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Complete List of Authors:	Martínez-González, Nahara; Institute of Primary Care, University of Zurich and University Hospital of Zurich Coenen, Samuel; Centre for General Practice, Department of Primary and Interdisciplinary Care (ELIZA), University of Antwerp - Campus Drie Eiken Plate, Andreas; Institute of Primary Care, University of Zurich and University Hospital of Zurich Colliers, Annelies; Centre for General Practice, Department of Primary and Interdisciplinary Care (ELIZA), University of Antwerp - Campus Drie Eiken Rosemann, Thomas; Institute of Primary Care, University of Zurich and University Hospital of Zurich Senn, Oliver; Institute of Primary Care, University of Zurich and University Hospital of Zurich Neuner-Jehle, Stefan; Institute of Primary Care, University of Zurich and University Hospital of Zurich
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BMJ Open Systematic Review Protocol

Title

The impact of interventions to improve the quality of prescribing and use of antibiotics in primary care patients with respiratory tract infections: a systematic review protocol

Authors

Research Associate Nahara Anani Martínez-González,[1] Associate professor Samuel Coenen,[2] Medical doctor Andreas Plate,[1] Medical doctor Annelies Colliers,[2] Professor Thomas Rosemann,[1] Assistant professor Oliver Senn,[1] Senior Researcher Stefan Neuner-Jehle [1]

Author affiliations

[1]Institute of Primary Care, University of Zurich and University Hospital of Zurich, Pestalozzistrasse 24, CH-8091 Zurich, Switzerland.

[2]Centre for General Practice, Department of Primary and Interdisciplinary Care (ELIZA), University of Antwerp - Campus Drie Eiken, Universiteitsplein 1, 2610, Wilrijk, Belgium.

Corresponding author

Nahara A. Martínez-González, Nahara.Martinez@usz.ch

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Abstract

Introduction: Antibiotic consumption is the main modifiable driver of Antimicrobial Resistance (AMR). Most antibiotics are used for infectious diseases of the respiratory tract (RTIs), the most common reason for primary care consultations. Antibiotics' inappropriate use often leads to RTI complications, increased incidence of adverse events, re-consultations, resource use, costs and AMR. We will systematically review the interventions aiming to improve the quality of prescribing and use of antibiotics for acute RTI including 1) interventions targeting healthcare professionals and patients, and 2) public health campaigns and regulatory interventions.

Methods and analysis: Eligible will be primary peer-reviewed and grey literature of studies conducted in in-hours and out-of-hours primary care (adults and children) patients: 1) healthcare professionals- and patient-based intervention studies evaluating the effectiveness, feasibility and acceptability in Randomised Controlled Trials (RCTs), quasi-RCTs and cluster-RCTs; and 2) public health campaigns and regulatory intervention studies evaluating the effectiveness in RCTs and other study designs. We will perform a comprehensive search with no language restriction in MEDLINE (EBSCOHost), EMBASE (Elsevier), The Cochrane Library (Wiley), CINHAL (EBSCOHost), PsychINFO (EBSCOHost), Scopus, LILACS, TRIP, and opengrey.eu. We will also hand-search the reference lists of included studies and relevant reviews. Primary outcome: quality of prescribing and use of antibiotics including the rates of (guideline-recommended) antibiotics prescribed and/or used. Secondary outcomes including delayed use will also be assessed. Reviewers will assess study eligibility and risk of bias, and will extract data. Data-permitting, meta-analyses will be incorporated.

Ethics and dissemination: This is a systematic review protocol. No confidential, personal or primary data will be collected. The review findings will be disseminated at national and international scientific meetings, and will be published in peer-review journals.

Registration: CRD42017035305.

Keywords: Systematic Review, Infectious Diseases, Acute Respiratory Tract Infections, Quality Of Antibiotic Use, Quality Of Antibiotic Prescribing, Prudent Antibiotic Use, Prescriptions, Anti-Bacterial Agents Use, Antibiotic Use

Strengths and limitations of this study

- First 'back-to-back' systematic review assessing both 1) healthcare professional and patient-based targeted interventions, and 2) public awareness campaigns and regulatory interventions that aim to improve prescribing quality and use of antibiotics for acute respiratory tract infection.
- First systematic review with a broad scope of international evidence from peer-reviewed and grey literature including all types of such interventions, expanded to adults and children, and in-hours and out-of-hours care.
- No language restriction and the number of searching sources will add to the comprehensiveness of this review.
- Our results will help healthcare professionals, policy makers and public health researchers making informed decisions about the interventions that provide the most benefits in optimising quality of prescribing and use of antibiotics.
- Our results may help design future interventions aiming to improve prescribing quality and use of antibiotics.
- The quality of studies and the significant heterogeneity of results might potentially limit the evidence in this review, which may challenge the interpretation of findings.

INTRODUCTION

Antimicrobial resistance (AMR) is a major threat to public health globally.[1] Drug-resistant infections lead to a higher risk of worse clinical outcomes and death than not drug-resistant infections.[2] If AMR continues to rise as in the last decades, 10 million people would be expected to die every year because of drug-resistant infections and could cause a global economic loss of 60-100 trillion USD between now and 2050.[3] Antibiotic consumption, particularly inappropriate drug use, is the main and modifiable driver of AMR.[4] The extent of antibiotic use has been consistently associated with the rate of AMR at the individual, community, and national levels.[5-6]

Most antibiotics used in humans are administered in primary care. In Europe, 80-90% of all antibiotics are prescribed in primary ambulatory care,[6-7] while in the USA at least 70% of patients visiting their family physician receive antibiotics.[7] Antibiotics are dispensed or sold inappropriately too, and they are taken incorrectly by the majority of consumers.[8] Most of this inappropriate use is still common for infectious diseases of the respiratory tract (RTIs),[9] one of the most prevalent reasons for patient encounters in general practice.[10] The common cold, acute sore throat, pharyngitis and tonsillitis, acute otitis media, rhinitis, acute sinusitis, laryngitis, and acute bronchitis are the most common acute RTIs. These are normally self-limiting and mostly improve without antibiotic therapy since they often have a viral cause.[11] However, self-medication with antibiotics is also most common for colds and upper RTIs in the USA[12-14] and Europe.[15] Inappropriate use of antibiotics often lead to increased incidence of adverse events, re-consultations, resource use, RTI complications and costs, and ultimately contribute to bacterial resistance.[4]

Inappropriate use of antibiotics is highly influenced by human behaviour at many levels of society. Many of such complex factors contribute greatly to the problem including lack of knowledge and concern[16] and underestimation of AMR,[17] patients expectation for antibiotics and the pressure on physicians to meet such expectations.[18] In addition, medicalising with antibiotics encourages patients to re-attend and to expect similar antibiotics behaviour in future episodes.[19]

There is a fast-growing body of literature about interventions designed to improve the quality of prescribing and use of antibiotics for RTIs. Multifaceted interventions, interventions

involving physicians and pharmacists, and patient education are more likely to reduce antibiotic prescribing rates and increase the use of recommended antibiotics, and improve antibiotic consumption.[20-21] Lowering antibiotic dispensing at general practices can also reduce AMR[22-23] and has positive effects on seeking behaviour (e.g. change in expecting antibiotics) for RTI.[24] Various systematic reviews also show that some of the outpatient interventions can safely improve or reduce antibiotic prescribing and use.[25-28] Yet, the Global Strategy by WHO to contain AMR recognizes that isolated interventions have little impact on improving antibiotic use.[29] In many countries, interventions are increasingly being integrated in system- and population- level strategies including public health campaigns and regulatory interventions to translate knowledge and recommendations into practice,[30] to change antibiotics behaviour and to reduce AMR.[31-34]

We hypothesise that interventions aiming to improve the quality of prescribing and use of antibiotics for RTI:

1) are more effective in resolving inappropriate use of antibiotic prescribing, dispensing (healthcare providers), and use (patients) when these integrate multifaceted interventions that target both patients and physicians; and

2) work better at reducing antibiotic use-related problems when these target healthcare professionals and patients in the context of public awareness campaigns (at the population level); but

3) are more effective in making a step-change for reducing antibiotic use-related problems when these are implemented at the system-level by regulatory interventions.

Objectives

The objectives of this study are: 1) to conduct a systematic review of the impact of interventions aiming to improve the quality of prescribing and use of antibiotics for the most common acute RTI; and to estimate the pooled effect of such interventions through meta-analyses if available data permits; 2) to analyse the prevalence of antibiotic prescribing rates over time before and after the implementation of campaigns and regulatory interventions.

Review questions

We will guide the systematic review with the following review questions:

1. What is the comparative effectiveness of interventions to improve antibiotic use on the quality of antibiotic prescribing (prescribing or not, and the type of antibiotic prescribed) and use in primary care patients with acute respiratory tract infection (RTI)?
2. What is the feasibility and acceptability of patient and clinician-based interventions to improve antibiotic use on antibiotic prescribing quality in patients with acute RTI in primary care general practice?

METHODS

Our systematic review protocol follows the guidance for the Preferred Reporting Items for Systematic reviews and Meta-analyses for Protocols (PRISMA-P),[35] and it is registered on PROSPERO (CRD42017035305).

Design

Systematic review of primary peer-reviewed and grey literature.

Eligibility criteria

Types of participants

Upper RTIs include acute pharyngitis, nasopharyngitis, rhinitis and common cold, otitis media (acute, chronic), acute mastoiditis, acute sinusitis, croup (laryngotracheobronchitis), epiglottitis, and diphtheria.[36] Lower RTIs include bronchitis (acute and chronic), bronchiolitis, influenza, chronic recurrent cough, pneumonia, acute exacerbation of COPD, and acute exacerbation of bronchiectasis.[36-38] RTIs might also be classified as acute if symptoms last for less than four weeks and no antibiotic therapy or diagnostics procedures have been followed. The most common acute RTIs include the common cold, acute sore throat, pharyngitis and tonsillitis, acute otitis media, rhinitis, acute sinusitis, laryngitis, and acute bronchitis.

We will include studies of the most common acute RTIs involving:

- adult and paediatric (and their parents) patients with an acute RTI
- carers or parents of patients with an acute RTI
- healthcare providers of patients with acute RTI in primary outpatient settings, including physicians (e.g. paediatricians and family physicians) of in-hours and out-of-hours *ambulatory* care services, and/or pharmacists.

We will exclude studies of exacerbations of COPD and/or other pre-existing chronic pulmonary diseases; and studies involving in-patients.

Types of interventions

Interventions to improve antibiotic use vary by whose behaviours they try to influence e.g. modify self-medication and expectations in consumers (patients, general public), or reduce prescribing and dispensing by health care professionals (clinicians, pharmacists). Through changing behaviour, these aim to improve patient outcomes, while limiting resistance, complications, adverse effects and costs. They might take the format of single or multifaceted interventions and can be classified by the approach used to influence antibiotic use behaviour, e.g. educational, clinical (e.g. delayed prescribing, point of care), system level strategies (e.g. review/feedback).[26-27]

We will include studies that evaluate the following interventions:

- healthcare professional (clinicians and/or pharmacists) and patient-based interventions
- public awareness campaigns: local, national, and 'choosing wisely' campaigns[39-40]
- regulatory interventions

Health care professional interventions target clinicians (physicians e.g. paediatricians and family physicians, and nurses) or pharmacists, while patient-based interventions target patients with acute RTI and/or their carers or parents. Public awareness campaigns are population-level strategies that target the general public. They are designed to raise public awareness and knowledge about antibiotic misuse through the distribution of mass media such as television, radio, internet, posters, leaflets, newspapers.[32] Their aim is to benefit the target population and/or the society altogether. Regulatory interventions are system-level strategies designed to outline a framework of requirements and legal practice of antibiotic use

(e.g. limiting prescribing and/or dispensing).[8, 41] Their goal is to enforce decision-making to improve the use of antibiotics.

Types of intervention comparators

- Other interventions to improve antibiotic use or one or more alternative interventions (single or multifaceted); and/or
- Usual care

Types of outcome measures

We will extract primary and secondary outcomes regardless of the outcome measurement instruments used, the outcome measure (e.g. prescribed individuals, prescriptions, items as numerators, and RTI patients or patient years "at risk" as denominators),[42-44] their nature (objective or subjective) and time points.

Primary outcomes

For all interventions, the primary outcome will be the quality of antibiotic prescribing and use including:

- rates and types of (any) antibiotics prescribed and/or used
- rates and types of guideline recommended antibiotics prescribed

Secondary outcomes

For studies of healthcare professional and patient-based interventions:

- rates and types of antibiotics prescribed as immediate and delayed use
- patients' adherence to immediate and/or delayed prescribing:
- antibiotic resistance (e.g. rates of patients with RTI with proven antibiotic resistant bacteria, and reduction of resistance as a result of the intervention);
- types and rates of medical complications (e.g. emergency visits, hospital admissions due to possible RTI (complications), and mortality);
- adverse effects of antibiotic use (e.g. nausea and diarrhoea);

- adverse effects of the intervention strategy (e.g. increased consultation times of physicians);
- the costs of healthcare services, programs and (dispensing) medication; healthcare utilization (e.g. length of consultations, tests ordered);
- consultation rates: re-consultation rates including re-consultations due to original infection but deteriorated (e.g. unplanned re-visits within 2-3 weeks of first consultation) and due to new RTI episodes;
- patient outcome (e.g. symptom severity, symptom resolution, disease duration, time to resume to school or work);
- outcomes of feasibility and acceptability of patient and clinician-based interventions in primary care general practice (e.g. uptake of interventions);
- patients' and clinicians' knowledge about antibiotic use; patients' participation rate in decision making about antibiotic use;
- patient satisfaction with care; quality of patient-healthcare provider communication

Other outcomes of interest: quality of life, use of non-antibiotic medication (e.g. over-the-counter medicines), sustainability of interventions (i.e. change in prescribing pattern over a period after the delivery of interventions), physicians' and patients' views and attitudes about antibiotic prescribing.

Depending on the resources available to conduct this review, we will also assess the secondary outcomes for studies of campaigns and regulatory interventions (e.g. antibiotic resistance, types and rates of medical complications, the costs of healthcare services, programs and (dispensing) medication, and healthcare utilization).

Types of studies

For healthcare professional (clinicians and/or pharmacists) and patient-based interventions, we will include studies of prospective, comparative and experimental design including parallel randomised controlled trials (RCTs), quasi-RCTs in which the method of allocation is not strictly random (e.g. allocation by alternation, date of birth, hospital number), and cluster-RCTs in which the method of allocation is by group (e.g. patients of the same physician) if they:

a) evaluate the effectiveness of interventions to improve antibiotic prescribing and/or use; and/or

b) evaluate the feasibility and acceptability of patient and clinician-based interventions to improve antibiotic use in primary care general practice

For public awareness (local, national, and 'choosing wisely') campaigns[39-40] and regulatory interventions, besides RCTs we will also include other study designs (e.g. non-randomised controlled trials, before and after studies with or without a contemporary control group) if they:

a) evaluate the effectiveness of interventions to improve antibiotic prescribing and/or use

If eligible, studies will be included regardless of the length of follow-up, publication year and country of origin, giving first priority to studies published in English (see study selection). We will not include systematic reviews and meta-analyses in this review. These will only be used for the identification of additional studies.

Types of setting

Studies carried-out in the following primary care settings will be included:

1) in-hours (e.g. paediatric and family practice clinics)
2) out-of-hours ambulatory care

We will exclude studies from in-patient settings.

Search methods

We will design and conduct a comprehensive search strategy, and will cross-check it with the strategies of two available systematic reviews.[25, 27] The search strategy will aim at identifying RCTs in humans evaluating interventions aiming to improve antibiotic use and prescribing including healthcare professional and patient-based interventions, as well as public awareness campaigns and regulatory interventions. The strategy will be revised by an information specialist and will follow the PICOTS (populations, interventions, comparisons, timing, and settings) approach. It will not be restricted to reporting language, population age or gender, publication date, country or outcomes.

We will search MEDLINE (EBSCOHost), EMBASE (Elsevier), The Cochrane Library (Wiley), CINHAL (EBSCOHost), PsychINFO (EBSCOHost) and Scopus from their inception. The

concepts and terminology will be considered and translated to fit all database searches. These may include 'respiratory tract infections' 'antibiotic', 'antimicrobial', 'anti-bacterial/anti-infective agents', 'prudent/judicious antibiotic use', 'prescribers/prescribing', 'interventions', 'strategies', 'stewardship', 'primary health care', 'outpatients', 'in-hours care' and 'after/out-of-hours care'. The strategy may also include the terminology specific to interventions to improve antibiotic prescribing and use e.g. 'education', 'point of care', 'audit or feedback', 'information/awareness campaign' and 'choosing wisely campaign'. We will also search for grey literature using the Latin American and Caribbean Literature on Health Sciences (LILACS), Turning Research Into Practice database (TRIP), and the system for information on grey literature in Europe (http://opengrey.eu/). We will identify additional publications through manually searching the reference lists of included studies and relevant reviews. The searches will be updated as required.

Study selection

All records identified by the electronic and manual searches will be merged and duplicate citations will be removed. We will give priority to the selection of publications reported in English; and depending on the resources available, we will also appraise the citations and publications of studies reported in Spanish and German and then other languages. The title and abstract of each citation will be screened and sifted in duplicate and independently by two reviewers. The full-text publications of selected citations will be obtained if they meet the eligibility criteria, appear relevant, or if eligibility is not clear; all will be evaluated independently by two reviewers. If studies reported in languages other than English are appraised, we will follow the recommendations proposed by the Centre for Research in Evidence Based Practice[45] to translate the abstracts of potentially relevant citations and full-texts of eligible publications. The final list of included studies will be confirmed and the reasons for excluding studies will be recorded. Differences in judgment of eligibility will be resolved by discussion or involvement of an arbitrator, or both.

Data extraction and management

Data extraction will be conducted by one reviewer and verified by a second reviewer. Studies reported across more than one publication will be identified and data will be extracted as one unit. If one publication reports more than one study, data will be extracted as separate studies, where possible. At data appraisal studies may be excluded if it becomes apparent that inclusion criteria are not met after closer evaluation. If studies reported in languages other than English are appraised, abstraction of data from publications eligible for inclusion will be confirmed with a native language speaker following the translation of full-text. Differences in data collection will be resolved by discussion or involvement of an arbitrator, or both. For each study, we will extract and record data as follows:

a) bibliographic details and descriptive study elements (design, care setting, number of facilities/sites, geographic distribution, start and end dates of study);
b) patient characteristics: inclusion/exclusion, age, sex, ethnicity, co-morbidities (e.g. asthma and COPD), population type served (e.g. urban), socioeconomic (higher versus lower income regions), educational level, regional differences (e.g. in a country: north versus south; deprived versus affluent; urban versus rural), time of year, number of randomised/enrolled participants and withdrawals;
c) provider characteristics: age, gender, experience (e.g. years in practice), number of clinicians per site;
d) RTI characteristics: type (e.g. upper RTI, acute otitis media, lower RTI, bronchitis), diagnostic method and/or tools used, signs and symptoms, antibiotic therapy prescribed (recommended/not recommended agents, doses, duration, route of administration) and antibiotic therapy previously used;
e) interventions/comparators characteristics: definition, description and components (tools used e.g. information leaflets, decision aids), interventions' intended target (patients or patients' parents/carer, physicians and/or pharmacists), delivery time (e.g. before consultation), duration, follow-up episodes; and
f) outcome details: the value of "appropriateness" and/or "inappropriateness" of antibiotics prescribing that has been adjudicated to an outcome by the study reviewers; outcome measurement tools/methods (validated or not), definitions and time points; the quantitative

results for each outcome; and any qualitative statements about the association between the outcomes and the intervention and comparison groups.

We will group together studies with similar definitions of appropriateness in prescribing. We will group studies' interventions into distinct categories by their components based on proposed classification systems.[26-27] Data will be organized by RTI type (e.g. upper RTI, acute otitis media, lower RTI, bronchitis), care setting, population (with distinction by targeted participants), intervention and sources of variation (e.g. regional differences in a country).

Risk of bias assessment

Two independent reviewers will assess in duplicate the quality features of included studies using criteria forms developed based on established guidelines; and will resolve differences by discussion or involvement of an arbitrator, or both. The criteria will cover the core items related to internal validity of RCTs,[46] i.e. methods of random sequence generation and concealment of allocation at randomisation, the use of blinding and intention to treat (ITT) analysis, and similarity between groups at baseline. Bias due to attrition will be considered of significant concern with a loss to follow-up of at least 20%; and adequate ITT if authors analysed participants based on their original group allocation. Blinding of patients and clinicians may not be possible due to the nature of interventions. It is however possible to perform blinded assessment of outcomes and to identify whether studies are prone to selective outcome reporting. Following the debate about scoring the quality of trials, discussed in depth by Juni et al.[47], we will not calculate a composite score. We will describe the studies' adequacy in each item with an overall judgment of the quality of evidence and generate summary tables with the quality profile of each study. For other (e.g. before and after and non-randomised) study designs, assessment criteria will be based on items from the Cochrane Collaboration's by EPOC,[48] the Newcastle-Ottawa Scale[49] and ROBINS-I.[50] Reporting criteria that will be assessed in all studies include the definition and reporting of primary and secondary outcomes, inclusion and exclusion criteria, 'a-priori' sample size calculation, and funding sources.

Data analysis

We will use the Cochrane Collaboration's analysis software RevMan 5.3[51] for statistical analyses and will follow available guidelines to incorporate cluster-RCTs.[46] For binary data, the intervention effect will be estimated using the unadjusted Risk Ratios or Odd Ratios with 95% confidence intervals (CI). For continuous data, the intervention effect will be estimated using the weighted mean differences or standardized mean differences if studies use different scales. The summary statistics and 95% CIs will be reported where sufficient detail allows their calculation. A p-value of <0.05 will be considered as statistically significant. One single estimate of a treatment effect will be produced for each individual study. Data permitting, outcome data will be combined and meta-analyses will be incorporated where appropriate (i.e. ≥2 studies per outcome). The pooled effect estimate(s) will be produced using the random effects model and will be retained if between-study heterogeneity is substantial. The fixed-effects model will be used otherwise. Available guidance will be used to estimate missing data.[46] We will assess between-study heterogeneity using the I^2 statistic[52] and by visual inspection of forest plots.[53] Values of heterogeneity are represented as low (below 25%), moderate (50%), severe (up to 75%) and very severe (more than 75%). We will also assess the impact of awareness and choosing wisely campaigns and regulatory interventions over time. The pooled rates of prescriptions due to RTI will be calculated and compared for data before and after (e.g. six months) the implementation of such interventions.

We will report the results using forest plots where appropriate and evidence-based summary of finding tables. We will synthesise all results descriptively including those where quantitative synthesis is not appropriate.

Subgroup and sensitivity analyses

We will perform subgroup and sensitivity analyses for the primary outcomes only, if enough data are available from the studies in review. We will conduct subgroup analyses in the following areas:

a) population and interventions characteristics: country (developing vs. developed), population (children and adults aged 18 years and older, gender, socioeconomic status and educational level, time of year), care setting (in-hours vs. out-of-hours care), acute

RTI type, antibiotic therapy, diagnostic method, intervention type and intended target (patients and/or physicians and/or pharmacists);

b) risk of bias and other methodological criteria: random sequence generation, allocation concealment, blinding, and attrition (lower levels: <20% vs. higher levels: ≥20%), and intention to treat; study size (small: N<200 vs. large: N≥200), and length of follow-up.

Sensitivity analyses will be performed by excluding studies with higher risk of bias, dubious criteria for inclusion, and unclear definitions of acute RTI or studies that do not differentiate between RTI type, and unclear/incomplete definitions of appropriate prescribing.

DISCUSSION

AMR due to antibiotic consumption is a global shared health priority and most antibiotics are administered in primary care where they are commonly used for the management of RTIs. Our systematic review will evaluate the interventions aiming to improve the quality of prescribing and use of antibiotics for acute RTI. To the best of our knowledge, this is the first 'back-to-back' systematic review on both 1) healthcare professional and patient-based targeted interventions, and 2) public awareness campaigns and regulatory interventions. The evaluation of these interventions will allow the comparison of their impact and assessment of their interaction providing thus unique information to policy makers.

A synthesis with a broader scope including international evidence from peer-reviewed and grey literature on all types of these interventions, expanded to adults and children, and including in-hours and out-of-hours care has not been performed. In addition, our search will have no language restrictions allowing the identification of evidence from non-English literature which could provide valuable findings. The results will provide estimates of the effectiveness as well as the feasibility and acceptability of such interventions, with an assessment of the methodological quality of the included studies. A thorough search run in a large number of sources will enable a comprehensive identification and assessment of data. The evidence in this review may be potentially limited by the quality of studies and the significant heterogeneity of the results, and this may challenge the interpretation of results. However, we expect that the review will produce a comprehensive and up-to-date evidence-based body of knowledge about the interventions that provide the most benefits towards a

more judicious antibiotic prescribing and use. This would ultimately help improve AMR. The results may help design future interventions, and will be of international interest to public health, primary healthcare professionals, policy makers and finally patients.

ETHICS AND DISSEMINATION

Formal ethical approval is not required given that this is a protocol for a systematic review, and no confidential personal and no primary data on interventions on patients will be collected. The findings of this review will be disseminated at national and international scientific meetings.

REGISTRATION AND PUBLISHING

This systematic review protocol is registered on the International Prospective Register of Systematic Reviews (http://www.crd.york.ac.uk/PROSPERO/): CRD42017035305. The reporting of the review will follow the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist[54] and the review findings will be published in peer-review journals.

Contributors

NM wrote the manuscript, conceived and designed the review, critically revised several drafts of the protocol and contributed to improvements in the protocol; will be involved in designing and testing the data extraction forms and screening of studies, extracting data and assessment of study quality. SC conceived and designed the review, critically revised several drafts of the protocol and contributed to improvements in the protocol. AP critically revised several drafts of the protocol and contributed to improvements in the protocol; will be involved in designing and testing the data extraction forms and screening of studies, extracting data and assessment of study quality. AC critically revised several drafts of the protocol and contributed to improvements in the protocol; will be involved in designing and testing the data extraction forms and screening of studies, extracting data and assessment of study quality. TR critically revised several drafts of the protocol and contributed to improvements in the protocol. OS conceived and designed the review, critically revised several drafts of the protocol and contributed to improvements in the protocol. SNJ conceived and designed the review, critically revised several drafts of the protocol and contributed to improvements in the protocol. All authors read and approved the final manuscript.

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Competing interest

The authors declared no competing interests.

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Title: The impact of interventions to improve the quality of prescribing and use of antibiotics in primary care patients with respiratory tract infections: a systematic review protocol

PRISMA-P 2015 Checklist

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	Page where reported in protocol
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	n/a
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2 (Protocol registration number: CRD42017035305)
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	18
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	18
Sponsor	5b	Provide name for the review funder and/or sponsor	18
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	18
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	4

Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	6,7
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	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	11
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	11
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	13
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)	12
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	13
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	13
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	9, 10
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	14
DATA			
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	15
	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)	15
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	15
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	15
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	15
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	14 (Risk of bias criteria based on the Cochrane Collaboration's

			tool)

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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The impact of interventions to improve the quality of prescribing and use of antibiotics in primary care patients with respiratory tract infections: a systematic review protocol

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BMJ Open Systematic Review Protocol

Title

The impact of interventions to improve the quality of prescribing and use of antibiotics in primary care patients with respiratory tract infections: a systematic review protocol

Authors

Research Associate Nahara Anani Martínez-González,[1] Associate professor Samuel Coenen,[2] Medical doctor Andreas Plate,[1] Medical doctor Annelies Colliers,[2] Professor Thomas Rosemann,[1] Assistant professor Oliver Senn,[1] Senior Researcher Stefan Neuner-Jehle [1]

Author affiliations

[1]Institute of Primary Care, University of Zurich and University Hospital of Zurich, Pestalozzistrasse 24, CH-8091 Zurich, Switzerland.

[2]Centre for General Practice, Department of Primary and Interdisciplinary Care (ELIZA), University of Antwerp - Campus Drie Eiken, Universiteitsplein 1, 2610, Wilrijk, Belgium.

Corresponding author

Nahara A. Martínez-González, Nahara.Martinez@usz.ch

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Supplementary file 1: PRISMA-P Checklist.

Supplementary file 2: Draft of preliminary full search strategy in Embase.

Abstract

Introduction: Respiratory tract infection (RTIs) are the most common reason for primary care (PC) consultations and for antibiotic prescribing and use. The majority of RTIs have a viral aetiology however, and antibiotic consumption is ineffective and unnecessary. Inappropriate antibiotic use contributes greatly to Antimicrobial Resistance (AMR) leading to complications, increased adverse events, re-consultations and costs. Improving antibiotic consumption is thus crucial to containing AMR, which has become an urgent priority worldwide. We will systematically review the evidence about interventions aimed at improving the quality of antibiotic prescribing and use for acute RTI.

Methods and analysis: We will include primary peer-reviewed and grey literature of studies conducted on in-hours and out-of-hours PC patients (adults and children): 1) Randomised Controlled Trials (RCTs), quasi-RCTs and/or cluster-RCTs evaluating the effectiveness, feasibility and acceptability of patient- and clinician-targeted interventions; and 2) RCTs and other study designs evaluating the effectiveness of public campaigns and regulatory interventions. We will search MEDLINE (EBSCOHost), EMBASE (Elsevier), The Cochrane Library (Wiley), CINHAL (EBSCOHost), PsychINFO (EBSCOHost), Web of Science, LILACS, TRIP, and opensgrey.eu without language restriction. We will also search the reference lists of included studies and relevant reviews. Primary outcomes include the rates of (guideline-recommended) antibiotics prescribed and/or used. Secondary outcomes include immediate or delayed use of antibiotics, and feasibility and acceptability outcomes. We will assess study eligibility and risk of bias, and will extract data. Data permitting, we will perform meta-analyses.

Ethics and dissemination: This is a systematic review protocol. We will not collect confidential, personal or primary data.

Registration: CRD42017035305.

Keywords: Systematic Review, Infectious Diseases, Acute Respiratory Tract Infections, Quality Of Antibiotic Use, Quality Of Antibiotic Prescribing, Prudent Antibiotic Use, Prescriptions, Anti-Bacterial Agents Use, Antibiotic Use

Strengths and limitations of this study

- First 'back-to-back' systematic review assessing both 1) healthcare professional and patient-targeted interventions, and 2) public campaigns and regulatory interventions that aim to improve prescribing quality and use of antibiotics for acute respiratory tract infection.
- First systematic review with a broad scope of international evidence from peer-reviewed and grey literature including all types of such interventions, expanded to adults and children, and in-hours and out-of-hours care.
- Searching a large number of sources and searching without language restrictions will add to the comprehensiveness of this review.
- Our results will help healthcare professionals, policy makers and public health researchers make informed decisions about the interventions that provide most benefits in optimising the quality of prescribing and use of antibiotics.
- Our results may help design future interventions aiming to improve prescribing quality and use of antibiotics.
- The quality of studies and the significant heterogeneity of results might limit the performance of meta-analyses and may challenge the interpretation of findings.

INTRODUCTION

Antimicrobial resistance (AMR) is a major threat to public health globally.[1] Drug-resistant infections lead to a higher risk of worse clinical outcomes and death than non-drug-resistant infections.[2] It is estimated that if AMR continues to rise, as it has in the last decades, 10 million people would die yearly from drug-resistant infections. This could cause a global economic loss of 60-100 trillion USD between now and 2050.[3] Antibiotic consumption, particularly inappropriate drug use, is the main and modifiable driver of AMR.[4] The extent of antibiotic use has been consistently associated with the rate of AMR at the individual, community, and national levels.[5-6]

Most antibiotics used in humans are administered in primary care. In Europe 80-90% of all antibiotics are prescribed in primary ambulatory care,[6-7] while in the USA at least 70% of patients visiting their family physician receive antibiotics.[7] Antibiotics are dispensed or sold inappropriately too, and they are taken incorrectly by the majority of consumers.[8] Most of this inappropriate use is still common for respiratory tract infections (RTIs),[9] and RTIs are a leading cause of patient encounters in general practice.[10] The common cold, acute sore throat, pharyngitis and tonsillitis, acute otitis media, rhinitis, acute sinusitis, laryngitis, and acute bronchitis are the most common acute RTIs. These are normally self-limiting, and since they often have a viral cause, they mostly improve without antibiotic therapy.[11] However, self-medication with antibiotics is also most common for colds and upper RTIs in the USA[12-14] and Europe.[15] Inappropriate use of antibiotics often lead to increased incidence of adverse events, re-consultations, resource use, RTI complications and costs, and ultimately contribute to bacterial resistance.[4]

Furthermore, the inappropriate use of antibiotics is highly influenced by human behaviour at many levels of society. Many complex factors contribute greatly to the problem, including lack of knowledge and concern,[16] underestimation of AMR,[17] and patients' expectations for antibiotics, as well as the pressure on physicians to meet these expectations.[18] In addition, medicalising with antibiotics encourages patients to re-visit and expect similar antibiotics behaviour in future episodes.[19]

There is a fast-growing body of literature about interventions designed to improve the quality of prescribing and use of antibiotics for RTIs. Multifaceted interventions, interventions

involving physicians and pharmacists, and patient education are more likely to reduce antibiotic prescribing rates and increase the use of recommended antibiotics, as well as improve antibiotic consumption.[20-21] Lowering antibiotic dispensing at general practices can also reduce AMR[22-23] and has positive effects on seeking behaviour for RTI (e.g. change in expecting antibiotics).[24] Various systematic reviews also show that some of the outpatient interventions can safely improve or reduce antibiotic prescribing and use.[25-28] Yet WHO Global Strategy to contain AMR recognizes that isolated interventions have little impact on improving antibiotic use.[29] In many countries, interventions are increasingly being integrated in system- and population- level strategies including public health campaigns and regulatory interventions to translate knowledge and recommendations into practice,[30] to change antibiotics behaviour and to reduce AMR.[31-34] This systematic review will appraise the existing evidence and estimate the effectiveness of interventions aiming to improve the quality of antibiotic prescribing and use for acute RTI in primary care. Our second objective is to assess the feasibility and acceptability of patient- and clinician-targeted interventions. We also expect to identify the intervention components that are most strongly associated with effectiveness.

We hypothesise that interventions aimed at improving the quality of antibiotic prescribing and use for RTIs: 1) are more effective in reducing inappropriate antibiotic prescribing, dispensing by healthcare professionals (clinicians and/or pharmacists), and use by patients, their carers or parents when multiple components are integrated to target both patients and healthcare professionals; and 2) work better at reducing antibiotic use-related problems when they target healthcare professionals and patients by means of public campaigns. We also hypothesise that such interventions are even more effective in making a step-change when they are implemented at the system-level by means of regulatory measures. In addition, knowing the feasibility and acceptability of patient- and clinician-targeted interventions may help explain their comparative effectiveness and guide their implementation in practice.

METHODS

Our systematic review protocol follows the guidance for the Preferred Reporting Items for Systematic reviews and Meta-analyses for Protocols (PRISMA-P),[35] and it is registered on PROSPERO (CRD42017035305).

Design

Systematic review of primary peer-reviewed and grey literature.

Review questions

We will guide this systematic review with the following questions:

1. What is the (comparative) effectiveness of interventions to improve antibiotic use on the quality of antibiotic prescribing and use in primary care patients with acute RTI?
2. What is the feasibility and acceptability of patient- and clinician-targeted interventions to improve antibiotic use on the quality of antibiotic prescribing and use in patients with acute RTI in primary care general practice?

These questions will also guide the identification of the interventions components that appear to be associated with success.

Eligibility criteria

Types of participants

We will include studies examining both adults and children of all ages presenting to primary care settings with a common acute RTI. The studies might also involve:

- adult patients and/or paediatric patients (together with their parents) with an acute RTI
- carers or parents of patients with an acute RTI
- healthcare providers of patients with acute RTI including physicians (e.g. paediatricians and family physicians) of in-hours and out-of-hours ambulatory care services and/or pharmacists

RTIs are labelled as acute if there is a sudden onset of symptoms lasting less than four weeks without diagnosis regardless of whether or not antibiotics are being prescribed.[36] RTIs are classified as upper RTIs or lower RTIs. Upper RTIs include acute pharyngitis,

nasopharyngitis, rhinitis and common cold, otitis media (acute, chronic), acute mastoiditis, acute sinusitis, croup (laryngotracheobronchitis), epiglottitis, and diphtheria.[37] Lower RTIs include bronchitis (acute and chronic), bronchiolitis, influenza, chronic recurrent cough, pneumonia, acute exacerbation of COPD, and acute exacerbation of bronchiectasis.[37-39] The most common acute RTIs include the common cold, acute cough, acute sore throat, pharyngitis and tonsillitis, acute otitis media, rhinitis, acute sinusitis, laryngitis, and acute bronchitis.

We will exclude studies of exacerbations of COPD and/or other pre-existing chronic pulmonary diseases; and studies involving in-patients.

Types of interventions and comparators

We will include studies that evaluate interventions relevant to improving antibiotic prescribing and use for RTIs based on previous reviews.[26-27] The interventions vary according to the behaviours they try to influence. These include modification of self-medication and expectations in consumers (patients, general public), or reduction of prescribing and dispensing by health care professionals (clinicians, pharmacists). Through changing behaviour, these aim to improve patient outcomes, while limiting resistance, complications, adverse effects and costs. They might take the format of single or multifaceted interventions and can be classified by the approach used to influence antibiotic use behaviour, e.g. educational, clinical (e.g. delayed prescribing, point of care), system level strategies (e.g. review/feedback).[26-27] We will focus on:

- healthcare professional (clinicians and/or pharmacists) and patient-targeted interventions
- public campaigns: local, national and international awareness and 'choosing wisely' campaigns[40-41]
- regulatory interventions

Comparators will include alternative interventions that also aim to improve antibiotic prescribing and use for RTIs including interventions consisting of one or multiple components, or usual care.

Health care professional interventions target clinicians (e.g. paediatricians and family physicians, and nurses) or pharmacists, while patient-targeted interventions target patients

with acute RTI and/or their parents or carers. Public awareness campaigns are population-level strategies that target the general public. They are designed to raise public awareness and knowledge about antibiotic misuse through mass media such as television, radio, internet, posters, leaflets and newspapers.[32] Their aim is to benefit the target population and/or the society altogether. Regulatory interventions are system-level strategies designed to outline a framework of requirements and legal practice of antibiotic use (e.g. limiting prescribing and/or dispensing).[8, 42] Their goal is to enforce decision-making to improve the use of antibiotics.

Types of outcome measures

We will extract primary and secondary outcomes to measure the effectiveness, feasibility and acceptability of interventions, regardless of the outcome measurement instruments used, the outcome measure (e.g. prescribed individuals, prescriptions, items as numerators, and RTI patients or patient years "at risk" as denominators),[43-45] their nature (objective or subjective) and time points.

EFFECTIVENESS

Primary outcomes

For all interventions to improve antibiotic use, the effect of interventions on the quality of antibiotic prescribing and use will be measured by means of:

- rates and types of (any) antibiotics prescribed and/or used for primary care patients with acute RTI
- rates and types of guideline-recommended antibiotics prescribed for primary care patients with acute RTI

Secondary outcomes

For healthcare professional and patient-targeted interventions, the effect of interventions on the quality of antibiotic prescribing and use will be measured by means of:

- rates and types of antibiotics prescribed as immediate and delayed use
- patients' adherence to immediate and/or delayed prescribing:

- antibiotic resistance (e.g. rates of patients with RTI with proven antibiotic resistant bacteria, and reduction of resistance as a result of the intervention);
- types and rates of medical complications (e.g. emergency visits, hospital admissions due to possible RTI (complications), and mortality);
- adverse effects of antibiotic use (e.g. nausea and diarrhoea);
- adverse effects of the intervention strategy (e.g. increased consultation times of physicians);
- the costs of healthcare services, programs and (dispensing) medication; healthcare utilization (e.g. length of consultations, tests ordered);
- consultation rates: re-consultation rates including re-consultations due to deterioration of original infection (e.g. unplanned re-visits within 2-3 weeks of first consultation) and due to new RTI episodes;
- patient outcome (e.g. symptom severity, symptom resolution, disease duration, time to resume school or work);
- patients' and clinicians' knowledge about antibiotic use;
- patients' participation rate in decision making about antibiotic use;
- patient satisfaction with care;
- quality of patient-healthcare provider communication

Depending on the number of reviewers available in our team, we may also assess the secondary outcomes for studies of campaigns and regulatory interventions (e.g. antibiotic resistance, types and rates of medical complications, the costs of healthcare services, programs and (dispensing) medication, and healthcare utilisation).

Other outcomes of interest: quality of life, use of non-antibiotic medication (e.g. over-the-counter medicines), sustainability of interventions (i.e. change in the prescribing pattern over a period after the delivery of interventions), physicians' and patients' views and attitudes towards antibiotic prescribing.

FEASIBILITY AND ACCEPTABILITY

Secondary outcomes

For patient- and clinician-targeted interventions, the feasibility and acceptability of interventions to improve the quality of antibiotic prescribing and use measured as, for example, satisfaction with the intervention or uptake of interventions.

Types of studies

For healthcare professional (clinicians and/or pharmacists) and patient-targeted interventions, we will include studies of prospective, comparative and experimental design including parallel randomised controlled trials (RCTs), quasi-RCTs in which the method of allocation is not strictly random (e.g. allocation by alternation, date of birth, hospital number), and cluster-RCTs in which the method of allocation is by group (e.g. patients of the same physician) if they:

a) evaluate the effectiveness of interventions to improve antibiotic prescribing and/or use for RTIs; and/or

b) evaluate the feasibility and acceptability of patient and clinician-targeted interventions to improve antibiotic use for RTIs in primary care general practice

For public awareness (local, national, and 'choosing wisely') campaigns[40-41] and regulatory interventions, besides RCTs, we will also include other study designs (e.g. non-randomised controlled trials, before and after studies with or without a contemporary control group) if they:

a) evaluate the effectiveness of interventions to improve antibiotic prescribing and/or use for RTIs

If eligible, studies will be included regardless of the length of follow-up, publication year and country of origin. We aim to include studies published in English and other languages. We will give priority to the inclusion of studies published in English. Depending on the number of reviewers available in our team, we will include studies published in languages other than English in the following order: Spanish, German and other languages (see study selection). We will not include systematic reviews and meta-analyses in this review, but we will use them to identify additional studies.

Types of setting

Studies carried-out in the following primary care settings will be included:

1) in-hours (e.g. paediatric and family practice clinics)

2) out-of-hours ambulatory care

We will exclude studies from in-patient settings.

Search methods

We will design and conduct a comprehensive search strategy, and will cross-check it with the strategies of two available systematic reviews.[25, 27] The search strategy will aim to identify RCTs in humans evaluating interventions aiming to improve antibiotic prescribing and use. These will include healthcare professional and patient-targeted interventions, as well as public awareness campaigns and regulatory interventions. We will develop a search strategy in collaboration with an information specialist, and will follow the PICOTS (populations, interventions, comparisons, timing, and settings) approach. It will not be restricted to reporting language, population age or gender, publication date, country or outcomes.

We will search MEDLINE (EBSCOHost), EMBASE (Elsevier), The Cochrane Library (Wiley), CINHAL (EBSCOHost), PsychINFO (EBSCOHost) and Web of Science from their inception until the date of the search. The concepts and terminology will be considered and translated to fit all database searches. These may include 'respiratory tract infections' 'antibiotic', 'antimicrobial', 'anti-bacterial/anti-infective agents', 'prudent/judicious antibiotic use', 'prescribers/prescribing', 'interventions', 'strategies', 'stewardship', 'primary health care', 'outpatients', 'in-hours care' and 'after/out-of-hours care'. The strategy may also include the terminology specific to interventions to improve antibiotic prescribing and use, such as 'education', 'point of care', 'audit or feedback', 'information/awareness' campaign and 'choosing wisely' campaign. We will also search for grey literature using the Latin American and Caribbean Literature on Health Sciences (LILACS), Turning Research Into Practice database (TRIP), and the system for information on grey literature in Europe (http://opengrey.eu/). We will identify additional publications by manually searching the reference lists of included studies and relevant reviews. We might update the searches of relevant databases before publication of the review to screen for further potentially eligible studies. Supplementary file 2 provides a draft of the full search strategy in Embase.

Study selection

We will merge all records identified by the electronic and manual searches, and will remove duplicate citations. We will prioritise the selection of studies published in English. Depending on the number of reviewers available in our team, we will also appraise the citations and publications of studies published in languages other than English in the following order: Spanish, German and other languages. Two reviewers will independently screen and sift the title and abstract of each citation. We will obtain the full-text publications of citations which meet the eligibility criteria, appear relevant, or for which eligibility is not clear. The full-text publications of selected citations will be independently evaluated by two reviewers. The recommendations proposed by the Centre for Research in Evidence Based Practice[46] will be followed in order to translate the abstracts of potentially relevant citations and full-texts of eligible publications reported in languages other than English for appraisal. The final list of included studies will be confirmed and the reasons for excluding studies recorded. Differences in judgment of eligibility will be resolved by discussion or involvement of an arbitrator, or both.

Data extraction and management

Data extraction will be conducted by one reviewer and verified by a second reviewer. Data from studies reported across more than one publication will be extracted as one unit. If more than one study is reported by a single publication, data will be extracted as separate studies where possible. Studies may be excluded at the data appraisal stage if it becomes apparent that they do not meet the inclusion criteria. If studies reported in languages other than English are appraised, data extraction from publications eligible for inclusion will be confirmed by a native-speaker following translation of full-text. Differences in data collection will be resolved by discussion or involving an arbitrator, or both. For each eligible study, data will be extracted and recorded as follows:

a) bibliographic details and descriptive study elements (design, care setting, number of facilities/sites, geographic distribution, start and end dates of study);
b) patient characteristics: inclusion/exclusion, age, sex, ethnicity, co-morbidities (e.g. asthma and COPD), population type served (e.g. urban), socioeconomic (higher versus lower

income regions), educational level, regional differences (e.g. in a country: north versus south; deprived versus affluent; urban versus rural), time of year, number of randomised/enrolled participants and withdrawals;

c) provider characteristics: age, gender, experience (e.g. years in practice), number of clinicians per site;

d) RTI characteristics: type (e.g. upper RTI, acute otitis media, lower RTI, bronchitis), diagnostic method and/or tools used, signs and symptoms, antibiotic therapy prescribed (recommended/not recommended agents, doses, duration, route of administration) and antibiotic therapy previously used;

e) interventions/comparators characteristics: definition, description and components (tools used e.g. information leaflets, decision aids), interventions' intended target (patients or patients' parents/carer, physicians and/or pharmacists), delivery time (e.g. before consultation), duration, follow-up episodes; and

f) outcome details: the value of "appropriateness" and/or "inappropriateness" that authors of eligible studies have adjudicated to antibiotics prescribing and/or use; outcome measurement tools/methods (validated or not), definitions and time points; the quantitative results for each outcome; and any qualitative statements about the association between the outcomes and the intervention and comparison groups.

We will group together studies with similar definitions of appropriateness in prescribing. We will group studies' interventions into distinct categories by their components based on proposed classification systems.[26-27] Data will be organized by RTI type (e.g. upper RTI, acute otitis media, lower RTI, bronchitis), care setting, population (with distinction by targeted participants), intervention and sources of variation (e.g. regional differences in a country).

Risk of bias assessment

The quality features of included studies will be assessed in duplicate by two independent reviewers using criteria forms based on established guidelines. Differences will be resolved by discussion or the involvement of an arbitrator, or both. The criteria will cover the core items related to the internal validity of RCTs,[47] i.e. methods of random sequence generation and concealment of allocation at randomisation, the use of blinding and intention to treat (ITT)

analysis, and similarity between groups at baseline. Blinding patients and clinicians may not be possible due to the nature of interventions. It is possible to perform blinded assessment of outcomes however, and to identify whether studies are prone to selective outcome reporting. Following the debate about scoring the quality of trials, discussed in depth by Juni et al.,[48] we will not calculate a composite score. The validity of eligible studies will be determined by rating the adequacy of each core item. RCTs of adequate quality will be those with an adequate generation of random sequence, concealment of allocation (at randomisation), and blinding of outcome assessors based on established guidelines [47]. Bias due to attrition will be considered as being of significant concern if there is a loss to follow-up of at least 20%; ITT will be considered adequate if authors analysed participants based on their original group allocation. We will describe the studies' adequacy in each item with an overall judgment on the quality of evidence, and generate summary tables with the quality profile of each study. For other study designs (e.g. before and after, and non-randomised), assessment criteria will be based on items from the Cochrane Collaboration's by EPOC,[49] the Newcastle-Ottawa Scale[50] and ROBINS-I.[51] In all studies, we will assess reporting criteria including the definition and reporting of primary and secondary outcomes, inclusion and exclusion criteria, 'a-priori' sample size calculation, and funding sources.

Data analysis

We will use the Cochrane Collaboration's analysis software RevMan 5.3[52] for statistical analyses, and will follow available guidelines to incorporate cluster-RCTs.[47] For binary data, the intervention effect will be estimated using the unadjusted Risk Ratios or Odd Ratios with 95% confidence intervals (CI). For continuous data, the intervention effect will be estimated using the weighted mean differences or standardized mean differences if studies use different scales. Where sufficient detail allows their calculation, the summary statistics and 95% CIs together with the exact p-values will be reported. One single estimate of a treatment effect will be produced for each individual study. Data permitting, outcome data will be combined and meta-analyses will be incorporated where appropriate (i.e. ≥2 studies per outcome). The pooled effect estimate(s) will be produced using the random effects model and will be retained if between-study heterogeneity is substantial. Otherwise the fixed-effects model will

be used. Available guidance will be used to estimate missing data.[47] We will assess between-study heterogeneity using the I^2 statistic[53] and by visual inspection of forest plots.[54] Values of heterogeneity are represented as low (below 25%), moderate (50%), severe (up to 75%), and very severe (more than 75%). We will also assess the impact of awareness and 'choosing wisely' campaigns and regulatory interventions over time. The pooled rates of prescriptions due to RTI will be calculated and compared for data before and after (e.g. six months) the implementation of such interventions.

We will report the results using forest plots where appropriate and evidence-based summary of finding tables. We will synthesise all results descriptively including those where quantitative synthesis is not appropriate.

Subgroup and sensitivity analyses

If enough data are available from the studies in review, we will perform subgroup and sensitivity analyses for the primary outcomes only. We will conduct subgroup analyses in the following areas:

a) population and interventions characteristics: country (developing vs. developed), population (children and adults aged 18 years and older, gender, socioeconomic status and educational level, time of year), care setting (in-hours vs. out-of-hours care), acute RTI type, antibiotic therapy, diagnostic method, intervention type and intended target (patients and/or physicians and/or pharmacists);

b) risk of bias and other methodological criteria: adequate (vs. other), random sequence generation, allocation concealment and blinding attrition (lower levels: <20% vs. higher levels: ≥20%), and intention to treat; study size (small: N<200 vs. large: N≥200), and length of follow-up.

We will perform sensitivity analyses by excluding studies with higher risk of bias, dubious criteria for inclusion, and unclear definitions of acute RTI or studies that do not differentiate

DISCUSSION

AMR due to antibiotic consumption is a shared global health priority and most antibiotics are administered in primary care where they are commonly used for the management of RTIs.

Our systematic review will evaluate the interventions aimed at improving the quality of prescribing and use of antibiotics for acute RTI. To the best of our knowledge, this is the first 'back-to-back' systematic review on both 1) healthcare professional and patient-targeted interventions, and 2) public awareness campaigns and regulatory interventions. The evaluation of these interventions will allow a comparison of their impact, providing unique information to policy makers.

A synthesis with a broader scope including international evidence from peer-reviewed and grey literature on all types of these interventions, expanded to adults and children, and including in-hours and out-of-hours care has never been performed. In addition, our search will have no language restrictions, thus allowing the identification of evidence from non-English literature. This could provide valuable findings. The results will provide estimates of the effectiveness, as well as the feasibility and acceptability of such interventions, with an assessment of the methodological quality of the included studies. A thorough search in a large number of sources will enable a comprehensive identification and assessment of data. The evidence in this review may be limited by the quality of studies and the significant heterogeneity of the results, and this may challenge the interpretation of results. We expect however that the review will produce a comprehensive and up-to-date evidence-based body of knowledge about the interventions which provide the most benefits towards more judicious antibiotic prescribing and use. This would ultimately help improve AMR. The results may help design future interventions, and will be of international interest to public health, primary healthcare professionals, policy makers and patients.

ETHICS AND DISSEMINATION

Formal ethical approval is not required given that this is a protocol for a systematic review and confidential personal or primary data on interventions on patients will not be collected. The findings of this review will be disseminated at national and international scientific meetings.

REGISTRATION AND PUBLISHING

This systematic review protocol is registered on the International Prospective Register of Systematic Reviews (http://www.crd.york.ac.uk/PROSPERO/): CRD42017035305. The

reporting of the review will follow the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist[55] and the review findings will be published in peer-review journals.

Contributors

NM wrote the manuscript, conceived and designed the review, critically revised several drafts of the protocol, and contributed to its improvement. NM will also be involved in designing and testing the data extraction forms, screening studies, extracting data, assessing study quality, and performing analysis. SC conceived and designed the review, critically revised several drafts of the protocol, and contributed to its improvement. AP critically revised several drafts of the protocol, and contributed to its improvement. AP will also be involved in designing and testing the data extraction forms, screening studies, extracting data, and assessing study quality. AC critically revised several drafts of the protocol and contributed to its improvement. AC will also be involved in designing and testing the data extraction forms, screening studies, extracting data, and assessing study quality. TR critically revised several drafts of the protocol, and contributed to its improvement. OS conceived and designed the review, critically revised several drafts of the protocol, and contributed to its improvement. SNJ conceived and designed the review, critically revised several drafts of the protocol, and contributed to its improvement. All authors read and approved the final manuscript.

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Competing interest

The authors declare no competing interests.

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Supplementary file 2: Search strategy in Embase (ELSEVIER).

No.	Search
1	'acute sinusitis'/exp OR 'acute otitis media'/exp OR 'common cold'/exp OR 'sore throat'/exp OR 'pharyngitis'/exp OR 'tonsillitis'/exp OR 'rhinitis'/exp OR 'rhinopharyngitis'/exp OR 'laryngitis'/exp OR ('bronchitis'/exp NOT 'chronic bronchitis'/exp) OR 'respiratory tract disease'/de OR 'pleurisy'/exp OR 'pneumonia'/exp OR 'coughing'/exp OR 'sneezing'/exp OR 'otalgia'/exp OR 'influenza'/exp OR flu:ab,ti OR influenza:ab,ti OR 'respiratory syncytial vir*':ab,ti OR rsv:ab,ti OR rti:ab,ti OR urti:ab,ti OR rhinit*:ab,ti OR pharyngit*:ab,ti OR nasopharyngit*:ab,ti OR rhinopharyngit*:ab,ti OR rhinorrhoea:ab,ti OR rhinorrhea:ab,ti OR tonsillit*:ab,ti OR laryngit*:ab,ti OR mononucleo*:ab,ti OR croup:ab,ti OR pseudocroup:ab,ti OR tracheobronchit*:ab,ti OR laryngotracheobronchit*:ab,ti OR pneumon*:ab,ti OR pleuropneumon*:ab,ti OR bronchopneumon*:ab,ti OR pleurisy:ab,ti OR cough*:ab,ti OR sneez*:ab,ti OR earache*:ab,ti OR (common NEAR/3 (cold OR colds)):ab,ti OR ((runny OR running OR discharg* OR congest* OR blocked OR stuff* OR dripping) NEAR/3 (nose* OR nasal)):ab,ti OR ((respiratory OR chest) NEAR/3 (infect* OR inflam*)):ab,ti OR (throat* NEAR/3 (inflam* OR infect*)):ab,ti OR (acute NEAR/3 (sinusit* OR bronchit* OR bronchiolit* OR 'otitis media' OR nasosinusit* OR rhinosinusit*)):ab,ti OR (acute NEAR/3 'middle ear*' NEAR/3 infect*):ab,ti
2	'antibiotic agent'/exp OR 'quinoline derived antiinfective agent'/exp OR 'sulfonamide'/exp OR antibacterial*:ti,ab OR 'anti bacterial*':ti,ab OR antibiotic*:ti,ab OR 'anti biotic*':ti,ab OR 'anti infective':ti,ab OR macrolide*:ti,ab OR 'beta lactam*':ti,ab OR antimicrobial*:ti,ab OR 'anti microbial*':ti,ab OR penicillin:ti,ab OR methicillin:ti,ab OR ampicillin:ti,ab OR azithromycin:ti,ab OR cephalexin:ti,ab OR fluoroquinolon*:ti,ab OR quinolon*:ti,ab OR quinolin*:ti,ab OR sulfonamid*:ti,ab OR sulphonamid*:ti,ab OR sulfamoyl:ti,ab OR 'amantadine'/exp OR 'amantadine sulfate'/exp OR 'arbidol'/exp OR 'rimantadine'/exp OR 'umifenovir'/exp OR 'zanamivir'/exp OR 'oseltamivir'/exp OR 'peramivir'/exp OR amantadine:ti,ab OR adamantanamine:ti,ab OR endantadine:ti,ab OR enzil:ti,ab OR amantix:ti,ab OR amantrel:ti,ab OR amazolon:ti,ab OR aminoadamantane:ti,ab OR aminoadamantine:ti,ab OR atarin:ti,ab OR boidan:ti,ab OR hofcomant:ti,ab OR infectoflu:ti,ab OR mantadan:ti,ab OR mantadix:ti,ab OR mantidan:ti,ab OR midantane:ti,ab OR nurelin:ti,ab OR padiken:ti,ab OR paritrel:ti,ab OR parkintrel:ti,ab OR 'pk merz':ti,ab OR prayanol:ti,ab OR protexin:ti,ab OR symadine:ti,ab OR symetrel:ti,ab OR symmetrel:ti,ab OR tregor:ti,ab OR viregyt:ti,ab OR virofral:ti,ab OR virosol:ti,ab OR virucid:ti,ab OR 'amantadine sulfate':ti,ab OR 'amantadine sulphate':ti,ab OR grippin:ti,ab OR 'arbidol':ti,ab OR 'rimantadin*':ti,ab OR flumadine:ti,ab OR flumandine:ti,ab OR gabirol:ti,ab OR germic:ti,ab OR remantadin:ti,ab OR remantadine:ti,ab OR 'ro22 1859':ti,ab OR roflual:ti,ab OR 'umifenovir':ti,ab OR 'zanamivir':ti,ab OR gg167:ti,ab OR 'gr 121167':ti,ab OR relenza:ti,ab OR 'oseltamivir':ti,ab OR tamiflu:ti,ab OR 'peramivir':ti,ab OR 'bcx 1812':ti,ab OR bcx1812:ti,ab OR peramiflu:ti,ab OR rapiacta:ti,ab OR rapivab:ti,ab OR 'rwj 270201':ti,ab OR rwj270201:ti,ab
3	'ambulatory care'/exp OR 'outpatient department'/exp OR 'general practice'/exp OR 'primary health care'/exp OR 'outpatient'/exp OR 'outpatient care'/exp OR 'home visit'/exp OR 'emergency health service'/exp OR 'pharmacist'/exp OR 'pharmacy technician'/exp OR 'pharmacy'/exp OR (ambulatory NEAR/3 (care OR setting? OR facilit* OR ward? OR department? OR service?)):ti,ab OR practi*:ti,ab OR physician*:ti,ab OR doctor*:ti,ab OR clinician*:ti,ab OR pharmacist*:ti,ab OR pharmacy:ti,ab OR pharmacies:ti,ab OR 'primary care':ti,ab OR 'primary health care':ti,ab OR 'primary healthcare':ti,ab OR 'after hour*':ti,ab OR afterhour*:ti,ab OR 'out of hour*':ti,ab OR ooh:ti,ab OR ((clinic OR clinics OR office) NEAR/3 (visit OR visits)):ti,ab OR ((health* OR medical) NEAR/2 (center OR centers OR centre*)):ti,ab OR outpatient*:ti,ab OR (emergency NEAR/3 (care OR setting* OR facility OR facilities OR ward OR wards OR department* OR service*)):ti,ab
4	#1 AND #2 AND #3

5	'rapid test'/exp OR 'chemiluminescence immunoassay'/exp OR 'immunofluorescence test'/exp OR 'inhalation test'/exp OR 'laboratory test'/exp OR 'gram staining'/exp OR 'calcitonin derivative'/exp OR 'blood cell count'/exp OR 'blood gas'/exp OR 'enzyme linked immunosorbent assay'/exp OR 'nucleic acid amplification'/exp OR 'latex agglutination test'/exp OR 'thorax radiography'/exp OR 'c reactive protein'/exp OR 'polymerase chain reaction'/exp OR 'colorimetry'/exp OR 'cell culture'/exp OR (('point of care' OR poc) NEAR/3 (diagnos* OR test* OR assay* OR kit OR kits)):ti,ab OR ((immediat* OR routine) NEAR/3 (test* OR diagnos*)):ti,ab OR ((rapid* OR quick* OR swift* OR office*) NEAR/3 (test* OR kit OR kits OR assay* OR swab*)):ti,ab OR (strep* NEAR/5 (test* OR kit OR kits OR assay* OR swab*)):ti,ab OR procalcitonin:ti,ab OR 'c-reactive protein*':ti,ab OR monospot*:ti,ab OR ((antibod* OR gram) NEAR/3 stain*):ti,ab OR (fluoresc* NEAR/3 antibod*):ti,ab OR ('reverse transcriptas*' NEAR/3 ('polymerase chain reaction*' OR pcr)):ti,ab OR ((singleplex* OR multiplex*) NEAR/3 ('polymerase chain reaction*' OR pcr)):ti,ab OR ((chest* OR thorac* OR thorax) NEAR/3 (radiogra* OR 'x ray*')):ti,ab OR ((leukocyt* OR 'white blood cell*' OR wbc OR neutrophil) NEAR/3 (test* OR count*)):ti,ab OR (blood NEAR/2 (gas OR gases) NEAR/3 (analy* OR test*)):ti,ab OR elisa:ti,ab OR immunoassay:ti,ab OR ((agglutinin OR coagglutinin OR 'breath based' OR inflammatory) NEAR/3 test*):ti,ab OR (cell NEAR/3 (culture* OR colon*)):ti,ab
6	'decision support system'/exp OR 'information system'/exp OR 'health personnel attitude'/exp OR 'patient information'/exp OR 'patient education'/exp OR 'health promotion'/exp OR 'practice guideline'/exp OR 'protocol compliance'/exp OR 'inappropriate prescribing'/exp OR 'drug misuse'/exp OR 'drug utilization'/exp OR 'absenteeism'/exp OR 'return to work'/exp OR intervention*:ti OR audit*:ti OR feedback:ti OR ((clinical OR clinician* OR performance OR outcome OR regulatory) NEAR/3 (intervention* OR audit* OR feedback OR review)):ti,ab OR (decision* NEAR/3 (make OR makes OR making OR made OR tool* OR system* OR method* OR approach*)):ti,ab OR ((drug* OR medical* OR pharmac*) NEAR/3 (utiliz* OR misuse OR misusage OR limit* OR restriction* OR banning)):ti,ab OR ((prescib* OR dispens* OR utiliz*) NEAR/3 (formular* OR restrict* OR control* OR banning)):ti,ab OR (attitud* NEAR/3 ('health personnel' OR doctor OR physician OR practitioner*)):ti,ab OR (practice* NEAR/3 pattern*):ti,ab OR (risk* NEAR/3 assess*):ti,ab OR ((education OR teach* OR information OR instruct*) NEAR/3 (professional OR 'interprofessional' OR material* OR method* OR campaign* OR strateg* OR patient* OR public OR program*)):ti,ab OR (communication NEAR/3 (skill* OR train* OR improve* OR strateg*)):ti,ab OR ((public OR health OR awareness OR local OR national OR regional OR wise*) NEAR/3 (campaign* OR strategy OR strategies)):ab OR campaign:ti OR strategy:ti OR strategies:ti OR ((professional* OR doctor* OR physician* OR practitioner*) NEAR/3 patient* NEAR/3 (relation* OR interaction OR request* OR ask*)):ti,ab OR ((guideline* OR protocol* OR workflow* OR recommendation* OR path*) NEAR/3 (adheren* OR comply* OR complian* OR obey*)):ti,ab OR ((professional* OR clinical*) NEAR/3 (competen* OR skill* OR abilit* OR knowledg*)):ti,ab OR ((inappropriat* OR imprudent* OR unreasonab* OR unwis* OR improper* OR unnecessar* OR useless* OR incorrect* OR worthless* OR useless* OR unneeded OR gratuitous* OR ineffect* OR overus* OR 'over us*') NEAR/3 (prescri* OR give OR gives OR giving OR issue OR issuing OR provid* OR use OR usage OR utiliz*)):ti,ab OR ((appropriat* OR judicious* OR judge* OR judging OR wise* OR prudent* OR sensible OR reasonabl* OR proper* OR necessar* OR useful* OR correct* OR worthwhile* OR needed OR effectiv* OR delay* OR postpon*) NEAR/3 (prescri* OR give OR gives OR giving OR issue OR issuing OR provid* OR use OR usage OR utiliz*)):ti,ab OR (('non antibiotic' OR nonantibiotic) NEAR/3 (prescribe* OR us*)):ti,ab OR ((critical* OR clinical*) NEAR/3 (path OR paths OR pathway* OR algorithm* OR 'prediction rule*')):ti,ab OR ((antibiotic* OR 'anti biotic*' OR 'anti microb*' OR antimicrob*) NEAR/3 steward*):ti,ab OR ((system* OR computer* OR electronic*) NEAR/3 (remind* OR alert*)):ti,ab OR ((econom* OR financ* OR regulatory OR dollar* OR cash OR money OR physician* OR provider* OR doctor* OR clinician* OR practitioner* OR nurse*) NEAR/3 (incentiv* OR reimburs*)):ti,ab OR ((worker* OR job OR jobs OR workplace* OR employe* OR student* OR school* OR daycare OR 'day care' OR pupil* OR child* OR infant* OR baby OR babies OR toddler*) NEAR/5 (keep* OR stay* OR remain*) NEAR/3 (home OR away)):ti,ab OR ((return* OR 'com* back') NEAR/5 (work* OR job OR jobs OR school* OR class OR daycare OR 'day care')):ti,ab
7	#5 OR #6
8	#4 AND #7

9	'randomized controlled trial'/exp OR 'randomization'/exp OR 'controlled study'/exp OR 'multicenter study'/exp OR 'phase 3 clinical trial'/exp OR 'phase 4 clinical trial'/exp OR 'double blind procedure'/exp OR 'single blind procedure'/exp OR random*:ab,ti OR crossover*:ab,ti OR 'cross over*':ab,ti OR 'cross over':ab,ti OR crossingover*:ab,ti OR factorial*:ab,ti OR assign*:ab,ti OR allocat*:ab,ti OR placebo*:ab,ti OR volunteer*:ab,ti OR ((singl* OR doubl* OR trebl* OR tripl*) NEAR/3 (blind* OR mask*)):ab,ti NOT ('animal'/exp OR 'nonhuman'/exp NOT 'human'/exp)
10	#4 AND #7 AND [systematic review]/lim
11	#8 AND #9
12	#10 OR #11
13	#10 OR #11 AND [conference abstract]/lim AND [1-1-2015]/sd NOT [7-4-2017]/sd
14	#10 OR #11 NOT [conference abstract]/lim
15	#13 OR #14

Supplementary file 1: PRISMA-P 2015 Checklist.

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	Page where reported in protocol
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	n/a
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2 (Protocol registration number: CRD42017035305)
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	19
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	19
Sponsor	5b	Provide name for the review funder and/or sponsor	19
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	19
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	4-6
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	7
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	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	12
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	12, Supplemental file 2
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	13
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)	13
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	13
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	13
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	9
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	14
DATA			
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	15
	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)	15
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	16
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	16
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	16
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	14, 15

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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