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Improving antibiotic prescribing by general practitioners: A protocol for a systematic review of interventions involving pharmacists

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Title of the study protocol:

Improving antibiotic prescribing by general practitioners: A protocol for a systematic review of interventions involving pharmacists

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ABSTRACT

Introduction

Antibiotic prescribing options in general practice (GP) for patients with infections are declining significantly due to imprudent antibiotic prescribing and emerging antibiotic resistance. To better improve antibiotic prescribing by general practitioners (GPs), pharmacist-GP collaborations have been promoted under antibiotic stewardship programs. However, there is insufficient information about whether and how pharmacists help GPs to more appropriately prescribe antibiotics. This systematic review aims to determine whether pharmacist-led or pharmacist involved interventions are effective at improving antibiotic prescribing by GPs within general practice.

Methods and analysis

A systematic review of English language randomised controlled trials (RCTs), cluster randomized trials (cRCTs), controlled before-after studies (CBAs) and interrupted time series (ITS) studies cited in MEDLINE, EMBASE, EMCARE, CINAHL plus, PubMed, PsycINFO, Cochrane CENTRAL, and WEB OF SCIENCE databases will be conducted. Studies will be included if a pharmacist is involved as the intervention provider and GPs are the intervention recipients in general practice or family practice setting. Data extraction and management will be conducted utilizing EPOC's data abstraction tools and a template for intervention description and replication (TDieR).The Cochrane and ROBINS-I risk of bias assessment tools will be used to assess the methodological quality of studies. Primary outcome measures include changes (overall and guidelines concordant) of GP prescribed antibiotics. Secondary outcomes include quality of antibiotic prescribing, delayed antibiotic use, acceptability, and feasibility of interventions. Meta-analysis for combined effect and Forest plots, $\chi 2$ test, and I^2 statistics for detailed heterogeneity and sensitivity analysis will be performed if data permits. We will use GRADE and PRISMA-P guidance to summarize and report findings.

Ethics and dissemination

No formal ethical approval is required as no primary, personal and confidential data is being collected in this study. The findings will be disseminated to national and international scientific sessions, in addition, to publishing in a peer reviewed journal.

Trial registration number: PROSPERO registration number CRD42017078478

Keywords: Antibiotic stewardship, Interventions, Pharmacist, General practitioner, Systematic review

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Strengths and Limitations of this study

- First systematic review assessing pharmacist-led or pharmacist involved interventions to improve GPs' antibiotic prescribing in primary care
- This review is solely based on general practice or family practice excluding aged care, nursing home, and dental care facilities in order to increase applicability of the findings
- Significant heterogeneity and quality of study may hinder meta-analysis and interpretation of findings
- The findings will support general practitioners, pharmacists, researchers, and health policy makers make informed decisions about effective and feasible interventions to introduce under antibiotic stewardship programs in general practice to improve quality of antibiotic prescribing and use of antibiotics.
- The results will help to understand how the expertise of pharmacist is utilized in general practice to promote rational use of antibiotics through GP-pharmacist collaborative intervention model.

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INTRODUCTION

Growing antibiotic resistance (AR) and a shortage of new effective antibiotics have become an urgent global threat to public health[1 2] with a risk of a significant rise in morbidity, mortality and health care costs .[2 3] AR annually causes 23000 death in America, 25 000 deaths in the European Union (EU) and 700, 000 deaths worldwide.[4] By 2050, it is predicted that there will be 10 million deaths annually and USD 100 trillion in global economic loss caused by drug-resistant bacterial infections if AR continues to rise at the same pace as in the last decades. [5] In the EU, it is estimated that AR could cause €1.5bn (£1.32bn; $1.7bn) per year loss due to a combination of treatment costs and lower productivity.[4]

Overprescribing and inappropriate prescribing of antibiotics are the principal and the modifiable driver of AR.[6 7] These prescribing practices significantly contribute to AR development at the individual, community, social, national and international levels.[8 9] The mechanism behind this association between AR and antibiotic use is the natural selection of pre-existing resistant bacteria with antibiotic use.[10] The most important risk factor for an individual patient to be affected with AR bacterial infection is the recent and recurrent use of antibiotics.[11 12] Furthermore, multiple courses and longer duration of antibiotic prescribing also accelerate higher rates of resistance.[6] Broad spectrum antibiotics (e.g. cephalosporin, fluoroquinolones) should not be prescribed if narrow-spectrum antibiotics remain effective, as they increase risk of multi-drug resistant urinary tract infections (UTIs), respiratory tract infections (RTIs), and *Clostridium difficile* infection (CDI).[13]

Over the ten years from 2000 to 2010, human consumption of antibiotics increased by 36% globally and similar trends was observed in the USA, Europe, UK and Australia.[14 15] Primary care is where the vast majority antibiotics are prescribed and dispensed [8 16 17] evidenced by 85%-95% antibiotics in Europe and nearly 70% of antibiotics in the USA are supplied in primary care. The major primary care antibiotic prescribers are general practitioners (GPs) or family practitioners (FPs) and ambulatory clinic physicians.[18] It is estimated that 50-90% of antibiotic prescriptions for RTIs are not indicated by published guidelines.[17 19-21] For UTIs, 80% of prescriptions are thought to be guideline incongruent and 46% of antibiotics prescribed for skin infection are inappropriate.[22]This inappropriate antibiotic prescribing leads to adverse effects, resource wasting, re-consultations, rising treatment costs, ineffective antibiotics and bacterial resistance.[6 23]

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Inappropriate prescribing of antibiotics are influenced by individual, interpersonal, social, organizational and national level barriers. Mostly these factors are behavioural and health system oriented.[24] More specifically, knowledge deficits in prescribers, the practice environment and prior experience of the practitioner, peer pressure, patient pressure, patients expectation, time constraints, diagnostic uncertainties, lack and/or ineffective communication between prescriber, pharmacist and patients[25 26] have been implicated in inappropriate antibiotic prescribing.

There is a major body of literature documenting numerous interventions (e.g. single, multicomponent and multifaceted) to reduce individual, interpersonal, community and societal level barriers and behaviours of clinicians related to antibiotic prescribing. These include promotion of narrow-spectrum over broad-spectrum antibiotics [27] use of antibiotic guidelines [28], a point of care diagnostic kits [29], group meetings [30], academic detailing [31], educational outreach and workshops[32], and audit and feedback.[33] However, the effect of interventions to improve clinicians antibiotics prescribing behaviours is unclear [34]. Over the last ten years, various systematic reviews[35-41] have explored the effectiveness of clinician targeted interventions to improve antibiotic prescribing. However, these reviews have generally examined in settings rather than solely focusing on general practice. A landmark Cochrane review focused solely on assessing interventions aimed at improving antibiotic prescribing by physicians based in ambulatory care[27] . Some of the systematic reviews showed intervention features to support primary care antibiotic stewardship programs since then.[21 42-46] Multifaceted interventions involving physicians, pharmacists and patients are more likely to produce a greater effect size.[47 48] However, this has been contradicted by a systematic review that concluded that single but focused interventions are more effective than multidimensional interventions at improving antibiotic selection by clinicians.[39] Another systematic review emphasized that intervention delivered by pharmacist are predominantly persuasive than medical practitioners and intervention included education, guideline development, reminder to physician and clinical audit and feedback.[49]

In many countries, interventions are being implemented at the health care system or practice level with the aim of achieving more collaborative care by physicians, pharmacists, and other health professionals to optimise antibiotic use.[50] Practitioner-pharmacist collaboration model [51] is one such example. Such collaboration is more firmly established in hospitals than in primary care. However, GPs and pharmacists are being engaged in antibiotic stewardship programs to improve GPs' antibiotic prescribing. [46 52] In family practice, an intervention

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involving pharmacotherapy audit meetings where family practitioners (FPs) and pharmacists collaborated to reduce antibiotic prescriptions in RTI was effective.[53] In the UK, utilization of antimicrobial pharmacists, infectious disease pharmacists, and community pharmacists are emerging to support GPs in right decision making about antibiotic prescribing. [54] An example is the Welch government funded AMR Pacesetter project [55] which was implemented to support GPs in adopting good antimicrobial stewardship. A primary care antimicrobial pharmacist led the project through auditing antimicrobial prescribing, developing an action plan in collaboration with GPs and delivering patient education to reduce 'patient pressure' on prescribing antibiotics by GPs. A 16.09% reduction of antimicrobials prescribing was achieved in 2015. Antimicrobial pharmacists' contribution to this reduction has been demonstrated as a positive step in tackling AR.[55] Other evidence supports the important role played by pharmacists as: a therapeutic adviser [56] ; a trainer of physicians [57 58]; an academic detailer [59 60] ; a medication reviewer and feedback provider to GPs[39] in collaboration with general practitioners [51] to improve antibiotic prescribing norms and culture.

Despite recommendations to utilize the expertise and clinical knowledge of pharmacist to ensure appropriate antibiotics use and improve stewardship[55] pharmacist involved intervention components of antibiotic stewardship programs are still under-researched. Understanding such interventions which are more likely to improve engagement between GPs and pharmacists and optimising antibiotic prescribing in general practice is a priority. However, no systematic review has yet explored which interventions involving pharmacists are effective at improving GPs' antibiotic prescribing. Hence there is insufficient information to design future GP-pharmacist collaborative models to optimise antibiotic use in the community.

This systematic review, therefore, aims to identify pharmacist-led or pharmacist involved interventions to improve antibiotic prescribing by GPs and to assess their effectiveness, feasibility, and acceptability. It is very difficult to make definitive conclusions regarding the effectiveness of interventions unless interventions are focused and very specific to a practice area.[61] This review will explore studies specific to general practice settings where the intervention is either pharmacist-led or pharmacist involved and the recipient is a general practitioner.

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METHODS

Guidance regarding the Preferred Reporting Items for Systematic review and Meta-analysis for Protocols (PRISMA-P) was used to develop this systematic review protocol. This protocol is registered on PROSPERO with trial no CRD42017078478.The planned period of this review study is from 1 June 2017 to 30 January 2018.

Study design

The selected studies will be either randomised controlled trials (RCTs) (including cluster parallel group and factorial), controlled before-after studies (CBAs) or interrupted time series analyses (ITS).The guidance on study design as recommended by the Effective Practice and Organisation of Care group (EPOC) that all RCTs must have at least two intervention and control sites and that interrupted times series studies must have a minimum of three time points both before and after the intervention will be followed. The EPOC study design algorithm will be used to determine the study design and to avoid ambiguous terminology.

Review question

The research question is: What pharmacist-led or pharmacist involved interventions are effective to improve antibiotics prescribing by GPs in primary care?

Eligibility criteria

Types of participants

We will include studies that examine interventions targeted at GPs or FPs within primary care. Intervention providers include either a pharmacist or pharmacologist alone or as part of a joint team consisting of GPs/clinicians/ microbiologists/ infectious disease experts in a general practice environment. No restrictions will be made on age, gender, ethnicity, and residence of participants. Intervention recipients include GPs or FPs. Physicians, nurses, dentists in aged care facilities, long- term care facilities, nursing homes or dental care facilities will be excluded. We will exclude any studies targeting health professionals working in inpatient settings, hospital settings or residential settings.

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Types of interventions and comparators

Studies will be included if they meet following conditions:

- Conduct interventions by either a pharmacist or Pharmacist-GP or pharmacist engaged in a multidisciplinary team to improve antibiotic prescribing within primary care settings.
- Investigate a single or multicomponent or multifaceted intervention with the primary objective of reducing quantity or improving quality (selection/appropriateness) of antibiotic prescribing
- Evaluate the effect of interventions based on changes in GPs' antibiotic prescribing
- Evaluate any type of intervention (e.g. educational, clinical, managerial or regulatory)
- Where GPs or family physicians in general practice receive the interventions
- Evaluate feasibility and acceptability of intervention
- Apply any mode of intervention delivery techniques
- Conduct the intervention at any time

Studies will be excluded when the -

- Intervention is delivered in an inpatient/hospital setting/ secondary care/ tertiary care, long-term care, residential care, ambulatory care, aged care facility, nursing home, or dental care facility
- Intervention doesn't include pharmacist(s) or any expert from pharmacy background
- Intervention is received by any professional other than GPs in primary care
- Intervention targets only patients as recipients
- Study evaluates no outcome measures related to GP antibiotics prescribing
- Intervention is delivered to nurses, physicians other than general practitioner or dentists.

Comparators will be alternative interventions that aim similarly to improve GPs antibiotic prescribing in any disease including single or multicomponent interventions.

Settings

Only studies in general practice/family practice will be included. General practice or family practice for this review will be defined as "*the first point of care where individuals and families in their communities are provided person centred, continuing, comprehensive and coordinated whole person health care* ".[62]

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Language

Only English language articles will be included.

Time

There will be no restrictions on study publishing date. The inception of databases until the date of search will be the time limit for the search strategy. Studies will be included regardless of intervention follow up time.

Study outcome measures

Primary and secondary outcomes will be measured to determine effectiveness, feasibility, and acceptability of interventions and distinguishing features of interventions (e.g. types, format and content).

Effectiveness

Primary outcomes

The effect of interventions to reduce the quantity and improve quality of antibiotic prescribing will be measured by:

- Change in total antibiotics (any type) prescribed by GPs or FPs
- Change in broad-spectrum antibiotic (individual or multiple) prescribing
- Change in antibiotic prescribing congruent with antibiotic guidelines or therapeutic guidelines or WHO listed alert antibiotic guides

Secondary outcome measures of effectiveness will include:

- Change in antibiotic dose and/or dose regimen on antibiotic prescriptions in response to any intervention
- Changes in consultation rates including re-consultation of patients with infections
- Change in antibiotic dispensing Rx/1000 patients where antibiotic prescribing data is not available
- Change of cases/visits where antibiotics were prescribed in response to deterioration of condition or adverse effect of antibiotics
- Clinician knowledge about antibiotic use and /or antibiotic resistance
- Cases of adverse effects of antibiotics
- Types of interventions
- Intervention components (e.g. types, formats, mode of delivery, providers)

The measurement unit of changes in prescribing will be a number or percent or proportion of prescribed antibiotics.

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Feasibility and acceptability

This will be assessed as a secondary outcome by assessing ease of implementation, required resources, acceptability, and satisfaction of the targeted clinicians after the intervention.

Data sources and search methods

Electronic Databases

We will conduct this systematic review and meta-analysis in accordance with the PRISMA-P guidelines.[63] A uniform search strategy will be developed and applied to the following databases: MEDLINE, EMBASE, EMCARE, PubMed, PsycINFO, Cochrane Central Register of Controlled Trials (CENTRAL), CINAHL plus and Web of Sciences. We will also manually search reference lists of retrieved articles and relevant articles. The databases will be searched from:

1. MEDLINE and Ovid (1946 to searched date)
2. EMBASE and Ovid (1974 to searched date
3. EMCARE (1995 to searched date)
4. PubMed (1974 to searched date)
5. PsycINFO (1806 to searched date)
6. Cochrane Central Register of Controlled Trials (CENTRAL) (date of inception—searched date
7. CINAHL PLUS (1982 to searched date)
8. Science Citation Index and Social Sciences Citation Index, ISI Web of Science (1975 to searched date)

Search terms and strategy

The search strategy will capture studies that include each of three groups of terms within PICO format: populations (pharmacists, GPs), intervention (any) and outcomes (antibiotics, prescribing practice changes and settings). Matched terms under each group against possible medical subject headings (MeSH) or keywords will be used in a systematic search as follows. Proposed search strategies are shown in appendix A using a MEDLINE database.

A. Population terms:

   Pharmacist: Pharmacists/ OR Pharmacist* OR (pharmacy or pharmacies) OR (retail pharmacist or community pharmacist or clinical pharmacist or antimicrobial pharmacist or infectious disease pharmacist)

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Physician: Family Physicians / OR General Practitioners / OR (GP* or family practitioner* general practitioner* or clinician* or doctor* or rural practitioner or family medicine practitioner)

B. Intervention terms

Intervention: intervention* or program* or health promotion* or education* or educational outreach* or training* or academic detailing* or educational meeting* or workshop or communication skill* or audit* or guideline* or group meeting* or decision support* or poster* or leaflet* or flyer* or incentive* or regulation or reminder* or consultation* or web based training* or electronic prescribing* or Medication review* or medication reconciliation* or drug review or stewardship or multi-prong* or strategy or single or multicomponent* or multi-component or multiple or multifaceted or multidisciplinary or multi-disciplinary or physician aid or physician-aid or collaborative or collaboration or counselling or pharmacist supported or pharmacist-led or pharmacist led or team based or team-based or shared

C. Outcome terms

Antibiotics: Anti-Bacterial Agents/ OR (antibacterial or anti-bacterial or antibiotic or anti-biotic or antimicrobial or anti-microbial or antibiotic* or antimicrob* or antibacteria* or antibacterial agent) OR Anti-infective agents/ or (broad spectrum or short spectrum or narrow spectrum or narrow-spectrum)

Practice changes: Drug Prescriptions/ OR Inappropriate prescribing/ OR Appropriate prescribing/ OR practice pattern, physicians/ OR (prescribe or prescription* or practice or practising or dispense or dispensing or stewardship or Antibiotic therapy or Antibiotic treatment or antibiotic prescribing or pattern* or behaviour or behaviour or reduce or reduced or reduction or reducing or increase or increasing or increased or change or changing or changed or optimize or optimise or optimizing or optimization or optimising optimisation or effect* or effective or effectiveness or influence or influenced or influencing or impact.

Settings: General practice / Primary health care/ OR (primary care or primary health care or primary healthcare)

Hand searching

We will manually search key journals (e.g. The LANCET Infectious Diseases, Journal of Antimicrobial Chemotherapy, Journal of Antimicrobial Agents, Biomed Central (http://www.biomedcentral.com/), British Medical Journal (BMJ), Annals of pharmacotherapy, International Journal of pharmacy practice (IJPP), JAMA, WHO's library databases (WHOLIS). If required, direct contact with authors will be undertaken to obtain other relevant

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articles. Cited original articles in relevant systematic reviews will also be retrieved and analyzed. We will update our literature search using the auto alert system in individual databases before publication of this review to avoid missing any potential articles.

Study selection

All electronically and manually searched records will be merged to remove duplicate citations. Two reviewers will then independently screen titles and abstracts to identify potentially eligible articles using the inclusion and exclusion criteria. Where there is uncertainty regarding whether an article meets eligibility criteria, the full text of the article will be reviewed against inclusion criteria. Discrepancies between the reviewers will be resolved through discussion until a consensus is reached. If necessary, a third reviewer will be consulted to resolve the disagreement. This process will minimize bias. If there is an information gap in a paper and/or a need for further clarification, the author will be contacted to clarify the issue by email. A PRISMA flow diagram will be used to maintain transparency in the article selection process and to record remaining studies in each stage of selection with a valid explanation regarding reasons of studies' exclusion.

Data extraction and management

A tailored version of EPOC's data abstraction tool[64] and the EPOC data collection checklist forms will be used as a guide to developing a data extraction form. This form will be adapted to answer the research question of this review and identify confounding factors. Additionally, recommendations for improving the consideration and description of interventions in a systematic review and a template for intervention description and replication (TDieR) checklist [65 66] will be followed. The developed data extraction form will be pilot tested by the data extractors (SKS, LH) to ensure that it has captured all the relevant information and that unnecessary resources are not wasted on data extraction [67] Feedback from the extractors will be used to modify the data extraction form to ensure its usability and completeness. Data extraction in duplicate will be accomplished independently. Any disagreements between two parties will be resolved through discussion. The third reviewer will arbitrate if a consensus is unreachable.

We will extract data on I) general information (title, author, year, study ID), II) aims and rationale III) study design (includes brief description of method limitation) IV) study period V) study participants and settings VI) intervention characteristics in details (e.g. component, types, format, delivery strategy, timing, provider and recipient characteristics, effect, feasibility, acceptability, sustainability), VII) intervention outcomes (control and intervention group results, effect, effect size, Confidence Interval (CI), Standard Deviation (SD) and VIII) recommendations and conclusions. The intervention results will be carefully extracted to

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make them statistically meta-analysable. If data presentation is problematic, unclear, missing or presented in a un-extractable form, the respective authors will be contacted for clarification by email with a response time limit of two weeks. If the author is unresponsive, then they will be classified as uncontactable. We will group interventions based on disease cases, intervention classes, effect size, country, provider population and sources of variation (e.g. seasonal and regional)

Assessment of risk of bias

Two reviewers (SKS and LH) will independently evaluate quality features of included articles utilizing established guidelines and criteria tools[68-71]. Internal validity of RCTs will be assessed using Cochrane risk of bias tools. [69] The domains of this tool will be selection bias (random sequence generation, allocation concealment), reporting bias (selective reporting), performance bias (blinding of participant and personnel), detection bias (blinding of outcome assessment), and attrition bias (incomplete outcome data). We will have significant concern about attrition bias if there exists a loss to follow up of at least 20%. We will avoid scoring the quality of the trials because of debates regarding scoring methods.[72] Each study will be categorized as high risk, low risk and unclear risk of bias under each of the criteria based on guidelines. [69] A study will be deemed as being at low risk of bias if it meets greater than or equal to four criteria out of six criteria with low risk of bias and the other two criteria must not be attrition or reporting bias. Studies will be considered as at unclear risk of bias if at least one domain has an unclear risk of bias and at most three domains have a low risk of bias. Studies with three domains with low risk of bias excluding attrition or reporting bias will be treated as studies with medium risk of bias. In studies where there are at least four domains at risk of bias or having random sequence generation bias, they will be considered as studies with high risk of bias. Based on this criteria, each study will be given an overall assessment of the low, moderate, or high risk of bias. The quality assessment tool will be piloted on a small sample of included studies (5). The quality assessment criteria for non-randomized studies (CBA and TSA) will be based on ROBINS-I risk assessment tools[70] and methodological quality criteria and guidance [72 73] from the Cochrane Collaborations.[68] We will also evaluate reporting criteria (e.g. outcome definition, sample size calculation, sources of funding) for each of the included studies. The findings of each trial's risk of bias assessment will be recorded in a summary table.

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Data synthesis and analysis

The findings of the included studies will be summarized in a table format for outcome measures including key information features regarding study types, design, number, participant characteristics, interventions, outputs and outcome measures. All the categorical variables of RCT, CBA and TSA trials (e.g. antibiotic prescribing rate) will be reported with the same unit with 95% confidence intervals (CI) and continuous variables with the mean difference (MD) and 95% CI. We will assess the proportion or volume or rate of I) overall changes of antibiotic prescribing II) changes in broad spectrum or WHO listed alert antibiotic prescribing III) changes in antibiotic prescribing adherence with a therapeutic guideline indicating appropriateness of GPs' antibiotic prescribing and IV) changes in antibiotic dose and /or dose regimen during prescribing after intervention. We will calculate the effect size of each study by subtracting pre-intervention differences (intervention group–control groups) and post-intervention differences. Absolute risk will be determined to express clinical significance. Summary statistics with 95% CIs and exact p-value will be reported if studies have sufficient data for calculations. The combined analyses will represent the real percentage change in the rate of antibiotic prescribing or appropriateness of prescribing that is intervention attributed.

Where appropriate, outcome data will be combined for meta-analysis. The pooled effect estimates will be generated using random-effects modelling to calculate inter study heterogeneity in the intervention effect size. Fixed effect modelling will be used if no substantial inter-study heterogeneity exists. For substantial inter-study heterogeneity, Forest plots [71], χ^2 test and I^2 statistic [69] will be used to compare the effect size of trials with and without characteristics (e.g. study features, context or intervention variation) of interest. The scale of heterogeneity will be low (<25%), moderate (50%), severe (up to 75%) and very severe (>75%). A meta-regression analysis will be performed to measure secondary outcomes if there are a substantial number of studies. A statistician will be approached if standardization is required across studies for meta-analysis of continuous outcomes.

We will explain our data within an analytic stratum using the median and interquartile range of effect sizes of trials. We will evaluate the association between type of intervention strategies and effect size, using the methods described above. In addition, we will assess other characteristics of studies as important confounders of the observed association.

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Assessment of confounders will be undertaken if the study characteristic meets two criteria: (1) if there is an independent association with the effect size and (2) where trials with that characteristic across the intervention types (e.g. clinician education only, or combined with audit and feedback) have an uneven distribution. We will use rank-sum tests to evaluate the association between each intervention trial characteristic and effect size, and Fisher exact test to evaluate uneven distributions of study characteristics over intervention types. We will specify $P < 0.05$ as statistically significant for this association. All analyses will be performed using STATA 13. Where quantitative analysis is not possible, evidence will be presented as a descriptive synthesis.

Unit of analysis errors

In case of a potential unit of analysis error of RCT and CBAs, methods for re-analysis as guided by EPOC, 2015, will be used. Incorrect analysis of cluster RCTs due to the absence of accounting for clustering will be handled with reanalysis if possible. If correction is not possible we will report the effect size without a standard error and confidence interval as they are unlikely to be accurate.

Reanalysis methods for inappropriate analysis

If appropriate, segmented time-series regression will be applied according to EPOC guidance to re-analyse the data of studied trials followed by a method described in Ramsay et al. [74]

Dealing with missing data

If any missing data exists within working trials, the respective authors will be contacted to avoid the inappropriate description of study results and to minimize the risk of bias in meta-analysis. [75] A guidance [69] will be followed to handle missing data.

Assessment of publication bias

The assessment of publication bias will be conducted by extrapolating the study trials effect estimate with inversion of trials standard error through the usage of a funnel plot. The assessment of the plots will be both visually and by Egger's test with a p-value < 0.1 considered as significant publication bias. [76]

Quality assessment of Evidence

The evidence summaries (intervention profiles and table of findings) will be formulated based on the guidance recommended by Grading of Recommendations Assessment, Development, and Evaluation (GRADE) working group[77] and the TDieR checklist. [65 66]

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Sensitivity analysis

A sensitivity analysis will be conducted to estimate the effect of study quality and effect of missing data on the meta-analysis of outcome measures. Two meta-analysis (one including all eligible studies and the second including only those studies defined by EPOC criteria as being high quality for quality assessment) will be performed to determine the effect of study quality. In case of unobtainable data, our plan will be I) to conduct complete case analysis following a method described in Ebrahim et al., 2013 and II) to perform sensitivity analysis of outcomes (continuous and dichotomous) to address the potential impact of missing data on meta-analysis utilizing a method discussed by AKL et al. [78]

Subgroup analysis

Should enough data be available, this review will conduct subgroup analysis for primary outcomes. Important varieties of exploratory subgroup analysis may be performed by I) provider population (pharmacist and/or GPs and/ or infectious disease expert), II) country settings (developed vs middle income vs low income), III) primary care setting (General practice vs ambulatory), IV) disease cases (among RTIs or RTI vs skin), V) risk of bias (high risk vs low risk of bias) VI) antibiotic classes VII) intervention types, VIII) mode of delivery of intervention IX) timing of intervention studies.

Dissemination

We will present our findings including GRADE evidence and descriptive evidence tables in Australia and at international scientific meetings, seminars, workshops, and conferences in addition to publishing in a peer-reviewed journal.

Discussion

To the best our knowledge, this is the first systematic review assessing pharmacist-led or pharmacist involved interventions to improve GPs' antibiotic prescribing in primary care. This review is solely focused on family practice or general practice settings. The findings may be more applicable to general practice due to less contextual variation led by different settings of care. This review will cover a large number of databases and other sources as well. Use of English language articles is a limitation of the review. Poor quality studies and heterogeneity in results that may lead to difficulty in interpreting findings.

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It is anticipated that the findings of this systematic review will be relevant to many stakeholders. Firstly, the review will present a comprehensive overview of pharmacy intervention features for primary care researchers and will additionally highlight any potential gaps in the current literature on this topic. Secondly, it will highlight international evidence from peer-reviewed literature on the effectiveness, feasibility, and acceptability of interventions with the assessment of methodological quality of relevant studies thereby increasing the applicability of the findings. Thirdly, the review could provide information regarding valuable interventions which may increase GP-pharmacist collaboration and more judicious antibiotic prescribing in general practice. Fourthly, the review may be useful for funders to better understand interventions which could be prioritised for future funding. This will be informed by ranking outcomes in an innovative approach. Finally, the findings may support general practitioners, pharmacist, researchers, and health policy makers to design future interventions to improve antibiotic prescribing by GPs in primary care.

REGISTRATION AND PUBLISHING

This systematic review protocol is registered on the International Prospective Register of Systematic Reviews (PROSPERO) with a trial number, CRD42017078478 (https://www.crd.york.ac.uk/prospero/#myprospero) dated 8 November 2017. A PRISMA-P checklist[63] will be used to report the review. The findings of the review will be published in international peer-reviewed journals.

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Contributors

Review concept was designed by DM and SKS. SKS and LH developed the study design and literature search strategies. Screening of literature was conducted by SKS and LH. Design of study quality risk assessment tools, data extraction tools, data synthesis and meta-analysis and statistical tests were developed by SKS, LH, and DM. SKS wrote this manuscript and also drafted the whole protocol according to PRISMA-P. Revision of the draft manuscript was undertaken by all authors.

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Competing interest

The authors have no conflicts of interest.

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Improving antibiotic prescribing by general practitioners: A protocol for a systematic review of interventions involving pharmacists

A Systematic Review & Meta-Analysis

Review Protocol

Organization, City, Country	: Monash University, Melbourne, Australia
Prepared by	: Sajal K. Saha
Project leader & Supervisor	: Professor Danielle Mazza
Research team members	: Sajal K. Saha, Lesley Hawes

Starting Date: 1 June 2017

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PRISMA-P guided Systematic Review Protocol

Section and topic	Item No	Checklist item
ADMINISTRATIVE INFORMATION		
Title: *Improving antibiotic prescribing by general practitioners: A protocol for a systematic review of interventions involving pharmacists*		
Identification	1a	A systematic review protocol
Update	1b	First systematic review to the best our knowledge
Registration	2	PROSPERO registration trial no. CRD42017078478
Authors: Sajal K. Saha, Lesley Hawes, Danielle Mazza		
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; **Sajal K. Saha (SKS)** PhD fellow Department of General Practice, Monash University, Australia. Building 1, 270 Ferntree Gully Road, Notting Hill 3168 National Centre for Antimicrobial Stewardship, Doherty Institute, Melbourne e-mail: Sajal.saha@monash.edu **Lesley Hawes (LH)** PhD fellow Department of General Practice, Monash University. Building 1, 270 Ferntree Gully Road, Notting Hill 3168 National Centre for Antimicrobial Stewardship, Doherty Institute, Melbourne e-mail: Lesley.Hawes@monash.edu **Danielle Mazza (DM)** MD, MBBS, FRACGP, DRANZCOG, Grad Dip Women's Health, GAICD Professor, Head of Department of General Practice School of Primary and Allied Health Care Faculty of Medicine Nursing and Health Sciences Monash University Building 1, 270 Ferntree Gully Rd, Notting Hill, VIC 3168, Australia e-mail: Danielle.mazza@monash.edu

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		Guarantor **Danielle Mazza** e-mail: Danielle.mazza@monash.edu
Contributions	3b	**Contributions of protocol authors** Concept was designed by DM and SKS. SKS wrote this protocol, designed the study, and developed literature search strategies. Screening of literatures was conducted by SKS & LH. Design of study quality risk assessment tools, development of data extraction tools, data synthesis and meta-analysis design and designing of statistical tests were developed by SKS, LH and DM. The drafting of whole protocol was done according to PRISMA-P by SKS. All authors and research team members revised the protocol draft. **Guarantor of the review** Professor Danielle Mazza Department of General Practice Monash University, Australia
Amendments	4	N/A
Support:		
Sources	5a	This systematic review study received no specific grant from any funding agency. SKS as a PhD student is supported by a Faculty of Medicine, Nursing & Health Sciences and Monash International Post Graduate Scholarship (MIPRS) from Monash University in Australia.
Sponsor	5b	N/A
Role of sponsor or funder	5c	Department of General Practice, Monash University has supported with physical resources to develop this protocol
INTRODUCTION		
Rationale	6	Growing antibiotic resistance (AR) and a shortage of new effective antibiotics have become an urgent global threat to public health[1 2] with a risk of a significant rise in morbidity, mortality and health care costs .[2 3] AR annually causes 23000 death in America, 25 000 deaths in the European Union (EU) and 700, 000 deaths worldwide.[4] By 2050, it is predicted that there will be 10 million deaths annually and USD 100 trillion in global economic loss caused by drug resistant bacterial infections if AR continues to rise at the same pace as in the last decades. [5] In the EU, it is estimated that AR could cause €1.5bn (£1.32bn; $1.7bn) per year loss due to a combination of treatment costs and lower productivity.[4] Overprescribing and inappropriate prescribing of antibiotics are the principal and

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modifiable driver of AR.[6 7] These prescribing practices significantly contribute to AR development at the individual, community, social, national and international levels.[8 9] The mechanism behind this association between AR and antibiotic use is the natural selection of pre-existing resistant bacteria with antibiotic use.[10] The most important risk factor for an individual patient to be affected with AR bacterial infection is the recent and recurrent use of antibiotics.[11 12] Furthermore, multiple courses and longer duration of antibiotic prescribing also accelerate higher rates of resistance.[6] Broad spectrum antibiotics (e.g. cephalosporin, fluoroquinolones) should not be prescribed if narrow-spectrum antibiotics remain effective, as they increase risk of multidrug resistant urinary tract infections (UTIs), respiratory tract infections (RTIs), and *Clostridium difficile* infection (CDI).[13]

Over the ten years from 2000 to 2010, human consumption of antibiotics increased by 36% globally and similar trends was observed in the USA, Europe, UK and Australia.[14 15] Primary care is where the vast majority antibiotics are prescribed and dispensed [8 16 17] evidenced by 85%-95% antibiotics in Europe and nearly 70% of antibiotics in the USA are supplied in primary care. The major primary care antibiotic prescribers are general practitioners (GPs) or family practitioners (FPs) and ambulatory clinic physicians.[18] Estimates are that 50-90% of antibiotics prescribed for respiratory tract infections (RTI) are not indicated by published guidelines.[17 19-21] For urinary tract infections 80% of prescriptions are thought to be guideline incongruent and in skin infection 46% of antibiotics prescribed are inappropriate.[22]This inappropriate antibiotic prescribing leads to adverse effects, resource wasting, re-consultations, rising treatment costs, ineffective antibiotics and bacterial resistance.[6 23]

Influencing factors of this inappropriate prescribing are individual, interpersonal, social, organizational and national level barriers. Mostly these factors are behavioural and health system oriented.[24] More specifically, knowledge deficits in prescribers, the practice environment and prior experience of practitioner, peer pressure, patient pressure, patients expectation, time constraints, diagnostic uncertainties, lack and/or ineffective communication between prescriber, pharmacist and patients[25 26] have been implicated in inappropriate antibiotic prescribing.

There is a major body of literature documenting numerous interventions (e.g.

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single, multicomponent and multifaceted) to reduce individual, interpersonal, community and societal level barriers and behaviours of clinicians related to antibiotic prescribing. These include promotion of narrow-spectrum over broad-spectrum antibiotics [27] use of antibiotic guidelines [28], point of care diagnostic kits [29], group meetings [30], academic detailing [31], educational outreach and workshops[32], and audit and feedback.[33] However, the effect of interventions to improve clinicians antibiotics prescribing behaviours is unclear [34]. Over the last ten years, various systematic reviews[35-41] have explored the effectiveness of clinician targeted interventions to improve antibiotic prescribing. However, these reviews have generally examined in settings rather than solely focusing on general practice. A landmark Cochrane review focused solely on assessing interventions aimed at improving antibiotic prescribing by physicians based in ambulatory care[27] . Some of the systematic reviews showed intervention features to support primary care antibiotic stewardship programs since then.[21] [42-46] Multifaceted interventions involving physicians, pharmacists and patients are more likely to produce a greater effect size.[47] [48] However, this has been contradicted by a systematic review that concluded that single but focused interventions are more effective than multidimensional interventions at improving antibiotic selection by clinicians.[39]

In many countries, interventions are being implemented at the health care system or practice level with the aim of achieving more collaborative care by physicians, pharmacists and other health professionals to optimise antibiotic use.[49] Practitioner-pharmacist collaboration models [50] is one such example. Such collaboration is more firmly established in hospitals than in primary care. However, GP and pharmacists are being engaged in antibiotic stewardship programs to improve GPs antibiotic prescribing. [46] [51] In family practice, an intervention involving pharmacotherapy audit meetings where family practitioners (FPs) and pharmacists collaborated to reduce antibiotic prescriptions in RTI was effective.[52] In the UK, utilization of antimicrobial pharmacists, infectious disease pharmacists, and community pharmacists are emerging to support GPs in right decision making about antibiotic prescribing. [53] An example is the Welch government funded AMR Pacesetter project [54] which was implemented to support GPs in adopting good antimicrobial stewardship. A primary care antimicrobial pharmacist led the project through auditing antimicrobial prescribing, developing an action plan in collaboration with GPs and delivering patient education to reduce 'patient pressure'

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		on prescribing antibiotics by GPs. A 16.09% reduction of antimicrobials prescribing was achieved in 2015. Antimicrobial pharmacists' contribution to this reduction has been demonstrated as a positive step in tackling AR.[54] Other evidence supports the important role played by pharmacists as : a therapeutic adviser [55] ; a trainer of physicians [56 57]; an academic detailer [58 59] ; a medication reviewer and feedback provider to GPs[39] in collaboration with general practitioners [50] to improve antibiotic prescribing norms and culture. Despite recommendations to utilise the expertise and clinical knowledge of pharmacist to ensure appropriate antibiotics use and improve stewardship[54] pharmacist involved intervention components of antibiotic stewardship programs are still under researched. Understanding such interventions which are more likely to improve engagement between GPs and pharmacists and optimising antibiotic prescribing in general practice is a priority. However, no systematic review has yet explored which interventions involving pharmacists are effective at improving GP antibiotic prescribing. Hence there is insufficient information to design future GP-pharmacist collaborative models to optimise antibiotic use in the community. This systematic review therefore aims to identify pharmacist-led or pharmacist involved interventions to improve GP antibiotic prescribing and to assess their effectiveness, feasibility and acceptability. It is very difficult to make definitive conclusions regarding effectiveness of interventions unless interventions are focused and very specific to a practice area.[60] This review will explore studies specific to general practice settings where the intervention is either pharmacist led or pharmacist involved and the recipient is a general practitioner.
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO) Q.1 What pharmacist-led or pharmacist involved interventions are effective to improve antibiotics prescribing by GPs in primary care?

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		Specific objectives 1. To identify what pharmacist–led or pharmacist involved interventions are effective to improve antibiotic prescribing by general Practitioners 2. To explore feasibility, acceptability and sustainability of these interventions 3. To explore interventions which may enhance GP-pharmacist collaboration in optimizing GPs' antibiotic prescribing
METHODS		
Eligibility criteria	8	**Inclusion and exclusion criteria** Types of Study design The selected studies will be either randomised controlled trials (RCTs) (including cluster parallel group and factorial), controlled before-after studies (CBAs) or interrupted time series analyses (ITS).The guidance on study design as recommended by the Effective Practice and Organisation of Care group (EPOC) that all RCTs must have at least two intervention and control sites and that interrupted times series studies must have a minimum of three time points both before and after the intervention will be followed. The EPOC study design algorithm will be used to determine the study design and to avoid ambiguous terminology Types of interventions and comparators Studies will be included if they meet following conditions: • Conduct interventions by either a pharmacist or pharmacologist alone or pharmacist engaged in a multidisciplinary team to improve antibiotic prescribing within primary care settings. • Investigate a single or multicomponent or multifaceted intervention with the primary objective of reducing quantity or improving quality (selection/appropriateness) of antibiotic prescribing • Evaluate the effect of interventions based on changes in GPs' antibiotic prescribing • Evaluate any type of intervention (e.g. educational, clinical, managerial or regulatory) • Where GPs or family physicians in general practice receive the interventions • Apply any mode of intervention delivery techniques • Evaluate the feasibility and acceptability of GP targeted intervention • Conduct the intervention at any time Studies will be excluded when the -

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		• Intervention is delivered in an inpatient/hospital setting/ secondary care/ tertiary care, long term care, residential care, ambulatory care, aged care facility, nursing home, or dental care facility • Intervention doesn't include pharmacist/s • Intervention is received by any professional other than GPs in primary care • Intervention targets only patients as recipients • Study evaluates no outcome measures related to GP antibiotics prescribing • Intervention is delivered to nurses, physicians other than general practitioners or dentists. Comparators will be alternative interventions that aim similarly to improve GPs antibiotic prescribing in any disease including single or multicomponent interventions. Types of participants/ population We will include studies that examine interventions targeted at GPs or FPs within primary care. Intervention providers include either a pharmacist alone or as part of joint team consisting of GPs/clinicians/ microbiologists/ infectious disease experts in a general practice environment. No restrictions will be made on age, gender, ethnicity and residence of participants. Intervention recipients includes GPs or FPs. Physicians, nurses, dentists in aged care facilities, long term care facilities, nursing homes or dental care facilities will be excluded. We will exclude any studies targeting health professionals working in inpatient settings, hospital settings or residential settings. Settings Only studies in general practice / family practice will be included. General practice or family practice for this review will be defined as "*the first point of care where individuals and families in their communities are provided person centred, continuing, comprehensive and coordinated whole person health care* ".[61] Language Only English language articles will be included. Time There will be no restrictions on study publishing date. The inception of databases until date of search will be the time limit for the search strategy. Studies will be included regardless of intervention follow up time.

Information sources	9	**Data sources and search methods** Electronic Databases We will conduct this systematic review and meta-analysis in accordance with the PRISMA-P guidelines.[62] A uniform search strategy will be developed and applied to the following databases: MEDLINE, EMBASE, EMCARE, PubMed, PsycINFO, Cochrane Central Register of Controlled Trials (CENTRAL), CINAHL plus and Web of Sciences. We will also manually search reference lists of retrieved articles and relevant articles. The databases will be searched from: 1. MEDLINE and Ovid (1946 to searched date) 2. EMBASE and Ovid (1974 to searched date 3. EMCARE (1995 to searched date) 4. PubMed (1974 to searched date) 5. PsycINFO (1806 to searched date) 6. Cochrane Central Register of Controlled Trials (CENTRAL) (date of inception—searched date 7. CINAHL PLUS (1982 to searched date) 8. Science Citation Index and Social Sciences Citation Index, ISI Web of Science (1975 to searched date) Hand searching We will manually search key journals (e.g. The LANCET Infectious Diseases, Journal of Antimicrobial Chemotherapy, Journal of Antimicrobial Agents, Biomed Central (http://www.biomedcentral.com/), British Medical Journal (BMJ), Annals of pharmacotherapy, International Journal of pharmacy practice (IJPP), JAMA, WHO's library databases (WHOLIS). If required, direct contact with authors will be undertaken to obtain other relevant articles. Cited original articles in relevant systematic reviews will also be retrieved and analysed. We will update our literature search using auto alert system in individual databases before publication of this review to avoid missing any potential articles.
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 Search terms and strategy The search strategy will capture studies that include each of three groups of terms within PICO format: populations (pharmacists, GPs), intervention (any) and

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outcomes (antibiotics, prescribing practice changes and settings). Matched terms under each group against possible medical subject headings (MeSH) or keywords will be used in a systematic search as follows. Proposed search strategies are shown in appendix A using a MEDLINE database.

A. Population terms:

Pharmacist: Pharmacists/ OR Pharmacist* OR (pharmacy or pharmacies) OR (retail pharmacist or community pharmacist or clinical pharmacist or antimicrobial pharmacist or infectious disease pharmacist)

Physician: Family Physicians / OR General Practitioners / OR (GP* or family practitioner* general practitioner* or clinician* or doctor* or rural practitioner or family medicine practitioner)

B. Intervention terms

Intervention: intervention* or program* or health promotion* or education* or educational outreach* or training* or academic detailing* or educational meeting* or workshop or communication skill* or audit* or guideline* or group meeting* or decision support* or poster* or leaflet* or flyer* or incentive* or regulation or reminder* or consultation* or web based training* or electronic prescribing* or Medication review* or medication reconciliation* or drug review or stewardship or multi-prong* or strategy or single or multicomponent* or multi-component or multiple or multifaceted or multidisciplinary or multi-disciplinary or physician aid or physician-aid or collaborative or collaboration or counselling or pharmacist supported or pharmacist-led or pharmacist led or team based or team-based or shared

C. Outcome terms

Antibiotics: Anti-Bacterial Agents/ OR (antibacterial or anti-bacterial or antibiotic or anti-biotic or antimicrobial or anti-microbial or antibiotic* or antimicrob* or antibacteria* or antibacterial agent) OR Anti-infective agents/ or (broad spectrum or short spectrum or narrow spectrum or narrow-spectrum)

Practice changes: Drug Prescriptions/ OR Inappropriate prescribing/ OR Appropriate prescribing/ OR practice pattern, physicians/ OR (prescribe or prescription* or practice or practising or dispense or dispensing or stewardship or Antibiotic therapy or Antibiotic treatment or antibiotic prescribing or pattern* or behaviour or behaviour or reduce or reduced or

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		reduction or reducing or increase or increasing or increased or change or changing or changed or optimize or optimise or optimizing or optimization or optimising optimisation or effect* or effective or effectiveness or influence or influenced or influencing or impact. *Settings:* General practice / Primary health care/ OR (primary care or primary health care or primary healthcare)
Study records:		
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review The covidence software will be used individually by two reviewers to keep study records at each steps of inclusion and exclusion phase with logical reasons of exclusion criteria. A PRISMA flow diagram will be used to maintain transparency in the article selection process and to record remaining studies in each stage of selection with valid explanation regarding reasons of studies' exclusion.
Selection process	11b	**Study selection** All electronically and manually searched records will be merged to remove duplicate citations. Two reviewers will then independently screen titles and abstracts to identify potentially eligible articles using the inclusion and exclusion criteria. Where there is uncertainty regarding whether an article meets eligibility criteria, the full text of the article will be reviewed against inclusion criteria. Discrepancies between the reviewers will be resolved through discussion until consensus is reached. If necessary, a third reviewer will be consulted to resolve the disagreement. This process will minimize bias. If there is an information gap in a paper and/or a need for further clarification, the author will be contacted to clarify the issue by email. A PRISMA flow diagram will be used to maintain transparency in the article selection process and to record remaining studies in each stage of selection with valid explanation regarding reasons of studies' exclusion.
Data collection process	11c	**Data extraction and management** A tailored version of EPOC's data abstraction tool[63] and the EPOC data collection checklist forms will be used as a guide to develop a data extraction form. This form will be adapted to answer the research question of this review and identify confounding factors. Additionally, recommendations for improving the consideration

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		and description of interventions in a systematic review and a template for intervention description and replication (TDieR) checklist [64 65] will be followed. The developed data extraction form will be pilot tested by the data extractors (SKS, LH) to ensure that it has captured all the relevant information and that unnecessary resources are not wasted on data extraction [66] Feedback from the extractors will be used to modify the data extraction form to ensure its usability and completeness. Data extraction in duplicate will be accomplished independently. Any disagreements between two parties will be resolved through discussion. The third reviewer will arbitrate if consensus is unreachable.
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 We will extract data on: I) general information (title, author, year, study ID), II) aims and rationale III) study design (includes brief description of method limitation) IV) study period V) study participants and settings VI) intervention characteristics in details (e.g. component, types, format, delivery strategy, timing, provider and recipient characteristics, effect, feasibility, acceptability, sustainability), VII) intervention outcomes (control and intervention group results, effect, effect size, Confidence Interval (CI), Standard Deviation (SD) and VIII) recommendations and conclusions. The intervention results will be carefully extracted to make them statistically meta-analysable. If data presentation is problematic, unclear, missing or presented in un-extractable form, the respective authors will be contacted for clarification by email with a response time limit of two weeks. If the author is unresponsive, then they will be classified as uncontactable. We will group interventions based on disease cases, intervention classes, effect size, country, provider population and sources of variation (e.g. seasonal and regional)
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale Study Outcome measures Primary and secondary outcomes will be measured to determine effectiveness, feasibility and acceptability of interventions and distinguishing features of interventions (types, format and content etc).

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		Effectiveness Primary outcomes The effect of interventions to reduce quantity and improve quality of antibiotic prescribing will be measured by: • Change in total antibiotics (any type) prescribed by GPs or FPs • Change in broad spectrum antibiotic (individual or multiple) prescribing • Change in antibiotic prescribing congruent with antibiotic guidelines or therapeutic guidelines or WHO listed alert antibiotic guides Secondary outcome measures of effectiveness will include: • Change in antibiotic dose and/or dose regimen on antibiotic prescriptions in response to any intervention • Changes in consultation rates including re-consultation of patients with infections • Change in antibiotic dispensing Rx/1000 patients where antibiotic prescribing data is not available • Change of cases/visits where antibiotics were prescribed in response to deterioration of condition or adverse effect of antibiotics • Clinician knowledge about antibiotic use and /or antibiotic resistance • Cases of adverse effects of antibiotics • Types of interventions • Intervention components (e.g. types, formats, mode of delivery, providers) Measurement unit of changes in prescribing will be a number or percent or proportion of prescribed antibiotics. **Feasibility and acceptability** This will be assessed as a secondary outcome by assessing ease of implementation, required resources, acceptability and satisfaction of the targeted clinicians after the intervention.
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 **Assessment of risk of bias** Two reviewers (SKS and LH) will independently evaluate quality features of included articles utilizing established guidelines and criteria tools[67-70]. Internal validity of RCTs will be assessed using Cochrane risk of bias tools. [68] The domains of this tool will be selection bias (random sequence generation, allocation

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		concealment), reporting bias (selective reporting), performance bias (blinding of participant and personnel), detection bias (blinding of outcome assessment), and attrition bias (incomplete outcome data). We will have significant concern about attrition bias if there exist a loss to follow up of at least 20%. We will avoid scoring the quality of the trials because of debates regarding scoring methods.[71] Each study will be categorized as high risk, low risk and unclear risk of bias under each of the criteria based on guidelines. [68] A study will be deemed as being at low risk of bias if it meets greater than or equal to four criteria out of six criteria with low risk of bias and the other two criteria must not be attrition or reporting bias. Studies will be considered as at unclear risk of bias if at least one domain has unclear risk of bias and at most three domains have low risk of bias. Studies with three domains with low risk of bias excluding attrition or reporting bias will be treated as studies with medium risk of bias. In studies where there are at least four domains at risk of bias or having random sequence generation bias they will be considered as studies with high risk of bias. Based on this criteria, each study will be given an overall assessment of low, moderate, or high risk of bias. The quality assessment tool will be piloted on a small sample of included studies (5). The quality assessment criteria for non-randomized studies (CBA and TSA) will be based on ROBINS-I risk assessment tools[69] and methodological quality criteria and guidance [71 72] from the Cochrane Collaborations.[67] We will also evaluate reporting criteria (e.g. outcome definition, sample size calculation, sources of funding) for each of the included studies. The findings of each trial's risk of bias assessment will be recorded in a summary table.
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised The findings of the included studies will be summarized in a table format for outcome measures including key information features regarding study types, design, number, participant characteristics, interventions, outputs and outcome measures. All the categorical variables of RCT, CBA and TSA trials (e.g. antibiotic prescribing rate) will be reported with the same unit with 95% confidence intervals (CI) and continuous variables with mean difference (MD) and 95% CI. We will

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		assess the proportion or volume or rate of I) overall changes of antibiotic prescribing II) changes in broad spectrum or WHO listed alert antibiotic prescribing III) changes in antibiotic prescribing adherence with a therapeutic guideline indicating appropriateness of GPs' antibiotic prescribing and IV) changes in antibiotic dose and /or dose regimen during prescribing after intervention. We will calculate the effect size of each study by subtracting pre intervention differences (intervention group–control groups) and post intervention differences. Absolute risk will be determined to express clinical significance. Summary statistics with 95% CIs and exact p-value will be reported if studies have sufficient data for calculations. The combined analyses will represent the real percentage change in the rate of antibiotic prescribing or appropriateness of prescribing that is intervention attributed.
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 I2, Kendall's τ) Where appropriate, outcome data will be combined for meta-analysis. The pooled effect estimates will be generated using random-effects modelling to calculate inter study heterogeneity in the intervention effect size. Fixed effect modelling will be used if no substantial inter study heterogeneity exists. For substantial inter study heterogeneity, Forest plots [70], χ^2 test and I^2 statistic [68] will be used to compare the effect size of trials with and without characteristics (e.g. study features, context or intervention variation) of interest. The scale of heterogeneity will be low (<25%), moderate (50%), severe (up to 75%) and very severe (>75%). A meta-regression analysis will be performed to measure secondary outcomes if there are a substantial number of studies. A statistician will be approached if standardisation is required across studies for meta-analysis of continuous outcomes. We will explain our data within an analytic stratum using the median and interquartile range of effect sizes of trials. We will evaluate the association between type of intervention strategies and effect size, using the methods described above. In addition, we will assess other characteristics of studies as important confounders of the observed association. Assessment of confounders will be undertaken if the study characteristic meets two criteria: (1) if there is an independent association with the effect size and (2) where trials with that characteristic across the intervention types (e.g. clinician education only, or combined with audit and feedback) have an uneven distribution. We will use rank-sum tests to evaluate the

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	association between each intervention trial characteristic and effect size, and Fisher exact test to evaluate uneven distributions of study characteristics over intervention types. We will specify $P < 0.05$ as statistically significant for this association. All analyses will be performed using STATA 13.Where quantitative analysis is not possible, evidence will be presented as a descriptive synthesis.
15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression) **Unit of analysis errors** In case of potential unit of analysis error of RCT and CBAs, methods for re-analysis as guided by EPOC, 2015, will be used. Incorrect analysis of cluster RCTs due to absence of accounting for clustering will be handled with reanalysis if possible. If correction is not possible we will report the effect size without a standard error and confidence interval as they are unlikely to be accurate. **Reanalysis methods for inappropriate analysis** If appropriate, segmented time series regression will be applied according to EPOC guidance to reanalyse the data of studied trials followed by a method described in Ramsay et al. [73] **Dealing with missing data** If any missing data exists within working trials, the respective authors will be contacted to avoid inappropriate description of study results and to minimize risk of bias in meta-analysis. [74] A guidance [68] will be followed to handle missing data. **Sensitivity analysis** A sensitivity analysis will be conducted to estimate the effect of study quality and effect of missing data on meta-analysis of outcome measures. Two meta-analyses (one including all eligible studies and the second including only those studies defined by EPOC criteria as being high quality for quality assessment) will be performed to determine the effect of study quality. In case of unobtainable data, our plan will be I) to conduct complete case analysis following a method described in Ebrahim et al., 2013 and II) to perform sensitivity analysis of outcomes (continuous and dichotomous) to address the potential impact of missing data on meta-analysis utilizing a method discussed by AKL et al. [77]

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		Subgroup analysis Should enough data be available, this review will conduct subgroup analysis for primary outcomes. Important varieties of exploratory subgroup analysis may be performed by: I) provider population (pharmacist and/or GPs and/ or infectious disease expert), II) country settings (developed vs middle income vs low income), III) primary care setting (General practice vs ambulatory), IV) disease cases (among RTIs or RTI vs skin), V) risk of bias (high risk vs low risk of bias) VI) antibiotic classes VII) intervention types, VIII) mode of delivery of intervention IX) timing of intervention studies.
15d		If quantitative synthesis is not appropriate, describe the type of summary planned If data are not appropriate for meta-analysis, a narrative synthesis will be conducted through combining results into forest plot with omission of pooled estimate. A narrative synthesis framework developed by Rogers et al., 2009 will be used to ensure that the narrative synthesis is a rigorous and transparent process. Priority will be given to high quality trials and special cautions will be given to the results which are highly prone to bias.
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies) **Assessment of publication bias** The assessment of publication bias will be conducted by extrapolating the study trials effect estimate with inversion of trials standard error through usage of a funnel plot. The assessment of the plots will be both visually and by Egger's test with a p-value < 0.1 considered as significant publication bias. [75]
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE) **Quality assessment of Evidence** The evidence summaries (intervention profiles and table of findings) will be formulated based on guidance recommended by Grading of Recommendations Assessment, Development, and Evaluation (GRADE) working group[76] and the TDieR checklist. [64 65]

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Improving antibiotic prescribing by general practitioners: A protocol for a systematic review of interventions involving pharmacists

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Title of the study protocol

Improving antibiotic prescribing by general practitioners: A protocol for a systematic review of interventions involving pharmacists

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Abstract

Introduction Effective antibiotic options in general practice (GP) for patients with infections are declining significantly due to imprudent antibiotic prescribing and emerging antibiotic resistance. To better improve antibiotic prescribing by general practitioners (GPs), pharmacist-GP collaborations have been promoted under antibiotic stewardship programs. However, there is insufficient information about whether and how pharmacists help GPs to more appropriately prescribe antibiotics. This systematic review aims to determine whether pharmacist-led or pharmacist involved interventions are effective at improving antibiotic prescribing by GPs within general practice.

Methods and analysis A systematic review of English language randomized controlled trials (RCTs), cluster randomized trials (cRCTs), controlled before-after studies (CBAs) and interrupted time series (ITS) studies cited in MEDLINE, EMBASE, EMCARE, CINAHL plus, PubMed, PsycINFO, Cochrane CENTRAL, and WEB OF SCIENCE databases will be conducted. Studies will be included if a pharmacist is involved as the intervention provider and GPs are the intervention recipients in GP setting. Data extraction and management will be conducted utilizing Effective Practice and Organization of Care (EPOC) data abstraction tools and a template for intervention description and replication (TIDieR).The Cochrane and ROBINS-I risk of bias assessment tools will be used to assess the methodological quality of studies. Primary outcome measures include changes (overall, broad spectrum, and guidelines concordance) of GP prescribed antibiotics. Secondary outcomes include quality of antibiotic prescribing, delayed antibiotic use, acceptability, and feasibility of interventions. Meta-analysis for combined effect and Forest plots, $\chi 2$ test, and I^2 statistics for detailed heterogeneity and sensitivity analysis will be performed if data permits. GRADE and PRISMA-P guidance will be used to report findings.

Ethics and dissemination No formal ethics approval is required as no primary, personal or confidential data is being collected in this study. The findings will be disseminated to national and international scientific sessions and published in a peer reviewed journal.

Trial registration number PROSPERO registration number CRD42017078478.

Keywords Antibiotic stewardship, Interventions, Pharmacist, General practitioner, Systematic review

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Strengths and limitations of this study

- To the best of our knowledge, this will be the first systematic review assessing pharmacist-led or pharmacist involved interventions to improve antibiotic prescribing by GPs.
- This review is solely focused on general practice or family practice which may increase applicability of the findings.
- An expected heterogeneity in design and varying methodological quality across study which may hinder meta-analysis and interpretation of findings.
- Searches of this review will be limited to only English language studies.

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Introduction

Growing antibiotic resistance (AR) and a shortage of new effective antibiotics have become an urgent global threat to public health[1 2] with a risk of a significant rise in morbidity, mortality and health care costs .[2 3] AR annually causes 23000 death in America, 25 000 deaths in the European Union (EU) and 700, 000 deaths worldwide.[4] By 2050, it is predicted that there will be 10 million deaths annually and USD 100 trillion in global economic loss caused by drug-resistant bacterial infections if AR continues to rise at the same pace as in the last decades.[5] Over-prescribing and inappropriate prescribing of antibiotics are the principal and the modifiable driver of AR.[6 7]

Primary care is where the majority antibiotics are prescribed and dispensed [8-10] as evidenced by 85%-95% antibiotics in Europe and nearly 70% of antibiotics in the USA are supplied in primary care. The major primary care antibiotic prescribers are general practitioners (GPs) or family practitioners (FPs) and ambulatory clinic physicians.[11] It has been reported that in respiratory tract infections (RTIs), urinary tract infections (UTIs), and in skin infections, guideline incongruent antibiotic prescription rates in primary care were 50-90%, [10 12-14] 80% and 46% [15] respectively. Inappropriate antibiotic prescribing eventually leads to adverse effects, resource wasting, re-consultations, rising treatment costs, ineffective antibiotics and bacterial resistance.[6 16]Inappropriate prescribing of antibiotics are influenced by individual, interpersonal, social, organizational and national level barriers. Mostly these factors are behavioural and health system oriented.[17] More specifically, knowledge deficits among prescribers, the practice environment and prior experience of the practitioner, peer pressure, patient pressure, patients expectation, time constraints, diagnostic uncertainties, lack and/or ineffective communication between prescriber, pharmacist and patients[18 19] have been implicated in inappropriate antibiotic prescribing practices.

There is a major body of literature documenting many interventions to cut the established barriers and behaviours of clinicians related to antibiotic prescribing. Over the last ten years, various systematic reviews[20-26] have explored the effectiveness of clinician targeted interventions to improve their antibiotic prescribing in inpatient and outpatient settings. However, no reviews were solely focused on general practice. [27] Multifaceted interventions involving physicians, pharmacists and patients are more likely to produce a greater effect size in reducing antibiotic prescribing and increasing guideline recommended antibiotic prescribing.[28 29] although another review concluded that single but focused interventions are more effective than multidimensional interventions at improving antibiotic choice by

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clinicians.[24] According to the WHO global strategies against antimicrobial resistance (AMR), isolated interventions have little effect on improving the quality of antibiotic prescribing.[30]

Pharmacists play an active role in improving the appropriateness of antibiotic prescribing practice by GPs through the provision of expert advice, education and training, liaison with regards to formulary, the provision of resistance data, raising awareness of guideline-adherence and policy-guided antibiotic prescribing.[31 32]In many countries, these interventions are being increasingly integrated at the health care system or practice level with the aim of achieving more collaborative care by physicians, pharmacists, and other health professionals to optimise antibiotic use.[33] Practitioner-pharmacist collaboration model [34] is such an example. Such collaboration is more firmly established in hospitals rather than in primary care. Burdet et al's., 2016 review outlined four specific workable models of collaboration in primary care focused on relationship, conceptual and attitudinal models amongst GP and pharmacists but their effectiveness and acceptability was inconclusive and under-researched.[35] As GPs and pharmacists are being increasingly engaged in antibiotic stewardship programs, a workable intervention model is inevitable to improve GPs' antibiotic prescribing in community setting. [36 37] Vervloet et al's., 2015 showed that FPs and pharmacists collaborative pharmacotherapy audit meeting to reduce antibiotic prescriptions in RTI was effective.[38] In the UK, utilization of antimicrobial pharmacists, infectious disease pharmacists, and community pharmacists are emerging to support GPs in right decision making about antibiotic prescribing. [39]AMR Pacesetter project [40] which was implemented to support GPs in adopting good antimicrobial stewardship in primary care through auditing antimicrobial prescribing, developing an action plan in collaboration with GPs and delivering patient education to reduce 'patient pressure' on prescribing antibiotics by GPs. A 16.09% reduction of antimicrobials prescribing was achieved in 2015 which has highlighted the contribution of antimicrobial pharmacists to this effective collaboration with GPs as a positive step in tackling community AR.[40] The evidences of other intervention studies supports the important role of pharmacists to GP as a therapeutic adviser [41] ; a trainer [31 42] ; an academic detailer [43 44] ; a reviewer of medication prescription and feedback provider [24] to improve their antibiotic prescribing norms and culture. This evidence clearly shows the importance of pharmacists in supporting GPs to foster prudent prescribing practice of antibiotics. Therefore, it is crucial to explore the evidences of effective interventions where pharmacists play a role as interventionist to GPs to improve quality of antibiotic prescribing.

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Understanding such interventions which are more likely to improve engagement between GPs and pharmacists and optimising antibiotic prescribing in general practice is a priority. However, no systematic review has yet explored which interventions involving pharmacists are effective at improving GPs' antibiotic prescribing. Hence there is insufficient information to design future GP-pharmacist collaborative models to optimise antibiotic use in the community. This systematic review, therefore, aims to find pharmacist-led or pharmacist involved interventions to improve antibiotic prescribing by GPs and to assess their effectiveness. The second objective of this review is to explore the feasibility and acceptability of the interventions if data permits. It is very difficult to make definitive conclusions regarding the effectiveness of interventions unless interventions are focused and very specific to a practice area.[45] This review will explore studies specific to general practice settings where the intervention is either pharmacist-led or pharmacist involved and the recipient is a general practitioner.

Methods

Guidance regarding the Preferred Reporting Items for Systematic review and Meta-analysis for Protocols (PRISMA-P) was used to develop this systematic review protocol. This protocol is registered on PROSPERO with trial no. CRD42017078478.The planned period of this review study is from 1 June 2017 to 30 January 2018.

Study design

The selected studies will be either randomised controlled trials (RCTs) (including cluster parallel group and factorial), controlled before-after studies (CBAs) or interrupted time series analyses (ITS).The guidance on study design as recommended by the Effective Practice and Organisation of Care group (EPOC) that all RCTs must have at least two intervention and control sites and that interrupted times series studies must have a minimum of three time points both before and after the intervention will be followed. The EPOC study design algorithm will be used to determine the study design and to avoid ambiguous terminology.

Review question

The research question is: What pharmacist-led or pharmacist involved interventions are effective to improve antibiotic prescribing by GPs in primary care?

Eligibility criteria

Types of participants

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We will include studies that examine interventions targeted at GPs or FPs within primary care. Intervention providers include either a pharmacist alone or as part of a team consisting of pharmacist/others (e.g. GPs/clinicians/ microbiologists/ infectious disease experts) in a general practice environment. No restrictions will be made on age, gender, ethnicity, and residence of participants. Intervention recipients include GPs or FPs. Physicians, nurses or dentists practitioners working in aged care facilities, long- term care facilities, nursing homes or dental care facilities will be excluded. We will exclude any studies targeting health professionals working in inpatient settings, hospital settings or residential settings as well.

Types of interventions and comparators

Studies will be included if they meet following conditions-

- Conduct interventions by either a pharmacist(s) alone or a pharmacist(s) engaged in a multidisciplinary team to improve antibiotic prescribing by GPs.
- Investigate a single or multicomponent or multifaceted intervention with the primary objective of reducing quantity or improving quality (selection/appropriateness) of antibiotic prescribing
- Evaluate the effect of interventions based on changes in GPs' antibiotic prescribing
- Evaluate any type of intervention (e.g. educational, clinical, managerial or regulatory)
- Where GPs or FPs in general practice receive the interventions
- Apply any mode of intervention delivery techniques
- Conduct the intervention at any time

Studies will be excluded when the -

- Intervention is delivered in an inpatient/hospital setting/ secondary care/ tertiary care, long-term care, residential care, ambulatory care, aged care facility, nursing home, or dental care facility
- Intervention doesn't include pharmacist(s)
- Study evaluates no outcome measures related to GP's antibiotics prescribing

We will include alternative intervention studies that aim to improve antibiotic prescribing compared with control or usual care.

Settings

Only studies in general practice/family practice will be included. General practice or family practice for this review will be defined as "*the first point of care where individuals and*

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families in their communities are provided person centred, continuing, comprehensive and coordinated whole person health care ".[46]

Language

Only English language articles will be included.

Time

There will be no restrictions on study publishing date. The inception of databases until the date of search will be the time limit for the search strategy. Studies will be included regardless of intervention follow-up time.

Study outcome measures

Effectiveness

Primary outcomes

The effect of interventions to reduce the quantity and improve quality of antibiotic prescribing will be measured by:

- Change in total antibiotics prescribed by GPs or FPs
- Change in broad-spectrum antibiotic prescribing
- Change in antibiotic prescribing congruent with published antibiotic guidelines or therapeutic guidelines or WHO listed alert antibiotic guides

Secondary outcomes

- Change in antibiotic dose and/or dose regimen on antibiotic prescriptions in response to any intervention
- Changes in consultation rates including re-consultation of patients with infections
- Change in antibiotic dispensing Rx/1000 patients where antibiotic prescribing data is not available
- Change of cases/visits where antibiotics were prescribed in response to deterioration of condition or adverse effect of antibiotics
- Clinician knowledge about antibiotic use and /or antibiotic resistance
- Cases of adverse effects of antibiotics
- Types of interventions
- Intervention components (e.g. types, formats, mode of delivery, providers)

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The measurement unit of antibiotic prescribing will be a number or percent or proportion of prescribed antibiotics. Antibiotic prescribing rate will be defined as number of antibiotic prescription divided by total number of patient visits /prescription during a designated interval. The rate of antibiotic prescribing adherence with guidelines will be defined as the number of recommended antibiotic prescription divided by total number of patient visits/prescription during a designated period.

Feasibility and acceptability

Secondary outcomes

These outcomes will be assessed as secondary outcomes by assessing ease of implementation, required resources, acceptability, and satisfaction of the targeted clinicians after the intervention.

Data sources and search methods

Electronic Databases

We will conduct this systematic review and meta-analysis in accordance with the PRISMA-P guidelines.[47] A uniform search strategy will be developed and applied to the following databases: MEDLINE, EMBASE, EMCARE, PubMed, PsycINFO, Cochrane Central Register of Controlled Trials (CENTRAL), CINAHL plus and Web of Sciences. We will also manually search reference lists of retrieved articles and relevant articles. The databases will be searched from:

1. MEDLINE and Ovid (1946 to searched date)
2. EMBASE and Ovid (1974 to searched date
3. EMCARE (1995 to searched date)
4. PubMed (1974 to searched date)
5. PsycINFO (1806 to searched date)
6. Cochrane Central Register of Controlled Trials (CENTRAL) (1889—searched date)
7. CINAHL PLUS (1982 to searched date)
8. Science Citation Index and Social Sciences Citation Index, ISI Web of Science (1975 to searched date)

Search terms and strategy

The search strategy will capture studies that include each of three groups of terms within PICO format: populations (pharmacists, GPs), intervention (any) and outcomes (antibiotics, prescribing practice changes and settings). Matched terms under each group against

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possible medical subject headings (MeSH) or keywords as follows will be used in a systematic search through 8 databases.

A. Population terms:

Pharmacist: Pharmacists/ OR Pharmacist* OR (pharmacy or pharmacies) OR (retail pharmacist or community pharmacist or clinical pharmacist or antimicrobial pharmacist or infectious disease pharmacist)

Physician: Family Physicians / OR General Practitioners / OR (GP* or family practitioner* general practitioner* or clinician* or doctor* or rural practitioner or family medicine practitioner)

B. Intervention terms

Intervention: intervention* or program* or health promotion* or education* or educational outreach* or training* or academic detailing* or educational meeting* or workshop or communication skill* or audit* or guideline* or group meeting* or decision support* or poster* or leaflet* or flyer* or incentive* or regulation or reminder* or consultation* or web based training* or electronic prescribing* or medication review* or medication reconciliation* or drug review or stewardship or multi-prong* or strategy or single or multicomponent* or multi-component or multiple or multifaceted or multidisciplinary or multi-disciplinary or physician aid or physician-aid or collaborative or collaboration or counselling or pharmacist supported or pharmacist-led or pharmacist led or team based or team-based or shared

C. Outcome terms

Antibiotics: Anti-Bacterial Agents/ OR (antibacterial or anti-bacterial or antibiotic or anti-biotic or antimicrobial or anti-microbial or antibiotic* or antimicrob* or antibacteria* or antibacterial agent) OR Anti-infective agents/ or (broad spectrum or short spectrum or narrow spectrum or narrow-spectrum)

Practice changes: Drug Prescriptions/ OR Inappropriate prescribing/ OR Appropriate prescribing/ OR practice pattern, physicians/ OR (prescribe or prescription* or practice or practising or dispense or dispensing or stewardship or Antibiotic therapy or Antibiotic treatment or antibiotic prescribing or pattern* or behaviour or behaviour or reduce or reduced or reduction or reducing or increase or increasing or increased or change or changing or changed or optimize or optimise or optimizing or optimization or optimising optimisation or effect* or effective or effectiveness or influence or influenced or influencing or impact.

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Settings: General practice / Primary health care/ OR (primary care or primary health care or primary healthcare)

Hand searching

We will manually search key journals (e.g. The LANCET Infectious Diseases, Journal of Antimicrobial Chemotherapy, Journal of Antimicrobial Agents, Biomed Central (http://www.biomedcentral.com/), British Medical Journal (BMJ), Annals of pharmacotherapy, International Journal of pharmacy practice (IJPP), JAMA, WHO's library databases (WHOLIS). If required, direct contact with authors will be undertaken to obtain other relevant articles. Cited original articles in relevant systematic reviews will also be retrieved and analyzed. We will update our literature search using the auto alert system in individual databases before publication of this review to avoid missing of any potential articles.

Study selection

All electronically and manually searched records will be merged to remove duplicate citations. Two reviewers will independently screen titles and abstracts to identify eligible articles using the inclusion and exclusion criteria. Where there is uncertainty regarding whether an article meets eligibility criteria, the full text of the article will be reviewed to determine final inclusion.. Discrepancies between the reviewers will be resolved through discussion until a consensus is reached. If necessary, a third reviewer will be consulted to resolve the disagreement. . If there is an information gap in a paper and/or a need for further clarification, the author will be contacted to clarify the issue by email. A PRISMA flow diagram will be used to maintain transparency in the article selection process and to record remaining studies in each stage of selection with a valid explanation regarding reasons of studies' exclusion.

Data extraction and management

A tailored version of EPOC's data abstraction tool[48] and the EPOC data collection checklist forms will be used as a guide to developing a data extraction form. This form will be adapted to answer the research question of this review and identify confounding factors. Additionally, recommendations for improving the consideration and description of interventions in a systematic review and a template for intervention description and replication (TIDieR) checklist [49 50] will be followed. The developed data extraction form will be pilot tested by the data extractors (SKS, LH) to ensure that it has captured all the relevant information. [51] Feedback from the extractors will be used to modify the data extraction form to ensure its usability and completeness. Data extraction in duplicate will be accomplished independently.

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Any disagreements between two parties will be resolved through discussion. The third reviewer will arbitrate if a consensus is unreachable.

We will extract data on I) general information (title, author, year, study ID), II) aims and rationale III) study design (includes brief description of method limitation) IV) study period V) study participants and settings VI) intervention characteristics in details (e.g. component, types, format, delivery strategy, timing, provider and recipient characteristics, effect, feasibility, acceptability, sustainability), VII) intervention outcomes (e.g. control and intervention group results, effect, effect size, confidence interval (CI), standard deviation (SD), odds ratio (OR) and VIII) recommendations and conclusions. The intervention results will be carefully extracted to make them statistically meta-analysable. If data presentation is problematic, unclear, missing or presented in an un-extractable form, the respective authors will be contacted for clarification by email with a response time limit of two weeks. If the author is unresponsive, then they will be classified as uncontactable. We will group interventions based on disease cases, intervention types, effect size, country, provider population and sources of variation (e.g. seasonal and regional).

Assessment of risk of bias

Two reviewers (SKS and LH) will independently evaluate quality features of included articles utilizing established guidelines and criteria tools.[52-55] Internal validity of RCTs will be assessed using Cochrane risk of bias tools. [53] The domains of this tool will be selection bias (random sequence generation, allocation concealment), reporting bias (selective reporting), performance bias (blinding of participant and personnel), detection bias (blinding of outcome assessment), and attrition bias (incomplete outcome data). We will avoid scoring the quality of the trials because of debates regarding scoring methods.[56] Each study will be categorized as high risk, low risk and unclear risk of bias under each of the criteria based on guidelines. [53] A study will be deemed as being at low risk of bias if it meets greater than or equal to four criteria out of six criteria with low risk of bias and the other two criteria must not be attrition or reporting bias. Studies will be considered as at unclear risk of bias if at least one domain has an unclear risk of bias and at most three domains have a low risk of bias. Studies with three domains with low risk of bias excluding attrition or reporting bias will be treated as studies with medium risk of bias. In studies where there are at least four domains at risk of bias or having random sequence generation bias, they will be considered as studies with high risk of bias. Based on this criteria, each study will be given an overall assessment of the low, moderate, or high risk of bias. The quality assessment tool will be piloted on a small sample of included studies (5). The quality assessment criteria for non-randomized studies (CBA

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and ITS) will be based on ROBINS-I risk assessment tools[54] and methodological quality criteria and guidance [56 57] from the Cochrane Collaborations.[52] We will also evaluate reporting criteria (e.g. outcome definition, sample size calculation, sources of funding) for each of the included studies. The findings of each trial's risk of bias assessment will be recorded in a summary table.

Data synthesis and analysis

The findings of the included studies will be summarized in a table format for outcome measures including key information features regarding study types, design, number, participant characteristics, interventions, outputs and outcome measures. All the categorical variables of RCT, CBA and ITS trials (e.g. antibiotic prescribing rate) will be reported with the same unit with 95% confidence intervals (CI) and continuous variables with the mean difference (MD) and 95% CI. As primary outcomes, we will assess the proportion or volume or rate of I) overall changes of antibiotic prescribing II) changes in broad spectrum and III) changes in antibiotic prescribing adherence with a therapeutic guideline indicating appropriateness of GPs' antibiotic prescribing. We will calculate the effect size of each study by subtracting pre-intervention differences (intervention group–control groups) and post-intervention differences. Absolute risk may be determined to express clinical significance. Summary statistics with 95% CIs and exact p-value will be reported if studies have sufficient data for calculations. The combined analyses will represent the real percentage change in the rate of antibiotic prescribing or appropriateness of prescribing that is intervention attributed.

Where appropriate, outcome data will be combined for meta-analysis. The pooled effect estimates will be generated using random-effects modelling to calculate inter study heterogeneity in the intervention effect size. Fixed effect modelling will be used if no substantial inter-study heterogeneity exists. For substantial inter-study heterogeneity, Forest plots [55], χ^2 test and I^2 statistic [53] will be used to compare the effect size of trials with and without characteristics (e.g. study features, context or intervention variation) of interest. The scale of heterogeneity will be low (<25%), moderate (50%), severe (up to 75%) and very severe (>75%). A meta-regression analysis will be performed to measure potential sources of heterogeneity if there are a substantial number of studies. A statistician will be approached if standardization is required across studies for meta-analysis of continuous outcomes.

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We will explain our data within an analytic stratum using the median and interquartile range of effect sizes of trials. We will evaluate the association between type of intervention strategies and effect size, using the methods described above. In addition, we will assess other characteristics of studies as important confounders of the observed association. Assessment of confounders will be undertaken if the study characteristic meets two criteria: (1) if there is an independent association with the effect size and (2) where trials with that characteristic across the intervention types (e.g. clinician education only, or combined with audit and feedback) have an uneven distribution. We will use rank-sum tests to evaluate the association between each intervention trial characteristic and effect size, and Fisher exact test to evaluate uneven distributions of study characteristics over intervention types. We will specify $P < 0.05$ as statistically significant for this association. All analyses will be performed using STATA 13. Where quantitative analysis is not possible, evidence will be presented as a descriptive synthesis.

Unit of analysis errors

In case of a potential unit of analysis error of RCT and CBAs, methods for re-analysis as guided by EPOC, 2015, will be used. Incorrect analysis of cluster RCTs due to the absence of accounting for clustering will be handled with reanalysis if possible. If correction is not possible we will report the effect size without a standard error and confidence interval as they are unlikely to be accurate.

Reanalysis methods for inappropriate analysis

If appropriate, segmented time-series regression will be applied according to EPOC guidance to re-analyse the data of studied trials followed by a method described in Ramsay et al. [58]

Dealing with missing data

If any missing data exists within working trials, the respective authors will be contacted to avoid the inappropriate description of study results and to minimize the risk of bias in meta-analysis. [59] A guidance [53] will be followed to handle missing data.

Assessment of publication bias

The assessment of publication bias will be conducted by extrapolating the study trials effect estimate with inversion of trials standard error through the usage of a funnel plot. The assessment of the plots will be both visually and by Egger's test with a p-value < 0.1 considered as significant publication bias. [60]

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Quality assessment of Evidence

The evidence summaries (intervention profiles and table of findings) will be formulated based on the guidance recommended by Grading of Recommendations Assessment, Development, and Evaluation (GRADE) working group[61] and the TIDieR checklist. [49 50]

Sensitivity analysis

A sensitivity analysis will be conducted to estimate the effect of study quality and effect of missing data on the meta-analysis of outcome measures. Two meta-analysis (one including all eligible studies and the second including only those studies defined by EPOC criteria as being high quality for quality assessment) will be performed to determine the effect of study quality. In case of unobtainable data, our plan will be I) to conduct complete case analysis following a method described in Ebrahim et al., 2013 and II) to perform sensitivity analysis of outcomes (continuous and dichotomous) to address the potential impact of missing data on meta-analysis utilizing a method discussed by AKL et al. [62]

Subgroup analysis

Should enough data be available, this review will conduct subgroup analysis for primary outcomes. Important varieties of exploratory subgroup analysis may be performed by I) provider population, II) country settings (e.g. developed vs middle income vs low income), III) study design, IV) disease cases (among RTIs or RTI vs skin), V) risk of bias (high risk vs low risk of bias) VI) antibiotic classes VII) intervention types, VIII) mode of delivery of intervention IX) Follow up timing of intervention studies.

Ethics and dissemination

No formal ethical approval is required as no primary, personal and confidential data is being collected in this study .We will present our findings including GRADE evidence and descriptive evidence tables in Australia and at international scientific meetings, seminars, workshops, and conferences in addition to publishing in a peer-reviewed journal.

Discussion

To the best our knowledge, this is the first systematic review assessing pharmacist-led or pharmacist involved interventions to improve GPs' antibiotic prescribing in primary care. This review is solely focused on family practice or general practice settings. The findings will be more applicable to general practice due to less contextual variation led by different settings of care. This review will cover a large number of databases and other journal sources as well.

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Use of English language articles is a limitation of the review. Poor quality studies and heterogeneity in results may lead to difficulty in interpreting findings.

It is anticipated that the findings of this systematic review will be relevant to many stakeholders. Firstly, the review will present a comprehensive overview of pharmacy intervention features for primary care researchers and will additionally highlight any potential gaps in the current literature on this topic. Secondly, it will highlight international evidence from peer-reviewed literature on the effectiveness, feasibility, and acceptability of interventions with the assessment of methodological quality of relevant studies thereby increasing the applicability of the findings. Thirdly, the review could provide information regarding valuable interventions which may increase GP-pharmacist collaboration and more judicious antibiotic prescribing in general practice. Fourthly, the review may be useful for funders to better understand interventions which could be prioritized for future funding. This will be informed by ranking outcomes in an innovative approach. Finally, the findings may support general practitioners, pharmacist, researchers, and health policy makers to design future interventions to improve antibiotic prescribing by GPs in primary care.

Registration and publishing

This systematic review protocol is registered on the International Prospective Register of Systematic Reviews (PROSPERO) with a trial number, CRD42017078478 (https://www.crd.york.ac.uk/prospero/#myprospero) dated 8 November 2017. A PRISMA-P checklist[47] will be used to report the review. The findings of the review will be published in international peer-reviewed journals.

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Contributors

Review concept was designed by DM and SKS. SKS and LH developed the study design and literature search strategies. Screening of literature was conducted by SKS and LH. Design of study quality risk assessment tools, data extraction tools, data synthesis and meta-analysis and statistical tests were developed by SKS, LH, and DM. SKS wrote this

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manuscript and also drafted the whole protocol according to PRISMA-P. Revision of the draft manuscript was undertaken by all authors.

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Competing interest

The authors have no conflicts of interest.

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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	Protocol Page No
ADMINISTRATIVE INFORMATION			
Title:			1
Identification	1a	Identify the report as a protocol of a systematic review	
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	2
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	16
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	16
Sponsor	5b	Provide name for the review funder and/or sponsor	
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	
INTRODUCTION			3-6
Rationale	6	Describe the rationale for the review in the context of what is already known	5-6
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	6
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	6-8
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	9
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	10
Study records:			

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Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	11-12
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)	11
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	11
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	11
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	8
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	12
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	
	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)	13
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	14
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	14
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	14
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	14

*** 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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