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Written information for patients on the use of antibiotics in acute upper respiratory infections in primary care

Intervention Protocol

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[Intervention Protocol]

Written information for patients on the use of antibiotics in acute upper respiratory infections in primary care

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

To determine the effect of patient information on antibiotic use in patients presenting to primary care settings with URTIs.

BACKGROUND

Description of the condition

Respiratory infections are a heterogeneous group of diseases that are traditionally divided into upper respiratory tract infections (URTI) or lower respiratory tract infections (LRTI). These infections are typically defined as above or below the vocal folds, respectively. URTI infections are commonly caused by viruses and usually present with nasal stuffiness and discharge, sneezing, sore throat and cough. Other symptoms include hoarseness, headache, malaise and lethargy (Heikkinen 2003). Viral transmission is via contact with bodily secretions or, less commonly, air transmission (via particle aerosols) (Heikkinen 2003). On average, children are subjected to six to eight URTI per year; and adults, to two to four per year (Heikkinen 2003). There is evidence to suggest that antibiotics have little or no effect on common URTI including acute otitis media (AOM) (Venekamp 2013), acute bronchi-

tis (Smith 2014), pharyngitis (Spinks 2013) and acute laryngitis (Revez 2013). However, antibiotics continue to be prescribed for URTI (Arnold 2005; Teng 2004). The likely mechanism is that viruses infect endogenous (human) host cells and multiply within these host cells, whereas bacteria multiply on an extracellular level (Lee 2009). This is important because antibiotics target extracellular bacterial multiplication, without damaging host cells, a phenomenon known as selective toxicity (Lee 2009). Antibiotic therapy cannot inhibit intracellular viral multiplication (Lee 2009). We will not consider LRTI, such as pneumonia, in this review because it is accepted practice to treat pneumonia with antibiotics.

Description of the intervention

As mentioned above, URTI are generally caused by viruses (Heikkinen 2003), hence antibiotics have no effect but are still prescribed and requested (Arnold 2005). Guidelines and education alone have had little impact on the behaviour of both doctors

and patients (Arnold 2005). However, some patient information materials have had some effect, particularly when combined with other interventions including delayed prescribing (where patients are asked to wait a few days before considering using antibiotics) (Spurling 2013) and behavioural interventions (Meeker 2014). Written information may also form part of shared decision-making interventions, public health campaigns or be given alongside alternative symptomatic treatments for URTI. Given the breadth of written information use, we anticipate that this review will include interventions that vary in content, style and quality. The aim of this review is to explore the effect of written patient information, displayed in a paper or electronic form, or both, and any associated change in antibiotic use.

How the intervention might work

Knowledge of illness and treatment, beliefs about the benefits or harms of a taking a treatment and expectations of treatment outcome are known to influence medication-taking behaviour (Jackson 2014; Michie 2011). Written information about antibiotics for acute respiratory infections may target these determinants of antibiotic-taking behaviour and thereby, change patients' antibiotic use. Patients who receive antibiotics for the treatment of an URTI are more likely to re-consult their doctor for further antibiotics in the future (Moore 2009). If written information was able to prevent patients taking antibiotics, this would potentially interrupt this cycle, reduce reconsultation rates and subsequent antibiotic use.

Why it is important to do this review

Respiratory tract infections are the most common reason for patients to consult primary care physicians (Francis 2009). About 20% of children who present with a respiratory tract infection return during the same illness episode, even though most of these visits are unnecessary (Francis 2009). Complications of respiratory tract infections are rare, with little or no benefit from treatment with antibiotics (Francis 2009). Antibiotics have common adverse reactions (including rash, abdominal pain, diarrhoea and vomiting) (Berman 1997; Niemela 1999), and overprescribing may contribute to community bacterial resistance (Costelloe 2010). Therefore, tools to decrease inappropriate antibiotic prescribing are needed in order to reduce adverse effects and the development of community antibiotic resistance. Written information in paper or electronic format, or both, used with or without a co-intervention, is a simple, cheap and potentially effective means to improve antibiotic prescribing for respiratory infections.

OBJECTIVES

To determine the effect of patient information on antibiotic use in patients presenting to primary care settings with URTIs.

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomised controlled trials (RCTs) that compare information about antibiotics for acute respiratory infections with no information. Trials that include information as the only intervention and those that include information as an add-on intervention will be included.

1. Information versus no information.

2. Information + intervention-X versus no information + intervention-X (for example, where Intervention-X was delayed prescribing or other intervention).

We will also include studies that compare information and another intervention with a control (for example, usual care).

Types of participants

Patients of all ages defined as having a URTI. When children are involved, the intervention may be directed to the parent/guardian. We will exclude patients with LRTIs and those with chronic lung conditions, such as chronic obstructive pulmonary disease (COPD).

Types of interventions

Any written information, in both paper (for example, handout, booklet, poster) or electronic (for example, video) format, given to a patient with the aim of informing them about antibiotics for acute respiratory infections, either as the main or as an add-on intervention. This information must occur at the time of prescribing, i.e. immediately prior or during. We will exclude studies that offer information after prescribing, for example, pharmacists educating via package inserts. Information must include details about antibiotics for acute respiratory infections but it does not have to be exclusive. Further, we will exclude interventions where only verbal information is given.

Types of outcome measures

We will extract the following outcomes at the end of treatment and end of follow-up. We will exclude studies that do not report our primary outcome.

Primary outcomes

1. Antibiotic use subsequent to the index consultation.

Secondary outcomes

1. Reconsultation.
2. Resolution of symptoms.
3. Patient knowledge about antibiotics for acute respiratory infection.
4. Patient satisfaction with consultation.
5. Complications.
 - i) Adverse drug reaction due to the prescribed antibiotics.
 - ii) Disease complications, for example, pneumonia or mastoiditis.

*Note: If sufficient studies report 'time to resolution' data, then we will use this as a further secondary outcome, dividing the time into three zones where the majority of studies can provide data.

Search methods for identification of studies

Electronic searches

We will search CENTRAL (latest issue), which contains the Cochrane Acute Respiratory Infections Group's Specialised Register, MEDLINE (1946 to current date), EMBASE (2010 to current date), CINAHL (1981 to current date), LILACS (1982 to current date) and Web of Science (1955 to current date).

We will use the search strategy described in [Appendix 1](#) to search MEDLINE and CENTRAL. We will combine the MEDLINE search with the Cochrane Highly Sensitive Search Strategy for identifying randomised trials in MEDLINE ([Lefebvre 2011](#)). We will adapt the search strategy to search EMBASE ([Appendix 2](#)), CINAHL ([Appendix 3](#)), LILACS ([Appendix 4](#)) and Web of Science ([Appendix 5](#)). We will not use any language or publication restrictions.

Searching other resources

We will search the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) and www.clinicaltrials.gov for completed and ongoing trials. We will review the reference lists of retrieved articles.

Data collection and analysis

Selection of studies

We will scan abstracts to identify if they might meet the inclusion criteria. We will check the references of the selected trials to try and identify any other articles. Two review authors (JOS, RH) will independently apply the inclusion criteria to the full-text articles. Two review authors (JOS, RH) will independently assess the methodological quality of the included trials. We will resolve disagreements by discussion.

Data extraction and management

We will extract data using a standardised form. We will include the following information.

1. Age and gender of participants.
2. Number of participants.
3. Literacy level of participants (measured by highest level of education or other methods employed by authors).
4. Description of intervention content, intensity (dose and duration), mode of delivery and fidelity to intervention, where available.
5. Antibiotic use.
6. Reconsultation rates.
7. Symptom resolution.
8. Complications such as adverse drug reactions and disease complications.

As information contained in handouts could vary widely, we will contact all trial authors directly to request copies of their information handouts.

Assessment of risk of bias in included studies

Two review authors (JOS, RH) will independently assess the methodological quality of each of the study trials using the 'Risk of bias' domains set out in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)). The domains are as follows.

Selection bias

Random sequence generation: two review authors (JOS, RH) will independently assess the method used to generate the allocation sequence and whether this method was adequate to produce comparable groups.

Allocation concealment: two review authors (JOS, RH) will independently assess the method used to conceal the allocation sequence to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment.

Performance bias

Blinding of participants and personnel: two review authors (JOS, RH) will independently assess the measures used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. Further, the two review authors

will search for any information stated as to whether the intended blinding was effective.

Detection bias

Blinding of outcome assessment: two review authors (JOS, RH) will independently assess the measures used, if any, to blind outcome assessors from knowledge of which intervention a participant received. Further, the two review authors (JOS, RH) will search for any information relating to whether the intended blinding was effective.

Attrition bias

Incomplete outcome data: two review authors (JOS, RH) will independently assess the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. State whether attrition and exclusions were reported, the numbers in each intervention group (compared to total randomised participants), reasons for attrition/exclusions where reported, and any re-inclusions in analyses performed by review authors.

Reporting bias

Selective reporting: two review authors (JOS, RH) will independently assess whether the possibility of selective outcome reporting was examined by authors, and elaborate on what was found.

Other bias

Other sources of bias: two review authors (JOS, RH) will independently assess whether authors state any important concerns about bias not addressed in the other domains in the tool.

Two individual review authors (JOS, RH) will assess the quality of the studies that meet the inclusion criteria. All review authors (JOS, RH, PG) will then meet and resolve any disagreements. If possible we will reconstruct intention-to-treat (ITT) analyses.

Measures of treatment effect

We will analyse data using RevMan 5.3 (RevMan 2014). As the primary and secondary outcomes are dichotomous, we will use risk ratios as the main measure of effect. We will also calculate and report a number needed to treat to benefit (NNTB) for any statistically significant outcomes.

Unit of analysis issues

We will use the patient as the unit of analysis. If there are includable trials that use cluster designs, we will use an analysis adjusted for within-cluster correlations.

Dealing with missing data

We will write to trial authors for clarification of any missing data. If a study outcome has more than 20% missing data, we will exclude it from the primary analysis but include it in a sensitivity analysis.

Assessment of heterogeneity

We will assess the presence of heterogeneity in two steps. First, we will assess obvious heterogeneity at face value by comparing populations, settings, interventions and outcomes before deciding whether it is appropriate to pool studies using a fixed-effect analysis, a random-effects analysis, or to not pool studies. If pooling is done, we will assess statistical heterogeneity by means of the I^2 statistic (Higgins 2011). Thresholds for the interpretation of the I^2 statistic can be misleading, since the importance of inconsistency depends on several factors. We plan to use the guide to interpretation as outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011): 0% to 40%: might not be important; 30% to 60%: may represent moderate heterogeneity; 50% to 90%: may represent substantial heterogeneity; 75% to 100%: considerable heterogeneity.

Assessment of reporting biases

We will search www.clinicaltrials.gov and other appropriate trials databases for unpublished studies. We will contact trial authors to request any unreported outcomes.

Data synthesis

We will analyse differences in antibiotic use via a risk ratio (RR) with a 95% confidence interval (CI) calculated by the Mantel-Haenszel method using a fixed-effect model.

Subgroup analysis and investigation of heterogeneity

We will conduct a subgroup analysis of the impact of patient information based on whether or not delayed prescribing was also used. That is, we will group all trials by whether they used a delayed antibiotic prescription or not. Factorial studies (2 x 2 of delayed prescription x handout) will contribute to both groups.

Sensitivity analysis

If a study outcome has more than 20% missing data, we will exclude it from the primary analysis but include it in a sensitivity analysis (see [Dealing with missing data](#) above). We plan to conduct sensitivity analyses to determine the robustness of results to intervention intensity and fidelity.

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* Indicates the major publication for the study

APPENDICES

Appendix I. MEDLINE (Ovid) search strategy

- 1 exp Respiratory Tract Infections/ (267266)
- 2 (respiratory adj3 infection*).tw. (28715)
- 3 (urti or lrti).tw. (840)
- 4 Otitis Media/ (14775)
- 5 otitis media.tw. (14693)
- 6 exp Sinusitis/ (14844)
- 7 sinusit*.tw. (10651)
- 8 (acute adj3 (rhinosinusit* or nasosinusit* or rhinit*)).tw. (563)
- 9 exp Pharyngitis/ (12604)
- 10 (pharyngit* or nasopharyngit* or tonsillit*).tw. (7293)
- 11 sore throat*.tw. (2858)
- 12 exp Laryngitis/ (4019)
- 13 laryngit*.tw. (1215)
- 14 croup.tw. (1010)
- 15 Cough/ (10867)
- 16 cough*.tw. (29125)
- 17 Common Cold/ (3273)
- 18 common cold*.tw. (2458)
- 19 coryza.tw. (350)
- 20 Influenza, Human/ (29323)
- 21 (influenza* or flu).tw. (73727)
- 22 Bronchitis/ (19330)
- 23 bronchit*.tw. (17051)
- 24 exp Bronchiolitis/ (5874)
- 25 bronchiolit*.tw. (6755)
- 26 or/1-25 (374954)
- 27 exp Anti-Bacterial Agents/ (481743)
- 28 antibiotic*.tw,nm. (210904)
- 29 27 or 28 (569485)
- 30 Patient Education as Topic/ (63802)

31 Pamphlets/ (2825)
 32 (pamphlet* or brochure* or leaflet* or booklet*).tw. (17230)
 33 (flyer* or flier*).tw. (616)
 34 information pack*.tw. (205)
 35 information sheet*.tw. (472)
 36 (cards or postcard*).tw. (7421)
 37 (handout* or guidebook*).tw. (669)
 38 (print* adj2 (material* or information* or guide or guides or instruction* or advice or advis*).tw. (979)
 39 or/30-38 (89662)
 40 26 and 29 and 39 (267)

Appendix 2. EMBASE (Elsevier) search strategy

#51 #42 AND #50
 #50 #45 NOT #49
 #49 #46 NOT #48
 #48 #46 AND #47
 #47 'human'/de
 #46 'animal'/de OR 'nonhuman'/de OR 'animal experiment'/de
 #45 #43 OR #44
 #44 random*:ab,ti OR placebo*:ab,ti OR crossover*:ab,ti OR 'cross over':ab,ti OR trial:ti OR allocat*:ab,ti OR (doubl* NEXT/1
 blind*):ab,ti
 #43 'randomized controlled trial'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp
 #42 #24 AND #27 AND #41
 #41 #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40
 #40 'health literacy'/de
 #39 'consumer health information'/de
 #38 'information dissemination'/de
 #37 'persuasive communication'/de
 #36 (patient* NEAR/3 (literatur* OR material* OR information* OR guide* OR guides OR instruction*)):ab,ti
 #35 ((print* OR written OR text*) NEAR/3 (material* OR information* OR guide OR guides OR instruction* OR advice OR advis*
 OR messag* OR note OR notes)):ab,ti
 #34 handout*:ab,ti OR guidebook*:ab,ti
 #33 card:ab,ti OR cards:ab,ti OR postcard*:ab,ti
 #32 (information NEAR/2 (pack* OR sheet*)):ab,ti
 #31 flyer*:ab,ti OR flier*:ab,ti
 #30 pamphlet*:ab,ti OR brochure*:ab,ti OR leaflet*:ab,ti OR booklet*:ab,ti
 #29 'publication'/de
 #28 'patient education'/de
 #27 #25 OR #26
 #26 antibiotic*:ab,ti
 #25 'antibiotic agent'/exp
 #24 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR
 #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23
 #23 bronchit*:ab,ti OR bronchiolit*:ab,ti
 #22 'bronchitis'/exp
 #21 influenza*:ab,ti OR flu:ab,ti
 #20 'influenza'/exp
 #19 coryza:ab,ti
 #18 'common cold'/de OR 'common cold symptom'/de
 #17 cough*:ab,ti
 #16 'coughing'/de

#15 croup:ab,ti
 #14 ((throat* OR 'middle ear' OR tonsil* OR sinus* OR larynx* OR pharynx* OR bronch*) NEAR/3 (inflamm* OR infect*)):ab,ti
 #13 laryngit*:ab,ti
 #12 'laryngitis'/de
 #11 'sore throat'/de
 #10 pharyngit*:ab,ti OR nasopharyngit*:ab,ti OR rhinopharyngit*:ab,ti OR tonsillit*:ab,ti
 #9 'pharyngitis'/exp
 #8 (acute NEAR/3 (rhinosinusit* OR nasosinusit* OR rhinit*)):ab,ti
 #7 sinusit*:ab,ti
 #6 'sinusitis'/exp
 #5 'otitis media':ab,ti
 #4 'otitis media'/exp
 #3 urti:ab,ti OR lrti:ab,ti
 #2 (respiratory NEAR/3 infection*):ab,ti
 #1 'respiratory tract infection'/exp

Appendix 3. CINAHL (Ebsco) search strategy

S52 S42 and S51 S
 S51 S43 or S44 or S45 or S46 or S47 or S48 or S49 or S50
 S50 (MH "Quantitative Studies")
 S49 TI placebo* OR AB placebo*
 S48 (MH "Placebos")
 S47 TI random* OR AB random*
 S46 TI ((singl* or doubl* or tripl* or trebl*) W1 (blind* or mask*)) OR AB ((singl* or doubl* or tripl* or trebl*) W1 (blind* or mask*))
 S45 TI clinic* trial* OR AB clinic* trial*
 S44 PT clinical trial
 S43 (MH "Clinical Trials+")
 S42 S25 and S28 and S41
 S41 S29 or S30 or S31 or S32 or S33 or S34 or S35 or S36 or S37 or S38 or S39 or S40
 S40 (MH "Information Literacy")
 S39 (MH "Communication")
 S38 (MH "Consumer Health Information")
 S37 TI (patient* N3 (literatur* or material* or information* or guide or guides or instruction*)) OR AB (patient* N3 (literatur* or material* or information* or guide or guides or instruction*))
 S36 TI ((print* or written or text*) N3 (material* or information* or guide or guides or instruction* or advice or advis* or messag* or note or notes)) OR AB ((print* or written or text*) N3 (material* or information* or guide or guides or instruction* or advice or advis* or messag* or note or notes))
 S35 TI (handout* or guidebook*) OR AB (handout* or guidebook*)
 S34 TI (card or cards or postcard*) OR AB (card or cards or postcard*)
 S33 TI (information N2 (pack* or sheet*)) OR AB (information N2 (pack* or sheet*))
 S32 TI (flyer* or flier*) OR AB (flyer* or flier*)
 S31 TI (pamphlet* or brochur* or leaflet* or booklet*) OR AB (pamphlet* or brochur* or leaflet* or booklet*)
 S30 (MH "Pamphlets")
 S29 (MH "Patient Education")
 S27 TI antibiotic* OR AB antibiotic*
 S26 (MH "Antibiotics+")
 S25 S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9 or S10 or S11 or
 S12 or S13 or S14 or S15 or S16 or S17 or S18 or S19 or S20 or S21 or S22 or S23 or S24
 S24 TI (bronchit* or bronchiolit*) OR AB (bronchit* or bronchiolit*)
 S23 (MH "Bronchitis+")
 S22 TI (influenza* or flu) OR AB (influenza* or flu)

S21 (MH "Influenza+")
 S20 TI coryza OR AB coryza
 S19 TI common cold* OR AB common cold*
 S18 (MH "Common Cold")
 S17 TI cough* OR AB cough*
 S16 (MH "Cough")
 S15 TI croup OR AB croup
 S14 TI ((throat* or middle ear* or tonsil* or sinus* or larynx* or pharynx* or bronch*) N3 (inflam* or infect*)) OR AB ((throat* or middle ear* or tonsil* or sinus* or larynx* or pharynx* or bronch*) N3 (inflam* or infect*))
 S13 TI laryngit* OR AB laryngit*
 S12 (MH "Laryngitis+")
 S11 TI sore throat* OR AB sore throat*
 S10 TI ((pharyngit* or nasopharyngit* or rhinopharyngit* or tonsillit*)) OR AB ((pharyngit* or nasopharyngit* or rhinopharyngit* or tonsillit*))
 S9 (MH "Pharyngitis")
 S8 TI (acute N3 (rhinosinusit* or nasosinusit* or rhinit*)) OR AB (acute N3 (rhinosinusit* or nasosinusit* or rhinit*))
 S7 TI sinusit* OR AB sinusit*
 S6 (MH "Sinusitis+")
 S5 TI otitis media OR AB otitis media
 S4 (MH "Otitis Media+")
 S3 TI (urti or lrti) OR AB (urti or lrti)
 S2 TI respiratory N3 infection* OR AB respiratory N3 infection*
 S1 (MH "Respiratory Tract Infections+")

Appendix 4. LILACS (BIREME) search strategy

(MH:"Anti-Bacterial Agents" OR Antibacterianos OR Antibacterianos OR antibiotic\$ OR MH:D27.505.954.122.085\$ OR Antibacterianos OR Antibióticos) AND (MH:"Patient Education as Topic" OR "Educación del Paciente" OR "Educação de Pacientes" OR Pamphlets OR Folletos OR Folhetos OR Panfletos OR Libretos OR Livretos OR booklet\$ OR brochur\$ OR flyer\$ OR fier\$ OR card OR cards OR postcard\$ OR handout\$ OR guidebook\$ OR MH:"Consumer Health Information" OR "Información de Salud al Consumidor" OR "Informação de Saúde ao Consumidor" OR MH:I02.233.332.186\$ OR MH:N02.421.143.827.407.228\$ OR N02.421.726.407.228\$ OR MH:"Persuasive Communication" OR "Comunicación Persuasiva" OR "Comunicação Persuasiva" OR MH:"Information Dissemination" OR "Diseminación de Información" OR "Disseminação de Informação" OR "information sheet" OR "information sheets" OR "information pack" OR "information packs" OR "information package" OR "printed information" OR "printed instructions" OR "printed guides" OR "patient information" OR "patient instructions")

Appendix 5. Web of Science (Thomson Reuters) search strategy

# 6	123	#5 AND #4 <i>Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, CCR-EXPANDED, IC Timespan=All years</i>
# 5	1,623,616	TOPIC: (random* or placebo* or ((singl* or doubl*) NEAR/1 blind*) or crossover* or "cross-over" or allocat*) OR TITLE: (trial) <i>Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, CCR-EXPANDED, IC Timespan=All years</i>

(Continued)

# 4	282	#3 AND #2 AND #1 <i>Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, CCR-EXPANDED, IC Timespan=All years</i>
# 3	181,671	TOPIC: (pamphlet* or brochur* or leaflet* or booklet* or flyer* or flier* or (information NEAR/3 (pack* or sheet*)) or card or cards or postcard* or handout* or guidebook* or ((print* or written or text*) NEAR/3 (material* or information* or guide or guides or instruction* or advice or advis* or messag* or note or notes)) or ((patient* or consumer*) NEAR/3 (literatur* or material* or information* or guide or guides or instruction*))) <i>Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, CCR-EXPANDED, IC Timespan=All years</i>
# 2	225,746	TOPIC: (antibiotic* or anti-bacterial*) <i>Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, CCR-EXPANDED, IC Timespan=All years</i>
# 1	218,318	TOPIC: ((respiratory NEAR/3 infection*) or urti or lrti or “otitis media” or sinusit* or (acute NEAR/1 (rhinosinusit* or nasosinusit* or rhinit*)) or pharyngit* or nasopharyngit* or rhinopharyngit* or tonsillit* or “sore throat” or “sore throats” or laryngit* or ((throat* or “middle ear” or tonsil* or sinus* or laryn* or pharyn* or bronch*) NEAR/3 (infect* or inflam*)) or croup or cough* or “common cold” or “common colds” or coryza or influenza* or flu or bronchit* or bronchiolit*) <i>Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, CCR-EXPANDED, IC Timespan=All years</i>

CONTRIBUTIONS OF AUTHORS

PG conceived the idea for the study. PG and AMcC helped draft the protocol. JO and RT wrote the protocol. All authors checked and agreed the final version.

DECLARATIONS OF INTEREST

Jack W O’Sullivan: none known.

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Amanda McCullough: none known.

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