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Point-of-care tests for urinary tract infections: Protocol for a systematic review and meta-analysis of diagnostic test accuracy

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Title: *Point-of-care* tests for urinary tract infections: Protocol for a systematic review and meta-analysis of diagnostic test accuracy.

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ABSTRACT: *(BMJ Open Protocol format)*

Introduction

Urinary tract infections (UTIs) are the second most common type of infection worldwide, accounting for a large number of primary care consultations and antibiotic prescribing. Current diagnosis is based on an empirical approach, relying on symptoms and occasional use of urine dipsticks. The diagnostic gold standard is still urine culture, although it is not routinely recommended for uncomplicated UTIs in the community, due to time to diagnosis (48h). Rapid point-of-care tests have been developed, but their diagnostic accuracy has not been compared. Our objective is to systematically review and meta-analyse the diagnostic accuracy of currently available point-of-care tests for urinary tract infections.

Methods and analysis

Studies evaluating the diagnostic accuracy of point-of-care tests for urinary tract infections will be included. Pubmed, Web of Science, EMBASE and Cochrane Database of Systematic Reviews were searched from inception to the 1st June 2019. Data extraction and risk of bias assessment will be assessed using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool. Meta-analysis will be performed depending on data availability and heterogeneity.

Ethics and dissemination

This is a systematic review protocol and therefore formal ethical approval is not required, as no primary, identifiable, personal data will be collected. Patients or the public were not involved in the design of our research. However, the findings from this review will be shared with key stakeholders, including patient groups, clinicians and guideline developers, and will also be presented and national and international conferences.

Registration

The protocol is registered in PROSPERO, registration number: CRD42018112019

Keywords

Systematic Review, Urinary Tract Infections, Infectious Diseases, Diagnostic Accuracy, Point-of-care tests.

Strengths and limitations of this study

- Antimicrobial resistance is an increasing worldwide public health concern, with resistance among gram-negatives (most common microorganisms in urinary tract infections) being a burden in Europe. Improving diagnosis is one of the key streams of antimicrobial stewardship, and the use of point-of-care tests has been shown very effective in improving antibiotic use in both primary and secondary care settings, with the potential of reversing or flattening resistance trends related to lower antimicrobial use.
- To our knowledge, this is the first systematic review that formally analyses and compares the diagnostic accuracy of currently available point-of-care tests for UTI diagnosis.
- The results from this study will help identify the best available point-of-care test to diagnose UTIs in the primary care setting.
- It is likely significant heterogeneity will be found as all available tests will be explored. Random-effects meta-analysis will be performed to account for this.
- Studies involving paediatric population (<18 years old) or populations with certain conditions (detailed in exclusion criteria) will be excluded, as well as studies aimed at screening of asymptomatic bacteriuria, which may affect the generalisability of the results out with these situations.

INTRODUCTION:

Urinary tract infections (UTIs) are the second most common cause of infection in primary [1] and secondary care [2] and most women experience at least one episode of acute uncomplicated cystitis in their lifetime. In the United Kingdom, UTIs account for 1-3% of all consultations in primary care each year [1]. UTIs are also responsible for a major part of antibiotic prescriptions, accounting for up to 15% of antimicrobial use in the community, with antibiotic use been described as one of the main factors contributing to the emergence of antimicrobial resistance (AMR) [3]. The rise of AMR has been postulated as one of the major challenges for health care worldwide [4]. It is related to increased morbidity, mortality and cost, particularly in vulnerable populations such as the elderly [4]. The World Health Organization Global Action Plan to Reduce Antimicrobial Resistance [5] includes improving antimicrobial use across all human and animal health, and environment settings through a One Health approach. Rates of AMR amongst gram-negative bacteria have progressively increased in the last decade in the European Union [6], with particularly concerning rise of carbapenemase-producing and extended-spectrum-beta-lactamase organisms [7].

Currently, most clinical guidelines recommend that primary care diagnosis and management of uncomplicated UTI should be done empirically [8][9], thus based on clinical symptoms. Although this approach has proven to be cost-effective [10], prescribing without diagnostic certainty increases the use of potentially unnecessary antibiotics, and contributes to the problem of antimicrobial resistance [11]. Up to 90% of patients presenting to primary care with urinary symptoms receive an antibiotic [7,12] but it is unclear how many will have a proven infection. Available evidence on how well symptoms predict the presence of a true UTI has shown diverging results, when compared to gold standard (urine culture). The probability of a female patient presenting to primary care with typical UTI symptoms and having a real infection is estimated to be between 50-80%, with the greatest predictability for haematuria, and if combined with a positive urine dipstick [13,14]. Therefore, alternative tests with enhanced diagnostic accuracy could potentially reduce inappropriate antimicrobial use in this context.

The gold standard for UTI diagnosis is urine culture from a midstream, clean urine catch. However, it is slow, requiring at least 24–48 hours to report the causative microorganism and provide an antibiotic resistance profile [15]. As previously mentioned, urine culture is not always performed, especially in primary care and emergency departments, where diagnosis of most UTIs occurs [16] . As result of this, different point-of-care tests (POC) have been developed aiming to provide a more rapid and accurate method for detecting infection. Point-of-care testing is defined as ‘diagnostic testing, performed at or near the site where clinical care is delivered’ [17]. POC test diagnostic accuracy is influenced dramatically from pre-test probability in different subpopulations [19] and consequently, its ability to detect or discard infection can be variable [20][21]. Potentially, an ‘ideal’ POC would allow for more timely

identification of UTIs, facilitating improved, targeted treatment, and reduced inappropriate antibiotic use. Indirect methods, such as urine dipsticks, which detect host inflammatory response rather than bacterial presence, have become the main POCT for UTIs [22]. Other techniques include culture-based devices, enzymatic assays and semi-automated urine analysers [23]. Previous reports suggest that their diagnostic accuracy could be greater than that of simpler urine dipsticks [16]. These tests could provide relevant information to clinicians to prescribe antimicrobials more accurately, reducing antibiotic-related harms (including resistance), and costs [24]. However, it is difficult to ascertain which POC could be better for diagnosing UTIs in general and in specific situations.

Our aim is to systematically review and meta-analyse the diagnostic test accuracy of currently available point-of-care tests for urinary tract infections, as compared to gold standard (urine culture).

METHODS AND ANALYSIS

Eligibility criteria

Randomized clinical trials (RCTs), cluster RCTs, evaluation studies, observational studies and regulatory or approval evidence reports (if available), evaluating point-of-care diagnostic tests for UTI in symptomatic patients versus urine culture (gold standard) [7] will be included, from both primary or secondary care settings. No particular index test was pre-specified in our review search criteria, as we aimed to capture and compare all available tests. However, only those tests that could be categorised as 'point-of-care test' will be included, defined as the tests that can be carried out in close proximity to the patient, without involvement of laboratory facilities [25]. Inclusion criteria are detailed in **Box 1**, following the PIRD approach (Participants, Index test, Target condition, Reference standard) for including studies in systematic reviews of diagnostic test accuracy [26].

Box 1. Inclusion criteria

Participants:	Adults
Presentation:	Symptomatic UTIs (dysuria, polyuria, urgency and/or suprapubic pain)[13]
Index test(s):	Any point-of-care diagnostic test
Target condition:	Urinary Tract Infections
Reference Standard:	Urine culture

Studies with the following characteristics will be excluded:

- Studies evaluating the detection of asymptomatic bacteriuria in pregnancy.
- Studies performed only in children.
- Tests aimed at detecting sexually transmitted infections, or non-bacterial infections (e.g. schistosomiasis).
- Tests based on biomarkers needing laboratory facilities.
- Studies whose main outcome measure is to detect complications of urinary infections (e.g. CT scans or other imaging techniques).
- Clinical algorithms or self-reported symptom tests.
- Specific populations will be excluded: urinary catheterized patients, kidney transplantation, terminal kidney failure or immunocompromised patients, patients with spinal cord injury or neurogenic bladder.

Information sources & Search

MEDLINE, Web of Science, EMBASE and Cochrane Database of Systematic Reviews were searched from database inception to 8th October 2018 with no language restrictions. Only studies involving human health were included. The search included a combination of the following terms: "Urinary Tract Infections/diagnosis", "Diagnostic Tests, Routine", Point-of-Care Systems", "Point-of-Care Testing", "point-of-care testing", 'near-patient testing,' 'RDT', "poct", "Diagnostic Technics and Procedures", "Techni* and Procedures, Diagnostic", "rapid diagnostic test*", AND "Urinary Tract Infections", "Pyuria", "Bacteriuria", "uti", AND "sensitivity", "specificity". The full search strategy is available in **Appendix 1** and online in PROSPERO's database [27].

Study selection

Three reviewers (DFN, AAL and VHS) will independently assess study eligibility for inclusion. A calibration exercise assessing 10% of the results by title and abstract will be done in duplicate. After title and abstract screening, selected articles will be screened full-text. Discrepancies will be solved by discussion. Another reviewer will be involved as necessary (FS).

Data collection process

A standardised data extraction form will be developed. The review team (DFN, AAL and VHS) will independently extract the data from all studies. Study authors will be contacted if no data is available.

Diagnostic accuracy measures

A 2x2 contingency table with true positives, true negatives, false positives and false negatives will be extracted from each study. Accuracy outcome measures will include: sensitivity, specificity, positive and negative predictive values.

Definitions for data extraction

From each study, besides the accuracy-related data already specified, we will extract the following predefined set of characteristics:

- Device/Product name.
- Manufacturer/ Country of origin.
- Regulatory approval status in the EU and US.
- Type of sample used (clean urine midstream catch, or other).
- Method principle (culture-based, enzymatic assay, other).
- Analysis time (time required, in minutes).
- Additional training required.
- Need for supplementary equipment (e.g. sterilizer, centrifuge…).
- Type of result provided if the test is positive (presence of infection, bacterial load, antibiotic sensitivity, indirect method for detection).
- The threshold for positivity detection, in Unit Forming Colonies (UFC).
- Population tested.
- Secondary outcomes: Mortality, Hospitalisation, Quality of life (QoL) measures and or patients' preferences, if reported.

Risk of bias

Methodological quality assessment will be conducted using the QUADAS-2 tool (Quality Assessment of Diagnostic Accuracy studies) [28].

Synthesis of results

A narrative description summarising the pre-specified characteristics of each test, and a paired sensitivity-specificity forest plot, will be provided. Meta-analysis will be performed depending on available data, sources of heterogeneity, comparability between methods and ability to aggregate data. If enough data is available, random-effects meta-analysis will be performed for each index test. The bivariate model will be used to ascertain summary sensitivity and specificity if all studies in the group use the same threshold value for positivity. If index tests use different threshold values, the hierarchical summary ROC model will be used instead, to obtain summary sensitivity and specificity for each threshold value. Sources of heterogeneity will be investigated, regarding index test used, threshold for detection, target population included in the study and its given (if reported) pre-test probability. Subgroup analysis will be explored and performed depending on the heterogeneity found.

Patients and Public Involvement

Patients or the public were not involved in the design of our research. However, the findings from this review will be shared with key stakeholders, including patient groups, clinicians and guideline developers, and will also be presented and national and international conferences.

ETHICS AND DISSEMINATION

Ethical approval was explored with the University of St Andrews School of Medicine Research and Ethics Committee but was not necessary due to the nature of the research (literature review). Results from this review will be shared with key stakeholders, including patient groups, clinicians and guideline developers, and will potentially inform future diagnostic and treatment pathways.

Authors' contributions:

VHS conceived the idea. The protocol was developed by DFN, FS, AAL and VHS. DFN performed the search strategy. VHS, DFN and AAL will contribute to design the data extraction form, screen manuscripts, extract data from individual studies and assess study quality. FS will act as a third reviewer in case of discrepancy. DFN redacted the original draft of the protocol. All authors reviewed and contributed to subsequent drafts and read and approved the final draft.

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Competing interests' statement:

The authors declare no competing interests related to the production of this review.

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APPENDIX 1 – SEARCH STRATEGY

PUBMED

(("Urinary Tract Infections/diagnosis"[Mesh]) OR ("Diagnostic Tests, Routine"[Mesh]) OR ("Point-of-Care Systems"[Mesh]) OR ("Point-of-Care Testing"[Mesh]) OR ("point-of-care testing"[tw]) OR ('near-patient testing'[tw]) OR ('RDT'[tiab]) OR ("poct"[tw]) OR ("Diagnostic Technics and Procedures"[Mesh]) OR ("Techni* and Procedures, Diagnostic"[Mesh]) OR ("rapid diagnostic test*"[tiab])) AND (("Urinary Tract Infections"[Mesh]) OR ("Pyuria"[Mesh]) OR ("Bacteriuria"[Mesh]) OR ("uti"[tiab])) AND (("sensitivity"[tiab]) OR ("specificity"[tiab]))

EMBASE

('urinary tract infection$'/exp OR 'uti'/exp OR 'pyuria'/exp OR 'bacteriuria'/exp) AND ('urinary tract infections diagnosis'/exp OR 'rapid diagnostic test'/exp OR 'point of care test'/exp OR 'poct'/exp OR 'near patient'/exp)

Web of Science

TS=(urinary tract infection* OR pyuria OR bacteriuria OR uti) AND TS=(point of care OR point-of-care OR near-patient OR diagnostic test* OR poct) AND TS=(sensitivity OR specificity)

Cochrane Database of Systematic Reviews

“Urinary tract infections” AND “diagnosis”

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Primary Subject Heading:	General practice / Family practice
Secondary Subject Heading:	Infectious diseases, Health services research, Diagnostics
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Introduction

Urinary tract infections (UTIs) are the second most common type of infection worldwide, accounting for a large number of primary care consultations and antibiotic prescribing. Current diagnosis is based on an empirical approach, relying on symptoms and occasional use of urine dipsticks. The diagnostic reference standard is still urine culture, although it is not routinely recommended for uncomplicated UTIs in the community, due to time to diagnosis (48h). Faster Point-of-care tests have been developed, but their diagnostic accuracy has not been compared. Our objective is to systematically review and meta-analyse the diagnostic accuracy of currently available point-of-care tests for urinary tract infections.

Methods and analysis

Studies evaluating the diagnostic accuracy of point-of-care tests for urinary tract infections will be included. Pubmed, Web of Science, EMBASE and Cochrane Database of Systematic Reviews were searched from inception to the 1st June 2019. Data extraction and risk of bias assessment will be assessed using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool. Meta-analysis will be performed depending on data availability and heterogeneity.

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Keywords

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Strengths and limitations of this study *(first point deleted)*

- To our knowledge, this is the first systematic review that formally analyses and compares the diagnostic accuracy of currently available point-of-care tests for UTI diagnosis.
- The results from this study will help identify the best available point-of-care test to diagnose UTIs in the primary care setting.
- It is likely significant heterogeneity will be found as all available tests will be explored, and meta-analysis will be performed to account for this.
- Studies involving paediatric population (<18 years old) or populations with certain conditions (detailed in exclusion criteria) will be excluded, as well as studies aimed at screening of asymptomatic bacteriuria, which may affect the generalisability of the results out with these situations.

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Currently, most clinical guidelines recommend that primary care diagnosis and management of uncomplicated UTI should be done empirically [8][9], thus based on clinical symptoms. Although this approach has proven to be cost-effective [10], prescribing without diagnostic certainty increases the use of potentially unnecessary antibiotics, and contributes to the problem of antimicrobial resistance [11]. Up to 90% of patients presenting to primary care with urinary symptoms receive an antibiotic [7,12] but it is usually without further investigation, so it is unclear how many will have a proven infection. Available evidence on how well symptoms predict the presence of a true UTI has shown diverging results, when compared to gold standard (urine culture). The probability of a female patient presenting to primary care with typical UTI symptoms and having a confirmed infection is estimated to be between 50-80%, with the greatest predictability for haematuria, and if combined with a positive urine dipstick [13,14]. Therefore, alternative tests with enhanced diagnostic accuracy could potentially reduce inappropriate antimicrobial use in this context.

The gold standard for UTI diagnosis is urine culture from a midstream, clean urine catch, but as previously mentioned, urine culture is not always performed, especially in primary care and emergency departments, where diagnosis of most UTIs occurs [15]. Urine culture is slow, requiring at least 24-48 hours to report the causative microorganism and provide an antibiotic resistance profile [16], and symptoms are usually distressing enough to prompt on the day empirical management, as since acutely unwell patients with UTI symptoms may not be prepared to wait up to 48 hours for a culture result. Current clinical guidelines also advocate empirical treatment if symptoms are sufficiently suggestive of a diagnosis of UTI [9]. Empirical decision-making will often result in the patient getting an antibiotic without infection confirmation. As result of this, different point-of-care tests (POCT) have been

developed aiming to provide a more rapid and accurate method for detecting infection. Point-of-care testing has been defined as 'a test to support clinical decision making, performed nearby the patient and on any part of the patient's body or its derivates, to help the patient and healthcare professional upon the best management approach during or very close to the time of the consultation, with results available at the time of clinical decision making' [17]. POCT diagnostic accuracy is influenced dramatically from pre-test probability in different subpopulations [18] and consequently, its ability to detect or discard infection can be variable [19][20]. Potentially, an 'ideal' POCT would allow for more timely identification of UTIs, facilitating improved, targeted treatment, and reduced inappropriate antibiotic use. Indirect methods, such as urine dipsticks, which detect host inflammatory response rather than bacterial presence, have become the main POCT for UTIs [21]. Other techniques include culture-based devices, enzymatic assays and semi-automated urine analysers [22]. Previous reports suggest that their diagnostic accuracy could be greater than that of simpler urine dipsticks [16]. These tests could provide relevant information to clinicians to prescribe antimicrobials more accurately, reducing antibiotic-related harms (including resistance), and costs [23]. However, it is difficult to ascertain which POCT could be better for diagnosing UTIs in general and in specific situations.

Our aim is to systematically review and meta-analyse the diagnostic test accuracy of currently available point-of-care tests for urinary tract infections, as compared to gold standard (urine culture).

METHODS AND ANALYSIS

Eligibility criteria

Randomized clinical trials (RCTs), cluster RCTs, evaluation studies, observational studies and regulatory or approval evidence reports (if available), evaluating point-of-care diagnostic tests for UTI in symptomatic patients versus urine culture (reference standard) [7] will be included, from both primary or secondary care settings. No particular index test was pre-specified in our review search criteria, as we aimed to capture and compare all available tests. However, only those tests that could be categorised as 'point-of-care test' will be included, defined as above [17]. Inclusion criteria are detailed in **Box 1**, following the PIRD approach (Participants, Index test, Target condition, Reference standard) for including studies in systematic reviews of diagnostic test accuracy [24].

Box 1. Inclusion criteria

Participants:	Adults
Presentation:	Symptomatic UTIs (dysuria, polyuria, urgency and/or suprapubic pain)[13]
Index test(s):	Any point-of-care diagnostic test
Target condition:	Urinary Tract Infections
Reference Standard:	Urine culture

The search strategy uses broad terms for defining UTI with the aim of capturing all potentially relevant studies looking at POCT used in symptomatic UTIs. Classical symptoms include those mentioned in Box 1 above, and we will also examine different symptoms / combinations and UTI definition used in each study. Exclusion criteria will be applied and are detailed below. These include:

- Studies evaluating the detection of asymptomatic bacteriuria in pregnancy.
- Studies performed only in children.
- Tests aimed at detecting sexually transmitted infections, or non-bacterial infections (e.g. schistosomiasis).
- Tests based on biomarkers needing laboratory facilities.
- Studies whose main outcome measure is to detect complications of urinary infections (e.g. CT scans or other imaging techniques).
- Clinical algorithms or self-reported symptom tests.
- Specific populations will be excluded: urinary catheterized patients, kidney transplantation, terminal kidney failure or immunocompromised patients, patients with spinal cord injury or neurogenic bladder.

Information sources & Search

MEDLINE, Web of Science, EMBASE and Cochrane Database of Systematic Reviews were searched from database inception to 1st June 2019 with no language restrictions. Only studies involving human health were included. The search included a combination of the following terms: "Urinary Tract Infections/diagnosis", "Diagnostic Tests, Routine", Point-of-Care Systems", "Point-of-Care Testing", "point-of-care testing", 'near-patient testing,' 'RDT', "poct", "Diagnostic Technics and Procedures", "Techni* and Procedures, Diagnostic", "rapid diagnostic test*", AND "Urinary Tract Infections", "Pyuria", "Bacteriuria", "uti", AND "sensitivity", "specificity". The full search strategy is available in **Appendix 1** and online in PROSPERO's database [25].

Data management

Search results will be stored in EndNote version X8.2 bibliography management software. To synthetize and develop study selection, data extraction and quality assessment we will use Covidence platform [26].

Study selection

Three reviewers (DFN, AAL and VHS) will independently assess study eligibility for inclusion. A calibration exercise assessing 10% of the results by title and abstract will be done in duplicate. After title and abstract screening, selected articles will be screened full-text. Discrepancies will be solved by discussion. Another reviewer will be involved as necessary (FS).

Data collection process

A standardised data extraction form will be developed. The review team (DFN, AAL and VHS) will independently extract the data from all studies. Study authors will be contacted if no data is available. All articles will be double-extracted, and risk of bias will be double-assessed. Discrepancies will be evaluated and solved by discussion, and if no agreement, a third reviewer will be involved.

Diagnostic accuracy measures

A 2x2 contingency table with true positives, true negatives, false positives and false negatives will be extracted from each study. Accuracy outcome measures will include: sensitivity, specificity, positive and negative predictive values.

Definitions for data extraction

From each study, besides the accuracy-related data already specified, we will extract the following predefined set of characteristics:

- Device/Product name.
- Manufacturer/ Country of origin.
- Regulatory approval status in the EU and US.
- Type of sample used (clean urine midstream catch, or other).
- Method principle (culture-based, enzymatic assay, other).
- Analysis time (time required, in minutes).
- Additional training required.
- Need for supplementary equipment (e.g. sterilizer, centrifuge…).
- Cost.
- Type of result provided if the test is positive (presence of infection, bacterial load, antibiotic sensitivity, indirect method for detection).
- The threshold for positivity detection, in Unit Forming Colonies (UFC).

- Population tested.
- UTI definition used.
- Secondary outcomes: Mortality, Hospitalisation, Quality of life (QoL) measures and or patients' preferences, if reported.

Risk of bias

Methodological quality assessment will be conducted using the QUADAS-2 tool (Quality Assessment of Diagnostic Accuracy studies) [27].

Synthesis of results

A narrative description summarising the pre-specified characteristics of each test, and a paired sensitivity-specificity forest plot, will be provided. Meta-analysis will be performed depending on available data, sources of heterogeneity, comparability between methods and ability to aggregate data. If enough data is available, random-effects meta-analysis will be performed for each index test. The bivariate model will be used to ascertain summary sensitivity and specificity if all studies in the group use the same threshold value for positivity. If index tests use different threshold values, the hierarchical summary ROC model will be used instead, to obtain summary sensitivity and specificity for each threshold value. Sources of heterogeneity will be investigated, regarding index test used, threshold for detection, target population included in the study and its given (if reported) pre-test probability. Subgroup analysis will be explored and performed depending on the heterogeneity found and available data, analysing separately studies looking at each POCT, and also different population groups (differentiating adults from elderly patients).

Patients and Public Involvement

Patients or the public were not involved in the design of our research. However, the findings from this review will be shared with key stakeholders, including patient groups, clinicians and guideline developers, and will also be presented and national and international conferences.

ETHICS AND DISSEMINATION

Ethical approval was explored with the University of St Andrews School of Medicine Research and Ethics Committee but was not necessary due to the nature of the research (literature review). Results from this review will be shared with key stakeholders, including patient groups, clinicians and guideline developers, and will potentially inform future diagnostic and treatment pathways.

Authors' contributions:

VHS conceived the idea. The protocol was developed by DFN, FS, AAL and VHS. DFN performed the search strategy. VHS, DFN and AAL will contribute to design the data extraction form, screen manuscripts, extract data from individual studies and assess study quality. FS will act as a third reviewer in case of discrepancy. DFN redacted the original draft of the protocol. All authors reviewed and contributed to subsequent drafts and read and approved the final draft.

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Competing interests' statement:

The authors declare no competing interests related to the production of this review.

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APPENDIX 1 – SEARCH STRATEGY

PUBMED

(("Urinary Tract Infections/diagnosis"[Mesh]) OR ("Diagnostic Tests, Routine"[Mesh]) OR ("Point-of-Care Systems"[Mesh]) OR ("Point-of-Care Testing"[Mesh]) OR ("point-of-care testing"[tw]) OR ('near-patient testing'[tw]) OR ('RDT'[tiab]) OR ("poct"[tw]) OR ("Diagnostic Technics and Procedures"[Mesh]) OR ("Techni* and Procedures, Diagnostic"[Mesh]) OR ("rapid diagnostic test*"[tiab])) AND (("Urinary Tract Infections"[Mesh]) OR ("Pyuria"[Mesh]) OR ("Bacteriuria"[Mesh]) OR ("uti"[tiab])) AND (("sensitivity"[tiab]) OR ("specificity"[tiab]))

EMBASE

('urinary tract infection$'/exp OR 'uti'/exp OR 'pyuria'/exp OR 'bacteriuria'/exp) AND ('urinary tract infections diagnosis'/exp OR 'rapid diagnostic test'/exp OR 'point of care test'/exp OR 'poct'/exp OR 'near patient'/exp)

Web of Science

TS=(urinary tract infection* OR pyuria OR bacteriuria OR uti) AND TS=(point of care OR point-of-care OR near-patient OR diagnostic test* OR poct) AND TS=(sensitivity OR specificity)

Cochrane Database of Systematic Reviews

“Urinary tract infections” AND “diagnosis”

Appendix 2: PRISMA-P 2015 Checklist

This checklist has been adapted from Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 **4**:1

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	☒	☐	2
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	☐	☒	NA
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	☒	☐	63
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	☐	☐	8-32
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	☒	☐	267-273
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	☐	☒	NA
Support					
Sources	5a	Indicate sources of financial or other support for the review	☒	☐	274-279
Sponsor	5b	Provide name for the review funder and/or sponsor	☐	☒	NA
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	☐	☒	NA
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	☒	☐	83-143
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	☒	☐	144-146
METHODS					

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	☒	☐	148-182
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	☒	☐	184-186
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	☒	☐	186-192
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	☒	☐	193-196
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	☒	☐	197-202
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	☒	☐	203-208
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	☒	☐	209-232
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	☒	☐	209-212
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	☒	☐	234-236
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	☒	☐	237-251
	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 (e.g., I^2, Kendall's tau)	☒	☐	241-246
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	☒	☐	246-251
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	☒	☐	238-239
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	☐	☒	NA

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	☐	☒	NA

BMJ Open

Point-of-care tests for urinary tract infections: Protocol for a systematic review and meta-analysis of diagnostic test accuracy

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Primary Subject Heading:	General practice / Family practice
Secondary Subject Heading:	Infectious diseases, Health services research, Diagnostics
Keywords:	Diagnostic microbiology < INFECTIOUS DISEASES, Epidemiology < INFECTIOUS DISEASES, Molecular diagnostics < INFECTIOUS DISEASES, Urinary tract infections < UROLOGY

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Title: Point-of-care tests for urinary tract infections: Protocol for a systematic review and meta-analysis of diagnostic test accuracy.

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ABSTRACT

Introduction

Urinary tract infections (UTIs) are the second most common type of infection worldwide, accounting for a large number of primary care consultations and antibiotic prescribing. Current diagnosis is based on an empirical approach, relying on symptoms and occasional use of urine dipsticks. The diagnostic reference standard is still urine culture, although it is not routinely recommended for uncomplicated UTIs in the community, due to time to diagnosis (48h). Faster point-of-care tests have been developed, but their diagnostic accuracy has not been compared. Our objective is to systematically review and meta-analyse the diagnostic accuracy of currently available point-of-care tests for urinary tract infections.

Methods and analysis

Studies evaluating the diagnostic accuracy of point-of-care tests for urinary tract infections will be included. Pubmed, Web of Science, EMBASE and Cochrane Database of Systematic Reviews were searched from inception to the 1st June 2019. Data extraction and risk of bias assessment will be assessed using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool. Meta-analysis will be performed depending on data availability and heterogeneity.

Ethics and dissemination

This is a systematic review protocol and therefore formal ethical approval is not required, as no primary, identifiable, personal data will be collected. Patients or the public were not involved in the design of our research. However, the findings from this review will be shared with key stakeholders, including patient groups, clinicians and guideline developers, and will also be presented and national and international conferences.

Registration

The protocol is registered in PROSPERO, registration number: CRD42018112019

Keywords

Systematic Review, Urinary Tract Infections, Infectious Diseases, Diagnostic Accuracy, Point-of-care tests.

Strengths and limitations of this study

- To our knowledge, this is the first systematic review that formally analyses and compares the diagnostic accuracy of currently available point-of-care tests for UTI diagnosis.
- The results from this study will help identify the best available point-of-care test to diagnose UTIs in the primary care setting.
- It is likely significant heterogeneity will be found as all available tests will be explored, and meta-analysis will be performed to account for this.
- Studies involving paediatric population (<18 years old) or populations with certain conditions (detailed in exclusion criteria) will be excluded, as well as studies aimed at screening of asymptomatic bacteriuria, which may affect the generalisability of the results out with these situations.

INTRODUCTION:

Urinary tract infections (UTIs) are the second most common cause of infection in primary [1] and secondary care [2] and most women experience at least one episode of acute uncomplicated cystitis in their lifetime. In the United Kingdom, UTIs account for 1-3% of all consultations in primary care each year [1]. UTIs are also responsible for a major part of antibiotic prescriptions, accounting for up to 15% of antimicrobial use in the community, with antibiotic use been described as one of the main factors contributing to the emergence of antimicrobial resistance (AMR) [3]. The rise of AMR has been postulated as one of the major challenges for health care worldwide [4]. It is related to increased morbidity, mortality and cost, particularly in vulnerable populations such as the elderly [4]. The World Health Organization Global Action Plan to Reduce Antimicrobial Resistance [5] includes improving antimicrobial use across all human and animal health, and environment settings through a One Health approach. Rates of AMR amongst gram-negative bacteria have progressively increased in the last decade in the European Union [6], with particularly concerning rise of carbapenemase-producing and extended-spectrum-beta-lactamase organisms [7].

Currently, most clinical guidelines recommend that primary care diagnosis and management of uncomplicated UTI should be done empirically [8][9], thus based on clinical symptoms. Although this approach has proven to be cost-effective [10], prescribing without diagnostic certainty increases the use of potentially unnecessary antibiotics, and contributes to the problem of antimicrobial resistance [11]. Up to 90% of patients presenting to primary care with urinary symptoms receive an antibiotic [7,12] but it is usually without further investigation, so it is unclear how many will have a proven infection. Available evidence on how well symptoms predict the presence of a true UTI has shown diverging results, when compared to gold standard (urine culture). The probability of a female patient presenting to primary care with typical UTI symptoms and having a confirmed infection is estimated to be between 50-80%, with the greatest predictability for haematuria, and if combined with a positive urine dipstick [13,14]. Therefore, alternative tests with enhanced diagnostic accuracy could potentially reduce inappropriate antimicrobial use in this context.

The gold standard for UTI diagnosis is urine culture from a midstream, clean urine catch, but as previously mentioned, urine culture is not always performed, especially in primary care and emergency departments, where diagnosis of most UTIs occurs [15]. Urine culture is slow, requiring at least 24-48 hours to report the causative microorganism and provide an antibiotic resistance profile [16], and symptoms are usually distressing enough to prompt on the day empirical management, since acutely unwell patients with UTI symptoms may not be prepared to wait up to 48 hours for a culture result. Current clinical guidelines also advocate empirical treatment if symptoms are sufficiently suggestive of a diagnosis of UTI [9]. Empirical decision-making will often result in the patient getting an antibiotic without infection confirmation. As result of this, different point-of-care tests (POCT) have been

developed aiming to provide a more rapid and accurate method for detecting infection. Point-of-care testing has been defined as 'a test to support clinical decision making, performed nearby the patient and on any part of the patient's body or its derivates, to help the patient and healthcare professional upon the best management approach during or very close to the time of the consultation, with results available at the time of clinical decision making' [17]. POCT diagnostic accuracy is influenced dramatically from pre-test probability in different subpopulations [18] and consequently, its ability to detect or discard infection can be variable [19][20]. Potentially, an 'ideal' POCT would allow for more timely identification of UTIs, facilitating improved, targeted treatment, and reduced inappropriate antibiotic use. Indirect methods, such as urine dipsticks, which detect host inflammatory response rather than bacterial presence, have become the main POCT for UTIs [21]. Other techniques include culture-based devices, enzymatic assays and semi-automated urine analysers [22]. Previous reports suggest that their diagnostic accuracy could be greater than that of simpler urine dipsticks [16]. These tests could provide relevant information to clinicians to prescribe antimicrobials more accurately, reducing antibiotic-related harms (including resistance), and costs [23]. However, it is difficult to ascertain which POCT could be better for diagnosing UTIs in general and in specific situations.

Our aim is to systematically review and meta-analyse the diagnostic test accuracy of currently available point-of-care tests for urinary tract infections, as compared to gold standard (urine culture).

METHODS AND ANALYSIS

Eligibility criteria

Randomized clinical trials (RCTs), cluster RCTs, evaluation studies, observational studies and regulatory or approval evidence reports (if available), evaluating point-of-care diagnostic tests for UTI in symptomatic patients versus urine culture (reference standard) [7] will be included, from both primary or secondary care settings. No particular index test was pre-specified in our review search criteria, as we aimed to capture and compare all available tests. However, only those tests that could be categorised as 'point-of-care test' will be included, defined as above [17]. Inclusion criteria are detailed in **Box 1**, following the PIRD approach (Participants, Index test, Target condition, Reference standard) for including studies in systematic reviews of diagnostic test accuracy [24].

Box 1. Inclusion criteria

Participants:	Adults
Presentation:	Symptomatic UTIs (variously defined) [13]
Index test(s):	Any point-of-care diagnostic test
Target condition:	Urinary Tract Infections
Reference Standard:	Urine culture

The search strategy uses broad terms for defining UTI with the aim of capturing all potentially relevant studies looking at POCT used in symptomatic UTIs. Classical symptoms include those mentioned in Box 1 above, and we will also examine different symptoms / combinations and UTI definition used in each study. Exclusion criteria will be applied and are detailed below. These include:

- Studies evaluating the detection of asymptomatic bacteriuria in pregnancy.
- Studies performed only in children.
- Tests aimed at detecting sexually transmitted infections, or non-bacterial infections (e.g. schistosomiasis).
- Tests based on biomarkers needing laboratory facilities.
- Studies whose main outcome measure is to detect complications of urinary infections (e.g. CT scans or other imaging techniques).
- Clinical algorithms or self-reported symptom tests.
- Specific populations will be excluded: urinary catheterized patients, kidney transplantation, terminal kidney failure or immunocompromised patients, patients with spinal cord injury or neurogenic bladder.

Information sources & Search

MEDLINE, Web of Science, EMBASE and Cochrane Database of Systematic Reviews were searched from database inception to 1st June 2019 with no language restrictions. Only studies involving human health were included. The search included a combination of the following terms: "Urinary Tract Infections/diagnosis", "Diagnostic Tests, Routine", Point-of-Care Systems", "Point-of-Care Testing", "point-of-care testing", 'near-patient testing,' 'RDT', "poct", "Diagnostic Technics and Procedures", "Techni* and Procedures, Diagnostic", "rapid diagnostic test*", AND "Urinary Tract Infections", "Pyuria", "Bacteriuria", "uti", AND "sensitivity", "specificity", "likelihood ratio", "predictive value", "diagnostic accuracy", "AUC", "PPV", "NPV", among other. The full search strategy is available in **Appendix 1** and online in PROSPERO's database [25].

Data management

Search results will be stored in EndNote version X8.2 bibliography management software. To synthetize and develop study selection, data extraction and quality assessment we will use Covidence platform [26].

Study selection

Three reviewers (DFN, AAL and VHS) will independently assess study eligibility for inclusion. A calibration exercise assessing 10% of the results by title and abstract will be done in duplicate. After title and abstract screening, selected articles will be screened full-text. Discrepancies will be solved by discussion. Another reviewer will be involved as necessary (FS).

Data collection process

A standardised data extraction form will be developed. The review team (DFN, AAL and VHS) will independently extract the data from all studies. Study authors will be contacted if no data is available. All articles will be double-extracted, and risk of bias will be double-assessed. Discrepancies will be evaluated and solved by discussion, and if no agreement, a third reviewer will be involved.

Diagnostic accuracy measures

A 2x2 contingency table with true positives, true negatives, false positives and false negatives will be extracted from each study. Accuracy outcome measures will include: sensitivity, specificity, positive and negative predictive values.

Definitions for data extraction

From each study, besides the accuracy-related data already specified, we will extract the following predefined set of characteristics:

- Device/Product name.
- Manufacturer/ Country of origin.
- Regulatory approval status in the EU and US.
- Type of sample used (clean urine midstream catch, or other).
- Method principle (culture-based, enzymatic assay, other).
- Analysis time (time required, in minutes).
- Additional training required.
- Need for supplementary equipment (e.g. sterilizer, centrifuge…).
- Cost.
- Type of result provided if the test is positive (presence of infection, bacterial load, antibiotic sensitivity, indirect method for detection).
- The threshold for positivity detection, in Unit Forming Colonies (UFC).

- Population tested.
- UTI definition used.
- Secondary outcomes: Mortality, Hospitalisation, Quality of life (QoL) measures and / or patients' preferences, if reported.

Risk of bias

Methodological quality assessment will be conducted using the QUADAS-2 tool (Quality Assessment of Diagnostic Accuracy studies) [27].

Synthesis of results

A narrative description summarising the pre-specified characteristics of each test, and a paired sensitivity-specificity forest plot, will be provided. Meta-analysis will be performed depending on available data, sources of heterogeneity, comparability between methods and ability to aggregate data. If enough data is available, random-effects meta-analysis will be performed for each index test. The bivariate model will be used to ascertain summary sensitivity and specificity if all studies in the group use the same threshold value for positivity. If index tests use different threshold values, the hierarchical summary ROC model will be used instead, to obtain summary sensitivity and specificity for each threshold value. Sources of heterogeneity will be investigated, regarding index test used, threshold for detection, target population included in the study and its given (if reported) pre-test probability. Subgroup analysis will be explored and performed depending on the heterogeneity found and available data, analysing separately studies looking at each POCT, and also different population groups (differentiating adults from elderly patients).

Patients and Public Involvement

Patients or the public were not involved in the design of our research. However, the findings from this review will be shared with key stakeholders, including patient groups, clinicians and guideline developers, and will also be presented and national and international conferences.

ETHICS AND DISSEMINATION

Ethical approval was explored with the University of St Andrews School of Medicine Research and Ethics Committee but was not necessary due to the nature of the research (literature review). Results from this review will be shared with key stakeholders, including patient groups, clinicians and guideline developers, and will potentially inform future diagnostic and treatment pathways.

Authors' contributions:

VHS conceived the idea. The protocol was developed by DFN, FS, AAL and VHS. DFN performed the search strategy. VHS, DFN and AAL will contribute to design the data extraction form, screen manuscripts, extract data from individual studies and assess study quality. FS will act as a third reviewer in case of discrepancy. DFN redacted the original draft of the protocol. All authors reviewed and contributed to subsequent drafts and read and approved the final draft.

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Competing interests' statement:

The authors declare no competing interests related to the production of this review.

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APPENDIX 1 – SEARCH STRATEGY

PUBMED

(("Urinary Tract Infections/diagnosis"[Mesh]) OR ("Diagnostic Tests, Routine"[Mesh]) OR ("Point-of-Care Systems"[Mesh]) OR ("Point-of-Care Testing"[Mesh]) OR ("point-of-care testing"[tw]) OR ('near-patient testing'[tw]) OR ('RDT'[tiab]) OR ("poct"[tw]) OR ("Diagnostic Technics and Procedures"[Mesh]) OR ("Techni* and Procedures, Diagnostic"[Mesh]) OR ("rapid diagnostic test*"[tiab])) AND (("Urinary Tract Infections"[Mesh]) OR ("Pyuria"[Mesh]) OR ("Bacteriuria"[Mesh]) OR ("uti"[tiab])) AND (("sensitivity"[tiab]) OR ("specificity"[tiab]) OR "likelihood ratio"[tiab]) OR ("predictive value"[tiab]) OR ("diagnostic accuracy"[tiab]) OR ("DOR"[tiab]) OR ("AUC"[tiab]) OR ("PPV"[tiab]) OR ("NPV"[tiab]))

EMBASE

('urinary tract infection$'/exp OR 'uti'/exp OR 'pyuria'/exp OR 'bacteriuria'/exp) AND ('urinary tract infections diagnosis'/exp OR 'rapid diagnostic test'/exp OR 'point of care test'/exp OR 'poct'/exp OR 'near patient'/exp)

Web of Science

TS=(urinary tract infection* OR pyuria OR bacteriuria OR uti) AND TS=(point of care OR point-of-care OR near-patient OR diagnostic test* OR poct) AND TS=(sensitivity OR specificity OR likelihood ratio OR predictive value* OR diagnostic accuracy OR DOR OR AUC OR PPV OR NPV)

Cochrane Database of Systematic Reviews

“Urinary tract infections” AND “diagnosis”

PRISMA-P 2015 Checklist

This checklist has been adapted for use with protocol submissions to *Systematic Reviews* from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 **4**:1

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	☒	☐	1-4
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	☐	☒	NA
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	☒	☐	63
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	☐	☐	5-32
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	☒	☐	269-275
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	☐	☒	NA
Support					
Sources	5a	Indicate sources of financial or other support for the review	☒	☐	276-281
Sponsor	5b	Provide name for the review funder and/or sponsor	☐	☒	NA
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	☐	☒	NA
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	☒	☐	83-146
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	☒	☐	144-146
METHODS					
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	☒	☐	148-182

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	☒	☐	183-194
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	☒	☐	183-194
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	☒	☐	195-198
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	☒	☐	199-204
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	☒	☐	205-210
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	☒	☐	211-234
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	☒	☐	211-214
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	☒	☐	236-238
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	☒	☐	239-253
	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 (e.g., I^2, Kendall's tau)	☒	☐	244-250
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	☒	☐	250-253
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	☒	☐	240-243
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	☐	☒	NA
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	☐	☒	NA