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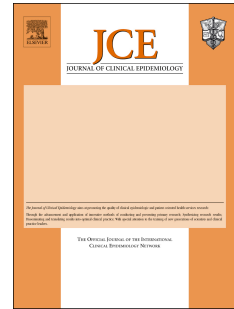
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The TRIP database showed most Acute Respiratory Infections questions were already addressed by Cochrane reviews

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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 ≥ 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

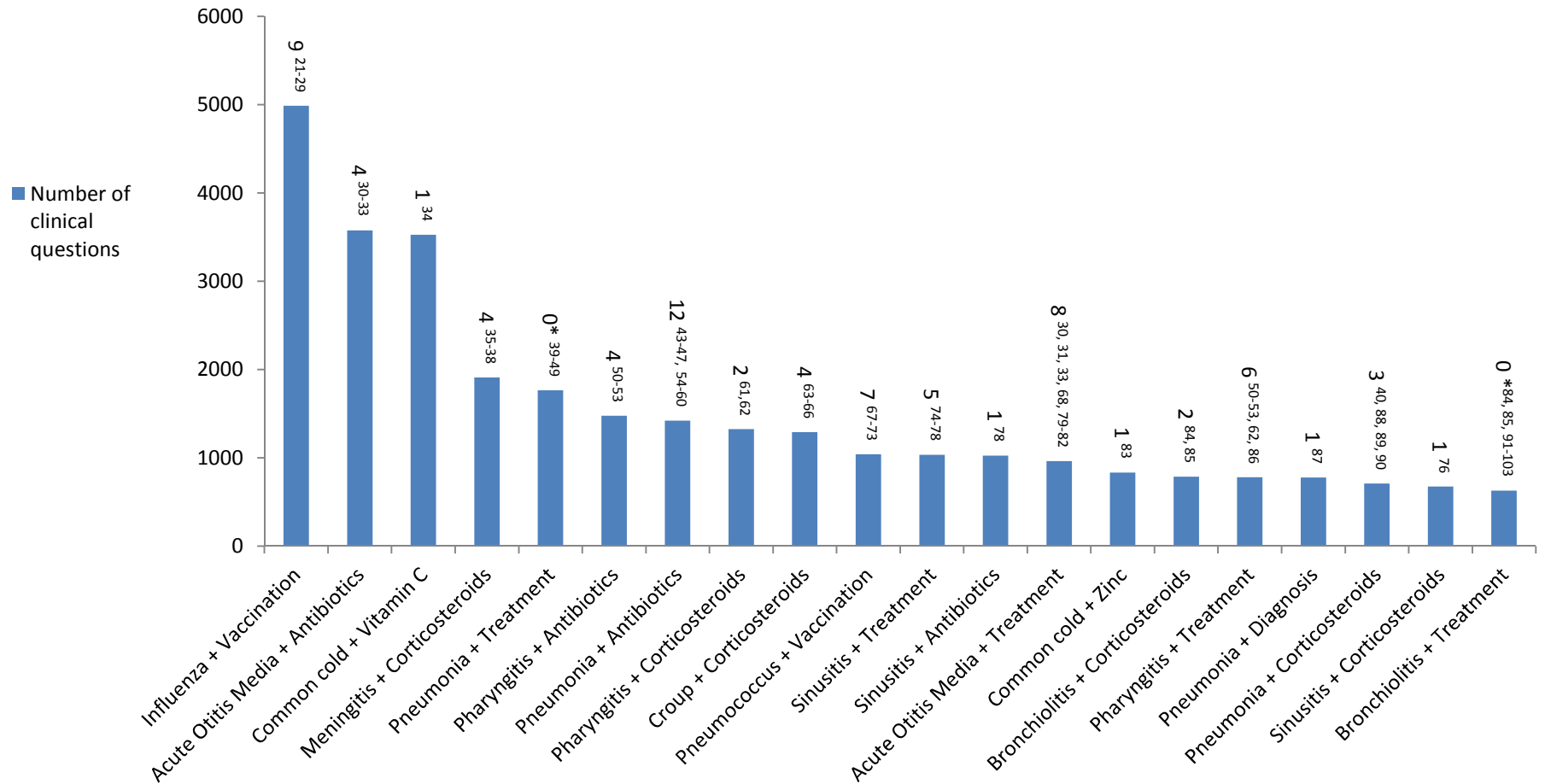
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The most frequent full clinical questions were: *influenza + vaccination* 4,989 (12%); *acute otitis media + antibiotics* 3578 (9%); *common cold + vitamin C* 3,528 (9%); *meningitis + corticosteroids* 1,910 (5%); and *pneumonia + general treatment* 1,765 (4%), Figure 1, (Appendix Table 4 lists all topics with ≥ 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 Carter has nothing to disclose.

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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.

References

- [1] The Cochrane Collaboration. Cochrane: about us. 2018. Accessed 14 May, 2018 Available at: <http://www.cochrane.org/about-us>
- [2] Useem J, Brennan A, LaValley M, Vickery M, Ameli O, Reinen N, et al. Systematic Differences between Cochrane and Non-Cochrane Meta-Analyses on the Same Topic: A Matched Pair Analysis. PLoS One. 2015;10:e0144980. 10.1371/journal.pone.0144980: 10.1371/journal.pone.0144980
- [3] Bero LA, Binder L. The Cochrane Collaboration review prioritization projects show that a variety of approaches successfully identify high-priority topics. J Clin Epidemiol. 2013;66:472-3. 10.1016/j.jclinepi.2012.03.015: 10.1016/j.jclinepi.2012.03.015
- [4] The Cochrane Collaboration. Cochrane Strategy to 2020. 2016. Available at: http://community-archive.cochrane.org/sites/default/files/uploads/Strategy%20to%202020_updated_Final_Feb2016.pdf
- [5] Nasser M, Welch V, Tugwell P, Ueffing E, Doyle J, Waters E. Ensuring relevance for Cochrane reviews: evaluating processes and methods for prioritizing topics for Cochrane reviews. J Clin Epidemiol. 2013;66:474-82. 10.1016/j.jclinepi.2012.01.001: 10.1016/j.jclinepi.2012.01.001
- [6] Welsh E, Stovold E, Karner C, Cates C. Cochrane Airways Group reviews were prioritized for updating using a pragmatic approach. J Clin Epidemiol. 2015;68:341-6
- [7] Wale JL, Belizan M, Nadel J, Jeffrey C, Vij SL. The Cochrane Library review titles that are important to users of health care, a Cochrane Consumer Network project. Health Expect. 2013;16:e146-63. 10.1111/j.1369-7625.2011.00723.x: 10.1111/j.1369-7625.2011.00723.x
- [8] Cochrane Tobacco Addiction Group. Cochrane Tobacco Addiction Priority setting workshop. 2016. Accessed 16 November, 2016 Available at: <http://tobacco.cochrane.org/priority-setting-workshop>
- [9] Synnot A, Bragge P, Lowe D, Nunn JS, O'Sullivan M, Horvat L, et al. Research priorities in health communication and participation: international survey of consumers and other stakeholders. BMJ Open. 2018;8:e019481. 10.1136/bmjopen-2017-019481: 10.1136/bmjopen-2017-019481
- [10] Synnot A. Stakeholder priorities for research in health communication and participation: findings from the Cochrane Consumers and communication priority setting project. 2016. Available at: http://www.latrobe.edu.au/data/assets/pdf_file/0005/751361/CKA8075_LaTrobeUni.LTU.Cochrane_PriorityReport_FINAL_WEB.pdf
- [11] Cochrane Acute Respiratory Infections. Cochrane Acute Respiratory Infections About us. 2018. Accessed 08 May, 2018 Available at: <http://ari.cochrane.org/welcome>
- [12] Alloo J, Vallath S, Del Mar C, Carter M, Thorning S, Clark J. Determining the gaps between Cochrane reviews and trials of effectiveness of interventions for acute respiratory infections: an audit. Systematic Reviews. 2017;6:82. 10.1186/s13643-017-0472-0: 10.1186/s13643-017-0472-0
- [13] Scott A. Setting research priorities in systematic reviews: Cochrane Acute Respiratory Infections Group's Stakeholder Engagement Project J Clin Epidemiol. 2018
- [14] Trip Database Ltd. Trip: about. 2017. Accessed 10 May, 2018 Available at: <https://www.tripdatabase.com/about>
- [15] Brassey J. Trip database blog: Survey ended, start of analysis. Trip; 2011.

- [16] Stevens GA, Fitterling L, Kelly FV. Trip Database: Turning Research into Practice for Evidence-Based Care. Med Ref Serv Q. 2017;36:391-8. 10.1080/02763869.2017.1369288: 10.1080/02763869.2017.1369288
- [17] Meats E, Brassey J, Heneghan C, Glasziou P. Using the Turning Research Into Practice (TRIP) database: how do clinicians really search? J Med Libr Assoc. 2007;95:156-63. 10.3163/1536-5050.95.2.156: 10.3163/1536-5050.95.2.156
- [18] Brassey J, Elwyn G, Price C, Kinnersley P. Just in time information for clinicians: a questionnaire evaluation of the ATTRACT project. BMJ. 2001;322:529-30
- [19] Ely JW, Osheroff JA, Gorman PN, Ebell MH, Chambliss ML, Pifer EA, et al. A taxonomy of generic clinical questions: classification study. BMJ. 2000;321:429-32
- [20] Ely JW, Osheroff JA, Maviglia SM, Rosenbaum ME. Patient-care questions that physicians are unable to answer. J Am Med Inform Assoc. 2007;14:407-14. 10.1197/jamia.M2398: 10.1197/jamia.M2398

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

Diagnosi s	Synonyms
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

Prognosi	Synonyms

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

[21] Bitterman R, Eliakim-Raz N, Vinograd I, Zalmanovici TA, Leibovici L, Paul M. Influenza vaccines in immunosuppressed adults with cancer. Cochrane Database Syst Rev: John Wiley & Sons, Ltd; 2018.

[22] Cates CJ, Rowe BH. Vaccines for preventing influenza in people with asthma. Cochrane Database Syst Rev: John Wiley & Sons, Ltd; 2013.

[23] Demicheli V, Jefferson T, Ferroni E, Rivetti A, Di PC. Vaccines for preventing influenza in healthy adults. Cochrane Database Syst Rev: John Wiley & Sons, Ltd; 2018.

[24] Dharmaraj P, Smyth RL. Vaccines for preventing influenza in people with cystic fibrosis. *Cochrane Database Syst Rev*: John Wiley & Sons, Ltd; 2014.

ACCEPTED MANUSCRIPT

[25] Goossen GM, Kremer LC, van de Wetering MD. Influenza vaccination in children being treated with chemotherapy for cancer. *Cochrane Database Syst Rev*: John Wiley & Sons, Ltd; 2013.

[26] Jefferson T, Di PC, Al-Ansary LA, Ferroni E, Thorning S, Thomas RE. Vaccines for preventing influenza in the elderly. *Cochrane Database Syst Rev*: John Wiley & Sons, Ltd; 2010.

[27] Jefferson T, Rivetti A, Di PC, Demicheli V. Vaccines for preventing influenza in healthy children. *Cochrane Database Syst Rev*: John Wiley & Sons, Ltd; 2018.

[28] Salam RA, Das JK, Dojo SC, Lassi ZS, Bhutta ZA. Impact of Haemophilus influenzae type B (Hib) and viral influenza vaccinations in pregnancy for improving maternal, neonatal and infant health outcomes. *Cochrane Database Syst Rev*: John Wiley & Sons, Ltd; 2015.

[29] Thomas RE, Jefferson T, Lasserson TJ. Influenza vaccination for healthcare workers who care for people aged 60 or older living in long-term care institutions. *Cochrane Database Syst Rev*: John Wiley & Sons, Ltd; 2016.

[30] Kozyrskyj AL, Klassen TP, Moffatt M, Harvey K. Short-course antibiotics for acute otitis media. *Cochrane Database Syst Rev*: John Wiley & Sons, Ltd; 2010.

[31] Leach AJ, Morris PS. Antibiotics for the prevention of acute and chronic suppurative otitis media in children. *Cochrane Database Syst Rev*: John Wiley & Sons, Ltd; 2006.

[32] Venekamp RP, Burton MJ, van DTM, van dHGJ, van ZA, Schilder AG. Antibiotics for otitis media with effusion in children. *Cochrane Database Syst Rev*: John Wiley & Sons, Ltd; 2016.

[33] Venekamp RP, Sanders SL, Glasziou PP, Del Mar CB, Rovers MM. Antibiotics for acute otitis media in children. *Cochrane Database Syst Rev*: John Wiley & Sons, Ltd; 2015.

[34] Hemilä H, Chalker E. Vitamin C for preventing and treating the common cold. *Cochrane Database Syst Rev*: John Wiley & Sons, Ltd; 2013.

[35] Brouwer MC, McIntyre P, Prasad K, van dBD. Corticosteroids for acute bacterial meningitis. *Cochrane Database Syst Rev*: John Wiley & Sons, Ltd; 2015.

[36] Ogunlesi TA, Odigwe CC, Oladapo OT. Adjuvant corticosteroids for reducing death in neonatal bacterial meningitis. *Cochrane Database Syst Rev*: John Wiley & Sons, Ltd; 2015.

[37] Prasad K, Singh MB, Ryan H. Corticosteroids for managing tuberculous meningitis. *Cochrane Database Syst Rev*: John Wiley & Sons, Ltd; 2016.

[38] Thanaviratnanich S, Thanaviratnanich S, Ngamjarus C. Corticosteroids for parasitic eosinophilic meningitis. *Cochrane Database Syst Rev*: John Wiley & Sons, Ltd; 2015.

[39] Arthur LE, Kizor RS, Selim AG, van DML, Seoane L. Antibiotics for ventilator-associated pneumonia. *Cochrane Database Syst Rev*: John Wiley & Sons, Ltd; 2016.

[40] Chen Y, Li K, Pu H, Wu T. Corticosteroids for pneumonia. *Cochrane Database Syst Rev*: John Wiley & Sons, Ltd; 2011.

[41] Hemilä H, Louhiala P. Vitamin C for preventing and treating pneumonia. *Cochrane Database Syst Rev*: John Wiley & Sons, Ltd; 2013.

- [42] Jefferson T, Jones MA, Doshi P, Del MCB, Hama R, Thompson MJ, et al. Neuraminidase inhibitors for preventing and treating influenza in adults and children. *Cochrane Database Syst Rev*: John Wiley & Sons, Ltd; 2014.
- [43] Lassi ZS, Imdad A, Bhutta ZA. Short-course versus long-course intravenous therapy with the same antibiotic for severe community-acquired pneumonia in children aged two months to 59 months. *Cochrane Database Syst Rev*: John Wiley & Sons, Ltd; 2017.
- [44] Lodha R, Kabra SK, Pandey RM. Antibiotics for community-acquired pneumonia in children. *Cochrane Database Syst Rev*: John Wiley & Sons, Ltd; 2013.
- [45] Martí-Carvajal AJ, Conterno LO. Antibiotics for treating community-acquired pneumonia in people with sickle cell disease. *Cochrane Database Syst Rev*: John Wiley & Sons, Ltd; 2016.
- [46] Pakhale S, Mulpuru S, Verheij TJ, Kochen MM, Rohde GG, Bjerre LM. Antibiotics for community-acquired pneumonia in adult outpatients. *Cochrane Database Syst Rev*: John Wiley & Sons, Ltd; 2014.
- [47] Pugh R, Grant C, Cooke RP, Dempsey G. Short-course versus prolonged-course antibiotic therapy for hospital-acquired pneumonia in critically ill adults. *Cochrane Database Syst Rev*: John Wiley & Sons, Ltd; 2015.
- [48] Shah PB, Meleveedu R, Elayaraja S, James S, Sathiyasekaran BW. Interventions for treating community-acquired pneumonia: an overview of Cochrane systematic reviews. *Cochrane Database Syst Rev*: John Wiley & Sons, Ltd; 2014.
- [49] Shah PB, Meleveedu R, James S, Elayaraja S, Sathiyasekaran BW. Interventions for treating hospital-acquired pneumonia: an overview of Cochrane systematic reviews. *Cochrane Database Syst Rev*: John Wiley & Sons, Ltd; 2014.
- [50] Altamimi S, Khalil A, Khalaiwi KA, Milner RA, Pusic MV, Al OMA. Short-term late-generation antibiotics versus longer term penicillin for acute streptococcal pharyngitis in children. *Cochrane Database Syst Rev*: John Wiley & Sons, Ltd; 2012.
- [51] Ng GJ, Tan S, Vu AN, Del Mar CB, van DML. Antibiotics for preventing recurrent sore throat. *Cochrane Database Syst Rev*: John Wiley & Sons, Ltd; 2015.
- [52] Spinks A, Glasziou PP, Del Mar CB. Antibiotics for sore throat. *Cochrane Database Syst Rev*: John Wiley & Sons, Ltd; 2013.
- [53] van Driel ML, De SAI, Habraken H, Thorning S, Christiaens T. Different antibiotic treatments for group A streptococcal pharyngitis. *Cochrane Database Syst Rev*: John Wiley & Sons, Ltd; 2016.
- [54] Eliakim-Raz N, Robenshtok E, Shefet D, Gafter-Gvili A, Vidal L, Paul M, et al. Empiric antibiotic coverage of atypical pathogens for community-acquired pneumonia in hospitalized adults. *Cochrane Database Syst Rev*: John Wiley & Sons, Ltd; 2012.
- [55] Enuh HA, Enuh CU, Ezedunukwe IR, Diaz KT, Nfonoyim J. Aerosolised antibiotics for the management of healthcare-associated pneumonia (HCAP) and ventilator-associated pneumonia (VAP). *Cochrane Database Syst Rev*: John Wiley & Sons, Ltd; 2017.
- [56] Haider BA, Lassi ZS, Bhutta ZA. Short-course versus long-course antibiotic therapy for non-severe community-acquired pneumonia in children aged 2 months to 59 months. *Cochrane Database Syst Rev*: John Wiley & Sons, Ltd; 2008.
- [57] Jiang L, Mu D, Zhang L, Gui G, Duan Y, Wan C. Antibiotics for hospital-acquired pneumonia in children. *Cochrane Database Syst Rev*: John Wiley & Sons, Ltd; 2016.

- [58] Lassi ZS, Kumar R, Das JK, Salam RA, Bhutta ZA. Antibiotic therapy versus no antibiotic therapy for children aged two to 59 months with WHO-defined non-severe pneumonia and wheeze. *Cochrane Database Syst Rev*: John Wiley & Sons, Ltd; 2014.
- [59] Rodriguez-Barrientos R, López-Alcalde J, Rodríguez-Fernández C, Muñoz-Gutiérrez J, Gómez-García M, Molero-García JM, et al. Short-course versus long-course therapy of the same antibiotic for community-acquired pneumonia in adolescent and adult outpatients. *Cochrane Database Syst Rev*: John Wiley & Sons, Ltd; 2011.
- [60] Rojas-Reyes MX, Granados RC. Oral antibiotics versus parenteral antibiotics for severe pneumonia in children. *Cochrane Database Syst Rev*: John Wiley & Sons, Ltd; 2006.
- [61] Adams NP, Bestall JC, Lasserson TJ, Jones P, Cates CJ. Fluticasone versus placebo for chronic asthma in adults and children. *Cochrane Database Syst Rev*: John Wiley & Sons, Ltd; 2008.
- [62] Hayward G, Thompson MJ, Perera R, Glasziou PP, Del Mar CB, Heneghan CJ. Corticosteroids as standalone or add-on treatment for sore throat. *Cochrane Database Syst Rev*: John Wiley & Sons, Ltd; 2012.
- [63] Edmonds ML, Milan SJ, Camargo JCA, Pollack CV, Rowe BH. Early use of inhaled corticosteroids in the emergency department treatment of acute asthma. *Cochrane Database Syst Rev*: John Wiley & Sons, Ltd; 2012.
- [64] Kew KM, Quinn M, Quon BS, Ducharme FM. Increased versus stable doses of inhaled corticosteroids for exacerbations of chronic asthma in adults and children. *Cochrane Database Syst Rev*: John Wiley & Sons, Ltd; 2016.
- [65] Khemani RG, Randolph A, Markovitz B. Corticosteroids for the prevention and treatment of post-extubation stridor in neonates, children and adults. *Cochrane Database Syst Rev*: John Wiley & Sons, Ltd; 2009.
- [66] Russell KF, Liang Y, O'Gorman K, Johnson DW, Klassen TP. Glucocorticoids for croup. *Cochrane Database Syst Rev*: John Wiley & Sons, Ltd; 2011.
- [67] Chang CC, Singleton RJ, Morris PS, Chang AB. Pneumococcal vaccines for children and adults with bronchiectasis. *Cochrane Database Syst Rev*: John Wiley & Sons, Ltd; 2009.
- [68] Fortanier AC, Venekamp RP, Boonacker CW, Hak E, Schilder AG, Sanders EA, et al. Pneumococcal conjugate vaccines for preventing otitis media. *Cochrane Database Syst Rev*: John Wiley & Sons, Ltd; 2014.
- [69] Golos M, Eliakim-Raz N, Stern A, Leibovici L, Paul M. Conjugated pneumococcal vaccine versus polysaccharide pneumococcal vaccine for prevention of pneumonia and invasive pneumococcal disease in immunocompetent and immunocompromised adults and children. *Cochrane Database Syst Rev*: John Wiley & Sons, Ltd; 2016.
- [70] Lucero MG, Dulalia VE, Nillos LT, Williams G, Parreño RAN, Nohynek H, et al. Pneumococcal conjugate vaccines for preventing vaccine-type invasive pneumococcal disease and X-ray defined pneumonia in children less than two years of age. *Cochrane Database Syst Rev*: John Wiley & Sons, Ltd; 2009.
- [71] Moberley S, Holden J, Tatham DP, Andrews RM. Vaccines for preventing pneumococcal infection in adults. *Cochrane Database Syst Rev*: John Wiley & Sons, Ltd; 2013.
- [72] Sadlier C, Bennett K, Matthews A, Mockler D, Wilson F, Bergin C. Pneumococcal vaccine for preventing *Streptococcus pneumoniae* infection in HIV-infected individuals. *Cochrane Database Syst Rev*: John Wiley & Sons, Ltd; 2016.
- [73] Walters JA, Tang JNQ, Poole P, Wood-Baker R. Pneumococcal vaccines for preventing pneumonia in chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*: John Wiley & Sons, Ltd; 2017.

[75] Zalmanovici TA, Barua A, Pertzov B. Cyclamen europaeum extract for acute sinusitis. *Cochrane Database Syst Rev*: John Wiley & Sons, Ltd; 2018.

[76] Venekamp RP, Thompson MJ, Hayward G, Heneghan CJ, Del MCB, Perera R, et al. Systemic corticosteroids for acute sinusitis. *Cochrane Database Syst Rev*: John Wiley & Sons, Ltd; 2014.

[77] Shaikh N, Wald ER. Decongestants, antihistamines and nasal irrigation for acute sinusitis in children. *Cochrane Database Syst Rev*: John Wiley & Sons, Ltd; 2014.

[78] Ahovuo-Saloranta A, Rautakorpi U-M, Borisenko OV, Liira H, Williams JJW, Mäkelä M. Antibiotics for acute maxillary sinusitis in adults. *Cochrane Database Syst Rev*: John Wiley & Sons, Ltd; 2015.

[79] Venekamp RP, Mick P, Schilder AG, Nunez DA. Grommets (ventilation tubes) for recurrent acute otitis media in children. *Cochrane Database Syst Rev*: John Wiley & Sons, Ltd; 2018.

[80] Ranakusuma RW, Pitoyo Y, Safitri ED, Thorning S, Beller EM, Sastroasmoro S, et al. Systemic corticosteroids for acute otitis media in children. *Cochrane Database Syst Rev*: John Wiley & Sons, Ltd; 2018.

[81] Norhayati MN, Ho JJ, Azman MY. Influenza vaccines for preventing acute otitis media in infants and children. *Cochrane Database Syst Rev*: John Wiley & Sons, Ltd; 2017.

[82] Azarpazhooh A, Lawrence HP, Shah PS. Xylitol for preventing acute otitis media in children up to 12 years of age. *Cochrane Database Syst Rev*: John Wiley & Sons, Ltd; 2016.

[83] Hemilä H, Chalker E. Zinc for preventing and treating the common cold. *Cochrane Database Syst Rev*: John Wiley & Sons, Ltd; 2017.

[84] Fernandes RM, Bialy LM, Vandermeer B, Tjosvold L, Plint AC, Patel H, et al. Glucocorticoids for acute viral bronchiolitis in infants and young children. *Cochrane Database Syst Rev*: John Wiley & Sons, Ltd; 2013.

[85] Blom DJ, Ermers M, Bont L, van WJB, Van AWM. Inhaled corticosteroids during acute bronchiolitis in the prevention of post-bronchiolitic wheezing. *Cochrane Database Syst Rev*: John Wiley & Sons, Ltd; 2011.

[86] van DML, De SAI, Habraken H, Thorning S, Christiaens T. Different antibiotic treatments for group A streptococcal pharyngitis. *Cochrane Database Syst Rev*: John Wiley & Sons, Ltd; 2016.

[87] Huang Y, Wu T, Zeng L, Li S. Chinese medicinal herbs for sore throat. *Cochrane Database Syst Rev*: John Wiley & Sons, Ltd; 2012.

[88] Wang K, Gill P, Perera R, Thomson A, Mant D, Harnden A. Clinical symptoms and signs for the diagnosis of *Mycoplasma pneumoniae* in children and adolescents with community-acquired pneumonia. *Cochrane Database Syst Rev*: John Wiley & Sons, Ltd; 2012.

[89] Kew KM, Seniukovich A. Inhaled steroids and risk of pneumonia for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*: John Wiley & Sons, Ltd; 2014.

[90] Ewald H, Raatz H, Boscacci R, Furrer H, Bucher HC, Briel M. Adjunctive corticosteroids for *Pneumocystis jirovecii* pneumonia in patients with HIV infection. *Cochrane Database Syst Rev*: John Wiley & Sons, Ltd; 2015.

[91] Zhang L, Mendoza-Sassi RA, Wainwright C, Klassen TP. Nebulised hypertonic saline solution for acute bronchiolitis in infants. *Cochrane Database Syst Rev*: John Wiley & Sons, Ltd; 2017.

[92] Ventre K, Haroon M, Davison C. Surfactant therapy for bronchiolitis in critically ill infants. *Cochrane Database Syst Rev*: John Wiley & Sons, Ltd; 2010.

ACCEPTED MANUSCRIPT

[93] Umoren R, Odey F, Meremikwu MM. Steam inhalation or humidified oxygen for acute bronchiolitis in children up to three years of age. *Cochrane Database Syst Rev*: John Wiley & Sons, Ltd; 2011.

[94] Roqué iFM, Giné-Garriga M, Granados RC, Perrotta C, Vilaró J. Chest physiotherapy for acute bronchiolitis in paediatric patients between 0 and 24 months old. *Cochrane Database Syst Rev*: John Wiley & Sons, Ltd; 2016.

[95] Liu F, Ouyang J, Sharma AN, Liu S, Yang B, Xiong W, et al. Leukotriene inhibitors for bronchiolitis in infants and young children. *Cochrane Database Syst Rev*: John Wiley & Sons, Ltd; 2015.

[96] Liet J-M, Ducruet T, Gupta V, Cambonie G. Heliox inhalation therapy for bronchiolitis in infants. *Cochrane Database Syst Rev*: John Wiley & Sons, Ltd; 2015.

[97] Jat KR, Mathew JL. Continuous positive airway pressure (CPAP) for acute bronchiolitis in children. *Cochrane Database Syst Rev*: John Wiley & Sons, Ltd; 2015.

[98] Jat KR, Chawla D. Surfactant therapy for bronchiolitis in critically ill infants. *Cochrane Database Syst Rev*: John Wiley & Sons, Ltd; 2015.

[99] Hartling L, Bialy LM, Vandermeer B, Tjosvold L, Johnson DW, Plint AC, et al. Epinephrine for bronchiolitis. *Cochrane Database Syst Rev*: John Wiley & Sons, Ltd; 2011.

[100] Gadomski AM, Scribani MB. Bronchodilators for bronchiolitis. *Cochrane Database Syst Rev*: John Wiley & Sons, Ltd; 2014.

[101] Farley R, Spurling GK, Eriksson L, Del Mar CB. Antibiotics for bronchiolitis in children under two years of age. *Cochrane Database Syst Rev*: John Wiley & Sons, Ltd; 2014.

[102] Enriquez A, Chu I-W, Mellis C, Lin W-Y. Nebulised deoxyribonuclease for viral bronchiolitis in children younger than 24 months. *Cochrane Database Syst Rev*: John Wiley & Sons, Ltd; 2012.

[103] Beggs S, Wong ZH, Kaul S, Ogden KJ, Walters JA. High-flow nasal cannula therapy for infants with bronchiolitis. *Cochrane Database Syst Rev*: John Wiley & Sons, Ltd; 2014.

