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Probiotics for preventing acute otitis media in children

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To assess the effects of probiotics to prevent the occurrence and reduce the severity of acute otitis media in children.

BACKGROUND

Description of the condition

Acute otitis media (AOM) is one of the most common childhood diseases. It is characterised by effusion of the middle ear and rapid onset of symptoms such as ear pain, otorrhoea (discharge from the ear), fever, and malaise (AAP 2013). Although AOM has low mortality, it has high morbidity (Stool 1989); by two years of age, 70% of children have had at least one episode of AOM, and 20% to 30% of children have experienced three or more episodes (Hatakka 2007). Globally, the incidence rate of AOM is estimated at 10.85% (the equivalent of 709 million cases of AOM each year); the incidence rate varies, from a low of 3.64% in Central Europe to 43.37% in central sub-Saharan Africa (Monasta 2012).

Clinical care guidelines for treatment of AOM vary internationally. For mild-moderate cases, 'watchful waiting' has now been adopted in many high-income countries, although this remains infrequent in low-income countries (Tamir 2017). Most guide-

lines recommend amoxicillin as first-line treatment, with some exceptions: amoxicillin-clavulanate in some high-income countries, penicillin V in Scandinavian countries, and other first-line treatments in low-income countries include trimethoprim-sulfamethoxazole, cephalexin, cloxacillin, and others (Tamir 2017). Although AOM is one of the main reasons for antibiotic prescription in children (Hendley 2002), the rates of antibiotic prescription for AOM vary internationally, from 56% of consultations for AOM in the Netherlands, Akkerman 2005, to 95% in North America (Froom 2001). However, using antibiotics in prophylaxis and treatment of AOM leads to the development of antibiotic resistance, and identification of alternatives to antibiotics for prevention or treatment of AOM is becoming urgent (Cohen 2013; Hatakka 2007; Niittynen 2012).

Description of the intervention

The World Health Organization (WHO) defines probiotics as live micro-organisms that confer a health benefit on the host when

administered in adequate amounts (FAO-WHO 2006). Microorganisms used as probiotics include: *Lactobacillus* (e.g. *L. acidophilus*, *L. fermentum*), *Bifidobacterium* (e.g. *B. bifidum*, *B. lactis*), *Streptococcus* (e.g. *S. thermophilus*) species, and *Saccharomyces* (e.g. *S. boulardii*) species (Niittynen 2012). Probiotics are available in multiple forms: as tablets or powders (regulated as dietary supplements), as a food ingredient (e.g. yogurts or kefir) (Wang 2016), or directly applied by spray to the throat (Roos 2001). Probiotics are not currently part of clinical practice. Probiotics can be used by adults and children (Wang 2016). In people with unimpaired immune systems, probiotics do not have any known harmful effects (Marteau 2002).

How the intervention might work

Since otitis media is associated with colonisation by pathogenic bacteria in the nasopharynx, and disruption of the balance of the normal microbiota (Hatakka 2007), probiotics may act by restoring the normal microbiota (i.e. by overwhelming the pathogens with healthy commensals), rather than by attempting to kill pathogens with antibiotics, although the mechanisms of any probiotics benefit are unclear (Hao 2015). They may act by stabilising gut microbiota; modulating immune function; competing with pathogens for essential nutrients and adhesion sites on epithelial surfaces; producing bacteriocins or other inhibitory substances (Hao 2015; Hatakka 2007; Niittynen 2012).

Why it is important to do this review

Because antibiotic use leads to increased antibiotic resistance, (O'Neill 2014), other options (including probiotics) are attracting greater interest (Hatakka 2007). The most recent Cochrane Review on the use of probiotics for preventing acute respiratory tract infections did not include studies with AOM as an outcome on the grounds that otitis-prone children may have immunodeficiencies (Hao 2015). Several other Cochrane Reviews have investigated other interventions for the prevention of otitis media. These include xylitol (Azarpazhooh 2016), pneumococcal conjugate vaccines (Fortanier 2014), influenza vaccines (Norhayati 2015), and antibiotics (Leach 2013).

OBJECTIVES

To assess the effects of probiotics to prevent the occurrence and reduce the severity of acute otitis media in children.

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomised controlled trials (RCTs), irrespective of type (e.g. cluster, parallel, cross-over). We will include studies reported as full text, those published as abstracts only, and unpublished data.

Types of participants

We will include children (aged up to 18 years) diagnosed with acute otitis media (AOM) by a clinician.

We will exclude children with the following comorbidities or characteristics: chromosomal and genetic disorders; craniofacial abnormalities, including cleft palate; those taking systemic corticosteroids or with immune deficiency status; and those with cystic fibrosis or primary ciliary dyskinesia.

Types of interventions

We will include trials comparing probiotics (including: *Lactobacillus spp.*, *Bifidobacterium spp.*, *Streptococcus spp.*, and *Saccharomyces spp.*) with placebo or usual care or lack of treatment. We will include probiotics of any composition (e.g. powder, drink, spray). We will include studies that include a co-intervention (including antibiotics) that is applied to both the intervention and control groups, and we will perform a subgroup analysis for those studies.

Types of outcome measures

Primary outcomes

1. Incidence of AOM.
2. Severity of AOM.
3. Adverse events (e.g. gastrointestinal side effects).

Secondary outcomes

1. Median duration of AOM episodes (days).
2. Difference between probiotic and non-probiotic groups in use of antibiotics to treat AOM (e.g. dose, duration)
3. Time off school (for the child) (e.g. in days or hours)
4. Time off work (for the parent or carer) (e.g. in days or hours)
5. Difference between probiotic and non-probiotic groups in hearing loss, if AOM occurs.
6. Serous/secretory otitis media.
7. Reduction in referrals to a specialist (e.g. for glue ear).
8. Reduction in other infections (respiratory and gastrointestinal).

9. Compliance with taking probiotics (e.g. measured by pill count or weight of the spray bottle).
10. Quality of life measures (using any validated quality of life measure).
11. Difference in use of other treatments (e.g. differences in dosage of analgesics, decongestants).

Search methods for identification of studies

Electronic searches

We will search the following databases from inception to present.

- Cochrane Acute Respiratory Infections Group Specialized Register
- CENTRAL (Cochrane Central Register of Controlled Trials)
- MEDLINE (PubMed)
- Embase
- CINAHL (Cumulative Index to Nursing and Allied Health Literature)
- Web of Science
- LILACS (Latin American and Caribbean Health Sciences Literature database)

We will use the search strategy described in [Appendix 1](#) to search PubMed. We will combine the PubMed search with the Cochrane Highly Sensitive Search Strategy for randomised trials: sensitivity and precision-maximising version (2008 revision) ([Lefebvre 2011](#)). We will not impose any language, publication date, or publication status restrictions. We will convert the search for use in the other databases.

We will also conduct a search of ClinicalTrials.gov (www.clinicaltrials.gov) and the WHO International Clinical Trials Registry Platform (apps.who.int/trialsearch/) to identify published registered trials, as well as ongoing studies.

Where relevant, for completed trials that appear to be unpublished, we will contact trial investigators for unpublished data.

We will run backward (cited) and forward (citing) citation analyses for all included studies. We will also use the similar article feature in PubMed and the shared citation matcher in Web of Science to identify any potential trials missed by the search strategy.

Searching other resources

We will contact experts in the field to identify additional unpublished materials.

Data collection and analysis

Selection of studies

Two review authors (AMS, JC) will independently screen titles and abstracts for inclusion of all the potential studies we identify as a result of the search.

We will retrieve the full-text study reports/publication, and two review authors (AMS, JC) will independently screen the full text and identify studies for inclusion, and identify and record reasons for exclusion of the ineligible studies. Any disagreements will be resolved through discussion or by consulting a third review author (CDM) when necessary. We will identify and exclude duplicates and collate multiple reports of the same study so that each study rather than each report is the unit of interest in the review. We will record the selection process in sufficient detail to complete a PRISMA flow diagram and 'Characteristics of excluded studies' table ([Moher 2009](#)). We will not impose any language restrictions.

Data extraction and management

We will use a data collection form for study characteristics and outcome data that has been piloted on at least one study in the review. Two review authors (AMS, JC) will extract the following study characteristics from included studies.

1. Methods: study location, study design, study objective, study duration
2. Participants: N, type of participants, mean age, age range, gender, comorbidities, number of previous episodes of otitis media, diagnostic criteria
3. Interventions: probiotic type, duration, dose, comparison, other permitted interventions (e.g. concomitant analgesics, decongestants), other prohibited interventions (e.g. analgesics, decongestants)
4. Outcomes: primary and secondary outcomes specified and collected, and time points reported
5. Notes: funding for trial, and notable conflicts of interest of trial authors

Two review authors (AMS, JC) will independently extract outcome data from the included studies. We will note in the 'Characteristics of included studies' table if outcome data are not reported in a useable way. Any disagreements will be resolved by consensus or by involving a third review author (CDM). One review author (EB) will transfer data into the Review Manager 5 file ([RevMan 2014](#)). We will double-check that data are entered correctly by comparing the data presented in the systematic review with the study reports. A second review author (CDM) will spot-check study characteristics for accuracy against the trial report.

Assessment of risk of bias in included studies

Two review authors (AMS, JC) will independently assess risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)). Any disagreements will be resolved by discussion or by involving

another review author (EB, CDM). We will assess the risk of bias according to the following domains.

1. Random sequence generation
2. Allocation concealment
3. Blinding of participants and personnel
4. Blinding of outcome assessment
5. Incomplete outcome data
6. Selective outcome reporting
7. Other bias

We will grade each potential source of bias as high, low, or unclear and provide a quote from the study report together with a justification for our judgement in the 'Risk of bias' table. We will summarise the 'Risk of bias' judgements across different studies for each of the domains listed. Where necessary, we will consider blinding separately for different key outcomes. Where information on risk of bias relates to unpublished data or correspondence with a trialist, we will note this in the 'Risk of bias' table.

When considering treatment effects, we will take into account the risk of bias for the studies that contribute to that outcome.

Assessment of bias in conducting the systematic review

We will conduct the review according to this published protocol and report any deviations from it in the 'Differences between protocol and review' section of the systematic review.

Measures of treatment effect

We will enter the outcome data for each study into the data tables in Review Manager 5 to calculate the treatment effects (RevMan 2014). We will use risk ratios for dichotomous outcomes, rate ratios for outcomes measured as rates (e.g. adverse events), and mean differences or standardised mean differences for continuous outcomes.

We will undertake meta-analyses only where this is meaningful, that is if the treatments, participants, and the underlying clinical question are similar enough for pooling to make sense. If meta-analysis is possible, we will use a random-effects model for high heterogeneity and a fixed-effect model for low heterogeneity.

Unit of analysis issues

We will use the participant as the unit of analysis, except for any cluster RCTs.

Dealing with missing data

We will contact investigators or study sponsors to verify key study characteristics and obtain missing numerical outcome data where possible (e.g. when a study is identified as abstract only). Where this is not possible, and the missing data are thought to introduce

serious bias, we will explore the impact of including such studies in the overall assessment of results by a sensitivity analysis.

If numerical outcome data such as standard deviations or correlation coefficients are missing, and they cannot be obtained from the authors, we will calculate them from other available statistics such as P values according to the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Assessment of heterogeneity

We will use the I^2 statistic to measure heterogeneity among the trials in each analysis. If we identify substantial heterogeneity, we will report it and explore possible causes by prespecified subgroup analysis. We will consider an I^2 statistic value of 0% to 40% to be low heterogeneity, 41% to 60% as moderate heterogeneity, 61% to 90% substantial heterogeneity, and over 91% to be considerable heterogeneity (Higgins 2011).

Assessment of reporting biases

If we are able to pool more than 10 trials, we will create and examine a funnel plot to explore possible small-study and publication biases.

Data synthesis

We will pool data from studies we judge to be clinically homogeneous using Review Manager 5 software (RevMan 2014). If more than one study provides useable data in any single comparison, we will perform a meta-analysis. As sizeable heterogeneity is expected in terms of populations, probiotics studied, etc., we will use the random-effects model. If an insufficient volume of evidence exists to perform a meta-analysis, we will report outcomes in a narrative format.

GRADE and 'Summary of findings' table

We will create a 'Summary of findings' table using the following outcomes: incidence of AOM, severity of AOM, adverse events, median duration of AOM episodes, difference between groups in antibiotic use, time off school (child), time off work (parent or carer). We will use the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness, and publication bias) to assess the quality of a body of evidence as it relates to the studies that contribute data to the meta-analyses for the prespecified outcomes (Atkins 2004). We will use methods and recommendations described in Section 8.5 and Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), employing GRADEpro GDT software (GRADEpro GDT 2014). We will justify all decisions to down- or upgrade the quality of studies using footnotes, and we will make comments to aid the reader's understanding of the review where necessary.

Subgroup analysis and investigation of heterogeneity

We plan to carry out the following subgroup analyses.

1. Child's age (\leq two years: see [Rovers 2006](#))
2. Type of probiotic
3. Children with severe AOM (fever > 39 °C; bilateral otitis; or perforation of the tympanic membrane, see [Rovers 2006](#))
4. Studies that include a co-intervention (including antibiotics) that is applied to both the intervention and control groups

We will use the Chi² test to test for subgroup interactions in Review Manager 5 ([RevMan 2014](#)).

Sensitivity analysis

We plan to carry out the following sensitivity analysis.

1. Including versus excluding studies with two or more domains rated as at high risk of bias

ACKNOWLEDGEMENTS

The authors would like to acknowledge and thank the authors of [Crosby 2004](#), whose withdrawn protocol partly informed development of this protocol. Parts of the [Background](#) are based on a Cochrane Review by [Venekamp 2015](#). One of the present authors (CDM) is also an author of [Crosby 2004](#) and [Venekamp 2015](#). The [Methods](#) section of this protocol is based on a standard template developed by the Cochrane Airways Group and adapted by the Cochrane Acute Respiratory Infections Group. We wish to thank the following people for commenting on the draft of this protocol: Catherine Marshall, Jenny Negus, Roderick Venekamp, Tal Marom, Robert Ware, and Zulfiqar Bhutta.

REFERENCES

Additional references

AAP 2013

American Academy of Pediatrics (AAP). Clinical practice guidelines: diagnosis and management of acute otitis media. *Pediatrics* 2013;**131**(3):e964–99.

Akkerman 2005

Akkerman AE, Kuyvenhoven MM, van der Wouden JC, Verhij TJM. Analysis of under- and overprescribing of antibiotics in acute otitis media in general practice. *Journal of Antimicrobial Chemotherapy* 2005;**56**:569–74.

Atkins 2004

Atkins D, Best D, Briss PA, Eccles M, Falck-Ytter Y, Flottorp S, et al. GRADE Working Group. Grading quality of evidence and strength of recommendations. *BMJ* 2004;**328**(7454):1490.

Azarpazhooh 2016

Azarpazhooh A, Lawrence HP, Shah PS. Xylitol for preventing acute otitis media in children up to 12 years of age. *Cochrane Database of Systematic Reviews* 2016, Issue 8. DOI: 10.1002/14651858.CD007095.pub3

Cohen 2013

Cohen R, Martin E, de la Rocque F, Thollot F, Pecquet S, Werner A, et al. Probiotics and prebiotics in preventing episodes of acute otitis media in high-risk children: a randomized double-blind, placebo-controlled study. *Pediatric Infectious Disease Journal* 2013;**32**(8):810–4.

FAO-WHO 2006

Food, Agriculture Organization of the United Nations. World Health Organization (FAO-WHO). Probiotics in food: health and nutritional properties and guidelines for evaluation. www.fao.org/3/a-a0512e.pdf (accessed 7 March 2017).

Fortanier 2014

Fortanier AC, Venekamp RP, Boonacker CWB, Hak E, Schilder AGM, Sanders EAM, et al. Pneumococcal conjugate vaccines for preventing otitis media. *Cochrane Database of Systematic Reviews* 2014, Issue 4. DOI: 10.1002/14651858.CD001480.pub4

Froom 2001

Froom J, Culpepper L, Green LA, de Melker RA, Grob P, Heeren T, et al. A cross-national study of acute otitis media: risk factors, severity, and treatment at initial visit. Report from the International Primary Care Network (IPCN) and the Ambulatory Sentinel Practice Network (ASPN). *Journal of the American Board of Family Practice* 2001;**14**:406–17.

GRADEpro GDT 2014 [Computer program]

GRADE Working Group, McMaster University. GRADEpro GDT. Hamilton (ON): GRADE Working Group, McMaster University, 2014.

Hao 2015

Hao Q, Dong BR, Wu T. Probiotics for preventing acute upper respiratory tract infections. *Cochrane Database of Systematic Reviews* 2015, Issue 2. DOI: 10.1002/14651858.CD006895.pub3

Hatakka 2007

Hatakka K, Blomgren K, Pohjavuori S, Kajjalainen T, Poussa T, Leinonen M, et al. Treatment of acute otitis media with probiotics in otitis-prone children - a double-blind, placebo-controlled randomised study. *Clinical Nutrition* 2007;**26**:314–21.

Hendley 2002

Hendley JO. Otitis media. *New England Journal of Medicine* 2002;**347**(15):1169–74.

Higgins 2011

Higgins JP, Green S, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Leach 2013

Leach AJ, Morris PS. Antibiotics for the prevention of acute and chronic suppurative otitis media in children. *Cochrane Database of Systematic Reviews* 2013, Issue 7. DOI: 10.1002/14651858.CD004401.pub2

Lefebvre 2011

Lefebvre C, Manheimer E, Glanville J. Chapter 6: Searching for studies. In: Higgins JP, Green S, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Marteau 2002

Marteau PR. Probiotics in clinical conditions. *Clinical Reviews in Allergy and Immunology* 2002;**22**(3):255–73.

Moher 2009

Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA Statement. *BMJ* 2009;**339**:2535.

Monasta 2012

Monasta L, Ronfani L, Marchetti F, Montico M, Vecchi Brumatti L, Bavcar A, et al. Burden of disease caused by otitis media: systematic review and global estimates. *PLoS ONE* 2012;**7**(4):e36226.

Niittynen 2012

Niittynen L, Pitkaranta A, Korpela R. Probiotics and otitis media in children. *International Journal of Otorhinolaryngology* 2012;**76**(4):465–70.

Norhayati 2015

Norhayati MN, Ho JJ, Azman MY. Influenza vaccines for preventing acute otitis media in infants and children. *Cochrane Database of Systematic Reviews* 2015, Issue 3. DOI: 10.1002/14651858.CD010089.pub2

O'Neill 2014

O'Neill J, Davies S, Rex J. Antimicrobial resistance: tackling a crisis for the health and wealth of nations. amr-review.org/sites/default/files/AMR%20Review%20Paper%20-%20Tackling%20a%20crisis%20for%20the%20health%20and%20wealth%20of%20nations_1.pdf (accessed 7 March 2017).

RevMan 2014 [Computer program]

Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager 5 (RevMan 5). Version 5.3. Copenhagen: Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Roos 2001

Roos K, Hakansson EG, Holm S. Effect of recolonisation with “interfering” alpha streptococci on recurrences of acute and secretory otitis media in children: randomised placebo controlled trial. *BMJ* 2001;**322**:1–4.

Rovers 2006

Rovers MM, Glasziou P, Appelman CL, Burke P, McCormick DP, Damoiseaux RA, et al. Antibiotics for acute otitis media: a meta-analysis with individual patient data. *Lancet* 2006;**368**(9545):1429–35.

Stool 1989

Stool SE, Field MJ. The impact of otitis media. *Pediatric Infectious Disease Journal* 1989;**8**(Suppl 1):11–4.

Tamir 2017

Tamir SO, Sibbald A, Rupa V, Marchisio P, Homoe P, Daniel SJ, et al. Guidelines for the treatment of acute otitis media: why are there worldwide differences?. *Current Otorhinolaryngology Reports* 2017;**5**(2):101–7.

Venekamp 2015

Venekamp RP, Sanders SL, Glasziou PP, Del Mar CB, Rovers MM. Antibiotics for acute otitis media in children. *Cochrane Database of Systematic Reviews* 2015, Issue 6. DOI: 10.1002/14651858.CD000219.pub4

Wang 2016

Wang Y, Li X, Ge T, Xiao Y, Liao Y, Cui Y, et al. Probiotics for prevention and treatment of respiratory tract infections in children. *Medicine* 2016;**95**(31):e4509.

References to other published versions of this review**Crosby 2004**

Crosby Z, Williamson I, Del Mar C, Little P. Probiotics for the prevention of acute otitis media in children. *Cochrane Database of Systematic Reviews* 2004, Issue 4. DOI: 10.1002/14651858.CD004978

* Indicates the major publication for the study

APPENDICES

Appendix I. PubMed (National Library of Medicine) search strategy

(Probiotics[Mesh] OR “Synbiotics”[Mesh] OR Lactobacillus[Mesh] OR Bifidobacterium[Mesh] OR Saccharomyces[Mesh] OR “Streptococcus thermophilus”[Mesh] OR “Cultured Milk Products”[Mesh] OR Antibiosis[Mesh] OR “Lactococcus”[Mesh] OR Probiotics[tiab] OR Probiotic[tiab] OR Synbiotics[tiab] OR Synbiotic[tiab] OR Lactobacillus[tiab] OR Lactobacilli[tiab] OR Bifidobacteria[tiab] OR Bifidobacterium[tiab] OR Saccharomyces[tiab] OR Saccharomyce[tiab] OR “Microbial dietary supplements”[tiab] OR Yoghurt[tiab] OR “Fermented milk”[tiab] OR “Cultured Milk”[tiab] OR “Fermented Dairy”[tiab] OR Acidophilus[tiab] OR Antibiosis[tiab] OR “Microbial Antagonism”[tiab] OR “Microbial Antagonisms”[tiab] OR “Bacterial Interferences”[tiab] OR “Bacterial Interference”[tiab] OR “Streptococcus thermophilus”[tiab] OR “Bacillus laterosporus”[tiab] OR “Pediococcus acidilactici”[tiab] OR Lactococcus[tiab] OR Lactis[tiab])

AND

(“Respiratory Tract Infections”[Mesh] OR “Respiratory tract infection”[tiab] OR “Respiratory tract infections”[tiab] OR “Respiratory infection”[tiab] OR “Respiratory infections”[tiab] OR urti[tiab] OR uri[tiab] OR ari[tiab] OR “Otitis Media”[Mesh] OR “Otitis Media”[tiab] OR “Glue ear”[tiab] OR AOM[tiab] OR OME[tiab] OR (“Middle Ear”[tiab] AND (Infection[tiab] OR Infections[tiab] OR Inflammation[tiab] OR Inflammations[tiab])))

AND

((Randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR randomised[tiab] OR placebo[tiab] OR “drug therapy”[sh] OR randomly[tiab] OR trial[tiab] OR groups[tiab])

NOT (Animals[Mesh] not (Animals[Mesh] and Humans[Mesh])))

CONTRIBUTIONS OF AUTHORS

Draft the protocol: AMS, KG, EB, KR, JC, PL, CDM

Develop the search strategy: JC

Run the search strategy: JC

Obtain copies of studies: JC

Select which studies to include: AMS, JC

Extract data from studies: AMS, JC

Enter data into Review Manager 5: AMS, JC, EB

Carry out the analysis: EB

Interpret the analysis: AMS, KG, EB, KR, JC, PL, CDM

Draft the final review: AMS, KG, EB, KR, JC, PL, CDM

Check correct use of grammar: CDM

Update the review: AMS, CDM

DECLARATIONS OF INTEREST

Anna M Scott: Salary funded by the Centre for Research Excellence in Minimising Antibiotic Resistance from Acute Respiratory Infections (CREMARA), which itself is funded by the National Health and Medical Research Council (NHMRC), Australia.

Elaine Beller: This review was supported in part by research grants from the NHMRC, Australia, to the Centre for Evidence-Based Practice, Bond University.

Justin Clark: Salary funded by the Centre for Research Excellence in Minimising Antibiotic Resistance from Acute Respiratory Infections (CREMARA), which itself is funded by the National Health and Medical Research Council (NHMRC), Australia.

Kristian Roos: I am a minor shareholder of a small biomedical company (ESSUM AB). This company has been doing research for many years with probiotic bacteria. ESSUM AB has no patent in probiotic bacteria that might be used for acute otitis media, and ESSUM has no intention of doing research into acute otitis media.

Keith Grimwood: None known.

Paul Little: A study PL was Chief Investigator for, had placebo and probiotic tablets provided by a commercial company that makes probiotic (Cultech).

Chris Del Mar: reports CREMARA institutional funding (NHMRC); Cochrane Acute Respiratory Infections Group institutional funding (NHMRC); institutional and personal funding from the Australian Commission on Safety and Quality in Health Care for the development of patient decision aids; personal consulting funding for shared decision-making implementation (BUPA, UK); American College of Physicians (ACP) Journal Club editorial work; consultancy/providing advice to a pharmaceutical company about a proposed vaccine that might be effective against otitis media in children.

SOURCES OF SUPPORT

Internal sources

- There are no internal sources of support to report., Other.

External sources

- There are no external sources of support to report., Other.