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The cost and cost-effectiveness of point-of-care testing and treatment for sexually transmitted and genital infections in pregnancy in low- and middle-income countries: A systematic review protocol

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TITLE:

The cost and cost-effectiveness of point-of-care testing and treatment for sexually transmitted and genital infections in pregnancy in low- and middle-income countries: A systematic review protocol

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ABSTRACT

Introduction

Sexually transmitted and genital infections (STIs) greatly burden low- and middle-income countries (LMIC). When untreated in pregnancy, they increase the risk of adverse pregnancy and birth outcomes; yet early detection and treatment reduces this risk. The introduction of point-of-care (POC) tests have the potential to improve STI detection and treatment in LMICs. The widespread implementation of screening in antenatal clinics has been hindered by barriers, including economic costs. To date there have been no systematic reviews which explore the cost and cost-effectiveness of POC testing of STIs in pregnancy in LMICs. The objective of this protocol is to outline the methods that will help synthesize and appraise the evidence on the cost and cost-effectiveness of POC testing and treatment of STIs in pregnancy in LMICs. Drivers of cost-effectiveness in different contexts, and the quality of economic evaluations will also be explored.

Methods & Analysis

We will conduct two independent literature searches in three databases; MEDLINE, Embase and Web of Science. We will search google scholar and hand search reference lists for additional literature. Two reviewers will screen titles, abstracts and full texts; when necessary a third reviewer will resolve discrepancies. Only cost and cost-effectiveness studies of POC testing and treatment of STIs, including syphilis, chlamydia, trichomonas, gonorrhoea and bacterial vaginosis, in pregnancy in LMIC will be included. All selected studies will be quality-assessed using the CHEERS checklist and risk of bias. Between study heterogeneity will be explored and depending on variation between studies, a meta-analysis or narrative synthesis will be conducted. The study is on-going and we anticipate completion by 31 May, 2019.

Ethics and dissemination

The systematic review will use published literature, not patient data, therefore ethical approval is not required. The results will be published in a peer-reviewed open source journal and presented an international conference.

Keywords

Point-of-Care, sexually transmitted infections, genital infections, cost-effectiveness, costs, pregnancy, antenatal care

Prospero Registration number: CRD42018109072.

ARTICLE SUMMARY

Strengths and limitations of this study

- This systematic review is, to the best of our knowledge, the first to synthesize costing and cost-effectiveness analyses of point-of-care testing of sexually transmitted and genital infections in pregnancy in low- and middle- income countries.
- This review includes studies on both common curable sexually transmitted and genital infections in low- and middle- income countries.
- We will conduct a meta-analysis, however if there is between-study heterogeneity of outcome measures we will conduct a narrative synthesis.
- The results of this review will fill the gap in knowledge pertaining to the relative cost-effectiveness of testing for sexually transmitted and genital infections in pregnancy in low- and middle- income countries, which is pertinent to reducing their prevalence.
- The review is limited to how studies empirically depict costs and cost-effectiveness.

INTRODUCTION

Globally, the growing burden of sexually transmitted and genital infections (STIs)[1] alarming, and the majority of infections occur in low and middle income countries (LMICs) [1]. In 2012, the World Health Organization (WHO) estimated that there were 357.4 million new cases of STIs, half of which were attributed to trichomonas and chlamydia infections [2]. When left untreated, STIs can have adverse effects on sexual and reproductive health, neonatal health and child health [3]. Among pregnant women, untreated STIs are associated with increased risk of ectopic pregnancy, miscarriage and pre-term delivery [4]. Adverse birth outcomes associated with STIs in pregnancy, include still birth, low birth weight (LBW), neonatal death, and neonatal eye and respiratory infections following intrapartum transmission [5].

Several studies have indicated that the early detection and treatment of STIs in pregnancy could reduce the risk of adverse pregnancy and birth outcomes [6]. There is strong evidence to suggest that the

[1] This protocol refers to sexually transmitted infections and genital infections collectively as STIs, which is consistent with an associated study, the WANTIM trial. Please refer to ISRCTN registry www.isrctn.com/ISRCTN37134032

detection and treatment of HIV and syphilis early in pregnancy reduces adverse pregnancy and birth outcomes [7]. However, few studies, and most are based in high income countries, investigate the detection and treatment of gonorrhoea, chlamydia, trichomonas and bacterial vaginosis, early in pregnancy to prevent adverse outcomes, which means that more evidence is required to support this [6]. This is largely because up until recently detection of these common STIs required laboratory-based testing, which is relatively expensive and thus fairly uncommon in LMIC [3]. As a result, STI screening programs in many LMICs rely on syndromic management of the curable genital STIs; a WHO-endorsed strategy based on clinical symptoms and signs without laboratory confirmation. [8]. This strategy has been shown to have limited sensitivity and specificity for the detection of genital STIs, particularly among pregnant women where asymptomatic infection appears to be more common [7-10]. Other factors, which act as barriers to screening and subsequent treatment, such poor infrastructure and high operational costs, emphasise the difficulties associated with laboratory-based screening programs in resource-poor settings [9, 11].

Advances in STI detection have played a key role in improving screening coverage and subsequent treatment in LMICs. The widespread adoption of rapid point-of-care (POC) testing for HIV and syphilis, is perhaps a signal of this [12-14]. These tests allow women to be tested, diagnosed and treated in a single visit to a health facility [12-14]. There is evidence that suggests the introduction of POC tests for HIV and syphilis at antenatal (ANC) clinics have reduced the rate of perinatal and infant morbidity and mortality[3].

The evidence on the effectiveness of POC testing and treatment of STIS in pregnancy is mixed, and cannot single-handedly drive the implementation of STI screening programs at ANC clinics. POC testing also presents a particularly challenging scenario. On the one hand, the unit cost-per-test is higher owing to the loss of economies of scale offered by automation (typically centralised laboratories), but on the other hand, it offers the potential of substantial savings through enabling rapid delivery of results and treatment, avoiding the need for recall and loss of clients requiring treatment, and the associated reduction of facility costs [12-14]. Thus, health system challenges, for example budgetary constraints, program costs and accessibility, are key considerations for optimal program implementation [15, 16]. Economic evaluations, which consider program health outcomes, such as birth outcomes, and their associated costs, provide the relative cost-effectiveness of implementation can help address these considerations and inform resource allocation. This is particularly important for LMICs, where there may be competing priorities for relatively scarce resources [16]. To date there have been no systematic reviews which explore the cost and cost-effectiveness of POC testing of STIs in pregnancy in LMICs.

The objective of this protocol is to outline the aims and detail the methods that will help synthesize and appraise the evidence on the cost and cost-effectiveness of POC testing and treatment of STIs in pregnancy in LMICs. Drivers of cost-effectiveness in different contexts, and the quality of the economic evaluations will also be explored.

METHODS

Study type, participants and intervention

The systematic review will only consider peer-reviewed studies of cost and cost-effectiveness analyses (CEAs) of the POC testing and treatment of STIs. Specifically, the review will include studies that focus on POC testing and treatment of syphilis, chlamydia, trichomonas gonorrhoea, and bacterial vaginosis in LMICs, where the burden of STIs is the greatest [7-10]. Only interventions targeting pregnant women will be considered.

The review will not be restricted to cost analyses and CEAs conducted within the framework of randomised controlled trials. It will take a comprehensive approach and include pilot studies and feasibility analyses, as well as modelling studies.

Inclusion and Exclusion Criteria

Pre-determined inclusion and exclusion criteria will be applied after the initial literature search. We will only include full peer-reviewed articles and exclude book chapters, commentaries, conference publications/abstracts, editorials, letters, meeting outcomes, recommendations, protocols and reviews. We will also exclude all studies that are not in English. Studies of populations other than pregnant women and on infections other than syphilis, gonorrhoea, chlamydia or trichomonas will also be excluded. The focus of the studies included must be a POC test for STIs. Specifically diagnostic tools that require only one visit, where the test is conducted and result is received at the same visit, the test is simple, accurate and non-invasive, it is user-friendly, compact, durable and sturdy [17]. We will only include studies conducted in LMICs. The LMIC classification is directly sourced from the World Bank list comprised in 2018 [18].

Search strategy

The literature search for this systematic review will be independently conducted by two reviewers (OPMS and NB) and comprise of three stages. First, three pre-selected electronic databases, MEDLINE,

Embase and Web of Science, will be searched using keywords and MeSH terms, spanning relevant subject matter. These terms are presented in Table 1. Boolean operators will be included - "OR" within each group of keywords and MeSH terms to indicate the areas of interest, and "AND" to combine each group and find articles related to the main objective of the systematic review.

Table 1: Proposed keywords and MeSH terms for the literature search

Themes	Proposed keywords and MeSH terms
Economic evaluations	Cost-effectiveness OR cost benefit analysis (mesh term) OR cost analysis
Sexually transmitted and genital infections	Sexually transmitted infections OR Sexually transmitted Diseases OR Gonorrhoea OR Chlamydia OR Trichomonas OR Syphilis OR Bacterial Vaginosis
Point-of-Care testing	Point-of-care testing OR point-of-care OR rapid OR bedside OR near-to-patient OR test OR lateral flow OR screening
Pregnancy	Pregnancy OR pregnant women OR ANC OR antenatal

The second stage aims to identify additional literature using Google Scholar, which may capture articles missed by the database searches and finally, a hand-search of references included in the final set of articles will be conducted.

Data Analysis

All citations found through the literature search will be exported into End note X8 and all duplicates will be removed, after which the multi-stage screening process will begin. Literature included in this review will be reported according to the PRISMA guidelines and data will be analysed using Microsoft Excel 2013 and presented in tables.

The screening process, illustrated in Figure 1, shows the proposed PRISMA flow diagram for this review. OPMS and NB will independently screen all titles and abstracts to collate a final set of articles for review. Where discrepancies arise a third researcher, VW, will make the final decision to include or exclude literature.

Figure 1

Insert Figure 1 here

The CHEERS checklist [19] will be used to appraise the quality of each article included in the review. The quality appraisal of each article will be independently undertaken by two researchers (OPMS and NB) similar to the initial screening process. In case of discrepancies a third researcher, VW, will help arbitrate. Careful consideration will also be given to publication bias across studies and selective reporting within studies.

After the initial appraisal, data will be extracted into a data extraction form in Microsoft Excel 2013. We do not anticipate a high degree of homogeneity in the reporting of cost effectiveness outcomes. We propose to first conduct a narrative synthesis, focussing on a discussion of the costs and cost effectiveness of the POC testing programs, and their budgetary impact, reflecting on the scale of implementation of the programs. We will also explore and discuss program and context-related factors that might affect relative cost-effectiveness in different settings. Where outcomes are comparable, the review will compare the cost effectiveness outcomes, Cost-Effectiveness Ratios and Incremental Cost Effectiveness Ratios and the extent to which interventions are deemed cost-effective compared to relevant investment options [20]. This will allow us to explore whether there is a significant variation in the intervention programmes, economic evaluation methods, costs and outcomes. We will conduct tests of heterogeneity to confirm this, in order to guide the possibility of conducting a meta-analysis.

Study dates

This study is ongoing; the anticipated date of completion is 31 May 2019.

Ethics and dissemination

The systematic review will use published literature, not patient data, therefore ethical approval is not required. The results of this review will be published in a peer-reviewed, open access journal and presented an international conference.

DISCUSSION

STIs in pregnancy have multiple adverse effects and left untreated can be harmful to both mothers and babies. Most cases occur in LMICs, therefore highlighting the need for affordable and cost-effective interventions in low-resource settings. This, combined with shrinking health care budgets in LMICs, raised concerns about the quality and efficiency of health care delivery systems in these countries. Collating current evidence on cost-effectiveness is an important first step in assessing the value of this testing strategy and planning its efficient and equitable implementation. To our knowledge, the

proposed review is the first to consolidate evidence on the costs and cost-effectiveness of antenatal POC testing and treatment in LMICs, and to discuss the methodological differences between studies, including their limitations.

Contributions

OPMS drafted the manuscript, while initial revisions were provided by NB, AJV and VW. RA, CL and WP provided feedback and revisions to the manuscript. All authors read, provided feedback and approved the final manuscript.

Funding sources/ sponsors:

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Patient consent

Not required.

Ethics approval

This systematic review does not use individual personal data and therefore does not require ethical committee approval.

Provenance and peer review

Not commissioned; externally peer reviewed.

Competing Interests

None declared

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Figure 1: Prisma flow diagram of the search selection for this systematic review

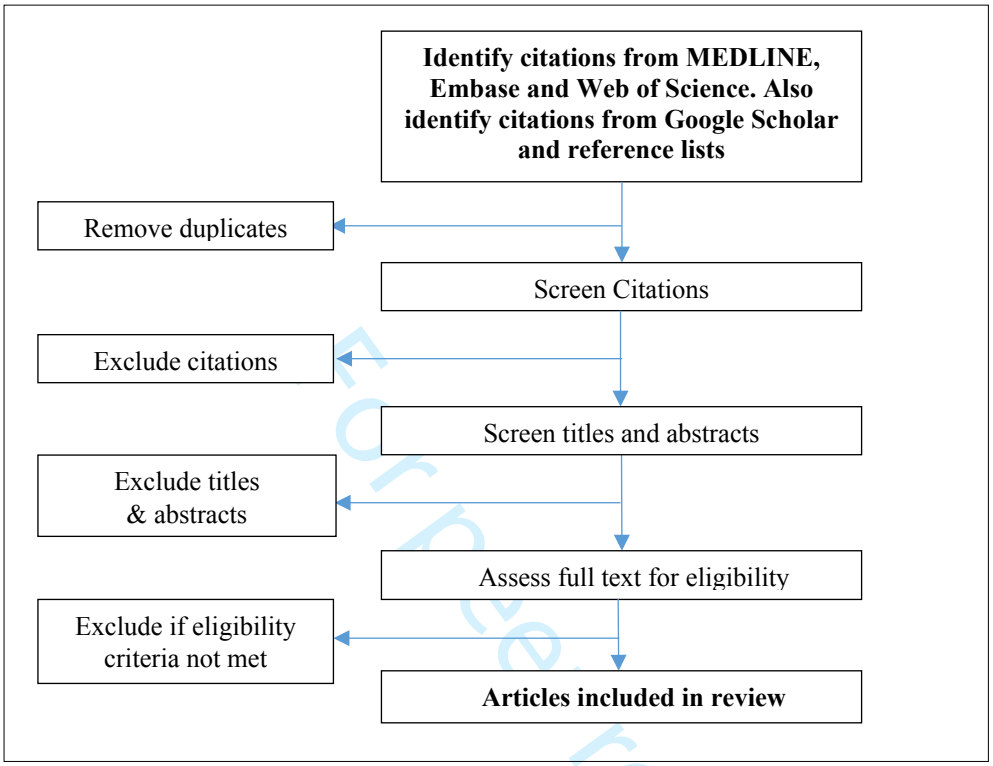
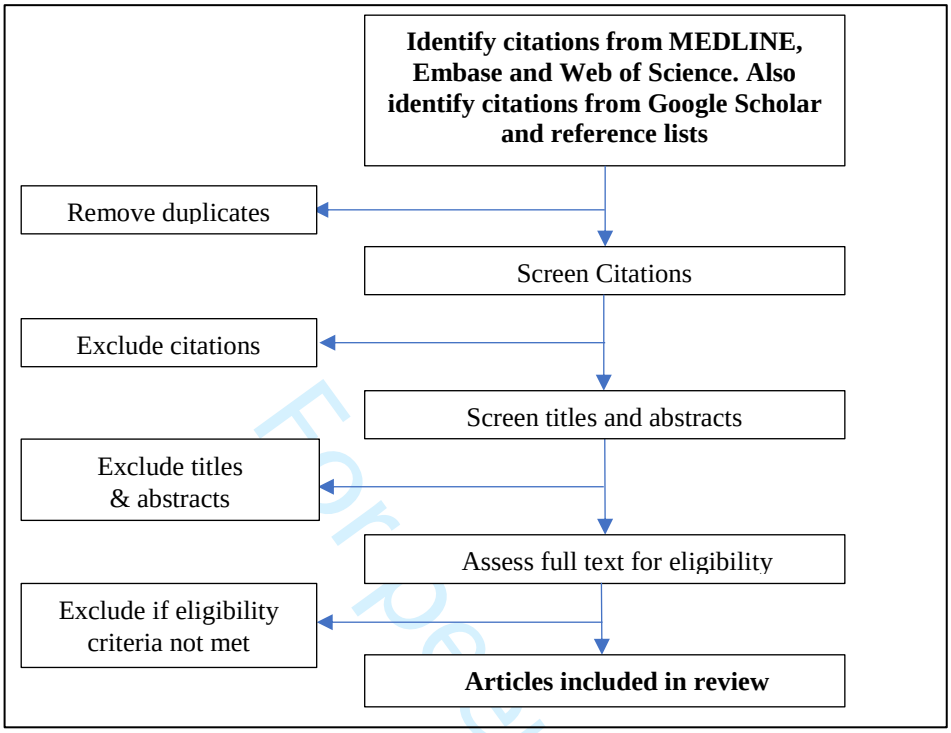


Figure 1: Prisma flow diagram of the search selection for this systematic review



PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol

Section and topic	Item No	Checklist item	Reported on page number
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	3
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	8
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	N/A
Support:			
Sources	5a	Indicate sources of financial or other support for the review	8
Sponsor	5b	Provide name for the review funder and/or sponsor	8
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	N/A
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	3-5
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	5
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	5-7
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	5-7

Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	5-7
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	5-7
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	5-7
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	5-7
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	5-7
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	7
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	7
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	7
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	7
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	7
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	7
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	7
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	7-8

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

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Primary Subject Heading:	Health economics
Secondary Subject Heading:	Health services research, Obstetrics and gynaecology, Public health
Keywords:	point-of-care, sexually transmitted infections, genital infections, cost-effectiveness, costs, pregnancy

TITLE:

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ABSTRACT

Introduction

The economic and health burden of sexually transmitted and genital infections (henceforth, STIs) in low- and middle- income countries (LMICs) is substantial. Left untreated, STIs during pregnancy can result in several adverse pregnancy and birth outcomes. Timely diagnosis and treatment at point-of-care (POC) can potentially improve these outcomes. Despite the availability and promotion of new POC diagnostics for STIs as a key component of antenatal care in LMICs, their widespread use has been limited, owing to the high economic costs faced by individuals and health systems. To date there have been no systematic reviews which explore the cost and cost-effectiveness of POC testing of STIs in pregnancy in LMICs. The objective of this protocol is to outline the methods that will synthesize and appraise the existing literature on the cost and cost-effectiveness of POC testing and treatment of STIs in pregnancy in LMICs to inform resource allocation.

Methods & Analysis

We will conduct literature searches in MEDLINE, Embase and Web of Science. To find additional literature we will search Google Scholar and hand search reference lists of included papers. Two reviewers will independently search the databases, screen titles, abstracts and full texts; when necessary a third reviewer will resolve disputes. Only cost and cost-effectiveness studies of POC testing and treatment of STIs, including syphilis, chlamydia, trichomonas, gonorrhoea and bacterial vaginosis, in pregnancy in LMICs will be included. Quality of reporting will be assessed using the CHEERS checklist. We will also assess risk of publication bias. Inter-study heterogeneity will be explored and depending on variation between studies, a meta-analysis or narrative synthesis will be conducted.

Ethics and dissemination

Ethical approval is not required as the review will use published literature. The results will be published in a peer-reviewed open source journal and presented at an international conference.

Keywords

Point-of-Care testing, sexually transmitted infections, genital infections, cost-effectiveness, costs, pregnancy, antenatal care

Prospero Registration number: CRD42018109072.

ARTICLE SUMMARY

Strengths and limitations of this study

- This systematic review is, to the best of our knowledge, the first to synthesize evidence on the costs and cost-effectiveness of point-of-care testing and treatment of common and curable sexually transmitted and genital infections in pregnancy in low- and middle- income countries.
- This review will assess the completeness of reporting practices and identify areas for improvement in the field.
- If the inter-study heterogeneity of results may prevent a meta-analysis, we will conduct a narrative synthesis of findings.
- The review is limited to how studies empirically depict costs and cost-effectiveness.
- The review is limited to English language studies published in peer-reviewed journals.

INTRODUCTION

Globally, the growing burden of common curable sexually transmitted and genital infections such as chlamydia, gonorrhoea, syphilis, trichomonas and bacterial vaginosis (henceforth, STIs)[1] is alarming. The majority of infections occur in low and middle income countries (LMICs) [1]. The World Health Organization (WHO) estimated that in 2012 there were 357.4 million new cases of chlamydia, gonorrhoea, syphilis and trichomonas [2]. Left untreated, these STIs can have adverse effects on sexual and reproductive health, neonatal and child health [3]. During pregnancy, these untreated STIs are associated with an increased risk of adverse pregnancy and birth outcomes, including miscarriage, pre-term delivery, still birth, low birth weight (LBW), neonatal death, and neonatal eye and respiratory infections following intrapartum transmission [4, 5].

There is strong evidence to suggest that the detection and treatment of HIV and syphilis early in pregnancy reduces adverse pregnancy and birth outcomes [6, 7]. Several studies have indicated that the early detection and treatment of STIs in pregnancy could reduce the risk of adverse pregnancy and birth outcomes [5, 7-9]. However, despite high prevalence rates in LMICs few studies in these settings investigate the detection and treatment of common, curable STIs early in pregnancy to prevent adverse outcomes [5, 8]. This is largely because up until recently the accurate detection of these STIs in

[1] This protocol refers to sexually transmitted infections and genital infections collectively as STIs, which is consistent with an associated study, the WANTIM trial. Please refer to ISRCTN registry www.isrctn.com/ISRCTN37134032

pregnancy required laboratory-based testing, which is a relatively expensive form of diagnosis in LMICs [3]. Other factors include poor infrastructure, limited human resources and high operational costs [8, 10, 11].As a result, clinicians in many LMICs rely on the WHO-endorsed strategy of syndromic management to diagnose and treat symptomatic STIs, which is based on presentation of clinical symptoms and signs without laboratory confirmation [10]. This strategy has limited specificity for accurate diagnosis, particularly among pregnant women where asymptomatic infections are common [9, 10, 12].

Advances in STI detection have played a key role in improving diagnosis and subsequent treatment in LMICs. The widespread adoption of point-of-care (POC) testing for HIV and syphilis, is perhaps a signal of this [13-15]. These tests allow patients to be tested, diagnosed and treated in a single visit to a health facility [13-15]. There is evidence that suggests the introduction of POC tests for HIV and syphilis at antenatal clinics has reduced the rate of perinatal and infant morbidity and mortality in many LMICs [5-7]. This evidence, however, cannot single-handedly drive the implementation of STI screening programs. POC testing also presents a particularly challenging scenario. On the one hand, the unit cost-per-test is higher owing to the loss of economies of scale offered by automation, typically by centralised laboratories. On the other hand, it offers the potential of substantial savings through enabling the rapid delivery of results and treatment, avoiding the need for recall and loss of patients requiring treatment, and the associated reduction of facility costs [13-15]. Economic evaluations provide evidence on the relative cost-effectiveness of implementation and can help address these considerations and inform resource allocation. While the number of studies analysing the cost and cost-effectiveness of POC testing and treatment of STIs in pregnancy in LMICs is increasing, there have been no systematic reviews synthesizing this body of literature.

The objective of this protocol is to identify, synthesise and appraise the existing evidence on the costs and cost effectiveness of POC testing and treatment of common, curable STIs (namely, chlamydia, gonorrhoea, syphilis, trichomonas and bacterial vaginosis) in pregnancy in LMICs. The specific objectives of this review are:

1. Identify and synthesise the evidence on the cost and cost-effectiveness of POC testing and treatment for STIs in pregnancy in LMICs;

2. Appraise the quality of reporting economic evaluations using the consolidated health economics evaluation reporting standards (CHEERS) checklist; and

3. Identify the key -drivers of costs and cost-effectiveness of POC testing and treatment for STIs in pregnancy in LMICs.

METHODS

Study type, participants and intervention

The systematic review will only consider peer-reviewed cost and cost-effectiveness analyses of POC testing and treatment of STIs. We define a POC test as a diagnostic tool that requires only one visit, where the test is conducted and the result is received during the same visit. The test is simple, accurate (both specific and sensitive) and non-invasive, it is user-friendly, compact, durable and sturdy [16]. Specifically, the review will include studies that focus on POC testing and treatment of common, curable STIs, namely syphilis, chlamydia, trichomonas gonorrhoea, and bacterial vaginosis among pregnant women [8-10, 12]. Only studies based in LMICs, where the burden of STIs is the greatest will be included. Lastly, the review will take a comprehensive approach by including cost and cost-effectiveness analyses conducted within a framework of randomised control trials, pilot and feasibility studies and modelling studies.

Exclusion Criteria

Pre-determined exclusion criteria will be applied after the initial literature search. We will only include full peer-reviewed articles and exclude book chapters, commentaries, conference publications/abstracts, editorials, letters, meeting outcomes, recommendations, protocols and reviews. We have opted to exclude grey literature in this review. Grey literature tends to focus on study conclusions without a rigorous methodological description that could facilitate evaluating study quality. Although another limitation, during the title and abstract screening, we will exclude studies that are not in English. This reflects the language proficiency of the study team. Studies of populations other than pregnant women and on infections other than syphilis, gonorrhoea, chlamydia, trichomonas or bacterial vaginosis will also be excluded. The focus of the studies included must be a POC test for STIs and comparators include, but are not limited to, no screening, syndromic management and existing screening programs. We will exclude all studies not conducted in LMICs. The LMIC classification is directly sourced from the World Bank list comprised in 2018 [17].

Search strategy

The literature search for this systematic review will be independently conducted by two reviewers (OPMS and NB). First, OPMS and NB will independently search three pre-selected electronic databases, MEDLINE, Embase and Web of Science, using keywords and MeSH terms, spanning relevant subject matter. The search terms determined by OPMS, NB, LC, AV and VW, in consultation

with experienced medical librarians are presented in Table 1. The search terms selected reflect relative search sensitivity and specificity, whereby a comprehensive search is balanced with identifying a manageable number of citations. Boolean operators will be included - "OR" within each group of keywords and MeSH terms to indicate the areas of interest, and "AND" to combine each group and find articles related to the main objective of the systematic review.

Table 1: Proposed keywords and MeSH terms for the literature search

Themes	Proposed keywords and MeSH terms
Economic evaluations	Cost-effectiveness OR cost benefit analysis (mesh term) OR cost analysis
Sexually transmitted and genital infections	Sexually transmitted infections OR Sexually transmitted Diseases OR Gonorrhoea OR Chlamydia OR Trichomonas OR Syphilis OR Bacterial Vaginosis
Point-of-Care testing	Point-of-care testing (mesh term) OR point-of-care OR rapid OR bedside OR near-to-patient OR test OR lateral flow OR screening
Pregnancy	Pregnancy OR pregnant women OR ANC OR antenatal

OPMS and NB will then independently search for literature using Google Scholar. The first 100 results will be screened to identify additional literature, which may capture articles missed by the database searches. Finally, OPMS and NB will each conduct a hand-search of references included in the final set of articles.

Data Extraction and Analysis

All citations found through the literature search will be exported into Endnote X8 (Thomson Reuters) and duplicates will be removed. OPMS and NB will independently screen all titles, keywords and abstracts to collate a set of articles for full-text review based on the inclusion and exclusion criteria. OPMS and NB will then independently review the full-texts of selected studies and apply the inclusion and exclusion criteria to compile the final set of studies to be included in the review. In the case of disputes VW will make the final decision to include or exclude studies. Literature included in this review will be reported according to the PRISMA guidelines. The screening process, illustrated in Figure 1, shows the proposed PRISMA flow diagram for this review.

Figure 1

Insert Figure 1 here

Data will be extracted into Microsoft Excel 2013 and will include details on the authors, title, type of intervention, comparator, study setting, study design, perspective adopted, time horizon, and key results of each study. The CHEERS checklist [18] will be used to appraise the quality of reporting practices for each article reporting on a cost-effectiveness analysis to gauge their transparency and clarity in reporting . For cost analyses (i.e. partial economic evaluations), we will use a subset of relevant criteria in the CHEERS checklist. The appraisal will be independently undertaken by OPMS and NB and in case of disputes, VW will arbitrate. Careful consideration will also be given to publication bias across studies and selective reporting within studies.

Data extracted for the analysis will include total cost of the intervention, unit cost, cost-effectiveness and incremental cost -effectiveness ratios (such as cost per outcome and cost per DALY averted), cost savings to the health system, budget impact estimates. We will also extract data on context-related factors that could affect the costs and cost effectiveness of interventions. This will allow us to explore a wide range of intervention programmes, economic evaluation methods, costs and outcomes and to identify and discuss the variation in drivers of costs and cost-effectiveness. A high degree of heterogeneity in the primary studies is anticipated – including differences in cost-effectiveness outcomes, study designs, and health interventions and comparators- which will limit our ability to conduct a meta-analysis. If this is confirmed through tests of heterogeneity then a narrative synthesis will be undertaken using Stata IC version 14.0 (College Station, TX, USA).

Study dates

This study is ongoing; the anticipated date of completion is 31 July 2019.

Patient and public involvement

Patients and/or the public were not directly involved in the development of this systematic review protocol.

Ethics and dissemination

The systematic review will use published literature, not patient data, therefore ethical approval is not required. The results of this review will be published in a peer-reviewed, open access journal and presented an international conference.

DISCUSSION

Common, curable STIs in pregnancy have multiple adverse effects and left untreated can be harmful to both mothers and babies. LMICs have the highest burden of STIs, highlighting the need for affordable and cost-effective screening interventions in these settings. Collating current evidence on costs and cost-effectiveness of POC testing and treatment of STIs in pregnancy is an important first step in understanding the value of these tests in highly resource-constrained health systems. It also provides an opportunity to gauge the quality of reporting conventions used in the different studies. To our knowledge, this represents the first systematic review on this topic.

Contributions

OPMS drafted the manuscript, while initial revisions were provided by NB, AJV and VW. RA, CL and WP provided feedback and revisions to the manuscript. All authors read, provided feedback on and approved the final manuscript.

Funding sources/ sponsors:

WANTAIM is a partnership of academic and governmental institutions in Papua New Guinea, Australia and Europe. The trial is funded by a Joint Global Health Trials award from the UK Department for International Development, the UK Medical Research Council and the Wellcome Trust (MR/N006089/1); a Project Grant from the Australian National Health and Medical Research Council (GNT1084429); and a Research for Development award from the Swiss National Science Foundation (IZ07Z0_160909/1). All employee institutions listed by the Investigators contributed through provision of facilities and/or salary contributions. In addition, OPMS and RA are is supported by The University of New South Wales Scientia Higher Degree Candidate Scholarship Scheme.

Patient consent

Not required.

Ethics approval

This systematic review does not use individual personal data and therefore does not require ethical committee approval.

Provenance and peer review

Not commissioned; externally peer reviewed.

Competing Interests

None declared

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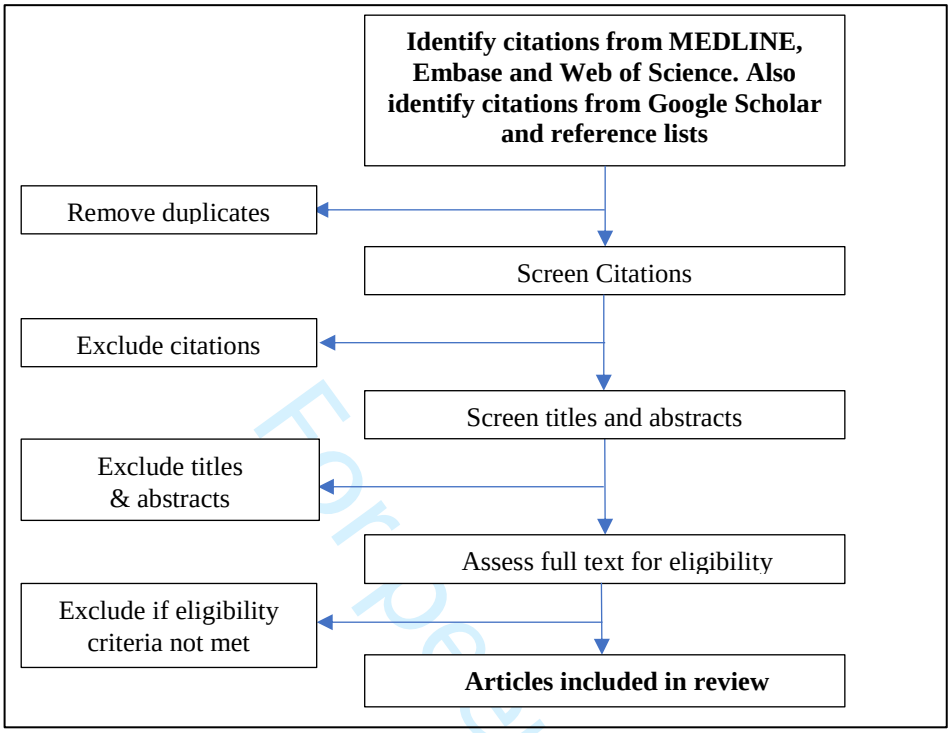
Figure 1: Prisma flow diagram of the search selection for this systematic review



PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol

Section and topic	Item No	Checklist item	Reported on page number
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	3
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	8
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	N/A
Support:			
Sources	5a	Indicate sources of financial or other support for the review	8
Sponsor	5b	Provide name for the review funder and/or sponsor	8
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	N/A
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	3-5
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	5
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	5-7
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	5-7

Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	5-7
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	5-7
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	5-7
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	5-7
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	5-7
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	7
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	7
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	7
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	7
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	7
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	7
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	7
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	7-8

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

BMJ Open

The cost and cost-effectiveness of point-of-care testing and treatment for sexually transmitted and genital infections in pregnancy in low- and middle-income countries: A systematic review protocol

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Primary Subject Heading:	Health economics
Secondary Subject Heading:	Health services research, Obstetrics and gynaecology, Public health
Keywords:	point-of-care, sexually transmitted infections, genital infections, cost-effectiveness, costs, pregnancy

TITLE:

The cost and cost-effectiveness of point-of-care testing and treatment for sexually transmitted and genital infections in pregnancy in low- and middle-income countries: A systematic review protocol

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ABSTRACT

Introduction

The economic and health burden of sexually transmitted and genital infections (henceforth, STIs) in low- and middle- income countries (LMICs) is substantial. Left untreated, STIs during pregnancy may result in several adverse pregnancy and birth outcomes. Timely diagnosis and treatment at point-of-care (POC) can potentially improve these outcomes. Despite the availability and promotion of POC diagnostics for STIs as a key component of antenatal care in LMICs, their widespread use has been limited, owing to the high economic costs faced by individuals and health systems. To date there have been no systematic reviews which explore the cost or cost-effectiveness of POC testing and treatment of STIs in pregnancy in LMICs. The objective of this protocol is to outline the methods that will compare, synthesize and appraise the existing literature in this domain.

Methods & Analysis

We will conduct literature searches in MEDLINE, Embase and Web of Science. To find additional literature we will search Google Scholar and hand search reference lists of included papers. Two reviewers will independently search databases, screen titles, abstracts and full texts; when necessary a third reviewer will resolve disputes. Only cost and cost-effectiveness studies of POC testing and treatment of STIs, including syphilis, chlamydia, trichomonas, gonorrhoea and bacterial vaginosis, in pregnancy in LMICs will be included. Published checklists will be used to assess quality of reporting practices and methodological approaches. We will also assess risk of publication bias. Inter-study heterogeneity will be assessed and depending on variation between studies, a meta-analysis or narrative synthesis will be conducted.

Ethics and dissemination

Ethical approval is not required as the review will use published literature. The results will be published in a peer-reviewed open source journal and presented at an international conference.

Keywords

Point-of-Care testing, sexually transmitted infections, genital infections, cost-effectiveness, costs, pregnancy, antenatal care

Prospero Registration number: CRD42018109072.

ARTICLE SUMMARY

Strengths and limitations of this study

- This systematic review is, to the best of our knowledge, the first to synthesize evidence on the costs and cost-effectiveness of point-of-care testing and treatment of common and curable sexually transmitted and genital infections in pregnancy in low- and middle- income countries.
- This review will assess the completeness of reporting practices and identify areas for improvement in the field.
- If the inter-study heterogeneity of results may prevent a meta-analysis, we will conduct a narrative synthesis of findings.
- The review is limited to how studies empirically depict costs and cost-effectiveness.
- The review is limited to studies published in peer-reviewed journals.

INTRODUCTION

Globally, the growing burden of common curable sexually transmitted and genital infections such as chlamydia, gonorrhoea, syphilis, trichomonas and bacterial vaginosis (henceforth, STIs) is alarming. The majority of infections occur in low and middle income countries (LMICs) [1]. The World Health Organization (WHO) estimated that in 2012 there were 357.4 million new cases of chlamydia, gonorrhoea, syphilis and trichomonas [2]. Left untreated, these STIs can have adverse effects on sexual and reproductive health, neonatal and child health [3-5]. During pregnancy, untreated STIs are associated with an increased risk of adverse pregnancy and birth outcomes, including miscarriage, pre-term delivery, still birth, low birth weight (LBW), neonatal death, and neonatal eye and respiratory infections following intrapartum transmission [6-11].

There is strong evidence to suggest that the detection and treatment of HIV and syphilis early in pregnancy reduces adverse pregnancy and birth outcomes [12-15]. Several studies have indicated that the early detection and treatment of STIs, such as Chlamydia, Trichomonas and Gonorrhoea, in pregnancy could reduce the risk of adverse pregnancy and birth outcomes [16, 17]. However, despite high prevalence rates in LMICs few studies in these settings investigate the detection and treatment of common, curable STIs early in pregnancy to prevent adverse outcomes. This is largely because up until recently the accurate detection of these STIs in pregnancy required laboratory-based testing, which is a relatively expensive form of diagnosis in LMICs [18]. Other factors include poor infrastructure, limited

human resources and high operational costs [19, 20].As a result, clinicians in many LMICs rely on the WHO-endorsed strategy of syndromic management to diagnose and treat symptomatic STIs, which is based on presentation of clinical symptoms and signs without laboratory confirmation [18, 19, 21]. This strategy has limited specificity for accurate diagnosis, particularly among pregnant women where asymptomatic infections are common [19, 22].

Advances in STIs detection have played a key role in improving diagnosis and subsequent treatment in LMICs. The widespread adoption of point-of-care (POC) testing for HIV and syphilis, is perhaps a signal of this [23]. These tests allow patients to be tested, diagnosed and treated in a single visit to a health facility [24]. There is evidence that suggests the introduction of POC tests for HIV and syphilis at antenatal clinics has reduced the rate of perinatal and infant morbidity and mortality in many LMICs [25, 26]. This evidence, however, cannot single-handedly drive the implementation of STIs screening programs. POC testing also presents a particularly challenging scenario. On the one hand, the unit cost-per-test is higher owing to the loss of economies of scale offered by automation, typically by centralised laboratories. On the other hand, it offers the potential of substantial savings through enabling the rapid delivery of results and treatment, avoiding the need for recall and loss of patients requiring treatment, and the associated reduction of facility costs [27, 28]. Economic evaluations provide evidence on the relative cost-effectiveness of implementation and can help address these considerations and inform resource allocation. While the number of studies analysing the cost and cost-effectiveness of POC testing and treatment of STIs in pregnancy in LMICs is increasing, there have been no systematic reviews synthesizing this body of literature.

The objective of this protocol is to identify, compare, synthesise and appraise the existing evidence on the costs and cost effectiveness of POC testing and treatment of common, curable STIs (namely, chlamydia, gonorrhoea, syphilis, trichomonas and bacterial vaginosis) in pregnancy in LMICs. The specific objectives of this review are:

1. Identify and synthesise the evidence on the cost and cost-effectiveness of POC testing and treatment for STIs in pregnancy in LMICs;
2. Compare and contrast the key findings from existing literature on the cost and cost-effectiveness of POC testing and treatment for STIs in pregnancy in LMICs;
3. Identify the key -drivers of costs and cost-effectiveness of POC testing and treatment for STIs in pregnancy in LMICs; and
4. Appraise the quality of reporting and methodological approaches of using published checklists.

METHODS

Study type, participants and intervention

The systematic review will only consider peer-reviewed cost and cost-effectiveness analyses of POC testing and treatment of STIs. We define a POC test as a diagnostic tool that requires only one visit, where the test is conducted and the result is received at the same visit. The test is simple, accurate (both specific and sensitive) and non-invasive, it is user-friendly, compact, durable and sturdy [24]. Specifically, the review will include studies that focus on POC testing and treatment of common, curable STIs, namely syphilis, chlamydia, trichomonas gonorrhoea, and bacterial vaginosis among pregnant women. Only studies based in LMICs, where the burden of STIs is the greatest will be included. Lastly, the review will include cost and cost-effectiveness analyses conducted within a framework of randomised control trials, pilot and feasibility studies and modelling studies.

Exclusion Criteria

Pre-determined exclusion criteria will be applied after the initial literature search. We will only include full peer-reviewed articles and exclude book chapters, commentaries, conference publications/abstracts, editorials, letters, meeting outcomes, recommendations, protocols and reviews. We will also exclude grey literature from the review. Grey literature tends to focus on study conclusions without a rigorous methodological description that could facilitate evaluating study quality. Although another limitation, during the title and abstract screening, we will exclude studies that are not in English. This reflects the language proficiency of the study team. Studies of populations other than pregnant women and on infections other than syphilis, gonorrhoea, chlamydia, trichomonas or bacterial vaginosis will also be excluded. The focus of the studies included must be a POC test for STIs and comparators include, but are not limited to, no screening, syndromic management and existing screening programs. We will exclude all studies not conducted in LMICs. The LMIC classification is sourced from the World Bank list comprised in 2018 [29]. We will not apply date and/or time of publication limitations.

Search strategy

The literature search for this systematic review will be independently conducted by two reviewers (OPMS and NB). First, OPMS and NB will independently search three pre-selected electronic databases, MEDLINE, Embase and Web of Science, using keywords and MeSH terms, spanning relevant subject matter. The search terms determined by OPMS, NB, LC, AV and VW, in consultation with experienced medical librarians at University College London and the University of New South

Wales are presented in a condensed form in Table 1. The search terms selected reflect relative search sensitivity and specificity, whereby a comprehensive search is balanced with identifying a manageable number of citations. No restrictions will be applied to the literature search. Boolean operators will be included - "OR" within each group of keywords and MeSH terms to indicate the areas of interest, and "AND" to combine each group and find articles related to the main objective of the systematic review. Lastly, terms will be exploded and truncated where necessary.

Table 1: Proposed keywords and MeSH terms for the literature search

Themes	Proposed keywords and MeSH terms
Economic evaluations	Cost-effectiveness OR cost benefit analysis (mesh term) OR cost analysis
Sexually transmitted and genital infections	Sexually transmitted infections OR Sexually transmitted Diseases OR Gonorrhoea OR Chlamydia OR Trichomonas OR Syphilis OR Bacterial Vaginosis
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Figure 1: Prisma flow diagram of the search selection for this systematic review.

Insert Figure 1 here

Data will be extracted into Microsoft Excel 2013 and will include details on the authors, title, type of intervention, comparator, study setting, study design, perspective adopted, time horizon, and key cost and cost effectiveness indicators results of each study. The Drummond checklist will be used in this systematic review to assess the methodological quality of the included studies [30] in conjunction with the novel CHEERS checklist [31] to assess the consistency and transparency of reporting. The Drummond 10-item, 13-criteria checklist [30] is a simplified version of the more detailed 35-item Drummond version, providing comprehensive guidance on the methodological conduct of an economic evaluation. It is recommended in the Cochrane Handbook for Systematic Reviews of Interventions [32]. The appraisal will be independently undertaken by OPMS and NB and in case of disputes, VW will arbitrate. Careful consideration will also be given to publication bias across studies and selective reporting within studies.

Data extracted for the analysis will include, primary outcomes or endpoints, such as total cost of the intervention, unit costs, cost-effectiveness and incremental cost -effectiveness ratios (such as cost per outcome and cost per disability-adjusted life years (DALYs) averted), cost savings to the health system, budget impact estimates. We will also extract data on context-related factors, such as factors included in sensitivity analyses that could affect the costs and cost effectiveness of interventions. This will allow us to explore a wide range of intervention programmes, economic evaluation methods, costs and outcomes and to identify and discuss the variation in drivers of costs and cost-effectiveness. A high degree of heterogeneity in the primary studies is anticipated – including differences in cost-effectiveness outcomes, study designs, and health interventions and comparators- which will limit our ability to conduct a meta-analysis. If methodological heterogeneity is confirmed then a descriptive summary and narrative synthesis will be undertaken. Further, if a subset of studies have comparable cost effectiveness outcomes, and the sample is large enough to do a rigorous meta-analysis this will be conducted using Stata IC version 14.0 (College Station, TX, USA).

Study dates

This study is ongoing; the anticipated date of completion is 30 September 2019.

Patient and public involvement

Patients and/or the public were not directly involved in the development of this systematic review protocol.

Ethics and dissemination

The systematic review will use published literature, not patient data, therefore ethical approval is not required. The results of this review will be published in a peer-reviewed, open access journal and presented an international conference.

DISCUSSION

Common, curable STIs in pregnancy have multiple adverse effects and left untreated can be harmful to both mothers and babies. LMICs have the highest burden of STIs, highlighting the need for affordable and cost-effective screening interventions in these settings. Collating current evidence on costs and cost-effectiveness of POC testing and treatment of STIs in pregnancy is an important first step in understanding the value of these tests in highly resource-constrained health systems. It also provides an opportunity to gauge the quality of reporting conventions used in the different studies. To our knowledge, this represents the first systematic review on this topic.

Contributions

OPMS drafted the manuscript, while initial revisions were provided by NB, AJV and VW. RA, CL and WP provided feedback and revisions to the manuscript. All authors read, provided feedback on and approved the final manuscript.

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Patient consent

Not required.

Ethics approval

This systematic review does not use individual personal data and therefore does not require ethical committee approval.

Provenance and peer review

Not commissioned; externally peer reviewed.

Competing Interests

None declared

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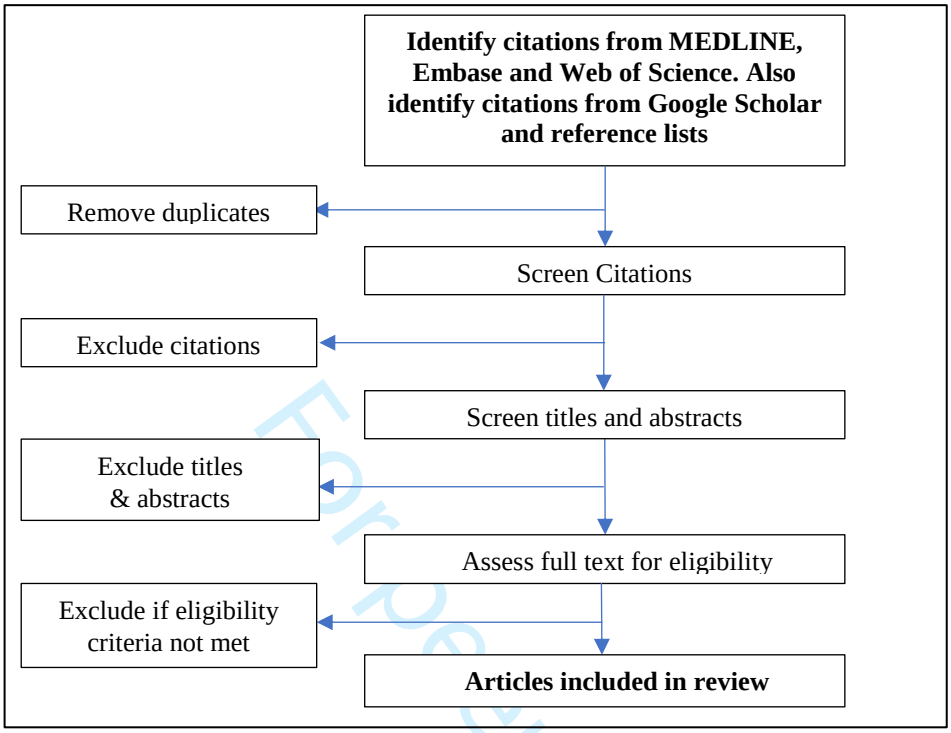
Figure 1: Prisma flow diagram of the search selection for this systematic review



PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol

Section and topic	Item No	Checklist item	Reported on page number
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	3
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	8
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	N/A
Support:			
Sources	5a	Indicate sources of financial or other support for the review	8
Sponsor	5b	Provide name for the review funder and/or sponsor	8
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	N/A
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	3-5
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	5
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	5-7
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	5-7

Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	5-7
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	5-7
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	5-7
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	5-7
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	5-7
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	7
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	7
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	7
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	7
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	7
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	7
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	7
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	7-8

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.