Are Patient Decision Aids Effective in Decreasing Antibiotic Prescription for Acute Upper Respiratory Tract Infections During General Practice and Emergency Department Encounters: A Systematic Review Protocol

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ABSTRACT

Background
Antibiotic resistance is a global issue that has a significant impact on patient morbidity and mortality. Evidence exists within the general practice and the emergency department setting to suggest that antimicrobial overuse is a significant contributor to resistance. Upper respiratory tract infections are a group of conditions for which antibiotics may be inappropriately prescribed. Patient decision aids are tools allowing for shared decision making between clinician and patient, incorporating patient values and the latest evidence into the decision of whether to prescribe antibiotics or not.

Objectives
To determine if patient decision aids are effective in decreasing antibiotic prescription for acute upper respiratory tract infections during general practice and emergency department encounters, and to comment on the depth of literature available in this field.

Methods and Analysis
We have established a protocol for a systematic review to assess the efficacy of patient decision aids in reducing antibiotic prescription for upper respiratory tract infections in general practices and emergency departments. A set of inclusion criteria has been established. We will include systematic reviews and randomised controlled trials only. A search strategy was formed and will be used in the Medline, Embase, ScienceDirect and Cochrane databases as well as sources of unpublished literature. Primary and secondary outcomes will focus on immediate and longer-term antibiotic prescription rate and patient decision aid efficacy. We have established a literature screening process and criteria for quantitative synthesis. Literature screening and study quality assessment will be carried out by two independent and blinded reviewers. We will use a single data extraction protocol.

Results
We are yet to start any formal data collection or analysis but have secured funding from Mackay Institute of Research and Innovation.

Ethics and Dissemination
It was decided that this systematic review protocol did not require ethical approval. Study sponsors will be communicated with regularly regarding the study, which will be published in a journal in the relevant field. Any updates to the protocol will be published as required.

Registration
Prospero registration number: CRD42017069598

Keywords
INTRODUCTION

Antibiotic resistance is a global health issue which negatively affects patient morbidity and mortality (1,2). Overuse of such drugs is a driver in rising antibiotic resistance, with inappropriate prescribing being the focus of global health bodies such as the World Health Organisation (3,4).

Two major areas of antibiotic prescription are emergency departments and general practices, and there is evidence of inappropriate prescription in both settings (6,7). This is especially evident regarding acute uncomplicated upper respiratory tract infections (URTI), which constitute a common reason for antibiotic prescriptions and outpatient physician visits (8,9). Although most URTIs are viral in origin, a survey of 568 general practices in the United Kingdom showed antibiotic prescription for URTIs ranged from 39 to 69% (10,11). In the United States, a retrospective cohort study of emergency departments also showed a 61% antibiotic prescription rate for the URTIs between 2001 and 2010 (12). Given the rise of drug resistant respiratory pathogens, this issue must be addressed (13).

Patient decision aids (PDA) are a promising tool in reducing antibiotic prescription. They are part of the shared decision making (SDM) concept, which allows clinicians and patients to make decisions together that align current evidence and patient values (14-16). PDAs are patient targeted summaries of evidence that aim to improve patient knowledge and decision-making ability (14,15). They include information about the decision being addressed and available management pathways with their individual harms and benefits, outlined such that patients are encouraged to consider their own values and preferences whilst making decisions (15). As patient expectations may influence the decision to prescribe antibiotics, PDAs may improve patient knowledge, decreasing the expectation for antibiotic prescription (8). An example of a relevant patient decision aid has been attached (See “Supplementary File Patient Decision Aid”) with permission from the original authors (17).

A literature review was conducted prior to this systematic review to briefly survey the current literature regarding the efficacy of patient decision aids in decreasing antibiotic prescription rates for upper respiratory tract infections in general practice and emergency encounters (See “Supplementary File Literature Review Ramasamy”) (Ramasamy, 2017). A search of The Cochrane Library, Embase and public PubMed databases was conducted, with the studies found summarised in table 1.
<table>
<thead>
<tr>
<th>Author</th>
<th>Title</th>
<th>Description</th>
</tr>
</thead>
</table>
| Legare et al. 2011 (17) | Training family physicians in shared decision making for the use of antibiotics for acute respiratory infections: a pilot clustered randomized controlled trial | **Intervention:** program promoting SDM to physicians, including PDA  

**Primary outcome measured:**  
Patient decision to immediately use antibiotics (reported by patient)  

**Relevant Results:**  
Baseline immediate antibiotic use decision rate pre-intervention - 56% (intervention group), 54% (control group)  
Post intervention (T1) 33% of intervention group reported immediate antibiotic use compared to 49% in control group – 16% difference, p value 0.08  
Post delayed intervention in control group (T2, 6 months post T1) 35% of intervention group reported immediate antibiotic use (– 2% difference from T1, 95% CI (-14 – 16)). 46% of control group reported immediate antibiotic use. Difference between change in intervention group and change in control group from T0 to T2 = -13 with 95% CI (-13 – 12)
| Legare et al. 2012 (18) | Training family physicians in shared decision-making to reduce the overuse of antibiotics in acute respiratory infections: a cluster randomized trial | **Intervention:** program promoting SDM to physicians, including PDA  
**Primary Outcome Measured:** Patient decision to immediately use antibiotics  
**Relevant Results:**  
Baseline immediate antibiotic use rate pre-intervention reported as 41.2% (intervention group), 39.2% (control group)  
27.2% of intervention group reported immediate antibiotic use post intervention, compared to 52.2% in control group– 25% difference, adjusted relative risk 0.5, 95% CI (0.3-0.7).  
2 weeks post intervention, patient adherence rate to antibiotic decision made initially was 87.7% in intervention group, 91.5% in control group -adjusted RR 1.0 with 95% CI (0.9-1.0)  
2 weeks post intervention, repeat consultation rate was 22.7% in intervention group, 15.2% in control group - adjusted RR 1.3, 95% CI (0.7 – 2.3) |
The literature review suggested that patient decision aids were effective in reducing antibiotic prescription in the context of a combination of further physician education regarding the decision aids, shared decision making and acute upper respiratory tract infections. However, the carrying out of a quantitative analysis was not considered due to resource constraints. It must also be noted that the inclusion criteria for the above literature review did not comment on whether interventions that focused on educating medical practitioners on how to use patient decision aids and the information within them would be considered as separate interventions from the patient decision aid itself. No primary research involving emergency departments was found, and it was also noted that many studies were found during literature screening that used interventions similar to patient decision aids but did not refer to them as such, raising the possibility that there was room for further optimisation of the search strategy and eligibility criteria. Given all of this and the relatively small amount of literature that was found, it is hard to derive any certain conclusion from the above review. This systematic review will look to build upon the previously conducted literature search, utilising input from senior librarians and experienced researchers to review and optimise the search strategy, keywords used and data analysis. More extensive literature access will also be utilised. It is hoped that a larger number of studies will found than in the previously conducted literature review. If not, the need for further research into this area may be highlighted.

**OBJECTIVE**

The objective of this systematic review is to assess whether patient decisions aids are effective in decreasing antibiotic prescription for acute upper respiratory tract infections during general practice and emergency department encounters. We will primarily aim to compare patient decision aids in this context to scenarios where no specific pre-planned intervention is used in the doctor patient interaction.
METHODS AND ANALYSIS

Target Outcomes

The primary outcome will be the proportion of patients who were prescribed antibiotics intended for immediate use.

We define immediate use as a script given for the intended use of antibiotic treatment starting on the same day as the consultation.

The secondary outcomes will include the proportion of patients who were prescribed antibiotics intended for delayed use and follow up markers reflecting longer term efficacy of the PDA, including the number of repeat consultations made for the same illness, the proportion of patients who received an antibiotic script for the same illness in a subsequent consultation and the proportion of antibiotic scripts intended for delayed use that were subsequently filled. We define the prescription of a script for delayed antibiotic use as one that is given in the context of a verbal agreement that the patient will only fill the antibiotic script if symptoms persist or worsen.

The follow up period is defined as being 2 days to 8 weeks post intervention in order to account for URTI symptoms, such as post infectious cough, which may persist for that long (19). Any deterioration in clinical condition would also be expected to occur within this time frame.

Inclusion Criteria

The criteria to assess study eligibility is outlined in Table 2

Table 2: Inclusion Criteria for the Literature Search

<table>
<thead>
<tr>
<th>Study Aspect</th>
<th>Inclusion Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>Immunocompetent general practice and/or emergency department patients of any age and gender. We will assume that participants are immunocompetent unless otherwise specified, in which case at least 90% of all participants must be immunocompetent. Patients with an acute upper respiratory infection, which (after consultation with an infectious disease physician and the literature) includes pharyngitis, rhinosinusitis, sinusitis, tonsillitis, laryngitis, otitis media, nasopharyngitis and rhinopharyngitis (9).</td>
</tr>
<tr>
<td>Intervention</td>
<td>To standardise the intervention, a patient decision aid will be defined</td>
</tr>
</tbody>
</table>
as a resource with all of the following characteristics

- Describes the decision, options available, risks and benefits of individual options
- Presents evidence based information
- Encourages patient involvement in decision making and management
- Encourages patients to consider their own values and preferences

Education on the use of patient decision aids will not be considered an additional intervention. We define such education as any effort that aims to improve clinicians’ direct knowledge of the patient decision aid or enhances their ability to utilise it within the clinician-patient interaction.

Studies that use a patient decision aid within a framework of multiple interventions will be included if results are available specifically for the efficacy of the patient decision aid in isolation.

<table>
<thead>
<tr>
<th>Comparison</th>
<th>The comparator will involve a clinician-patient interaction that does not include any pre-specified practices or interventions. Such interventions include patient focused information or evidence regarding antibiotic use for the patients’ illness that have been taught to clinicians prior to the interaction. A separate intervention will not be allowed as a comparator.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outcome</td>
<td>See “Target Outcomes” section above</td>
</tr>
<tr>
<td>Other</td>
<td>Literature in the English language only</td>
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<tr>
<td></td>
<td>Academic journals only</td>
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<tr>
<td></td>
<td>Electronic literature only</td>
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<td></td>
<td>Systematic reviews, randomised controlled trials only</td>
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</tbody>
</table>

**Search Strategy Formation**
The specific search strategy used has been created in collaboration with a senior librarian with experience in search strategy production.

The search will be conducted through the Clinician’s Knowledge Network (CKN). Scoping and preliminary searches were conducted through CKN to aid with keyword refinement and database selection. The electronic databases searched will include Medline (EBSCO Host interface, year 1946 onwards), Embase (Embase interface, year 1947 onwards), ScienceDirect (EBSCO host interface) and Cochrane Library (Wiley interface). The Web of Science (English interface, year 1900 onwards) database “Cited Reference” function will be used to search for studies that have previously cited studies found to pass level 3 literature screening. Sources searched for unpublished literature will include ClinicalTrials.gov and the “Google Advanced Search” interface of the Google search engine.

Keywords for the search will be created with input from the previous literature review, study authors and the senior librarian LP. A key difference from the literature review will be the exclusion of the term “bronchitis”, which upon further discussion will not be considered an upper respiratory tract infection. A search strategy will initially be created for the Medline database (See “Supplementary File Appendices”: appendix 1), and will then be translated into the syntax for the other databases as required.

The database search will be limited to systematic reviews, meta-analyses and randomised controlled trials. This will be done by utilising standardised search filters. The database searches will also be limited to papers in English and academic journals only.

**Literature Screening**

The results of the database searches will be exported to and stored in Endnote software. The citations inputted into this software will allow level one and two (study title and abstract respectively) screening. Full texts can then be obtained and imported for remaining studies. Results from each database and from each screening round will be kept in independent folders. Education regarding this software will be provided if screening personnel are unfamiliar with it.

The screening process will be carried out independently in duplicate by 2 blinded reviewers (SR and AG). Prior to screening, the Endnote software “Find Duplicate” function will be used to screen for duplicate copies of studies found from the search process. Manual screening of duplicate study records found using this function will be performed prior to deletion. Remaining papers will be sorted by author and manually screened by both reviewers independently to discover multiple reports of the same study and subsequently remove any further duplicates. Any discrepancies between reviewers will be resolved via discussion and then escalation for adjudication by a third party with senior research experience (MA) if required.

The process of selecting studies to be included in this review will involve 3 rounds of screening, with each round focusing on the study titles, abstracts and full papers respectively. Screening question forms will be developed for each round (see “Supplementary File Appendices”: appendix 2.1 – 2.3) based on the eligibility criteria listed above, and will be piloted on the first 10 studies chosen during each screening
round and any adjustments made. Studies will be deemed ineligible for further screening and inclusion if they do not meet the screening criteria at any round.

Systematic reviews and meta analyses that pass level 2 screening will have their reference lists undergo literature screening (the systematic review or meta-analysis itself will not undergo level three screening). The reference lists of any studies that pass level three screening will also be screened. The Web of Science “Cited Reference” function will also be used to search for further studies that have cited literature that has passed level three screening. Unpublished literature will be screened by utilising the “Google Advanced Search” function of the Google search engine and ClinicalTrials.gov.

A record of all studies excluded and included (including reasons for exclusion) at each round will be kept. After each round the inclusion and exclusion records will be compared, and any differences will be clarified and resolved with discussion. A third party with research experience will be contacted for clarification if required. Neither reviewer will be blinded to study title, author or institution. A flow diagram documenting the entire process will be created after the screening process.

The search will be carried out every two months post the initial literature screening to find any new literature.

Data Extraction

A data extraction template (see “Supplementary File Appendices”: appendix 3) will be created and piloted on the first 10 studies passing level 3 screening with any adjustments being made as required. We will use a single data extraction protocol, with results being verified by a second researcher. Any discrepancies between reviewers will be resolved via discussion and then escalation for adjudication by a third party with senior research experience (MA), if required. Any data missing from original studies will also be obtained by contacting the study authors. We will attempt to contact authors via email a maximum of 3 times. If this is unsuccessful, discussion between study authors and a third party with research experience will be carried out to determine the most appropriate way to proceed e.g. complete case analysis.

Data extracted will include:

Study details

design, date, number and size of intervention and control group, length of follow up, publication status, financial support source, proportion of patients lost to follow up and reasons why, time points of outcome measurement and conclusions

Methodology

intervention/s presented in study (including education regarding patient decision aids), non-intervention group treatment method, unit of randomisation and analysis, method of establishing decision aid in intervention group, method of obtaining patient decision aid specific results, patient decision aid specific outcomes measured with time points at which data was collected and reported
Patient demographics

age range, location of population, gender proportions, all diagnoses and/or presenting symptoms/signs, proportion who had previous clinical interactions for same illness within past four weeks, proportion of patients who were immunocompetent,

Patient decision aid details

name of decision aid, diseases targeted, does this patient decision aid fulfil the criteria given within the inclusion criteria?, distribution format, statistics presented, method of presentation of evidence, method of initiating patient input and/or reflection, treatment options presented, when decision aid was exposed to patients, any interventions focusing on patient decision aid education and use

Patient Decision Aid Specific Outcome Details

relevant intervention and non-intervention groups, number of participants in each and number of participants lost to follow up in each, raw data for each participant group (including time point of collection and reporting), processed data for each participant group e.g. mean + standard deviation with associated measure of statistical significance

Study and Data Analysis

Assessment of Bias

We will assess the risk of bias for all studies passing level 3 screening using the “Cochrane Collaboration's Tool for Assessing Risk of Bias”, which covers domains including random sequence generation, allocation concealment, blinding of participants, personnel and outcome assessors, the use of incomplete data for outcomes and selective reporting. This will be carried out independently by 2 reviewers, neither of whom will be blinded to the studies being analysed. Evidence regarding each domain will be described for all studies, with each study being graded as “high risk”, “low risk” or “unclear” for each domain. We will use the ORBIT classification system to help assess selective outcome reporting, which we will explore by comparing the outcomes reported to the outcomes projected to be reported on within study protocols (or within study methodologies if no protocol is found). Any uncertainties regarding any of the domains will be escalated to the authors of the original study for clarification. Differences in opinion between the two reviewers will be rectified with discussion and escalation to a third party with research experience if required.

We will assess publication bias using a funnel plot and the egger test providing at least ten studies pass level three screening. A significant p-value associated with the egger test will be interpreted as significant publication bias.
A sensitivity analysis will be performed with studies found to be at high risk of any type of bias if a quantitative synthesis/meta analysis is performed to assess the robustness of our results.

**Assessment of Inter Study Heterogeneity and Thresholds for Meta Analysis**

Clinical heterogeneity will be determined by comparing participants, interventions and outcomes measured between studies. Methodological heterogeneity will be determined by comparing study design and aspects of the study influencing risk of bias. This will be carried out by two researchers, who will make a decision regarding overall clinical and methodological heterogeneity between individual studies individually before comparing with each other. Any differences in opinion will be clarified with discussion and escalation to a third party with research experience if required. We will use the I squared test as a measure of statistical heterogeneity. A high level of statistical, clinical and/or methodological heterogeneity or inconsistencies in direction of effect between studies as concluded by researchers and statistical tests will preclude any meta analysis. An I squared threshold of 40% will be defined as significant to assist with the decision to perform a meta-analysis. A 95% confidence interval for this will be provided.

**Quantitative Synthesis/Meta Analysis**

If the collected studies are deemed homogenous as detailed above, a meta-analysis will be performed. The collection and analysis of continuous data will be preferred over dichotomous data. When any of the primary and secondary outcomes are represented using relative risk, odds ratio or risk difference, the raw data will be sought from the article or from the study authors in an attempt to present the data as continuous, using standardised or non-standardised mean difference with an associated confidence interval.

We will use the Review Manager (RevMan) software to assist with our quantitative synthesis. We will use both a random and fixed effects models as a sensitivity analysis to assess the robustness of the data obtained, but will put more emphasis on the random effects model results if we feel there is some level of clinical and statistical heterogeneity across the obtained studies. We will use the inverse variance fixed-effect and inverse variance random-effects model in RevMan to do this.

The primary unit of analysis will be at the level of individual participant randomisation. Each study will be assessed to determine if the unit of randomisation was consistent with the unit of analysis. It is expected that studies of non-standard design will be encountered. Cluster randomised trials will be assessed to determine if the cluster design was incorporated into any analyses performed. If this has not occurred, the intracluster correlation coefficient (ICC) will be taken from the study or found externally to account for the cluster design. If an external ICC is used, a sensitivity analyses will be performed. When studies with multiple treatment groups are analysed, all treatment arms will be presented but only those deemed relevant to the study will be included in analysis (namely where the patient decision aid group is compared to a non-intervention group). For studies with repeated observations at
different time points, individual patient data will be used to determine a single effect measure that incorporates all time points e.g. overall number of participants antibiotics were prescribed for.

When we cannot obtain missing data from study authors as was described previously, we will use complete case analysis (patients with missing data will be excluded from analysis). We will perform a sensitivity analysis on such studies during quantitative synthesis.

**Qualitative Synthesis**

A qualitative synthesis will be performed using text and tables regardless of whether a meta-analysis is performed to attempt to explain the findings across the included studies. The relationship between the findings of the different studies and the reason for any variability will be explored. Tables will be utilised to present relevant characteristics of the obtained studies and all outcomes relevant to this review. Information will be presented and discussed in order of outcomes (primary before secondary). Studies will be excluded from narrative analysis if any prior sensitivity analyses show they have considerable influence on the overall study results unless the study is the sole study looking at one of the outcomes or utilising one of the populations of interest.

**Overall Evidence Strength**

The strength of the body of the evidence will be judged using the Grades of Recommendation Assessment, Development and Evaluation (GRADE) system, which will judge the quality of the overall evidence base by critiquing against five domains (risk of bias, directness of evidence, heterogeneity, precision of effect estimates and risk of publication bias). Overall evidence body quality will be rated as high, moderate, low or very low. This assessment will exclude papers that have undergone sensitivity analyses (due to reasons stated above) and have been shown to significantly influence results.

**Inter-Rater Reliability**

For literature screening and data processing and analysis we will calculate inter-rater reliability to better assess the strength of our results. For categorical items we will be utilising the Cohen's kappa coefficient (k > 0.6 will be interpreted as good agreement) and for continuous data we will use intra class correlation coefficient (ICC > 0.6 will be interpreted as good agreement)

**RESULTS**

As of 10/5/2018, we are yet to start any data collection or analysis. We secured funding from the Mackay Institute of Research and Innovation in 2017. We hope for final publication during early 2019.

**DISCUSSION**
Our study aims to provide evidence that may influence the use of patient decision aids in primary care setting encounters for upper respiratory tract infections, potentially giving clinicians another tool to use when interacting with patients. Alongside answering our primary study question, we also hope to provide an insight into the depth of literature available in this field, highlighting any need for further primary research. We have provided a protocol based on input from experienced researchers and senior librarians which will utilise the major health related electronic databases for data collection. We believe that we will be able to deliver an accurate conclusion due to our proposed use of sensitivity analyses, bias analysis and grading of the evidence, as well as our use of multiple, independent literature screeners. However, we do appreciate that given our literature screen is limited to online databases and English language, we may our conclusions may not represent all existing research on this topic.

ETHICS AND DISSEMINATION

Ethical and Safety Considerations

Ethical approval was deemed unnecessary for this systematic review. Patient data that may identify individuals will not be collected.

Dissemination

Updates regarding this study will be communicated on a regular basis to study sponsor/funders. We will ultimately publish the full systematic review in a journal that is relevant to this field of research.

Any changes to the protocol will be reported with the date the amendment occurred, details of the amendment itself and the rationale behind the change

AUTHOR CONTRIBUTIONS/ACKNOWLEDGMENTS

SR performed the literature review that formed the basis of this systematic review. SR is responsible for drafting this protocol, developing the inclusion criteria and the primary and secondary outcomes of this study. SR developed the criteria and templates for literature screening, data extraction and bias assessment. SR developed the protocol for quantitative and qualitative synthesis. LP developed the search strategy with input from SR regarding key word selection. MA and JDS were consulted on methodology. AG will assist with literature screening and data extraction. All authors provided feedback on and approved the final copy of this protocol.

There is scope for contribution from further researchers, who will be acknowledged in the final systematic review if required.

COMPETING INTERESTS

None of the study authors have any competing interests to declare

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The financial support provided by the MIRI grants committee will assist with fees associated with presenting this systematic review at the Tropical Queensland Medical Conference 2017 and publishing it and the associated protocol within a research journal. If required, the hiring of a research assistant may also be funded. Database access will be provided by Queensland Health. No member of the MIRI grants committee will be involved in other parts of this study such as the design, literature search or data analysis and interpretation, nor will they contribute to the publication journal selection. All final decisions regarding this review will be made by the study authors.

REFERENCES


