Title

Cost-effectiveness of Screen-Triage-Treat approach with Primary HPV Testing for Cervical Cancer Screening in Low- and Middle-Income Countries: Protocol for a Systematic Review

Registration: The protocol will be registered in PROSPERO and University of Heidelberg repository HeiDOK

Authors and Affiliations:

Kavita Singh[1], Ziyue Zhang[1], Ines Böhret[1,] Hermann Bussmann[1], Andreas Ullirch[2], Malabika Sarker[3], Maurizio Grilli[4], Raymond Hutubessy[5], Quentin Wilm[6], Steffen Fleßa[7], Manuela de Allegri[1]

1. University of Heidelberg, Germany
2. Charité Berlin, Germany
3. Brown University, USA
4. University of Mannheim, Germany
5. World Health Organization, Geneva, Switzerland
6. Technical University of Berlin, Germany
7. University of Greifswald, Germany

Corresponding author

Dr. Kavita Singh, Ph.D.
Research Scientist, Health Economics and Health Financing Unit,
Heidelberg Institute of Global Health,
Im Neuenheimer Feld 130.3, 69120, Heidelberg, Germany
Email: kavita.singh@uni-heildeberg.de

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Introduction

Cervical cancer is a leading cause of mortality among women in low- and middle-income countries (LMICs). Early detection through screening is key to cervical cancer prevention. Visual inspection of the cervix with acetic acid (VIA) is a commonly used screening method in LMICs because of its relative simplicity and the possibility of getting immediate test results and offering treatment in the same visit.[1] However, due to the shortage of trained health workers, relatively poor awareness of screening among women, and challenges of technical quality with VIA, World Health Organization (WHO) has recommended in its newly released *Guideline of Screening and Treatment of Cervical Pre-cancer Lesions for Cervical Cancer Prevention* to "use HPV DNA detection as the primary screening rather than VIA or cytology for both general population and those at high risk of cervical cancer, e.g., HIV positive women". Alongside the recommendation of the new primary screening with HPV testing, WHO also introduced the "screen, triage, and treat approach, where the decision to treat is based on a positive primary screening test followed by a positive second test (a triage test)".[2]

Rationale: why is a systematic review needed?

Scarcity of resources in LMICs has meant that policymakers have to make active decisions about funding of interventions/strategies prioritized for inclusion in essential care packages for disease prevention/control to maximize benefit from the limited resources. Promoting effective prevention/care strategies without considering cost of intervention and the value of the health gain leads to inefficient use of public funds allocated for healthcare. More specifically, a systematic review of "screen-triage-treat" approach with primary HPV DNA testing is required for the following reasons:

1. Transitioning from cytology and/or VIA to HPV DNA testing presents challenges for healthcare providers, as it necessitates the establishment of new infrastructure, such as laboratories, and requires specialized training. Sufficient evidence of the incremental costs and cost-effectiveness of different screen-triage- treat algorithms is lacking, particularly more so in resource-constrained LMIC settings. Through a preliminary literature review on the topic "screen-triage-treat algorithms with HPV DNA primary test followed by triage testing" in PubMed, Google Scholar, Prospero, and Cochrane in January 2023, we found no systematic review published or planned to compare the incremental cost or cost-effectiveness of screening programs adopting the screen, triage, and treat algorithms in real-world context of LMICs.
2. More specifically regarding the two sample collection strategies for the HPV DNA primary screening, community-based HPV testing using self-sampling kits is considered one of the most promising screening methods to increase the uptake among hard-to-reach women in LMICs. Yet, there is a gap in literature of an economic evaluation to compare the community-based self-sampling versus facility-based provider-initiated sampling in LMIC.
3. Different screen, triage and treat algorithms may be suitable to different needs of the general population and high-risk population of HIV-positive women.
4. Furthermore, a comprehensive review is lacking about the methodological considerations applied in the economic evaluation of the newly recommended "screen, triage and treat" approach for cervical cancer screening in LMICs.

To fill these gaps, a systematic review, and a potential meta-analysis (if sufficient data are available) will be performed. The results from this review will enable policymakers, clinicians, and patient advocacy groups in the resource-constraint LMIC setting to make better "evidence-informed decisions".

Aim

To systematically review the economic evidence available on different cervical cancer Screen-, Triage-Treat algorithms with HPV DNA primary test of two sampling collection methods (self-sampling versus provider-sampling) followed by different triage tests (e.g. HPV DNA genotyping, colposcopy, VIA, or cytology) for the general population (eligible women for screening) as well as high risk HIV-positive women in low and middle-income countries (LMICs).

Specific objectives

1. To summarize and compare the incremental resource use, implementation cost, and incremental cost-effectiveness of adopting different algorithms using HPV DNA primary tests followed by triage tests (e.g., HPV DNA genotyping, colposcopy, VIA, or cytology) in LMICs.
2. To summarize and compare the resource use, implementation cost and cost-effectiveness of two sample collection methods (community-based self-sampling and facility-based provider-sampling) of the HPV-based primary screening as part of the screen-triage-treat approach for cervical cancer screening in LMICs.
3. To summarize and compare the resource use, implementation cost, and cost-effectiveness of different “Screen-triage-treat" methods in general population versus high-risk HIV-positive women.
4. To describe the methodological considerations applied in the economic evaluation studies (outcome, measures, analytical viewpoint, time horizon, discount rate, decision models) and assess the quality of economic evidence using standard CHEERS and Drummond checklists.[3,4]

METHODS

Search strategies and information sources

A systematic review will be performed following Preferred Reporting Items for Systematic Review and Meta-analysis Protocols (PRISMA-P) using literature from multiple databases including PubMed, Embase, Web of Science, CEA registry, NHS Economic Evaluation Database, Health Economic Evaluation Database (HEED), CINAHL, EconLit, ClinicalTrials.gov, WHO International Clinical Trials Registry Platform, and Cochrane Library.[5,6,7] These searches will be supplemented by a review of the bibliography sections of the selected literature to identify possible studies of interest. Grey literature and additional documents will also be identified from those produced by government agencies, international agencies, such as WHO, academic institutions, non-profit non-governmental organizations (NGOs), and internationally recognized news agencies. Relevant publications of the DCP3 (Disease Control Priority 3) project and WHO-CHOICE program will be completely hand-searched for relevant articles.[8] As the use of technical terms for indexing international literature in databases is often inconsistent or errant, we will define a search strategy with high sensitivity.

To ensure the comprehensiveness of the literature search in the PubMed database, combinations of medical subject-heading (MesH), and title and abstract screening ([tiab] will be used for each term, and all logical synonyms and iterations of the search combination will be included. Suitable terms of the aforementioned main concepts will be used in other databases based on the specific language, function, and characteristics of each database (See search strategy). The search will include all years up to 2023. Further the reference lists of identified relevant studies and reviews will be hand-searched. (Detailed search strategy customized for each database is included in the appendix).

Eligibility criteria

The PICOS (population, intervention, comparator, outcome, study design) framework for the review will be as follows:

PICOS	Inclusion criteria	Exclusion criteria
Population	Women and transgender men with a cervix who are eligible for cervical cancer screening in LMICs according to the respective national cervical screening guidelines. No age limit is applied.	populations from high-income countries, hysterectomized women and women with a previous history of cervical cancer
Intervention	HPV DNA tests as the primary screening followed by any triage tests after a positive primary test; Self-sampling or provider-sampling from the vagina or cervix are included.	Primary screening tests using VIA and/or cytology, HPV DNA tests followed directly by treatment without triage testing
Comparator	Any screen, triage, and treat strategy, screen and treat strategy, or no intervention	None
Outcomes	Cost-effectiveness measures, such as Incremental Cost-Effectiveness Ratio (ICER); Incremental Cost-utility Ratio (ICUR); cost difference; incremental costs, Years of Life Saved (YLS); Quality-Adjusted Life Years (QALY) and Disability-Adjusted Life Years (DALY); Cost per screen positive case & Cost per screen negative case	Clinical effectiveness only
Study design	Full (i.e., cost–benefit, cost-effectiveness and cost–utility analyses) or partial economic evaluations (i.e., cost-minimization analysis), trial based (any design) or decision model based. Studies will be included regardless of their economic perspective, publication year, language, and status (i.e., full article, protocols/registration record). In meta-analysis, only full articles reporting results will be included.	Systematic reviews, Mere cost analyses (i.e., studies that simply calculated the costs of the intervention but did not compare it to the costs of the control treatment), Commentaries/letters and -non-human trials
*All of the costs reported in the studies will be included.		

Study selection process

We will import search results into software such as Covidence. Our study selection will involve performing an exercise to calibrate reviewers to ensure reliability of screening. Two reviewers will apply our

eligibility criteria and independently screen a sample of 25 citations using online systematic review software (i.e., Covidence). We will calculate an inter-rater agreement for applying the eligibility criteria (using percent agreement) and will repeat this exercise in subsequent pilot screenings until we reach 90% agreement. We will utilize the systematic review software to screen the titles and abstracts of the remainder of potentially relevant articles after removing duplicate articles (level 1 screening). Two independent reviewers will then review full-text articles to assess eligibility (level 2 screening). Disagreements will be resolved through other reviewers on the research team to achieve consensus for both levels of screening.

Data collection

We will develop a standardized data abstraction form, which will be pilot tested on an initial sample of 2 included studies to ensure agreement between data extractors. The data from the articles included will be extracted and mapped independently by two reviewers. More specifically, we will collect information on characteristics of included studies and their results. To describe the characteristics of included studies, we will extract: year of study; details of interventions (screening strategies) and comparators; study design and source(s) of resource use, unit costs and (if applicable) effectiveness data; decision-making jurisdiction, geographical and organizational setting; analytic viewpoint; and time horizon for both costs and effects. Where information is missing, we will contact study authors to request additional details.

For outcome measures, estimates of specific items of resource use associated with intervention (screening strategy) and comparators along with their unit costs will be extracted in natural units (e.g., cost per screen detected positive case, cost per screen negative case, etc.). We will also collect information on the price year and currency used to calculate incremental cost estimates. Both a point estimate and a measure of uncertainty (e.g., standard error or confidence interval) will also be extracted for measures of incremental resource use, costs, and cost-effectiveness, if reported. Additionally, details of any sensitivity analyses undertaken will be collected.

Assessment of study quality

We will assess whether the published studies have described economic analyses methods, assumptions, decision models, and possible biases in a way that is transparent, so that the strength of economic studies can be determined. Since, the reliability of an economic evaluation is predicated on its use of reliable effectiveness data, part of the critical appraisal will involve considering sources of potential bias that applies to the randomized controlled trial (RCT).

In this review, the critical appraisal will therefore consist of the following three elements:

1. Assessment of the risk of bias in results of the effectiveness studies (RCT), using **Cochrane guidelines**.[9]
2. Assessment of the methodological quality of the economic evaluations, by using a modified **Drummond or CHEERS checklist** and '**Evers checklist**'.[3,4,10]
3. Assessment of the methodological quality of decision modelling studies will be undertaken by using standard **ISPOR guidelines** for decision modelling studies or '**Phillips checklist**' 2004.[11,12]

In general, factors that will be assessed for methodological quality are those related to applicability of findings, validity of individual studies, and certain design characteristics that affect interpretation of results. Further, four sources of bias will be checked in primary effectiveness studies: **selection bias, performance bias, and detection bias**. Two reviewers will independently assess methodological quality of selected studies. It is plausible that use of different data sources for measures of resource use, cost and/or cost-effectiveness will impact on results; therefore, sensitivity analysis will be performed to assess how the outcomes measures

are influenced by adding some of the excluded economic studies that didn't meet the minimum quality requirements of a good quality economic evaluation.

Analysing, interpreting, and reporting results

Presenting results in tables and narrative summary

We will use appropriate analytical methods (descriptive statistics and narrative synthesis) for summarising the results of this review. If applicable, a meta-analysis of resource use or cost data, or cost-effectiveness measures, may be considered. In addition to reporting the characteristics of included studies, a summary table of various checklists completed to inform assessments of the methodological quality of economic evaluations will be presented. Also, we will report a commentary on the main characteristics and results of included studies (measures of incremental resource use, cost, and cost-effectiveness). Costs will be presented in real currency (as of the year of study or adjusted to current year) as this will be relevant for the readers in the countries under study. Additionally, to facilitate comparison of cost estimates collected from different studies, an international exchange rate based on purchasing power parities (PPPs) will be used to convert cost estimates to a target currency i.e., international dollars, and gross domestic product (GDP) deflators will be used to convert cost estimates to a fixed price year.

Addressing reporting and publication biases

Publication bias will be detected by a funnel plot, if there are more than 5 studies assessing a particular "screen-triage-treat" approach. If asymmetry is seen, this will be discussed to consider reasons other than publication bias, for example selection bias, reporting bias, data irregularities, true heterogeneity, and artefact. Subgroup analysis will be performed to determine whether benefit varies across screening strategies, target population, or countries.

Heterogeneity and Sensitivity Analyses

We will test heterogeneity of intervention (screening strategy) effects among trials using the standard Chi-squared statistic (p-value) or the I^2 statistic. We will consider a p-value of >0.10 as statistically significant heterogeneity. Interpretation of I^2 for heterogeneity is as follows: 0% to 40%: may not be important; 30% to 60%: represents moderate heterogeneity; 50% to 90%: represents substantial heterogeneity; 75% to 100%: represents considerable heterogeneity We will explore the possible cause(s) of heterogeneity by doing various sensitivity analyses.[13]

Summary of findings

Results of this review will be reported in line with **PRISMA** (**P**referred **R**eporting **I**tems for **S**ystematic reviews and **M**eta-Analyses) 2015 checklist. The overall quality of evidence on outcomes will be presented using the **GRADE** (**G**rades of **R**ecommendation, **A**ssessment, **D**evelopment and **E**valuation) approach, which involves consideration of within-study risk of bias (methodological quality), directness of evidence, heterogeneity, precision of effect estimates and risk of publication bias.[14] We will rate overall quality of evidence at four levels: high, moderate, low, and very low.

Ethics and dissemination

As such, there are no ethical issues involved in this study as it's only a review of published economic evaluations and no patient data will be collected.

Findings from this review will be submitted for publication in peer-reviewed journals. They will be shared with decision makers, health professionals as brief policy notes. The study investigators will also disseminate

findings through professional conferences targeting primary and secondary care physicians, health economists, and public health policymakers more widely. While there has been an increasing interest in LMICs to scale-up the most cost-effective cervical cancer screening method, major research gaps will be identified through this review.

Significance

The review will provide an overview of the economic evidence on the screen, triage, treatment algorithms using HPV DNA primary screening followed by different triage testing, potentially contributing to prioritization of a specific sampling collection method for primary screening and/or particular triage test in future WHO Guidelines. The review will also provide an overview for the quality of the study design and methodology of the published literature in the area of cervical cancer screening methods.

References

1. Domgue JF, Valea FA. Is It Relevant to Keep Advocating Visual Inspection of the Cervix With Acetic Acid for Primary Cervical Cancer Screening in Limited-Resource Settings? DOI: 10.1200/JGO.17.00048. Journal of Global Oncology. 2017. No. 4. 1-5.
2. WHO. Guideline for Screening and Treatment of Cervical Pre-cancer Lesions for Cervical Cancer Prevention. Second Edition. 2021
3. Husereau D, Drummond M, Augustovski F, de Bekker-Grob E, Briggs AH, Carswell C, Caulley L, Chaiyakunapruk N, Greenberg D, Loder E, Mauskopf J, Mullins CD, Petrou S, Pwu RF, Staniszewska S, CHEERS 2022 ISPOR Good Research Practices Task Force. Consolidated Health Economic Evaluation Reporting Standards 2022 (CHEERS 2022) Statement: Updated Reporting Guidance for Health Economic Evaluations.
4. Drummond MF, Jefferson TO. Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. BMJ 1996;313:275-83.
5. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4(1):1. Available from: http://www.prisma-statement.org/Extensions/Protocols [Last accessed September 2023]
6. Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA, the PRISMA-P Group. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015: elaboration and explanation. BMJ 2015.349:g7647. Available from: http://www.prisma-statement.org/Extensions/Protocols [Last accessed September 2023]
7. Moher D, Altman DG, Liberati A, Tetzlaff J: PRISMA statement. Epidemiology 2011, 22(1):128. author reply 128.
8. World Health Organisation: Choosing Interventions that are Cost Effective (WHO-CHOICE). [Internet] Available from: https://www.who.int/news-room/feature-stories/detail/new-cost-effectiveness-updates-from-who-choice [Last accessed September 2023]
9. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.4 (updated August 2023). Cochrane, 2023. Available from www.training.cochrane.org/handbook. [Last accessed September 2023]

10. Evers S, Goossens M, de Vet H, van Tulder M, Ament A. Criteria list for assessment of methodological quality of economic evaluations: Consensus on Health Economic Criteria. Int J Technol Assess Health Care 2005;21:240-5.
11. Philips Z, Ginnelly L, Sculpher M, Claxton K, Golder S, Riemsma R, et al. Review of guidelines for good practice in decision-analytic modelling in health technology assessment. Health Technol Assess 2004;8(36). 10.3310/hta8360
12. Weinstein MC, O'Brien B, Hornberger J, et al. Principles of good practice of decision analytic modeling in health care evaluation: Report of the ISPOR Task Force on Good Research Practices-Modeling Studies. Value Health; 2003; 6(1):9-17.
13. Briggs A, Sculpher M: Sensitivity analysis in economic evaluation: a review of published studies. Health Econ 1995, 4:355-371.
14. Guyatt GH, Oxman AD, Schunemann HJ, et al. GRADE guidelines: a new series of articles in the Journal of Clinical Epidemiology. J Clin Epidemiol 2011; **64** (4): 380 – 82