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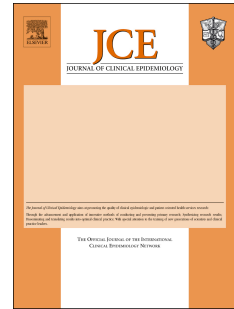
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# Accepted Manuscript

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**The TRIP database showed most Acute Respiratory Infections questions were already addressed by Cochrane reviews**

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## Abstract

### Objective

Cochrane systematic reviews require more methodological support from Cochrane Review Groups (CRGs) than is customary in journals, CRGs must prioritise reviews to conserve resources. The TRIP database provided a dataset of questions to guide prioritization for the Acute Respiratory Infections (ARI) CRG.

### Study Design and Setting

We extracted the ARI searches from the TRIP database (2010 to 2017) that contained at least one disease and one clinical management term, (defined as a 'search'), and tabulated these by frequency.

### Results

There were 314,346 ARI searches from which we inferred 45,497 clinical questions, covering 365 topics. In two thirds (30,541) these addressed only 20 clinical questions, of which *treatment* were the most frequent; followed by *diagnosis*, *mortality* and *prognosis*. The 5 most frequent clinical questions were "*Influenza + Vaccination*" 4,989 (12.1%), "*acute otitis media + antibiotics*" 3578 (8.7%), "*common cold + vitamin C*" 3528 (8.6%), "*meningitis + corticosteroids*" 1,910 (4.6%), "*pneumonia + general treatment*" 1765 (4.3%). The 20 most frequent clinical questions were addressed by Cochrane reviews or protocols.

### Conclusion

ARI questions are common and repeated often. Most may have been addressed by Cochrane reviews. The remainder form the basis of a priority list to assign resources for future Cochrane topics.

**Author keywords**

Research prioritization, Health priorities, Cochrane, Acute respiratory infections, Clinical questions, Database analysis

**Running title**

TRIP database showed most ARI questions already addressed by Cochrane

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**What is new****Key findings**

- Analysing a clinical question-answering databank is a novel way to achieve Cochrane review prioritisation
- Most clinical questions about acute respiratory infections addressed the same 20 topics, all treatment-type questions
- The 20 most-common topics already were already addressed by Cochrane reviews or protocols

**What this adds to what is known**

- This research prioritisation method provides an alternative to the common methods (Delphi processes with stakeholders; audits of research undertaken and systematically reviewed).

**What is the implication, what should change now**

- These prioritisation findings need to be implemented to improve transparency of Cochrane editorial decisions.

## Background

Cochrane is a global organisation which produces high quality, credible, systematic reviews (SR) of the literature [1, 2], and provides methodological support at several stages, which is provided by one of several editorial teams. Since editorial support is expensive and limited, Cochrane needs to prioritise review topics [3-5]. Prioritisation projects usually solicit the views of patients, their clinicians, and other stakeholders [6-10].

The Cochrane Acute Respiratory Infections (ARI) Group, responsible for synthesising evidence syntheses about diseases causing ARIs, has also embarked on a priority list of topics [11]. Two projects have been completed: one identified gaps between current Cochrane reviews and research that has been undertaken [12]; a second was a survey of topics that stakeholders wanted answered [13].

This third project sought to identify topics that stakeholders had asked of the TRIP database (previously known as *Turning Research Into Practice*), an search engine designed to assist clinicians find evidence. There have been >100 million searches of the TRIP database [14]. The largest group of searchers are medical doctors (45%), then information-specialists (20%), other health professional (9%), nurses (8%), pharmacists (8%), and patients or their carers (1%) [14, 15]. However, there is some uncertainty about these proportions because the survey used to collect these data were derived from a sub-sample of users, (only those registered) [14].

Most searches (67%) aim to answer clinical questions (67%) [15, 16]. Critical components of clinical questions can be inferred from the search terms. Accordingly, we could analyse the TRIP database for searches limited to ARIs, to determine the topics most frequently searched, and then rank them.

## Aims

To estimate the frequency of clinical questions asked about ARIs by users of the TRIP database for three question types (treatment, diagnosis, and prognosis).

## Methods

We obtained data containing all searches conducted in the TRIP database between 2010 and 2017, and focussed on the *keyword* field, which contained the search terms used, (eg "*xylitol otitis media*", "*tuberculosis*", "*transfer patient to the floor*" and "*eating disorder OR anorexia*", see Appendix 1, for more examples). Most searches in the TRIP database focused on the population, and few (12%) used Boolean operators [17]. To identify searches that were clinical questions, we selected only those with  $\geq 2$  different search terms, of which at least one was a *disease*, and at least one other a

*treatment, diagnosis or prognosis*. We tested this method on a convenient subsample of 1,543 searches, finding 972 (63%) satisfied this, and could be classified as clinical questions.

We now created two lists derived from search strategies used in Cochrane ARI Group reviews, and from our work on a previous prioritisation study [12]:

1. ARI *diseases* and their synonyms
2. *treatments, diagnoses, and prognoses*, and their synonyms.

This enabled us to infer clinical questions being asked, (eg, when *common cold* and *nasal irrigation* occurred together, we inferred the clinical question, *what is the efficacy of nasal irrigation for the common cold?*), (*Appendix Table 2* has a full list of search strings).

By re-combining the words of the clinical questions into a string, we could interrogate TRIP to identify clinical questions, and then the number of *diseases* (and their synonyms) combined with *treatments, diagnoses, or prognoses* (and their synonyms). The data were entered onto a spreadsheet, with *disease* along one axis and *treatments, diagnoses, or prognoses* along the other, *Table 1*. The 20 most common ARI clinical questions are displayed, *Figure 1*. We checked for Cochrane reviews for these 20 most common clinical questions, *Figure 1*, (also *Appendix Table 3*).

## Results

From 314,346 ARI searches conducted in TRIP, we could infer 45,497 questions. These addressed 365 different topics, most addressing the same question, with the 20 most frequent addressing 30,541 (two thirds, 67%) of the total.

*Treatment* was the most frequent clinical question type: 41,191 (91%); *diagnosis* 2,299 (5%); *mortality* 1,172 (2.6%); and *prognosis* 834 (1.8%). *Pneumonia* was the illness asked about most, 6,820 (15%); followed by *influenza* 6,495 (14%); *the common cold* 5,539 (12%) and *acute otitis media* 5,154 (11%), *Table 1*.



**Table 1: Total ARI clinical questions entered into TRIP**

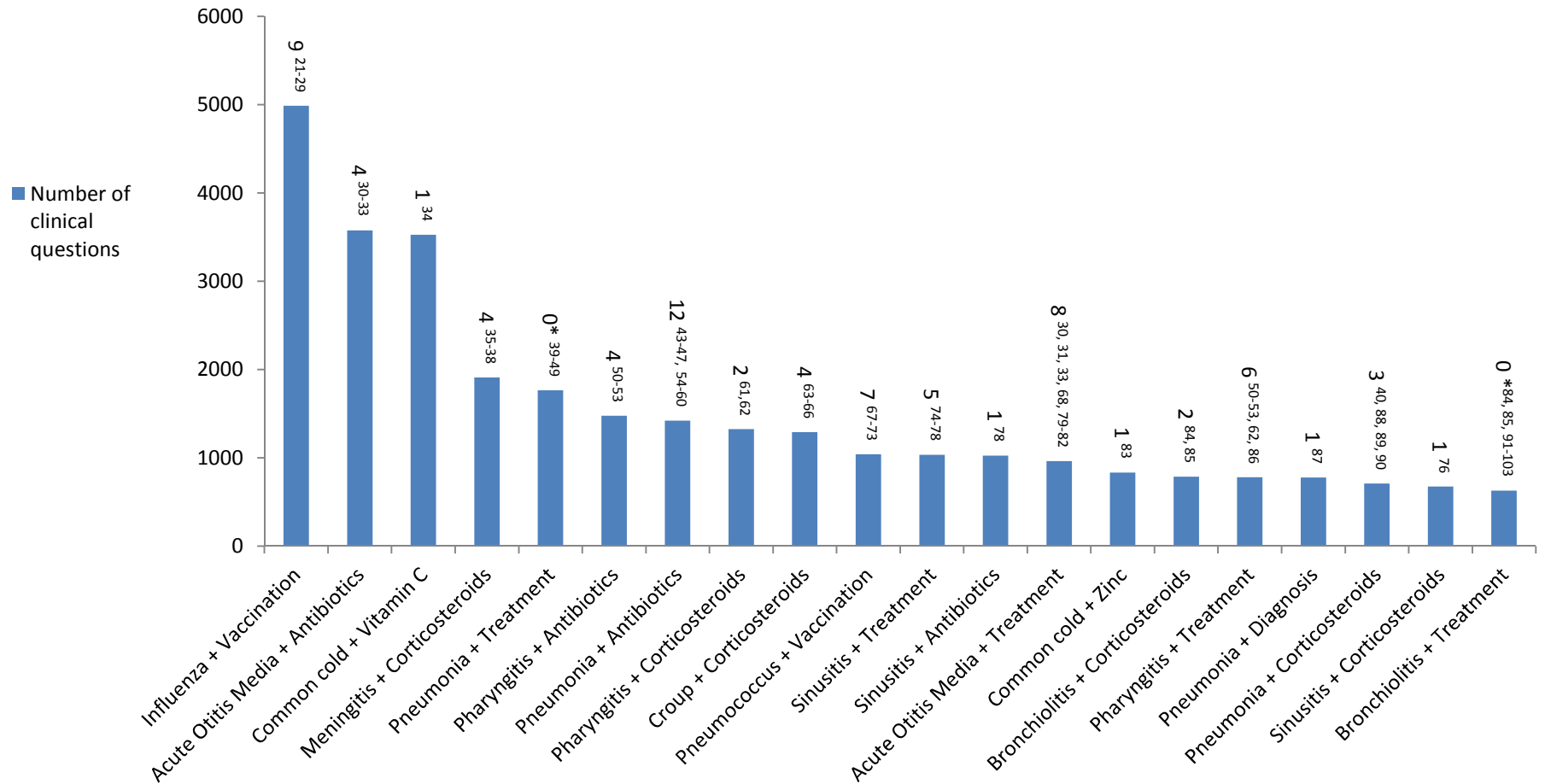
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The most frequent full clinical questions were: *influenza + vaccination* 4,989 (12%); *acute otitis media + antibiotics* 3578 (9%); *common cold + vitamin C* 3,528 (9%); *meningitis + corticosteroids* 1,910 (5%); and *pneumonia + general treatment* 1,765 (4%), Figure 1, (Appendix Table 4 lists all topics with  $\geq 100$  clinical questions)

There was at least one associated Cochrane review for each of 18 of the 20 most frequent clinical questions: the two outstanding clinical questions, one (*pneumonia + non-specific treatment*) had 9 completed Cochrane reviews (of specific treatments) that at least partly address it, and two Cochrane protocols that will answer it. The other (*bronchiolitis + non-specific treatment*) had 15 completed Cochrane reviews (of specific treatments) partly addressing it, Figure 1. (Appendix Table 3 lists top 20 topics with associated Cochrane reviews)

**Figure 1: Top 20 ARI Clinical Questions with corresponding Cochrane Reviews (CR)#**

\* = protocols and/or other CRs partially answer the question; # = available in the on-line supplement (Appendix 5)



**Discussion**

We found a wide spectrum of clinical questions. Some were much more frequent. *Treatment* clinical questions were much more frequent than *diagnosis* or *prognosis* ones. The questions were already addressed by existing Cochrane reviews or protocols.

Our study has some limitations. There is some uncertainty about who asks questions of the TRIP database. Our method of analysing the searches of the TRIP database made assumptions, particularly about what was being asked from the keywords, that may not have been valid.

However, our approach has some strengths. The enormous size of the dataset means sampling errors are very unlikely. Rather than relying on volunteers to nominate topics (diseases and clinical managements) to prioritise in surveys, which may not represent what participants themselves, let alone what others want to know, our method, which analysed what people actually did ask, is clearly more direct.

Our findings are largely concordant with other data on the most frequent type of clinical questions asked by doctors – mostly *treatment* (76%), although somewhat less than we found [18], perhaps because that study was of doctors only (we estimate 45% of TRIP users are doctors). Similarly, other studies of question-types asked have also found treatment questions of primary care physicians to be the most frequent [19, 20].

This information can be used for transparently prioritising proposed Cochrane ARI reviews and their updates in a climate of competing resources. It can be used in conjunction with our previous prioritisation projects, (a list of systematic review research gaps [12], and opinions from representatives of ARI experts and consumers [13]).

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Dr Del Mar reports grants from NHMRC (Australia), during the conduct of the study; grants from NHMRC (Australia), grants from Australian ACSQHC, personal fees from Elsevier and Blackwells publishers, outside the submitted work.

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**Appendix Table 1: examples of single and multiple topic searches entered into the Trip search interface**

Example of single topic searches entered	Examples of multiple topic searches entered
tuberculosis	xylitol otitis media
manuka honey	transfer patient to the floor
tuberculosis	pneumonia AND alcoholism
Typhoid fever	allergy to grass
fungal nail infection	Benzodiazepines cause respiratory depression with a shift of the CO2 response curve to the right
vitamin c	(Rotational coronary angiography) from:1990 to:2012
aids	(eating disorder OR anorexia) AND refeeding syndrome AND (control OR prevention OR monitoring)
inhibin b	Heart failure with preserved ejection fraction AND TREATMENT

**Appendix Table 2: Search terms used to identify ARI questions****a) Disease search terms**

Disease	Synonyms
Acute Otitis Media	Otitis media OR AOM OR Middle ear infection OR Middle ear infections OR Middle Ear Inflammation OR Middle Ear Inflammations OR Glue ear
Bronchiolitis	Bronchiolitides OR Inflamed bronchioles OR Inflammation of the bronchioles
Bronchitis	Bronchitides OR Inflamed bronchi OR Inflammation of the Bronchi OR Tracheobronchitis
Common cold	Common colds OR Cold OR Colds OR Rhinovirus OR Rhinoviruses OR Coryza OR Catarrh OR Catarrhs
Cough	Coughs OR Coughing
Croup	Pseudocroup OR Laryngotracheobronchitis OR Stridor
Infectious mononucleosis	Glandular Fever
Influenza	Flu

Laryngitis	Laryngitides
Measles	Chicken Pox
Meningitis	Meningitis OR Meningitides OR Meningitidis OR Meningeal
Mumps	
Nasopharyngitis	Nasopharyngitides
Pertussis	Whooping cough
Pharyngitis	Sore throats OR Sore throat OR Rhinopharyngitis OR Tonsillitis OR Tonsillitides
Pneumococcus	Pneumococcal
Pneumonia	Bronchopneumonia OR Pleuropneumonia OR Pleuropneumonia
Respiratory syncytial virus	RSV OR Respiratory Syncytial Viruses
Respiratory tract infection	Respiratory tract infections OR Respiratory infection OR Respiratory infections OR Respiratory inflammation OR Respiratory tract inflammation OR ARI OR URTI OR LRTI
Rhinorrhea	Rhinorrhoea
Rubella	
SARS	Severe Acute Respiratory Syndrome Virus OR Coronavirus
Sinusitis	Rhinosinusitis OR Sinus Infection OR Sinus Infections OR rhinitis OR nasosinusitis OR Nasosinusitis OR Runny nose
Wheeze	Wheezing

#### b) Treatment search terms

Intervention	Synonyms
Treatment	Treat OR Treating
Acupuncture	
Antibiotics	Anti-Bacterial Agents OR Antibiotic OR antibacterial OR anti-bacterials OR Anti-microbial OR Antimicrobial OR Antimicrobials OR amoxicillin OR amoxycillin OR penicillin OR ampicillin OR cotrimoxazole OR chloramphenicol OR trimethoprim OR sulphamethoxazole OR tmp smx
Anticholinergic	
Anticytokine	
Antihistamine	



Antitussive	Antitussives OR Cough Suppressants OR Decongestant OR expectorant OR oxymetazoline OR norepinephrine OR pseudoephedrine OR phenylephrine OR xylometazoline OR tramazoline OR Ephedrine OR ephedrin
Antiviral	Antivirals
Bronchodilator	
CAM	Complementary Therapies OR Complementary Therapy OR Complementary Medicine OR Alternative Medicine OR Alternative Medicines OR Alternative Therapies OR Alternative Therapy
Continuous positive airway pressure	CPAP OR Airway pressure
Corticosteroid	Corticosteroid OR Corticosteroids OR steroid OR Steroids OR glucocorticoid OR hydrocortisone OR cortisone OR triamcinolone OR prednisone OR prednisolone OR methylprednisolone OR dexamethasone OR cortisol
Counselling	
Deoxyribonuclease	
Education	
Exercise	Running OR Walking OR Jogging OR
Fluid therapy	
Glycerol	
Heliox	Helium OR heliox OR heo2 OR he-o2 OR "he o2"
Humidification	Steam
Immunoglobulin	Immunoglobulins OR RSV-igiv OR Respigam OR Palivizumab OR Synagis
Immunostimulant	
Immunotherapy	
Hand washing	Handwashing OR Hand-washing OR Hand hygiene
Masks	Mask
Infection control	Quarantine OR Isolation OR Isolate
Leukotriene	
Nasal irrigation	Nasal wash OR Saline wash OR Saline irrigation
NSAID	NSAIDs OR Non-Steroidal Anti-Inflammatory Agents OR Non-Steroidal Anti-Inflammatory Agent OR Ibuprofen
Oxygen therapy	

Paracetamol	Acetaminophen OR paracetamol OR acetaminophen OR acetaminophen OR tylenol
Physiotherapy	
Positioning	Posture OR Position OR Supine OR Prone OR Face down OR Lateral OR Upright OR Semirecumbent
Probiotic	Probiotics OR Lactobacillus OR Yoghurt OR Fermented milk OR Cultured Milk
Procalcitonin	Calcitonin
Public health	
Radiography	
Statins	
Surfactant	
Surgery	
Topical analgesia	Topical analgesic OR Topical analgesics OR Antipyrine OR Phenazone OR americaine otic OR aurafair OR auralgan OR auralgesic OR auraphene OR aurisan OR auroto OR dolotic OR lanaurine otocain OR omedia OR oticaine OR otigesic OR otocalm OR Rx-Otic OR sedaural OR tympagesic
Vaccination	Vaccine OR Vaccines
Vitamin A	
Vitamin C	
Xylitol	
Zinc	Galzin OR Zincteral OR Orazinc

**c) Diagnosis search terms**

<b>Diagnosi s</b>	<b>Synonyms</b>
Diagnosi s	Diagnostic OR Diagnoses OR Rapid antigen OR Rapid test OR Rapid tests OR adt OR radts OR rdt OR rdts OR Antigen detection OR Physical examination OR Physical exam OR Detection Test OR Detection tests OR Reagent OR Kit OR Kits OR Assay OR Assays OR Reagent OR Reagents OR Dipstick OR Dipsticks OR Predictive value OR Scores OR Score OR CENTOR OR Mclsaac OR Predict

**d) Prognosis search terms**

<b>Prognosi</b>	<b>Synonyms</b>

s	
Prognosis	Prognoses OR Prognostic OR Resolution OR Prediction OR Disease Progression OR Duration OR Progress OR Progression OR Self-limiting OR Self limiting OR Spontaneously remitting OR Spontaneously-remitting OR Resolve OR Resolves OR Resolution OR Severity of Illness
Mortality	Survival OR Life expectancy OR Death

**Appendix Table 3 Top 20 ARI Clinical Questions with corresponding Cochrane Reviews (CR)**

Rank	Topic	No. of searches	No. of Cochrane Reviews
1	Influenza + Vaccination	4989	9 [21-29]
2	Acute Otitis Media + Antibiotics	3578	4 [30-33]
3	Common cold + Vitamin C	3528	1 [34]
4	Meningitis + Corticosteroids	1910	4 [35-38]
5	Pneumonia + Non-specific treatment	1765	0* [39-49]
6	Pharyngitis + Antibiotics	1476	4 [50-53]
7	Pneumonia + Antibiotics	1422	12 [43-47, 54-60]
8	Pharyngitis + Corticosteroids	1324	2 [61, 62]
9	Croup + Corticosteroids	1292	4 [63-66]
10	Pneumococcus + Vaccination	1040	7 [67-73]
11	Sinusitis + Treatment	1036	5 [74-78]
12	Sinusitis + Antibiotics	1026	1 [78]
13	Acute Otitis Media + Treatment	963	8 [30, 31, 33, 68, 79-82]
14	Common cold + Zinc	832	1 [83]
15	Bronchiolitis + Corticosteroids	786	2 [84, 85]
16	Pharyngitis + Treatment	782	6 [50-52, 62, 86, 87]
17	Pneumonia + Diagnosis	778	1 [88]
18	Pneumonia + Corticosteroids	710	3 [40, 89, 90]

19	Sinusitis + Corticosteroids	674	1 [76]
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20	Bronchiolitis + Non-specific treatment	630	0* [84, 85, 91-103]

\* Cochrane protocols address this question and/or existing Cochrane reviews partially answer it.

**Appendix Table 4: List of topics with 100 or more searches**

Topic	No. of searches	% of searches
Influenza + Vaccination	4989	12.1
Acute Otitis Media + Antibiotics	3578	8.7
Common cold + Vitamin C	3528	8.6
Meningitis + Corticosteroids	1910	4.6
Pneumonia + Treatment	1765	4.3
Pharyngitis + Antibiotics	1476	3.6
Pneumonia + Antibiotics	1422	3.5
Pharyngitis + Corticosteroids	1324	3.2
Croup + Corticosteroids	1292	3.1
Pneumococcus + Vaccination	1040	2.5
Sinusitis + Treatment	1036	2.5
Sinusitis + Antibiotics	1026	2.5
Acute Otitis Media + Treatment	963	2.3
Common cold + Zinc	832	2.0
Bronchiolitis + Corticosteroids	786	1.9
Pharyngitis + Treatment	782	1.9
Pneumonia + Diagnosis	778	1.9
Pneumonia + Corticosteroids	710	1.7
Sinusitis + Corticosteroids	674	1.6
Bronchiolitis + Treatment	630	1.5

Common cold + Treatment	576	1.4
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Pneumonia + Mortality	567	1.4
Cough + Treatment	531	1.3
Pertussis + Vaccination	502	1.2
Meningitis + Treatment	477	1.2
Croup + Treatment	428	1.0
Bronchitis + Antibiotics	409	1.0
Influenza + Treatment	384	0.9
Measles + Vaccination	379	0.9
Sinusitis + Diagnosis	344	0.8
Meningitis + Antibiotics	313	0.8
Respiratory tract infection + Antibiotics	298	0.7
Pharyngitis + Diagnosis	293	0.7
Pneumonia + Vaccination	282	0.7
Influenza + Mortality	277	0.7
Pneumonia + Prognosis	268	0.7
Wheeze + Corticosteroids	247	0.6
Influenza + Diagnosis	221	0.5
Meningitis + Mortality	202	0.5
Rubella + Vaccination	192	0.5
Common cold + Antibiotics	186	0.5
Sinusitis + Immunotherapy	180	0.4
Bronchitis + Treatment	177	0.4
Pneumonia + Procalcitonins	177	0.4
Pneumonia + Physiotherapy	176	0.4

Bronchiolitis + CPAP	167	0.4
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Respiratory tract infection + Treatment	161	0.4
Meningitis + Diagnosis	157	0.4
Pertussis + Treatment	154	0.4
Acute Otitis Media + Corticosteroids	149	0.4
Acute Otitis Media + Prognosis	146	0.4
Acute Otitis Media + Diagnosis	137	0.3
Pneumonia + Probiotics	133	0.3
Sinusitis + Acupuncture	132	0.3
Cough + Antibiotics	129	0.3
Influenza + Antiviral	127	0.3
Mumps + Vaccination	126	0.3
Cough + Corticosteroids	115	0.3
Sinusitis + Antihistamine	114	0.3
Cough + Vaccination	110	0.3
Meningitis + Vaccination	110	0.3
Bronchiolitis + Physiotherapy	109	0.3
Pneumonia + Radiography	109	0.3
Bronchiolitis + Antibiotics	103	0.3
Influenza + Vitamin C	103	0.3

#### Appendix 5: List of Cochrane Reviews addressing the Clinical Questions

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