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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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Keywords:	point-of-care, sexually transmitted infections, genital infections, cost-effectiveness, costs, pregnancy

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Manuscripts

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3 1 **TITLE:**
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5 2 The cost and cost-effectiveness of point-of-care testing and treatment for sexually transmitted and
6 3 genital infections in pregnancy in low- and middle-income countries: A systematic review protocol
7
8 4

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52 27 **Word count:** 1586 words
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3 **28 ABSTRACT**
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5 **29 Introduction**
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8 **30 Sexually transmitted and genital infections (STIs) greatly burden low- and middle-income countries**
9 **31 (LMIC). When untreated in pregnancy, they increase the risk of adverse pregnancy and birth outcomes;**
10 **32 yet early detection and treatment reduces this risk. The introduction of point-of-care (POC) tests have**
11 **33 the potential to improve STI detection and treatment in LMICs. The widespread implementation of**
12 **34 screening in antenatal clinics has been hindered by barriers, including economic costs. To date there**
13 **35 have been no systematic reviews which explore the cost and cost-effectiveness of POC testing of STIs**
14 **36 in pregnancy in LMICs. The objective of this protocol is to outline the methods that will help synthesize**
15 **37 and appraise the evidence on the cost and cost-effectiveness of POC testing and treatment of STIs in**
16 **38 pregnancy in LMICs. Drivers of cost-effectiveness in different contexts, and the quality of economic**
17 **39 evaluations will also be explored.**
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26 **41 Methods & Analysis**
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29 **42 We will conduct two independent literature searches in three databases; MEDLINE, Embase and Web**
30 **43 of Science. We will search google scholar and hand search reference lists for additional literature. Two**
31 **44 reviewers will screen titles, abstracts and full texts; when necessary a third reviewer will resolve**
32 **45 discrepancies. Only cost and cost-effectiveness studies of POC testing and treatment of STIs, including**
33 **46 syphilis, chlamydia, trichomonas, gonorrhoea and bacterial vaginosis, in pregnancy in LMIC will be**
34 **47 included. All selected studies will be quality-assessed using the CHEERS checklist and risk of bias.**
35 **48 Between study heterogeneity will be explored and depending on variation between studies, a meta-**
36 **49 analysis or narrative synthesis will be conducted. The study is on-going and we anticipate completion**
37 **50 by 31 May, 2019.**
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46 **52 Ethics and dissemination**
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48 **53 The systematic review will use published literature, not patient data, therefore ethical approval is not**
49 **54 required. The results will be published in a peer-reviewed open source journal and presented an**
50 **55 international conference.**
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56 **57 Keywords**
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58 **58 Point-of-Care, sexually transmitted infections, genital infections, cost-effectiveness, costs, pregnancy,**
59 **59 antenatal care**
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5 61 **Prospero Registration number: CRD42018109072.**
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10 63 **ARTICLE SUMMARY**11
12 64 **Strengths and limitations of this study**

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- 14 65
- 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.
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- This review includes studies on both common curable sexually transmitted and genital infections in low- and middle- income countries.
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- We will conduct a meta-analysis, however if there is between-study heterogeneity of outcome measures we will conduct a narrative synthesis.
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- 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.
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- The review is limited to how studies empirically depict costs and cost-effectiveness.
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35 77 **INTRODUCTION**36
37 78 Globally, the growing burden of sexually transmitted and genital infections (STIs)¹ alarming, and the
38 79 majority of infections occur in low and middle income countries (LMICs) [1]. In 2012, the World Health
40 80 Organization (WHO) estimated that there were 357.4 million new cases of STIs, half of which were
41 81 attributed to trichomonas and chlamydia infections [2]. When left untreated, STIs can have adverse
42 82 effects on sexual and reproductive health, neonatal health and child health [3]. Among pregnant women,
43 83 untreated STIs are associated with increased risk of ectopic pregnancy, miscarriage and pre-term
44 84 delivery [4]. Adverse birth outcomes associated with STIs in pregnancy, include still birth, low birth
45 85 weight (LBW), neonatal death, and neonatal eye and respiratory infections following intrapartum
46 86 transmission [5].
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54 88 Several studies have indicated that the early detection and treatment of STIs in pregnancy could reduce
55 89 the risk of adverse pregnancy and birth outcomes [6]. There is strong evidence to suggest that the
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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

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3 90 detection and treatment of HIV and syphilis early in pregnancy reduces adverse pregnancy and birth
4 91 outcomes [7]. However, few studies, and most are based in high income countries, investigate the
5 92 detection and treatment of gonorrhoea, chlamydia, trichomonas and bacterial vaginosis, early in
6 93 pregnancy to prevent adverse outcomes, which means that more evidence is required to support this [6].
7
8 94 This is largely because up until recently detection of these common STIs required laboratory-based
9 95 testing, which is relatively expensive and thus fairly uncommon in LMIC [3]. As a result, STI screening
10 96 programs in many LMICs rely on syndromic management of the curable genital STIs; a WHO-endorsed
11 97 strategy based on clinical symptoms and signs without laboratory confirmation. [8]. This strategy has
12 98 been shown to have limited sensitivity and specificity for the detection of genital STIs, particularly
13 99 among pregnant women where asymptomatic infection appears to be more common [7-10]. Other
14 100 factors, which act as barriers to screening and subsequent treatment, such poor infrastructure and high
15 101 operational costs, emphasise the difficulties associated with laboratory-based screening programs in
16 102 resource-poor settings [9, 11].
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26 104 Advances in STI detection have played a key role in improving screening coverage and subsequent
27 105 treatment in LMICs. The widespread adoption of rapid point-of-care (POC) testing for HIV and
28 106 syphilis, is perhaps a signal of this [12-14]. These tests allow women to be tested, diagnosed and treated
29 107 in a single visit to a health facility [12-14]. There is evidence that suggests the introduction of POC tests
30 108 for HIV and syphilis at antenatal (ANC) clinics have reduced the rate of perinatal and infant morbidity
31 109 and mortality[3].
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39 111 The evidence on the effectiveness of POC testing and treatment of STIS in pregnancy is mixed, and
40 112 cannot single-handedly drive the implementation of STI screening programs at ANC clinics. POC
41 113 testing also presents a particularly challenging scenario. On the one hand, the unit cost-per-test is higher
42 114 owing to the loss of economies of scale offered by automation (typically centralised laboratories), but
43 115 on the other hand, it offers the potential of substantial savings through enabling rapid delivery of results
44 116 and treatment, avoiding the need for recall and loss of clients requiring treatment, and the associated
45 117 reduction of facility costs [12-14]. Thus, health system challenges, for example budgetary constraints,
46 118 program costs and accessibility, are key considerations for optimal program implementation [15, 16].
47 119 Economic evaluations, which consider program health outcomes, such as birth outcomes, and their
48 120 associated costs, provide the relative cost-effectiveness of implementation can help address these
49 121 considerations and inform resource allocation. This is particularly important for LMICs, where there
50 122 may be competing priorities for relatively scarce resources [16]. To date there have been no systematic
51 123 reviews which explore the cost and cost-effectiveness of POC testing of STIs in pregnancy in LMICs.
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3 125 The objective of this protocol is to outline the aims and detail the methods that will help synthesize and
4 126 appraise the evidence on the cost and cost-effectiveness of POC testing and treatment of STIs in
5 127 pregnancy in LMICs. Drivers of cost-effectiveness in different contexts, and the quality of the economic
6 128 evaluations will also be explored.
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11 12 130 **METHODS**

13 14 15 131 **Study type, participants and intervention**

16 132 The systematic review will only consider peer-reviewed studies of cost and cost-effectiveness analyses
17 133 (CEAs) of the POC testing and treatment of STIs. Specifically, the review will include studies that focus
18 134 on POC testing and treatment of syphilis, chlamydia, trichomonas gonorrhoea, and bacterial vaginosis
19 135 in LMICs, where the burden of STIs is the greatest [7-10]. Only interventions targeting pregnant women
20 136 will be considered.
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27 138 The review will not be restricted to cost analyses and CEAs conducted within the framework of
28 139 randomised controlled trials. It will take a comprehensive approach and include pilot studies and
29 140 feasibility analyses, as well as modelling studies.
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33 141

34 35 142 **Inclusion and Exclusion Criteria**

36 143 Pre-determined inclusion and exclusion criteria will be applied after the initial literature search. We will
37 144 only include full peer-reviewed articles and exclude book chapters, commentaries, conference
38 145 publications/abstracts, editorials, letters, meeting outcomes, recommendations, protocols and reviews.
39 146 We will also exclude all studies that are not in English. Studies of populations other than pregnant
40 147 women and on infections other than syphilis, gonorrhoea, chlamydia or trichomonas will also be
41 148 excluded. The focus of the studies included must be a POC test for STIs. Specifically diagnostic tools
42 149 that require only one visit, where the test is conducted and result is received at the same visit, the test is
43 150 simple, accurate and non-invasive, it is user-friendly, compact, durable and sturdy [17]. We will only
44 151 include studies conducted in LMICs. The LMIC classification is directly sourced from the World Bank
45 152 list comprised in 2018 [18].
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54 55 154 **Search strategy**

56 155 The literature search for this systematic review will be independently conducted by two reviewers
57 156 (OPMS and NB) and comprise of three stages. First, three pre-selected electronic databases, MEDLINE,

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3 157 Embase and Web of Science, will be searched using keywords and MeSH terms, spanning relevant
4 158 subject matter. These terms are presented in Table 1. Boolean operators will be included - “OR” within
5 159 each group of keywords and MeSH terms to indicate the areas of interest, and “AND” to combine each
6 160 group and find articles related to the main objective of the systematic review.
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11 162 *Table 1: Proposed keywords and MeSH terms for the literature search*

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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

13 164

14 165 The second stage aims to identify additional literature using Google Scholar, which may capture articles
15 166 missed by the database searches and finally, a hand-search of references included in the final set of
16 167 articles will be conducted.
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20 169 **Data Analysis**

21 170 All citations found through the literature search will be exported into End note X8 and all duplicates
22 171 will be removed, after which the multi-stage screening process will begin. Literature included in this
23 172 review will be reported according to the PRISMA guidelines and data will be analysed using Microsoft
24 173 Excel 2013 and presented in tables.
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27 174 The screening process, illustrated in Figure 1, shows the proposed PRISMA flow diagram for this
28 175 review. OPMS and NB will independently screen all titles and abstracts to collate a final set of articles
29 176 for review. Where discrepancies arise a third researcher, VW, will make the final decision to include or
30 177 exclude literature.
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34 179 *Figure 1*

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36 181 *Insert Figure 1 here*

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3 183 The CHEERS checklist [19] will be used to appraise the quality of each article included in the review.
4 184 The quality appraisal of each article will be independently undertaken by two researchers (OPMS and
5 185 NB) similar to the initial screening process. In case of discrepancies a third researcher, VW, will help
6 186 arbitrate. Careful consideration will also be given to publication bias across studies and selective
7 187 reporting within studies.
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14 189 After the initial appraisal, data will be extracted into a data extraction form in Microsoft Excel 2013.
15 190 We do not anticipate a high degree of homogeneity in the reporting of cost effectiveness outcomes. We
16 191 propose to first conduct a narrative synthesis, focussing on a discussion of the costs and cost
17 192 effectiveness of the POC testing programs, and their budgetary impact, reflecting on the scale of
18 193 implementation of the programs. We will also explore and discuss program and context-related factors
19 194 that might affect relative cost-effectiveness in different settings. Where outcomes are comparable, the
20 195 review will compare the cost effectiveness outcomes, Cost-Effectiveness Ratios and Incremental Cost
21 196 Effectiveness Ratios and the extent to which interventions are deemed cost-effective compared to
22 197 relevant investment options [20]. This will allow us to explore whether there is a significant variation
23 198 in the intervention programmes, economic evaluation methods, costs and outcomes. We will conduct
24 199 tests of heterogeneity to confirm this, in order to guide the possibility of conducting a meta-analysis.
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34 201 **Study dates**

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36 202 This study is ongoing; the anticipated date of completion is 31 May 2019.
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40 204 **Ethics and dissemination**

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42 205 The systematic review will use published literature, not patient data, therefore ethical approval is not
43 206 required. The results of this review will be published in a peer-reviewed, open access journal and
44 207 presented an international conference.
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50 209 **DISCUSSION**

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52 210 STIs in pregnancy have multiple adverse effects and left untreated can be harmful to both mothers and
53 211 babies. Most cases occur in LMICs, therefore highlighting the need for affordable and cost-effective
54 212 interventions in low-resource settings. This, combined with shrinking health care budgets in LMICs,
55 213 raised concerns about the quality and efficiency of health care delivery systems in these countries.
56 214 Collating current evidence on cost-effectiveness is an important first step in assessing the value of this
57 215 testing strategy and planning its efficient and equitable implementation. To our knowledge, the
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3 216 proposed review is the first to consolidate evidence on the costs and cost-effectiveness of antenatal POC
4 217 testing and treatment in LMICs, and to discuss the methodological differences between studies,
5 218 including their limitations.
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11 221 **Contributions**

12 222 OPMS drafted the manuscript, while initial revisions were provided by NB, AJV and VW. RA, CL and
13 223 WP provided feedback and revisions to the manuscript. All authors read, provided feedback and
14 224 approved the final manuscript.
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18 225

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27 234 South Wales Scientia Higher Degree Candidate Scholarship Scheme.
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35 236 **Patient consent**

36 237 Not required.
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40 239 **Ethics approval**

41 240 This systematic review does not use individual personal data and therefore does not require ethical
42 241 committee approval.
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46 243 **Provenance and peer review**

47 244 Not commissioned; externally peer reviewed.
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51 246 **Competing Interests**

52 247 None declared
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58 251 *commitment to STI prevention and control in achieving global sexual and reproductive health.*
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307 **Figure 1: Prisma flow diagram of the search selection for this systematic review**
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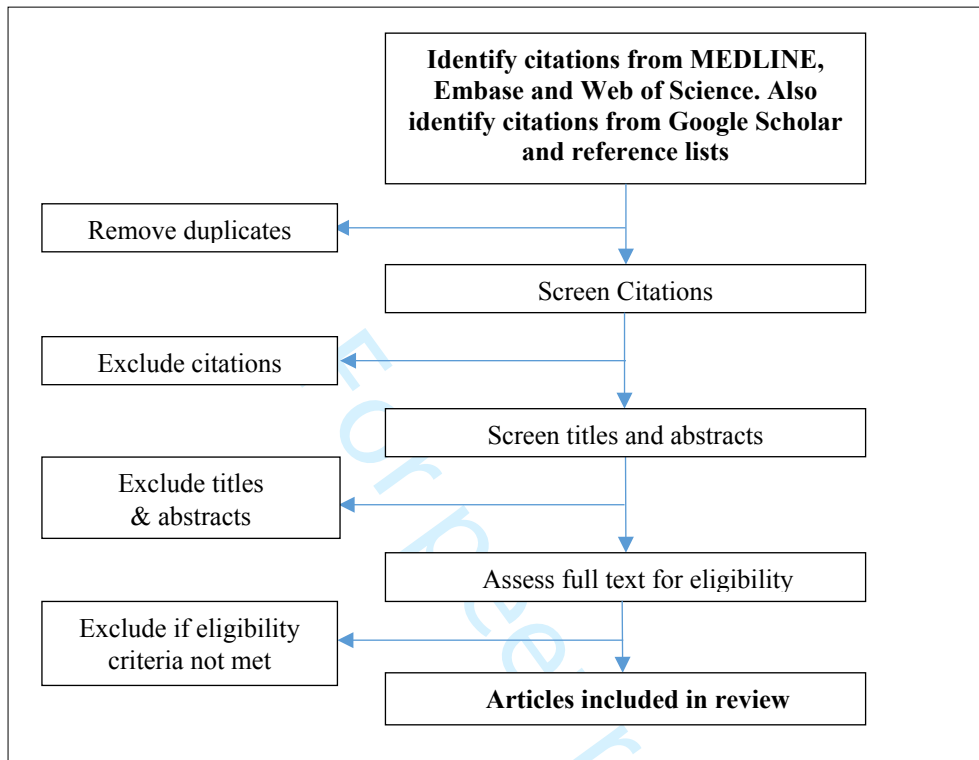
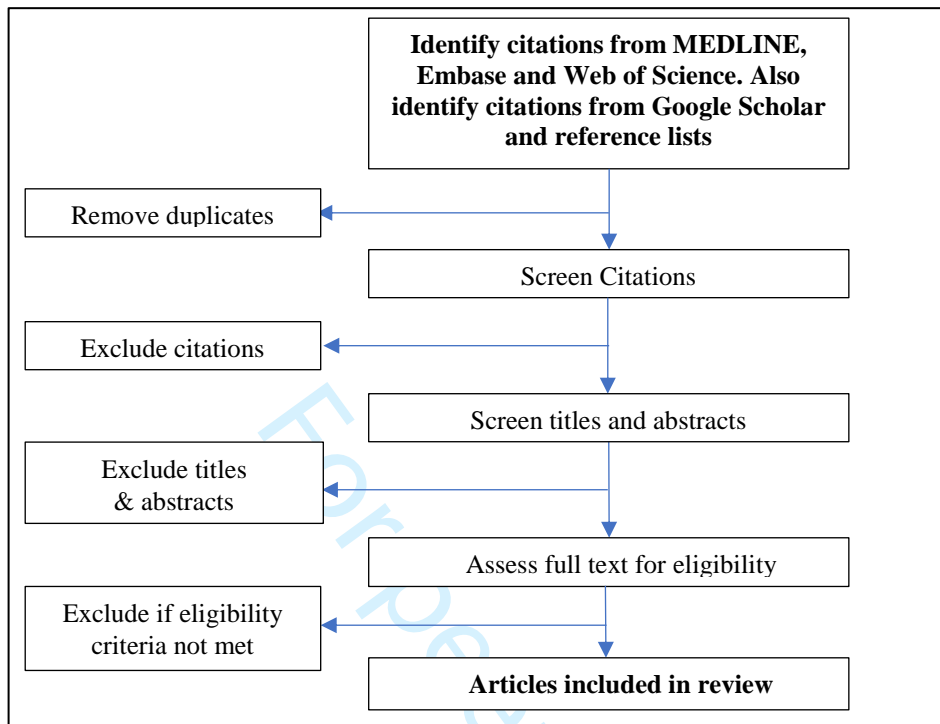


Figure 1: Prisma flow diagram of the search selection for this systematic review



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

Journal:	<i>BMJ Open</i>
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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

SCHOLARONE™
Manuscripts

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3 1 **TITLE:**
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5 2 The cost and cost-effectiveness of point-of-care testing and treatment for sexually transmitted and
6 3 genital infections in pregnancy in low- and middle-income countries: A systematic review protocol
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8 4

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52 27 **Word count:** 1723 words
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3 **28 ABSTRACT**
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5 **29 Introduction**
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8 30 The economic and health burden of sexually transmitted and genital infections (henceforth, STIs) in
9 31 low- and middle- income countries (LMICs) is substantial. Left untreated, STIs during pregnancy can
10 32 result in several adverse pregnancy and birth outcomes. Timely diagnosis and treatment at point-of-care
11 33 (POC) can potentially improve these outcomes. Despite the availability and promotion of new POC
12 34 diagnostics for STIs as a key component of antenatal care in LMICs, their widespread use has been
13 35 limited, owing to the high economic costs faced by individuals and health systems. To date there have
14 36 been no systematic reviews which explore the cost and cost-effectiveness of POC testing of STIs in
15 37 pregnancy in LMICs. The objective of this protocol is to outline the methods that will synthesize and
16 38 appraise the existing literature on the cost and cost-effectiveness of POC testing and treatment of STIs
17 39 in pregnancy in LMICs to inform resource allocation.
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26 **41 Methods & Analysis**
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28 42 We will conduct literature searches in MEDLINE, Embase and Web of Science. To find additional
29 43 literature we will search Google Scholar and hand search reference lists of included papers. Two
30 44 reviewers will independently search the databases, screen titles, abstracts and full texts; when necessary
31 45 a third reviewer will resolve disputes. Only cost and cost-effectiveness studies of POC testing and
32 46 treatment of STIs, including syphilis, chlamydia, trichomonas, gonorrhoea and bacterial vaginosis, in
33 47 pregnancy in LMICs will be included. Quality of reporting will be assessed using the CHEERS
34 48 checklist. We will also assess risk of publication bias. Inter-study heterogeneity will be explored and
35 49 depending on variation between studies, a meta-analysis or narrative synthesis will be conducted.
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44 **51 Ethics and dissemination**
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46 52 Ethical approval is not required as the review will use published literature. The results will be published
47 53 in a peer-reviewed open source journal and presented at an international conference.
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52 **55 Keywords**
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54 56 Point-of-Care testing, sexually transmitted infections, genital infections, cost-effectiveness, costs,
55 57 pregnancy, antenatal care
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59 **Prospero Registration number:** CRD42018109072.

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61 **ARTICLE SUMMARY**

62 **Strengths and limitations of this study**

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

72

73 **INTRODUCTION**

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

83

84 There is strong evidence to suggest that the detection and treatment of HIV and syphilis early in
85 pregnancy reduces adverse pregnancy and birth outcomes [6, 7]. Several studies have indicated that the
86 early detection and treatment of STIs in pregnancy could reduce the risk of adverse pregnancy and birth
87 outcomes [5, 7-9]. However, despite high prevalence rates in LMICs few studies in these settings
88 investigate the detection and treatment of common, curable STIs early in pregnancy to prevent adverse
89 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

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3 90 pregnancy required laboratory-based testing, which is a relatively expensive form of diagnosis in
4 91 LMICs [3]. Other factors include poor infrastructure, limited human resources and high operational
5 92 costs [8, 10, 11]. As a result, clinicians in many LMICs rely on the WHO-endorsed strategy of syndromic
6 93 management to diagnose and treat symptomatic STIs, which is based on presentation of clinical
7 94 symptoms and signs without laboratory confirmation [10]. This strategy has limited specificity for
8 95 accurate diagnosis, particularly among pregnant women where asymptomatic infections are common
9 96 [9, 10, 12].

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17 98 Advances in STI detection have played a key role in improving diagnosis and subsequent treatment in
18 99 LMICs. The widespread adoption of point-of-care (POC) testing for HIV and syphilis, is perhaps a
19 100 signal of this [13-15]. These tests allow patients to be tested, diagnosed and treated in a single visit to a
20 101 health facility [13-15]. There is evidence that suggests the introduction of POC tests for HIV and
21 102 syphilis at antenatal clinics has reduced the rate of perinatal and infant morbidity and mortality in many
22 103 LMICs [5-7]. This evidence, however, cannot single-handedly drive the implementation of STI
23 104 screening programs. POC testing also presents a particularly challenging scenario. On the one hand, the
24 105 unit cost-per-test is higher owing to the loss of economies of scale offered by automation, typically by
25 106 centralised laboratories. On the other hand, it offers the potential of substantial savings through enabling
26 107 the rapid delivery of results and treatment, avoiding the need for recall and loss of patients requiring
27 108 treatment, and the associated reduction of facility costs [13-15]. Economic evaluations provide evidence
28 109 on the relative cost-effectiveness of implementation and can help address these considerations and
29 110 inform resource allocation. While the number of studies analysing the cost and cost-effectiveness of
30 111 POC testing and treatment of STIs in pregnancy in LMICs is increasing, there have been no systematic
31 112 reviews synthesizing this body of literature.

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44 114 The objective of this protocol is to identify, synthesise and appraise the existing evidence on the costs
45 115 and cost effectiveness of POC testing and treatment of common, curable STIs (namely, chlamydia,
46 116 gonorrhoea, syphilis, trichomonas and bacterial vaginosis) in pregnancy in LMICs. The specific
47 117 objectives of this review are:

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50 118 1. Identify and synthesise the evidence on the cost and cost-effectiveness of POC testing and treatment
51 119 for STIs in pregnancy in LMICs;
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53 120 2. Appraise the quality of reporting economic evaluations using the consolidated health economics
54 121 evaluation reporting standards (CHEERS) checklist; and
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56 122 3. Identify the key -drivers of costs and cost-effectiveness of POC testing and treatment for STIs in
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58 123 pregnancy in LMICs.

124

125 **METHODS**

126 **Study type, participants and intervention**

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

137

138 **Exclusion Criteria**

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

151

152 **Search strategy**

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

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3 157 with experienced medical librarians are presented in Table 1. The search terms selected reflect relative
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5 158 search sensitivity and specificity, whereby a comprehensive search is balanced with identifying a
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7 159 manageable number of citations. Boolean operators will be included - “OR” within each group of
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9 160 keywords and MeSH terms to indicate the areas of interest, and “AND” to combine each group and find
10
11 161 articles related to the main objective of the systematic review.

12 162

13 163 *Table 1: Proposed keywords and MeSH terms for the literature search*

14 164

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

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16 166 OPMS and NB will then independently search for literature using Google Scholar. The first 100 results
17
18 167 will be screened to identify additional literature, which may capture articles missed by the database
19
20 168 searches. Finally, OPMS and NB will each conduct a hand-search of references included in the final set
21
22 169 of articles.

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24 171 **Data Extraction and Analysis**

25 172 All citations found through the literature search will be exported into Endnote X8 (Thomson Reuters)
26
27 173 and duplicates will be removed. OPMS and NB will independently screen all titles, keywords and
28
29 174 abstracts to collate a set of articles for full-text review based on the inclusion and exclusion criteria.
30
31 175 OPMS and NB will then independently review the full-texts of selected studies and apply the inclusion
32
33 176 and exclusion criteria to compile the final set of studies to be included in the review. In the case of
34
35 177 disputes VW will make the final decision to include or exclude studies. Literature included in this
36
37 178 review will be reported according to the PRISMA guidelines. The screening process, illustrated in
38
39 179 Figure 1, shows the proposed PRISMA flow diagram for this review.

40 180

41 181 *Figure 1*

42 182

43 183 *Insert Figure 1 here*

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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.

193

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).

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205 **Study dates**

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

207

208 **Patient and public involvement**

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

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212 **Ethics and dissemination**

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

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45 217 **DISCUSSION**

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7 218 Common, curable STIs in pregnancy have multiple adverse effects and left untreated can be harmful to
8 219 both mothers and babies. LMICs have the highest burden of STIs, highlighting the need for affordable
9 220 and cost-effective screening interventions in these settings. Collating current evidence on costs and
10 221 cost-effectiveness of POC testing and treatment of STIs in pregnancy is an important first step in
11 222 understanding the value of these tests in highly resource-constrained health systems. It also provides an
12 223 opportunity to gauge the quality of reporting conventions used in the different studies. To our
13 224 knowledge, this represents the first systematic review on this topic.

14
15 22516 226 **Contributions**

17 227 OPMS drafted the manuscript, while initial revisions were provided by NB, AJV and VW. RA, CL and
18 228 WP provided feedback and revisions to the manuscript. All authors read, provided feedback on and
19 229 approved the final manuscript.

20 230

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22 232 WANTAIM is a partnership of academic and governmental institutions in Papua New Guinea, Australia
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28 238 of facilities and/or salary contributions. In addition, OPMS and RA are supported by The University
29 239 of New South Wales Scientia Higher Degree Candidate Scholarship Scheme.

30 240

31 241 **Patient consent**

32 242 Not required.

33 243

34 244 **Ethics approval**

35 245 This systematic review does not use individual personal data and therefore does not require ethical
36 246 committee approval.

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38 248 **Provenance and peer review**

39 249 Not commissioned; externally peer reviewed.

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3 251 **Competing Interests**

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5 252 None declared

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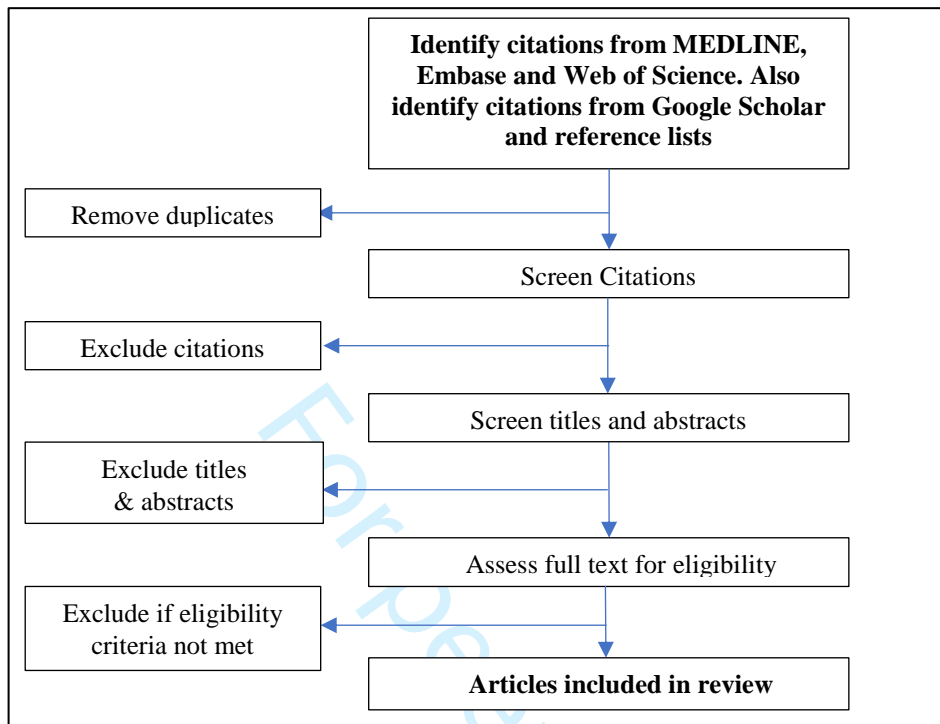
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For peer review only

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

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

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Manuscripts

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3 1 **TITLE:**
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5 2 The cost and cost-effectiveness of point-of-care testing and treatment for sexually transmitted and
6 3 genital infections in pregnancy in low- and middle-income countries: A systematic review protocol
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52 27 **Word count:** 1934 words
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28 **ABSTRACT**

29 **Introduction**

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

40 **Methods & Analysis**

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

51 **Ethics and dissemination**

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

55 **Keywords**

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

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3 59 **Prospero Registration number:** CRD42018109072.
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8 61 **ARTICLE SUMMARY**

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10 62 **Strengths and limitations of this study**

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12 63 • This systematic review is, to the best of our knowledge, the first to synthesize evidence on the
13 64 costs and cost-effectiveness of point-of-care testing and treatment of common and curable
14 65 sexually transmitted and genital infections in pregnancy in low- and middle- income countries.
15 66 • This review will assess the completeness of reporting practices and identify areas for
16 67 improvement in the field.
17 68 • If the inter-study heterogeneity of results may prevent a meta-analysis, we will conduct a
18 69 narrative synthesis of findings.
19 70 • The review is limited to how studies empirically depict costs and cost-effectiveness.
20 71 • The review is limited to studies published in peer-reviewed journals.
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31 73 **INTRODUCTION**

32 74 Globally, the growing burden of common curable sexually transmitted and genital infections such as
33 75 chlamydia, gonorrhoea, syphilis, trichomonas and bacterial vaginosis (henceforth, STIs) is alarming.
34 76 The majority of infections occur in low and middle income countries (LMICs) [1]. The World Health
35 77 Organization (WHO) estimated that in 2012 there were 357.4 million new cases of chlamydia,
36 78 gonorrhoea, syphilis and trichomonas [2]. Left untreated, these STIs can have adverse effects on sexual
37 79 and reproductive health, neonatal and child health [3-5]. During pregnancy, untreated STIs are
38 80 associated with an increased risk of adverse pregnancy and birth outcomes, including miscarriage, pre-
39 81 term delivery, still birth, low birth weight (LBW), neonatal death, and neonatal eye and respiratory
40 82 infections following intrapartum transmission [6-11].
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49 84 There is strong evidence to suggest that the detection and treatment of HIV and syphilis early in
50 85 pregnancy reduces adverse pregnancy and birth outcomes [12-15]. Several studies have indicated that
51 86 the early detection and treatment of STIs, such as Chlamydia, Trichomonas and Gonorrhoea, in
52 87 pregnancy could reduce the risk of adverse pregnancy and birth outcomes [16, 17]. However, despite
53 88 high prevalence rates in LMICs few studies in these settings investigate the detection and treatment of
54 89 common, curable STIs early in pregnancy to prevent adverse outcomes. This is largely because up until
55 90 recently the accurate detection of these STIs in pregnancy required laboratory-based testing, which is a
56 91 relatively expensive form of diagnosis in LMICs [18]. Other factors include poor infrastructure, limited

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3 92 human resources and high operational costs [19, 20]. As a result, clinicians in many LMICs rely on the
4 93 WHO-endorsed strategy of syndromic management to diagnose and treat symptomatic STIs, which is
5 94 based on presentation of clinical symptoms and signs without laboratory confirmation [18, 19, 21]. This
6 95 strategy has limited specificity for accurate diagnosis, particularly among pregnant women where
7 96 asymptomatic infections are common [19, 22].
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14 98 Advances in STIs detection have played a key role in improving diagnosis and subsequent treatment in
15 99 LMICs. The widespread adoption of point-of-care (POC) testing for HIV and syphilis, is perhaps a
16 100 signal of this [23]. These tests allow patients to be tested, diagnosed and treated in a single visit to a
17 101 health facility [24]. There is evidence that suggests the introduction of POC tests for HIV and syphilis
18 102 at antenatal clinics has reduced the rate of perinatal and infant morbidity and mortality in many LMICs
19 103 [25, 26]. This evidence, however, cannot single-handedly drive the implementation of STIs screening
20 104 programs. POC testing also presents a particularly challenging scenario. On the one hand, the unit cost-
21 105 per-test is higher owing to the loss of economies of scale offered by automation, typically by centralised
22 106 laboratories. On the other hand, it offers the potential of substantial savings through enabling the rapid
23 107 delivery of results and treatment, avoiding the need for recall and loss of patients requiring treatment,
24 108 and the associated reduction of facility costs [27, 28]. Economic evaluations provide evidence on the
25 109 relative cost-effectiveness of implementation and can help address these considerations and inform
26 110 resource allocation. While the number of studies analysing the cost and cost-effectiveness of POC
27 111 testing and treatment of STIs in pregnancy in LMICs is increasing, there have been no systematic
28 112 reviews synthesizing this body of literature.
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40 114 The objective of this protocol is to identify, compare, synthesise and appraise the existing evidence on
41 115 the costs and cost effectiveness of POC testing and treatment of common, curable STIs (namely,
42 116 chlamydia, gonorrhoea, syphilis, trichomonas and bacterial vaginosis) in pregnancy in LMICs. The
43 117 specific objectives of this review are:

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47 118 1. Identify and synthesise the evidence on the cost and cost-effectiveness of POC testing and treatment
48 119 for STIs in pregnancy in LMICs;
49 120 2. Compare and contrast the key findings from existing literature on the cost and cost-effectiveness of
50 121 POC testing and treatment for STIs in pregnancy in LMICs;
51 122 3. Identify the key -drivers of costs and cost-effectiveness of POC testing and treatment for STIs in
52 123 pregnancy in LMICs; and
53 124 4. Appraise the quality of reporting and methodological approaches of using published checklists.
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5 127 **METHODS**6
7 128 **Study type, participants and intervention**

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9 129 The systematic review will only consider peer-reviewed cost and cost-effectiveness analyses of POC
10 130 testing and treatment of STIs. We define a POC test as a diagnostic tool that requires only one visit,
11 131 where the test is conducted and the result is received at the same visit. The test is simple, accurate (both
12 132 specific and sensitive) and non-invasive, it is user-friendly, compact, durable and sturdy [24].
13 133 Specifically, the review will include studies that focus on POC testing and treatment of common,
14 134 curable STIs, namely syphilis, chlamydia, trichomonas gonorrhoea, and bacterial vaginosis among
15 135 pregnant women. Only studies based in LMICs, where the burden of STIs is the greatest will be
16 136 included. Lastly, the review will include cost and cost-effectiveness analyses conducted within a
17 137 framework of randomised control trials, pilot and feasibility studies and modelling studies.

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26 139 **Exclusion Criteria**

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29 140 Pre-determined exclusion criteria will be applied after the initial literature search. We will only include
30 141 full peer-reviewed articles and exclude book chapters, commentaries, conference publications/abstracts,
31 142 editorials, letters, meeting outcomes, recommendations, protocols and reviews. We will also exclude
32 143 grey literature from the review. Grey literature tends to focus on study conclusions without a rigorous
33 144 methodological description that could facilitate evaluating study quality. Although another limitation,
34 145 during the title and abstract screening, we will exclude studies that are not in English. This reflects the
35 146 language proficiency of the study team. Studies of populations other than pregnant women and on
36 147 infections other than syphilis, gonorrhoea, chlamydia, trichomonas or bacterial vaginosis will also be
37 148 excluded. The focus of the studies included must be a POC test for STIs and comparators include, but
38 149 are not limited to, no screening, syndromic management and existing screening programs. We will
39 150 exclude all studies not conducted in LMICs. The LMIC classification is sourced from the World Bank
40 151 list comprised in 2018 [29]. We will not apply date and/or time of publication limitations.

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51 153 **Search strategy**

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53 154 The literature search for this systematic review will be independently conducted by two reviewers
54 155 (OPMS and NB). First, OPMS and NB will independently search three pre-selected electronic
55 156 databases, MEDLINE, Embase and Web of Science, using keywords and MeSH terms, spanning
56 157 relevant subject matter. The search terms determined by OPMS, NB, LC, AV and VW, in consultation
57 158 with experienced medical librarians at University College London and the University of New South
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3 159 Wales are presented in a condensed form in Table 1. The search terms selected reflect relative search
4 160 sensitivity and specificity, whereby a comprehensive search is balanced with identifying a manageable
5 161 number of citations. No restrictions will be applied to the literature search. Boolean operators will be
6 162 included - “OR” within each group of keywords and MeSH terms to indicate the areas of interest, and
7 163 “AND” to combine each group and find articles related to the main objective of the systematic review.
8 164 Lastly, terms will be exploded and truncated where necessary.

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15 166 *Table 1: Proposed keywords and MeSH terms for the literature search*

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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

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31 169 OPMS and NB will then independently search for literature using Google Scholar. The first 100 results
32 170 will be screened to identify additional literature, which may capture articles missed by the database
33 171 searches. Finally, OPMS and NB will each conduct a hand-search of references included in the final set
34 172 of articles.

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174 **Data Extraction and Analysis**

42 175 All citations found through the literature search will be exported into Endnote X8 (Thomson Reuters)
43 176 and duplicates will be removed. OPMS and NB will independently screen all titles, keywords and
44 177 abstracts to collate a set of articles for full-text review based on the inclusion and exclusion criteria.
45 178 OPMS and NB will then independently review the full-texts of selected studies and apply the inclusion
46 179 and exclusion criteria to compile the final set of studies to be included in the review. In the case of
47 180 disputes VW will make the final decision to include or exclude studies. Literature included in this
48 181 review will be reported according to the PRISMA guidelines. The screening process, illustrated in
49 182 Figure 1, shows the proposed PRISMA flow diagram for this review.

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57 184 *Figure 1: Prisma flow diagram of the search selection for this systematic review.*

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7 188 Data will be extracted into Microsoft Excel 2013 and will include details on the authors, title, type of
8 189 intervention, comparator, study setting, study design, perspective adopted, time horizon, and key cost
9 190 and cost effectiveness indicators results of each study. The Drummond checklist will be used in this
10 191 systematic review to assess the methodological quality of the included studies [30] in conjunction with
11 192 the novel CHEERS checklist [31] to assess the consistency and transparency of reporting. The
12 193 Drummond 10-item, 13-criteria checklist [30] is a simplified version of the more detailed 35-item
13 194 Drummond version, providing comprehensive guidance on the methodological conduct of an economic
14 195 evaluation. It is recommended in the Cochrane Handbook for Systematic Reviews of Interventions [32].
15 196 The appraisal will be independently undertaken by OPMS and NB and in case of disputes, VW will
16 197 arbitrate. Careful consideration will also be given to publication bias across studies and selective
17 198 reporting within studies.
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27 200 Data extracted for the analysis will include, primary outcomes or endpoints, such as total cost of the
28 201 intervention, unit costs, cost-effectiveness and incremental cost -effectiveness ratios (such as cost per
29 202 outcome and cost per disability-adjusted life years (DALYs) averted), cost savings to the health system,
30 203 budget impact estimates. We will also extract data on context-related factors, such as factors included
31 204 in sensitivity analyses that could affect the costs and cost effectiveness of interventions. This will allow
32 205 us to explore a wide range of intervention programmes, economic evaluation methods, costs and
33 206 outcomes and to identify and discuss the variation in drivers of costs and cost-effectiveness. A high
34 207 degree of heterogeneity in the primary studies is anticipated – including differences in cost-
35 208 effectiveness outcomes, study designs, and health interventions and comparators- which will limit our
36 209 ability to conduct a meta-analysis. If methodological heterogeneity is confirmed then a descriptive
37 210 summary and narrative synthesis will be undertaken. Further, if a subset of studies have comparable
38 211 cost effectiveness outcomes, and the sample is large enough to do a rigorous meta-analysis this will be
39 212 conducted using Stata IC version 14.0 (College Station, TX, USA).
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214 **Study dates**

215 This study is ongoing; the anticipated date of completion is 30 September 2019.
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217 **Patient and public involvement**

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

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5 221 **Ethics and dissemination**

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7 222 The systematic review will use published literature, not patient data, therefore ethical approval is not
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9 223 required. The results of this review will be published in a peer-reviewed, open access journal and
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11 224 presented an international conference.

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15 226 **DISCUSSION**

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17 227 Common, curable STIs in pregnancy have multiple adverse effects and left untreated can be harmful to
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19 228 both mothers and babies. LMICs have the highest burden of STIs, highlighting the need for affordable
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21 229 and cost-effective screening interventions in these settings. Collating current evidence on costs and
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23 230 cost-effectiveness of POC testing and treatment of STIs in pregnancy is an important first step in
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25 231 understanding the value of these tests in highly resource-constrained health systems. It also provides an
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27 232 opportunity to gauge the quality of reporting conventions used in the different studies. To our
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29 233 knowledge, this represents the first systematic review on this topic.

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31 23432 235 **Contributions**

33 236 OPMS drafted the manuscript, while initial revisions were provided by NB, AJV and VW. RA, CL and
34
35 237 WP provided feedback and revisions to the manuscript. All authors read, provided feedback on and
36
37 238 approved the final manuscript.

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44
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53 247 of facilities and/or salary contributions. In addition, OPMS and RA are is supported by The University
54
55 248 of New South Wales Scientia Higher Degree Candidate Scholarship Scheme.

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57 24958 250 **Patient consent**

59 251 Not required.

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60 253 **Ethics approval**

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3 254 This systematic review does not use individual personal data and therefore does not require ethical
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5 255 committee approval.

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8 257 **Provenance and peer review**

9 258 Not commissioned; externally peer reviewed.

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13 260 **Competing Interests**

14 261 None declared

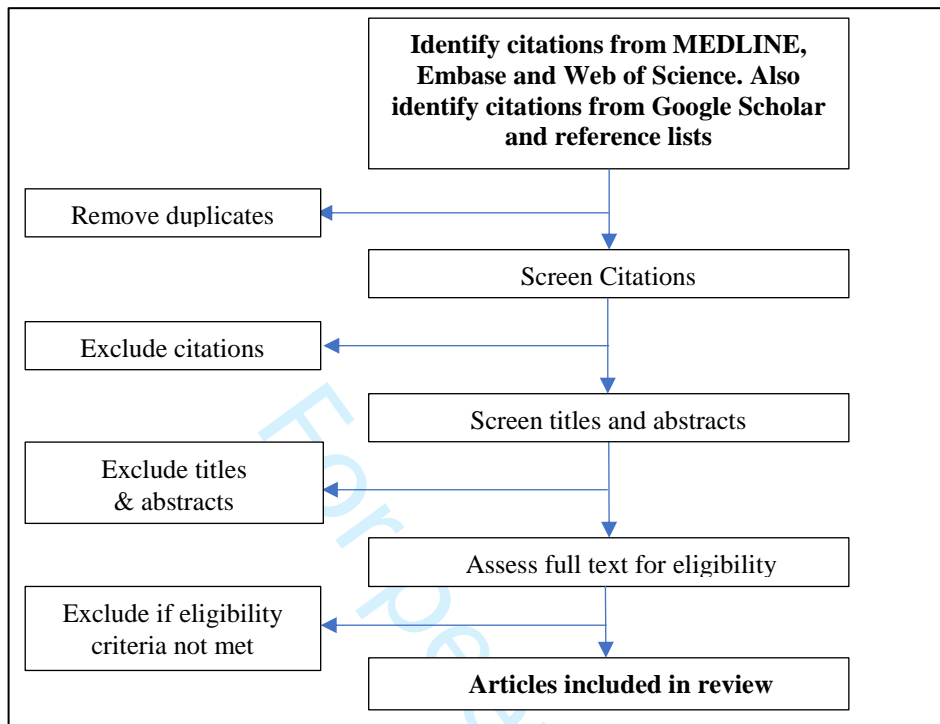
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- 46 344

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.