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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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ABSTRACT

Introduction Respiratory tract infections (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 antibiotic resistance (ABR) leading to complications, increased adverse events, reconsultations and costs. Improving antibiotic consumption is thus crucial to containing ABR, 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-targeted 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 (Latin American and Caribbean Literature on Health Sciences), TRIP (Turning Research Into Practice) 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 and so formal ethical approval is not required. We will not collect confidential, personal or primary data. The findings of this review will be disseminated at national and international scientific meetings.

Trial registration number PROSPERO trial (CRD42017035305).

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 which 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.

► The quality of studies and the significant heterogeneity of results might limit the performance of meta-analyses and may challenge the interpretation of findings.

► 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 and may help design such interventions in the future.

INTRODUCTION

Antibiotic resistance (ABR) 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 ABR 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 US$60–100 trillion between now and 2050.[3] Antibiotic consumption, particularly inappropriate drug use, is the main and modifiable driver of ABR.[4] The extent of antibiotic use has been consistently

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associated with the rate of ABR at the individual, community and national levels.[5][6]

Most antibiotics used in humans are administered in primary care (PC). In Europe, 80%–90% of all antibiotics are prescribed in primary ambulatory care,[6][7] whereas 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, reconsultations, 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 ABR[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 revisit 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 ABR[22][23] and has positive effects on seeking behaviour for RTIs (eg, 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 ABR recognises that isolated interventions have little impact on improving antibiotic use.[29] In many countries, interventions are increasingly being integrated in system-level 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 ABR.[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 RTIs in PC. Our second objective is to assess the feasibility and acceptability of patient-targeted 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-targeted 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) (see online supplementary file 1),[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:
► What is the (comparative) effectiveness of interventions to improve antibiotic use on the quality of antibiotic prescribing and use in PC patients with acute RTI?
► What is the feasibility and acceptability of patient-targeted and clinician-targeted interventions to improve antibiotic use on the quality of antibiotic prescribing and use in patients with acute RTI in PC 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 PC settings with a common acute RTI. The studies might 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 an acute RTI including physicians (eg, 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 <4 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 and 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 chronic obstructive pulmonary disease (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 inpatients.

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 and general public) or reduction of prescribing and dispensing by healthcare professionals (clinicians and 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, for example, educational, clinical (eg, delayed prescribing and point of care) and system level strategies (eg, 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.

Healthcare professional interventions target clinicians (eg, paediatricians and family physicians, and nurses) or pharmacists, whereas patient-targeted interventions target patients with acute RTIs 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 (eg, 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 (eg, prescribed individuals, prescriptions, items as numerators and patients with RTI 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 PC patients with acute RTI
► rates and types of guideline-recommended antibiotics prescribed for PC 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 (eg, 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 (eg, emergency visits, hospital admissions due to possible RTI (complications) and mortality);
► adverse effects of antibiotic use (eg, nausea and diarrhoea);
► adverse effects of the intervention strategy (eg, increased consultation times of physicians);
► the costs of healthcare services, programmes and (dispensing) medication; healthcare utilisation (eg, length of consultations and tests ordered);
► consultation rates: reconsultation rates including reconsultations due to deterioration of original infection (eg, unplanned revisits within 2–3 weeks of first consultation) and due to new RTI episodes;
► patient outcome (eg, symptom severity, symptom resolution, disease duration and 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 (eg, antibiotic resistance, types and rates of medical complications, the costs of healthcare services, programmes and (dispensing) medication, and healthcare utilisation).

Other outcomes of interest

Quality of life, use of non-antibiotic medication (eg, over-the-counter medicines), sustainability of interventions (ie, 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-targeted 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 (eg, allocation by alternation, date of birth and hospital number), and cluster-RCTs in which the method of allocation is by group (eg, patients of the same physician) if they: (1) evaluate the effectiveness of interventions to improve antibiotic prescribing and/or use for RTIs and/or (2) evaluate the feasibility and acceptability of patient-targeted and clinician-targeted interventions to improve antibiotic use for RTIs in PC 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 (eg, non-RCTs, before and after studies with or without a contemporary control group) if they 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 section). 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 PC settings will be included:
- ► in-hours (eg, paediatric and family practice clinics)
- ► out-of-hours ambulatory care.

We will exclude studies from inpatient settings.

Search methods

We will design and conduct a comprehensive search strategy and will crosscheck 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 (TRIP) database 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. Online 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 judgement 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: (1) bibliographic details and descriptive study elements (design, care setting, number of facilities/sites, geographic distribution, start and end dates of study); (2) patient characteristics: inclusion/exclusion, age, sex, ethnicity, comorbidities (eg, asthma and COPD), population type served (eg, urban), socioeconomic (higher vs lower income regions), educational level, regional differences (eg, in a country: north vs south, deprived vs affluent and urban vs rural), time of year, number of randomised/ enrolled participants and withdrawals; (3) provider characteristics: age, gender, experience (eg, years in practice) and number of clinicians per site; (4) RTI characteristics: type (eg, upper RTI, acute otitis media, lower RTI and bronchitis), diagnostic method and/or tools used, signs and symptoms, antibiotic therapy prescribed (recommended/not recommended agents, doses, duration and route of administration) and antibiotic therapy previously used; (5) interventions/comparators characteristics: definition, description and components (tools used, eg, information leaflets and decision aids), interventions' intended target (patients or patients' parents/ carer, physicians and/or pharmacists), delivery time (eg, before consultation), duration and follow-up episodes and (6) outcome details: the value of 'appropriateness' and/or 'inappropriateness' that authors of eligible studies have adjudicated to antibiotic 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 organised by RTI type (eg, upper RTI, acute otitis media, lower RTI and bronchitis), care setting, population (with distinction by targeted participants), intervention and sources of variation (eg, 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] that is, 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 Jüni 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 judgement on the quality of evidence and generate summary tables with the quality profile of each study. For other study designs (eg, before and after, and non-randomised), assessment criteria will be based on items from the Cochrane Collaboration's by Effective Practice and Organisation of Care,[49] the Newcastle-Ottawa Scale[50] and Risk Of Bias In Non-randomised Studies–of Interventions.[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 V.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 ORs with 95% CI. For continuous data, the intervention effect will be estimated using the weighted mean differences or standardised 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 (ie, two or more 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 (eg, 6 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: (1) population and interventions characteristics: country (developing vs developed), population (children and adults aged 18 years and older, gender, socioeconomic status and educational level, and 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) and (2) 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 ITT; 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. We will also exclude studies which do not differentiate between RTI type or which report unclear or incomplete definitions of appropriate prescribing.

ABR due to antibiotic consumption is a shared global health priority and most antibiotics are administered in PC 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 ABR. The results may help design future interventions and will be of international interest to public health, primary healthcare professionals, policy-makers and patients.

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 PRISMA checklist,[55] and the review findings will be published in peer-reviewed journals.

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