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[Intervention Review]

Antibiotics for prolonged wet cough in children

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ABSTRACT

Background

Cough is a frequent symptom presenting to doctors. The most common cause of childhood chronic (greater than fours weeks' duration) wet cough is protracted bacterial bronchitis (PBB) in some settings, although other more serious causes can also present this way. Timely and effective management of chronic wet or productive cough improves quality of life and clinical outcomes. Current international guidelines suggest a course of antibiotics is the first treatment of choice in the absence of signs or symptoms specific to an alternative diagnosis. This review sought to clarify the current evidence to support this recommendation.

Objectives

To determine the efficacy of antibiotics in treating children with prolonged wet cough (excluding children with bronchiectasis or other known underlying respiratory illness) and to assess risk of harm due to adverse events.

Search methods

We undertook an updated search (from 2008 onwards) using the Cochrane Airways Group Specialised Register, Cochrane Register of Controlled Trials (CENTRAL), MEDLINE, Embase, trials registries, review articles and reference lists of relevant articles. The latest searches were performed in September 2017.

Selection criteria

We included randomised controlled trials (RCTs) comparing antibiotics with a placebo or a control group in children with chronic wet cough. We excluded cluster and cross-over trials.

Data collection and analysis

We used standard methods as recommended by Cochrane. We reviewed results of searches against predetermined criteria for inclusion. Two independent review authors selected, extracted and assessed the data for inclusion. We contacted authors of eligible studies for further information as needed. We analysed data as 'intention to treat.'

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Main results

We identified three studies as eligible for inclusion in the review. Two were in the previous review and one new study was included. We considered the older studies to be at high or unclear risk of bias whereas we judged the newly included study at low risk of bias. The studies varied in treatment duration (from 7 to 14 days) and the antibiotic used (two studies used amoxicillin/clavulanate acid and one used erythromycin).

We included 190 children (171 completed), mean ages ranged from 21 months to six years, in the meta-analyses. Analysis of all three trials (190 children) found that treatment with antibiotics reduced the proportion of children not cured at follow-up (primary outcome measure) (odds ratio (OR) 0.15, 95% confidence interval (CI) 0.07 to 0.31, using intention-to -treat analysis), which translated to a number needed to treat for an additional beneficial outcome (NNTB) of 3 (95% CI 2 to 4). We identified no significant heterogeneity (for both fixed-effect and random-effects model the I^2 statistic was 0%). Two older trials assessed progression of illness, defined by requirement for further antibiotics (125 children), which was significantly lower in the antibiotic group (OR 0.10, 95% CI 0.03 to 0.34; NNTB 4, 95% CI 3 to 5). All three trials (190 children) reported adverse events, which were not significantly increased in the antibiotic group compared to the control group (OR 1.88, 95% CI 0.62 to 5.69). We assessed the quality of evidence GRADE rating as moderate for all outcome measures, except adverse events which we assessed as low quality.

Authors' conclusions

Evidence suggests antibiotics are efficacious for the treatment of children with chronic wet cough (greater than four weeks) with an NNTB of three. However, antibiotics have adverse effects and this review reported only uncertainty as to the risk of increased adverse effects when they were used in this setting. The inclusion of a more robust study strengthened the previous Cochrane review and its results.

PLAIN LANGUAGE SUMMARY

Antibiotics for prolonged moist cough in children

Background

Cough is the most common symptom which presents to doctors. Current recommendations suggest treating prolonged wet cough with antibiotics. We examined whether antibiotics are useful in treating children who have an ongoing persistent wet cough.

Study characteristics

We included randomised controlled trials that compared antibiotics with a placebo (pretend treatment) or control group. The children included in the trials had wet cough lasting more than 10 days.

The evidence is current to September 2017.

We found three studies that varied in a number of ways including different antibiotics (two studies used amoxicillin/clavulanate acid and one used erythromycin) and length of treatment was seven or 14 days.

The mean ages of the children ranged from 21 months to six years.

Key results

This review, involving 190 children with persistent wet cough, found that antibiotics were beneficial in curing the cough. The cure rate was one child cured for every three children treated. Antibiotics also prevented the illness from getting worse, thus avoiding a further course of antibiotics, for one in every four children treated. We found no clear evidence about whether antibiotics were associated with more side effects. We could not assess long-term results.

Reliability of the evidence

The reliability of the evidence was moderate when using antibiotics to cure cough and for illness progression, while it was only low for side effects of medicines.

Take home message

Antibiotics are effective in treating children with chronic (greater than four weeks) wet cough and could be considered when they present to doctors.

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SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Antibiotics compared to placebo for prolonged wet cough in children

Patient or population: prolonged wet cough in children
Setting: paediatric outpatients
Intervention: antibiotics
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with placebo	Risk with antibiotics				
Children not cured or substantially improved at follow-up (using intention-to-treat analysis) (measured as proportion of participants) Follow-up: range 7-14 days	76 per 100	32 per 100 (18 to 49)	**OR 0.15** (0.07 to 0.31)	190 (3 RCTs)	⊕⊕⊕◯ **Moderate**[a]	-
Children with progression of the disease resulting in additional medical therapy (complications) (measured as proportion of participants) Follow-up: range 7-14 days	36 per 100	5 per 100 (17 to 163)	**OR 0.10** (0.03 to 0.34)	125 (2 RCTs)	⊕⊕⊕◯ **Moderate**[b]	-
Children experiencing adverse effects of antibiotics (e.g. diarrhoea, nausea, skin rash, allergic reactions	5 per 100	10 per 100 (3 to 25)	**OR 1.88** (0.62 to 5.69)	190 (3 RCTs)	⊕⊕◯◯ **Low**[c]	-

(measured as proportion of participants))		

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **OR:** odds ratio; **RCT:** randomised controlled trial.

GRADE Working Group grades of evidence
High quality: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low quality: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low quality: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

[a]One study carrying 46% of the analysis weight was at high risk of bias due to lack of blinding. Downgraded one level for risk of bias (Darelid 1993).
[b]One study carrying 87% of the analysis weight was at high risk of bias due to lack of blinding. Downgraded one level for risk of bias (Darelid 1993).
[c]One study carrying 10% of the analysis weight was at high risk of bias due to lack of blinding and the result has been downgraded for imprecision due to wide CIs. Downgraded two levels for risk of bias and imprecision.

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BACKGROUND

Description of the condition

Internationally cough is consistently the most common symptom for presentation to primary care physicians (Britt 2016). In 2015 in Australia, data showed 9.4% of acute presentations to doctors were due to a coughing illnesses (Britt 2016). The magnitude of the problem is illustrated by the amount spent globally on non-prescription (over-the-counter) medications for cough. In the US, several billion dollars are spent annually on cough and cold pharmaceuticals (Irwin 2014). The burden to families of both acute and chronic cough in children is reflected in both the high frequency of medical visits and use of non-prescription medications (Anderson-James 2015; Marchant 2008). One study looking specifically at children with chronic cough found higher levels of parental stress and worry that resolved when the cough ceased, highlighting the need for appropriate and timely management (Marchant 2008).

Chronic childhood cough is defined as cough lasting more than four weeks, accepted internationally in all childhood cough guidelines other than two country-specific guidelines (Chang 2016a). In addition to the classification based on duration, cough can be classified as wet/productive or dry. As young children are usually unable to expectorate, the term 'wet' cough is used instead of the term 'productive' cough as used in adults (Chang 2003). Wet and dry cough can be clinically well differentiated by both physicians and parents (Chang 2005). Wet cough is representative of the presence of lower airway secretions (defined on bronchoscopy) and hence is a symptom with strong clinical validity (Chang 2005). In children with chronic wet cough, one systematic review found that the majority of studies described that most of these children had lower airway infection with common respiratory pathogens (*Haemophilus influenzae*, *Streptococcus pneumoniae*, *Moraxella catarrhalis*) in the bronchoalveolar lavage (BAL) or sputum (Chang 2016b).

One study investigating 108 children presenting with chronic cough found that protracted bacterial bronchitis (PBB) to be the final diagnosis in approximately 40% of the children (Marchant 2006). Since the first description of PBB (Marchant 2006), the diagnostic entity of PBB has been incorporated into cough guidelines and supported by prospective and retrospective research from many parts of the world (Chang 2016b; Chang 2016c; Kompare 2012; Wang 2015; Wurzel 2014).

Clinically PBB is now defined as a chronic (greater than four weeks) wet cough without specific signs or symptoms of alternative cause which responds to two weeks of appropriate antibiotic therapy (Chang 2016b). Initial a priori definitions of PBB included a positive BAL fluid culture with a growth of a bacterial species greater than 10^4 colony-forming units (CFU)/mL which showed growth of common respiratory pathogens (*Haemophilus influenzae*, *Streptococcus pneumoniae*, *Moraxella catarrhalis*) (Marchant 2006). However, it was impractical to do a flexible bronchoscopy and BAL on all children presenting with chronic wet cough and hence the clinical definition of PBB now used arose (Chang 2012; Chang 2016b). Internationally, numerous prospective and retrospective studies in children with chronic wet cough have found PBB to be the most common cause (Asilsoy 2008; Donnelly 2007; Kompare 2012; Usta 2014). A response to oral antibiotics is a universal finding in these studies as it is a key part of the clinical definition of PBB, yet the duration, although typically two to four weeks, and type of antibiotic varies in all studies and remains ill-defined in current literature (Chang 2016b).

Given the definition of PBB and the current recommendations to treat children with chronic wet cough who do not have any other specific cough pointers (e.g. clubbing, chest wall deformity, etc.) with antibiotics, a review that clarifies the current evidence for the use of antibiotics in children with chronic wet cough would inform and guide clinical practice.

Description of the intervention

Antibiotics are the mainstay of treating bacterial infections for all ages. There are different forms of antibiotics that can be used for respiratory system infections; oral (suspension, tablets, capsules), inhaled or intravenous. The reasons why antibiotics may be useful for children with wet cough are outlined below.

The most widely accepted antibiotic for treatment of wet cough is oral amoxicillin/clavulanic acid (as typical pathogens, such as *Haemophilus influenzae* and*Moraxella catarrhalis*, can be resistant to amoxicillin) although a macrolide, oral cephalosporin or trimethoprim-sulfamethoxazole are alternatives when a person has a history of penicillin hypersensitivity (Chang 2016c).

How the intervention might work

Studies that have examined the microbiology of the lower airways in children with chronic wet cough have shown common respiratory pathogens with *Haemophilus influenzae* being the most common found in 28% to 58% children, followed by*Streptococcus pneumoniae* (13% to 58%) and *Moraxella catarrhalis* (17% to 59%) (Chang 2006a; De Baets 2012; Douros 2011; Gedik 2015; Kompare 2012; Marchant 2006; Zgherea 2012). Marchant 2006 was the first study of PBB which described the same organisms that have been supported by subsequent studies into microbiology of PBB (Chang 2016c). Hence, given the known bacteriology of this condition, antimicrobials active against these common respiratory pathogens (*Haemophilus influenzae*, *Streptococcus pneumoniae*, *Moraxella catarrhalis*) are likely be effective in bacterial eradication and clinical cure with cough resolution.

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Why it is important to do this review

Appropriate management of children with chronic wet cough is important for several reasons as outlined below.

Attaining prompt resolution of chronic cough is important for parents. Irrespective of the cause of chronic cough, the high level of parental stress and worry and financial burden within this population has been clearly described (Marchant 2008). When the cough resolves, the health-related quality of life improves (generic and cough-specific) (Chang 2013).

As our knowledge of chronic childhood cough and PBB has progressed rapidly in recent years (Chang 2016c; Wurzel 2016), the importance of antibiotic treatment has been incorporated into international cough guidelines (Chang 2006b; Gibson 2010; Shields 2008); therefore, a systematic review of its effectiveness will highlight the suitability of this recommendation. Although it is suggested in all current guidelines that children receive antibiotic therapy, the duration varies with Australian guidelines suggesting two weeks as initial treatment trial (Gibson 2010), while the British Thoracic Society guidelines suggest all children receive four to six weeks of antibiotic therapy (Shields 2008). Hence, an evidence-based systematic review of RCTs, separating the analysis into short- and long-term treatment, is needed to inform current guidelines while also highlighting gaps in knowledge and therefore guide future research.

Further, it has been postulated that PBB, chronic suppurative lung disease and bronchiectasis lie within the same disease spectrum with PBB at the mild end and bronchiectasis at the severe end of this spectrum (Chang 2008; Goyal 2016a; Goyal 2016b). PBB if left untreated may lead to disease progression and radiological bronchiectasis. This is supported by the shared bacterial pathogens, airway neutrophilic inflammation and impaired airway clearance in the different diagnostic entities (Chang 2008), and in keeping with Coles vicious circle hypothesis whereby it is thought that persistent bacterial infection and the associated inflammation results in damage to the airway mucosa and wall over time hence altering airway clearance (Cole 1986). Furthermore, it is now thought that early bronchiectasis is reversible (Gaillard 2003), and hence timely treatment of children with chronic wet cough may interrupt this vicious cycle and preserve future lung health.

In our current era of antimicrobial stewardship, appropriate use of antibiotics is important. If antibiotics are not efficacious in improving clinical outcomes of children with chronic wet cough, they should not be used. If efficacious, their use should be promoted and the balance between benefit and adverse events described. This review will thus inform clinical practice.

OBJECTIVES

To determine the efficacy of antibiotics in treating children with prolonged wet cough (excluding children with bronchiectasis or other known underlying respiratory illness) and to assess risk of harm due to adverse events.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised controlled trials comparing antibiotics with a placebo medication or 'no treatment' control group. We excluded cross-over and cluster trials.

Types of participants

All trials that included children under 18 years of age with prolonged wet cough (longer than 10 days*). We planned a priori subgroup analyses for children under seven years of age and cough lasting over four weeks. Exclusion criteria: already known to have radiological evidence of bronchiectasis or lung histopathological evidence of bronchiectasis; already known to have a diagnosis of cystic fibrosis; cough related to *Mycoplasma pneumoniae* (which causes pneumonia), *Bordetella pertussis* (which causes whooping cough) and *Chlamydia;* presence of underlying cardiorespiratory condition (haemoptysis, recurrent pneumonia, chronic dyspnoea); current or recurrent wheeze (over two episodes); presence of the respiratory signs of clubbing or wheeze on auscultation (wheeze could be a sign of asthma); presence of any sign of systemic illness (failure to thrive, aspiration, neurological or developmental abnormality and immune deficiencies).

*Ideally, this review would include only studies recruiting children with cough persisting for four weeks or more (current definition of chronic cough in children), but as definitions have changed over time and this review dates back to 2005, this more inclusive cut-off has been maintained. See Overall completeness and applicability of evidence for further discussion.

Types of interventions

All randomised controlled comparisons of antibiotics versus placebo or control group in the management of prolonged wet cough. Antibiotics could be given via any route. We did not include trials comparing two or more antibiotics without a placebo arm.

We planned to evaluate three separate treatment regimens:

- short-term treatment (14 days or less);
- long-term antibiotics (more than 14 days);
- intravenous antibiotic treatment where antibiotics were given for at least five days.

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We included trials that allowed the use of other medications or interventions if all participants had equal access to such medications or interventions or if the additional therapies were regarded as ineffective.

Types of outcome measures

We made attempts to obtain data on at least one of the following outcome measures.

Primary outcomes

- Children not cured or not substantially improved at follow-up (measured as proportion of participants). We determined the children who failed to improve on treatment and the mean clinical improvement using the following hierarchy of assessment measures (i.e. where two or more assessment measures were reported in the same study, we used the outcome measure listed first).
    - Objective measurements of cough indices (cough frequency, cough receptor sensitivity, cough amplitude).
    - Symptomatic (Likert scale, visual analogue scale, level of interference of cough, cough diary, sputum production - quantity and colour, general well-being) - assessed by the child.
    - Symptomatic (Likert scale, visual analogue scale, level of interference of cough, cough diary, sputum production - quantity and colour, general well-being) - assessed by the parents/carers.
    - Symptomatic (Likert scale, visual analogue scale, level of interference of cough, cough diary, sputum production - quantity and colour, general well-being) - assessed by clinicians.
    - Airway markers (sputum or BAL) consistent with infection or inflammation.
    - Sputum volume alone.
    - Lung function tests alone.

Secondary outcomes

- Change in clinical state (mean difference).
- Difference in sputum, BAL or blood indices of inflammation or infection (mean improvement in markers of infection).
- Improvement in cough indices (cough diary, cough frequency, cough scores, quality of life) (measured as mean difference).
- Children with progression of the disease resulting in additional medical therapy (complications) (proportion of participants).
- Children experiencing adverse effects of antibiotics (e.g. diarrhoea, nausea, skin rash, allergic reactions (proportion of participants)).

For studies where data were not available on any of the prespecified outcome measures but the study was eligible for inclusion, we planned to describe the outcome measures in the Characteristics of included studies table. However, these studies would not have been included in the meta-analyses.

Search methods for identification of studies

Electronic searches

The last search for this review according to the method specified in the protocol was undertaken in 2010. For this update, we conducted a search of the following databases:

- the Cochrane Airways Group Register of Trials (searched 22 September 2017);
- Cochrane Central Register of Controlled Trials (CENTRAL), through the Cochrane Register of Studies Online (searched 22 September 2017);
- MEDLINE OvidSP (1950 to September 2017);
- Embase OvidSP (1974 to 22 September 2017).

The database search strategies are provided in Appendix 1. We also conducted a search of ClinicalTrials.gov (www.clinicaltrials.gov) and the World Health Organization (WHO) trials portal (www.who.int/ictrp/). We searched all databases from their inception to September 2017 and we imposed no restriction on language of publication. Elizabeth Stovold from the Cochrane Airways Group undertook the search.

Searching other resources

We checked reference lists of all primary studies and review articles for additional references. We searched relevant manufacturers' websites for trial information.

We searched for errata or retractions from included studies published in full-text on PubMed (www.ncbi.nlm.nih.gov/pubmed) on 22 September 2017.

Data collection and analysis

We included in the subsequent meta-analyses the results from studies that met the inclusion criteria and reported any of the outcomes of interest. We calculated odds ratios (OR) and 95% confidence interval (CI) (fixed-effects model) using the inverse of the variance of each study result for weighting (RevMan 2014). We calculated number needed to treat (NNT) from the pooled OR and its 95% CI applied to a specified baseline risk using an online calculator (Cates 2008). This calculator converts the risk in the placebo group to the corresponding odds, applies the OR to estimate the odds in the treated group, and converts that odds to the corresponding risk and calculates the risk difference, the inverse of which is the NNT. We assumed the cough indices to be normally distributed continuous variables and so we estimated the

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mean difference (MD) in outcomes. If studies reported outcomes using different measurement scales, we estimated the standardised mean difference (SMD). We described any heterogeneity between the study results and tested to see if it reached statistical significance using a Chi² test. We included the 95% CI estimated using a random-effects model whenever we had concerns about statistical heterogeneity.

We planned to test publication bias be tested by use of a funnel plot.

Selection of studies

The original selection of studies was reported in the previous review (Marchant 2005). Retrieval of studies for this update: from the title, abstract or descriptors, two review authors (JM, HP) independently reviewed literature searches and identified potentially relevant trials for full review. We also conducted searches of bibliographies and texts to identify additional studies. Using specific criteria, the same two review authors independently selected trials for inclusion in the review. We planned to resolve disagreement by third party adjudication (AC).

Two review authors (JM, HP) independently reviewed trials that satisfied the inclusion criteria. We recorded the following information: study setting; year of study; source of funding; participant recruitment details (including number of eligible children); inclusion and exclusion criteria; randomisation and allocation concealment method; numbers of participants randomised; blinding (masking) of participants, care providers and outcome assessors; dose and type of antibiotic therapy; duration of therapy; cointerventions; numbers of patients not followed up; reasons for withdrawals from study protocol (clinical, adverse effects, refusal and other); details on adverse effects of therapy; and whether intention-to-treat analyses were possible. We recorded the selection process in sufficient detail to complete the PRISMA flow diagram (Figure 1).

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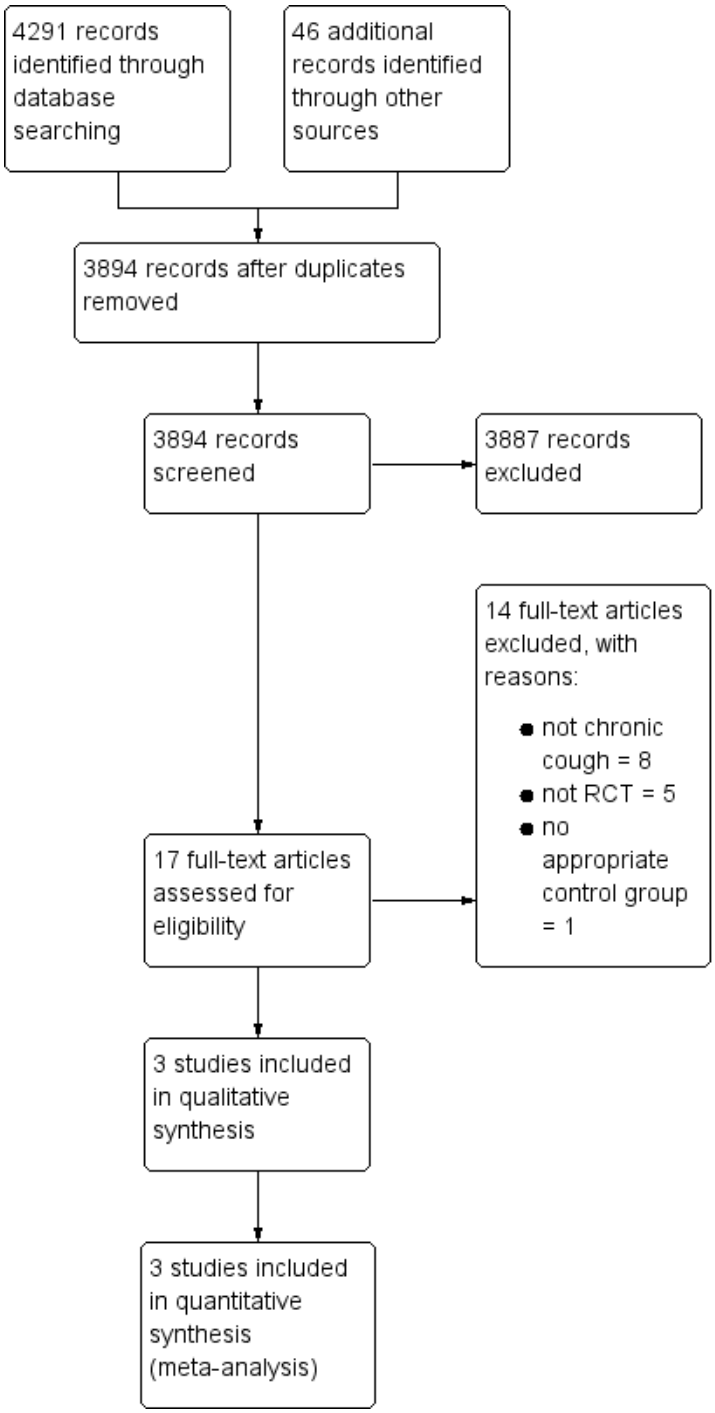
Figure 1. Study flow diagram.



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Data extraction and management

We extracted study characteristics from included studies.

- Methods: study design, total duration of study, number of study centres and location, study setting, withdrawals, date of study.
- Participants: number, mean age, age range, gender, length of cough, inclusion criteria and exclusion criteria.
- Interventions: antibiotic used, placebo, duration, concomitant medications and excluded medications.
- Outcomes: primary and secondary outcomes specified and collected, and time points.
- Notes: funding for trial, and notable conflicts of interest of trial authors.

Two review authors (JM, HP) independently extracted outcome data from included studies from searches. We noted in the Characteristics of included studies table if outcome data were not reported in a usable way. We planned to resolve disagreements by consensus or by involving a third review author (AC). One review author (JM) transferred data into Review Manager 5 (RevMan 2014). We double-checked that data were entered correctly by comparing the data presented in the systematic review with the study reports. A second review author (HP) checked the studies' characteristics for accuracy against the trial report.

Assessment of risk of bias in included studies

Two review authors (JM, HP) independently assessed risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We planned to resolve any disagreements by discussion or by involving another review author (AC). We assessed the risk of bias according to the following domains.

- Random sequence generation.
- Allocation concealment.
- Blinding of participants and personnel.
- Blinding of outcome assessment.
- Incomplete outcome data.
- Selective outcome reporting.
- Other bias.

We graded each potential source of bias as high, low or unclear and provided a quote from the study report together with a justification for our judgement in the 'Risk of bias' table. We then summarised the risk of bias judgements across different studies for each of the domains listed. We planned to assess blinding separately for different key outcomes where necessary (e.g. for unblinded outcome assessment, risk of bias for all-cause mortality may be very different than for a participant-reported pain scale).

Where information on risk of bias related to unpublished data or correspondence with a trial author, we noted this in the 'Risk of bias' table. One review author (PM) independently undertook the risk of bias assessment for Marchant 2012 as several review authors also authored this trial. In addition, the Cochrane Airways editorial staff independently agreed the judgements of risk of bias for Marchant 2012.

When considering treatment effects, we took into account the risk of bias for the studies that contributed to that outcome.

Measures of treatment effect

We analysed dichotomous data as ORs. We undertook meta-analyses only where it was meaningful (i.e. if the treatments, participants and the underlying clinical question were similar enough for pooling to make sense).

We narratively described skewed data which was reported as medians and interquartile (IQR) ranges.

Where a trial reported multiple arms, we included only the relevant arms. Where we combined two comparisons (e.g. drug A versus placebo and drug B versus placebo) in the same meta-analysis, we halved the control group to avoid double counting.

For continuous outcomes, we planned to record the mean relative change from baseline for each group or mean post-treatment or postintervention values and standard deviation (SD). If standard errors or CIs had been reported, we planned to calculate the SDs and then a pooled estimate of treatment effect by the MD and 95% CI (fixed-effect model) using Review Manager 5 (RevMan 2014)

Unit of analysis issues

We calculated OR for the dichotomous outcome variables of each individual study, using a modified intention-to-treat analysis. This analysis assumed that children not available for outcome assessment had not improved (and probably represented a conservative estimate of effect). An initial qualitative comparison of all the individually analysed studies examined whether pooling of results (meta-analysis) was reasonable. This took into account differences in study populations, inclusion/exclusion criteria, interventions, outcome assessment and estimated effect size.

Dealing with missing data

We contacted investigators or study sponsors in order to verify key study characteristics and obtain missing numerical outcome data where possible (e.g. when a study was identified as abstract only). Where this was not possible, and we thought the missing data might introduce serious bias, we explored the impact of including

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such studies in the overall assessment of results with a sensitivity analysis.

Assessment of heterogeneity

We described any heterogeneity between study results and tested to see if it reached statistical significance using a Chi² test. We planned to report the 95% CI estimated using a random-effects model whenever we had concerns about statistical heterogeneity. Heterogeneity was considered significant when the P value was less than 0.10 (Higgins 2011). We then used the I² statistic to measure heterogeneity among the trials in each analysis,
where heterogeneity was categorised such that a value of under 25% was considered low, 25% to 75% was considered moderate and over 75% was considered a high degree of heterogeneity (Higgins 2011).

Assessment of reporting biases

We were not able to pool more than 10 trials, so did not create and examine a funnel plot to explore possible small-study and publication biases.

Data synthesis

We included in the subsequent meta-analyses the results from studies that met the inclusion criteria and reported any of the outcomes of interest. We calculated the summary weighted OR and 95% CI (fixed-effect model) using Review Manager 5 (RevMan 2014). We calculated numbers needed to treat for an additional beneficial outcome (NNTB) from the pooled OR and its 95% CI applied to a specified baseline risk using an online calculator (Cates 2008).

'Summary of findings' table

We created a 'Summary of findings' table using the following outcomes:

- children not cured or not substantially improved at follow-up (using intention-to-treat analysis);
- children with progression of the disease resulting in additional antibiotic therapy (complications) (proportion participants);
- children experiencing adverse effects of antibiotics (e.g. diarrhoea, nausea, skin rash, allergic reactions (proportion participants)).

We used 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 related to the studies which contributed data to the meta-analyses for the prespecified outcomes. We then used methods and recommendations described in Section 8.5 and Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), using GRADEpro GDT software (GRADEpro GDT). We justified all decisions to downgrade or upgrade the quality of studies using footnotes and we made comments to aid the reader's understanding of the review where necessary.

Subgroup analysis and investigation of heterogeneity

We planned the following a priori subgroup analyses.

- Age (children seven years or younger versus children eight years or older).
- Control type (placebo versus no placebo/usual treatment).
- Variation in the inclusion criteria (e.g. short duration therapy 14 days or less versus long duration therapy longer than 14 days).
- Antibiotic types (oral antibiotics versus intravenous antibiotics; studies using same antibiotic and duration).

Sensitivity analysis

We planned the following sensitivity analyses to assess the impact of the potentially important factors on the primary outcome.

- Intention to treat but only including participants not lost to follow-up (available-data analysis).
- Model used: fixed effect versus random effects, risk ratio (RR) versus OR.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies tables.

Results of the search

The updated Airways Group register/search, combined with original searches, identified 4291 potentially relevant titles (see Figure 1). We identified an additional 46 titles through searches of ClinicalTrials.gov and the WHO trials portal. We obtained 17 papers for consideration for inclusion in the review after the initial assessment of the abstracts. We excluded 14 papers as the study involved children with acute cough rather than chronic cough, or were non-randomised studies or reviews. In this updated review, we included one new study (Marchant 2012).

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Included studies

We included three studies in total (see Characteristics of included studies table). The three studies included 190 randomised children with 171 children completing the trial (Darelid 1993; Gottfarb 1994; Marchant 2012).

Study design

The three studies included were single-centred studies and none received support from commercial interests. Two studies were conducted in a paediatric outpatient clinic in Sweden and both recruited children with over 10 days of cough (Darelid 1993; Gottfarb 1994). Marchant 2012 recruited children with chronic wet cough (greater than three weeks' duration) from a paediatric respiratory outpatient clinic in Australia. Although the inclusion criteria for duration of cough was short, the cough duration of the participants were longer in all the RCTs (described below under 'Participants'). A subgroup of children from one RCT had flexible bronchoscopy (FB) performed pretreatment and their BAL data were consistent with PBB (Marchant 2012).

One study was an open randomised study comparing erythromycin and a no treatment control group (Darelid 1993). Two studies compared amoxicillin/clavulanic acid and placebo in a double-blind RCT (Gottfarb 1994; Marchant 2012). Two studies used a dosage regimen equal to current recommended treatment dosage (Darelid 1993; Marchant 2012). The dosage in Gottfarb 1994 was lower (dosage 20 mg/kg/day) than currently recommended doses (22.5 mg/kg/day to 45 mg/kg/day) (Kemp 1997). Although the studies used two different antibiotics, both would treat the respiratory pathogens found in the nasopharyngeal aspirates of these children and organisms in BAL in other studies on chronic cough in children (Chang 2006a; Gedik 2015; Zgherea 2012). The children in one study all received oxymetazoline nose drops and salbutamol mixture was allowed and recorded in both groups (Darelid 1993). Neither of these treatments should have influenced the outcome since they were available to both groups. The other two trials did not allow cointerventions (Gottfarb 1994; Marchant 2012). One trial measured compliance by the return of the medication bottles (Marchant 2012). Darelid 1993 reported 97% of participants completed the erythromycin medication; however, they failed to state how this was assessed.

Participants

All three studies reported different length of cough in their participants. Around 50% of children had cough of greater than three weeks' duration in Darelid 1993, the mean length of cough was three to four weeks in Gottfarb 1994, and median length of cough was 11 to 15 weeks in Marchant 2012. The median age of participants in Darelid 1993 was not provided but 63% of the participants were aged one to three years. Median age of children in Gottfarb 1994 was 2.6 years. Likewise, the children in Marchant 2012 were preschool age with a median of 1.75 to 2.8 years. Although two studies did not specifically mention the quality of cough, contact with the authors confirmed that at least 75% of children had wet cough (Darelid 1993; Gottfarb 1994). Also, as both studies included nasopharyngeal aspirates which grew a range of bacterial pathogens, it is highly likely that these children had wet cough.

Interventions

The antibiotics and their duration varied in the studies. Two studies compared amoxicillin/clavulanic acid and placebo (Gottfarb 1994; Marchant 2012); however, the children in Gottfarb 1994 took the antibiotics for seven days, whereas the children in Marchant 2012 took the antibiotics for 14 days. The intervention arm in Darelid 1993 took erythromycin for seven days and the control group did not take any treatment.

Outcomes

Two studies used paediatrician assessment of clinical recovery as primary outcome measure but the day of assessment was different. Outcomes were assessed at day eight (Darelid 1993) and day 12 to 14 (Gottfarb 1994), so the results described only short-term effects. The primary outcome measure in both Swedish studies was paediatrician assessment of clinical outcome at follow-up. Participants were classified as cured or treatment failure. Both studies also reported parental assessment and used individual symptom scores as secondary outcome measures.

The Australian study used 'cough resolution' as their primary outcome (Marchant 2012). They defined this as an improvement of more than 75% from baseline cough score, or three days of being cough free for the study duration. Their secondary outcome measures were absolute change in cough score or change in verbal category descriptive (VCD). Thirty-seven of the 50 children underwent a bronchoscopy prior to commencing the intervention. The BAL microbiology in this subgroup identified typical respiratory pathogens including *Haemophilus influenzae* (14 children), *Streptococcus pneumonia* (nine children) and *Moraxella catarrhalis* (seven children). All these organisms were sensitive to amoxicillin/clavulanate acid.

Studies also documented adverse effects and progression of disease requiring further antibiotic therapy. Darelid 1993 also recorded and documented the elimination of nasopharyngeal pathogens in the intervention and control groups. Gottfarb 1994 excluded 15 children from the final analysis without indicating to which treatment group they were initially allocated. As contact with the authors was unsuccessful, we assumed that there were equal numbers of children in each group in the intention-to-treat analysis. Of the 15 children excluded, 12 had laboratory-confirmed *B pertussis* after randomisation which is a potential weakness of the study. Ideally the diagnosis of *B pertussis* would have been made prior

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to randomisation and then these children would not have been eligible to enter the study.

Excluded studies

We recorded the reasons for excluding the 14 studies in the Characteristics of excluded studies table. The reasons for exclusion were: children did not have a chronic cough (eight studies) or were not a randomised controlled trial comparing antibiotics with placebo or no-treatment control group (three studies) or were review articles (three studies).

Ongoing studies

We found no ongoing studies.

Risk of bias in included studies

Full details of risk of bias judgements can be found under the 'Risk of bias' section at the end of each study's details in the Characteristics of included studies table and are also summarised in Figure 2.

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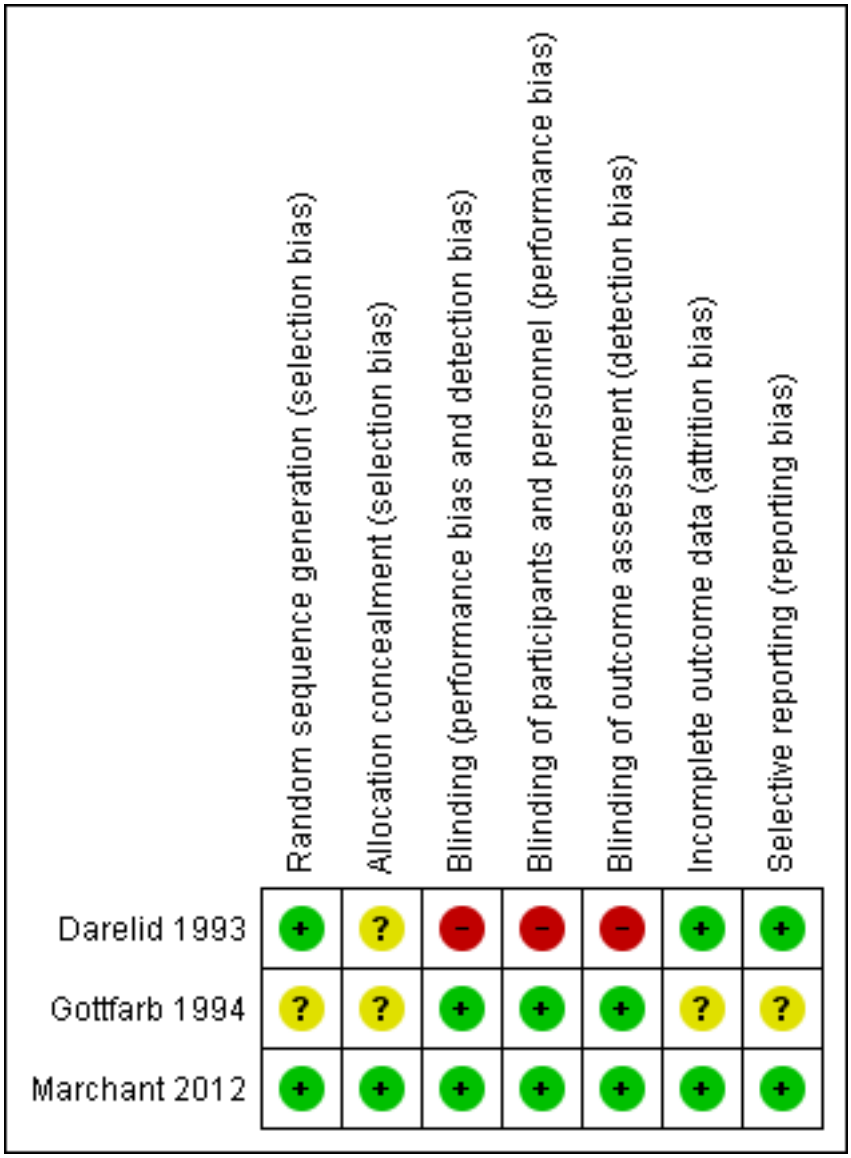
Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Two studies described generation of the randomisation sequence (Darelid 1993; Marchant 2012) and one study was unclear (Gottfarb 1994). We determined the method of allocation concealment to be adequate in one study (Marchant 2012), and unclear in two (Darelid 1993; Gottfarb 1994).

Blinding

Risk of detection bias was high in one study due to inadequate blinding of personnel, participants and outcome assessors (Darelid 1993). We judged the remaining two studies at low risk of bias due to adequate blinding (Gottfarb 1994; Marchant 2012).

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Incomplete outcome data

We assessed two studies at low risk of attrition bias (Darelid 1993; Marchant 2012). The other study was at unclear risk with 15 dropouts (Gottfarb 1994).

Selective reporting

We considered reporting bias to be low in two studies with all outcome measures being reported (Darelid 1993; Marchant 2012). We judged one study as unclear as there was not enough information provided in the published article (Gottfarb 1994).

Other potential sources of bias

We did not identify any other potential sources of bias in the included studies.

Effects of interventions

See: **Summary of findings for the main comparison** Antibiotics compared to placebo for prolonged wet cough in children

All included studies used only short-term treatment (14 days or less), that is, there were no studies of long-term treatment (more than 14 days) or intravenous antibiotics. Thus, all the effects of intervention refer to this group. See Summary of findings for the main comparison for the main comparisons

Primary outcome

Children not cured or not substantially improved at follow-up (measured as proportion of participants) (using intention-to-treat analysis)

We combined data from all included studies for children not cured or not substantially improved at follow-up. The number of children not cured at follow-up was 110 using an intention-to-treat analysis. The control event rate was 64% (Darelid 1993), 88% (Gottfarb 1994), and 84% (Marchant 2012) in the three studies. Treatment with antibiotics significantly reduced the proportion of children not cured at follow-up; the pooled OR effect estimate was 0.15 (95% CI 0.07 to 0.31; P < 0.00001; participants = 190, studies = 3; Analysis 1.1; Figure 3). These studies suggested that one child will be cured for every three children treated (NNTB 3, 95% CI 2 to 4) (Figure 4). Using GRADE, we assessed the strength of evidence to be moderate for this effect.

Figure 3. Forest plot of comparison: 1 Antibiotics versus no antibiotics/placebo for wet cough in children, outcome: 1.1 Children not cured or not substantially improved at follow-up (using intention-to-treat analysis).

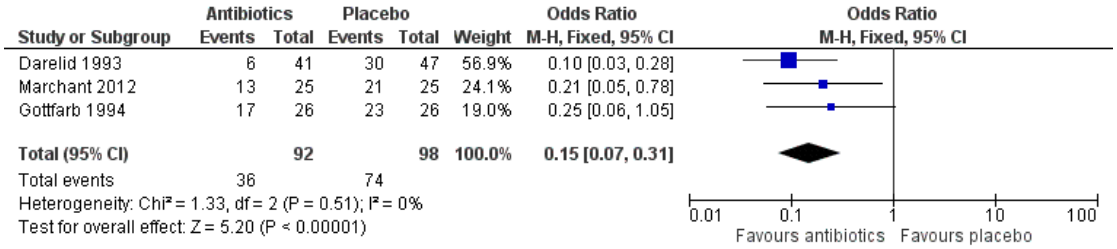

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Figure 4. In the control group, 75/100 people had not been cured over two weeks, compared to 31/100 (95% CI 17 to 48) for the active treatment group. Number needed to treat for an additional beneficial outcome 3 (95% CI 2 to 4).

Children not cured or not substantially improved at follow-up (measured as proportion of participants) (excluding those know to have *B pertussis*)

Two studies reported *B pertussis* data which could be combined for this outcome, hence we made the decision post-hoc to do an analysis excluding these children (Darelid 1993; Gottfarb 1994). The number of children not cured (excluding those with known *B pertussis*) was 17 in the antibiotics group versus 47 in the placebo group, which was statistically significant (OR 0.13, 95% CI 0.05 to 0.30; P < 0.00001; participants = 128; studies = 2; Analysis 1.4).

The data from Marchant 2012 could not be included in the meta-analysis as microbiological assessment for pertussis was not undertaken. However, they reported that 27/50 children had clinically important BAL microbiology (organism density of 10^4 or more CFU/mL BAL) with typical respiratory flora including *Haemophilus influenzae* (38%), *Streptococcus pneumoniae* (24%) and *Moraxella catarrhalis* (19%). They reported that all these organisms were sensitive to amoxicillin/clavulanate acid.

Secondary outcomes

Change in clinical state (mean difference)

All studies reported overall improvement in the antibiotic group but data could not be combined for this outcome.

Difference in sputum, bronchoalveolar lavage or blood indices of inflammation or infection (mean improvement in markers of infection)

Darelid 1993 examined clearance of potential pathogens from the nasopharynx using bacteriology. It found a significant higher elimination of *Moraxella catarrhalis* from the nasopharynx in treated (68%) versus untreated participants (20%; P < 0.001). There were

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similar results for *Streptococcus pneumoniae* (treated elimination 100%; untreated 23%; P < 0.0001). They also found a correlation with growth of *Moraxella catarrhalis* and persistent cough after the trial. In the untreated group, 80% of participants with untreated *Moraxella catarrhalis* continued to cough versus 33% of participants with no growth of this organism (P < 0.01). None of the studies provided data on the change in the analysis of sputum, BAL or blood indices of infection before and after treatment.

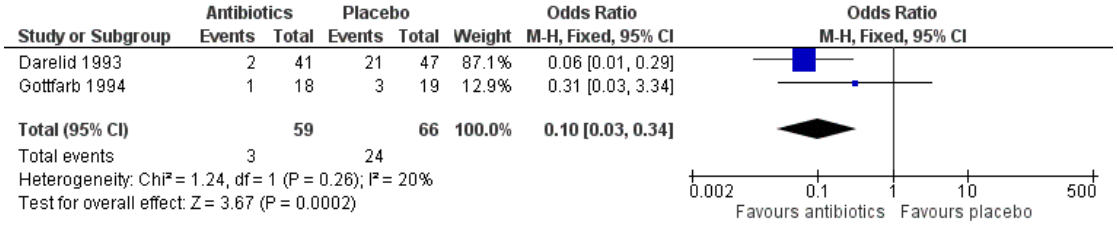
Improvement in cough indices (cough diary, cough frequency, cough scores, quality of life) (measured as mean difference)

All studies reported an improvement in a type of score that involved cough. These measures could not be combined due to the differing nature of the indices. Darelid 1993 used a score which combined cough frequency, morning temperature and level of daily activity, but provided no numerical value. Gottfarb 1994 looked at the number of coughing attacks in a 24-hour period but a single numerical value could not be obtained as data were expressed as proportion of children in each category. They reported a greater reduction in the coughing attacks in the antibiotic group compared to the placebo group. Marchant 2012 used a validated cough diary and reported a significant difference between the treatment group and the placebo group and found that the median improvement in cough score was significantly higher in the antibiotic group (1.5, IQR 0 to 2.5) compared to the control group (0.5, IQR -0.4 to 1.0; P = 0.02).

Children with progression of the disease resulting in additional medical therapy (complications) (proportion of participants)

Overall 125 children contributed data on this outcome (excluding the 15 dropouts in Gottfarb 1994). Marchant 2012 did not record further antibiotic use and therefore could not be included in this analysis. The overall control event rate for complications was 36% versus a treatment event rate of 5%. Progression of illness, as defined by requirement for further antibiotics in both studies (Darelid 1993; Gottfarb 1994), was significantly lower in the treatment group (OR 0.10, 95% CI 0.03 to 0.34; P = 0.0002; Analysis 1.2; Figure 5). The NNTB to avoid progression of disease was 4 (95% CI 3 to 5). Using GRADE, we assessed the quality the of evidence to be moderate for this effect.

Figure 5. Forest plot of comparison: 1 Antibiotics versus no antibiotics/placebo for wet cough in children, outcome: 1.4 Illness progression: participants with progression of disease resulting in additional medical therapy required.



Children experiencing adverse effects of antibiotics (e.g. diarrhoea, nausea, skin rash, allergic reactions) (proportion of participants)

In Darelid 1993, children in the erythromycin group had a reported adverse effect rate of 2% (Darelid 1993). These were diarrhoea and vomiting. It can be argued that these results should not been pooled as Darelid 1993 did not report any adverse effects for the control group. The rate of adverse effects in the study comparing amoxicillin/clavulanic acid and placebo was 12% for both treatment and control groups (Gottfarb 1994). Marchant 2012 also used amoxicillin/clavulanic acid at a significantly higher dosage than Gottfarb 1994, and as such the reported adverse effect rate in their study was higher at 20% in the treatment group and 8% in the control group. Pooling the results, assuming that no one in the control (no treatment) group in Darelid 1993 had any adverse events gave an OR of 1.88 (95% CI 0.62 to 5.69; P = 0.26; participants = 190; studies = 3; Analysis 1.3). Given the wide CIs, this finding remains uncertain and one can neither be certain of harm, or otherwise, from adverse effects of intervention.

Subgroup analyses

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Children under seven years of age

Two studies recruited children aged under seven years (Darelid 1993; Gottfarb 1994), and the mean age for the remaining study was under three years (SD 0.9) in both control and placebo group (Marchant 2012); hence, subgroup analysis was unnecessary.

Control type (placebo versus no placebo/usual treatment)

Two studies used a placebo (Gottfarb 1994; Marchant 2012). When compared to the one study that used a no-treatment control group (Darelid 1993), both subgroups continued to favour antibiotics over control and in terms of children not cured or substantially improved. The test indicated no significant difference between subgroups (Chi^2 = 1.30, df = 1 (P = 0.25), I^2 = 23.1%; Analysis 1.5). However, the test was an underpowered due to low number of studies included.

Variation in the inclusion criteria (cough duration longer than four weeks)

Although the two earlier studies had about 50% of children with prolonged wet cough for over four weeks, we could not extract disaggregated data for numbers of children not cured or substantially improved (Darelid 1993; Gottfarb 1994). Marchant 2012 was the sole study where children had been coughing for longer than four weeks (although inclusion criterion was over three weeks). Thus, for this subgroup analysis, we compared data from Marchant 2012, with data from the remaining two studies. Again, both subgroups favoured antibiotics over control and the test for subgroup difference was negative (Chi^2 = 0.28, df = 1 (P = 0.59), I^2 = 0%; Analysis 1.6). However, the test was underpowered due to low number of studies included.

Antibiotic types (differences in the medications used in the intervention group)

Two studies used amoxicillin/clavulanic acid (Gottfarb 1994; Marchant 2012). We compared these studies to the single study using erythromycin (Darelid 1993). Both subgroups favoured antibiotics over control in terms of the number of children not cured or substantially improved and the test for subgroup difference was negative (Chi^2 = 1.30, df = 1 (P = 0.25), I^2 = 23.1%). However, the test was underpowered due to low number of studies included.

Sensitivity analyses

Sensitivity analysis by intention to treat but only including participants not lost to follow-up (available data analysis) for primary outcome

Combining the data from the three included studies using data that were available (as opposed to intention to treat), the proportion of children randomised to the antibiotics arm were significantly less likely to be 'not cured' compared to controls (OR 0.14, 95% CI 0.07 to 0.29; P < 0.00001; participants = 171; studies = 3; Analysis 1.8). The effect size was slightly reduced compared to the intention-to-treat analysis. The NNTB for benefit at the end of study was 3 (95% CI 2 to 4). Using GRADE, we assessed the strength of evidence to be moderate for this outcome.

Sensitivity analysis for primary outcome model used: fixed effect versus random effects, risk ratio versus odds ratio

There was no difference when a random-effects model was used versus a fixed-effect model (OR for primary outcome 0.15 (fixed) versus 0.15 (random)). Both the Chi^2 and I^2 statistical tools show low level of heterogeneity between the studies, with I^2 = 0% and Chi^2 = 1.33 for the primary outcome measure.

In the primary outcome (clinical failure), the overall estimate of effect and degree of statistical heterogeneity were sensitive to the model used for meta-analysis although they were still significant (pooled RR 0.51, 95% CI 0.39 to 0.66 (fixed-effect model, I^2 = 81%); pooled RR 0.51, 95% CI 0.28 to 0.95 (random-effects model, I^2 = 81%). Both results significantly favoured use of antibiotics to prevent progression of disease.

DISCUSSION

Summary of main results

This updated review found three studies eligible for inclusion. We included a total of 190 children with mean ages of 21 months to six years (171 completed) in the meta-analysis. The two older studies were included in the previous review (Darelid 1993; Gottfarb 1994), and we found one newly included study (Marchant 2012). The studies varied in treatment duration (seven to 14 days) and antibiotic used (two studies used amoxicillin/clavulanate acid and one used erythromycin).

The meta-analysis of the three studies involving 190 children found that antibiotics were effective in treating children with a chronic wet cough (our primary outcome). Three children (95% CI 2 to 4) need to be treated to achieve one clinical cure. The meta-analysis of children with "clinical cure" showed that in the treatment group, the event rate was 61% compared to the control group which had an event rate of 24% (OR 0.15, 95% CI 0.07 to 0.31). In the subgroup and sensitivity analyses of the primary outcome, the data consistently significantly favoured the antibiotic arm (compared to controls).

We also found that children who received antibiotics were significantly less likely to have progression of illness, defined by requirement for further antibiotics, compared to children who did not receive antibiotics (OR 0.10, 95% CI 0.03 to 0.34; 125 children included in analysis). The NNTB was four (95% CI 3 to 5).

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One can neither be certain of harm, or otherwise, from adverse effects of the intervention and this finding remained uncertain with a high degree of imprecision. Data could not be combined for any other secondary outcomes.

In summary, this systematic review has strengthened the previous review (Marchant 2005) by the addition of a robust RCT (Marchant 2012). Some assumptions about the data in the older studies were made for both studies (cough quality and equal drop-outs in intervention and control groups) and the lack of data on quality of cough in these studies allows the possibility of greater clinical heterogeneity of participants than one would anticipate. Despite the limitations outlined above, this meta-analysis provided clear evidence that antibiotics are effective in the treatment of chronic wet cough in children.

Overall completeness and applicability of evidence

In children, chronic cough is defined as cough duration of over four weeks (Chang 2016a). Ideally, this review would be restricted to children with cough lasting over four weeks, or at least include a subanalysis of these studies. When the original review was undertaken (Marchant 2005), the sole published chronic cough guideline defined chronic cough as more than three to eight weeks (Irwin 1998), and since then, the definition of chronic cough has been revised. Earlier studies used over 10 days of cough as the definition of prolonged cough (Darelid 1993; Gottfarb 1994). Certainly this would be classified as subacute cough in the available paediatric literature (Chang 2001). A percentage of children with cough of 10 days will cease spontaneously before three weeks (Hay 2002). Neither of the authors of Darelid 1993 and Gottfarb 1994 were able to separate those with cough for 10 to 21 days versus those with over 21 days cough although both studies had a large percentage of children with cough over three weeks (mean duration of cough in Gottfarb 1994 was three to four weeks (SD not provided) and in Darelid 1993 50% of children were coughing for more than 21 days). The decision to include these studies that enrolled some children with shorter duration cough was made because although spontaneous resolution may occur in some children it should occur equally in both treatment and placebo groups. Therefore, it was unlikely to alter the review outcome but may have limited the strength of it. Marchant 2012 used an enrolment protocol which included more than three weeks of cough, which at study inception was the current definition of wet cough (Irwin 1990; Irwin 1998). However, the median duration of cough in this study ranged was 15 weeks (IQR 9 to 59) in the treatment group and 11 weeks (IQR 4 to 28) in the control group, hence it is probable the vast majority of this group had cough longer than four weeks' duration in keeping with current guidelines. In addition, these children therefore plausibly represent the more severe spectrum of disease, again unlikely to alter the review outcome favourably but may limit the strength of it.

Both earlier studies used physician-assessed 'clinical cure' as the outcome measure but these were undefined (Darelid 1993; Gottfarb 1994). Marchant 2012 used a previously validated cough diary (VCD score for daytime cough; Chang 1998). This objective measure increases the robustness and clinical validity of this RCT, and hence the updated meta-analysis.

Although neither of the earlier studies assessed specifically differences in sputum, BAL or blood indices of inflammation and infection (Darelid 1993; Gottfarb 1994), Darelid 1993 looked at the organisms grown on nasopharyngeal aspirate and the clearance of these post-treatment. It showed a significant elimination of *Moraxella catarrhalis* from the nasopharynx of treated participants. Marchant 2012 performed a bronchoscopy and BAL in a subgroup of participants, 19 in treatment group and 18 in control group, and found neutrophilic airway inflammation (median neutrophil percentage 34.5% to 38.5%) and a growth of significant organisms in the majority of children. The microbiology identified typical respiratory organisms *Streptococcus pneumoniae* (24%), *Haemophilus influenzae* (38%) and*Moraxella catarrhalis* (19%), which was consistent with numerous studies that have looked at the microbiology of wet cough in children (De Baets 2012; Gedik 2015; Kompare 2012; Zgherea 2012). This BAL data would suggest the majority of children within this cohort had a diagnosis consistent with PBB; that is, chronic wet cough without specific signs of alternative cause which responds to two weeks of antibiotic therapy (Chang 2016c).

The three studies chosen different antibiotics and dosages, erythromycin (dosage of 50 mg/kg/day; Darelid 1993), amoxicillin/clavulanic acid (dosage of 20 mg/kg/day; Gottfarb 1994), and amoxicillin/clavulanic acid (dosage 45 mg/kg/day; Marchant 2012). Darelid 1993 trialled erythromycin, a macrolide antibiotic, which has traditionally covered the common pathogens found in the lower respiratory tract such as *Streptococcus pneumoniae* and *Haemophilus influenzae* (as well as the atypical pathogens such as *Mycoplasma* species) (Alvarez-Elcoro 1999). Increasing emergence of macrolide resistance to the common pathogens may limit their usefulness in the future as illustrated by a study that found 13.7% of *Streptococcus pneumoniae* in school-aged children were resistant to erythromycin (Gazi 2004). In contrast Gottfarb 1994 and Marchant 2012 used amoxicillin/clavulanic acid, an antibiotic with broad coverage of the organisms likely to be found on BAL in children with chronic wet cough, namely *Streptococcus pneumoniae*,*Haemophilus influenzae* and*Moraxella catarrhalis* (Marchant 2006). In Gazi 2004, only 1.2% of *Haemophilus influenzae* were resistant to amoxicillin/clavulanic acid and none of the *Moraxella catarrhalis* or *Streptococcus pneumoniae*. Gottfarb 1994 chose a very low dosage schedule (20 mg/kg/day) compared with standard practice (45 mg/kg/day), which may limit the efficacy of the drug and so rate of clinical cure in the trial.

Both Darelid 1993 and Gottfarb 1994 used only seven days of antibiotic therapy, while Marchant 2012 used 14 days of antibiotic or placebo treatment, hence all had a short duration of therapy.

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Therefore, we were unable to compare short- and longer-duration antibiotic therapy. In addition, none of the studies included long-term follow-up of children, hence recurrence rates were unknown. Current best practice guidelines suggest 14 days' treatment in children with wet cough (Chang 2006b; Gibson 2010), and our review supported this recommendation. In contrast, the British Thoracic Society guidelines suggest four to six weeks of antibiotic treatment for chronic wet cough in childhood to prevent recurrence (Shields 2008). There were no data to compare resolution and recurrence rates in two versus four weeks of antibiotic therapy for chronic wet cough. Hence, our review was unable to provide answers to these contrasting recommendations from the guidelines. Well-designed RCTs involving longer duration of antibiotics and long-term follow-up are needed to address these important clinical questions.
The review's findings are limited to children who otherwise appear well and who do not have other signs of an underlying lung disease. Chronic wet cough can be caused by many diseases such as bronchiectasis, retained inhaled foreign body and bronchiolitis obliterans. Thus, children with chronic wet cough need to be assessed for the presence of other causes of chronic cough and this review cannot be extrapolated to these other causes.

Quality of the evidence

The 'Summary of findings' table summarised the evidence for the outcomes. Overall, we judged the quality of evidence to be moderate when using antibiotics to cure cough and also for illness progression, while evidence was low for reaction to medications. As Darelid 1993 was not blinded, this reduced our confidence in the accuracy of their reported study, and in particular they did not report adverse effects in their control group. Hence, the quality of the evidence for reaction to medications (adverse effects) should be considered low due to imprecision and is a finding of uncertainty. There were no concerns with indirectness, inconsistency or publication bias in this review and hence we did not deem other downgrades to be necessary.

Potential biases in the review process

Two review authors (JM, HP) independently screened the literature searches, selected studies, extracted outcome data and assessed risk of bias for each study. One review author (AC) independently checked the data extraction, risk of bias assessment and downgrading decisions for the 'Summary of findings' table. Some review authors (JM, HP, AC) were authors on the new included study, therefore, to decrease the risk of bias it was assessed independently by another review author (PM) who was not an author of the included study. Members of the Cochrane Airways editorial group independently checked the 'Risk of bias' and GRADE findings to minimise the risk of bias in the review process. The Cochrane Airways review editor (Christopher Cates) independently checked the data and analyses.

Agreements and disagreements with other studies or reviews

This systematic review has updated a previous Cochrane Review and has been strengthened by the addition of a small but well-designed and robust RCT (Marchant 2012). The findings of both Cochrane Reviews were in agreement, but the quality of evidence significantly increased in the updated review. This review's findings were consistent with one systematic review prepared under the auspices of the American College of Chest Physicians' Cough (ACCP) guideline panel (Chang 2016b). Likewise, this review's recommendations are consistent with the ACCP's guideline (Chang 2017).
Although these three small RCTs were the only available to date, numerous prospective and retrospective studies have agreed with our findings of the usefulness of antibiotics in wet cough (Asilsoy 2008; Marchant 2006; Usta 2014). One multicentre study of 187 children newly referred with cough found an odds ratio of 73.3 (95% CI 10 to 544.2) for antibiotics to be effective in the treatment of the cause of the coughing illness. Furthermore, they found 138 children within their cohort had PBB and their wet cough resolved with two weeks of antibiotic therapy (Chang 2015). Retrospective studies have found cough resolution in 77% (Pritchard 2015) to 95% (Donnelly 2007) of children with wet cough and PBB.
This review's findings were specific for chronic cough and differed from other Cochrane Reviews on antibiotics on acute cough and the common cold (which are not the same as chronic cough). Antibiotics have only minimal benefit (if any) in the treatment of acute bronchitis (Fahey 2004), and have no efficacy in treatment of the common cold (Arroll 2005).

AUTHORS' CONCLUSIONS

Implications for practice

The available evidence suggests that antibiotics are efficacious in young children with chronic wet cough with a number needed to treat for an additional beneficial outcome (NNTB) of clinical cure of three. The use of antibiotics in children with prolonged wet cough is also associated with a reduction in the progression of illness whereby children on antibiotics are less likely to require further antibiotics for treatment of complications. Antibiotics have adverse effects, which should be considered with this treatment option and this review has reported only uncertainty as to the risk of increased adverse effects in this setting. The conclusions of this review are applicable only to children with chronic wet cough (longer than four weeks' duration), which must be differentiated

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from acute cough where the role of antibiotics is clearly very different and has been addressed in other reviews. In addition, as there are many other causes of chronic wet cough (e.g. aspiration lung disease and bronchiectasis), this review is limited to children who do not have other symptoms suggestive of an underlying lung disease.

Implications for research

Well-designed randomised controlled trials (RCTs) of children with wet cough of over four weeks are needed to particularly assess the appropriate duration of antibiotic therapy for this condition, specifically trials comparing two weeks with longer-duration therapy of four weeks as suggested by some current international guidelines (Shields 2008). These RCTs should be placebo-controlled and double blind, and adverse events should be carefully measured and reported. The design of future RCTs should include objective measures of cough outcomes such as cough frequency, validated symptomatic measures such as a cough diary or a cough-specific quality of life tool, time to resolution of cough and recurrence. A clear and appropriate definition of clinical cure should be included in the trial design. Secondary measures, such as differences in sputum, bronchoalveolar lavage or blood indices of inflammation or infection, will also strengthen future trial outcomes. Future RCTs should incorporate sufficient longitudinal follow-up of these participants to assess recurrence.

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* *Indicates the major publication for the study*

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CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Darelid 1993

Methods	Open randomised study comparing erythromycin and no treatment (as control group) History and clinical examination performed at baseline. Obtained nasopharyngeal swab at baseline and 18-36 hours after last antibiotic dose. Repeated doctor's examination on day 8
Participants	88 children with cough > 10 days' duration. % of participants with cough > 3 weeks' duration was 50%. Approximately 75% of participants had wet cough Erythromycin group: n = 41; control group n = 47. No significant differences in any participant characteristics between groups Inclusion criteria: children aged 0.5-6 years attending 1 of 3 paediatric outpatient clinics with > 10 days of cough Exclusion criteria: children with allergy, asthma, cardiac disease, otitis media, tonsillitis, pneumonia or clinically suspected pertussis
Interventions	Treatment group: erythromycin ethylsuccinate suspension 50 mg/kg/day in 2 divided doses for 7 days Control group: no treatment All children received nose drops (oxymetazoline chloride). Salbutamol mixture (0.1 mg/kg/day) allowed and registered in both groups
Outcomes	• Clinical symptoms as recorded on a questionnaire by parents, including cough on 3-point scale (none, moderate or frequent), morning temperature and degree of activity of child (usual, reduced, bedridden) • Clinical examination on day 8 to assess cure or clinical failure (without knowledge of questionnaires) • Elimination of nasopharyngeal pathogens • Progression of disease requiring additional antibiotics (% complications), i.e. bacterial complications requiring further antibiotics and recurrent symptoms were recorded during therapy and for 3 months after • Adverse drug reactions
Notes	4 children in each group had received antibiotic treatment prior to enrolment for < 30 days Funding not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated table

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Darelid 1993 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	Insufficient information provided in the published article.
Blinding (performance bias and detection bias) All outcomes	High risk	Open study
Blinding of participants and personnel (performance bias) All outcomes	High risk	Parent and physician aware of treatment group. Physician blinded to daily cough questionnaire at day 8 review
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open study
Incomplete outcome data (attrition bias) All outcomes	Low risk	Only 1 participant withdrew from study
Selective reporting (reporting bias)	Low risk	No protocol available but results presented as ITT.

Gottfarb 1994

Methods	Randomised double-blind study comparing amoxicillin/clavulanic acid vs placebo Clinical data obtained at baseline and participants underwent nasopharyngeal aspirate and blood tests for *Bordetella pertussis* and *Mycoplasma pneumoniae*. A cough scoring system which combined number of coughing attacks per 24 hours, coughing attacks associated with vomiting and wheeze or crackles on auscultation obtained. At 2 weeks participants were followed up with repeat blood tests, nasopharyngeal aspirates and doctor assessment of clinical outcome. Parental assessment of treatment efficacy recorded. Number of coughing attacks per 24 hours recorded for each day of treatment
Participants	52 children with cough > 10 days duration. Mean duration of cough 3-4 weeks. Number with wet cough not reported Median age: amoxicillin/clavulanic acid: 2.7 years; placebo: 2.6 years (numbers per group not described). No significant differences in participant characteristics between groups Inclusion criteria: children aged 0.6-7 years with > 10 days of cough and > 7 points on cough score system Exclusion criteria: children with any signs of pneumonia, acute otitis media or clinical suspicion of *Bordetella pertussis* infection
Interventions	Treatment group: amoxicillin/clavulanic acid 20 mg/kg/day for 7 days Control group: placebo Children received no antitussive medication
Outcomes	• Paediatrician's assessment of clinical recovery on days 12-14 • Parental assessment of recovery on days 12-14 • Number of coughing attacks each day of treatment recorded until day 8

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	• Adverse events
Notes	Due to lack of information in paper and an inability to obtain data from authors about the dropouts with pertussis, we assumed that there were equal numbers of participants in each treatment group analysed (37 participants became 18 in one group and 19 in other)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Low risk	Stated double blind but no further information given in published paper; however, identical placebo used
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Stated double blind but no further information given in published paper
Blinding of outcome assessment (detection bias) All outcomes	Low risk	71% parents of the antibiotic group reported being satisfied with recovery vs 22% in the placebo group
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	26% attrition not included in final analysis
Selective reporting (reporting bias)	Unclear risk	No protocol available. Final numbers allocated to each group not reported

Marchant 2012

Methods	Parallel double-blind randomised controlled trial of amoxicillin/clavulanic acid vs placebo. Medical history including examination and given instructions for completion of diary card at enrolment. Telephone review conducted on day 7 and 14 of trial medications and clinical appointment arranged if still coughing at day 14. Parents returned diaries and medication bottles (for compliance checking) via post
Participants	50 children with chronic wet cough (> 3 weeks) Amoxicillin/clavulanic acid group n = 25; mean age: 1.75 (SD 0.9) years Placebo group n = 25; mean age: 2.8 (SD 0.9) years New referral to respiratory services at Royal Children's Hospital, Brisbane, Australia Inclusion criteria: aged 6 months to 18 years and chronic wet cough Exclusion criteria: presence of neurodevelopmental delay, cystic fibrosis, ex-premature

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	infant (< 37 weeks' gestation), chronic disease including interstitial lung disease or cardiac abnormalities, clinical suspension of bronchiectasis, haemoptysis, antibiotic use < 2 weeks ago, penicillin allergy or acutely unwell with fever or pneumonia
Interventions	Treatment group: amoxicillin/clavulanic acid 22.5 mg/kg twice daily for 14 days Control group: placebo twice daily for 14 days. Enrolled children completed cough diary cards for 5 days preintervention and total of 4 weeks after intervention Bronchoscopy and lavage conducted in 19 children in amoxicillin/clavulanic acid group and 18 children in placebo group
Outcomes	Primary outcome: cough resolution defined as improvement in baseline cough score (> 75% reduction in cough score) at end of trial or cessation of coughing for ≥ 3 days in trial Secondary outcomes: measures in absolute change in cough score and change in VCD score over study period
Notes	Funded by Royal Children's Hospital Foundation and TSANZ Career Development Fellowship

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation
Allocation concealment (selection bias)	Low risk	Concealed allocation and antibiotics dispensed by hospital pharmacy
Blinding (performance bias and detection bias) All outcomes	Low risk	Double blind; parent and study staff blinded
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blind. Medications provided by pharmacy
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double blind; parent and physician unaware of allocation group
Incomplete outcome data (attrition bias) All outcomes	Low risk	Only 3/50 (6%) participants lost to follow-up and were included in final analysis of primary outcome
Selective reporting (reporting bias)	Low risk	Trial registered before unblinding and analysis. Primary outcome measure consistent

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n: number of participants; ITT: intention to treat.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Dowell 1998	Review article on use of antibiotics for cough, pharyngitis and the common cold
Field 1966	Double-blind RCT of ampicillin vs placebo in infants with cough and expiratory wheeze (bronchiolitis). Excluded from review as all participants had wheeze, which was an exclusion criterion in our participants
Fiocchi 1988	RCT of domiodol vs placebo in children. Excluded as domiodol is a mucolytic not antibiotic
Friis 1984	Open randomised prospective trial of antibiotic vs control group in children with pneumonia. All had been unwell for < 1 week. Excluded as acute cough not chronic
Nevihostenyi 1980	Non-RCT. Study of 129 children aged 2-8 years who underwent endoscopy for investigation of chronic bronchitis
O'Brien 1998	Review article on the investigation and treatment of (including use of antibiotics) in children with acute, subacute and chronic cough
Schaad 1986	Double-blind RCT of bacterial lysate vs placebo in acute infections of the respiratory system; therefore, excluded as not antibiotic and not chronic infections
Shann 1985	Non-RCT. Review article on treatment of pneumonia
Stott 1976	RCT of doxycycline vs placebo in adults with acute cough of ≤ 1 weeks' duration. Excluded as adults and acute cough
Taylor 1977	Double-blind RCT of amoxicillin, co-trimoxazole and placebo in children with viral respiratory illnesses. Excluded as not chronic cough
Wald 1986	Excluded as cough due to acute sinusitis (i.e. not non-specific cough) and cough not chronic (< 30 days). Double-blind RCT of amoxicillin, amoxicillin/clavulanate potassium and placebo in 171 children aged 2-6 years with persistent nasal discharge or cough (or both). Children receiving antibiotic more likely to be cured then those receiving placebo (P < 0.05 at 10 days)
Yun 1983	RCT of antibiotics for sinusitis in children presenting with chronic cough. Excluded because no placebo or "no treatment" control group
Zanasi 2013	Excluded as non-RCT or chronic cough study
Zanasi 2015	Excluded as non-RCT or chronic cough study. Children with acute cough received either homeopathic syrup for 10 days or homeopathic syrup for 10 days and antibiotics for 7 days

RCT: randomised controlled trial.

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DATA AND ANALYSES

Comparison 1. Antibiotics versus no antibiotics/placebo for wet cough in children

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Children not cured or not substantially improved at follow-up (using intention-to-treat analysis)	3	190	Odds Ratio (M-H, Fixed, 95% CI)	0.15 [0.07, 0.31]
2 Illness progression: participants with progression of disease resulting in additional antibiotic therapy required (available data only)	2	125	Odds Ratio (M-H, Fixed, 95% CI)	0.10 [0.03, 0.34]
3 Children experiencing adverse effects of antibiotics (vomiting, diarrhoea, rash)	3	190	Odds Ratio (M-H, Fixed, 95% CI)	1.88 [0.62, 5.69]
4 Children not cured or not substantially improved at follow-up (excluding those known to have *B pertussis*)	2	128	Odds Ratio (M-H, Fixed, 95% CI)	0.13 [0.05, 0.30]
5 Subgroup analysis (placebo controlled): children not cured or substantially improved at follow-up	3	190	Odds Ratio (M-H, Fixed, 95% CI)	0.15 [0.07, 0.31]
5.1 Placebo controlled	2	102	Odds Ratio (M-H, Fixed, 95% CI)	0.22 [0.08, 0.60]
5.2 No placebo used	1	88	Odds Ratio (M-H, Fixed, 95% CI)	0.10 [0.03, 0.28]
6 Subgroup analysis (variation in inclusion criteria: cough duration): children not cured or not substantially improved at follow-up	3	190	Odds Ratio (M-H, Fixed, 95% CI)	0.15 [0.07, 0.31]
6.1 Cough duration < 4 weeks	2	140	Odds Ratio (M-H, Fixed, 95% CI)	0.13 [0.06, 0.31]
6.2 Cough duration > 4 weeks	1	50	Odds Ratio (M-H, Fixed, 95% CI)	0.21 [0.05, 0.78]
7 Subgroup analysis (antibiotics used): children not cured or not substantially improved at follow-up	3	190	Odds Ratio (M-H, Fixed, 95% CI)	0.15 [0.07, 0.31]
7.1 Amoxicilin/clavulanic acid use	2	102	Odds Ratio (M-H, Fixed, 95% CI)	0.22 [0.08, 0.60]
7.2 Other antibiotics used	1	88	Odds Ratio (M-H, Fixed, 95% CI)	0.10 [0.03, 0.28]
8 Sensitivity analysis: children not cured or not substantially improved at follow-up (using available data only)	3	171	Odds Ratio (M-H, Fixed, 95% CI)	0.14 [0.07, 0.29]

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Analysis 1.1. Comparison 1 Antibiotics versus no antibiotics/placebo for wet cough in children, Outcome 1 Children not cured or not substantially improved at follow-up (using intention-to-treat analysis).

Review: Antibiotics for prolonged wet cough in children

Comparison: 1 Antibiotics versus no antibiotics/placebo for wet cough in children

Outcome: 1 Children not cured or not substantially improved at follow-up (using intention-to-treat analysis)

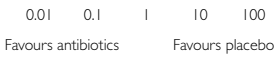
Study or subgroup	Antibiotics n/N	Placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Darelid 1993	6/41	30/47		56.9 %	0.10 [0.03, 0.28]
Marchant 2012	13/25	21/25		24.1 %	0.21 [0.05, 0.78]
Gottfarb 1994	17/26	23/26		19.0 %	0.25 [0.06, 1.05]
Total (95% CI)	**92**	**98**		**100.0 %**	**0.15 [0.07, 0.31]**

Total events: 36 (Antibiotics), 74 (Placebo)

Heterogeneity: Chi^2 = 1.33, df = 2 (P = 0.51); I^2 =0.0%

Test for overall effect: Z = 5.20 (P < 0.00001)

Test for subgroup differences: Not applicable



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Analysis 1.2. Comparison 1 Antibiotics versus no antibiotics/placebo for wet cough in children, Outcome 2 Illness progression: participants with progression of disease resulting in additional antibiotic therapy required (available data only).

Review: Antibiotics for prolonged wet cough in children

Comparison: 1 Antibiotics versus no antibiotics/placebo for wet cough in children

Outcome: 2 Illness progression: participants with progression of disease resulting in additional antibiotic therapy required (available data only)

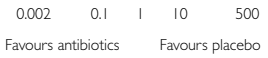
Study or subgroup	Antibiotics n/N	Placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Darelid 1993	2/41	21/47		87.1 %	0.06 [0.01, 0.29]
Gottfarb 1994	1/18	3/19		12.9 %	0.31 [0.03, 3.34]
Total (95% CI)	**59**	**66**		**100.0 %**	**0.10 [0.03, 0.34]**

Total events: 3 (Antibiotics), 24 (Placebo)

Heterogeneity: Chi^2 = 1.24, df = 1 (P = 0.26); I^2 =20%

Test for overall effect: Z = 3.67 (P = 0.00025)

Test for subgroup differences: Not applicable



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Analysis 1.3. Comparison 1 Antibiotics versus no antibiotics/placebo for wet cough in children, Outcome 3 Children experiencing adverse effects of antibiotics (vomiting, diarrhoea, rash).

Review: Antibiotics for prolonged wet cough in children

Comparison: 1 Antibiotics versus no antibiotics/placebo for wet cough in children

Outcome: 3 Children experiencing adverse effects of antibiotics (vomiting, diarrhoea, rash)

Study or subgroup	Antibiotics n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Gottfarb 1994	3/26	3/26		56.4 %	1.00 [0.18, 5.48]
Marchant 2012	5/25	2/25		34.0 %	2.88 [0.50, 16.48]
Darelid 1993	1/41	0/47		9.6 %	3.52 [0.14, 88.76]
Total (95% CI)	**92**	**98**		**100.0 %**	**1.88 [0.62, 5.69]**

Total events: 9 (Antibiotics), 5 (Control)

Heterogeneity: $Chi^2 = 0.90$, df = 2 (P = 0.64); $I^2 = 0.0\%$

Test for overall effect: Z = 1.12 (P = 0.26)

Test for subgroup differences: Not applicable

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Analysis 1.4. Comparison 1 Antibiotics versus no antibiotics/placebo for wet cough in children, Outcome 4 Children not cured or not substantially improved at follow-up (excluding those known to have *B pertussis*).

Review: Antibiotics for prolonged wet cough in children

Comparison: 1 Antibiotics versus no antibiotics/placebo for wet cough in children

Outcome: 4 Children not cured or not substantially improved at follow-up (excluding those known to have *B pertussis*)

Study or subgroup	Antibiotics n/N	Placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Darelid 1993	6/41	30/47		75.7 %	0.10 [0.03, 0.28]
Gottfarb 1994	11/20	17/20		24.3 %	0.22 [0.05, 0.98]
Total (95% CI)	**61**	**67**		**100.0 %**	**0.13 [0.05, 0.30]**

Total events: 17 (Antibiotics), 47 (Placebo)

Heterogeneity: $Chi^2 = 0.72$, df = 1 (P = 0.40); $I^2 = 0.0\%$

Test for overall effect: Z = 4.74 (P < 0.00001)

Test for subgroup differences: Not applicable

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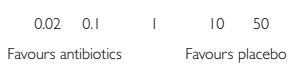
Analysis 1.5. Comparison 1 Antibiotics versus no antibiotics/placebo for wet cough in children, Outcome 5 Subgroup analysis (placebo controlled): children not cured or substantially improved at follow-up.

Review: Antibiotics for prolonged wet cough in children

Comparison: 1 Antibiotics versus no antibiotics/placebo for wet cough in children

Outcome: 5 Subgroup analysis (placebo controlled): children not cured or substantially improved at follow-up

Study or subgroup	Antibiotics n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
1 Placebo controlled					
Marchant 2012	13/25	21/25		24.1 %	0.21 [0.05, 0.78]
Gottfarb 1994	17/26	23/26		19.0 %	0.25 [0.06, 1.05]
Subtotal (95% CI)	**51**	**51**		**43.1 %**	**0.22 [0.08, 0.60]**
Total events: 30 (Antibiotics), 44 (Control)					
Heterogeneity: Chi^2 = 0.03, df = 1 (P = 0.86); I^2 =0.0%					
Test for overall effect: Z = 3.00 (P = 0.0027)					
2 No placebo used					
Darelid 1993	6/41	30/47		56.9 %	0.10 [0.03, 0.28]
Subtotal (95% CI)	**41**	**47**		**56.9 %**	**0.10 [0.03, 0.28]**
Total events: 6 (Antibiotics), 30 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 4.35 (P = 0.000014)					
Total (95% CI)	**92**	**98**		**100.0 %**	**0.15 [0.07, 0.31]**
Total events: 36 (Antibiotics), 74 (Control)					
Heterogeneity: Chi^2 = 1.33, df = 2 (P = 0.51); I^2 =0.0%					
Test for overall effect: Z = 5.20 (P < 0.00001)					
Test for subgroup differences: Chi^2 = 1.30, df = 1 (P = 0.25), I^2 =23%					



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Analysis 1.6. Comparison 1 Antibiotics versus no antibiotics/placebo for wet cough in children, Outcome 6 Subgroup analysis (variation in inclusion criteria: cough duration): children not cured or not substantially improved at follow-up.

Review: Antibiotics for prolonged wet cough in children

Comparison: 1 Antibiotics versus no antibiotics/placebo for wet cough in children

Outcome: 6 Subgroup analysis (variation in inclusion criteria: cough duration): children not cured or not substantially improved at follow-up

Study or subgroup	Antibiotics n/N	Placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
1 Cough duration < 4 weeks					
Darelid 1993	6/41	30/47		56.9 %	0.10 [0.03, 0.28]
Gottfarb 1994	17/26	23/26		19.0 %	0.25 [0.06, 1.05]
Subtotal (95% CI)	**67**	**73**		**75.9 %**	**0.13 [0.06, 0.31]**
Total events: 23 (Antibiotics), 53 (Placebo)					
Heterogeneity: Chi^2 = 1.04, df = 1 (P = 0.31); I^2 =4%					
Test for overall effect: Z = 4.65 (P < 0.00001)					
2 Cough duration > 4 weeks					
Marchant 2012	13/25	21/25		24.1 %	0.21 [0.05, 0.78]
Subtotal (95% CI)	**25**	**25**		**24.1 %**	**0.21 [0.05, 0.78]**
Total events: 13 (Antibiotics), 21 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.33 (P = 0.020)					
Total (95% CI)	**92**	**98**		**100.0 %**	**0.15 [0.07, 0.31]**
Total events: 36 (Antibiotics), 74 (Placebo)					
Heterogeneity: Chi^2 = 1.33, df = 2 (P = 0.51); I^2 =0.0%					
Test for overall effect: Z = 5.20 (P < 0.00001)					
Test for subgroup differences: Chi^2 = 0.28, df = 1 (P = 0.59), I^2 =0.0%					

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Analysis 1.7. Comparison 1 Antibiotics versus no antibiotics/placebo for wet cough in children, Outcome 7 Subgroup analysis (antibiotics used): children not cured or not substantially improved at follow-up.

Review: Antibiotics for prolonged wet cough in children

Comparison: 1 Antibiotics versus no antibiotics/placebo for wet cough in children

Outcome: 7 Subgroup analysis (antibiotics used): children not cured or not substantially improved at follow-up

Study or subgroup	Antibiotics n/N	Placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
1 Amoxicilin/clavulanic acid use					
Gottfarb 1994	17/26	23/26		19.0 %	0.25 [0.06, 1.05]
Marchant 2012	13/25	21/25		24.1 %	0.21 [0.05, 0.78]
Subtotal (95% CI)	**51**	**51**		**43.1 %**	**0.22 [0.08, 0.60]**
Total events: 30 (Antibiotics), 44 (Placebo)					
Heterogeneity: Chi^2 = 0.03, df = 1 (P = 0.86); I^2 =0.0%					
Test for overall effect: Z = 3.00 (P = 0.0027)					
2 Other antibiotics used					
Darelid 1993	6/41	30/47		56.9 %	0.10 [0.03, 0.28]
Subtotal (95% CI)	**41**	**47**		**56.9 %**	**0.10 [0.03, 0.28]**
Total events: 6 (Antibiotics), 30 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 4.35 (P = 0.000014)					
Total (95% CI)	**92**	**98**		**100.0 %**	**0.15 [0.07, 0.31]**
Total events: 36 (Antibiotics), 74 (Placebo)					
Heterogeneity: Chi^2 = 1.33, df = 2 (P = 0.51); I^2 =0.0%					
Test for overall effect: Z = 5.20 (P < 0.00001)					
Test for subgroup differences: Chi^2 = 1.30, df = 1 (P = 0.25), I^2 =23%					

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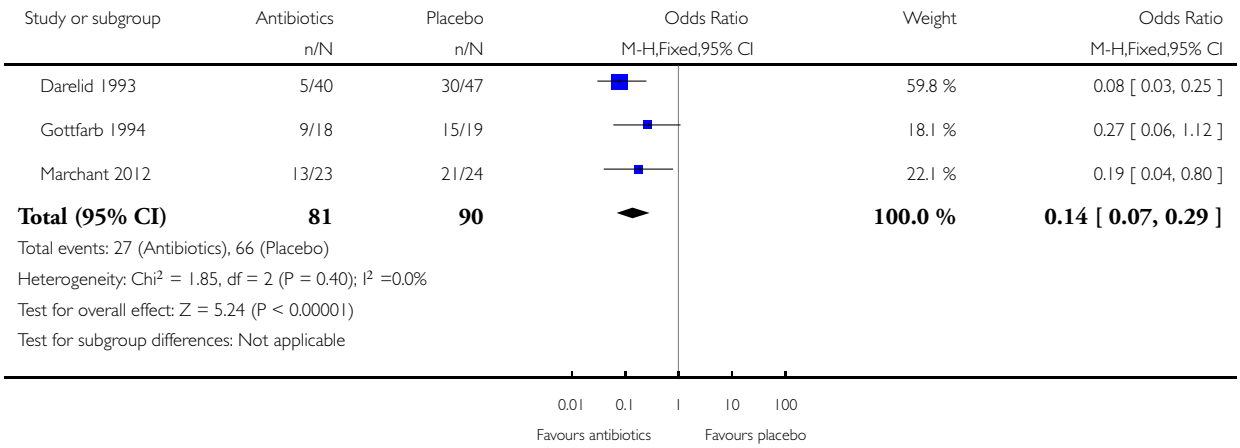
Analysis 1.8. Comparison 1 Antibiotics versus no antibiotics/placebo for wet cough in children, Outcome 8 Sensitivity analysis: children not cured or not substantially improved at follow-up (using available data only).

Review: Antibiotics for prolonged wet cough in children

Comparison: 1 Antibiotics versus no antibiotics/placebo for wet cough in children

Outcome: 8 Sensitivity analysis: children not cured or not substantially improved at follow-up (using available data only)



APPENDICES

Appendix 1. Database search strategies

Cochrane Airways Trials Register search strategy

#1 MeSH descriptor Cough explode all trees
#2 MeSH descriptor Bronchitis explode all trees
#3 cough* or bronchiti*
#4 (#1 OR #2 OR #3)
#5 MeSH descriptor Anti-Bacterial Agents explode all trees
#6 antibiot* or anti-biot* or antimicrob* or anti-microb* or antibacterial* or anti-bacterial* or erythromycin or amoxycillin or ampicillin or doxycycline
#7 (#5 OR #6)
#8 MeSH descriptor Child explode all trees
#9 MeSH descriptor Infant explode all trees
#10 MeSH descriptor Adolescent explode all trees
#11 MeSH descriptor Pediatrics explode all trees
#12 child* or paediat* or pediat* or adolesc* or infan* or toddler* or bab* or young* or preschool* or pre school* or pre-school* or newborn* or new born* or new-born* or neo-nat* or neonat*
#13 (#8 OR #9 OR #10 OR #11 OR #12)
#14 (#4 AND #7 AND #13)

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CENTRAL search strategy
#1 MeSH descriptor Cough explode all trees
#2 MeSH descriptor Bronchitis explode all trees
#3 cough* or bronchiti*
#4 (#1 OR #2 OR #3)
#5 MeSH descriptor Anti-Bacterial Agents explode all trees
#6 antibiot* or anti-biot* or antimicrob* or anti-microb* or antibacterial* or anti-bacterial* or erythromycin or amoxycillin or ampicillin or doxycycline
#7 (#5 OR #6)
#8 MeSH descriptor Child explode all trees
#9 MeSH descriptor Infant explode all trees
#10 MeSH descriptor Adolescent explode all trees
#11 MeSH descriptor Pediatrics explode all trees
#12 child* or paediat* or pediat* or adolesc* or infan* or toddler* or bab* or young* or preschool* or pre school* or pre-school* or newborn* or new born* or new-born* or neo-nat* or neonat*
#13 (#8 OR #9 OR #10 OR #11 OR #12)
#14 (#4 AND #7 AND #13)
MEDLINE search strategy
Topic search
1. exp COUGH/
2. exp Bronchitis/
3. (cough$ or bronchit$).mp.
4. 1 or 2 or 3
5. exp Anti-Bacterial Agents/
6. (antibiot$ or anti-biot$ or antimicrob$ or anti-microb$ or antibacterial$ or anti-bacterial$ or erythromycin or amoxycillin or ampicillin or doxycycline).mp.
7. 5 or 6
8. exp adolescent/ or exp child/ or exp infant/
9. exp Pediatrics/
10. (child$ or paediat$ or pediat$ or adolesc$ or infan$ or toddler$ or bab$ or young$ or preschool$ or pre school$ or pre-school$ or newborn$ or new born$ or new-born$ or neo-nat$ or neonat$).mp.
11. 8 or 9 or 10
12. 4 and 7 and 11
RCT filter
1. (clinical trial or controlled clinical trial or randomised controlled trial).pt.
2. (randomised or randomised).ab,ti.
3. placebo.ab,ti.
4. dt.fs.
5. randomly.ab,ti.
6. trial.ab,ti.
7. groups.ab,ti.
8. or/1-7
9. Animals/
10. Humans/
11. 9 not (9 and 10)
12. 8 not 11
Embase search strategy
Topic search
1. exp Coughing/
2. exp Bronchitis/
3. (cough$ or bronchit$).mp.
4. 1 or 2 or 3
5. exp Antibiotic Agent/

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6. (antibiot$ or anti-biot$ or antimicrob$ or anti-microb$ or antibacterial$ or anti-bacterial$ or erythromycin or amoxycillin or ampicillin or doxycycline).mp.
7. 5 or 6
8. Child/
9. Adolescent/
10. Infant/
11. exp pediatrics/
12. (child$ or paediat$ or pediat$ or adolesc$ or infan$ or toddler$ or bab$ or young$ or preschool$ or pre school$ or pre-school$ or newborn$ or new born$ or new-born$ or neo-nat$ or neonat$).mp.
13. or/8-12
14. 4 and 7 and 13

RCT filter

1. Randomized Controlled Trial/
2. Controlled Study/
3. randomisation/
4. Double Blind Procedure/
5. Single Blind Procedure/
6. Clinical Trial/
7. Crossover Procedure/
8. follow up/
9. exp prospective study/
10. or/1-9
11. (clinica$ adj3 trial$).mp.
12. ((singl$ or doubl$ or trebl$ or tripl$) adj5 (mask$ or blind$ or method$)).mp.
13. exp Placebo/
14. placebo$.mp.
15. random$.mp.
16. (latin adj3 square$).mp.
17. exp Comparative Study/
18. ((control$ or prospectiv$ or volunteer$) adj3 (trial$ or method$ or stud$)).mp.
19. (crossover$ or cross-over$).mp.
20. or/11-19
21. 10 or 20
22. exp ANIMAL/
23. Nonhuman/
24. Human/
25. 22 or 23
26. 25 not 24
27. 21 not 26

Appendix 2. Search history

Year of search	Number of references retrieved
2004	1550
2006	297
2008	365

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(*Continued*)

2010	567
2014	443
2016	683
2017	386

WHAT'S NEW

Last assessed as up-to-date: 22 September 2017.

Date	Event	Description
22 September 2017	New citation required and conclusions have changed	Conclusions strengthened by inclusion of more robust study.
22 September 2017	New search has been performed	Updated search, identified one new study. Refreshed background, abstract, PLS, results and discussion using required Cochrane headings. Changed definition short and long term (cut-off of 7 changed to 14). Methods updated as per Cochrane; new 'Risk of bias' tool, added 'Summary of findings' tables. Added subgroup analyses (numbers 2 to 4) and removed 6 sensitivity analyses

HISTORY

Protocol first published: Issue 2, 2004

Review first published: Issue 4, 2005

Date	Event	Description
8 October 2010	New search has been performed	New literature search run, no new studies found.
8 April 2008	Amended	Updated with searches until 19 March 2008; no new studies were eligible
6 July 2005	New citation required and conclusions have changed	Substantive amendment

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CONTRIBUTIONS OF AUTHORS

For the review:

- all reviewed the manuscript.

For update:

- JM and HP selection of articles from search, data extraction, data analysis and writing of review.
- PM: review of data and review of manuscript.
- AC: review of articles for inclusion, data extraction, double data entry, data analysis, writing of review.
- Justin Gaffney (author of original review) was removed as author from this update.

DECLARATIONS OF INTEREST

JM: none

HP: Employed as a senior lecturer at Griffith University, received a post doctoral fellowship from National Health Medical Research Council (ID. 1040830), received an early career fellowship from Asthma Australia

PM: Member of Expert Advisory Group on chronic suppurative otitis media and conjugate pneumococcal vaccines in Australia for GlaxoSmithKline

AC: Unrestricted, investigator-initiated grant from GlaxoSmithKline in an area unrelated to review topic. Consultancy work for Merck on an unrelated topic. Merck does not produce a drug relevant to this review.

Three of the authors (JM, AC, HP) have conducted an RCT on this topic, which was included in this updated review (Marchant 2012).

SOURCES OF SUPPORT

Internal sources

- The authors declared no internal funding was received for this systematic review update, Other.

External sources

- Australian Cochrane Airways Group Scholarship 2004, Australia.
- Asthma Australia, Australia.

Supporting HP through an early career fellowship

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

October 2004: during the review process the selection criteria were changed from RCTs comparing antibiotics to placebo medication to also include studies comparing antibiotics with a 'no treatment' control group. This was done because there were an insufficient number of placebo-controlled trials to be sure that the information obtained from unblinded studies would not be clinically useful. The inclusion criteria were changed to allow studies of children who had prolonged wet cough for more than 10 days. We planned to assess the impact of antibiotics on children with prolonged wet cough of more than three weeks (our preferred definition of chronic cough) as an a priori subgroup analysis. We also decided to include studies that were not exclusively limited to children with "wet sounding" cough if subgroup data were not available and more than 50% of children had a wet cough or other clinical features consistent with diagnosis (e.g. sputum production, excess secretions, etc.). The review used a summary weighted odds ratio rather than risk ratio as was stated in the protocol. This decision was made as it appeared the most clinically relevant analysis method particularly when converted to number needed to treat.

September 2017: the original protocol was written in 2004. Since this time, Cochrane methodology has become more rigorous. Therefore, this updated review has considered these changes and adapted as necessary. Helen Petsky was added as an author for the update in 2017.

INDEX TERMS

Medical Subject Headings (MeSH)

Anti-Bacterial Agents [*therapeutic use]; Chronic Disease; Cough [classification; *drug therapy]; Randomized Controlled Trials as Topic; Sputum [secretion]

MeSH check words

Child; Humans

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