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Strategies to reduce antibiotic use in women with uncomplicated urinary tract infection in primary care: protocol of a systematic review and meta-analysis including individual patient data

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ABSTRACT

Introduction Uncomplicated urinary tract infection (UTI) in women is a common reason to present in general practice and is usually treated with antibiotics to reduce symptom severity and duration. Results of recent clinical trials indicate that non-antibiotic treatment approaches can also be effective. However, it remains unclear which patients would benefit from antibiotic treatment and which can effectively and safely be treated without antibiotics. This systematic review and meta-analysis aims to estimate the effect of treatment strategies to reduce antibiotic use in comparison with immediate antibiotic treatment and to identify prognostic factors and moderators of treatment effects. A further aim is to identify subgroups of patients benefiting from a specific therapy.

Methods and analysis A systematic literature search will be performed to identify randomised controlled trials which investigated the effect of treatment strategies to reduce antibiotic use in female adults with uncomplicated UTI compared with immediate antibiotic treatment. Therefore, the primary outcome of the meta-analysis is incomplete recovery. Anonymised individual patient data (IPD) will be collected. Aggregate data will be used for pairwise comparisons of treatment strategies using meta-analysis models with random effects accounting for potential between-study heterogeneity. Potential effect moderators will be explored in meta-regressions. For IPD, generalised linear mixed models will be used, which may be adjusted for baseline characteristics. Interactions of baseline variables with treatment effects will be explored. These models will be used to assess direct comparisons of treatment, but might be extended to networks.

Ethics and dissemination The local institutional review and ethics board judged the project a secondary analysis of existing anonymous data which meet the criteria for waiver of ethics review. Dissemination of the results will be via published scientific papers and presentations. Key messages will be promoted for example, via social media or press releases.

PROSPERO registration number CRD42019125804.

Strengths and limitations of this study

- This is the first individual patient data (IPD) meta-analysis to evaluate the effectiveness of experimental strategies to reduce antibiotic use in women with uncomplicated urinary tract infection in comparison with immediate antibiotic treatment.
- A clinical prognostic model will be developed in order to identify women who can be treated without (immediate) antibiotics effectively and safely and to facilitate an individualised treatment approach.
- The use of IPD will allow for detailed modelling aimed towards personalised treatment recommendations.
- The joint analysis of data from several studies will enhance the external validity of findings and the assessment thereof.
- The set of included studies may be subject to selection biases (eg, reporting bias, data availability bias) and may be heterogeneous in design, study population and intervention used.

INTRODUCTION

Uncomplicated urinary tract infection (UTI) is a common condition affecting mostly women with a lifetime prevalence of 50% and is a common reason for women to present to general practice.[1 2] Generally, primary care guidelines recommend immediate antibiotics as a first-line treatment.[3] Consequently, UTI is among the most common causes for antibiotic prescription in primary care.[4–8]

Therefore, efforts to reduce their prescription are highly appreciated to reduce levels of antibiotic resistance. Physicians tend to overestimate the need and demand for antibiotics, and to prescribe them rather liberally although many women prefer non-antibiotic strategies to treat UTI if this is reliable and safe.[2 5 9] Furthermore, the selective effect of antibiotics on antimicrobial resistance increasingly forces physicians to prescribe second-line antibiotics.[10] Non-antibiotic treatment approaches as well as delayed prescription of antibiotics for UTI were tested in several randomised controlled trials (RCTs) showing reduced antibiotic use, but also delayed resolution of symptoms.[11–16] In most of these trials, the chosen strategies could substantially reduce the number of antibiotic courses in women with uncomplicated UTI, but this was traded off by a somewhat higher symptom severity or longer symptom duration and a few more cases of febrile UTI, worsening symptoms or pyelonephritis. Overall, the results of the trials suggest that symptomatic treatment is effective, but it may not be the method of choice for every woman with uncomplicated UTI. Thus, reducing antibiotic prescribing can be impeded by uncertainty regarding which patients with UTI symptoms would benefit from antibiotic treatment and which ones can effectively and safely be treated without (immediate) antibiotics.

There is a lack of guidance as to when immediate antibiotic treatment may be appropriate, and when alternative measures may be adequate. Physicians usually use symptoms, signs and a point-of-care test (mostly dipsticks) to diagnose UTI, but predicting the outcome of uncomplicated UTIs will enable individualised treatment recommendations.

Therefore, the meta-analysis aims to (1) estimate the effect of experimental strategies to reduce antibiotic use in women with uncomplicated UTI compared with immediate antibiotic treatment as standard care; (2) identify moderators that modify treatment effects comparing experimental strategies with immediate antibiotic treatment and (3) identify prognostic factors at baseline associated with disease course of UTI in women allocated to experimental strategies and to develop a clinical prediction model to support treatment decisions in women with UTI.

METHODS AND ANALYSIS

In this systematic review and meta-analysis, RCTs comparing different strategies to reduce antibiotic use in women with uncomplicated UTI presenting to primary care will be identified and investigated. Individual patient data (IPD) will be collected to compare strategies aimed at reducing antibiotic use in women with uncomplicated UTI and immediate antibiotic treatment as a standard of care. If IPD are not available, aggregated results of the studies will at least be used for the estimation of treatment effects. The feasibility of a network meta-analysis will be investigated in order to allow for direct and indirect treatment comparisons. The present meta-analysis will be conducted in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[17] The PRISMA checklist can be found in the online supplemental file 1.

Population

The primary target population are female adults (aged 18 or older) with symptoms of an acute UTI presenting in general practice. In case results are stated only for mixed adult/adolescent populations, these will be considered as well, but paediatric populations (all younger than 18 years) will be excluded.

Interventions

The intervention is any experimental strategy to reduce antibiotic use (eg, symptomatic treatment with non-steroidal anti-inflammatory drugs, herbal treatments, placebo or delayed antibiotic prescription).

Controls

The control is immediate antibiotic treatment as standard care.

Outcomes

Related to objectives (1) and (2) the primary outcome is incomplete clinical recovery; defined as more than slight symptoms (this applies to at least one of the scores for dysuria, frequency, urgency that were assessed last between days 3 and 7) at days 3–7 or occurrence of pyelonephritis, febrile UTI and sepsis or subsequent antibiotic treatment during a follow-up of at least 14 days. To assess the primary outcome with respect to UTI symptoms, we chose the time period of 3–7 days since most RCTs demonstrated the duration of moderately bad or worse symptoms within 3–4 days and a symptom resolution within 7 days in most of included patients.[12 15 16 18] With respect to the criteria pyelonephritis and subsequent antibiotic treatment, we chose a follow-up period of at least 14 days. Uncomplicated UTI is a short condition and most RCTs followed up the patients for about 4 weeks. A longer follow-up period did not reveal changes regarding the complications and occurrence of recurrent UTI.[19] For this reason and in order to include all available evidence on this topic, we chose a follow-up period of at least 14 days.

Secondary outcomes are antibiotic use (number of antibiotic courses) during a follow-up of at least 14 days, symptom burden at day 2, symptom burden at days 3–7, clinical recovery (defined as a symptom score of 0 for dysuria, frequency and urgency) at days 3–7 and recurrent UTI. Safety outcomes are complications (pyelonephritis, febrile UTI, sepsis) and (serious) adverse events within at least 14 days, related to the treatment or due to other reasons. Worsening of UTI symptoms will not be treated as adverse events as these are related to the outcome of the meta-analysis.

Related to objective (3), outcomes for prognostic factors at baseline will be associated with disease course of UTI in women allocated to experimental strategies. The outcomes will be: (a) recovery without antibiotics

within 14 days (b) subsequent antibiotic treatment within at least 14 days (due to persistent/worsening symptoms, symptom relapse) (c) complications (eg, febrile UTI, pyelonephritis). Candidate prognostic factors and moderators will include age, presence, severity and duration of patient-reported symptoms (eg, dysuria, frequency, urgency, lower abdominal pain), physician-reported physical examination findings (eg, fever, loin pain), point-of-care tests (eg, dipstick test results, C reactive protein, urine sediment, other point-of-care tests) and other additional variables like the bladder incubation time, at the initial consultation or inclusion, if available.[20] Although urine culture results are not available at the time of the treatment decisions, we will investigate the results (positive or negative for the presence of uropathogens and antimicrobial resistance) as possible antibiotic effect moderators.

Study designs

RCTs will be included in the meta-analysis.

Search strategy

A comprehensive literature search will be conducted in the following databases: MEDLINE, EMBASE, Web of Science, Latin American and Caribbean Health Sciences Literature (LILACS), the Cochrane Database of Systematic Reviews, the Cochrane Central Register of Controlled Trials, the Health Technology Assessment Database (HTA) at the Centre for Reviews and Dissemination and ClinicalTrials.gov.

Publications from 1990 onwards will be considered. If feasible, results will be filtered for 'Clinical Study', and the search will be repeated without filter, but with publication dates from 2018 onwards to retrieve studies that have only recently been added to the database and may not be completely indexed. The search terms including relevant Medical Subject Headings and keywords are (urinary tract infection OR urinary tract infections OR UTI OR bacteriuria OR pyuria OR cystitis OR pyelonephritis) AND (antibiotic OR antibiotics OR anti-bacterial agents OR anti-microbial). Detailed search strategies for each literature database can be found in tables 1–6 and under the Search strategies: additional databases section.

Reference lists of included studies and relevant reviews will be checked to identify any additional relevant articles that were not captured by the search.

Table 1 PubMed—search strategy: first search with filter 'Clinical Study' and '1990/01/01 to 2019/12/31'

Search	Query
1	"urinary tract infections"[MeSH Terms] OR ("urinary"[All Fields] AND "tract"[All Fields] AND "infections"[All Fields]) OR "urinary tract infections"(All Fields)
2	("urinary"[All Fields] AND "tract"[All Fields] AND "infection"[All Fields]) OR "urinary tract infection"[All Fields]
3	UTI[All Fields]
4	"bacteriuria"[MeSH Terms] OR "bacteriuria"[All Fields]
5	"pyuria"[MeSH Terms] OR "pyuria"[All Fields]
6	"cystitis"[MeSH Terms] OR "cystitis"[All Fields]
7	"pyelonephritis"[MeSH Terms] OR "pyelonephritis"[All Fields]
8	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7
9	"anti-bacterial agents"[Pharmacological Action] OR "anti-bacterial agents"[MeSH Terms] OR ("anti-bacterial"[All Fields] AND "agents"[All Fields]) OR "anti-bacterial agents"[All Fields]
10	"antibiotic"[All Fields] OR "antibiotics"[All Fields]
11	"anti-microbial" [All Fields] OR ("anti" [All Fields] AND "microbial" [All Fields])
12	#9 OR #10 OR #11
13	#8 AND #12
14	#8 AND #12 Filters: Clinical Study
15	#8 AND #12 Filters: Clinical Study; Publication date from 1990/01/01 to 2019/12/31

MeSH, Medical Subject Headings.

Search strategies: additional databases

Latin American and Caribbean Health Sciences Literature

(tw:((mh: 'urinary tract infections' OR "urinary tract infection" OR "urinary tract infection*" OR ("urinary" AND "tract" AND "infection*") OR "uti" OR mh: "bacteriuria" OR "bacteriuria" OR mh: "pyuria" OR "pyuria" OR mh: "cystitis" OR "cystitis" OR mh: "pyelonephritis" OR "pyelonephritis"))) AND (tw:((mh: "anti-bacterial agents" OR ("anti-bacterial" AND agents) OR "anti-bacterial agents" OR mh: "antibiotic agent" OR "antibiotic*" OR "anti-microbial" OR ("anti" AND "microbial")))) AND (tw:((mh: "random allocation" OR ("random" AND "allocation") OR "random allocation" OR "randomised" OR "randomized" OR "controlled" OR "Clinical"))) AND (tw:((mh: "clinical trials as a topic" OR ("clinical" AND "trial") OR "clinical trial" OR "trial" OR "study" OR mh: "randomized controlled trials as a topic"))) AND (instance:"regional") AND (db:("LILACS"))

HTA Database of the Center for Reviews and Dissemination (limitation 1990–2019)

((urinary tract infection*) AND (bacteriuria) OR (antibiotic*)) and (Project record:ZDT OR Full publication record:ZDT) IN HTA FROM 1990 TO 2019

ClinicalTrials.gov (applied filters: Interventional, Female, Adult (18–64), Older Adult (65+))

(Urinary Tract Infections OR bacteriuria OR pyuria OR cystitis OR pyelonephritis) AND (antibiotics OR antibiotic OR anti-bacterial OR anti-microbial)

Study selection and quality assessment

Screening of the search results for relevant studies will be done by two reviewers independently. Title and abstract will be screened and studies that clearly do not meet the

Table 2 PubMed—search strategy: additional search without filter 'Clinical Study' and from 2018 onwards (to retrieve studies that have only recently been added to the database and may not be completely indexed in PubMed)

Search	Query
1	"urinary tract infections"[MeSH Terms] OR ("urinary"[All Fields] AND "tract"[All Fields] AND "infections"[All Fields]) OR "urinary tract infections"[All Fields]
2	("urinary"[All Fields] AND "tract"[All Fields] AND "infection"[All Fields]) OR "urinary tract infection"[All Fields]
3	UTI(All Fields)
4	"bacteriuria"[MeSH Terms] OR "bacteriuria"[All Fields]
5	"pyuria"[MeSH Terms] OR "pyuria"[All Fields]
6	"cystitis"[MeSH Terms] OR "cystitis"[All Fields]
7	"pyelonephritis"[MeSH Terms] OR "pyelonephritis"[All Fields]
8	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7
9	"anti-bacterial agents"[Pharmacological Action] OR "anti-bacterial agents"[MeSH Terms] OR ("anti-bacterial"[All Fields] AND "agents"[All Fields]) OR "anti-bacterial agents"[All Fields]
10	"antibiotic"[All Fields] OR "antibiotics"[All Fields]
11	"anti-microbial"[All Fields] OR ("anti"[All Fields] AND "microbial"[All Fields])
12	#9 OR #10 OR #11
13	"random allocation"[MeSH Terms] OR ("random"[All Fields] AND "allocation"[All Fields]) OR "random allocation"[All Fields] OR "randomised"[All Fields] OR "randomised"[All Fields] OR "controlled"[All Fields] OR "clinical"[All Fields]
14	("clinical trials as topic"[MeSH Terms] OR ("clinical"[All Fields] AND "trials"[All Fields] AND "topic"[All Fields]) OR "clinical trials as topic"[All Fields] OR "trial"[All Fields]) OR "study"[All Fields]
15	#13 AND #14
16	"randomised controlled trials as topic"[MeSH Terms]
17	#15 OR #16
18	#8 AND #12 AND #17
19	#8 AND #12 AND #19 Filters: Publication date from 2018/01/01 to 2019/12/31

MeSH, Medical Subject Headings.

Table 3 EMBASE—search strategy: first search with filter 'Controlled Clinical Trial/Randomized Controlled Trial' and '1990/01/01 to 2019/12/31'

Search	Query
1	'urinary tract infection'/exp OR (urinary AND tract AND infection*) OR 'urinary tract infection'
2	uti
3	'bacteriuria'/exp OR bacteriuria
4	'pyuria'/exp OR pyuria
5	'cystitis'/exp OR cystitis
6	'pyelonephritis'/exp OR pyelonephritis
7	#1 OR #2 OR #3 OR #4 OR #5 OR #6
8	antiinfective agent'/exp OR ('anti-bacterial' AND agent*)
9	'antibiotic agent'/exp OR 'antibiotic*'
10	'anti-microbial' OR (anti AND microbial)
11	#8 OR #9 OR #10
12	#7 AND #11
13	#12 AND ('controlled clinical trial'/de OR 'randomized controlled trial'/de OR 'randomized controlled trial (topic)'/de)
14	#12 AND ('controlled clinical trial'/de OR 'randomized controlled trial'/de OR 'randomized controlled trial (topic)'/de) AND(1990–2019)/py
15	#12 AND ('controlled clinical trial'/de OR 'randomized controlled trial'/de OR 'randomized controlled trial (topic)'/de) AND(1990–2019)/py AND (embase)/lim
16	#12 AND ('controlled clinical trial'/de OR 'randomized controlled trial'/de OR 'randomized controlled trial (topic)'/de) AND(1990–2019)/py AND (medline)/lim
17	#14 NOT #16

inclusion criteria will be excluded. Any disagreements and all remaining studies will be rescreened by a third reviewer. For all studies still remaining, full texts will be reviewed according to the pre-specified inclusion criteria by the third reviewer. The decision about inclusion or exclusion of a study will be discussed with another independent reviewer. RCTs in uncomplicated acute UTI in adult (adolescent) female patients presenting in general practice with any intervention to reduce antibiotic treatment and (immediate) antibiotic treatment as control will be included. Conference abstracts will be excluded. If appropriate, IPD of trials that do not compare directly an intervention to reduce antibiotic treatment with (immediate) antibiotic treatment can be considered in explorative analyses to strengthen, if only indirectly, the outlined comparisons.

Study quality will be assessed independently by two reviewers using the Cochrane Collaboration's tool for assessing risk of bias focusing on sequence generation and allocation sequence concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias) and selective outcome reporting (reporting bias).[21] The potential for publication bias will be assessed using funnel plots (with and without studies lacking IPD) and corresponding asymmetry tests. To assess data availability bias characteristics

Table 4 EMBASE—search strategy: additional search without filter 'Controlled Clinical Trial/Randomized Controlled Trial' and from 2018 onwards (to retrieve studies that have only recently been added to the database and may not be completely indexed in EMBASE)

Search	Query
1	'urinary tract infection'/exp OR (urinary AND tract AND infection*) OR 'urinary tract infection'
2	uti
3	'bacteriuria'/exp OR bacteriuria
4	'pyuria'/exp OR pyuria
5	'cystitis'/exp OR cystitis
6	'pyelonephritis'/exp OR pyelonephritis
7	#1 OR #2 OR #3 OR #4 OR #5 OR #6
8	antiinfective agent'/exp OR ('anti-bacterial' AND agent*)
9	'antibiotic agent'/exp OR 'antibiotic*'
10	'anti-microbial' OR (anti AND microbial)
11	#8 OR #9 OR #10
12	'randomization'/exp OR (random AND allocation) OR randomi$ed
13	'clinical trial'/exp OR 'clinical study'/exp OR (clinical AND trial) OR (clinical AND study) OR 'controlled study'/exp OR 'controlled study'
14	#12 AND #13
15	'randomized controlled trial'/exp AND topic
16	#14 OR #15
17	#7 AND #11 AND #16
18	#7 AND #11 AND #16 AND(2018–2019)/py
19	#7 AND #11 AND #16 AND(2018–2019)/py AND (medline)/lim
20	#18 NOT #19

of the studies with IPD and those without IPD will be compared.[22]

Data extraction and IPD collection

For the IPD-meta-analysis anonymised data on individual patient level will be requested either in electronic form via standardised data extraction sheets and will be formatted in a consistent way to permit reanalysis. As the rating scales vary across some of the studies, the defined symptom severity for the primary and secondary outcomes may need to be rescaled. Data (baseline characteristics, outcomes and study characteristics) will be checked for accordance with the published data. If data appear inconsistent or unclear, this will be resolved by queries to the investigators. The investigators of currently nine available studies have been contacted in advance via personnel communication and agreed to provide IPD of their trials. Authors of further studies, which will be identified during the systematic literature search, will be contacted via email and asked to participate and to provide IPD of their trials. A comprehensive list of the requested variables are in the online supplemental file 2. If no IPD are accessible, aggregated data on baseline characteristics, treatments, symptoms and outcomes measures will be extracted from the publication in standardised forms by two reviewers independently.

Table 5 Cochrane Library (CENTRAL and CDSR) search strategy (limitation 1990–2019)

Search	Query (all text)
1	'urinary tract infection'
2	'urinary tract infections'
3	uti
4	'bacteriuria'
5	'pyuria'
6	'cystitis'
7	'pyelonephritis'
8	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7
9	'anti-bacterial agents'
10	'antibiotic'
11	'anti-microbial'
12	#9 OR #10 OR #11
13	#8 AND #12

CDSR, Cochrane Database of Systematic Reviews; CENTRAL, Cochrane Central Register of Controlled Trials.

Table 6 Web of Science—search strategy (limitation: article; 1990–2019)

Search	Query (all text)
1	ALL=("urinary tract infection*" OR UTI OR bacteriuria OR pyuria OR cystitis OR pyelonephritis) Indexes=SCI-EXPANDED Timespan=All years
2	ALL=(antibiotic* OR anti-microbial OR anti-bacterial) Indexes=SCI-EXPANDED Timespan=All years
3	#2 AND #1 Indexes=SCI-EXPANDED Timespan=All years
4	ALL=("random allocation") Indexes=SCI-EXPANDED Timespan=All years
5	ALL=(randomized OR randomised OR controlled OR clinical) Indexes=SCI-EXPANDED Timespan=All years
6	ALL=(trial OR study) Indexes=SCI-EXPANDED Timespan=All years
7	#6 AND #5 Indexes=SCI-EXPANDED Timespan=All years
8	#7 OR #4 Indexes=SCI-EXPANDED Timespan=All years
9	#8 AND #3 Indexes=SCI-EXPANDED Timespan=All years
10	(#8 AND #3) AND DOCUMENT TYPES: (Article) Indexes=SCI-EXPANDED Timespan=1990–2019

Analysis strategy and statistical methods

Pairwise meta-analysis methods will be used for estimating treatment effects (relative to standard treatment) based on relevant subsets of studies. Meta-analysis will be carried out if at least two studies are available for comparison. In order to include effect moderators or prognostic factors, analyses are generalised to meta-regressions. In all cases, analyses will be stratified by incorporating study-specific random effects, and, in a secondary analysis, possibly also centre-effects in IPD. IPD are considered via appropriate likelihoods (eg, binomial likelihoods for binary outcomes); study-level summary estimates (eg, log ORs) are included using an approximate normal likelihood (where appropriate). In a sensitivity analysis, we will also incorporate the IPD in terms of a summary estimate in a (technically simpler) two-stage meta-analysis. The investigation of prognostic factors (objective (3)) will require IPD. Prognostic factors will also be considered in terms of random effects, if supported by a better model fit, or otherwise as fixed effects. Missing data for certain patients in IPD will be imputed if necessary, given that the missing cases only make up a minority, and that these may plausibly be considered missing at random.[23] The models used all fall into the general class of generalised linear mixed models, a special type of hierarchical model accounting for variability at the patient-level as well as the study-level. In order to include also indirect evidence on treatment effects, the feasibility of a (joint) network meta-analysis will be explored.

Primary analyses will focus on ORs as effect measures, but relative risks will be explored as an alternative. Analyses will be performed using Bayesian methods with uninformative priors for treatment effects and weakly informative priors for between-study variability (heterogeneity), as these are better suited for the case of few studies only.[24] For objective (1), the variables urgency, frequency and dipstick results such as erythrocytes, leucocytes and nitrite will be included as main effects in the model.[25–27] Other additional variables (like age, further UTI symptoms, fever, urine culture results, C reactive protein, other point-of-care tests) will be considered in a variable selection stage. Concerning objective (2), symptom duration, worsening of symptoms and relapse will be considered as potential treatment effect moderators. Effect estimates (ORs or relative risks) will be quoted along with two-sided 95% credible intervals and posterior tail probabilities. Model building will be done using forward selection based on Bayes factors (if sensible and feasible), or approximations like information criteria (eg, the deviance information criterion). Besides pairwise comparisons of specific medications (eg, fosfomycin vs ibuprofen), groups of similar treatments will be grouped in broader categories (eg, first-line and second-line antibiotics, pain killers, herbal treatments, delayed prescription or placebo). Between-study variability will be visually explored in forest plots of (log) ORs and quantified using the SD parameter tau. Sensitivity of results to modelling approaches will be assessed for example, by varying prior assumptions for the heterogeneity, by considering subgroups of studies based on suitable geographical regions or by exclusion of individual studies based on quality criteria. The performance of prognostic models (objective (3)) will be assessed in an internal–external cross-validation fashion.[23] While the validation of prognostic models is fairly established, the evaluation of prediction models (objectives (1) and (2)) is an area of ongoing research.[28] For this purpose it may be possible to use, for example, a C-statistic approach.[29]

Descriptive summaries are used to describe study-characteristics and patient-characteristics, including as complete as possible details on missing values. Metric variables are characterised by mean and SD (and range, where appropriate) ordinal scaled variables by median and percentiles. Discrete variables are summarised by quoting absolute or relative frequencies.

We will use the R software (including appropriate add-on packages, for example, LME, JAGS, STAN, metafor, bayesmeta, MetaStan) for all statistical analyses.

To rate the confidence in cumulative evidence, the strength of the body of evidence (quality or certainty of evidence and strength of recommendation) will be assessed using The Grading of Recommendations Assessment, Development and Evaluation framework.[30]

Patient and public involvement

Our research team is collaborating with a patient advisory board consisting of about eight citizens which has recently been established at the Department of General Practice of the University of Wuerzburg (see http://www.allgemeinmedizin.uni-wuerzburg.de/forschung/buergerforum/). The board has been introduced to discuss the designs of the department's scientific studies to ensure that they are comprehensible and relevant for humans.[31] It has been invited to give feedback to the aims and outcomes of this review and will be involved to participate in development of the prognostic model. The group will also be involved as a patient advisory board of a practice-based research network in Bavaria (see http://www.allgemeinmedizin.uni-wuerzburg.de/forschung/forschungspraxennetz/).

ETHICS AND DISSEMINATION

The meta-analysis is based on previously published studies. The local institutional review and ethics board judged the project a secondary analysis of existing anonymous data which meet the criteria for waiver of ethics review. Data sharing statement according to current guidelines of the International Committee of Medical Journal Editors (ICMJE) will be required from authors providing IPD.

Dissemination of the results will be via published research papers in high-quality peer-reviewed open access journals and presentations at scientific meetings. Additionally, key messages will be promoted to clinicians and patients via direct mailings, communications via clinical research networks, social media, press releases or patient blogs. This work will aim to influence guidelines on

clinical management of UTI symptoms both on national (national guidelines) and international levels.

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Competing interests IG, GF, TF, EH, MM are involved in the following studies: 'REGATTA—reducing antibiotic use for uncomplicated urinary tract infection in general practice by treatment with uva-ursi'. Afshar K, Fleischmann N, Schmiemann G, Bleidorn J, Hummers-Pradier E, Friede T, Wegscheider K, Moore M, Gagyor I. 'Reducing antibiotic use for uncomplicated urinary tract infection in general practice by treatment with uva-ursi (REGATTA)—a double-blind, randomised, controlled comparative effectiveness trial'. BMC Complement Altern Med. 2018 Jul 3;18(1):203. doi: 10.1186/s12906-018-2266-x). IV was involved in the study: 'Vik I, Bollestad M, Grude N, Bærheim A, Damsgaard E, Neumark T, Bjerrum L, Cordoba G, Olsen IC, Lindbæk M. Ibuprofen versus pivmecillinam for uncomplicated urinary tract infection in women—a double-blind, randomised non-inferiority trial'. PLoS Med 15;5:e1002569. Doi.org/10.1371/journal.pmed.1002569. MM, ADH and PL are coauthors of the study: 'Moore M, Trill J, Simpson C, Webley F, Radford M, Stanton L, Maishman T, Glanopoulou A, Flower A, Eyles C, Willcox M, Hay AD, van der Werf E, Gibbons S, Lewith G, Little P, Griffiths G. Uva-ursi extract and ibuprofen as alternative treatments for uncomplicated urinary tract infection in women (ATAFUTI): a factorial randomised trial. Clinical Microbiology and Infection'. Doi.org/10.1016/j.cmi.2019.01.011. SH was involved in the study with the reference number 11. PL and MM were involved in the study with the reference number 12. SF and TM were involved in the study with the reference number 13. IG, EH were involved in the studies with the reference numbers 14 and 15. AK was involved in the study with the reference number 16.

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