

Health-Care Spending Attributable to Cervical Cancer: A Systematic Review

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Abstract Cervical cancer is the fourth most common cancer globally, due to an extremely low rate of screening and prohibitive prevention costs. Knowing the costs of screening will help planners and policymakers design, implement, and scale programs. The objective of this review is to quantify health care spending attributable to cervical cancer in sub-Saharan Africa. We searched PubMed and Google Scholar for English language publications detailing cost analyses of Human Papilloma Virus vaccination, different cervical cancer screening methods and pre-cancer treatment globally. The main outcome of interest was the cervical cancer prevention cost per woman. Expenditure data were extracted and a descriptive review was conducted for each included study. Among the screening strategies, Visual Inspection with Acetic acid (VIA) was the least expensive. In addition, preventative Cryotherapy without screening was the least expensive strategy for preventing cervical cancer in HIV-infected women compared to other strategies and their combinations. The screening costs for Pap, LEEP and colposcopy were relatively high. HPV Vaccination cost the highest among the cervical cancer prevention strategies reviewed. The varying costs for these proposed strategies provide options for program implementers including donors, insurance firms, and the Ministry of Health to efficiently plan based on the anticipated screening treatment coverage and program budgets.

Keywords Cervical Cancer, Direct Medical Expenditure, Cancer Prevention, Financial cost, Economic costs

1. Introduction

The prevailing drive and enthusiasm to achieve Universal Health coverage present an incredible opportunity to save the lives of women globally from cervical cancer. Health financing is crucial for achieving universal health coverage by raising adequate funds for health and rendering financial risk protection [1]. Cost concerns play an important role in whether or not women are screened and treated for cervical cancer. Moreover, cost concerns also limit strategies to ensure effective treatment for screen-positive women, which is an essential part of the cervical cancer prevention cascade. Generating practical data on the cost of alternative models of service delivery is imperative, as countries grapple with tough decisions about which interventions can be effectively implemented using innovative financing mechanisms and promote sustainability in the face of donor decline. Accurate cost estimates for preventive treatment for women who screen positive are pivotal for economic evaluations, policy decisions, and planning future medical care expenditures [2].

Globally, cervical cancer is the fourth most common cancer with an estimated 570,000 cases and 311,000 deaths forecast in 2018 [3]. More than 80% of cervical cancers occur in developing countries, where vaccination, screening, and treatment are limited [4]. The World Health Organization estimates that between 10 and 11 million cancers will be diagnosed each year in low- and middle-income countries by 2030 if no significant investments in cervical cancer prevention are made now [5]. The global age-standardized incidence rate is 14.1 per 100,000 woman years, compared to 40.1 per 100,000 woman years in Kenya [6]. The disparities in cervical cancer incidence reflect differences in investment in, access to and uptake of cervical cancer prevention programs.

Cervical cancer can be prevented through HPV vaccination and screening programs designed to identify and treat precancerous lesions known as high-grade squamous intraepithelial lesions (SIL) [7] [8]. Various technologies have been developed to detect and treat precancerous lesions including Pap smear, colposcopy, visual inspection with acetic acid or Lugol's iodine (VIA/VILI), HPV DNA testing, cone biopsy, Cryotherapy, and loop electrosurgical incision procedure (LEEP) [9] [10]. HPV vaccination programs are scaling up globally but implementation has been slow [11]. Besides, vaccination in most countries, mainly targets

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adolescent girls, leaving screening programs for women of reproductive age. High-risk human papilloma virus (HPV) testing [12] [13] [14] [15] and visual inspection with acetic acid (VIA) [16] [17] are recommended screening strategies that can be effectively coupled directly with preventive treatment in low-resource settings [18]. HPV testing has advantages over VIA, including a significantly higher sensitivity for precancerous lesions [19] [20] and a definitive result that allows for a simplified protocol with clear management options. However, there is no currently available point-of-care test for HPV, making same-day treatment strategies impossible [21].

Also, ensuring that women who test positive with VIA or HPV have access to safe, effective, and affordable treatment is crucial to reducing their risk for cervical cancer [22]. Cryotherapy is a simple means of treating women with precancerous cervical lesions [23] [24]. In low-resource settings, Cryotherapy is cost-effective and affordable, making it an ideal first-line treatment for visible lesions or cervical pre-cancer [25]. LEEP stands for Loop Electrosurgical Excision Procedure. It's a treatment that prevents cervical cancer. A small electrical wire loop is used to remove abnormal cells from your cervix. LEEP surgery may be performed after abnormal cells are found during a Pap test, colposcopy, or biopsy [26].

Financial issues can play an important role in whether or not women are screened and treated for cervical cancer. Women with lower incomes and those without health insurance are less likely to be screened [27]. This systematic review examined the cost of different cervical cancer

prevention strategies globally which is beneficial in planning the scale-up of cervical cancer prevention and ultimately achieving Universal Health Coverage. It provides cost estimates required to finance cervical cancer prevention.

2. Methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed in conducting this systematic review. This systematic review was not registered with PROSPERO.

Search strategy.

A systematic search for published literature in English was conducted on PubMed. Grey literature search was also conducted through the search engine Google Scholar. References of retrieved articles and reports were screened to identify additional potential published and unpublished studies. The key words used in the search were cervical cancer, prevention, costing, cost analysis, and their synonyms. The following search strategy was used; (((((cost) OR (healthcare cost)) AND (uterine cervix cancer)) OR (uterine cervix carcinoma)) OR (uterine cervix adenocarcinoma)) AND (Prevention)))). The PubMed search yielded a total of 115 studies. Non-empirical studies (commentaries, editorials, etc.) and studies that did not explicitly assess cost of the implementation strategies (knowledge, attitudes, and beliefs; incidence and prevalence; safety and efficacy) were excluded from the systematic review See figure 1 below.

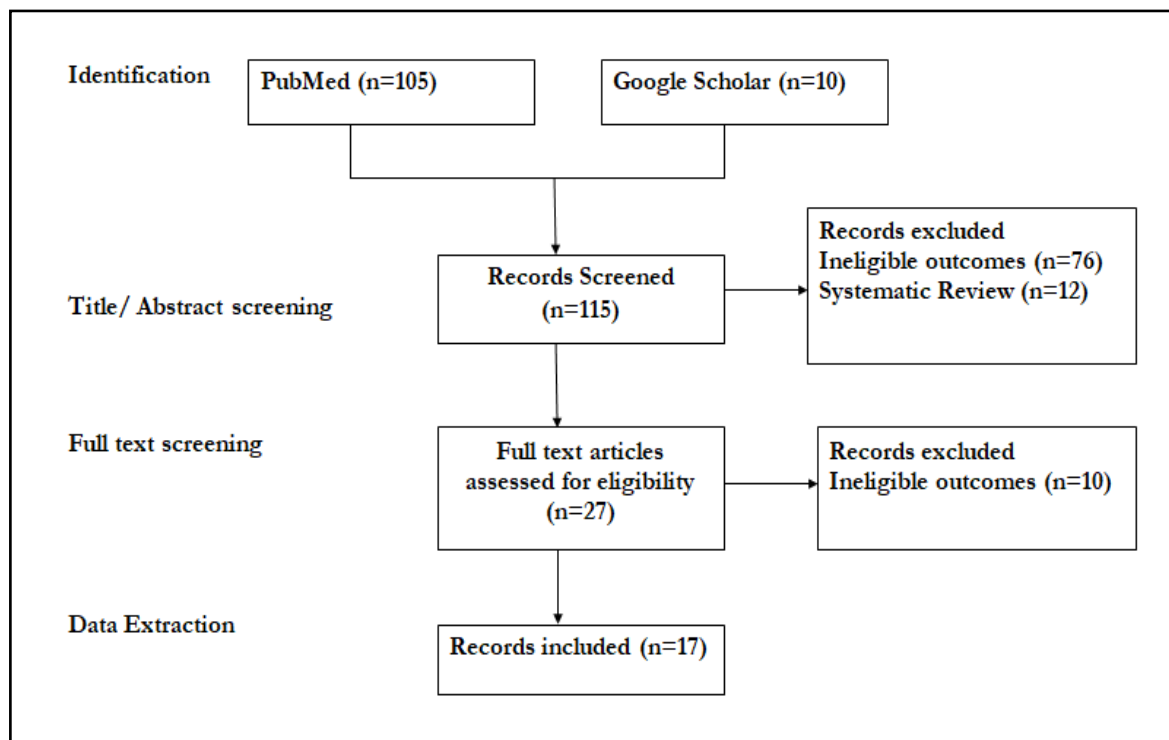


Figure 1. Literature screening process

Study eligibility

The following inclusion criterion was developed to identify original research that empirically measured the direct medical costs of implementation strategies to improve cervical cancer prevention.

- **Population:** Women of reproductive age (18-65) globally.
- **Intervention:** Cervical cancer screening/treatment
- **Comparator:** There was no comparator for this review.
- **Outcome:** Direct medical costs of cervical cancer screening/treatment.

The studies had no publication restriction date and adopted both societal and clinic perspectives of the costs of cervical cancer prevention.

Study selection

The initial database search yielded 115 results. Two reviewers independently screened the titles and abstracts of the search results to identify eligible articles. Titles and abstracts of the identified articles were screened to exclude duplicates ($n=12$) and studies not relevant to the topic ($n=76$). The remaining articles ($n=27$) were reviewed in full text. Seventeen studies met the eligibility criteria and an additional 10 articles were excluded.

Data extraction

The 17 articles that fit the inclusion criteria were extracted for the following implementation-related content: title, author, publication year, objective, country, study design,

data source, type of costs, and quality of publication, program and findings. All information related to the study objective was then extracted from each publication reviewed into an extraction matrix (MS Excel file) then synthesized and presented in narrative form.

Quality Assessment

We assessed the risk of bias in included studies using recommended risk of bias tools. We summarized the certainty of evidence using the GRADE tool [28].

3. Results

Study characteristics are summarized in Table 1. The studies included were published between 2005 and 2019. The 17 studies were conducted in 30 sites, 25 in sub-Saharan Africa, two in Southern Asia, and three in South America. While majority of studies (16) included in the review only estimated economic costs, one estimated both financial and economic costs of cervical cancer prevention. Seven publications reviewed were based on secondary data while the ten studies were based on primary data. The publications reviewed estimated the costs of VIA, Papanicolaou smear (Pap), HPV vaccination, HPV DNA screening, and Colposcopy/Biopsy as cervical cancer screening strategies. The studies also estimated the costs of Cryotherapy or Loop electrosurgical excision procedure as treatment strategies for pre-cancer.

Table 1. Study characteristics

	Author(S)	Title	Country	Program	Data source	Type of cost
1	Mvundura 2014	Estimating the costs of cervical cancer screening in high-burden Sub-Saharan African countries	Benin, Burundi, Cape verde, Comoros, Gambia, Ghana, Guinea, Guinea-Bissau, Lesotho, Liberia, Malawi, Mali, Mauritania, Mozambique, Nigeria, Rwanda, Senegal, Sierra Leone, Swaziland, Tanzania, Uganda, Zambia and Zimbabwe.	VIA, Cryotherapy or Loop electrosurgical excision procedure.	Secondary data	Financial and economical
2	Campos 2017	The Cost-Effectiveness of Visual Triage of Human Papillomavirus-Positive Women in Three Low- and Middle-Income Countries	India, Nicaragua, and Uganda	(i) HPV alone, followed by cryotherapy for all eligible HPV-positive women; and (ii) HPV testing with VIA triage for HPV-positive women, followed by cryotherapy for eligible women who were also VIA-positive (HPV-VIA).	Secondary data	Economic
3	Goldie 2005	Cost-effectiveness of cervical-cancer screening in five developing countries	India, Kenya, Peru, South Africa, and Thailand	VIA and HPV DNA	Primary data	Economic
4	Nelson 2016	Cost-Effectiveness of Screening and Treatment for Cervical Cancer in Tanzania: Implications	Tanzania	VIA and Cryotherapy	Primary data	Economic

		for other Sub-Saharan African Countries				
5	Quentin 2011	Costs of cervical cancer screening and treatment using visual inspection with acetic acid (VIA) and cryotherapy in Ghana: the importance of scale	Ghana	VIA and Cryotherapy.	Primary data	Economic
6	Shen 2018	Cost of HPV screening at community health campaigns (CHCs) and health clinics in rural Kenya	Kenya	HPV-based cervical cancer screening via self-collection.	Primary data	Economic
7	Sinanovic 2009	The potential cost-effectiveness of adding a human papillomavirus vaccine to the cervical cancer screening programme in South Africa	South Africa	HPV vaccination, HPV DNA screening and VIA screening	Secondary data	Economic
8	Zimmermann-2017	Cost-effectiveness of cervical cancer screening and preventative cryotherapy at an HIV treatment clinic in Kenya	Kenya	(VIA), Papanicolaou smear (Pap), and testing for human papillomavirus (HPV) and cryotherapy	Primary data	Economic
9	Campos 2015	Cervical cancer screening in low-resource settings: A cost-effectiveness framework for valuing tradeoffs between test performance and program coverage	Uganda	VIA, HPV DNA, Cytology, Colposcopy/Biopsy, Cryotherapy, LEEP,	Secondary data	Economic
10	Gelband 2016	Costs, affordability, and feasibility of an essential package of cancer control interventions in low-income and middle-income countries: key messages from Disease Control Priorities, 3rd edition	Nigeria, India, and Brazil	Screen and treat precancerous lesions and early-stage cervical cancer	Secondary data	Economic
11	Wilm Quentin 2010,	Costs of cervical cancer screening in Ghana.	Ghana	VIA and cryotherapy	Primary data	Economic
12	Ju-Fang Shi 2012	Estimation of the costs of cervical cancer screening, diagnosis and treatment in rural Shanxi Province, China: a micro-costing study	China	Visual inspection, self-sampled careHPV (Qiagen USA) screening, clinician-sampled careHPV, colposcopy and biopsy	Primary data	Economic
13	Rosa Legood 2005	Screening for cervical cancer in India: How much will it cost? A trial based analysis of the cost per case detected	India	VIA, cytology and HPV testing	Primary data	Economic
14	Vodicka 2019	Estimating the costs of HIV clinic integrated versus non-integrated treatment of pre-cancerous cervical lesions and costs of cervical cancer treatment in Kenya	Kenya	colposcopy, cryotherapy, Loop Electrosurgical Excision Procedure (LEEP), and treatment of cancer.	Primary data	Economic
15	Lince-Deroche, 2015	Costs and Cost Effectiveness of Three Approaches for Cervical Cancer Screening among HIV-Positive Women in Johannesburg, South Africa	South Africa	Conventional cytology (Pap), visual inspection with acetic acid (VIA) and HPV DNA testing	Primary data	Economic
16	Mezei 2018	Community-based HPV self-collection versus visual inspection with acetic acid in Uganda: a cost-effectiveness analysis of the ASPIRE trial	Uganda	The self-collected HPV test, VIA, cryotherapy treatment, colposcopy, and biopsy.	Secondary data	Economic

17	Campos 2017	To expand coverage, or increase frequency: Quantifying the tradeoffs between equity and efficiency facing cervical cancer screening programs in low-resource settings	Uganda	careHPV, Colposcopy, Colposcopy and biopsy, cryotherapy and LEEP	Secondary data	Economic
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Table 2. Table of evidence

	Author(S)	Title	Country	Objectives	Program	Findings	Quality
1	Mvundura 2014	Estimating the costs of cervical cancer screening in high-burden Sub-Saharan African countries	Benin, Burundi, Cape verde, Comoros, Gambia, Ghana, Guinea, Guinea-Bissau, Lesotho, Liberia, Malawi, Mali, Mauritania, Mozambique, Nigeria, Rwanda, Senegal, Sierra Leone, Swaziland, Tanzania, Uganda, Zambia and Zimbabwe.	To estimate the capital investment and recurrent costs of national cervical cancer screening and pre-cancer treatment programs in 23 high-incidence countries in Sub-Saharan Africa in order to provide estimates of the investment required to tackle the burden of cervical cancer in this region.	VIA, Cryotherapy or Loop electrosurgical excision procedure.	Cost per woman screened in a screen-and-treat program was either US \$3.33 or US \$7.31, and cost per woman treated was either US \$38 or US \$71 depending on the location of cryotherapy equipment.	Good
2	Campos 2017	The Cost-Effectiveness of Visual Triage of Human Papillomavirus-Positive Women in Three Low- and Middle-Income Countries	India, Nicaragua, and Uganda	To determine the cost-effectiveness of VIA triage for HPV-positive women in low-resource settings.	(i) HPV alone, followed by cryotherapy for all eligible HPV-positive women; and (ii) HPV testing with VIA triage for HPV-positive women, followed by cryotherapy for eligible women who were also VIA-positive (HPV-VIA).	The direct medical cost for careHPV (provider collection) was 9.24, 15.61, and 8.78 for India, Nicaragua, and Uganda respectively. careHPV (self-collection at the clinic) cost 8.90, 13.48 and 8.48 for India, Nicaragua, and Uganda respectively. VIA cost 3.55, 9.61 and 2.90 or India, Nicaragua, and Uganda respectively.	Good
3	Goldie 2005	Cost-effectiveness of cervical-cancer screening in five developing countries	India, Kenya, Peru, South Africa, and Thailand	Using primary data from studies in countries with diverse epidemiologic profiles and resources (India, Kenya, Peru, South Africa, and Thailand), we assessed the cost-effectiveness of alternative strategies to reduce the rate of death from cervical cancer	VIA and HPV DNA	Total screening costs, including laboratory, laboratory transport, and QA/QC, for VIA, was 1.82, 2.31, 4.13, 14.21, 2.08 for India Kenya Peru S. Africa, and Thailand respectively. HPV DNA cost 10.48, 12.30, 13.12, 21.21, and 11.21 for India Kenya Peru S. Africa and Thailand respectively.	Good
4	Nelson 2016	Cost-Effectiveness of Screening and Treatment for Cervical Cancer in Tanzania:	Tanzania	To compare the institutional cost per person of screening and treatment between two groups	VIA and Cryotherapy	Total screening cost for VIA was US \$1.45 while the Total cryotherapy cost was US \$28.97.	Good

		Implications for other Sub-Saharan African Countries		of patients—those screened and those not screened before treatment for cervical cancer at Ocean Road Cancer Institute (ORCI) in Dar es Salaam, Tanzania—and to perform a cost-effectiveness analysis of the ORCI cervical cancer screening program.			
5	Quentin 2011	Costs of cervical cancer screening and treatment using visual inspection with acetic acid (VIA) and cryotherapy in Ghana: the importance of scale	Ghana	To estimate the incremental costs of visual inspection with acetic acid (VIA) and cryotherapy at cervical cancer screening facilities in Ghana; to explore determinants of costs through modelling; and to estimate national scale-up and annual programme costs.	VIA and Cryotherapy.	Incremental economic costs per woman screened with VIA ranged from 4.93 US\$ to 14.75 US\$, and costs of cryotherapy were between 47.26 US\$ and 84.48 US\$ at surveyed facilities. Under base case assumptions, our model estimated the costs of VIA to be 6.12 US\$ per woman and those of cryotherapy to be 27.96 US\$. Sensitivity analysis showed that the number of women screened per provider and treated per facility was the most important determinants of costs. National annual programme costs were estimated to be between 0.6 and 4.0 million US\$ depending on assumed coverage and adopted screening strategy.	Good
6	Shen 2018	Cost of HPV screening at community health campaigns (CHCs) and health clinics in rural Kenya	Kenya	To estimate the costs of cervical cancer screening with a community-based health campaign strategy, and furthermore, compares the costs of two cervical cancer screening interventions in Kenya.	HPV-based cervical cancer screening via self-collection.	The mean cost per woman screened was \$25.00 for CHCs [median: \$25.09; Range: \$22.06-30.21] and \$29.56 for clinics [\$28.90; \$25.27-37.08]. Clinics had higher costs than CHCs for personnel (\$14.27 vs. \$11.26) and capital (\$5.55 vs. \$2.80). Screening costs were higher for clinics at \$21.84, compared to \$17.48 for CHCs. In contrast, CHCs had higher outreach costs (\$3.34 vs. \$0.17). After modeling a reduction in staffing, clinic per-screening costs (\$25.69) were approximately equivalent to CHCs.	Good
7	Sinanovic 2009	The potential cost-effectiveness of adding a human papillomavirus vaccine to the cervical cancer screening	South Africa	This study was designed to answer the question of whether a cervical cancer prevention programme that incorporates an HPV	HPV vaccination, HPV DNA screening and VIA screening	The societal cost per vaccinated girl was US \$570. The most costly screening strategy is HPV DNA test (\$309 per women), followed by cervical cytology (\$93) and	Good

		programme in South Africa		vaccine is potentially more cost-effective than the current strategy of screening alone. It was part of a broader study exploring challenges and barriers to potential HPV vaccine introduction in the public sector in South Africa.		VIA (\$75).	
8	Zimmermann -2017	Cost-effectiveness of cervical cancer screening and preventative cryotherapy at an HIV treatment clinic in Kenya	Kenya	This study evaluated the potential cost-effectiveness of cervical cancer screening in HIV treatment clinics in Nairobi, Kenya.	(VIA), Papanicolaou smear (Pap), and testing for human papillomavirus (HPV) and cryotherapy	Costs of cryotherapy, VIA, Pap, and HPV for women with CD4 200-500 cells/mL were \$99, \$196, \$219, and \$223 from a societal perspective and \$19, \$94, \$124, and \$113 from a clinic perspective, with 17.3, 17.1, 17.1, and 17.1 years of life expectancy, respectively. Women at higher CD4 counts (>500 cells/mL) given cryotherapy VIA, Pap, and HPV resulted in better life expectancies (19.9+ years) and lower cost (societal: \$49, \$99, \$115, and \$102; clinic: \$13, \$51, \$71, and \$56). VIA was less expensive than HPV unless HPV screening could be reduced to a single visit.	Good
9	Campos 2015	Cervical cancer screening in low-resource settings: A cost-effectiveness framework for valuing tradeoffs between test performance and program coverage	Uganda	This study aims to develop a framework for examining health and economic tradeoffs between screening test sensitivity, population coverage and follow-up of screen-positive women, to help decision makers identify where program investments yield the greatest value.	VIA, HPV DNA, Cytology, Colposcopy/ Biopsy, Cryotherapy, LEEP,	Direct medical costs for screening, diagnosis, and treatment of precancer, and total costs for treatment of invasive cancer (2005 I\$) for VIA test procedure was 1.63. HPV DNA test procedure cost 10.22 while cryotherapy cost 21.53.	Good
10	Gelband 2016	Costs, affordability, and feasibility of an essential package of cancer control interventions in low-income and middle-income countries: key messages from Disease Control Priorities, 3rd edition	Nigeria, India, and Brazil	To identify potentially cost-effective, feasible, and affordable interventions that address large disease burdens in LMICs	Screen and treat precancerous lesions and early-stage cervical cancer	Screen and treat precancerous lesions and early-stage cervical cancer 0.26, 0.29 and 0.87 for low-income countries (US\$), Lower-middle-income countries (US\$) and Upper-middle-income countries respectively	Good
11	Wilm	Costs of cervical	Ghana	To estimate 1) the	VIA and	Costs at surveyed facilities	Good

	Quentin 2010, (Programme for SRH HIV, Research Briefing 2)	cancer screening in Ghana.		costs of VIA and cryotherapy at existing VIA/cryotherapy sites in Ghana, and 2) the resource requirements for scaling up to a national screening and management programme.	cryotherapy	ranged from 7.30 to 21.86 GHS (4.93 to 14.75 US\$) for VIA, and from 70.04 to 125.19 GHS (47.26 and 84.48 US\$) per woman treated with cryotherapy. Salary costs accounted for the largest share of incremental costs of VIA at all facilities (45-61%). Equipment (cryoguns and probes) was responsible for the largest share of costs of cryotherapy.	
12	Ju-Fang Shi 2012	Estimation of the costs of cervical cancer screening, diagnosis and treatment in rural Shanxi Province, China: a micro-costing study	China	The aim of this study was to use a micro-costing approach and a societal perspective to estimate aggregated costs associated with cervical cancer screening, diagnosis and treatment in rural China.	Visual inspection, self-sampled careHPV (Qiagen USA) screening, clinician-sampled careHPV, colposcopy and biopsy	Under the base case assumption of a high-volume screening initiative (11,475 women screened annually per county), the aggregated direct medical costs of visual inspection, self-sampled careHPV (Qiagen USA) screening, clinician-sampled careHPV, colposcopy and biopsy were estimated as US\$2.64, \$7.49, \$7.95, \$3.90 and \$5.76, respectively. Screening costs were robust to screening volume (<5% variation if 2,000 women screened annually), but costs of colposcopy/biopsy tripled at the lower volume. Direct medical costs of Loop Excision, Cold-Knife Conization and Simple and Radical Hysterectomy varied from \$61–\$544, depending on the procedure and whether conducted at county or prefecture level. Direct non-medical expenditure varied from \$0.68–\$3.09 for screening/diagnosis and \$83–\$494 for pre-cancer/cancer treatment.	Good
13	Rosa Legood 2005	Screening for cervical cancer in India: How much will it cost? A trial based analysis of the cost per case detected	India	Estimated the total costs and detection rates for each cluster and used these data to calculate an average cluster cost and detection rate for each screening approach.	VIA, cytology and HPV testing	The average total costs per 1,000 women eligible for screening were US\$3,917, US\$6,609 and US\$11,779 with VIA, cytology and HPV respectively. The cost of detecting a case of CIN2/31 using VIA was \$522 (95% CI \$429–\$652). Our results suggest that more CIN2/31 cases would be detected in the same population if cytology were used instead of VIA and each additional case would cost US\$1065 (95% CI	Good

						<p>\$713– \$2175). Delivering cervical cancer screening is potentially expensive in a low-income country although costs might be lower outside a trial setting. We found screening with VIA to be the least expensive option, but it also detected fewer cases of CIN2/31 than other methods; its long-term cost-effectiveness will depend on the long-term benefits of early detection. Cytology was more effective at detecting cases than VIA but was also more expensive. Our findings indicate that HPV may not be a cost effective screening strategy in India at current consumable prices.</p>	
14	Vodicka 2019	Estimating the costs of HIV clinic integrated versus non-integrated treatment of pre-cancerous cervical lesions and costs of cervical cancer treatment in Kenya	Kenya	To estimate the modified societal costs of cervical cancer treatment in Kenya; and to compare the modified societal costs of treatment for pre-cancerous cervical lesions integrated into same-day HIV care compared to “non-integrated” treatment when the services are not coordinated on the same day.	colposcopy, cryotherapy, Loop Electrosurgical Excision Procedure (LEEP), and treatment of cancer.	<p>From the modified societal perspective, per-procedure costs of colposcopy were \$41 (integrated) vs. \$91 (non-integrated). Per-procedure costs of cryotherapy were \$22 (integrated) vs. \$46 (non-integrated), whereas costs of LEEP were \$50 (integrated) and \$99 (non-integrated). This represents cost savings of \$25 for cryotherapy and \$50 for colposcopy and LEEP when provided on the same day as an HIV-care visit. Treatment for cervical cancer cost \$1,345–\$6,514, depending on stage. Facility-based palliative care cost \$59/day.</p>	Good
15	Lince-Deroche, 2015	Costs and Cost Effectiveness of Three Approaches for Cervical Cancer Screening among HIV-Positive Women in Johannesburg, South Africa	South Africa	To estimate the costs and cost-effectiveness of conventional cytology (Pap), visual inspection with acetic acid (VIA) and HPV DNA testing for detecting cases of CIN2+ among HIV-infected women currently taking antiretroviral treatment at a public HIV clinic in Johannesburg, South Africa.	Conventional cytology (Pap), visual inspection with acetic acid (VIA) and HPV DNA testing	<p>VIA was least costly in both scenarios. In the higher volume scenario, the average cost per procedure was US\$ 3.67 for VIA, US\$ 8.17 for Pap and US\$ 54.34 for HPV DNA.</p>	Good
16	Mezei 2018	Community-based HPV	Uganda	Evaluated the cost-effectiveness of	The self-collected	The direct medical costs for the Self-collected HPV test	Good

		self-collection versus visual inspection with acetic acid in Uganda: a cost-effectiveness analysis of the ASPIRE trial		the Advances in Screening and Prevention of Reproductive Cancers (ASPIRE) trial, conducted in Kisenyi, Uganda	HPV test, VIA, cryotherapy treatment, colposcopy, and biopsy.	was US\$12.73, while VIA cost US\$14.64. The cost per cryotherapy treatment was US\$5.85 while colposcopy and biopsy cost US\$52.25 per woman.	
17	Campos 2017	To expand coverage, or increase frequency: Quantifying the tradeoffs between equity and efficiency facing cervical cancer screening programs in low-resource settings	Uganda	The objective was to quantify the health benefits, distributional equity, cost-effectiveness and financial impact of expanding screening coverage to more women versus increasing screening frequency for a select population	careHPV, Colposcopy, Colposcopy and biopsy, cryotherapy and LEEP	Direct medical costs for careHPV (cervical specimen) was 8.78. Colposcopy was 7.08 while Colposcopy and biopsy cost 32.90. Finally, cryotherapy and LEEP costs were 13.49 and 139.54 respectively.	Good

Cost of screening and treatment of pre-cancer VIA and Cryotherapy costs

A number of studies estimated the costs of VIA screening and Cryotherapy treatment. Mvundura *et al* (2014) found the average costs per woman screened with VIA and treated to be considerably higher for the single-visit treatment scenario, at US \$7.31 and US \$70.91 respectively, compared to the two-visit scenario, at US \$3.33 and US \$37.58 respectively [29]. Campos *et al* (2017) estimated VIA cost 3.55, 9.61 and 2.90 or India, Nicaragua, and Uganda respectively [30]. Goldie *et al* (2005) found the total screening costs, including laboratory, laboratory transport, and QA/QC, for VIA, to be 1.82, 2.31, 4.13, 14.21, 2.08 for India Kenya Peru S. Africa, and Thailand respectively [31]. Nelson *et al* (2016) found the screening cost per woman for VIA as US \$1.45 while the total Cryotherapy cost was US \$28.97. This was a single-visit screening service in which women could screen through VIA, and if an abnormality is found, they were treated through Cryotherapy. These screening costs are lower than the costs found in Mvundura *et al* (2014). The lower cost in Tanzania may be because Mvundura *et al* (2014) assumed that screening costs across all Sub-Saharan African countries were the same, whereas this study focused exclusively on Tanzania [32]. Quentin *et al* (2011) also estimated the incremental costs of visual inspection with acetic acid (VIA) and Cryotherapy at cervical cancer screening facilities in Ghana. The incremental economic costs per woman screened with VIA ranged from 4.93 US\$ to 14.75 US\$, and costs of Cryotherapy were between 47.26 US\$ and 84.48 US\$ at surveyed facilities. Results from surveyed facilities showed high variability of VIA and Cryotherapy costs in Ghana. VIA costs lie closer to figures previously published for South Africa (10.63 US\$) than to those estimated for Kenya (1.31 US\$) [31] and were also above costs reported for India (4.68 US\$) [33]. Sinanovic *et al* (2009) also estimated the cost of VIA and found the societal

cost per vaccinated girl to be \$75 [34]. Zimmermann *et al* (2017) estimated costs of Cryotherapy and VIA, for women with CD4 200-500 cells/mL to be \$99 and \$196 from a societal perspective and \$19 and \$94 from a clinic perspective. Women with higher CD4 counts (>500 cells/mL) were given Cryotherapy and VIA at a lower cost (societal: \$49 and \$99) and (clinic: \$13 and \$51). The cost for universal, prophylactic Cryotherapy without prior cervical cancer screening was found to be \$99 and \$19 from a societal and provider perspective, respectively [35]. Campos *et al* (2015) found the direct medical costs for screening and treatment of precancer through VIA to be 1.63 while Cryotherapy cost 21.53 [36]. The VIA screening costs are closer to those reported by for India by Goldie *et al* (2005) [37] while the Cryotherapy treatment costs are closer to that reported Nelson *et al* (2011) [32]. Ju-Fang Shi *et al* (2012) found the direct medical costs of visual inspection to be US\$2.64 [38]. Lince-Deroche *et al* (2015) reported the cost per case detected through VIA at US\$ 3.67 [39]. Mezei *et al* (2018) estimated the direct medical costs for VIA at US\$14.64 while the cost per Cryotherapy treatment was US\$5.85 per woman [40]. Finally, Campos *et al* (2017) estimated the direct medical costs for Cryotherapy at 13.49 [41].

HPV DNA screening costs

Ten studies estimated the costs of HPV DNA testing. Campos *et al* (2017) estimated the cost of cervical cancer screening thorough careHPV and VIA in three countries. The direct medical cost for careHPV through provider collection, was higher at 9.24, 15.61, and 8.78 for India, Nicaragua, and Uganda respectively compared to self-collection at the clinic which cost 8.90, 13.48 and 8.48 for India, Nicaragua, and Uganda respectively [30]. Goldie *et al* (2005) estimated the cost of HPV DNA screening to be 10.48, 12.30, 13.12, 21.21, and 11.21 for India Kenya Peru S. Africa and Thailand respectively [31]. Shen *et al* (2018)

estimated the cost of HPV screening at community health campaigns (CHCs) and health clinics in rural Kenya. The study found that the CHC was less expensive (\$25.00 per screening) than HPV based-screening at government clinics (\$29.56 per screening), at a difference of \$4.56 per screening. Sinanovic *et al* (2009) reported societal cost per for HPV DNA test at \$309 per women [34]. Zimmermann *et al* (2017) found the costs of HPV for women with CD4 200-500 cells/mL at \$223 from a societal perspective and \$113 from a clinic perspective. It cost women with higher CD4 counts (>500 cells/mL) \$102 from a societal perspective and \$56 from a clinic perspective [35]. Campos *et al* (2015) found the direct medical costs for HPV DNA screening to be 10.22 [36]. The cost of self-sampled careHPV (Qiagen USA) screening and clinician-sampled careHPV, were estimated as US\$7.49 and \$7.95 respectively as reported by Ju-Fang Shi *et al* (2012) [38]. Vodicka *et al* (2019) estimated the modified societal costs of cervical cancer treatment in Kenya and compared the modified societal costs of treatment for pre-cancerous cervical lesions integrated into same-day HIV care compared to “non-integrated” treatment when the services were not coordinated on the same day. From the modified societal perspective, per-procedure costs of Cryotherapy were \$22 (integrated) vs. \$46 (non-integrated). This represents cost savings of \$25 for Cryotherapy when provided on the same day as an HIV-care visit [42]. Lince-Deroche *et al* (2015) reported the cost per case detected through HPV DNA at US\$ 54.34 [39]. Mezei *et al* (2018) estimated the direct medical costs for the Self-collected HPV test at US\$12.73 per woman [40]. Finally Campos *et al* (2017) estimated the direct medical costs for careHPV (cervical specimen) at 8.78 [41].

Pap Screening Costs

Three studies estimated the cost of Pap screening. Zimmermann *et al* (2017) found the costs Pap for women with CD4 200-500 cells/mL to be \$219, from a societal perspective and \$124 from a clinic perspective. The cost of Pap for women at higher CD4 counts (>500 cells/mL) was \$115 from a societal perspective and \$71 from a clinic perspective [35]. Lince-Deroche *et al* (2015) reported the cost per case detected through Pap testing at US\$ 8.17 [39]. Mezei *et al* (2018) estimated the direct medical costs for colposcopy and biopsy at US\$52.25 per woman [40].

HPV Vaccination Costs

Sinanovic *et al* (2009) estimated the cost of HPV vaccination and found the societal cost per vaccinated girl to be US \$570 [34].

Colposcopy costs

Ju-Fang Shi *et al* (2012) estimated the direct medical costs of colposcopy and biopsy to be \$3.90 and \$5.76, respectively [38]. Vodicka *et al* (2019) from a modified societal perspective, found per-procedure costs of colposcopy to be \$41 (integrated) vs. \$91 (non-integrated) [42]. Campos *et al* (2017) estimated the direct medical costs for Colposcopy at 7.08 while Colposcopy and biopsy cost 32.90 [41].

LEEP

Vodicka *et al* (2019) from a modified societal perspective, found the per-procedure costs of LEEP to be \$50 (integrated) and \$99 (non-integrated) [42]. Ju-Fang Shi *et al* (2012) reported the direct medical costs of Loop Excision, Cold-Knife Conization and Simple and Radical Hysterectomy from \$61–544, depending on the procedure and whether conducted at county or prefecture level [38]. Finally Campos *et al* (2017) estimated the direct medical costs for LEEP costs at 139.54.

4. Discussion

The findings of this review show that among the screening strategies, VIA was the least expensive. In addition, preventative Cryotherapy without screening was the least expensive strategy for preventing cervical cancer in HIV-infected women compared to VIA, Pap, HPV, and their combinations. The screening costs for Pap, LEEP and colposcopy were relatively high. HPV Vaccination cost the highest among the cervical cancer prevention strategies reviewed.

The variability in costs can be attributed to a number of factors including: strategy, such as those for laboratory equipment and supplies, specimen transport, and training for and supervision of particular techniques. The variability can also be attributed variations in underlying assumptions, methods for cost calculations, and data availability for each study. The perspective adopted by a study influences the cost per woman screened as reported in Sinanovic *et al* (2009) and Zimmermann *et al* (2017). Studies that adopted the societal perspective reported higher costs compared to those that adopted the provider perspective.

Variability in the cost per woman screened and treated may also be possible through economies of scale. By spreading fixed costs (capital goods and equipment) over increased screening participants, the screening and treatment costs reduce. In addition, cost reductions can be attributed to bulk purchases, sharing of services, and reduced personnel downtime. Recent studies have found that large-scale HIV prevention and treatment programs are associated with decreased unit costs when scaled up, across multiple countries [43] [44].

Integration of cervical cancer prevention services into HIV treatment programs offers significant cost savings as reported by Vodicka *et al* (2019). This finding is consistent with that of a study in Zambia which found that increasing linkages and improving integration of HIV and sexual and reproductive health services led to more cost-effective service delivery [45]. However, it is important to come to an understanding as to whether integrated care is to be considered an intervention or whether it is to be interpreted, and evaluated, as a complex strategy to innovate and implement long-lasting change in the way services are delivered, including multiple changes at multiple levels.

Single and two-visit scenario is a major cost driver. The

costs of same day treatment of cervical precancer has also been shown to be less expensive by Zimmermann *et al* (2017) [35]. However, implementers should also be aware of potential diseconomies that may arise from longer wait times and disenrollment, and provider burnout due to expanding the services in a very resource-constrained setting [46].

5. Study Limitation

This study does not estimate costs for linkage to treatment. Although this underestimates the total cost of cervical cancer prevention, our estimates are designed to be of direct budgetary and programmatic relevance to actual screening and treatment of precancer.

6. Conclusions

To better plan effective cervical cancer prevention programs, a systematic review is needed to compare the cost-effectiveness of alternative screening and treatment programs. Moreover, new mathematical models have been developed to delineate the natural history of cervical cancer and assess the clinical benefits and cost-effectiveness of alternative cancer screening strategies. These models take into account differences in the relative effectiveness and requirements of various recruitment strategies, screening tests, treatment approaches, and follow-up protocols for a given country setting. Cost-effectiveness analysis of these interventions is crucial to understand how to stage these interventions for cervical cancer prevention.

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