Cost and Cost-Effectiveness of Cervical Precancerous Lesion Treatment in Low- and Middle-Income Countries: A Systematic Review

Grace John Mallange

Master's Thesis

Centre for International Health, Department of Global Public Health and Primary Care
Faculty of Medicine
University of Bergen, Norway
2023

Supervisor:

1. Professor Oddvar Martin Kaarbøe (PhD), Department of Global Public Health and Primary Care University of Bergen
2. Dr. Amani Thomas Mori (PhD), Bergen Center for Ethics and Priority Settings (BCEPS), Department of Global Public Health and Primary Care, University of Bergen

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This thesis is submitted in partial fulfilment of the requirements for the degree of Master of Philosophy in Global Health at the University of Bergen.

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ACRONYMS AND ABBREVIATIONS

CDSR	-	Cochrane Database of Systematic Reviews
CEA	-	Cost-Effectiveness Analysis
CENRAL	-	Cochrane Central Register of Controlled Trials
CiCERO	-	Criteria for Cost-Effectiveness Review Outcomes
CIN	-	Cervical Intraepithelial Neoplasia
CKC	-	Cold Knife Conization
CPI	-	Consumer Price Index
DARE	-	Database of Abstracts of Reviews of Effects
DCP	-	Disease Control Priorities
FIGO	-	International Federation of Obstetrics and Gynaecology
GNI	-	Gross National Income
HEE	-	Health Economic Evaluation
HPV	-	Human Papilloma Virus
ICER	-	Incremental Cost-Effectiveness Ratio
INAHTA	-	The International Network of Agencies for Health Technology Assessment
LEEP	-	Loop Electrosurgical Excision Procedure
NHS EED	-	National Health Service Economic Evaluation Databases
PRISMA	-	Preferred Reporting Items for Systematic Review and Meta-Analyses
PROSPERO	-	The International Prospective Register of Systematic Reviews
SDGs	-	Sustainable Development Goals
UHC	-	Universal Health Coverage
UNICEF	-	United Nations International Children's Emergency Fund
VIA	-	Visual Inspection with Acetic Acid

ACKNOWLEDGEMENT

First, I would like to express my heartfelt gratitude to my esteemed supervisors, Prof. Oddvar Martin Kaarbøe and Dr. Amani Thomas Mori, for their invaluable supervision, mentorship, support, teachings, and patience while I worked on my project. I learned a lot under their supervision and they made the learning experience impactful.

Second, thanks to the NORPART-2018/10207 Muhimbili-Bergen University Partnership to Enhance Pharmacy Education and Research (PEPER) project for funding my studies at the Centre for International Health (CIH), Department of Global Public Health and Primary Care, Faculty of Medicine, University of Bergen, Norway.

Third, I would like to express my deepest gratitude to the management, professors, lecturers, and all staff members at CIH for their dedication and commitment to impact knowledge and guide me throughout my study period in Norway. Special thanks go to my Master's in Global Health colleagues and classmates for their continued support, cooperation, and invaluable contributions during my studies and this project. Without them, this journey would not have been easy.

Last, I'd also like to thank my parents, siblings, and friends for their encouragement and support throughout my studies. It would have been impossible to complete my studies without the tremendous understanding, encouragement, and unending support of my wonderful husband and two amazing boys. I would like to express my gratitude to them, in particular, for being a source of energy that was the driving force throughout my studies.

ABSTRACT

Background: Cervical cancer is the second leading cause of cancer mortality in women in low- and middle-income countries (LMICs). About 90% of all cervical cancer mortality occurs in LMICs. WHO recommends the use of thermal ablation, cryotherapy, loop electrosurgical excision procedure (LEEP), and cold knife colonization (CKC) for the treatment of precancerous lesions and as the second prevention for cervical cancer. This study aims to collate data about the cost and cost-effectiveness of the recommended strategies for the treatment of cervical precancerous lesions in LMIC to help policy-makers, managers, program officers, and other health professionals to make informed resource allocation decisions.

Methods: A systematic search of published and unpublished literature was conducted to identify cost and cost-effectiveness studies of cervical precancerous lesions treatment in LMICs. The search was conducted in MEDLINE, EMBASE, and Web of Science databases, and grey literature. The search was limited to the English language and without time restriction. The review was registered in PROSPERO with registration number CRD42022333979. Rayyan and Endnote Software were used for screening the identified studies, which was done by two reviewers independently followed by risk of bias assessment. Cost and cost-effectiveness data were extracted and converted to 2021 US Dollars using relevant Consumer Price Indices.

Results: 99 studies were identified and after removing duplicates and screening, eight studies were included in the analysis. The provider cost for treatment of cervical precancerous lesions using cryotherapy ranged from $3.85 in Tanzania to $134.35 in South Africa, and for LEEP it ranged from $74.66 in Tanzania to $596.73 in South Africa. for CKC, the cost ranged from $335.03 in India to $766.86 in Thailand. One study from Kenya reported the cost of $52.89 for cryotherapy and $113.20 for LEEP, from the societal perspective. Only one cost-effectiveness study was identified, which reported that cryotherapy was more cost-effective than LEEP with an Incremental Cost-effectiveness Ratio (ICER) per disease-free case of $566.81 (2021 USD) in South Africa.

Conclusion: The number of cost and cost-effectiveness studies for the recommended treatment strategies of cervical precancerous lesions in LMICs is scarce. However, the few existing studies show that treatment costs for cervical precancerous lesions in LMIC vary widely and are high relative to the Gross National Income (GNI) per capita of their respective countries. More studies should be conducted on cost and cost-effectiveness of the recommended treatment strategies to provide information for evidence-based decisions.

CHAPTER ONE

1.0 INTRODUCTION

1.1 Background

Cervical cancer is one of the most life-threatening non-communicable diseases caused by long-term complications of Human Papilloma virus (HPV) infection(1). HPV is a double-stranded DNA passed from one person to another during sexual intercourse. It is found in 99.7% of cervical cancer specimens and can be categorized according to its carcinogenic properties as high and low risk(2). Infection by high-risk HPV strands such as HPV 16 and 18 strands increases the risk of cervical cancer. Almost 90% of HPV infections will become inactive or disappear within 12 to 24 months(3). Of about 50% of women who HPV will infect at some point in their lifetime, only 10% of the women will first develop precancerous cervical lesions. The precancerous lesions may take between 10 to 20 years to advance into invasive cervical cancer(4). Therefore, cervical cancer is preventable and associated with long survival and good quality of life if these precancerous lesions are detected and treated early.

Cervical precancerous lesions, also known as Cervical Intraepithelial Neoplasia (CIN), are alterations in cell structure that occur in the transformation zone (TZ). This is the area between the cervix (vaginal section) and the endocervix, which forms the cervical canal(5) Transformation zone consists of changing cells, hence the name, and is the most common area where abnormal cells can develop into precancerous lesions. These lesions are not cancer, but if left undiagnosed and untreated, they will progress to invasive cervical cancer(6). According to the World Health Organization (WHO), cervical pre-cancerous lesions are classified into three stages: Cervical Intraepithelial Neoplasia (CIN) 1, CIN 2, and CIN 3. Studies have shown that between 70% to 80% of stage 1 precancerous lesions will spontaneously regress or remain undetected(7). While stages 2 and 3 precancerous lesions, which are collectively known as CIN2+, will progress to invasive cervical cancer if not treated promptly(8).

The World Bank uses Gross National Income (GNI) per capita to classify the world's economies. GNI per capita is calculated by dividing a country's annual final income earned by its citizen living inside and outside the country divided by its total population(9,10). There are four groups,

which include the upper-income countries, which have GNI per capita of $13,205 and above; upper-middle-income countries with GNI per capita of $4,256 to $13,205; lower-middle-income countries with GNI per capita of $1,086 to $4,255; and low-income economies with GNP per capita of $1,085 or less(11). Low- and middle-income countries (LMICs) are sometimes called developing countries.

According to the World Bank, currently, there are 54 LMICs, which include Angola, Algeria, Bangladesh, Benin, Bhutan, Bolivia, Cabo Verde, Cambodia, Cameroon, Comoros, Congo, Republic, Cote d'Ivoire, Djibouti, India, Indonesia, Iran, Islamic Republic, Kenya, Kiribati, Kyrgyz Republic, Lao People's Democratic Republic, Lebanon, Lesotho, Samoa, Philippines, Sao Tome and Principe, Senegal, Solomon Islands, Sri Lanka, Solomon Islands, Tanzania, Tunisia, Tajikistan, Timor-Leste, Ukraine, Uzbekistan, Vanuatu, Vietnam, West Bank and Gaza, Nepal, Egypt, Arab Republic, El Salvador, Zimbabwe, Myanmar, Morocco, Mongolia, Mauritania, Micronesia, Federated States, Nicaragua, Nigeria, Eswatini, Ghana, Haiti, Pakistan, Papua New Guinea and Honduras(11).**Figure 1 Figure 1**depicts a classification of countries for the fiscal year 2023 based on their GNP per capita in 2021(12).

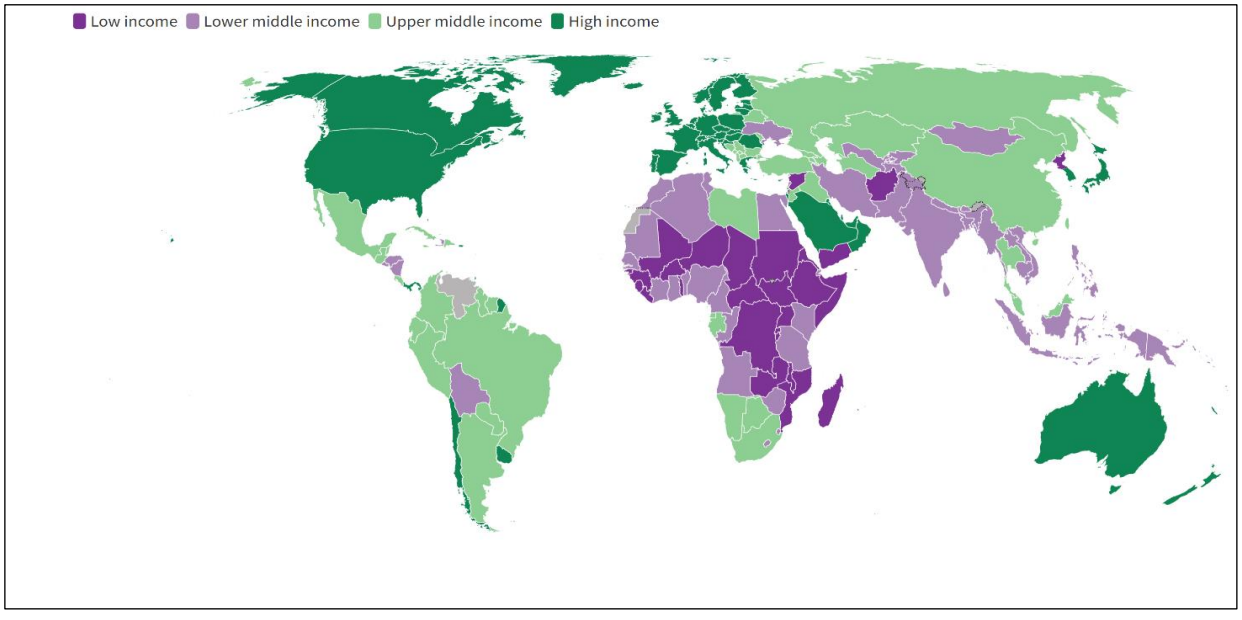

Figure 1: World classification according to income and region, Source: World Bank,2023(12)

1.1.1 The burden of Cervical Cancer

Cervical cancer also known as cervix uteri was ranked the fourth most frequently diagnosed cancer in women and the leading cause of cancer mortality among women globally in 2020(13). According to the Global Cancer Observatory (GLOBOCAN), which is an online database run by the International Agency for Research in Cancer (IAR), providing global cancer statistics in 185 countries, cervical cancer contributed to about 341,831(3.4%) deaths and about 604,127 new cases of cancer in 2020(14). Also, the WHO predicted that the number of deaths due to cervical cancer will raise to 82.3 million by 2040(15).

As shown in the map in **Figure 2Figure 1**, cervical cancer is the second leading cause of cancer deaths among women worldwide, affecting 41 nations. These countries are mostly found in the East, West, and South of Africa, as well as South America, South and central Asia. The majority of these nations with high cervical cancer death rates are LMICs.

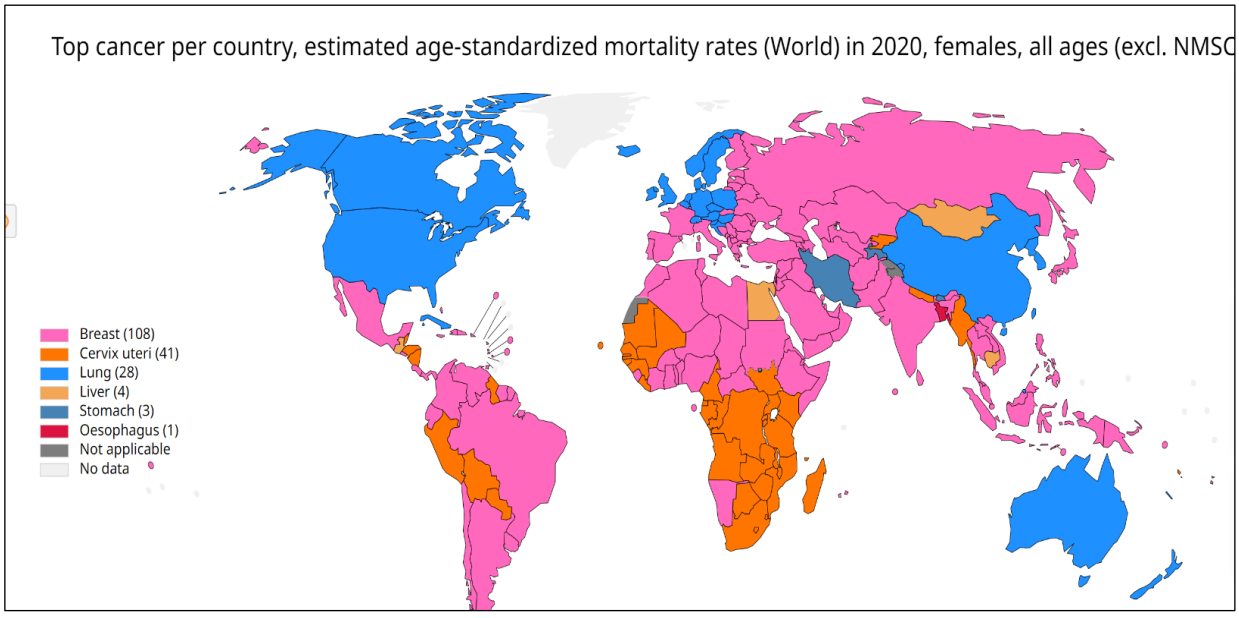

Figure 2: World Map showing Top Cancer per Country Mortality Rates Among Women in 2020. Source, GLOBOCAN 2020(14)

According to the Institute of Health Metrics and Evaluation (IHME), cervical cancer contributed 1.09% of total deaths and 0.75% of total DALYs globally, while in LMICs it contributed 1.03% of total deaths and 0.65% of total DALYs(16). In LMICs, cervical cancer was the second leading

cause of death among women contributing to the incidence of 236,826 (15.9%) and mortality of 146,196 (9.8%)(13). About 90% of all cervical cancer mortality occurs in LMICs. For example, in Tanzania, cervical cancer is the most common cancer among women aged 15-45 years with an incidence rate of 10,241 and a mortality rate of 6,525 deaths per year(17). In LMICs, 60% of women with cervical cancer die, compared to only 30% in high-income countries(18). This inequality in the cervical cancer burden is attributed to the low availability and poor access to quality healthcare services in LMICs. In addition to poor access, underutilization of healthcare services, particularly among vulnerable groups, is a significant contributor to high mortality among women with cervical cancer(19). Furthermore, the majority of women with cervical cancer in LMIC, seek care in formal health facilities very late when the disease has already advanced due to the low availability of early screening and diagnosis services(20).

Figure 3Figure 3, represents cancer incidence rates in 2020 among both men and women in LMICs, where cervical cancer is the second most incident cancer among both sexes.

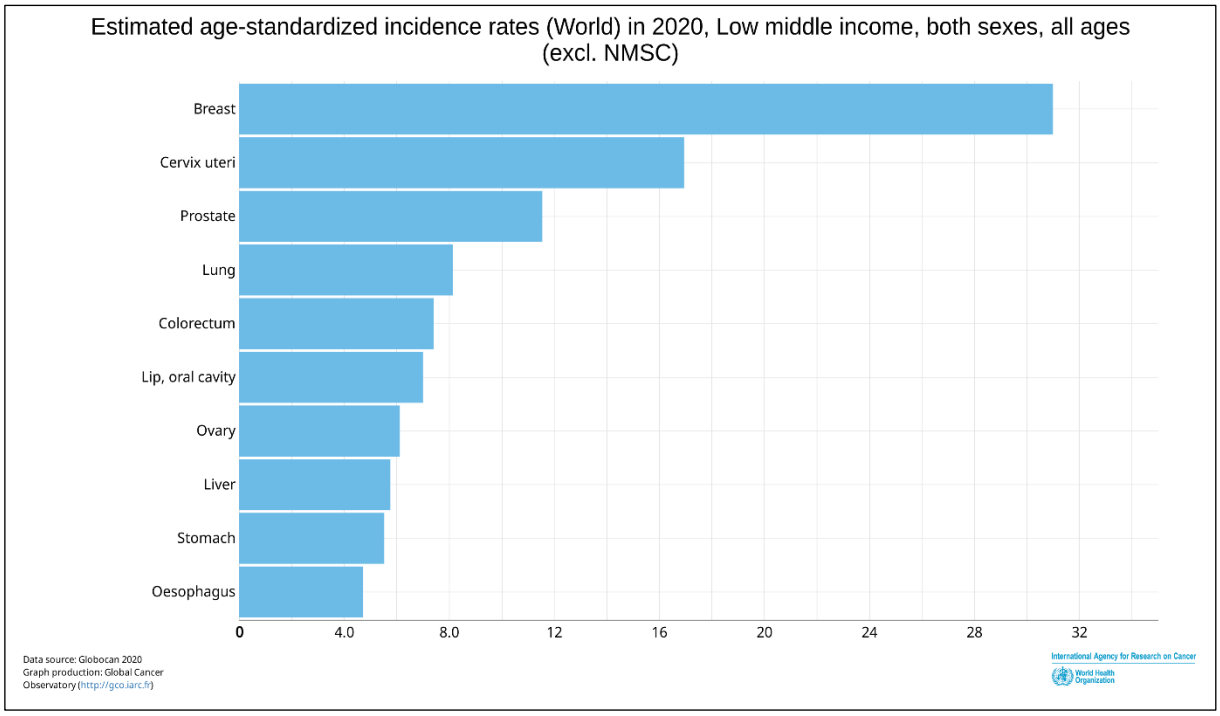

Figure 3: Estimated Age-Standardized Cancer Incidence Rate in 2020 in Low Middle-Income Countries. Source, GLOBALCAN 2020(14)

1.1.2 Cervical Cancer and Sustainable Development Goals (SDGs)

The burden of cervical cancer is closely linked to some of the Sustainable Development Goals (SDG)(21). Cervical cancer is more prevalent in low-income areas than in high-income areas(22), and as previously explained about 90% of cervical cancer deaths occur in LMICs. Also, women with low socioeconomic status are the most vulnerable to cervical cancer than their counterparts, which influences their health-seeking behaviours(23). In these circumstances, cervical cancer is linked to poverty. Poor countries cannot afford universal coverage for screening and treatment of precancerous cervical cancer lesions or cervical cancer. Poor women can also not afford to pay for these treatments in the expensive private sector. Therefore, ending poverty in all related forms and in all places as Goal 1 of the SDGs will reduce and eventually eliminate the devastating effect of cervical cancer.

Goal 3 of the SDGs aims to ensure healthy lives and promote the well-being of all people of all ages. Moreover, target 3.4 of this goal focuses on reducing by one-third the premature mortality from non-communicable diseases such as cervical cancer(24). The increased prevalence and mortality rates of cervical cancer in LMICs significantly impact achieving goal 3 of SDGs and precisely the target mentioned above.

Goal 5 of the SDGs aims to achieve gender equality and empower all women and girls. Cervical cancer primarily affects women, and most face barriers to healthcare, education, and economic opportunities that might help them fight the disease(23). According to research, over 85% of those diagnosed with cervical cancer are young, illiterate women from the poorest countries(18). Empowering these women and girls and giving them equal access to healthcare, education, and economic opportunities will put them in a position to be conscious of their health and seek healthcare services as needed. This would prevent and protect women from diseases such as cervical cancer, hence SDGs achievement.

Goal 10 of the SDGs is to reduce inequalities within and between countries. Cervical cancer burden and access to cervical cancer prevention and control strategies differ between and within nations. Every year, about 266,000 people worldwide die from cervical cancer, with LMICs accounting for almost 90% of these deaths(13). Furthermore, within countries, high-poverty areas will have a higher incidence of cervical cancer than low-poverty areas(22). The

achievement of SDGs is more dependent on the adoption of effective and efficient cervical cancer prevention and control strategies such as HPV vaccine, regular screening, diagnosis, treatment, and care(25).

Given the high burden of cervical cancer incidence and mortality rates, as well as the disease's underlying disparities. WHO devised a global strategy to accelerate cervical cancer elimination(18). This global strategy aims to eliminate cervical cancer as a public health problem by 2030, with an age-adjusted incidence of less than 4 per 100,000 women-years(18). Measurable targets were developed, such as fully vaccinating 90% of girls by the age of 15 with HPV vaccine; screening 70% of women by the age of 35 and again by the age of 45 with a high-performance test; and treating 90% of women with cervical precancerous lesions and managing 90% of women diagnosed with invasive cervical cancer(18)**.** When the high-burden countries implement HPV vaccination to all girls by the age of 15, together with twice-a-year screening in women aged 35 to 45, it will be possible to eliminate cervical cancer by 100% in all countries by 2120(26).

1.1.3 Prevention, Screening, and Treatment of Cervical Precancerous Lesion

1.1.3.1 HPV vaccination

There are effective and approved interventions for reducing the burden of cervical cancer, such as HPV vaccination as a primary preventive measure and regular screening, and early detection of the disease as secondary prevention(27–30). HPV vaccination has been available since 2006. It was originally recommended by WHO in 2009 for use in pre-adolescent girls aged 9 to 14 years old to prevent cervical cancer and other HPV illnesses (31). Boys and older women are considered the secondary target groups. WHO recommends one to two doses of HPV vaccines for girls aged 9 to 14 years and girls or women aged 15 to 25 years and two doses with six-month intervals for women aged 21 and older(32). By 2020, 107 (55%) of WHO member countries had launched HPV vaccination programs, but just 41% of the LMICs had done so by the end of 2019(33).

GAVI-the Vaccine Alliance, is a public-private collaboration founded in 2000 that brings together various organizations such as WHO, UNICEF, the Bill and Melinda Gates Foundation, the World Bank, vaccine manufacturers etc(34). GAVI was established to promote health equity

by establishing and expanding equal access to new and underused vaccines such as HPV in the world's poorest countries, strengthening countries' health and immunization systems, and introducing new innovative immunization technology(35). By 2021, approximately 24 of the 57 GAVI-supported countries had already initiated their national HPV vaccination program with GAVI funding(36). Many barriers face HPV vaccination implementation in LMICs, including a lack of political will, funding, resource allocation, delivery strategies, and other social and cultural factors(37). As a result, further efforts are required to guarantee that all countries include HPV vaccination in their national immunization programs.

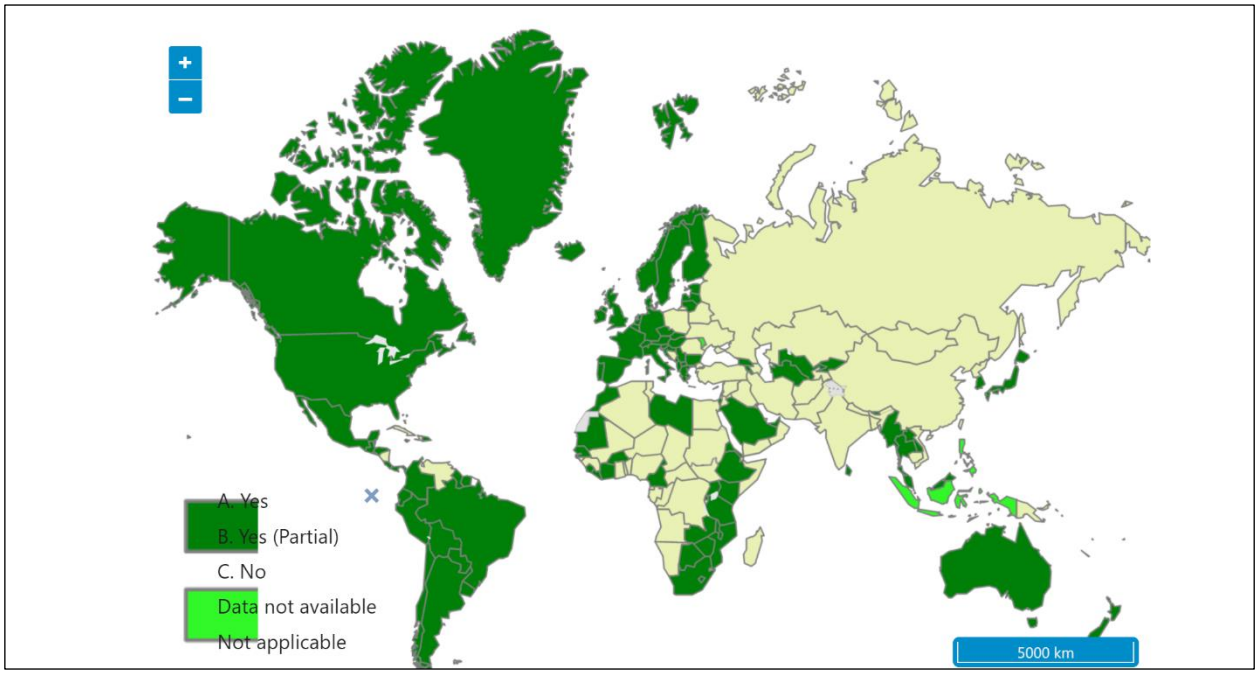

Figure 4: Countries which included HPV Vaccines in National Immunization Program as of April, 2023. Source, WHO HPV Dashboard, 2023(38)

As shown in **Figure 4**, approximately 126 countries have fully implemented HPV vaccination into their National Immunization Program, three countries have partially implemented it, and 65 countries have not implemented HPV. It also shows that while all countries in North and South America have fully or partially implemented HPV vaccination programs in their national immunization programs, only a few countries in Asia and Africa have done so.

Implementation of HPV vaccination only to girls by the age of 15 years alone is expected to avert 60 million cases and reduce the prevalence of cervical cancer by 89% in LMICs in the next century(26). Countries with a current incidence of more than 25 cases per 100,000 women years, especially sub-Saharan Africa cannot eliminate cervical cancer with HPV vaccination alone(26). Therefore, to reach the WHO global cervical cancer elimination target of incidence of less than 4 cases per 100,000 women-year by 2030, HPV vaccination is required to be used with other strategies such as screening and treatment of diagnosed women(39).

HPV vaccination in LMICs is expected to be cost-effective if the cost per vaccinated girl is less than $10-$25, and this includes the cost of three doses of HPV vaccines and delivery cost(40). However, a systematic review reported mean financial cost per fully immunized girl ranged from $5.48 in Tanzania, $5.71 (Peru, Uganda, Vietnam), $17.95 and $36.9 (Mozambique) to $ $40.03 (Zimbabwe), while the mean economic cost per fully immunized girl which includes monetary and non-monetary implication for HPV vaccination implementation strategies ranged from $9.55 (Peru, Uganda, Vietnam), $9.76 (Tanzania), $52.29 (Mozambique) and $91.19 (Zimbabwe)(41).

1.1.3.2 Screening

The recommended secondary prevention strategy for cervical cancer is regular screening and early detection(27,30). Its goal is to detect precancerous alterations that, if treated early, can prevent the development of aggressive cervical cancer(4). Women who participate in organized screening programs reduce their risk of cervical cancer by 41% to 92%(42). In 2013, WHO launched a screening and treatment program which recommended women be screened and, if positively diagnosed, be treated during a single visit to the health centre(8). In 2021, the second edition of WHO guidelines for screening and treatment of precancerous lesions for cervical prevention was published(43). In these guidelines, WHO recommended screening tests, including HPV DNA test, visual inspection with acetic acid (VIA), and cytology (pap smear)(8,43). The HPV DNA test detects the presence of DNA of high-risk human papillomavirus, which can induce cell alterations, while cytology/pap smear and VIA tests detect the presence of abnormal cells (precancer cells)(44). As a primary screening test, the

WHO advises screening for cervical cancer is beneficial beginning at the age of 30-49 years and again at intervals of every 5 to 10 years(43).

In addition to the "screen and treat" approach, WHO recommended the "screen, diagnosis, and treat" approach. The choice of which approach to be used depends on the local context in terms of the availability of resources to conduct the recommended approach, such as qualified personnel and equipment, costs, potential benefits and harms, and potential for loss to follow-up after treatment. In the “screen and treat” approach, the potential for loss to follow-up is reduced because screening and treatment are done immediately without regard for diagnosis. However, in the “screen, diagnose, and treat” approach, a positively screened woman is subjected to a confirmatory test (diagnosis) using colonoscopy or biopsy to histologically confirm the presence and severity of precancerous lesions before being treated(45).

A study conducted in Burkina Faso reported that the average cost per screening test ranged from $3.2 for VIA to24.8 for cytology(46). Another study conducted in five countries in developing countries reported that one or two screening visits using VIA or HPV test reduce the lifetime risk of cervical cancer by up to 36% and cost less than $500 per life of year saved(47). In a systematic review of the cost-effectiveness of cervical cancer screening in LMICs, it was reported that HPV testing was most effective compared to cytology and VIA in reducing cervical cancer incidences. HPV testing and VIA were more cost-effective than cytology in LMICs(30).

1.1.3.3 Treatment

Early detection of cervical precancerous lesions alone cannot reduce the impact of cervical cancer disease burden if positively screened women do not receive timely treatment of lesions. The treatment of cervical precancerous lesions is considered more effective compared to the treatment of advanced staged cervical cancer and posttreatment surveillance(4). WHO recommended three treatment options for cervical precancerous lesions, which included cryotherapy, Loop Electrosurgical Excision Procedure (LEEP), and Cold Knife Conization (CKC)(8,43).

However, there were challenges in implementing cryotherapy in LMIC, which included the need for refrigerant gas (N_20 and CO_2) and the transportation of bulky and heavy gas containers. In this regard, in 2019 WHO recommended thermal ablations an alternative

treatment option for these settings(48). WHO formulated both of these guidelines based on evidence from clinical, epidemiological, and economic evaluation models. According to some studies, cryotherapy and LEEP are the most commonly used and cost-effective treatment methods in both low- and high-income settings, whereas CKC is less cost-effective due to its implementation costs, including the need for operating rooms, highly trained specialists, anesthesia and the risk of pre-cancer lesions (CIN2+) recurrence(49,50). Therefore, in LMIC settings, WHO recommends using thermal ablative or cryotherapy for the treatment of patients with pre-cancer lesions (CIN2+), followed by LEEP if patients are not eligible for thermal ablation and cryotherapy. CKC should be used only if a patient is not eligible for all the treatment options mentioned 48).

Figure 5 depicts the decision-making process in the screen-and-treat approach. When using VIA as a primary screening test, if a patient tests negative, she will be rescreened after three years. If she tests positive, her eligibility for ablative treatment (cryotherapy or thermal ablation) is determined, and then she is treated if eligible. If she is not eligible, she will be treated with LEEP or CKC (if LEEP is unavailable). If a Histology test is available, it will be applied to the cells removed by LEEP. If the cells are less than CIN 3, the patient will be monitored for a year (post-treatment follow-up after one year). In addition, if a histology test is not available, the patient will be followed up after a year. However, if a patient is suspected of having invasive cervical cancer at the outset or after a histology test, the patient will be evaluated, biopsied, and managed further.

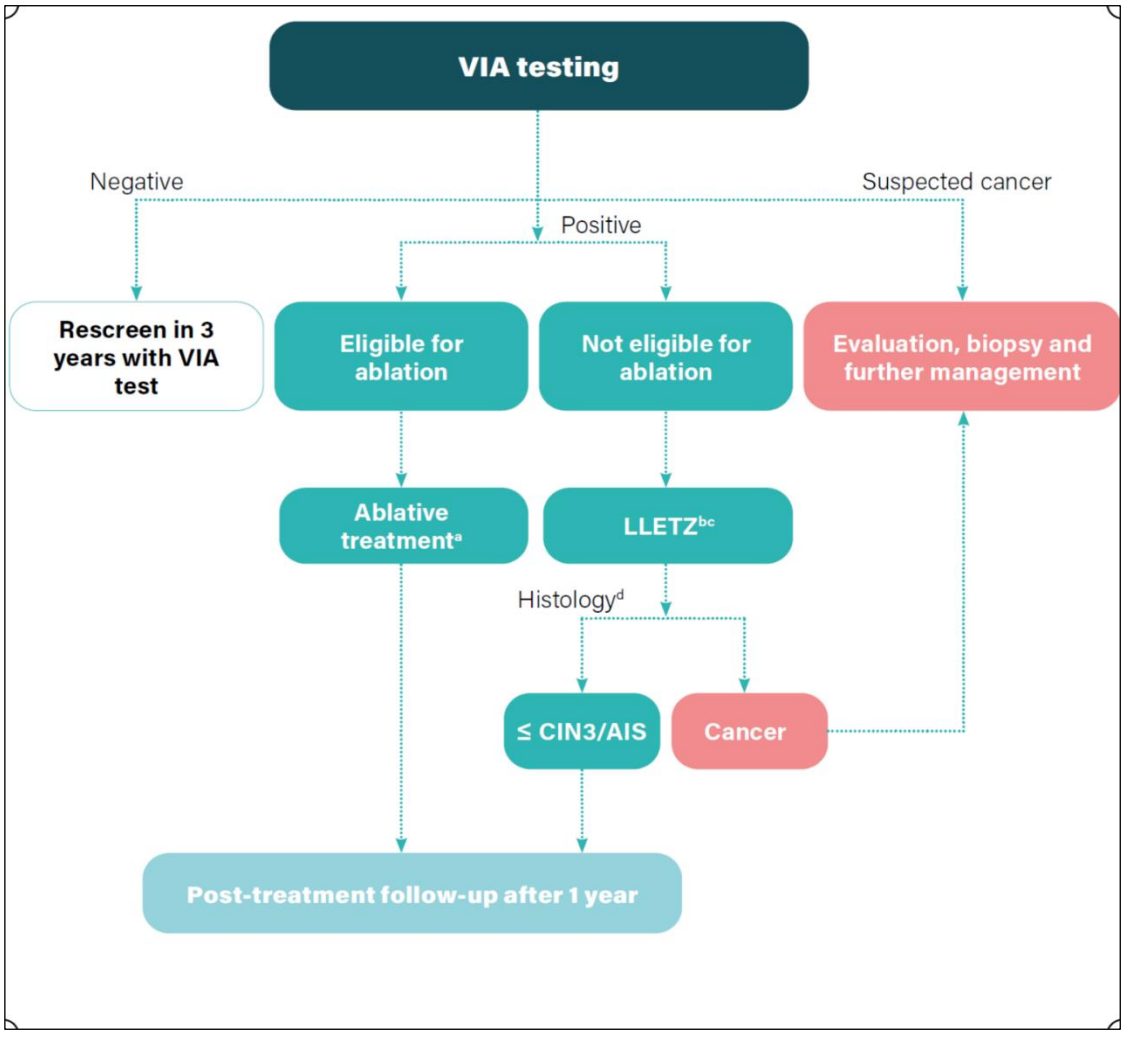

Figure 5: Decision flow for Screen and Treat Approach. Source WHO, 2021(43).

Studies have been conducted showing the effectiveness and safety of cervical precancerous lesion treatment using cryotherapy, LEEP, thermal ablation, and CKC(50–52). The following subsections describe the recommended treatment methods for cervical precancerous lesion and their implementation in different countries:

a) Cryotherapy

Cryotherapy is one of the two ablative treatment interventions recommended for the treatment of cervical precancerous lesions. It is a procedure in which abnormal tissue is frozen and destroyed using an extremely cold liquid or an instrument known as a cryoprobe. Liquid nitrogen, liquid nitrous oxide, or compressed argon gas are used to cool cryoprobes. Cryotherapy can be performed at all healthcare facilities levels by healthcare professionals who are conversant with pelvic examination and trained in cryotherapy treatment. The procedure takes about 15 minutes, can be performed without anesthesia and is well tolerated with mild discomfort(53). Cryoablation and cryosurgery are other terms for the same procedure. A patient is eligible for cryotherapy if the entire lesion and squamocolumnar junction are visible and the lesions do not cover more than three-quarters of the ectocervix. If the lesions extend beyond the cryoprobe being used or into the endocervical canal, or if the lesions are suspicious of invasive cancer, the patient is not eligible for cryotherapy(45).

The most widely used cryotherapy devices have an estimated cost between $1,700 and $2,000, with additional tips costing approximately $200 each. In addition to the cost of the machine, the required gas and related costs can range from $13 to $38 per treatment. These prices may increase significantly because of distribution costs and taxes specific to each country(53). Cryotherapy is considered to be effective and safe, with no risk of serious consequences and a cure rate of 89.5% for less severe lesions(54). In a project implemented in six African countries in 2009, 19,579 women were checked for VIA and treated with cryotherapy if positive. According to the project, 87.7% of VIA-positive diagnoses were eligible for cryotherapy, with 63.4% receiving cryotherapy within a week of initial screening. As a result, VIA and cryotherapy were introduced into cervical cancer preventive services in these countries' reproductive health facilities(55). Integration of the screen and treat program utilizing VIA and cryotherapy into normal health services is very plausible; however, public awareness, health care staff training, and health system improvements are required to address patients' demands(56).

b) Loop Electrosurgical Excision Procedures

The loop electrosurgical excision procedure (LEEP) is a surgical procedure used to remove cells and tissue from a woman's lower genital tract by heating a wire loop with an electric current. It is used to help diagnose and treat abnormal or cancerous conditions; therefore, this treatment serves a double purpose. An electric current is passed through the fine wire loop during LEEP to remove a thin layer of abnormal tissue and remove the lesions and the entire transformation zone. This tissue will be tested in a laboratory to assess the severity of the disease. LEEP can also be used to remove abnormal cells, allowing healthy tissue to grow. The procedure is performed at secondary-level health facilities, takes about 30 minutes under local anesthesia and should be performed by a competent healthcare worker. Eligibility of LEEP is a positive screening test and if lesions are not suspected to be invasive cervical cancer(45). The LEEP device, including the electrosurgical unit and smoke evacuator, generally costs approximately$3,500 and is made by several companies (53). Studies have demonstrated LEEP to be effective in high-grade lesions, with cure rates of 90% for CIN 1, 85.5% for CIN 2, and 72.7% for CIN 3 in low-resource countries(57). LEEP was also reported to have a low disease recurrence rate(58).

c) Thermal Ablation

Thermal ablation is another ablative treatment method used to treat cervical precancerous lesions. The procedure is also known as thermocoagulation or cold coagulation. It uses portable equipment, which is heated by electricity to 100^{o}C and applied for 20 – 40 seconds to destroy the cervical precancerous lesions. This treatment method was recommended by WHO in 2019 to treat cervical precancerous lesions in low-resource settings because it is easy to use and cheaper compared to other methods(48). It is advantageous compared to cryotherapy, which requires refrigerant gas stored in bulk containers, which are heavy and expensive to transport. Another advantage is that primary healthcare workers can administer it without the use of anesthesia. The updated device customized for use in LMICs is projected to cost approximately $2,500 and offers cost-saving benefits by requiring high-level disinfection (HLD) rather than autoclave sterilization of the probe(53). A systematic review reported the efficacy of cold coagulation with a cure rate of 96% for CNI 1 and 95% for CNI 2 - 3(59). According to a

modelling study conducted in China, self-collected HPV tests combined with thermal ablation are the most cost-effective strategies for cervical cancer prevention in China, with ICER ranging from -$3214.1 to $8900.2 per QALY gained(60).

d) CKC

Cold knife cone (CKC) or Conization of the cervix or cold knife cone biopsy is a surgical procedure used to treat or diagnose cervical dysplasia (cervical lesions). It is the excision of a cone-shaped portion of the cervix to remove a cervical lesion and the entire transformation zone, including the inner and outer cervix. Using a scalpel or laser knife, a cone-shaped piece of abnormal tissue is removed from the cervix. The number of tissues removed depends on the size of precancer lesions and the likelihood of finding invasive cervical cancer. Following that, some of the tissues are examined under a microscope for signs of disease, such as cervical cancer. CKC is conducted at the hospital level with the necessary equipment and infrastructure and by trained personnel with surgical skills, such as surgeons or gynaecologists. The procedure takes less than an hour and is performed under general anesthesia(53). CKC should be reserved for cases that cannot be resolved with cryotherapy or LEEP, such as in the presence of glandular pre-cancer (contained within the columnar epithelium of the canal) or micro-invasive cancer lesions (contained within cervical epithelium) of the cervix(45). Certain cervical conditions, such as genital warts, may also benefit from CKC(61). CKC decreases the risk of residual disease compared to LEEP(52). A study conducted in China reported the direct medical cost of treatment of cervical precancerous lesions in a hospital setting using CKC was $120.85(62).

1.1.4 Economic Burden of Cervical Cancer and Precancerous Lesions in LMIC

Apart from the epidemiological and clinical burden of cervical cancer, cervical cancer, like other types of cancers, imposes a high economic burden on the health system and society in general. Cancer prevention and treatment in LMICs have been underfunded, resulting in an estimated 5% of global cancer resources spent in countries hosting 80% of the global cancer burden(63). A systematic review in the US estimated the cost of treating cervical cancer at $441 million annually in 2010 US dollars(64). Another study reported the mean cost of premalignant lesions associated with HPV infection was estimated to be $ 2,853 per patient, of which 68.57% was direct medical costs, while the mean cost of cervical cancer was $ 39,327 per patient, with 57.9% related to indirect costs(65). Another study conducted in Belgium reported that from the

healthcare payer perspective, reported the total annual cost associated with the management of cervical cancer was $7.75 million, and for the management of precancerous lesions (CIN 1, 2 and 3), the total annual cost was $2.35 million(66).

A study conducted in Eswatini reported that the estimated total annual cost for cervical cancer was $19 million (ranging between $14 million and $24 million). Direct cost represented the majority of the costs at 72% ($13.7 million), of which total pre-cancerous treatment costs were 0.7% ($94,161). The management of invasive cervical cancer was the main cost driver, with costs attributable to treatment of stages III & IV representing $1.7 million and $8.7 million, respectively. Indirect costs contributed 27% ($5.3 million), out of which productivity loss due to premature mortality represented the majority at 67% ($3.5 million)(67).

Few primary studies have been conducted in LMIC to evaluate the cost and cost-effectiveness of these treatment methods for cervical precancerous lesions(68–70). However, there is no systematic review conducted on the cost and cost-effectiveness of cervical precancerous lesions treatment in LMIC. Therefore, this study aims to collate data about the cost and cost-effectiveness of the recommended strategies for treating cervical precancerous lesions in LMIC to help policy-makers, managers, program officers, and other health professionals make informed resource allocation decisions.

1.2 Problem Statement

The cervical cancer burden is 18 times higher in LMICs compared to higher-income countries(71). In particular, cervical cancer mortality is highest in Africa, Latin America, the Caribbean, and Asia (72,73). Many African countries such as Malawi, Tanzania, Zambia, Comoro and Guinea have 10 to 20 folds higher incidence and mortality rates of cervical cancer compared to countries such as Iran, Saudi Arabia, Syria, Egypt and Switzerland(74). This variation is associated with economic, social, and cultural factors causing limited availability, utilization, and implementation of effective prevention and treatment programs(75). However, while cryotherapy, Loop Electrosurgical Excision Procedure (LEEP), CKC, and thermal ablation are highly recommended for the treatment of precancerous cervical lesions, the cost and cost-effectiveness evidence are not readily available to policymakers and healthcare

workers in LMICs where cervical cancer is most prevalent. This could contribute to their low uptake and implementation in these countries, hence contributing to the high burden of cervical cancer. Therefore, this review aims to fill this gap by providing evidence-based information on cost and cost-effectiveness of strategies for the treatment of cervical precancerous lesions in LMICs. The information which is necessary for policymakers, program managers, health facilities, healthcare professionals and other relevant stakeholders in the selection of strategies and resources allocations for the prevention and treatment of cervical cancer.

1.3 Rationale

Inequalities in cervical cancer observed in LMICs are not only due to resource scarcity but also due to pervasive inequity (75). To improve the availability and accessibility of cervical cancer control and care interventions in LMICs, these interventions should be included in national healthcare benefits packages to ensure equity and reduce poverty amongst the affected population, as envisioned in the Universal Health Coverage (UHC) agenda. UHC is one of the global health agenda's driving forces, and it is one of the indicators of the Sustainable Development Goals (SDGs 2030)(76). According to WHO, UHC is achieved when "all people and community can use the promotive, preventive, curative, rehabilitative, palliative health services they need, of sufficient quality to be effective, while also ensuring that the use of these services do not expose the users to financial hardship"(77).

Moreover, Disease Control Priorities (DCP) Economic Evaluation for Health is a project that aims to build capacity and provide technical assistance to LMICs in developing their health intervention priority setting. The project uses the cost-effectiveness of the listed healthcare interventions for various diseases to ensure that the most cost-effective interventions are chosen to ensure equity and poverty reduction in the population as the country moves closer to universal health coverage(78). DCP has recommended cervical cancer control and care interventions, which include Human Papilloma virus (HPV) immunization; Screening for cervical cancer and precancerous lesions; Treatment of cervical precancerous lesions; Treatment of cervical cancer; and post-treatment surveillance for cervical cancer.

This project is linked to Bergen Centre for Priority-Setting (BCEPS) projects in Tanzania, Ghana, Nepal, and Africa CDC that aims to support the revision of NCD benefit packages in the respective countries and build competencies in health economics and priority-setting. When the evidence for cost and cost-effective interventions is available (as some of the criteria for priority setting), it will facilitate the process of fair choices when prioritizing healthcare interventions during the revision of the benefit packages for NCDs, which will improve the access and utilization of healthcare services, especially to the most vulnerable population and provide financial risk protection. The cost and cost-effectiveness evidence collated by this study will be useful in the revision of benefit packages, treatment guidelines for cervical precancerous lesions, and other relevant healthcare policies.

1.4 Main Research Question

What is the available cost and cost-effectiveness evidence for interventions against cervical precancerous lesions in LMICs?

1.4.1 Specific Research Questions

i) What are the costs of interventions used for the treatment of cervical precancerous in LMICs
ii) Which are the most cost-effective intervention for the treatment of cervical precancerous lesions in LMICs
iii) How do the costs and cost-effectiveness for the treatment of cervical precancerous lesions vary between different countries in LMICs
iv) What are the gaps in the literature on evidence of cost and cost-effectiveness for the treatment of cervical precancerous lesions to inform future research?

1.5 Main Objective

To systematically review and summarize current evidence on costs and cost-effectiveness of treatment interventions for cervical precancerous lesions in LMICs.

1.5.1 Specific objectives

i) To estimate/summarize the costs of treatment interventions for cervical precancerous lesions in LMICs;

ii) To summarize the cost-effectiveness of treatment interventions for cervical precancerous lesions in LMICs;

iii) To describe how costs and cost-effectiveness of treatment of cervical precancerous lesions vary between LMIC settings

iv) To identify gaps in the literature on evidence of cost-effectiveness for the treatment of cervical precancerous lesions to inform future research.

CHAPTER TWO

2.0 METHODS

2.1 Study Design

This is a systematic review study. According to Cochrane collaboration definition, "A systematic review attempts to identify, appraise and synthesize all the empirical evidence that meets pre-specified eligibility criteria to answer a specific research question. Researchers conducting systematic reviews use explicit, systematic methods that are selected to minimise bias, to produce more reliable findings to inform decision making"(79). This review was conducted and reported according to recommendations of the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines(80,81).

2.2 Study Registration

To avoid bias and unintended duplication of efforts and resources, the study was registered in The International Prospective Register of Systematic Reviews (PROSPERO)(82) with registration number **CRD42022333979**. The registration is also advantageous in the promotion of transparency, reproducibility, and usability of the systematic review(83).

2.3 Search Strategy

The review included published and unpublished study materials. The search for articles followed three steps shown below:

a) A preliminary search in PUBMED to identify relevant keywords contained in the title, abstract and subject descriptors;
b) Then identified terms and synonyms were used to develop a search strategy which was used in a comprehensive literature search in databases such as EMBASE (Ovid), Web of Science and MEDLINE (Ovid);
c) Lastly, a search for relevant references and bibliographies of articles obtained in stage (b) above was conducted.

Table 1:Search Strategy

Categories	Search Terms	
	EMBASE	MEDLINE
Cervical Cancer	Uterine cervical cancer; Uterine cervical neoplasia; Uterine cervix tumor; papillomavirus infection; cervical cancer	Uterine cervical cancer; Uterine cervical neoplasms; papillomavirus infection; cervical cancer; cervix tumor
Treatments for Precancerous Lesion	LEEP, Cryotherapy, CKC, thermal ablation	LEEP, Cryotherapy; CKC, thermal ablation
Cost-effectiveness	Cost-effectiveness analysis; Cost-benefit analysis; cost analysis; economic evaluation	Cost-effectiveness analysis; Cost-benefit analysis; costs and cost analysis; economic evaluation
Cost	Costs; Costing; cost analysis; cost measures; affordability	Costs; Costing; cost analysis; cost measures; affordability
Low- and Middle-Income Countries	Developing countries; Africa; Sub-Saharan Africa; South America; Latin America; South Asia	Developing countries; Africa; Sub Saharan Africa; South America; Latin America; South Asia
List of Countries in LMIC	Afghanistan; Albania; Algeria; Angola; Antigua; Barbuda; Argentina; Armenia; Azerbaijan; Bangladesh; Belarus; Belize; Benin; Bhutan; Bolivia; Bosnia; Herzegovina; Botswana; Brazil; Burkina Faso; Burundi; Cabo Verde; Cambodia; Cameroon; Central	Afghanistan; Albania; Algeria; Angola; Antigua; Barbuda; Argentina; Armenia; Azerbaijan; Bangladesh; Belarus; Belize; Benin; Bhutan; Bolivia; Bosnia; Herzegovina; Botswana; Brazil; Burkina Faso; Burundi; Cabo Verde; Cambodia; Cameroon; Central

Categories	Search Terms	
	EMBASE	MEDLINE
	African Republic; Chad; China (People's Republic of); Colombia; Comoros; Democratic Republic of Congo; Congo; Costa Rica; Côte d'Ivoire; Cuba; Djibouti; Dominica; Dominican Republic; Ecuador; Egypt; El Salvador; Equatorial Guinea; Eritrea; Eswatini; Ethiopia; Fiji; Gabon; Gambia; Georgia; Ghana; Grenada; Guatemala; Guinea; Guinea-Bissau; Guyana; Haiti; Honduras; India; Indonesia; Iran; Iraq; Jamaica; Jordan; Kazakhstan; Kenya; Kiribati; Democratic People's Republic of Korea; Kosovo; Kyrgyzstan Lao People's Democratic Republic; Lebanon; Lesotho; Liberia; Libya; North Macedonia; Madagascar; Malawi; Malaysia; Maldives; Mali; Marshall Islands; Mauritania; Mauritius; Mexico; Micronesia; Moldova; Mongolia; Montenegro; Montserrat; Morocco; Mozambique; Myanmar; Namibia; Nauru; Nepal; Nicaragua; Niger; Nigeria; Niue; Pakistan; Palau; Panama; Papua New Guinea; Paraguay; Peru;	African Republic; Chad; China (People's Republic of); Colombia; Comoros; Democratic Republic of Congo; Congo; Costa Rica; Côte d'Ivoire; Cuba; Djibouti; Dominica; Dominican Republic; Ecuador; Egypt; El Salvador; Equatorial Guinea; Eritrea; Eswatini; Ethiopia; Fiji; Gabon; Gambia; Georgia; Ghana; Grenada; Guatemala; Guinea; Guinea-Bissau; Guyana; Haiti; Honduras; India; Indonesia; Iran; Iraq; Jamaica; Jordan; Kazakhstan; Kenya; Kiribati Democratic People's Republic of Korea; Kosovo; Kyrgyzstan; Lao People's Democratic Republic; Lebanon; Lesotho; Liberia; Libya; North Macedonia; Madagascar; Malawi; Malaysia; Maldives; Mali Marshall Islands; Mauritania; Mauritius; Mexico; Micronesia; Moldova; Mongolia; Montenegro; Montserrat; Morocco; Mozambique; Myanmar; Namibia; Nauru; Nepal; Nicaragua; Niger; Nigeria; Niue; Pakistan; Palau; Panama; Papua New Guinea;

Categories	Search Terms	
	EMBASE	MEDLINE
	Philippines; Rwanda; Saint Helena; Samoa; São Tomé and Príncipe; Senegal; Serbia; Sierra Leone; Solomon Islands; Somalia; South Africa; South Sudan; Sri Lanka; Saint Lucia; Saint Vincent and the Grenadines; Sudan; Suriname; Syrian Arab Republic; Tajikistan; Tanzania; Thailand; Timor-Leste; Togo; Tokelau; Tonga; Tunisia; Turkey; Turkmenistan; Tuvalu; Uganda; Ukraine; Uzbekistan; Vanuatu; Venezuela; Vietnam; Wallis and Futuna; West Bank and Gaza Strip Yemen; Zambia; Zimbabwe	Paraguay; Peru; Philippines; Rwanda; Saint Helena Samoa; São Tomé and Príncipe; Senegal; Serbia; Sierra Leone; Solomon Islands; Somalia; South Africa; South Sudan; Sri Lanka; Saint Lucia; Saint Vincent and the Grenadines; Sudan; Suriname; Syrian Arab Republic; Tajikistan; Tanzania; Thailand; Timor-Leste; Togo; Tokelau; Tonga; Tunisia; Turkey; Turkmenistan; Tuvalu; Uganda;; Ukraine; Uzbekistan; Vanuatu; Venezuela; Vietnam; Wallis and Futuna; West Bank and Gaza Strip Yemen; Zambia; Zimbabwe

Other databases which were used for extensive search include:

- Global Health Cost-Effectiveness Analysis Registry (GH CEAR)
- Cochrane Database of Systematic Reviews (CDSR)
- Health Economic Evaluation (HEE) such as the National Health Service Economic Evaluation Databases (NHS EED), International Health Technology Assessment Database (INAHTA)

In addition, a search to identify potential additional studies, including unpublished studies and published studies, was conducted using the following sources:

The systematic scanning of the reference lists of eligible studies and review articles; and grey literature search and citation tracking in Google and Google Scholar to retrieve further references.

2.4 Inclusion and Exclusion Criteria

To assess the cost and cost-effectiveness of treatment interventions for cervical precancerous lesions using LEEP, Cryotherapy, thermal ablation, and CKC in LMICs, the following were the inclusion and exclusion criteria for studies included in the review:

2.4.1 Criteria according to PICO(T)

a) Types of Participants/Population

Women positively diagnosed with cervical precancerous lesions in low- and middle-income countries undergoing treatment using cryotherapy, thermal ablation, LEEP or CKC.

b) Type of Intervention

Studies with interventions related to economic evaluation for the treatment of cervical precancerous lesions using thermal ablation, cryotherapy, LEEP, and CKC

c) Types of Comparators

No restriction on the comparator. Studies with no comparator or alternative comparators other than interventions were included as long they clearly described the comparator used.

d) Types of Outcome Measures

Cost and cost-effectiveness presented in the economic evaluation studies for the treatment of cervical precancerous lesions using LEEP, CKC, thermal ablation, and Cryotherapy were included. Which included treatment costs and ICER of using one treatment method over another.

e) Time

The review did not consider the time limit in the search. All cost and cost-effectiveness studies (published and unpublished) which were available in the searched databases up to July 2022 and were conducted in LMIC were included.

2.4.2 Other Criteria

a) Economic Evaluation studies

The review included full economic evaluation studies such as trial-based, non-trial biased, decision model, and simulation model studies. Qualitative studies, study protocols, conference abstracts, comments, and notes were excluded.

b) Language

Only studies written in English language were included.

c) There was no restriction on sample size, economic evaluation perspective or follow-up time.

2.5 Perspective

Economic evaluation studies that collected data from all perspectives, such as provider's, household, and societal perspectives, were included.

2.6 Study Selection Procedures

Endnote 20 and Rayyan software were used in the study selection process. Two reviewers (GM & ATM) independently reviewed the studies according to the inclusion and exclusion criteria. The selection of studies followed two steps as follows:

i) First, using Rayyan software, the two reviewers independently screened for titles and abstracts against the selection criteria;

Secondly, using Endnote 20, the two reviewers independently conducted full-text screening for

required studies. When there was disagreement or conflicting views, the reviewers conducted a meeting to further review the relevant articles before making a final decision. There was no unresolved disagreement about the studies inclusion and exclusion; therefore, there was no need for arbitration.

2.7 Data Extraction

The Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist(84) was used to structure the data extraction form to capture all the necessary variables in costing and cost-effectiveness studies. Data extracted included the name of the primary author, year of publication, year in which the data was collected, study type, the country in which data was collected, costing perspective used, the outcome of interest, the currency used, and cost or cost-effectiveness information. To reduce introduction of bias, data extraction was conducted independently by two reviewers (GM &ATM). A standardized and pre-piloted Excel form was used to record the extracted information, which included:

- Name of Authors
- Year of Publication
- Country
- Study design
- Currency unit
- Study perspective
- Time horizon
- Methods for collecting resource use
- Price year
- Costs categories
- Total/average intervention costs
- ICER
- Uncertainty analysis
- Sensitivity analysis

Any inconsistency between reviewers over data extraction process was resolved through discussions.

2.8 Critical Appraisal

To ensure the quality of the review process, the PRISMA checklist was used as a guideline for review(80). Also, Drummond's checklist, 2015 Criteria for Assessment of Economic Evaluation Studies(85,86) was used to assess the risk of bias of selected cost and cost-effectiveness studies. The checklist was also adapted to evaluate costing studies. The checklist consists of ten items, including the research question; description of the study or intervention; study design; measurements; identification; valuation of costs and consequences; discounting; incremental analysis; results with sensitivity and uncertainty; and discussion of results(87).

The following questions are used to evaluate whether the study abides by these ten items:

i) Was a well-defined question posed?
ii) Was a comprehensive description of the competing alternatives offered?
iii) Was the evidence of the effectiveness of the program offered?
iv) Were all important and relevant costs and consequences identified?
v) Were all important and relevant costs and consequences measured accurately?
vi) Were all important and relevant costs and consequences have been properly valued?
vii) Were the costs and consequences adjusted for different times?
viii) Was an incremental analysis of costs and consequences of competing alternatives done?
ix) Was the effect of uncertainty (sensitivity analysis) investigated in estimating the costs and consequences?
x) Were the presentation and analysis of all issues related to users of the results included?

The scoring system developed by Doran(88) was adopted where each item on the checklist was awarded 1 point. Aggregated results of quality assessment for 1-3 points were regarded as poor, 4-7 points average and 8-10 point good. The risk of bias assessment was conducted independently by two reviewers (GM&AM) for completeness and accuracy.

2.9 Data Analysis and Reporting

Descriptive statistic was used to summarize extracted data. Costs and cost-effectiveness data were presented using tables and detailed explanations. Costs were categorized per cervical cancer treatment methods such as cost for cryotherapy, LEEP, or CKC and per costing perspective if its provider or household perspective or both (societal). Household costs were further disaggregated into direct costs and indirect costs. Direct costs could be further disaggregated into direct medical costs, i.e., those paid for the treatment procedure, such as registration, consultation, laboratory test, and medicines, and direct non-medical costs, such as transport, meals, and drinks. Indirect costs are those associated with loss of productivity for not being able to work because one is away seeking healthcare, taking care of a patient, or incapacitation due to disease. Provider costs were also disaggregated into two classes: capital costs, which are fixed one-time costs to buy buildings, equipment, etc., and recurrent costs, which are regular expenditure costs repeatedly incurred for the provision of goods and services such as salaries, utility bills etc. Sometimes provider costs can be categorized as direct medical costs, which are the costs incurred to deliver healthcare services such as personnel/staff, equipment, consumables, medicines etc, and direct non-medical costs, which may include program monitoring and evaluation, housekeeping, re-training of personnel etc.

Base year costs in USD ($) were recorded before adjustment to 2021 US Dollars using relevant US Consumer Price Indices (CPI)(89). If costs were reported in local currency, they were converted to USD using the prevailing exchange rate when cost data were collected before being adjusted to the year 2021. Adjusted costs in USD were obtained by taking 2021 midyear CPI divided by mid-year CPI for the base year multiplied by base year cost.

2.10 Ethical Clearance

This was a review study and hence did not require ethical clearance.

CHAPTER THREE

3.0 RESULTS

99 studies were identified, of which 34 were duplicates. The remaining 65 unique studies were subjected to screening by reading the titles and abstracts, and as a result, 33 studies were excluded because they were not relevant. Full-text screening and assessment for eligibility were conducted for the remaining 32 articles, of which 8 were included in the review **Figure 6**.

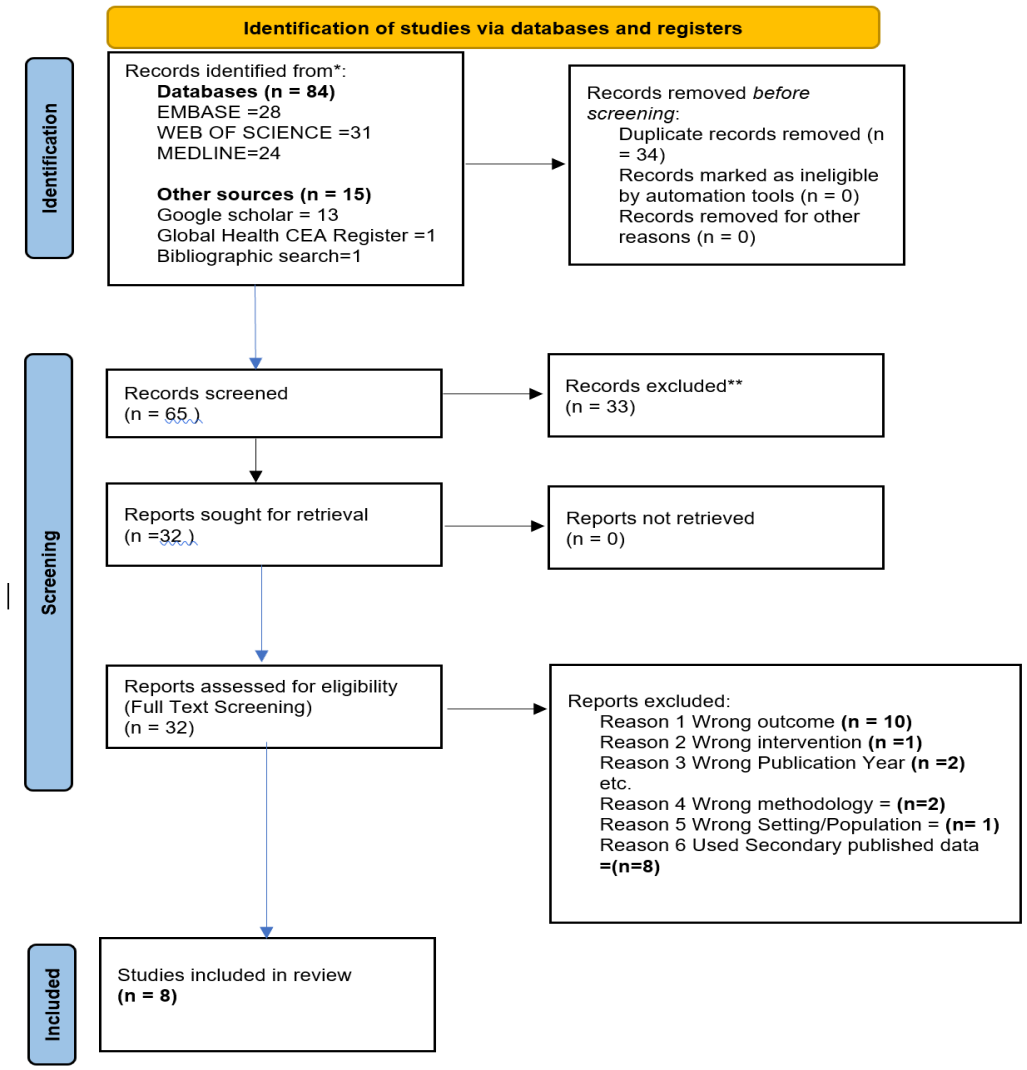

Figure 6: PRISMA Flow diagram showing articles included and excluded in the systematic review

3.1 Summary characteristics

Table 2 shows the characteristics of the included studies. Most of the studies used a cross-sectional design, and data were collected from households, healthcare facilities (providers), and societal perspectives. Most of the included studies used micro-costing or ingredient approaches which identify in detail all the resource items used. Out of the eight included studies, seven were relatively recent and were published in the year 2010 or after, except one, which was published in the year 2005.

Table 2: Study Characteristics

No.	Author & Year	Country	The approach used/Study type	Outcome of Interest
1.	Vodicka EL. et al (2019)(69)	Kenya	Micro-costing study	HIV clinic integrated versus nonintegrated Cost of treatment of precancerous lesion using cryotherapy and LEEP Perspective: Societal perspective
2.	Quentin W. et al. (2011)(70)	Ghana	Cost analysis using ingredient approach	Cost of cervical cancer screening and treatment using visual inspection with acetic acid (VIA) and cryotherapy. Perspective: Provider perspective
3.	WHO Report (2020)(90)	Tanzania	Used "Bottom-up" or Ingredient approach. Presented in terms of financial cost and economic cost[1]	National estimated costs for cervical cancer prevention and control Perspective: Public provider perspective
4.	Nelson S. et al (2016)(91)	Tanzania	Cross-sectional study. Costing using an ingredient approach	Cryotherapy Cost Perspective: Provider perspective

No.	Author & Year	Country	The approach used/Study type	Outcome of Interest
5.	Lince-Deroche N. et al (2018)(92)	South Africa (SA)	Micro costing study and cost-effectiveness analysis	Cost and ICER for treatment of cervical dysplasia using cryotherapy and LEEP
6.	Goldie SJ. et al. (2005)(47)	India, Kenya, Peru, South Africa, Thailand	Cost analysis using the quantity-and-price approach	Cost data for cryotherapy, LEEP and CKC Perspective: Societal perspective
7.	Campos NG. et al (2015)(93)	India, Nicaragua, Uganda	Cost analysis using ingredient approach	Cost of precancerous lesion treatment using cryotherapy and LEEP in India, Nicaragua and Uganda. Perspective: Societal perspective
8.	Campos NG, Maza M. et al (2015)(68)	El Salvador	Cost analysis using the micro-costing approach	Cost estimates for treatment of cervical precancerous lesion using Cryotherapy and LEEP. Perspective: Societal perspective.

3.2 Distribution of studies

Figure 7 shows the distribution of countries where the included cost and cost-effectiveness studies were conducted. Out of the Eight included studies, two studies reported costs of cervical precancerous lesion treatment from more than one country(47,93). In South America, studies were conducted in three countries, including El Salvador (1), Nicaragua (1) and Peru (1); Asia studies were conducted in three countries, including India (2) and Thailand (1); lastly in Africa studies were conducted in seven countries including Ghana (1), Tanzania (2), South Africa (2), Kenya (2) and Uganda (1).

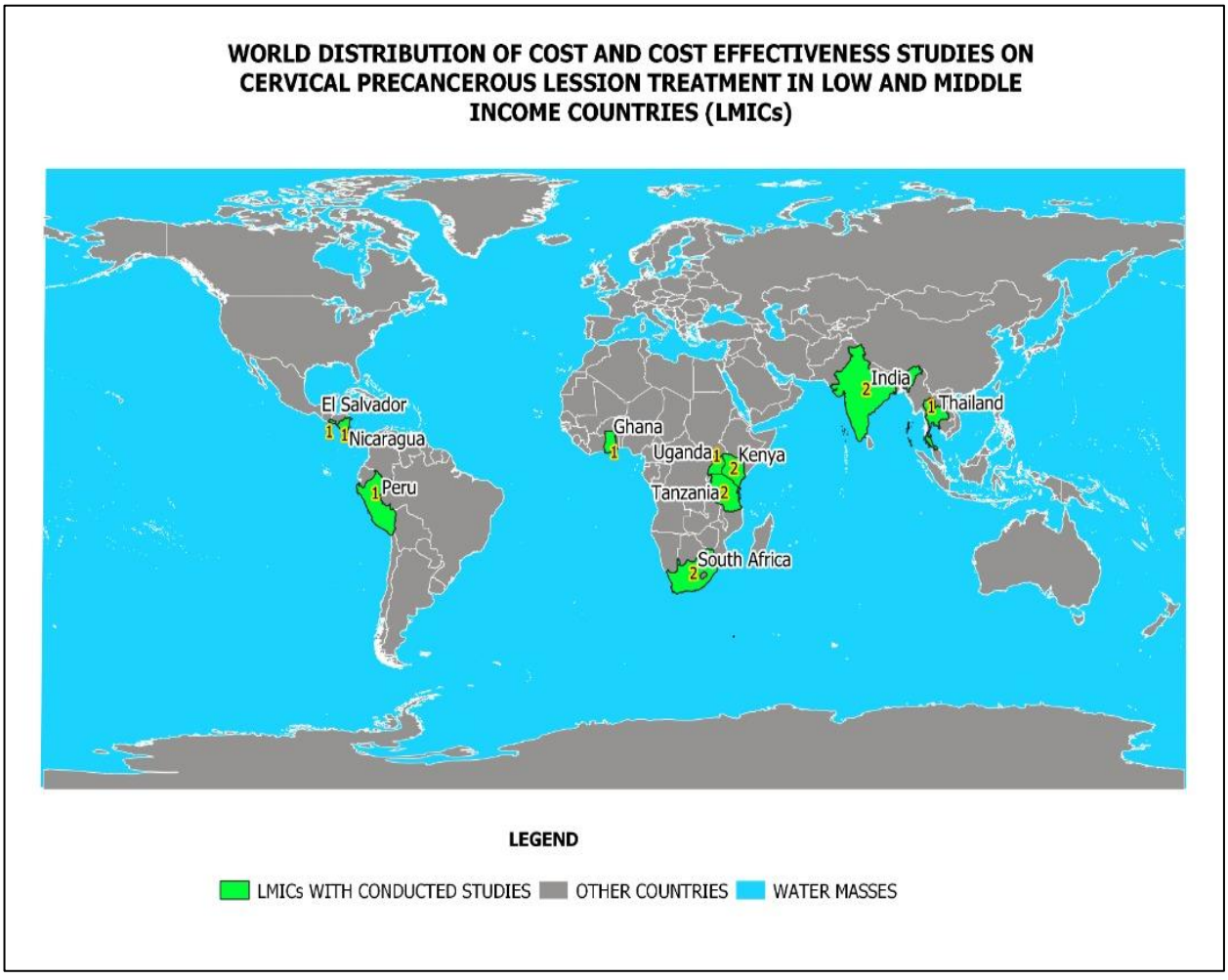

Figure 7:World Map showing where the Studies were conducted Key: The numbers in the map indicates number of times each country appeared in the eight included studies.

3.3 Risk of Bias Assessment

Table 2 shows the results of the risk of bias assessment. Out of eight studies, four were of good quality(68,69,92,93); three were of average quality(47,70,90), and one was of poor quality(91). Most studies provided a well-defined problem and description of interventions to be compared, identified, measured and valued all the relevant costs and effectiveness. However, most studies did not clearly include a presentation and analysis of all issues related to users of the results, especially for policymakers.

Table 3: Risk of Bias Assessment

Criteria		Was a well-defined question posed?	Was a comprehensive description of the competing alternatives offered?	Was the evidence of the effectiveness of the program offered?	Were all important and relevant costs and consequences identified?	Were all important and relevant costs and consequences measured accurately?	Were all important and relevant costs and consequences have been properly valued?	Were the costs and consequences adjusted for different times?	Was an incremental analysis of costs and consequences of competing alternatives done?	Was the effect of uncertainty (sensitivity analysis) investigated in estimating the costs and consequences?	Were the presentation and analysis of all issues related to users of the results included?	Overall Study Quality
No.	Study											
1.	Vodicka E. L et al(69)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	NA	Good
2.	Quentin W. et al.(70)	Yes	Yes	No	No	No	NA	Yes	Yes	Yes	NA	Average
3.	WHO Report(90)	Yes	NA	No	Yes	Yes	NA	Yes	No	No	NA	Average
4.	Nelson S. et al(91)	Yes	NA	Yes	No	NA	Yes	NA	No	No	NA	Poor
5.	Lince-Deroche N. et al (92)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NA	Good
6.	Goldie S.J et al(47)	NA	Yes	Yes	Yes	NA	NA	Yes	No	Yes	NA	Average
7.	Campos N.G et al (93)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NA	Good
8.	Campos N. G, Maza M. et al(68)	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	NA	Good

Scores:

1-3 (Poor); 4-7 (Average); 8-10 (Good)

3.4 Cost of Cervical Precancerous Lesion Treatment

Table 4 A, B and C show the cost of treatment of cervical precancerous lesions in LMICs. A total of 8 studies from 10 countries reported the cost of treatment for cervical precancerous lesions using cryotherapy/cryosurgery, loop electrosurgical excision procedure (LEEP) and CKC. The number of studies reporting treatment cost of cryotherapy (n=7), cryosurgery (n=1), LEEP (n=6) and CKC (n=1).

Error! Reference source not found.A further shows treatment costs (in 2021 USD) of cervical precancerous lesions from the provider perspective, which are the cost incurred by healthcare providers to provide cervical precancerous lesions to affected patients. Cryotherapy (n=7) cost ranges from $3.85 in Tanzania(90) to $151.47 in South Africa(47); LEEP (n= 5) costs ranges from $53.28 in El Salvador(68) to $596.73 in South Africa(47); and CKC (CKC) (n=1) costs ranges from $335.03 in India(47) to $766.86 in Thailand(47). These studies had different costing approaches and used different costing items. The most common costing items in the included studies which were included in all of these studies, are personnel/staff, consumables and equipment costs. However, some studies included costs for building, infrastructures and training costs while most studies did not include these costing items.

Table 4B shows the patient's perspective costs, which are incurred by patients when seeking/accessing cervical precancerous treatment. These costs include patient's time costs/loss of productivity (costs of time used for travelling, waiting and receiving care), cost of meals and transportation costs. Three studies reported treatment costs using cryotherapy in 5 countries where costs of transportation (n=5) ranged from $0.1 - $15.39; meals (n=1) $1.15; and patient's time cost (n=5) ranged from $0.82 - $4.79. One study reported treatment costs using cryosurgery in 5 countries where transportation cost (n=5) ranged from $1.10 - $31.74; loss of productivity cost (n=3) ranging from $0.47 - $7.56, and meals costs were not reported. Also, four studies reported treatment costs using LEEP in 8 countries where two countries (India and Kenya) appeared twice in different studies; transportation cost (n=10) ranging from $3.31 - $47.91, meals cost (n=1) $2.30; and loss of productivity cost (n=10) ranging $0.47 - $14.31. Lastly, one study reported treatment costs using CKC in 5 countries, with transportation cost (n=5) ranging from $17.46 – $49.80; loss of productivity cost (n=5) ranging from $0.47 - $7.56.

Table 4C shows the only one study(69) which reported the total societal cost of treatment of cervical precancerous lesions using cryotherapy and LEEP, where the total cost included direct medical costs for the procedure, personnel time, supplies, other direct medical costs incurred by patients, lab cost, overhead cost, patient transport, meals, child/elderly care and loss of productivity. The total treatment cost from a societal perspective (2021 USD) for cryotherapy is $52.89, and LEEP is $113.20.

Table 4: Cost (USD) of Cervical Precancerous lesions Treatment

Table 4A: Provider's Perspective

Study	Country	Base year	Perspective	Direct Cost Base Year	Direct Cost 2021(USD)
Cryotherapy					
Quentin W.[ii]	Ghana	2009	Provider	27.96	35.22
WHO Report[iii]	Tanzania	2018	Provider	3.57	3.85
Nelson S.[iv]	Tanzania	2014	Provider	28.97	33.03
Lince-Deroche N.[‡‡]	South Africa	2015	Provider	118	134.35
Goldie SJ.[**]	India	2000	Provider	16.55	26.08
	Kenya			25.18	39.68
	Peru			13.61	21.45
	South Africa			96.11	151.47
	Thailand			45.11	71.09
	India	2011	Provider	38.13	45.89

[ii] It is an incremental economic cost of cryotherapy per woman treated. Costing of resources included capital (building, equipment) and recurrent (personnel and supplies), counselling (pre & post treatment), cryotherapy treatment and follow up visits

[iii] Included service delivery cost (staff, supplies, infrastructure and capital cost) and program support activities costs (training, microplanning, social mobilization, supervision and monitoring and evaluation

[‡‡] Included costs of personnel, consumables, equipment and laboratory costs

[**] Included costs categorised as direct medical cost (staff, disposable supplies, equipment and specimen transport)

Study	Country	Base year	Perspective	Direct Cost Base Year	Direct Cost 2021(USD)
Campos NG.***	Nicaragua			33.04	39.77
	Uganda			13.49	16.24
Campos NG****	El Salvador	2012	Provider	22.56	26.71
LEEP (Loop Electrosurgical Excision Procedure)					
WHO Report†	Tanzania	2018	Public Provider Perspective	69.24	74.66
Lince-Deroche N.‡‡	South Africa	2015	Provider Perspective	162.56	185.08
Goldie SJ.**	India	2000	Provider	95.96	151.23
	Kenya			222.33	350.40
	Peru			173.43	273.33
	South Africa			378.63	596.73
	Thailand			324.39	511.24

*** Direct Medical Costs (included staff time, clinical supplies, drugs, clinical equipment)

**** Included cost of treatment of cervical precancerous lesions at clinic level and at hospital level. Also, the Direct medical cost included staff time, disposable supplies, laboratory and equipment use.

‡‡ Included costs of personnel, consumables, equipment and laboratory costs

Study	Country	Base year	Perspective	Direct Cost Base Year	Direct Cost 2021(USD)
Campos NG.***	India	2011	Provider	NA	NA
	Nicaragua			133.64	160.85
	Uganda			139.54	167.95
Campos NG.****	El Salvador	2012	Provider	45	53.28
Cold Knife Conization (CKC)					
Goldie SJ.**	India	2000	Provider	212.58	335.03
	Kenya			291.58	459.53
	Peru			394.17	621.22
	South Africa			458.48	722.57
	Thailand			486.58	766.86

*** Direct Medical Costs (included staff time, clinical supplies, drugs, clinical equipment)

**** Included cost of treatment of cervical precancerous lesions at clinic level and at hospital level. Also, the Direct medical cost included staff time, disposable supplies, laboratory and equipment use.

**Included costs categorised as direct medical cost (staff, disposable supplies, equipment and specimen transport)

Table 4B: Patient Perspective

Study	Country	Base Year	Transport at Base Year	Transport 2021	Meals at Base Year	Meals in 2021	Loss of Productivity at Base Year	Loss of Productivity in 2021
Cryotherapy								
Campos NG.[v]	India	2011	0.08	0.1	-	-	1.14	1.37
	Nicaragua		0.69	0.83	-	-	1.14	1.37
	Uganda		4.46	5.37	-	-	0.68	0.82
Vodicka E.[vi]	Kenya	2014	13.50	15.39	1.01	1.15	6.28	7.16
Campos NG.[vii]	El Salvador	2012	0.75	0.89	-	-	4.05	4.79
Cryosurgery								
Goldie SJ.	India	2000	0.7	1.10	-	-	0.3	0.47
	Kenya		10.18	16.04	-	-	0.76	1.20
	Peru		17.17	27.06	-	-	1.81	2.85
	South Africa		20.14	31.74	-	-	4.80	7.56
	Thailand		2.40	3.78	-	-	1.82	2.87
LEEP (Loop Electrosurgical Excision Procedure)								
Vodicka EL.	Kenya	2014	27	30.78	2.02	2.30	12.55	14.31

[v] Women time costs spent on travelling, waiting for treatment and receiving treatment

[vi] Indirect non-medical cost (transport and meals) and indirect cost (loss of productivity)

[vii] Patient time costs associated with travelling, waiting and receiving care and transportation costs

Study	Country	Base Year	Transport at Base Year	Transport 2021	Meals at Base Year	Meals in 2021	Loss of Productivity at Base Year	Loss of Productivity in 2021
Cryotherapy								
Goldie SJ.[viii]	India	2000	13.95	21.99	-	-	0.30	0.47
	Kenya		20.97	33.05	-	-	0.76	1.19
	Peru		28.86	45.48	-	-	1.81	2.85
	South Africa		30.40	47.91	-	-	4.80	7.56
	Thailand		10.63	16.75	-	-	1.82	2.19
Campos NG.	India	2011	15.29	18.40	-	-	1.14	1.37
	Nicaragua		2.75	3.31	-	-	1.14	1.37
	Uganda		10.87	13.08	-	-	0.68	0.81
Campos NG,	El Salvador	2012	3	3.55	-	-	8.82	10.44
Cold Knife Conization (CKC)								
Goldie SJ.	India	2000	14.03	22.11	-	-	0.30	0.47
	Kenya		21.16	33.35	-	-	0.76	1.19
	Peru		29.31	46.19	-	-	1.81	2.85
	South Africa		31.60	49.80	-	-	4.80	7.56
	Thailand		11.08	17.46	-	-	1.82	2.87

[viii] Women time cost (travelling, waiting and receving care) and transportation costs

Table 4C: Societal Perspective

Study	Country	Base Year	Perspective	Direct medical Cost at Base Year	Indirect Costs			Total Treatment Cost at Base Year	Total Treatment Cost in 2021
Cryotherapy									
Vodicka E.[†]	Kenya	2014	Societal Perspective	21.40	13.50	1.01	6.28	46.40	52.89
LEEP (Loop Electrosurgical Excision Procedure)									
Vodicka E.[†]	Kenya	2014	Societal Perspective	49.13	27	2.02	12.55	99.30	113.20

[†] Included cost of treatment of cervical precancerous lesions when integrated in HIV Clinic services versus when not integrated

[†] It is the only study which reported total cost of treatment of precancerous lesion from **societal perspective,** included; direct medical costs (staff, supplies, lab cost and out of pocket cost incurred by patients such as consultation/hospital charges); direct non-medical cost (transport, meals and overhead); and indirect cost (loss of productivity)

3.5 Cost-effectiveness of Cervical Precancerous Lesion Treatment

Table 5 shows the cost-effectiveness analysis of cryotherapy when compared to LEEP to treat HIV-positive women with CIN2+. The study reported that LEEP was more efficacious than cryotherapy. However, the difference was not significant. The performed economic evaluation indicated that LEEP was strongly dominated by cryotherapy, meaning cryotherapy was more effective and less costly. Cryotherapy remained to be more cost-effective than LEEP in all sensitivity and scenario analysis conducted.

Table 5: Cost-effectiveness analysis comparing cryotherapy versus LEEP for Treatment of CIN2+ among HIV-positive women (2015$), intention to treat analysis

Study	Country	Cost Reported Year	Perspective	Strategy	Total cost	Incremental cost	Effectiveness	Incremental Effectiveness	ICER
Lince-Deroche N.(92)	South Africa	2015	Provider	Cryotherapy	11,800.47	-	84	-	-
				LEEP	16,256.18	4,455.72	79	-5	dominated

CHAPTER FOUR

4.0 DISCUSSION

4.1 Summary of findings

This review identified eight studies conducted in ten LMICs on the cost and cost-effectiveness of precancerous lesion treatment. All eight studies reported the costs from the provider or societal perspective(47,68–70,90–93). Only one study compared the cost-effectiveness of cryotherapy versus LEEP for treating cervical precancerous lesions(92). Seven of the eight studies were rated to be of good quality(47,68–70,90,92,93) and one of low quality(91).

The review indicates that cryotherapy is the cheapest treatment intervention for cervical precancerous lesions amongst the three reported WHOs recommended treatment interventions. Its cost, from the provider's perspective, ranges from $3.85 in Tanzania(90) to $151.47 in South Africa(47). The cost of cryotherapy was $52.89 from a societal perspective in Kenya(69). LEEP was the second most cheap treatment, with its cost ranging from $53.28 in El Salvador(68) to $596.73 in South Africa from the provider perspective(47). The cost of LEEP was $113.20 in Kenya from a societal perspective(69). CKC (CKC) was the most expensive treatment intervention, with direct costs ranging from $335.03 in India to $766.86 in Thailand from the provider's perspective(47).

Only one study reported the cost-effectiveness of cryotherapy versus LEEP. The economic evaluation indicated that cryotherapy was more effective and less costly and remained more cost effective than LEEP in all sensitivity and scenario analysis (94). Scarcity of economic evaluation studies of cervical precancerous lesion treatment has also been documented by WHO as a gap during the development of its guidelines for recommendation of cervical precancerous treatment methods(8,43,48).

The study by Goldie et al was the oldest study we included in the analysis and was published in 2005(47). This study was conducted in five countries in LMICs including Kenya, India, South Africa, Peru, and Thailand. Most of the reported costs of treatment strategies for cervical precancerous lesions from this study were within range of our reported costs, hence making this

study prominent in the analysis to date. It is the only study that reported the cost of CKC. Also, all of the upper ranges of our reported costs came from this study. The higher range costs may be due to inflation because the costs in the study were collected in 2000 USD.

Another study conducted in South Africa, reported the average cost of cryotherapy and LEEP per randomized patient (initial treatment cost) and per case cured at 12 months of follow-up (94). The cost at 12 months included initial treatment and diagnosis costs at 12 and 6 months, as well as LEEP costs for patients who were re-treated after diagnosis at six months and were found still to have CIN2+ after initial treatment with cryotherapy or LEEP. The average initial cost for treatment using cryotherapy was $118, and at 12 months was $140.90. On the other hand, the average initial treatment cost for LEEP was $162.56, and at 12 months, it is $205.59. These results indicate there is not much difference in initial treatment costs for the treatment of cervical precancerous lesions using cryotherapy and LEEP as compared to their respective treatment costs after 12 months of follow-up, which shows that both treatment options were effective.

There are only few studies on the economics of treating cervical precancerous lesions in LMICs. The review also found that cryotherapy was the most commonly used treatment method for precancerous treatment in lower-level health facilities and LEEP was used in higher-level health facilities. No study on thermal ablation was found during our review period. Lack of studies may be attributed by the unavailability of quality data and the capacity to conduct economic evaluation studies(95–97).

4.2 Comparison with high-income countries

The costs reported in these studies from LMICs are comparable to those from high-income settings. A study conducted in China reported that LEEP was $77.31 cheaper compared to CKC, which was $152.22 (in 2021 USD)(62). Also, another study conducted in German reported the cost of cryotherapy, estimated at $31.64, while LEEP and CKCere were estimated at $2392, respectively(98). However, a study conducted in Israel contrasted with the results of our systematic review where a unit cost for treatment of cervical precancerous lesion using CKC was cheaper by $103.46 compared to LEEP, which was $204.43 while cryotherapy remained to

be the cheapest treatment intervention which was $31.16 (99). Say that differences in costs could be due to what organization of the healthcare system etc.

Our review, also observed that LEEP is conducted in higher-level hospitals and not performed in lower-level hospitals (68,93), which is in line with a study conducted in China(100) and German (98). In Germany, cervical precancerous lesions are treated by various techniques, including office-based laser coagulation, CKC and hospital-based LEEP. It was estimated that cryotherapy was $331.64 while CKC was $2392.51 and LEEP was $2392.51 (2021USD)(98).

4.3 Methodological issues

The observed variations in costs for the same procedure between countries, for example, cryotherapy and LEEP in Tanzania(90) and South Africa(47), were due to differences in the costing approaches used, cost items included, perspectives, and the inflation rate. The study conducted in Tanzania used WHO Cervical Cancer Prevention and Control Costing (C4P-ST tool) which has been developed to assist LMICs in planning and costing cervical cancer control strategies. It estimates additional resources required to add cervical cancer screening and treatment to an existing health program and provides estimates of the cost per screening or treatment service of cervical cancer. However, the study conducted in South Africa(92), used micro-costing approach to collect data on personnel, consumables, equipment, and laboratory costs. From the provider's perspective, included cost items varied from personnel, laboratory, supplies, and equipment as direct medical costs. However, some studies included training costs(70), overhead costs(69), consultation fees and service fees (69). All studies that used the households' perspective included transportation costs and patient time cost/loss of productivity cost (time used by patient for travelling, waiting and receiving care), but there was one study which also included the cost of meals(69).

There were four studies which reported direct medical costs from a provider's perspective including the same costing items such as personnel, supplies and equipment (47,68,91,93). The reported direct medical costs for cryotherapy ranged from $16.24 - $151.47, the upper range cost was from a study (South Africa) which is from a study published in 2005(47). However, when we included studies from 2010 to July 2022, costs for cryotherapy ranged between $16.24 to $45.89. LEEP costs ranged from $53.28 to $596.75 the upper range cost (South Africa) was

also from a similar study published in 2005(47). But when we include studies from 2010 to July 2022, the LEEP costs range from $53.28 to $167.95. This show that the wide cost range may be because of outdated cost data or inflation rates. However, the difference may also be due to the high treatment costs of cervical precancerous lesions in South Africa. Another study conducted in South Africa which was published in 2018 with 2015 costs data(92) reported average cost per patient for diagnosis and treatment of cervical precancerous lesions using cryotherapy was $134.35 and LEEP $185.08. These treatment costs are still high, especially for cryotherapy treatment, compared to costs from other countries reported in this review.

4.4 Integration of interventions for cervical cancer prevention

One study conducted in Kenya has reported the cost of treatment of cervical precancerous lesions when integrated with HIV services and when not integrated with HIV services(69). It was reported that, when fully integrated with an HIV clinic, the treatment cost of cervical precancerous lesions using cryotherapy is $21.67, while the non-integrated cost for treatment of cervical precancerous lesions was $46.40. When fully integrated with an HIV clinic, the cost of treatment of cervical precancerous lesions using LEEP is $49.80, while when not integrated, the cost is $99.30. These results show the importance of integrating healthcare services into the existing system to increase the capacity of the healthcare system and provide continuity of care which will lead to timely access of care, equity in healthcare delivery, delivery of quality services and efficient use of resources(101,102).

A study reported that the cumulative incidence of cervical cancer among unvaccinated women was 94 cases per 100,000 persons compared to 47 cases per 100,000 persons in vaccinated women by the age of 30 years. For girls who initiated HPV vaccination before 17 years of age, the cumulative incidence becomes 4 cases per 100,000 persons by the age of 28 years(103). This shows that, as much as HPV vaccination is regarded as the most cost-effective and primary preventive measure for invasive cervical cancer. However, it will not be 100% effective in preventing invasive cervical cancer when used as the only preventive measure. With this regard, secondary preventive measures such as screening and treatment of cervical precancerous lesions is crucial to ensure effective and efficient prevention of invasive cervical cancer, especially in

LMICs where less than 30% of these countries have included HPV vaccination in their national vaccination programs and coverage is 8% compared to global coverage of 13%(33).

As per the WHO-recommended screen and treat program, screening and treatment of cervical precancerous lesions in positively detected women is done in a single visit. Cervical precancerous lesion screening and therapy go hand in hand. Despite the fact that our study focused solely on the treatment costs and cost-effectiveness of cervical precancerous lesions, the majority of treatment cost data were derived from cost-effectiveness studies for cervical screening or/and treatment of cervical precancer utilizing the treatment options(47,68,70,91,93). Another review may be conducted by combining the cost and cost-effectiveness of screening and treatment of cervical precancerous lesions in LMICs.

While the screen and treat program for cervical cancer is an important prevention intervention, countries must exercise caution when adopting and implementing the program due to concerns about overdiagnosis and overtreatment. Studies have reported overdiagnosis and overtreatment of cervical precancerous lesions(104,105), with some screening strategies producing more overdiagnosis compared to others(104). Overdiagnosis and overtreatment of cervical precancerous lesions, if neglected, may result in increased costs and underestimation of the cost-effectiveness of interventions/programs(106). As a result, cost and cost-effectiveness studies should account for overdiagnosis and overtreatment of cervical precancerous lesions, during cost-effectiveness analysis, by utilizing cancer mortality as the end outcome or lifetime as the time horizon(106).

The incidence and mortality rates due to cervical cancer are higher in countries with lower Human Development Index(13) and among women with poor socioeconomic status(23). Therefore, in order to achieve a global strategy for cervical cancer elimination and meet the set targets of 90-70-90 by 2030(18), inequity and poverty, which causes disproportion of cervical cancer burden, especially in LMICs should be addressed. Similar global efforts used to improve maternal health should be implemented urgently to address these inequities. Furthermore, these efforts will contribute to the achievement of SDGs such as poverty reduction, healthy lives and well-being, gender equality and women's empowerment, and equality within and between countries.

4.5 Strengths and Limitations

To our knowledge, this is the first systematic review of the cost and cost-effectiveness of treating cervical precancerous lesions in LMICs. Also, risk of bias assessment showed that studies included mostly had good quality, as among eight included studies, four (50%) had good quality during risk of bias assessment, three (40%) had average quality and only one (10%) had poor quality.

Our review has several limitations, first is the fact that our search was limited to English, which means we may have missed some studies published in other languages. Second, the included studies also used different costing approaches to calculate costs, such as micro-costing, bottom-up or ingredient approach, and also included different cost items. This may have contributed to the differences in costs observed; as a consequence, we were unable to aggregate the costs into meaningful means or medians. Third, our review only focused on cost and cost effectiveness of treatment of cervical precancerous lesions. However, as recommended by WHO in screen and treat program, screening and treatment of cervical precancerous lesions are done simultaneously. With this, during our review, we observed that most studies included both screening and treatment of cervical precancerous lesions and cervical cancer. Although the search was conducted systematically, a few studies that focused on cost and cost effectiveness of cervical cancer screening and included a small part of precancer treatment might have been missed during the search. Therefore, the inclusion of the cost and cost-effectiveness of screening and treatment of cervical precancerous lesions to obtain comprehensive results of the review should be considered in the future.

Conclusion

According to this review, only a few cost and cost-effectiveness studies on the treatment strategies for cervical precancerous lesions exists in LMICs. The few existing studies show that cryotherapy was the least costly treatment intervention for the treatment of cervical precancerous lesions compared to LEEP and CKC. Although, WHO recommended thermal ablation as the most affordable treatment intervention in LMICs when compared to cryotherapy, our review could not find any economic evaluation study comparing these strategies. The review also observed the importance of integrating healthcare services (such as the treatment of cervical precancerous lesions) into the existing healthcare delivery systems, which increases the efficiency and effectiveness of service delivery, especially in this era of emergence and the increased burden of non-communicable diseases. High patient out-of-pocket costs call for policies advocating for free and universal health coverage for cervical cancer control and care, which should be prioritized on both national and international agendas. Otherwise, these costs will hinder access to cervical cancer interventions, undermining efforts to ensure equity and reduce poverty in the region. Furthermore, more cost and cost-effectiveness studies, particularly from a societal standpoint, should be conducted to inform evidence-based decision-making.

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Appendices

i) PRISMA Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving	

		rationale.	
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2 for each meta-analysis.	

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	
Additional	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-	

analysis		regression [see Item 16]).	
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	

ii) Drummond's Checklist 2015; Criteria for Assessment of Economic Evaluation Studies

1) Was a well-defined question posed?
2) Was a comprehensive description of the competing alternatives offered?
3) Was the evidence of the effectiveness of the program offered?
4) Were all important and relevant costs and consequences identified?
5) Were all important and relevant costs and consequences measured accurately?
6) Were all important and relevant costs and consequences have been properly valued?
7) Were the costs and consequences adjusted for different times?
8) Was an incremental analysis of costs and consequences of competing alternatives done?
9) Was the effect of uncertainty (sensitivity analysis) investigated in estimating the costs and consequences?
10) Were the presentation and analysis of all issues related to users of the results included?