomizedcontrolledtrial[Filter] OR systematicreview[Filter]))) AND ((ffrft[Filter]) AND (booksdocs[Filter] OR clinicaltrial[Filter] OR clinicaltrialphasei[Filter] OR clinicaltrialphaseii[Filter] OR clinicaltrialphaseiii[Filter] OR clinicaltrialphaseiv[Filter] OR controlledclinicaltrial[Filter] OR journalarticle[Filter] OR meta-analysis[Filter] OR multicenterstudy[Filter] OR observationalstudy[Filter] OR pragmaticclinicaltrial[Filter] OR randomizedcontrolledtrial[Filter] OR review[Filter] OR systematicreview[Filter]) AND (fft[Filter]) AND (english[Filter])) AND ((ffrft[Filter]) AND (booksdocs[Filter] OR clinicaltrial[Filter] OR clinicaltrialphasei[Filter] OR clinicaltrialphaseii[Filter] OR clinicaltrialphaseiii[Filter] OR clinicaltrialphaseiv[Filter] OR controlledclinicaltrial[Filter] OR journalarticle[Filter] OR meta-analysis[Filter] OR multicenterstudy[Filter] OR observationalstudy[Filter] OR pragmaticclinicaltrial[Filter] OR randomizedcontrolledtrial[Filter] OR review[Filter] OR	7	21-Jan-20	6

			systematicreview[Filter]) AND (fft[Filter]) AND (english[Filter]))) AND (LEEP)			
		Embase	(cervical AND cancer) AND (leep OR 'loop electrosurgical excision') AND ('meta analysis'/de OR 'randomized controlled trial'/de OR 'systematic review'/de) AND ('article'/it OR 'conference abstract'/it OR 'conference paper'/it OR 'conference review'/it OR 'review'/it) AND [2010-2020]/py	37	5-Jan-21	
	HPV self-sampling	PubMed	((("Uterine Cervical Neoplasms"[Mesh]) AND (("2006/1/1"[Date - Publication] : "2019/1/25"[Date - Publication])) AND ((ffrft[Filter]) AND (meta-analysis[Filter] OR randomizedcontrolledtrial[Filter] OR systematicreview[Filter])) AND ((ffrft[Filter]) AND (meta-analysis[Filter] OR randomizedcontrolledtrial[Filter] OR systematicreview[Filter]))) AND ((ffrft[Filter]) AND (booksdocs[Filter] OR clinicaltrial[Filter] OR clinicaltrialphasei[Filter] OR clinicaltrialphaseii[Filter] OR clinicaltrialphaseiii[Filter] OR clinicaltrialphaseiv[Filter] OR controlledclinicaltrial[Filter] OR journalarticle[Filter] OR meta-analysis[Filter] OR multicenterstudy[Filter] OR observationalstudy[Filter] OR pragmaticclinicaltrial[Filter] OR randomizedcontrolledtrial[Filter] OR review[Filter] OR systematicreview[Filter]) AND (fft[Filter]) AND (english[Filter])) AND ((ffrft[Filter]) AND (booksdocs[Filter] OR clinicaltrial[Filter] OR clinicaltrialphasei[Filter] OR clinicaltrialphaseii[Filter] OR clinicaltrialphaseiii[Filter] OR clinicaltrialphaseiv[Filter] OR controlledclinicaltrial[Filter] OR journalarticle[Filter] OR meta-analysis[Filter] OR multicenterstudy[Filter] OR observationalstudy[Filter] OR pragmaticclinicaltrial[Filter] OR randomizedcontrolledtrial[Filter] OR review[Filter] OR systematicreview[Filter]) AND (fft[Filter]) AND (english[Filter]))) AND (HPV self-sampl* OR HPV self-collect*)	50	21-Jan-20	13
		Embase	(hpv AND 'self sampl*' OR hpv) AND 'self collect*' AND (cervical AND cancer) AND ('meta analysis'/de OR 'randomized controlled trial'/de OR 'systematic review'/de) AND ('article'/it OR 'conference abstract'/it OR 'conference paper'/it OR 'conference review'/it OR 'review'/it) AND [2010-2020]/py	57	5-Jan-21	

Appendix 2.2 Data abstraction

	Author	Year	Study name	Study Design	Location	Population	Intervention	Intervne tion # dose	Comparison	Comparison # dose	Outcomes	Sample size
Efficacy	Huh et al.(46)	2017	"Final efficacy, immunogenicity, and safety analyses of a nine-valent human papillomavirus vaccine in women aged 16-26 years: a randomised, double-blind trial"	RCT	18 countries	16-26yo women	9vHPV	3 (0, 2, 6)	4vHPV	3 (0, 2, 6)	HSIL, persistent HPV infections, antibody titer	14,215 9vHPV (n=7,106) 4vHPV (n=7,109)
	Paavonen et al.(326)	2009	PATRICIA	RCT	14 countries	15-25 yo women	2vHPV	3 (0, 1, 6)	Hep A vaccine	3 (0, 1, 6)	CIN2+, persistent infections with 16/18 and other HR types	16,162 Vaccine (n=8,093) Control (n=8,069)
	Apter et al.(327)	2015	PATRICIA	RCT	14 countries	15-25 yo women	2vHPV	3 (0, 1, 6)	Hep A vaccine	3 (0, 1, 6)	CIN2+, persistent infections with 16/18 and other HR types	18,644 Vaccine (n=9,319) Control (n=9,325)
	Garland et al.(44)	2007	FUTURES I	RCT	16 countries	16-24yo women	4vHPV	3	Placebo	3	Any CIN or AIS Antibody titer	5,455 Vaccine (n=2,723) Control (n=2,732)
	Futures II study group(45)	2007	FUTURES II	RCT	16 countries	15-26 yo women	4vHPV	3	Placebo	3	HSIL or CIN2+, AIS, CC	12,167 Vaccine (n=5,305) Control (n=5260)

	Kahn et al.(201)	2013	"Immunogenicity and safety of the human papillomavirus 6, 11, 16, 18 vaccine in HIV-infected young women"	RCT	US and PR	HIV+ 16-23yo women	4vHPV	3 (0, 2, 6)	HIV-neg women	3 (0, 2, 6)	Antibody titer	366 Vaccine (n=69; no ART n=30; ART) Control (n=267 HIV negative)
	Kojic et al.(202)	2014	AIDS Clinical Trials Group	RCT	US, Brazil, South Africa	HIV+ 13-45yo women	4vHPV	3 (0, 2, 6)	Stratum A (>350 Cells/μL) Stratum B (201–350 Cells/μL) Stratum C (≤200 Cells/μL)	3 (0, 2, 6)	Immunogenicity	315 Stratum A (n=127) Stratum B (n=95) Stratum C (n=93)
	Giacomet et al.(203)	2014	"Safety and immunogenicity of a quadrivalent human papillomavirus vaccine in HIV-infected and HIV-negative adolescents and young adults"	Matched cohort	Italy	HIV+ 13-27yo men and women	4vHPV	3 (0, 2, 6)	HIV-neg	3 (0, 2, 6)	Immunogenicity	92 Virally suppressed HIV+ (n=46) HIV negative (n=46)
	McClymont et al.(204)	2019	HPV in HIV Study Group	Cohort	Canada	HIV+ 13-66yo women	4vHPV	3 (0, 2, 6)	Unvaccinated HIV+ Unvaccinated HIV-	3 (0, 2, 6)	6 month persistent HPV CIN2+	279

	Mugo et al.(205)	2018	"Quadrivalent HPV vaccine in HIV-1-infected early adolescent girls and boys in Kenya: Month 7 and 12 post vaccine immunogenicity and correlation with immune status"	Noninferiority	Kenya	HIV+ 9-14yo girls and boys	4vHPV	3 (0, 2, 6)	Vaccinated historical HIV+ and HIV- controls	3 (0, 2, 6)	Immunogenicity	189 Girls (n=100) Boys (n=80)
	Levin et al.(206)	2010	IMPAACT PACTG P1047	RCT	US	HIV+ 7-12yo girls and boys	4vHPV	3 (0, 2, 6)	Placebo	3 (0, 2, 6)	Immunogenicity	126 4vHPV (n=96) Placebo (n=30)
	Weinberg et al.(207)	2012	IMPAACT PACTG P1047	RCT	N/A	HIV+ 7-12yo girls and boys	4vHPV	3 (0, 2, 6) + booster at 24 months	Delayed 4vHPV	3 (0, 2, 6)	Immunogenicity	126 Immediate injection (n=96) Delayed (n=30)
	Toft et al.(208)	2014	"Comparison of the immunogenicity of Cervarix® and Gardasil® human papillomavirus vaccines for oncogenic non-vaccine serotypes HPV-31, HPV-33, and HPV-45 in HIV-infected adults"	RCT	Denmark	HIV+ men and women, median age 44.5-47.0	4vHPV	3 (0, 1.5, 6)	2vHPV	3 (0, 1.5, 6)	Immunogenicity	91 4vHPV (n=46) 2vHPV (n=45)
	Faust et al.(209)	2016	"Human Papillomavirus neutralizing and cross-reactive antibodies induced in HIV-positive subjects after vaccination with quadrivalent and bivalent HPV vaccines"	RCT	Denmark	HIV+ men and women, median age 44.5-47.0	4vHPV	3 (0, 1.5, 6)	2vHPV	3 (0, 1.5, 6)	Seroconversion rate	91 4vHPV (n=46) 2vHPV (n=45)
	Arbyn, Xu (328)	2018	"Efficacy and safety of prophylactic HPV vaccines. A Cochrane review of randomized trials"	Meta-analysis	Global	N/A	Any HPV vaccine types	N/A	N/A	N/A	1) CIN2+, CIN3+, and AIS related to the HPV types	26 trials

											included in the vaccine 2) Any CIN2+, CIN3+, and AIS irrespective of HPV types	
	Signorelli et al.(329)	2017	"Human papillomavirus 9-valent vaccine for cancer prevention: a systematic review of the available evidence"	Systematic review	All studies were multi-center multi-countries trials	N/A	9vHPV	N/A	N/A	N/A	Efficacy, immunogenicity and safety, and registered, completed, and ongoing RCTs	10 articles
Population effectiveness	Patel et al.(330)	2018	"The impact of 10 years of human papillomavirus (HPV) vaccination in Australia: what additional disease burden will a nonavalent vaccine prevent?"	Non-systematic literature review	Australia	N/A	Any HPV vaccine types	N/A	N/A	N/A	Burden of HPV-associated cancers and diseases in Australia	N/A
	Steben et al.(331)	2018	"A Review of the Impact and Effectiveness of the Quadrivalent Human Papillomavirus Vaccine: 10 Years of Clinical Experience in Canada"	Systematic Review	Canada	N/A	4vHPV	N/A	N/A	N/A	HPV infection, HPV associated anogenital warts, and/or HPV-associated cervical dysplasia or cervical intraepithelial neoplasia	7 articles
	Spinner et al.(332)	2019	"Human Papillomavirus Vaccine Effectiveness and Herd Protection in Young Women"	Surveillance study	US	N/A	4vHPV 9vHPV	N/A	N/A	N/A	1) Prevalence of vaccine type HPV in adolescent and young adult women who were vaccinated (to assess vaccine effectiveness)	1580

											2) Prevalence of vaccine-type HPV in women who were unvaccinated (to assess herd protection)	
Durability	Artemchuk et al.(333)	2019	Finnish Maternity Cohort biobank	Cohort	Finland	Pregnant women who received HPV vaccine	4vHPV 2vHPV	4v: 3 (0, 2, 6) 2v: (0, 1, 6)	Age matched unvaccinated, HPV sero positive women	None	Immune response durability	4vHPV (n=79) 2vHPV (n=11) Unvaccinated (n=125)
	Guevara et al.(334)	2017	"Antibody persistence and evidence of immune memory at 5years following administration of the 9-valent HPV vaccine"	Cohort	Europe and Latin America	17-26yo women at vaccination	9vHPV	3 (0, 2,6)	N/A	N/A	Immune response durability	150
	Kjaer et al.(335)	2020	FUTURE II	Cohort	Nordic countries	16-23 at enrollment	4vHPV	3 (0, 2,6)	N/A	N/A	HPV 16/18 related CIN2+	2,121
	Kreimer et al.(90)	2015	CVT and PATRICIA	Cohort	Costa Rica	15-25yo women	2vHPV	3 (0, 1, 6)	Hep A vaccine	3 (0, 1,6)	Persistent HPV, CIN2+	22,327 2vHPV (n=11,104) Hep A Vaccine (n=11,209)
	Safaeian et al.(187)	2018	CVT	Cohort	Costa Rica	18-25yo women	2vHPV	3 (0, 1, 6)	N/A	N/A	Persistent HPV, CIN2+	2vHPV (n=2043)
	Tsang et al.(336)	2020	CVT	Cohort	Costa Rica	18-25yo women	2vHPV	3 (0, 1, 6)	Unvaccinated women	N/A	HPV 31/33/45 infection	At the final visit in the 9-11 year loss to follow-up cohort 3-doses (n=2,102)

												Control (n=2,379)
Coverage	Bruni et al.(28)	2016	“Global estimates of human papillomavirus vaccination coverage by region and income level: a pooled analysis”	Systematic review	Global	N/A	Any HPV vaccines	N/A	N/A	N/A	HPV vaccine coverage	N/A
	Gallagher et al.(337)	2017	“Human papillomavirus (HPV) vaccine coverage achievements in low and middle-income countries 2007-2016”	Descriptive analysis	59 LMICs	N/A	Any HPV vaccines	N/A	N/A	N/A	HPV vaccine coverage	6 national programs 48 demo project

Appendix 3.3 Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist—Items to include when reporting economic evaluations of health interventions (338)

Section/item	Item Number	Recommendation	Reported on page Number
Title and abstract			
Title	1	Identify the study as an economic evaluation or use more specific terms such as "cost-effectiveness analysis", and describe the interventions compared.	70
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	70-71
Introduction			
Background and objectives	3	Provide an explicit statement of the broader context for the study.	
		Present the study question and its relevance for health policy or practice decisions.	73
Methods			
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analyzed, including why they were chosen.	74-76
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	74-76
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	77
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	N/A*
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	78
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	78-79
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	80
Measurement of effectiveness	11a	*Single study-based estimates:* Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	N/A*

Section/item	Item Number	Recommendation	Reported on page Number
	11b	*Synthesis-based estimates:* Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.	N/A*
Measurement and valuation of preference based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	N/A*
Estimating resources and costs	13a	*Single study-based economic evaluation:* Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	78-80
	13b	*Model-based economic evaluation:* Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	N/A*
Currency, price date, and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	78
Choice of model	15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.	N/A*
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	78-80
Analytical methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	78-82
Results			
Study parameters	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	Table 3.1, Figure 3.4
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	Table 3.2

Section/item	Item Number	Recommendation	Reported on page Number
Characterizing uncertainty	20a	*Single study-based economic evaluation:* Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact of methodological assumptions (such as discount rate, study perspective).	82-85
	20b	*Model-based economic evaluation:* Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	N/A*
Characterizing heterogeneity	21	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	85
Discussion			
Study findings, limitations, generalizability, and current knowledge	22	Summarize key study findings and describe how they support the conclusions reached. Discuss limitations and the generalizability of the findings and how the findings fit with current knowledge.	86-89
Other			
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support.	15
Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.	15

* Items suitable for cost-effectiveness analysis rather than micro-costing analysis were deemed not applicable (N/A)

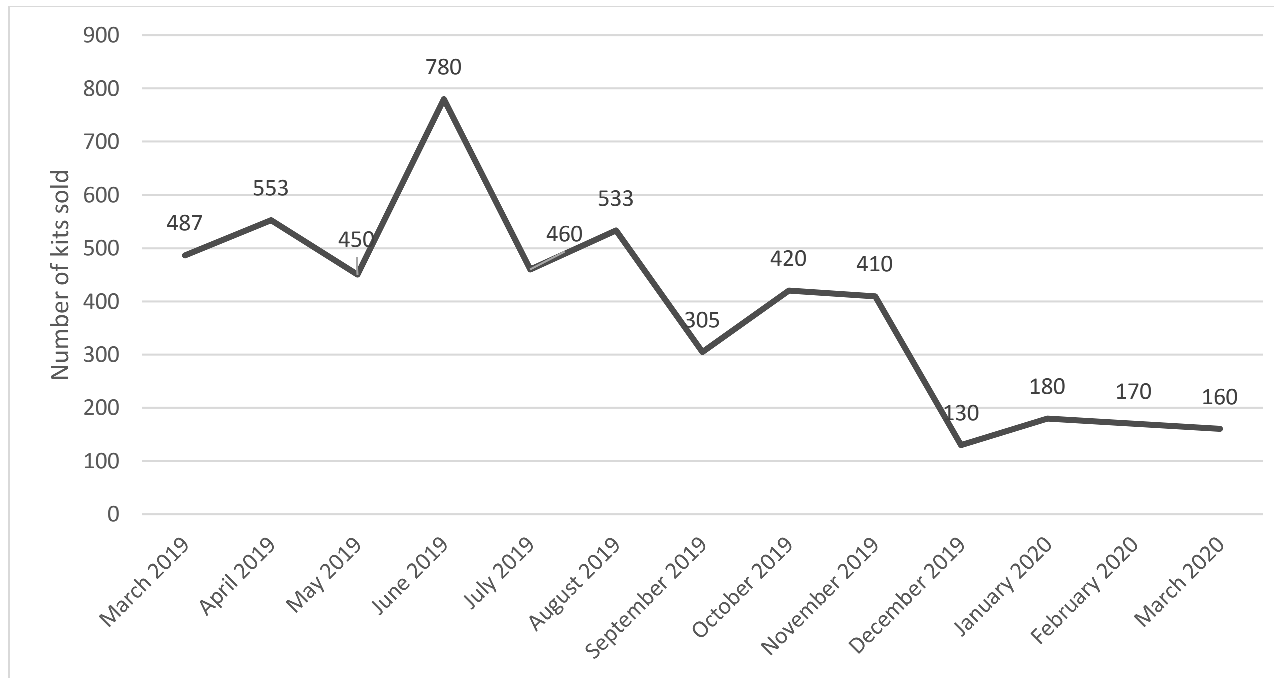
Appendix 3.4 Program output and average time per program activity provided by Hope Ladies

	Output	Minutes of activity	Minutes in transit	Total minutes	Total hours	Total months*
Recruitment and Training	(# trained)					
First meeting	62	90	60	9,300	155	1.1
Second meeting	62	120	60	11,160	186	1.4
Initial training	62	480	120	37,200	620	4.5
				57,660	**961**	**7.0**
Kit distribution	(# kits)					
Home visit	9,764	90	60	1,464,600	24,410	178.2
Initial kits purchase	24	0	30	720	12	0.1
Sample collection and delivery to leader	24	0	30	720	12	0.1
				1,466,040	**24,434**	**178.4**
Follow up	(# women)					
Paper results pick up	48	0	30	1,440	24	0.2
HPV negative women counseling	4,296	30	60	386,640	6,444	47.0
HPV-positive women follow up	586	60	60	70,320	1,172	8.6
HPV-positive women seen in clinic	365	60	60	43,800	730	5.3
				502,200	**8,370**	**61.1**
Annual total for all Hope Ladies				**2,025,900 minutes**	**33,765 hours**	**246 months**
Annual total per person **				**32,676 minutes**	**545 hours**	**4 months**

*Assuming 137 working hours per month

**For 62 Hope Ladies

Appendix 3.5 HPV self-sampling kit trend



Appendix 4.6 Relational and financial empowerment survey

ENGLISH TRANSLATION

The survey will take at most 10 minutes and will be given orally.
Research Question(s):

- Does the implementation of a combination of a microfinancing and peer-education program called the **Hope model** increase relational empowerment and financial autonomy within the household for the peer-educators and the women they serve in Ventanilla, Peru?

To understand how the Hope initiative impacts the Hope ladies' relational empowerment

1. Insight to women's impact of the Hope micro-business services in promoting women's social awareness and their capacity to influence social norms and practices
    a. Would you say that your number of social contacts in and outside of the family has increased since the beginning of your Hope Lady journey?
        i. Can respond on a 4-point scale: "strongly disagree" (0), " disagree" (1), " agree" (2), "strongly agree" (3).
    b. Would you say that you have been able to help other women in times of need since the beginning of your Hope Lady journey?
        i. Can respond on a 4-point scale: "strongly disagree" (0), " disagree" (1), " agree" (2), "strongly agree" (3).
    c. Would you say that you have been able to increase your visits to a healthcare provider unaccompanied to satisfy personal needs since the beginning of your Hope Lady journey?
        i. Can respond on a 4-point scale: "strongly disagree" (0), " disagree" (1), " agree" (2), "strongly agree" (3).
    d. Would you say you have felt confident due to learning about your reproductive health and how to prevent certain diseases compared to the beginning of your Hope Lady journey?
        i. Can respond on a 4-point scale: "strongly disagree" (0), " disagree" (1), " agree" (2), "strongly agree" (3).

To understand how the Hope initiative impacts financial autonomy for the Hope ladies

2. Assessing Financial independence based on autonomy/influence from three questions, based on the past and present, representing a Hope Lady's autonomy and influence in purchases.
    a. In the present, can you decide how to spend any household monetary earnings?
        i. Can respond on a 4-point scale: "often" (3), "sometimes" (2), "rarely" (1), or "never" (0).
    b. In the past, could you decide how to spend any household monetary earnings?
        i. Can respond on a 4-point scale: "often" (3), "sometimes" (2), "rarely" (1), or "never" (0).
    c. In the present, do you have a say in the purchase of large household assets?
        i. Can respond on a 4-point scale: "often" (3), "sometimes" (2), "rarely" (1), or "never" (0).
    d. In the past, could you have a say in the purchase of large household assets?
        i. Can respond on a 4-point scale: "often" (3), "sometimes" (2), "rarely" (1), or "never" (0).
    e. What are your top 3 biggest household expenditures?

SPANISH TRANSLATION

Encuesta de relacional y financiera empoderamiento
La encuesta tomará como máximo 10 minutos y el contenido se dará oralmente.
Pregunta(s) de investigación:

- ¿La implementación de una combinación de un programa de microfinanciación y educación entre pares llamado modelo Hope aumenta el empoderamiento relacional y la autonomía financiera dentro del hogar para las educadoras pares y las mujeres a las que sirven en Ventanilla, Perú?

Para entender cómo la iniciativa Hope impacta el empoderamiento relacional de las Hope Ladies

1. Conocimiento del impacto de las mujeres de los servicios de microempresas Hope en la promoción de la conciencia social de las mujeres y su capacidad para influir en las normas y prácticas sociales.
    a. ¿Diría que su número de contactos sociales dentro y fuera de la familia ha aumentado desde el comienzo de su viaje Hope Lady?
        i. Puede responder en una escala de 4 puntos: "totalmente en desacuerdo" (0), "en desacuerdo" (1), "de acuerdo" (2), "muy de acuerdo" (3).
    b. ¿Diría que ha podido ayudar a otras mujeres en momentos de necesidad desde el comienzo de su viaje Hope Lady?
        i. Puede responder en una escala de 4 puntos: "totalmente en desacuerdo" (0), "en desacuerdo" (1), "de acuerdo" (2), "muy de acuerdo" (3).
    c. ¿Diría que ha podido aumentar sus visitas a un proveedor de atención médica no acompañado para satisfacer sus necesidades personales desde el comienzo de su trabajo Hope Lady?
        i. Puede responder en una escala de 4 puntos: "totalmente en desacuerdo" (0), "en desacuerdo" (1), "de acuerdo" (2), "muy de acuerdo" (3).
    d. ¿Diría que se ha sentido confiado debido a aprender sobre su salud reproductiva y cómo prevenir ciertas enfermedades en comparación con el comienzo de su trabajo Hope Lady?
        i. Puede responder en una escala de 4 puntos: "totalmente en desacuerdo" (0), "en desacuerdo" (1), "de acuerdo" (2), "muy de acuerdo" (3).

Comprender cómo la iniciativa Hope impacta la autonomía financiera de las Hope Ladies

1. Evaluar la independencia financiera basada en la autonomía / influencia de tres preguntas, basadas en el pasado y el presente, que representan la autonomía e influencia de Hope Lady en las compras.
    a. En el presente, ¿puedes decidir cómo gastar los ingresos monetarios de su hogar?
        i. Puede responder en una escala de 4 puntos: "a menudo" (3), "a veces" (2), "rara vez" (1) o "nunca" (0).
    b. En el pasado, ¿podría decidir cómo gastar los ingresos monetarios de su hogar?
        i. Puede responder en una escala de 4 puntos: "a menudo" (3), "a veces" (2), "rara vez" (1) o "nunca" (0).
    c. En el presente, ¿a usted se le permite opinar sobre la compra de grandes activos domésticos?
        i. Puede responder en una escala de 4 puntos: "a menudo" (3), "a veces" (2), "rara vez" (1) o "nunca" (0).

d. En el pasado, ¿a usted se le permitía opinar sobre la compra de grandes activos domésticos?
    i. Puede responder en una escala de 4 puntos: "a menudo" (3), "a veces" (2), "rara vez" (1) o "nunca" (0).
e. ¿Cuáles son sus 3 mayores gastos domésticos más importantes?

Appendix 4.7 Summary of deductive content analysis

General category	Sub-categories	Pre-determined codes and sub-categories	Sub-themes (Counts)	Quotes
Resource	Individual	Gender norms and roles within the household (ICWR) Relationships as an individual within household and community context (RLT)	Role in the household sometimes conflicting with the role as a Hope Lady (n= 15, References –35)	P17: I have a baby. When she grows a little more, I don't think I will have any obstacles in the Hope Project. (age 35) P3: I have my mother-in-law in my care. She needs me to take care of her...because she cannot get out of bed. I go [out to sell the kits], but with the thought, 'what if she suddenly falls out of bed,' or I do not know she will urinate on herself. With that thought I go, sometimes I say, 'I continue or I do not continue,' and sometimes I stop. My friends tell me, 'Don't stop, keep going for us.' (age 33) P2: I have to take my son to school, I have to cook and sometimes because of those issues they [the women who screened positive] don't go to the hospital [for triage]. (age 45) P5: Unfortunately, my mother passed away and I have stayed with my father…I do not have that time to reestablish myself with the Hope Project. My father lives far away and my father is an eighty-three-year-old person. That is the impediment I have, my dad doesn't want to come here! So, I have to go to his house to see him. (age 33) P8: Unfortunately, I have not had enough time, because how I tell the truth, sometimes I am left alone with the store, the house, the kitchen, the baby, the homework, and the school. I have lacked time, but if I had dedicated the time to it, the way one works, I bet I would have achieved more goals…the truth is, I have five children, and so many responsibilities that the time doesn't pay off. (age 44)
	Community	Relationships as a collective identity (e.g., Hope Ladies) (RLT)	Camaraderie with other Hope Ladies (n= 9, References – 20)	P10: We would agree with other colleagues [Hope Ladies]…and we would go out in a group, because it is less tedious [than] when you are alone. (age 64) P19: We are working with Cayetano throughout this project, so that [the Hope Project] grows and we can amplify the good work. (age 54)
	Community	Relationships as a collective identity (e.g., Hope Ladies) (RLT)	Recognition from the community as a resource for women (n= 10, References – 12)	P2: They [the community women] talk to me more because you know in the hospital they will hardly talk to them like we [Hope Ladies] talk to them. They are always be afraid to ask the doctor, or that [the doctors] will ask if they have not understood. We as leaders of our community know our neighbors…They comment on the program [Hope Project] and they look for us and they call us about this topic. (age 45) P3: sometimes, my difficulties are the lack of communication, sometimes the ladies doubt, when you go you have not heard anywhere, they say: but, it will be true or it will be false because, well, it is 10 soles or how much, sometimes They

				come to fool us, sometimes, no! no! no! Suddenly, it's a lie, they close the door! Sometimes it is discouraging when you go somewhere they have not heard of us before, and they close the door on us. But now there is a lot of communication, [Hope Project] has been on TV, they have been on the radio. The community has listened, so when we knock on the door we say: we are from Hope! They say, "Oh that program! I was waiting at my house for a knock on my door!" (age 33) P13: Sometimes, the women [in the community] think we are doctors and nurses and ask us about women's illnesses... so we correct them and find out who they should go to. (age 47)
Agency	Individual	Self-confidence (ICWR)	Confidence to speak about reproductive health Improved ability to communicate and express themselves (n= 12, References – 19)	P11: Well, in my case, it has helped me to have more confidence in words, that is, in being able to express myself with confidence what I am talking about. (age 33) P3: [Hope Project] has also helped me to express myself, because before I did not speak...But, this program has helped me connecting with other people, more than economically. (age 33) P13: [The Hope Project] has taught me to talk to women and lose my shame. We [the Hope Ladies] lose our fear with the talks and training. Hope's support has been very important to us because we have educated ourselves through it. (age 47) P16: The first thing is to learn to know and love ourselves [to be take the test]. Above all the love of oneself. (age 47)
	Individual	Self-efficacy (ICWR)	Increased knowledge (n= 20, References – 27)	P7: Well, with hope, I have lost the shame of communicating with people, because before I was not capable, when I started I was very shy, but now I have enough skills. I have acquired that with [Hope Project] because of the training that they also give us, they support us in everything that we do, we also consult with them. (age 46) P9: I have learned a lot and of which, well, it is quite beneficial, because that way I am educating myself, that is, I am learning and I am really glad that these programs exist because they educate you, you learn from this, so it's very good! I really congratulate the program, because if it weren't for this, I wouldn't even have taken the test. (age 44) P16: There were two ladies in particular [from the 2015 pilot] that we saved her from cervical cancer. One had her uterus removed. She thanked me, she wanted to pay me, so, I said no. You feel good because you say, 'well I did something good and look here is the result.' I felt very good. (age 47)

| | Community | Evolving social order (RLT) | Ability to speak against machismo culture and advocate for women to make autonomous decisions

(n= 18, References – 27) | P4: Yes, it is an important factor, for the husbands to give them permission. Many times they say, "No, my husband does not want to" and they have to talk with the husband. That is, more than anything, machismo. (age 50)

P10: Women are well trodden, sometimes it depends a lot… I say to them, "Who is the one who is going to show their body [to the doctor]? Who is the one who is going to get sick? Your husband or you?" …There are cultural barriers…because the liberation of women is also being imposed! (age 64)

…Once a lady had her motorcycle, and she tells me get on, she made me go to talk to the husband, but the husband told her "for what do you bring the [Hope] lady, if you want to do it, do it." But it depends on the women... it [machismo] is not much [of a barrier], they always consider [their husbands], but it is not an obstacle.

P5: We are not talking about the test anymore; we talked and encountered different problems. We are like a heart doctor, they already believe us [heart] doctors, because they ask us different things. We try to do that, to be able to lift the woman, so that they are not left saying 'Oh, I'm going to ask my husband's permission!' (age 33)

P6: The empowerment that [the Hope Project] brings to us, that other institutions cannot, is women's self-realization, their power to decide themselves, not to ask their partner. (age 48)

P6: I discovered how much violence [there is in the homes], already. (age 48)

P7: Machismo. Of the men who ... I have had quite a few cases in which they have not been allowed to take the test or the woman has to ask for permission. I tell her, "You don't have to ask for permission! Because he is not your dad, he is your partner, he is your husband...You are your body." That is machismo. (age 46)

We always try to solve the doubts that people have, and also empower women, because sometimes some women do not want to do it, because first they have to consult with the husband first, then what we do it is to say to her, "She is the own owner of her body, of her health! There are men who do not want to let them get tested. But if [you have HPV] it is your body that will suffer the consequences." We help them, so that they can become aware that the decision is in oneself, and that we do not depend on anyone. We say, "We have come alone and we are going to leave alone, so each one is the owner of what to do and what decisions to make." And that is what I have learned with Hope Project.

P16: Many women say, 'Oh, I'm going to tell my husband!' and the husbands say 'No, how are you going to do such nonsense test!' I say to the women, 'why do |

				you have to consult them? You are the owner of your person, you are a woman, health is yours not his…you have to take care of yourself.' (age 47)
	Community	Change in behaviors (RLT)	Performing or buying HPV self-sampling kits in secret (n= 3, References – 4)	P2: Mostly women do it [HPV self-sampling] secretly (age 45) P3: As I said, of 100%, there is always 1%, husbands who do not want [HPV self-sampling]. But they [wives of husbands who do not want HPV self-sampling] do it in secret. Many women do it in secret [without telling their husbands]. (age 33) P16: [some women say] "I'm going to pay you secretly, come on a day my husband is not here." (age 47)
	Community	Change in relational dynamics (new approaches, values, attitudes, behaviors, and ideologies) (RLT)	Violence (n= 5, References – 7)	P6: I discovered how much violence [there is in the homes], already. (age 48) P20: No, they [the spouses] don't let women get tested [for HPV]. That's where I've discovered how much violence there is. [The men] made me work harder, thinking about what I should do to meet with the women. (age 51) P11: Some women don't do [the test] out of fear of [their spouses]. They say, 'my husband will ask me why I'm taking the test! He will tell me perhaps it's because I doubt him [his fidelity]'. (age 33)
Achievement	Individual	Control over assets (ICWR)	Increased economic assets (n= 13, References – 24)	P2: Of course, it has helped me a lot, because, sometimes, here my husband does not earn more, weekly, sometimes, it helps me for my children's bus fares, which is daily for school. My husband does not bring daily, he is paid weekly. And you have to wait that week, while I go do this work. (age 45) P3: It has helped me a lot, because in my free time I earn something else, to support my household, to help my husband with something. (age 33) P20: Yes, it helps [financially]. It is a job that helps you financially and that you are also helping other people, other women, I think it does help you financially. (age 51)
	Individual	Financial autonomy (ICWR)	Improved ability to make financial decisions (n= 8, References – 17)	P16: I'm the one who works. I am a mother and father, I have a daughter and I am the one who says how much money comes into my house and how much I am going to spend. I try to balance what is my priority. (age 47) P5: I have always managed the house expenses, although I don't [work], I have always tried to solve all the house expenses. [My husband] is the one who contributes. (age 33) P20: Of course, the income [from the Hope Project] helps me! (age 51)
	Community	Relationship as an outcome (RLT)	Widened social network Technology skills development	P2: Now they call us, they leave our numbers, and other people who have never met call us, and you get to know more people. (age 45)

			(n= 11, References – 18)	P5: Social networks...the cell phone for me was nothing more like the phone that you go and answer, nothing at all! now I know, well, I chat everything. (age 33) P7: Yes, I have also learned a lot with social networks, because before joining [Hope Project], I did not even know I did not have a touch phone, I had a [phone with buttons], which was only to receive calls and messages and my daughters always told me, "Mommy, and why don't you change!" [And I'd say,] "No! I don't want anything, I don't know anything." I didn't know how to use it at all. And when I joined Hope Project, it was practically indispensable, well, the telephone and they [the administrators] themselves have taught me to use it, they have taught me to enter the page, to enter the data, all those things, so they have taught us all that there; I have also learned everything about technology with hope, because before I didn't even care to pick up a phone, but now I do. (age 46) P18: Social networking apps, even though I already used them, it helped me to handle much more than before. Now we are in the time where everything is handled by the computer. (age 41) P13: I learned new skills to buy things online, enter the data into the system, to send it to the laboratory, and to write by WhatsApp…I have learned to communicate with people [using apps]. (age 47)

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VITA

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