Cochrane Library

Cochrane Database of Systematic Reviews

Delayed antibiotic prescriptions for respiratory infections (Review)

Spurling GKP, Del Mar CB, Dooley L, Foxlee R, Farley R

Spurling GKP, Del Mar CB, Dooley L, Foxlee R, Farley R.
Delayed antibiotic prescriptions for respiratory infections.
Cochrane Database of Systematic Reviews 2017, Issue 9. Art. No.: CD004417.
DOI: 10.1002/14651858.CD004417.pub5.

www.cochranelibrary.com

WILEY

TABLE OF CONTENTS

[Intervention Review]

Delayed antibiotic prescriptions for respiratory infections

Geoffrey KP Spurling[1], Chris B Del Mar[2], Liz Dooley[3], Ruth Foxlee[4], Rebecca Farley[1]

[1]Discipline of General Practice, School of Medicine, The University of Queensland, Brisbane, Australia. [2]Centre for Research in Evidence-Based Practice (CREBP), Bond University, Gold Coast, Australia. [3]Faculty of Health Sciences and Medicine, Bond University, Gold Coast, Australia. [4]Cochrane Editorial Unit, Cochrane, London, UK

Contact address: Geoffrey KP Spurling, Discipline of General Practice, School of Medicine, The University of Queensland, Herston, Brisbane, Queensland, 4029, Australia. g.spurling@uq.edu.au, geoffspurling@optusnet.com.au.

Editorial group: Cochrane Acute Respiratory Infections Group.
Publication status and date: New search for studies and content updated (conclusions changed), published in Issue 9, 2017.

Citation: Spurling GKP, Del Mar CB, Dooley L, Foxlee R, Farley R. Delayed antibiotic prescriptions for respiratory infections. *Cochrane Database of Systematic Reviews* 2017, Issue 9. Art. No.: CD004417. DOI: 10.1002/14651858.CD004417.pub5.

ABSTRACT

Background

Concerns exist regarding antibiotic prescribing for respiratory tract infections (RTIs) owing to adverse reactions, cost, and antibacterial resistance. One proposed strategy to reduce antibiotic prescribing is to provide prescriptions, but to advise delay in antibiotic use with the expectation that symptoms will resolve first. This is an update of a Cochrane Review originally published in 2007, and updated in 2010 and 2013.

Objectives

To evaluate the effects on clinical outcomes, antibiotic use, antibiotic resistance, and patient satisfaction of advising a *delayed* prescription of antibiotics in respiratory tract infections.

Search methods

For this 2017 update we searched the Cochrane Central Register of Controlled Trials (CENTRAL) (the Cochrane Library, Issue 4, 2017), which includes the Cochrane Acute Respiratory Infection Group's Specialised Register; Ovid MEDLINE (2013 to 25 May 2017); Ovid Embase (2013 to 2017 Week 21); EBSCO CINAHL Plus (1984 to 25 May 2017); Web of Science (2013 to 25 May 2017); WHO International Clinical Trials Registry Platform (1 September 2017); and ClinicalTrials.gov (1 September 2017).

Selection criteria

Randomised controlled trials involving participants of all ages defined as having an RTI, where *delayed* antibiotics were compared to *immediate* antibiotics or *no* antibiotics. We defined a *delayed* antibiotic as advice to delay the filling of an antibiotic prescription by at least 48 hours. We considered all RTIs regardless of whether antibiotics were recommended or not.

Data collection and analysis

We used standard Cochrane methodological procedures. Three review authors independently extracted and collated data. We assessed the risk of bias of all included trials. We contacted trial authors to obtain missing information.

Main results

For this 2017 update we added one new trial involving 405 participants with uncomplicated acute respiratory infection. Overall, this review included 11 studies with a total of 3555 participants. These 11 studies involved acute respiratory infections including acute otitis media (three studies), streptococcal pharyngitis (three studies), cough (two studies), sore throat (one study), common cold (one study), and a variety of RTIs (one study). Five studies involved only children, two only adults, and four included both adults and children. Six studies were conducted in a primary care setting, three in paediatric clinics, and two in emergency departments.

Studies were well reported, and appeared to be of moderate quality. Randomisation was not adequately described in two trials. Four trials blinded the outcomes assessor, and three included blinding of participants and doctors. We conducted meta-analysis for antibiotic use and patient satisfaction.

We found no differences among *delayed*, *immediate*, and no prescribed antibiotics for clinical outcomes in the three studies that recruited participants with cough. For the outcome of fever with sore throat, three of the five studies favoured *immediate* antibiotics, and two found no difference. For the outcome of pain related to sore throat, two studies favoured *immediate* antibiotics, and three found no difference. One study compared *delayed* antibiotics with no antibiotic for sore throat, and found no difference in clinical outcomes.

Three studies included participants with acute otitis media. Of the two studies with an *immediate* antibiotic arm, one study found no difference for fever, and the other study favoured *immediate* antibiotics for pain and malaise severity on Day 3. One study including participants with acute otitis media compared *delayed* antibiotics with *no* antibiotics and found no difference for pain and fever on Day 3.

Two studies recruited participants with common cold. Neither study found differences for clinical outcomes between *delayed* and *immediate* antibiotic groups. One study favoured *delayed* antibiotics over *no* antibiotics for pain, fever, and cough duration (moderate quality evidence for all clinical outcomes - GRADE assessment).

There were either no differences for adverse effects or results favoured *delayed* antibiotics over *immediate* antibiotics (low quality evidence - to GRADE assessment) with no significant differences in complication rates.

Delayed antibiotics resulted in a significant reduction in antibiotic use compared to *immediate* antibiotics prescription (odds ratio (OR) 0.04, 95% confidence interval (CI) 0.03 to 0.05). However, a *delayed* antibiotic was more likely to result in reported antibiotic use than *no* antibiotics (OR 2.55, 95% CI 1.59 to 4.08) (moderate quality evidence - GRADE assessment).

Patient satisfaction favoured *delayed* over *no* antibiotics (OR 1.49, 95% CI 1.08 to 2.06). There was no significant difference in patient satisfaction between *delayed* antibiotics and *immediate* antibiotics (OR 0.65, 95% CI 0.39 to 1.10) (moderate quality evidence - GRADE assessment).

None of the included studies evaluated antibiotic resistance.

Authors' conclusions

For many clinical outcomes, there were no differences between prescribing strategies. Symptoms for acute otitis media and sore throat were modestly improved by *immediate* antibiotics compared with *delayed* antibiotics. There were no differences in complication rates. Delaying prescribing did not result in significantly different levels of patient satisfaction compared with immediate provision of antibiotics (86% versus 91%) (moderate quality evidence). However, delay was favoured over *no* antibiotics (87% versus 82%). *Delayed* antibiotics achieved lower rates of antibiotic use compared to *immediate* antibiotics (31% versus 93%) (moderate quality evidence). The strategy of *no* antibiotics further reduced antibiotic use compared to delaying prescription for antibiotics (14% versus 28%).

Delayed antibiotics for people with acute respiratory infection reduced antibiotic use compared to *immediate* antibiotics, but was not shown to be different to *no* antibiotics in terms of symptom control and disease complications. Where clinicians feel it is safe not to prescribe antibiotics immediately for people with respiratory infections, *no* antibiotics with advice to return if symptoms do not resolve is likely to result in the least antibiotic use while maintaining similar patient satisfaction and clinical outcomes to delaying prescription of antibiotics. Where clinicians are not confident in using a no antibiotic strategy, a *delayed* antibiotics strategy may be an acceptable compromise in place of *immediate* prescribing to significantly reduce unnecessary antibiotic use for RTIs, and thereby reduce antibiotic resistance, while maintaining patient safety and satisfaction levels.

Editorial note: As a living systematic review, this review is continually updated, incorporating relevant new evidence as it becomes available. Please refer to the Cochrane Database of Systematic Reviews for the current status of this review.

PLAIN LANGUAGE SUMMARY

Delayed antibiotic prescriptions for respiratory tract infections

Review question

We investigated the effect of *delaying* antibiotic prescription compared to *immediate* prescription or *no* antibiotics for people with respiratory tract infections including sore throat, middle ear infection, cough (bronchitis), and the common cold. We included all RTIs regardless of whether antibiotics were indicated or not. We also evaluated antibiotic use, patient satisfaction, antibiotic resistance, reconsultation rates, and use of supplemental therapies. This is an update of a review published in 2007, 2010, and 2013.

Background

Prescribing too many antibiotics increases the risk of adverse reactions and results in higher healthcare costs and increased antibacterial resistance.

One strategy to reduce unnecessary antibiotic prescribing is to provide an antibiotic prescription, but with advice to delay filling the prescription. The prescriber assesses that *immediate* antibiotics are not immediately required, expecting that symptoms will resolve without antibiotics.

Study characteristics

Evidence is current to 25^{th} May 2017. We included 11 trials with a total of 3555 participants evaluating prescribing strategies for people with respiratory tract infections. Ten of these studies compared strategies of *delaying* antibiotics with *immediate* antibiotics. Four studies compared *delayed* antibiotics with *no* antibiotics. Of the 11 studies, five included only children (1173 participants), two included only adults (594 participants), and four included children and adults (1761 participants). The studies investigated a variety of respiratory tract infections. One study involving 405 participants was new for this update.

Key results

There were no differences between *immediate*, *delayed*, and *no* antibiotics for many symptoms including fever, pain, feeling unwell, cough, and runny nose. The only differences were small and favoured *immediate* antibiotics for relieving pain, fever, and runny nose for sore throat; and pain and feeling unwell for middle ear infections. Compared to *no* antibiotics, *delayed* antibiotics led to a small reduction in how long pain, fever, and cough persisted in people with colds. There was little difference in antibiotic adverse effects, and no significant difference in complications.

Patient satisfaction was similar for people who trialled *delayed* antibiotics (86% satisfied) compared to *immediate* antibiotics (91% satisfied), but was greater than *no* antibiotics (87% versus 82% satisfied). Antibiotic use was greatest in the *immediate* antibiotic group (93%), followed by *delayed* antibiotics (31%), and *no* antibiotics (14%).

In the first month after the initial consultation, two studies indicated that participants were no more likely to come back and see the doctor for *delayed* or *immediate* prescribing groups. Excluding the first month, one study found that participants were no more likely to return to see the doctor in the 12 months after the *delayed* or *immediate* prescription for another respiratory infection, and another study found that participants were more likely to come back and see the doctor in the next 12 months if they had had an *immediate* prescription compared to a *delayed* prescription.

Two studies including children with acute otitis media reported on the use of other medicines in *delayed* and *immediate* antibiotic groups. There was no difference in the use of ibuprofen, paracetamol, and otic drops in one study. In the other study, fewer spoons of paracetamol were used in the *immediate* antibiotic group compared with the *delayed* antibiotic group on the second and third day after the child's initial presentation. No included studies evaluated herbal or other forms of complementary medicine.

No included studies evaluated antibiotic resistance.

Quality of the evidence

Overall, the quality of the evidence was moderate according to GRADE assessment.

When doctors feel it is safe not to *immediately* prescribe antibiotics, advising *no* antibiotics but to return if symptoms do not resolve, rather than *delayed* antibiotics, will result in lower antibiotic use. However, patient satisfaction may be greater when a *delayed* prescribing strategy is used. Using a *delayed* antibiotic strategy will still result in a significant reduction in antibiotic use compared to the use of *immediate* antibiotics.

Editorial note: This is a living systematic review. Living systematic reviews offer a new approach to review updating in which the review is continually updated, incorporating relevant new evidence as it becomes available. Please refer to the Cochrane Database of Systematic Reviews for the current status of this review.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Delayed **antibiotics compared to** *immediate* **antibiotics for respiratory infections**

Patient or population: respiratory infections
Setting: primary care, emergency department, paediatric outpatients
Intervention: *delayed* antibiotics
Comparison: *immediate* antibiotics

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with *immediate* antibiotics	Risk with *delayed* antibiotics				
Clinical outcomes assessed with: pain, malaise, fever follow up: range 1 days to 7 days	10 included studies contributing data to this comparison measured clinical outcomes. For the 4 studies including participants with cough or common cold there was no evidence of difference for clinical outcomes. 5 studies included clinical outcome data for the presentation of sore throat, and for most clinical outcomes we found no evidence of difference. 2 studies measured clinical outcomes for participants with acute otitis media with 1 finding no evidence of difference in clinical outcomes, and the other favouring immediate antibiotics for malaise and pain severity on Day 3. There were sufficient outcome data to pool results for some clinical outcome measures. For participants with otitis media and sore throat, results favoured immediate antibiotics over *delayed* antibiotics for reducing pain and malaise severity on Day 3. For participants with common cold and otitis media, there was no evidence of differences in the number of participants with fever on Days 3 to 6		-	2419 (10 RCTs)	⊕⊕⊕◯ MODERATE	[1]

Antibiotic use: *delayed* versus immediate antibiotics	930 per 1000	348 per 1000 (286 to 401)	OR 0.04 (0.03 to 0.05)	1963 (7 RCTs)	⊕⊕⊕◯ MODERATE	[1]
Patient satisfaction: *delayed* versus immediate antibiotics	909 per 1000	866 per 1000 (795 to 916)	OR 0.65 (0.39 to 1.10)	1633 (6 RCTs)	⊕⊕⊕◯ MODERATE	[1]
Reconsultation rate: *delayed* versus immediate antibiotics	109 per 1000	113 per 1000 (63 to 196)	OR 1.04 (0.55 to 1.98)	379 (2 RCTs)	⊕⊕⊕◯ MODERATE	[1]
Adverse effects of antibiotics (Adverse effects) assessed with: diarrhoea, vomiting, rash follow-up: range 1 days to 7 days	The outcome of diarrhoea was measured by 4 studies and results favoured *delayed* antibiotics in 2 studies, and there was no evidence of difference the other 2. The outcome of vomiting was measured by 3 studies with no evidence of difference in 2, and results favouring immediate antibiotics in a third. The results for rash, measured by 2 studies, were sufficiently homogenous to conduct meta-analysis, and results showed no evidence of difference		-	1303 (5 RCTs)	⊕⊕◯◯ LOW	[12]

*__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; **RR:** Risk ratio; **OR:** Odds ratio;

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

[1] Downgraded 1 level because more than half of studies were not adequately blinded and did not adequately report allocation concealment
[2] Downgraded 1 level as results were inconsistent (I^2 = 93% for vomiting, I^2 = 72% for diarrhoea, I^2 = 0% for rash)

BACKGROUND

Description of the condition

Over the past 70 years antimicrobials have transformed medicine, greatly reducing morbidity and mortality. However, the development of resistance to antimicrobials has increased substantially in recent decades. Each year in the USA, at least 2 million people acquire infections with antibiotic-resistant bacteria, causing approximately 23,000 deaths (CDC 2017). The most significant cause for the development of resistance is considered to be excessive and inappropriate use of antibiotics for both humans, Goossens 2005; Sun 2012, and animals (Kempf 2016). A number of recent systematic reviews suggest that antibiotics only slightly modify the course of respiratory tract infections (RTIs) including acute otitis media (Venekamp 2015), sore throat (Spinks 2013), and acute bronchitis (Smith 2014), and have no effect on the common cold (Arroll 2013). Despite this, most antibiotics continue to be prescribed in primary care and mainly for people with RTIs (Goossens 2005; WHO 2014).

Description of the intervention

Strategies to reduce inappropriate antibiotic prescribing aim to reduce antibiotic resistance, adverse drug-related events, and healthcare costs (AHRQ 2016).

One strategy is to advise patients to delay filling prescriptions, and to fill it only if symptoms persist or deteriorate. *delayed* antibiotics have been advocated as a means of demonstrating to patients that antibiotics are not always necessary, without making them feel under-serviced (Arroll 2002b). Two ways of using this strategy have been deployed: giving the patient the antibiotic prescription (with instructions not to use unless there is deterioration), and making the prescription available at the clinic (to be picked up in the event of deterioration).

How the intervention might work

Delaying antibiotics may provide a feeling of safety for both patient and clinician should illness deteriorate. This intervention provides the safety of having a prescription of antibiotics available, yet an educational way of experiencing whether the illness resolves spontaneously without their use.

A systematic review showed that using *delayed* antibiotics for people with RTIs significantly reduced antibiotic prescribing (Arroll 2003a). The reduction ranged from a risk ratio (RR) of 0.77 (95% confidence interval (CI) 0.73 to 0.81) to RR 0.25 (95% CI 0.19 to 0.34) (Dowell 2001; Little 1997).

Why it is important to do this review

The *delayed* antibiotic strategy has been advocated as a safety net for avoiding rare but important complications of initially uncomplicated RTIs, and reducing antibiotic use, while enabling adequate control of symptoms and providing high levels of patient satisfaction (Little 2005b).

This review asked specifically what effect *delayed* antibiotics have on clinical outcomes for people with RTIs compared to *immediate* antibiotic provision and *no* antibiotics. It also evaluated the available data on antibiotic use, patient satisfaction, and antibiotic resistance for three prescribing strategies (*delayed* antibiotics, *immediate* antibiotics, and *no* antibiotics). This is a Cochrane Review update (Spurling 2007; Spurling 2010; Spurling 2013).

While previous versions of this systematic review have not supported the strategy of *delayed* antibiotic prescribing over *no* antibiotics, recommendations for delay persist in international guidelines, and continue to be discussed in the literature (De la Poza Abad 2016; NICE 2016).

A 2016 review that investigated strategies to improve antibiotic prescribing for people with uncomplicated RTIs prepared for the Agency for Healthcare Research and Quality in the USA highlighted the need for ongoing, systematic evaluation of these strategies, and the importance of ensuring that policy and practice is informed by a strong and up-to-date evidence base (AHRQ 2016). AHRQ 2016 also highlighted the need for further research reporting on resistance.

Following the publication of this 2017 review update, it will be maintained as a living systematic review. This means we will be continually running the searches, and incorporating any newly identified evidence (for more information about the living systematic review approach being piloted by Cochrane, see Appendix 1). We believe a living systematic review approach is appropriate for this review for the following reasons. First, the review addresses an important topic for clinical practice; second, this review has been identified as a priority review (Cochrane 2017); and third, we are planning to use this living systematic review as the basis of a living recommendation in a clinical practice guideline (Appendix 2).

OBJECTIVES

To evaluate the effects on clinical outcomes, antibiotic use, antibiotic resistance, and patient satisfaction of advising a *delayed* prescription of antibiotics in respiratory tract infections.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs). We included studies reported as full text, those published as abstract only, and unpublished data. Open randomised trials that did not include blinding were accepted for inclusion.

Types of participants

We included adults and children diagnosed with RTIs.

Types of interventions

We included trials that investigated use of the following.

1. *Delayed* antibiotic use, defined as a strategy involving the use of or advice to use antibiotics more than 48 hours after the initial consultation.
2. Immediate antibiotic use, defined as the immediate use of a prescription of oral antibiotics given at the initial consultation.
3. No antibiotic use, defined as no prescription of antibiotics at the initial consultation.

Types of outcome measures

Primary outcomes

We aimed to compare *delayed* antibiotics with *immediate* antibiotics and *delayed* antibiotics with*no* antibiotics.

1. Clinical outcomes for sore throat, acute otitis media, bronchitis (cough), and common cold (we included duration and severity measures for the following symptoms: pain, malaise, fever, cough, and rhinorrhoea).
2. Antibiotic use.
3. Patient satisfaction (measured on a four- to six-point Likert scale; we defined satisfaction as including moderately satisfied, very satisfied, and extremely satisfied).
4. Antibiotic resistance.

Secondary outcomes

1. Adverse effects of antibiotics.
2. Complications of disease.
3. Reconsultation.
4. Use of other therapies such as simple analgesia, e.g. paracetamol and ibuprofen.

Search methods for identification of studies

Electronic searches

For this 2017 update we searched the Cochrane Central Register of Controlled Trials (CENTRAL) (the Cochrane Library, Issue 4, to 25 May, 2017), which includes the Cochrane Acute Respiratory Infection Group's Specialised Register; Ovid MEDLINE In-Process & Other Non-Indexed Citations, Ovid MEDLINE Daily, and Ovid MEDLINE (2013 to 25 May 2017); Ovid Embase Classic+Embase (2013 to 2017 Week 21), EBSCO CINAHL Plus (1984 to 25 May 2017); Web of Science (2013 to 25 May 2017); WHO International Clinical Trials Registry Platform (1 September 2017); and ClinicalTrials.gov (1 September 2017).

In previous versions of this review, we searched MEDLINE using keywords and MeSH terms in conjunction with the highly sensitive search strategy designed by Cochrane for identifying RCTs (Dickersin 1994). We applied no trial filters for this update. Search strategies for all five databases can be found in Appendix 3.

We applied no language restrictions in any of the electronic database searches, but applied date restrictions to most of the databases, as this was an updated search.

These database searches are now being re-run using auto-alerts to deliver the monthly yield search by email. We will review search methods and strategies approximately yearly to ensure that they reflect any terminology changes in the topic area or in the databases.

Searching other resources

We checked reference lists of all primary studies and review articles for additional references. We planned to contact experts in the field to identify additional unpublished materials. As additional steps to inform the living systematic review, we will contact corresponding authors of ongoing studies as they are identified, and ask them to share early or unpublished data. We will also contact the corresponding authors of any newly included studies for advice as to other relevant studies. We will conduct citation tracking of included studies in Web of Science Core Collection on an ongoing basis, using citation alerts in Web of Science Core Collection.

Data collection and analysis

Selection of studies

Two review authors (RFo, GS) independently screened titles and abstracts of all potential studies identified by the search for inclusion in the review. We retrieved the full-text study reports, and three review authors (CDM, LD, GS) independently screened the full texts and identified studies for inclusion, and identified and recorded reasons for exclusion of the ineligible studies. Any disagreements were resolved through discussion or by consulting a third review author (RFo). We identified and excluded duplicates and collated multiple reports of the same study so that each study, rather than each report, was the unit of interest in the review. We recorded the selection process and completed a PRISMA flow diagram and 'Characteristics of excluded studies' table (Moher 2009). We did not impose any language restrictions. For the monthly searches, we will immediately screen any new citations retrieved.

Data extraction and management

We used a data collection form for study characteristics and outcome data that was piloted on at least one study in the review. Two review authors (LD, CDM) extracted study characteristics from the included studies. We extracted the following study characteristics.

1. Methods: study design, total duration of study, details of any 'run in' period, number of study centres and location, study setting, withdrawals, and date of study.
2. Participants: N, mean age, age range, gender, severity of condition, diagnostic criteria, baseline lung function, smoking history, inclusion criteria, and exclusion criteria.
3. Interventions: intervention, comparison, concomitant medications, and excluded medications.
4. Outcomes: primary and secondary outcomes specified and collected, and time points reported.
5. Notes: funding for trial, and notable conflicts of interest of trial authors.

Two review authors (LD, CDM) independently extracted outcome data from the included studies. We noted in the 'Characteristics of included studies' table if outcome data were not reported in a usable way. Any disagreements were resolved by consensus or by involving a third review author. One review author (RFo) 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 (GS) spot-checked study characteristics for accuracy against the trial report.

Assessment of risk of bias in included studies

Two review authors (LD, CDM) independently assessed risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). Any disagreements were resolved by discussion or by involving third review author (GS). We assessed risk of bias according to the following domains.

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

We graded each potential source of bias as high, low, or unclear and provided quotes from the study together with a justification for our judgement in 'Risk of bias' tables. We summarised the 'Risk of bias' judgements across different studies for each of the domains listed. We considered blinding separately for different key outcomes where necessary. Where information on risk of bias related to unpublished data or correspondence with a trialist, we noted this in 'Risk of bias' tables.

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

Assessment of bias in conducting the systematic review

We conducted the review according to the published protocol and reported any deviations from it in Differences between protocol and review.

Measures of treatment effect

We entered outcome data for each study into data tables in Review Manager 5 to calculate the treatment effects (RevMan 2014). We used odds ratio for dichotomous outcomes and mean differences or standardised mean differences for continuous outcomes.

We undertook meta-analyses only where this was meaningful, that is if treatments, participants, and the underlying clinical question were sufficiently similar for pooling to make sense.

Unit of analysis issues

The unit of analysis for each outcome was the individual study participant.

Dealing with missing data

We planned to contact investigators or study sponsors to verify key study characteristics and to obtain missing numerical outcome data where possible (e.g. when we identified a study as abstract only). Where this was not possible, and the missing data were thought to introduce serious bias, we planned to explore the impact of including such studies in the overall assessment of results by a sensitivity analysis.

We also planned that if numerical outcome data were missing, such as standard deviations or correlation coefficients, and they were not obtainable from the study authors, we would calculate these from other available statistics, such as P values, according to the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Assessment of heterogeneity

We used the I^2 statistic to measure heterogeneity among the trials in each analysis. If we identified substantial heterogeneity, we planned to report this and explore for possible causes in subgroup analysis.

Assessment of reporting biases

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

Data synthesis

We have reported much of the data in this review as a narrative synthesis describing outcome measures. As previously indicated, we pooled results where heterogeneity was satisfactorily low. We have conducted meta-analysis where results were sufficiently homogenous.

GRADE and 'Summary of findings' table

We created two 'Summary of findings' tables. One table dealt with the comparison of *delayed* antibiotics versus *immediate* antibiotics and included clinical outcomes, antibiotics use, patient satisfaction, adverse effects of antibiotics, and reconsultation rates (Summary of findings for the main comparison). The second table deals with the comparison of *delayed* antibiotics versus *no* antibiotics, and included clinical outcomes, antibiotics use, patient satisfaction, and adverse effects of antibiotics. 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 relates to the studies that contribute data to the meta-analyses for these outcomes (Atkins 2004). We used methods and recommendations described in Section 8.5 and Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), employing GRADEpro GDT software (GRADEpro GDT 2014). We justified all decisions to down- or upgrade the quality of studies using footnotes, and made comments to aid the reader's understanding of the review where necessary.

When we identify new evidence (studies, data or information) that meets the review inclusion criteria, we will immediately assess risk of bias and extract the data and incorporate it in the synthesis, as appropriate.

Subgroup analysis and investigation of heterogeneity

We considered subgroup analyses for all outcomes and included year of publication, clinical presentation, setting, and differences in the intervention. We considered subgroup analyses for studies including only children versus those including only adults where data were available.

We described two subgroup analyses that showed differences in outcomes. We further explored heterogeneity of antibiotic use in *delayed* antibiotic arms in analyses of different delay strategy methods; we also investigated heterogeneity of patient satisfaction with respect to blinding of outcome assessors and participants.

Sensitivity analysis

We conducted sensitivity analysis according to risk of bias.

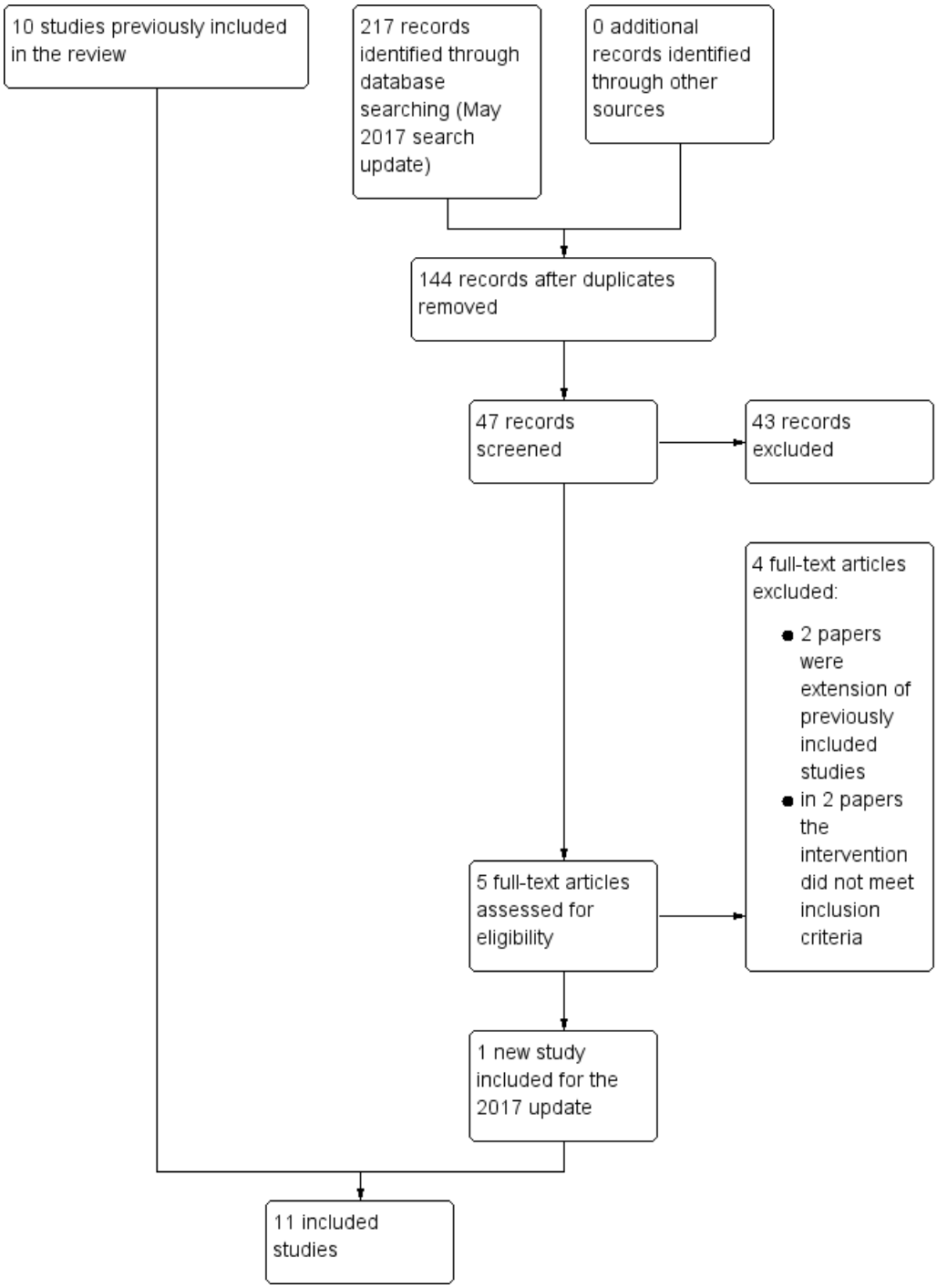
RESULTS

Description of studies

Results of the search

We identified 217 records in this update. We removed 73 duplicates and 97 records that were clearly not relevant based on title alone, leaving 47 records. We assessed titles and abstracts, and retrieved four full-text reports. Of these, one met our inclusion criteria (Figure 1). Of the remaining three, one was an excluded study (Agnew 2013), and the other two reported longer-term outcome data from studies that were already included in the review. Little 2006 reported long-term outcome data for the Little 2001 study, and Moore 2009 reported longer-term outcome data for Little 2005a. We considered these reports to be part of the originally included studies.

Figure 1. Study flow diagram.



Included studies

We included 11 trials involving a total of 3555 participants. Ten trials compared immediate provision of antibiotics with *delayed* antibiotics; four trials investigated sore throat (pharyngitis); two trials considered acute otitis media (AOM); two evaluated cough (bronchitis); one investigated common cold; and one included a number of acute upper RTIs.

Of the 11 included trials, 1357 participants were randomised to receive *delayed* antibiotics. In 10 of these trials, 1168 participants were allocated to receive *immediate* antibiotics, and in four trials 564 participants were allocated to receive *no* antibiotics. Four studies compared the prescribing strategy of *no* antibiotics with *delayed* antibiotics (Chao 2008; De la Poza Abad 2016; Little 1997; Little 2005a). These four trials investigated the presentations of pharyngitis/sore throat (De la Poza Abad 2016; Little 1997), bronchitis (cough) (De la Poza Abad 2016; Little 2005a), AOM (Chao 2008), and the common cold/rhinosinusitis (De la Poza Abad 2016). Please see the Characteristics of included studies table for details of the included trials.

Motives for studying *delayed* antibiotics

Early studies of sore throat were designed as efficacy trials to identify the rate of relapse of group A beta-haemolytic streptococcus (GABHS) throat in immediate versus *delayed* antibiotic groups (El-Daher 1991; Gerber 1990; Pichichero 1987). Subsequent trials comparing *delayed* antibiotics and *immediate* antibiotics were conducted with a view to evaluate the use of*delayed* antibiotics to reduce the use of antibiotics for upper respiratory tract infections (Arroll 2002a; De la Poza Abad 2016; Dowell 2001; Little 1997; Little 2001; Spiro 2006).

Population

Of the 11 included studies, five included only children (Chao 2008; El-Daher 1991; Little 2001; Pichichero 1987; Spiro 2006), two included only adults (De la Poza Abad 2016; Dowell 2001), and four included both adults and children (Arroll 2002a; Gerber 1990; Little 1997; Little 2005a).

Setting

Of the 11 included studies, six were conducted in a primary care setting (Arroll 2002a; De la Poza Abad 2016; Dowell 2001; Little 1997; Little 2001; Little 2005a), three in paediatric clinics (El-Daher 1991; Gerber 1990; Pichichero 1987), and two in emergency departments (Chao 2008; Spiro 2006).

Excluded studies

Two of the studies identified in searches were extensions of previously included studies (Little 2006; Moore 2009). We excluded one RCT because it compared usual delayed antibiotics with a post-dated script for delayed antibiotics, and did not include either an *immediate* antibiotic or a *no* antibiotic arm (Worrall 2010). We excluded one new study for this update because it investigated information leaflets rather than prescribing strategies (Agnew 2013). We excluded a total of nine studies; the other seven studies were not RCTs (Cates 1999; De la Poza Abad 2013; Fischer 2009; Little 2014; Newson 2009; Siegel 2003; Vouloumanou 2009).

Risk of bias in included studies

Overall, we assessed the included studies as at low risk of bias. Studies were most likely to be assessed as at unclear or moderate risk of bias for the domains of allocation concealment and blinding. Almost all studies showed a low risk of bias for all other domains. We assessed randomisation of studies as low risk for all of the included studies except for two, for which the randomisation was unclear. We assessed allocation concealment as low risk of bias for four studies, unclear for two studies, and high risk of bias for the five remaining studies. We assessed blinding as low risk of bias in three studies and high risk of bias for the remaining eight studies. For incomplete data, we assessed 10 studies as at low risk of bias and the remaining study as at high risk of bias. We assessed selective reporting as low risk of bias in 10 studies and unclear in one study. We detected no other biases apart from bias associated with funding source. Two studies were funded by pharmaceutical companies and were assessed as at high risk of bias. We assessed two studies for which the funding source was not described as at unclear risk of bias. The remaining seven studies were funded by state institutions or specialist college and were assessed as at low risk of bias. Summaries of the risk of bias in included studies are provided in Figure 2 and Figure 3.

Figure 2. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.

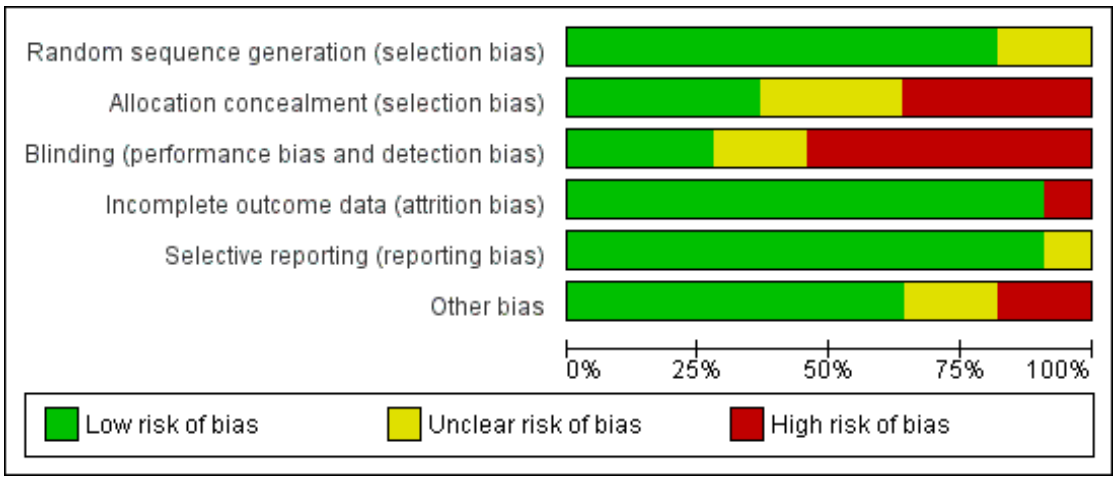
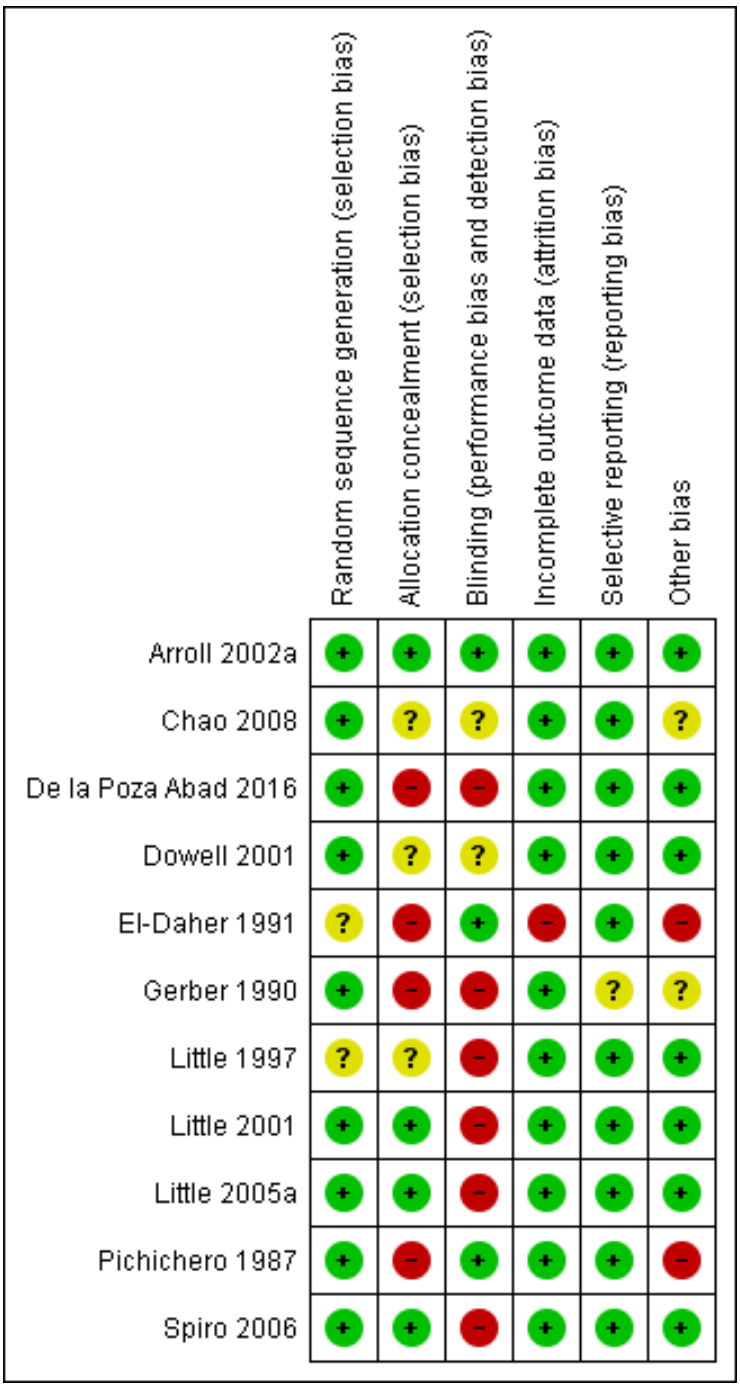


Figure 3. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.



Allocation

Nine studies reported using random number tables or computer-generated randomisation and were assessed as at low risk of bias. Two studies did not describe randomisation methods and were assessed as at unclear risk of bias (El-Daher 1991; Little 1997). Four trials described adequate allocation concealment using opaque envelopes and were assessed as at low risk of bias (Arroll 2002a; Little 2001; Little 2005a; Spiro 2006). We assessed the remaining studies as at unclear or high risk of bias.

Blinding

Seven studies attempted to blind some or all aspects of the study, that is participants, prescribing doctors, and outcome assessors were blinded. We assessed three studies as at low risk of bias because they attempted to blind participants and prescribing doctors without indicating if the outcome assessor was blinded (Arroll 2002a; El-Daher 1991; Pichichero 1987). In one study, participants were informed only that they would be given one of two sets of instructions about taking antibiotics for their colds. Participants read an information sheet and completed a consent form. Participants were thus blinded to what the other group would take (Arroll 2002a). Two studies used placebo (tablets) to blind participants (El-Daher 1991; Pichichero 1987). We assessed the remaining eight studies as at high risk of bias in this domain. Of these eight studies, the outcomes assessor, but not participants or prescribing doctors, were blinded in four studies (Chao 2008; Dowell 2001; Little 2005a; Spiro 2006). No blinding was reported in the other four studies (De la Poza Abad 2016; Gerber 1990; Little 1997; Little 2001).

Incomplete outcome data

We assessed one study as at high risk of bias for incomplete data reporting because the numbers of participants enrolled did not match the numbers of participants analysed, and this disparity was not explained (El-Daher 1991). We assessed all other studies as at low risk of bias, with no or very small numbers of participant dropout.

Selective reporting

Gerber 1990 reported all clinical outcomes as one aggregated outcome and was assessed as at unclear risk of bias. We assessed all of the other studies as at low risk of bias because they reported on their predetermined outcome measures.

Other potential sources of bias

Six included studies received grants from research bodies funded by the national government where the trial was conducted (Arroll 2002a; De la Poza Abad 2016; Little 1997; Little 2001; Little 2005a; Spiro 2006). One study received funding from their relevant specialist college (Dowell 2001). We assessed these seven studies as at low risk of bias. We assessed two studies as at high risk of bias because they received funding from pharmaceutical companies. One study, El-Daher 1991, was funded by Biochemie GmbH and the local university. Another study, Pichichero 1987, was funded by both a philanthropic organisation and a pharmaceutical company (Eli Lilly). Two studies did not describe the funding source (Chao 2008; Gerber 1990), and we have assessed them as at unclear risk of bias.

Effects of interventions

See: **Summary of findings for the main comparison** Delayed antibiotics compared to immediate antibiotics for respiratory infections; **Summary of findings 2** Delayed antibiotics compared to No antibiotics for respiratory infections

We assessed the effects of interventions using all 11 included studies. Details of the interventions are presented in Table 1 as per reporting recommendations published in 2017 (Hoffman 2017). Assessing the effectiveness of antibiotic prescribing strategies was complicated by the heterogeneity of RTIs considered by the included studies. This heterogeneity is important because clinical outcomes are known to be influenced by antibiotics in different ways depending on the type of RTI. For example, antibiotics have been shown to reduce pain in otitis media (Venekamp 2015), but make no difference to the symptoms of the common cold (Kenealy 2013). Additionally, authors of studies measuring the same RTI reported clinical outcomes in a variety of ways which could not readily be compared even after we obtained raw study data. However, we did combine the outcomes of pain (Days 3 to 6; Analysis 1.1, Analysis 1.2), malaise (Days 3 to 6; Analysis 2.1, Analysis 2.2), and fever (Days 3 to 6; Analysis 3.1, Analysis 3.2), and conducted meta-analysis where this was not precluded by heterogeneity. Other clinical outcomes are presented in Table 2 for the comparison of *delayed* antibiotics versus *immediate* antibiotics, and in Table 3 for the comparison of *delayed* antibiotics versus *no* antibiotics.

De la Poza Abad 2016 divided its *delayed* antibiotic arm into two parts, that is a patient-led prescription strategy and a prescription collection strategy. The patient-led prescription strategy involved the doctor providing the patient with a prescription that they could fill at a pharmacy if they decided they needed to take antibiotics based on their assessment of their symptoms. The prescription collection strategy involved patients returning to the primary care

health service to collect their prescription, and then filling it at a pharmacy if they decided they required antibiotics based on their assessment of their symptoms. The clinical outcomes of this study are presented in Table 2 and Table 3.

Regarding the other primary outcomes, we conducted meta-analyses for antibiotic use (Analysis 4.1, Analysis 4.2) and patient satisfaction (Analysis 5.1, Analysis 5.2). No data were available for antibiotic resistance.

The secondary outcomes of adverse effects of antibiotics (Analysis 6.1, Analysis 6.2, Analysis 6.3) and reconsultation (Analysis 7.1) are presented with meta-analysis where there was sufficient homogeneity of included study data.

Subgroup analysis

For most subgroups, there were insufficient data to justify subgroup analysis. However, we did analyse the two different strategies of delaying antibiotics (prescription at consult with advice to delay and return to collect prescription). Regarding study population, two studies included only adult participants (De la Poza Abad 2016; Dowell 2001), and neither study contributed data that could be compared with other studies. Five studies included only child participants (Chao 2008; El-Daher 1991; Little 2001; Pichichero 1987; Spiro 2006); when these studies were analysed separately there were no changes to important outcome results except for the outcome of patient satisfaction. However, just one study involving only children measured patient satisfaction for *delayed* antibiotics versus *immediate* antibiotics (Little 2001). Additionally, just one study involving only children measured patient satisfaction for *delayed* antibiotics versus *no* antibiotics (Chao 2008). We have reported the results of the subgroup analysis for patient satisfaction below in the appropriate section.

Primary outcomes

1. Clinical outcomes for sore throat, acute otitis media, bronchitis, and common cold

The results for clinical outcomes were based on moderate-quality evidence according to GRADE assessment, and are summarised in Summary of findings for the main comparison for *delayed* versus *immediate* antibiotics, and Summary of findings 2 for *delayed* versus *no* antibiotics.

Sore throat

Five included studies specifically examined sore throat (N = 1573) (De la Poza Abad 2016; El-Daher 1991; Gerber 1990; Little 1997; Pichichero 1987).

Delayed antibiotics versus immediate antibiotics

Pain was not significantly different for *delayed* and immediate antibiotic groups in three studies (N = 939) (Gerber 1990; Little 1997; Pichichero 1987) (Table 2). In one study (El-Daher 1991), pain was reported by a higher proportion of participants in the *delayed* antibiotic group (N = 118) on Day 3 compared to the immediate antibiotic group (N = 111) with an odds ratio (OR) of 14.51 (95% confidence interval (CI) 7.14 to 29.50) (Table 2). Participants in the *delayed* antibiotic arms (N = 91) of the study by De la Poza Abad 2016 reported longer pain duration than participants in the immediate antibiotic arm (N = 94) with a mean difference (MD) of 2.01 days (95% CI 0.75 to 3.26). For participants given a script at the time of consultation this difference was smaller with a MD of 1.30 days (95% CI -0.34 to 2.94) than for participants required to return to pick up the script where the MD was 3.00 days (95% CI -1.03 to 4.95) (Table 2).

Two studies measured malaise (Day 3) for *delayed* and immediate antibiotic groups, with one study finding no evidence of difference in malaise severity on Day 3 (N = 114) (Table 2) (Pichichero 1987). The other study detected a much higher proportion of participants with malaise on Day 3 in the *delayed* antibiotic group (N = 118) compared to the immediate antibiotic group (N = 111), with an OR of 16.49 (95% CI 5.68 to 47.83) (Table 2) (El-Daher 1991).

Five studies measured fever for *delayed* and *immediate* antibiotics groups (N = 1573) (De la Poza Abad 2016; El-Daher 1991; Gerber 1990; Little 1997; Pichichero 1987). Two studies did not report fever in a way that could be readily compared with other studies (Gerber 1990; Little 1997). Two studies found fever severity on Day 3 to be higher for participants in the *delayed* antibiotic group than in the immediate antibiotic group (N = 343) (El-Daher 1991; Pichichero 1987), with a pooled MD of 0.53 °C (95% CI 0.31 to 0.74) (N = 343) (Analysis 1.1). One study found that the median number of days of fever experienced by participants in the *delayed* antibiotic group (N = 235) was one day longer than for the immediate antibiotic group (N = 247) (P = 0.04) (Little 1997). However, in one study (N = 405) (De la Poza Abad 2016), the number of days with fever was not significantly different for participants in the *delayed* antibiotic group compared to the immediate antibiotic group (Table 2).

Delayed antibiotics versus no antibiotics

Two studies that recruited participants with sore throat compared the prescribing strategy of *delayed* antibiotics with *no* antibiotics (N = 1117) (De la Poza Abad 2016; Little 1997). These studies found no evidence of difference in any clinical outcome between these two prescribing strategies (Table 3).

Complications

Data on complications of sore throat such as rheumatic fever, poststreptococcal glomerulonephritis, and peritonsillar abscess were not reported in any of the five studies evaluating sore throat for the three prescribing strategies of immediate, *delayed*, and *no* antibiotics.

Acute otitis media

Three included studies recruited participants with AOM (N = 830) (Chao 2008; Little 2001; Spiro 2006).

Delayed antibiotics versus immediate antibiotics

Two studies (N = 598) compared the prescribing strategies of *delayed* antibiotics versus *immediate* antibiotics for AOM (Little 2001; Spiro 2006). One of these studies (N = 283) measured pain and fever on Days 4 to 6 and found no evidence of difference (Table 2) (Spiro 2006). In the other study (N = 315) (Little 2001), pain and malaise on Day 3 were reported by a greater proportion of participants randomised to the *delayed* antibiotics group compared to the *immediate* antibiotics group (Table 2) (Little 2001). Further analysis of earache from one trial found that the *delayed* antibiotic prescribing strategy did not significantly increase risk of earache at three months (OR 0.89, 95% CI 0.48 to 1.65) or one year (OR 1.03, 95% CI 0.60 to 1.78) (Little 2006).

Delayed antibiotics versus no antibiotics

Only one study compared *delayed* antibiotics with *no* antibiotics (N = 232) (Chao 2008). In this study, no significant difference was detected for the outcomes of pain or fever for participants in *delayed* antibiotic and immediate antibiotic groups (Table 3). This trial also advised participants in the no antibiotic arm to return in two to three days if symptoms did not resolve (Chao 2008).

Complications

Data on complications of AOM such as mastoiditis, rheumatic fever, and poststreptococcal glomerulonephritis were not reported in any of the three studies evaluating AOM for the prescribing strategies of immediate and *delayed* antibiotics. However, Spiro 2006 and Chao 2008 reported that no serious adverse events had occurred in participants in their studies (N = 515).

Bronchitis (cough)

Delayed antibiotics versus immediate antibiotics

Three studies examined the prescribing strategies of immediate versus *delayed* antibiotics for the clinical presentation of cough (N = 1401) (De la Poza Abad 2016; Dowell 2001; Little 2005a). None of the studies found any difference in clinical outcomes including pain, fever, and cough (Table 2).

Delayed antibiotics versus no antibiotics

De la Poza Abad 2016 and Little 2005a (N = 1212) also evaluated *delayed* antibiotics versus *no* antibiotics, finding no evidence of difference in clinical outcomes (Table 3).

Complications

One participant in the no antibiotic group (N = 273) of one study developed pneumonia, and recovered with antibiotics in hospital (Little 2005a). Another study (N = 405) reported that there were no evidence of differences in complication rates between the *delayed* and immediate antibiotic groups (De la Poza Abad 2016). The third study (N = 189) did not report on complications in the immediate and *delayed* antibiotic groups (Dowell 2001).

Common cold

Delayed antibiotics versus immediate antibiotics

Two studies examined *immediate* antibiotics versus *delayed* antibiotics (N = 534) and found no evidence of difference between the two prescribing strategies for fever, cough, pain, malaise, and rhinorrhoea except for the outcome of fever severity on Day 7 which favoured *delayed* antibiotics (Table 2) (Arroll 2002a; De la Poza Abad 2016).

Delayed antibiotics versus no antibiotics

De la Poza Abad 2016 (N = 405) compared *delayed* antibiotics with *no* antibiotics and found a reduction in pain duration in the patient-led prescription *delayed* antibiotic strategy and reductions in fever and cough duration for both delay strategies (patient-led prescription and prescription collection) compared with *no* antibiotics (Table 3). There was no evidence of difference between *delayed* and no antibiotic prescribing groups for the outcome of nasal mucosity (Table 3).

Pooling of clinical outcomes (*delayed* versus *immediate* antibiotics)

Sufficient study data were available to allow the pooling of results for the outcomes of pain (Days 3 to 6), pain severity (Day 3), malaise (Day 3), malaise severity (Day 3), fever (Days 3 to 6), and fever severity (Day 3) for the comparison of *delayed* versus *immediate* antibiotics. We conducted meta-analysis for study data where results were sufficiently homogenous. Data were insufficient to pool results for the comparison *delayed* versus *no* antibiotics.

Pain

There was significant heterogeneity of study data for the outcome of pain on Days 3 to 6 (Analysis 1.1). For three studies there was no evidence of difference examining the clinical conditions of common cold and otitis media (Arroll 2002a; Little 2001; Spiro 2006). One study that included participants with sore throat favoured *immediate* antibiotics (El-Daher 1991). Meta-analysis for the two studies that measured pain severity on Day 3 found in favour of *immediate* antibiotics with an MD of 0.35 (95% CI 0.13 to 0.57) (Analysis 1.2).

Malaise

There was significant heterogeneity of study data for the outcome of malaise on Day 3 (Analysis 2.1). However, both studies found in favour of *immediate* antibiotics. One study included participants with otitis media (Little 2001), the other participants with sore throat (El-Daher 1991). Meta-analysis of the two studies measuring malaise severity on Day 3 found in favour of *immediate* antibiotics with an MD of 0.29 (95% CI 0.09 to 0.48) (Analysis 2.2). One of these studies recruited participants with sore throat (Pichichero 1987), the other participants with AOM (Little 2001).

Fever

Two studies provided data that could be combined for the outcome of fever on Days 3 to 6 (Arroll 2002a; Spiro 2006). Meta-analysis of these data found no evidence of difference with an OR of 0.86 (95% CI 0.54 to 1.38) (Analysis 3.1). The three studies providing data on fever severity on Day 3 provided heterogenous results. One study including participants with the common cold found no evidence of difference in fever severity on Day 3 with an MD of -0.24 (95% CI -0.48 to -0.00) (Arroll 2002a). Two studies found results favouring *immediate* antibiotics; both studies included participants with sore throat (Analysis 3.2). The first study was Pichichero 1987 (MD 0.40, 95% CI 0.05 to 0.75), and the second was El-Daher 1991 (MD 0.90, 95% CI 0.50 to 1.30) (Analysis 3.2).

2. Antibiotic use

Delayed antibiotics versus immediate antibiotics

The three included studies published before 1992 investigated the concern that *immediate* antibiotics for streptococcal pharyngitis might impair the body's immune response and predispose the patient to a relapse of pharyngitis (El-Daher 1991; Gerber 1990; Pichichero 1987). Antibiotic use in both immediate and *delayed* antibiotic groups was close to 100% as intended. Seven of the included studies published after 1992 (N = 2840) evaluated *delayed* antibiotics as a way to reduce antibiotic use for respiratory infections compared to *immediate* antibiotics (Arroll 2002a; De la Poza Abad 2016; Dowell 2001; Little 1997; Little 2001; Little 2005a; Spiro 2006). All seven studies found that antibiotic use was significantly reduced in the *delayed* antibiotic group compared to the immediate antibiotic group. There were significant differences in the way antibiotics were *delayed*, which may have resulted in the marked heterogeneity of this result. Of the eight studies published after 1991, four had the *delayed* script kept at reception to be picked up (N = 2023) (Dowell 2001; Little 1997; Little 2001; Little 2005a), while in three the script was issued to patients with instructions to delay (N = 644) (Arroll 2002a; Chao 2008; Spiro 2006). De la Poza Abad 2016 was specifically designed to determine the relative efficacy and safety of two delayed strategies: one where the delayed script was kept at the primary care centre to be picked up (prescription collection) and one where the script was issued to patients with instructions to delay (patient-led prescription). For the delayed arms of the five studies where the script was left at reception, antibiotics were used in 27% of cases (196/718) compared with use of antibiotics in 38% of cases (154/403) where antibiotics were issued to patients with instructions to delay (Analysis 4.1). One included study compared *delayed* antibiotics with *no* antibiotics and did not include an immediate antibiotic prescribing arm (Chao 2008). Of the eight trials conducted after 1992 that included a *delayed* antibiotic arm, we found 350 prescriptions filled out for 1121 participants (31.2%) (Analysis 4.1). Pooled results of these studies showed that *delayed* antibiotics resulted in a significant reduction in antibiotic use compared to *immediate* antibiotics (OR 0.04, 95% CI 0.03 to 0.05) (Analysis 4.1). This evidence is moderate quality according to GRADE assessment (Summary of findings for the main comparison).
Seven trials published after 1992 provided immediate antibiotic arms measuring this outcome, resulting in 882 out of 948 participants (93.0%) filling prescriptions (Analysis 4.1).

Delayed antibiotics versus no antibiotics

Four studies compared *delayed* antibiotics with *no* antibiotics (N = 1241) (Chao 2008; De la Poza Abad 2016; Little 1997; Little 2005a). Pooled results of these studies showed that 77 out of 564

participants in the no antibiotic arms filled scripts (13.7%). More participants in the *delayed* antibiotic groups filled prescriptions compared with the no antibiotic groups (OR 2.55, 95% CI 1.59 to 4.08) (Analysis 4.2). This evidence is moderate quality according to GRADE assessment (Summary of findings 2).

3. Patient satisfaction

Delayed antibiotics versus immediate antibiotics

Patient satisfaction was measured in six (of eight) studies since 1992 (N = 1663) that evaluated *delayed* prescribing (Analysis 5.1) (Arroll 2002a; De la Poza Abad 2016; Dowell 2001; Little 1997; Little 2001; Little 2005a). The pooled result for all six studies showed no evidence of difference between the number of participants in the *delayed* antibiotic group who were satisfied or very satisfied compared to the immediate antibiotic group (OR 0.65, 95% CI 0.39 to 1.10) (Analysis 5.1). For the same outcome, we obtained a similar OR of 0.62 (95% CI 0.38 to 1.01) for the three studies that included elements of blinding (N = 1125) (Arroll 2002a; Dowell 2001; Little 2005a). Similarly, the three studies without any blinding (N = 1432) found an OR for this outcome of 0.64 (95% CI 0.27 to 1.55) (De la Poza Abad 2016; Little 1997; Little 2001). For the six studies addressing this outcome, 91% of participants in the *immediate* antibiotics arms were satisfied or very satisfied compared with 86% of participants in the *delayed* antibiotics arms. The one study that involved only child participants found in favour of *immediate* antibiotics, with an OR of 0.32 (95% CI 0.16 to 0.65) (Little 2001). These results are based on moderate-quality evidence according to GRADE assessment (Summary of findings for the main comparison).

Delayed antibiotics versus no antibiotics

Four studies examined patient satisfaction for *delayed* antibiotics compared with *no* antibiotics (N = 1234) (Chao 2008; De la Poza Abad 2016; Little 1997; Little 2005a). The pooled result of all four studies showed that more participants were satisfied or very satisfied in the *delayed* antibiotic group compared with the no antibiotic group (OR 1.49, 95% CI 1.08 to 2.06) (Analysis 5.2). The number needed to treat with *delayed* antibiotics rather than *no* antibiotics to achieve a satisfied or very satisfied patient is 22.5. Fixed-effect and random-effects analyses gave similar results. The two trials that blinded the outcome assessor found a similar OR for this outcome (OR 1.42, 95% CI 0.92 to 2.19) (N = 1039) (Chao 2008; Little 2005a). Similarly, the two unblinded trials found an OR of 1.58 (95% CI 0.97 to 2.55) (N = 1117) (De la Poza Abad 2016; Little 1997). For the four studies addressing this outcome, 87% of participants in the *delayed* antibiotic group were satisfied or very satisfied compared with 82% in the *no* antibiotics group. The one study that involved only child participants found no evidence of difference, with an OR of 2.00 (95% CI 0.65 to 6.18) (Chao 2008). These results are based on moderate-quality evidence according to GRADE assessment (Summary of findings 2).

4. Antibiotic resistance

None of the included studies evaluated antibiotic resistance.

Secondary outcomes

1. Adverse effects of antibiotics

Seven studies reported on the adverse effects of antibiotics (N = 2707) (Arroll 2002a; Chao 2008; El-Daher 1991; Little 1997; Little 2001; Little 2005a; Spiro 2006).

Delayed antibiotics versus *immediate* antibiotics

Heterogeneity of outcomes for adverse events may be due to differences in antibiotic prescribing recommendations for different RTIs. This is likely to have contributed to the heterogeneity evident for these outcomes, preventing pooling of results except for the outcome of rash, for which there was no significant difference (OR 1.03, 95% CI 0.54 to 1.97). Overall results for adverse effects comparing *delayed* and *immediate* antibiotics are presented for the outcomes of vomiting (N = 888) (Analysis 6.1), diarrhoea (N = 1073) (Analysis 6.2), and rash (N = 1027) (Analysis 6.3). The evidence presented below is low quality evidence according to GRADE assessment owing to concerns about bias from lack of blinding, concerns about allocation concealment, and heterogeneity of outcome data (Summary of findings for the main comparison).

Sore throat

Little 1997 found no evidence of difference for diarrhoea, vomiting, rash, and stomachache for participants in *delayed* and immediate antibiotic groups. El-Daher 1991 found more vomiting associated with *delayed* compared to *immediate* antibiotics.

Acute otitis media

Little 2001 and Spiro 2006 found reduced diarrhoea in the *delayed* antibiotic group. Spiro 2006 found no evidence of difference between *delayed* and *immediate* antibiotics for vomiting, and Little 2001 found no evidence of difference for rash.

Cough

Little 2005a found no evidence of difference for adverse effects.

Common cold

There was no significant difference between *delayed* and immediate antibiotic groups for diarrhoea, a potential adverse effect of antibiotics (Arroll 2002a).

Delayed antibiotics versus *no* antibiotics

There were too few studies measuring adverse effects of antibiotics for the comparison of *delayed* versus *no* antibiotics to justify pooling results. Little 1997 (N = 712) found no evidence of difference for the outcome of vomiting in participants with sore throat (OR 0.68, 95% CI 0.34 to 1.36). Little 1997 also found no evidence of difference for the outcome of diarrhoea (OR 1.57, 95% CI 0.80 to 3.07). In the study by Chao 2008 (N = 232) of children with AOM there were no reports of diarrhoea in either the *delayed* or *no* antibiotics group. Little 1997 found no evidence of difference for the outcome of rash between *delayed* antibiotics and *no* antibiotics (OR 0.51, 95% CI 0.24 to 1.10). These results were assessed as moderate-quality evidence according to GRADE assessment (Summary of findings 2).

2. Complications of disease

There was no significant difference in complication rates between the three prescribing strategies. Five studies reported on complications or serious adverse effects (N = 1856) (Arroll 2002a; Chao 2008; De la Poza Abad 2016; Little 2005a; Spiro 2006). More details of disease complications are reported above under clinical outcomes for each disease category.

3. Reconsultation rates

Reconsultation rates were similar between *delayed* and immediate antibiotic groups in two studies. Pooling resulted in an OR of 1.04 (95% CI 0.55 to 1.98) (N = 379) (Analysis 7.1). Subsequent consultation rates in the 12 months (excluding the first month) were also similar between *delayed* and immediate antibiotic groups in one study (Little 2001). Participants with sore throat in one study were more likely to intend to consult again if they received *immediate* antibiotics compared to those who received *delayed* antibiotics (Little 1997). These results are based on moderate quality evidence according to GRADE assessment (Summary of findings for the main comparison).

4. Use of other therapies

Three studies reported on use of other medicines (N = 1802) (Little 1997; Little 2001; Spiro 2006). In one study (Little 1997), there was no evidence of difference in analgesic use for participants with sore throat presenting to primary care in immediate, *delayed*, and no antibiotic prescribing groups. Two studies looked at analgesic use in children with AOM. One study evaluating children presenting to primary care found less paracetamol was consumed in the immediate antibiotic group compared with the *delayed* antibiotic group (Little 2001). The other study, which evaluated children presenting to an emergency department, found no evidence of difference between groups in paracetamol and ibuprofen use (Spiro 2006).

ADDITIONAL SUMMARY OF FINDINGS [Explanation]

Delayed **antibiotics compared to** *no* **antibiotics for respiratory infections**

Patient or population: respiratory infections
Setting: Primary care, emergency department
Intervention: *delayed* antibiotics
Comparison: *No* antibiotics

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with *no* antibiotics	Risk with *delayed* antibiotics				
Clinical outcomes (clinical outcomes) assessed with: pain, fever, cough, nasal mucosity, follow-up: range 1 days to 16 days	4 studies measured clinical outcomes for this comparison. 2 studies recruited participants with sore throat, one study recruited participants with otitis media, and 1 study recruited participants with cough, and for these studies there was no evidence of differences found. 1 study recruited participants with the common cold, and found results favouring *delayed* antibiotics for pain, fever, and cough duration, but no evidence of difference for nasal mucosity		-	955 (4 RCTs)	⊕⊕⊕◯ MODERATE	[1]
Antibiotic use: *delayed* versus *no* antibiotics	137 per 1,000	287 per 1,000 (201 to 392)	OR 2.55 (1.59 to 4.08)	1241 (4 RCTs)	⊕⊕⊕◯ MODERATE	[1]
Patient satisfaction: *delayed* versus *no* antibiotics	824 per 1,000	875 per 1,000 (835 to 906)	OR 1.49 (1.08 to 2.06)	1235 (4 RCTs)	⊕⊕⊕◯ MODERATE	[1]
Adverse effects of antibiotics (adverse effects) assessed with: vomiting, diarrhoea, rash,	2 studies measured adverse effects. 1 recruited participants with sore throat, and 1 with otitis media. Neither study found any difference in adverse effects		-	566 (2 RCTs)	⊕⊕⊕◯ MODERATE	[1]

follow-up: range 1 days to 7 days				

*__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; **RR:** Risk ratio; **OR:** Odds ratio;

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

[1] Downgraded 1 level for inadequate blinding for all studies, and allocation concealment not adequately reported for more than half of studies

DISCUSSION

Summary of main results

Results for clinical outcomes were often heterogeneous. For most outcomes there was no evidence of difference between *delayed* antibiotics and both immediate and no antibiotic prescribing strategies. Insufficient data precluded pooling of study data for the comparison of *delayed* and *no* antibiotics. Where data could be pooled for the strategies of *delayed* and *immediate* antibiotics, results favoured *immediate* antibiotics for pain severity on Day 3 (participants presented with otitis media and sore throat) and malaise severity on Day 3 (participants presented with otitis media and sore throat). There was no evidence of differences in the number of participants with fever on Days 3 to 6 (participants presented with the common cold and otitis media). All strategies appear to have similar safety with no advantage for *delayed* antibiotics over either *no* antibiotics or *immediate* antibiotics for disease complications. *delayed* and no antibiotic strategies markedly reduced the use of antibiotics for RTIs compared to *immediate* antibiotics. The least antibiotic use was in the no antibiotic group, followed by *delayed* and then immediate antibiotic groups. The number needed to treat to prevent one antibiotic prescription using the *delay* strategy was 1.6 compared to *immediate* antibiotics. The number needed to treat to prevent one antibiotic prescription using a no antibiotic strategy compared to a *delayed* antibiotic strategy was 7.0. Patient satisfaction was highest in the immediate antibiotic group, with 91% being moderately satisfied, very satisfied, or extremely satisfied with the consultation. The *delayed* antibiotic group was more satisfied (87%) than the no antibiotic group (83%). These high satisfaction results may reflect patient involvement in studies, where treating physicians were more thorough in their explanations than usual (Hawthorne effect) (French 1950; Levitt 2011). No data were available regarding antibiotic resistance.

Overall completeness and applicability of evidence

Studies comparing *delayed* and *immediate* antibiotics have been performed with two different motives. The studies of Pichichero 1987, Gerber 1990, and El-Daher 1991 were concerned that *immediate* antibiotics for streptococcal pharyngitis might impair the body's immune response and predispose the patient to a relapse of pharyngitis. These studies are useful for determining the effect of *delayed* versus *immediate* antibiotics on the clinical course of suspected streptococcal pharyngitis. Seven of the remaining studies were conducted to determine if the strategy of *delayed* antibiotics reduces the number of prescriptions filled for RTIs while maintaining patient safety and satisfaction (Arroll 2002a; De la Poza Abad 2016; Dowell 2001; Little 1997; Little 2001). The most recent study, De la Poza Abad 2016, further aimed to explore the relative efficacy and safety of two *delayed* prescribing strategies.
Useful data were collected for many symptom outcomes in all studies but were not always reported in a way that could be analysed or compared with other studies. This problem was partially overcome by obtaining raw data from some trial authors. The eight studies conducted after 1992 all reported useful data on antibiotic use, and seven reported useful data on patient satisfaction.
Four trials compared *delayed* antibiotics with *no* antibiotics.
There were no data on levels of antibiotic resistance.

Quality of the evidence

All but one trial, El-Daher 1991, were adequately randomised and accounted for incomplete data. El-Daher 1991 did find large differences for clinical outcomes for sore throat in favour of *immediate* antibiotics compared to *delayed* antibiotics.
The assessed interventions did not lend themselves to blinding. However, three trials attempted to blind participants and doctors (Arroll 2002a; El-Daher 1991; Pichichero 1987). In four studies the outcomes assessor was blinded, but neither participants nor caregivers were blinded (Chao 2008; Dowell 2001; Little 2005a; Spiro 2006).
Otherwise, studies were well reported. The GRADE assessments of the meta-analyses of outcomes for antibiotic use and patient satisfaction were moderate (Summary of findings for the main comparison; Summary of findings 2). GRADE assessments of clinical outcome data and reconsultation rates were moderate (Summary of findings for the main comparison, Summary of findings 2). GRADE assessments of adverse effects of antibiotics for the comparison of *delayed* antibiotics versus *immediate* antibiotics was low owing to concerns about lack of blinding, inadequate reporting of allocation concealment, and heterogeneity of results (Summary of findings for the main comparison).

Potential biases in the review process

Heterogeneity of RCTs was one limitation of this review. Heterogeneity may have resulted from variable clinical presentations, differences in delay method, differences in antibiotic use, and quality of included studies. Potential for type I error (falsely positive results) is another limitation of this review given the large number of reported clinical outcome results. For example, multiple outcome measures are reported for the clinical outcomes comparing *delayed* and immediate antibiotic groups.

Agreements and disagreements with other studies or reviews

Findings for certain clinical outcomes may have been anticipated. Systematic reviews on antibiotics for sore throat and AOM found

that the time of greatest benefit for symptoms is apparent at Days 3 or 4 after treatment was started (Spinks 2013; Venekamp 2015). Delaying antibiotics by 48 hours or more would thus overshoot this zenith. Nor is it surprising that we found more adverse reactions to antibiotics from *immediate* antibiotics in line with known adverse events from comparison RCTs with *no* antibiotics.

We found the greatest difference in clinical outcomes in the only trial of *delayed* antibiotics conducted in a country not considered to be a high-income economy according to the World Bank at the time of publication (World Bank 2017). El-Daher 1991 favoured *immediate* antibiotics over *delayed* antibiotics. This trial was also the least methodologically sound, but it highlighted that concerns expressed about *delayed* antibiotics for children, the elderly, and those with language or cultural difficulties may also need to be extended to lower socioeconomic populations (Datta 2008; Johnson 2007).

A parallel RCT of people with acute infective conjunctivitis similarly reported shortest symptom duration with *immediate* antibiotics, followed by *delayed* and then *no* antibiotics (the last resulting in least antibiotic use). There was no evidence of difference between groups for patient satisfaction (Everitt 2006).

Worrall 2010 compared *delayed* prescriptions dated either the day of the office visit or two days later, but did not compare *delayed* with either *immediate* or *no* antibiotics. This study demonstrated no significant difference between groups in terms of antibiotic use. Randomised controlled trials comparing *delayed* with *no* antibiotics and concluding that they were both acceptable alternatives to *immediate* antibiotics as a means of reducing antibiotic prescriptions led to a recommendation for *delayed* instead of *no* antibiotics to address concerns about risks of complications (Little 2001; Little 2005a; Little 2005b). Doctors worried about the risk of serious infective complications consequent to adopting a no antibiotic rather than *delayed* antibiotic strategy might take comfort from a UK observational study showing that reduced prescribing resulted in no increase in admissions to hospital for peritonsillar abscess or rheumatic fever (Sharland 2005), although mastoiditis might be a risk at the rate of 2500 children needing to be treated with antibiotics to prevent one case (Van Zuijlen 2001). Just over a third (35%) of parents in the AOM trials used their *delayed* script, suggesting that the number of *delayed* scripts required to prevent one case of mastoiditis would be significantly higher than 2500 (Chao 2008; Little 2001; Spiro 2006). A large cohort study (28,883 participants) recruiting people with symptoms and signs of lower RTI found no evidence of difference in hospitalisation or death regardless of antibiotic prescribing strategies, which included *immediate*, *delayed*, and *no* antibiotics (Little 2017). Doctors often find it difficult to identify patients at risk of serious complications from respiratory infections (Kumar 2003). Patients probably perform even less well, despite their self confidence in making this decision if given a *delayed* antibiotic prescription. This concern is supported by empirical data: respiratory disease severity does not correlate with patients' immediate preference for an antibiotic prescription (Macfarlane 1997). We did not find any significant difference for complication rates between prescribing strategies.

There is little controversy within published guidelines that *immediate* antibiotics are recommended for patients who appear to be seriously unwell, fit multiple criteria indicating bacterial tonsillitis, are under six months of age with AOM, have bilateral AOM, or have AOM with otorrhoea (Tan 2008). American guidelines also recommend *immediate* antibiotics for children under the age of two with definite AOM (OMTG 2004). It seems then that for the majority of respiratory infections that do not meet these criteria, clinicians have the option of *delayed* or *no* antibiotics. Where doctors are confident in not prescribing antibiotics, it seems clear that *no* antibiotics will result in the least antibiotic use, and therefore less antibiotic resistance. Concerns about patient and doctor satisfaction with *no* antibiotics appear to be driving the use of a *delayed* strategy. Some doctors use the delay strategy to reduce antibiotic use, empower patients, and save the patient time and money without jeopardising the doctor-patient relationship (Arroll 2002b). A qualitative study found that while some participants appreciated the option of controlling the decision as to whether and when to take antibiotics, others expected "the physician to decide" (Arroll 2002b). One physician expressed concern that patients might view *delayed* prescribing as physician incompetence, which was substantiated by comments from some patients. In this review, we found higher levels of patient satisfaction with a strategy of *delayed* antibiotics compared with *no* antibiotics (number needed to treat for an additional beneficial outcome: 22.5 patients). Shared decision-making and education campaigns for doctors have been proposed as ways of helping doctors and patients avoid unnecessary antibiotic use (Butler 2001; Legare 2007; Sung 2006). One suggestion is that *delayed* antibiotics may in time become redundant as doctors and their patients become more reassured of the safety of not using antibiotics (Arroll 2003b). Meanwhile, a *delayed* antibiotics strategy may be an acceptable compromise to reduce antibiotics prescribing for RTIs and thereby reduce antibiotic resistance.

AUTHORS' CONCLUSIONS

Implications for practice

A strategy of*immediate* antibiotics is more likely to confer the modest benefits of antibiotics on clinical outcomes such as symptoms for acute otitis media and sore throat than *delayed* antibiotics (moderate quality evidence according to GRADE assessment). There was no evidence of differences in complication rates between immediate and *delayed* antibiotics or between *delayed* and *no* antibiotics. *Immediate* antibiotics had similarly high levels of patient satisfaction to *delayed* antibiotics (91% versus 86% - moderate quality evidence according to GRADE assessment). *Delayed*

antibiotics had higher levels of patient satisfaction than *no* antibiotics (87% versus 82% - moderate quality evidence according to GRADE assessment). *Delayed* antibiotic prescribing strategies achieved markedly lower rates of antibiotic use compared to *immediate* antibiotics (31% versus 93% - moderate quality evidence according to GRADE assessment). Requiring the patient to return for a prescription resulted in even lower antibiotic use (27%) than giving a prescription at the time of the consultation with instructions to fill the prescription if symptoms worsened (38%). *No* antibiotics achieved lower rates still of antibiotic use compared to *delayed* antibiotics (14% versus 28% - moderate quality evidence according to GRADE assessment).

Delayed antibiotics for respiratory infections is a strategy that reduces antibiotic use compared to *immediate* antibiotics, maintains similar patient satisfaction to *immediate* antibiotics, and does not result in greater numbers of complications compared with *immediate* antibiotics. *Delayed* antibiotics results in more antibiotic use than *no* antibiotics, but also slightly greater patient satisfaction compared to *no* antibiotics, and minimal differences for symptom control and complications compared with *no* antibiotics.

In patients with respiratory infections where clinicians, informed by relevant guidelines, feel it is safe not to prescribe antibiotics immediately, *no* antibiotics with advice to return if symptoms do not resolve results in the least antibiotic use, while maintaining high levels of patient satisfaction and patient safety. Where clinicians are not confident in using a no antibiotic strategy, a *delayed* antibiotics strategy may be an acceptable compromise in place of immediate prescribing to significantly reduce unnecessary antibiotic use for respiratory tract infections, and thereby reduce antibiotic resistance, without significantly compromising patient safety or satisfaction levels.

Implications for research

Further research into antibiotic prescribing strategies for respiratory infections may best be focused on identifying patient groups at high risk of disease complications, enhancing doctors' communication with patients to maintain satisfaction, ways of reducing doctors' anxieties about not prescribing antibiotics for respiratory infections, and policy measures to reduce unnecessary antibiotic prescribing for respiratory tract infections. Future randomised controlled trials of delaying antibiotics as an intervention should fully report symptoms, patient satisfaction, doctor satisfaction, and disease complications as well as changes in prescription rates. They should also include a no antibiotic arm. Measurement and reporting of antibiotic resistance would also be welcome in this setting.

ACKNOWLEDGEMENTS

The review authors wish to thank the following people for commenting on the 2010 updated review: Alison Thomas, Bill Hueston, Max Bulsara, and Tom Fahey. We also thank the following people for commenting on the 2013 update: Amanda Roberts, Sandra Arnold, Bill Hueston, Sree Nair, and Tom Fahey. We thank the following people for commenting on the 2017 update: Esther Martin Lopez, Shunjie Chua, Terry Neeman, Deepak Chawla, Tom Fahey, and Roger Damoiseaux.

REFERENCES

References to studies included in this review

Arroll 2002a ***{published and unpublished data}***
Arroll B, Kenealy T, Kerse N. Do delayed prescriptions reduce the use of antibiotics for the common cold? A single-blind controlled trial. *Journal of Family Practice* 2002;**51**(4): 324–8.

Chao 2008 ***{published data only (unpublished sought but not used)}***
Chao J, Kunkov S, Reyes L, Lichten S, Crain E. Comparison of two approaches to observation therapy for acute otitis media in the emergency department. *Pediatrics* 2008;**121** (5):1352–6.

De la Poza Abad 2016 ***{published data only}***
* De la Poza Abad M, Dalmau GM, Bakedano MM, González AI, Criado YC, Anadón SH, et al. Prescription strategies in acute uncomplicated respiratory infections. *JAMA* 2016;**176**(1):21–9. [DOI: 10.1001/jamainternmed.2015.7088]
EUCTR2011-005741-13-ES. Delayed antibiotic prescription for respiratory infections in children. www.clinicaltrialsregister.eu/ctr-search/search?query=eudract˙number:2011-005741-13 12 December 2011.
NCT01363531. Clinical Trial for the Assessment of Delayed Antibiotic Treatment Strategies in the Non-complicated Acute Respiratory Tract Infections in General Practice. clinicaltrials.gov/show/NCT01363531 18 May 2011.

Dowell 2001 ***{published data only}***
Dowell J, Pitkethy M, Bain J, Martin S. A randomised controlled trial of delayed antibiotic prescribing as a strategy for managing uncomplicated respiratory tract infection in primary care. *British Journal of General Practice* 2001;**51** (464):200–5.

El-Daher 1991 ***{published data only}***
El-Daher N, Rawashedeh N, Al-Khalil I, Abu-ektaish F. Immediate versus delayed treatment of group A beta-haemolytic streptococcal pharyngitis with penicillin V. *Pediatric Infectious Disease Journal* 1991;**10**(2):126–30.

Gerber 1990 *{published data only}*
Gerber M, Randolph M, DeMeo K, Kaplan E. Lack of impact of early antibiotic therapy for streptococcal pharyngitis on recurrence rates. *Journal of Pediatrics* 1990; **117**(6):853–8.

Little 1997 *{published data only}*
Little P, Williamson I, Warner G, Gould C, Gantley M, Kinmonth AL. Open randomised trial of prescribing strategies in managing sore throat. *BMJ* 1997;**314**(7082): 722–7.

Little 2001 *{published and unpublished data}*
* Little P, Gould C, Williamson I, Moore M, Warner G, Dunleavey J. Pragmatic randomised controlled trial of two prescribing strategies for childhood acute otitis media. *BMJ* 2001;**322**(7282):336–42.
Little P, Moore M, Warner G, Dunleavy J, Williamson I. Longer term outcomes from a randomised trial of prescribing strategies in otitis media. *British Journal of General Practice* 2006;**56**(524):176–82.

Little 2005a *{published data only}*
ISRCTN92319172. Randomised controlled trial of a leaflet and three prescribing strategies for the management of acute lower respiratory tract illness. Acute Cough Trial. isrctn.com/ISRCTN92319172 23 October 2000.
* Little P, Rumsby K, Kelly J, Watson L, Moore M, Warner G, et al. Information leaflet and antibiotic prescribing strategies for acute lower respiratory infection. *JAMA* 2005; **293**(24):3029–35.
Moore M, Little P, Rumsby K, Kelly J, Watson L, Warner G, et al. Effect of antibiotic prescribing strategies and an information leaflet on longer-term reconsultation for acute lower respiratory tract infection. *British Journal of General Practice* 2009;**59**(567):728–34.

Pichichero 1987 *{published data only}*
Pichichero M, Disney F, Talpey W, Green J, Francis A, Roghmann K, et al. Adverse and beneficial effects of immediate treatment of group A beta-haemolytic streptococcal pharyngitis with penicillin. *Pediatric Infectious Disease Journal* 1987;**6**(7):635–43.

Spiro 2006 *{published data only}*
Spiro DM, Tay KY, Arnold DH, Dziura JD, Baker MD, Shapiro ED. Wait-and-see prescription for the treatment of acute otitis media: a randomized controlled trial. *JAMA* 2006;**296**(10):1235–41.

References to studies excluded from this review

Agnew 2013 *{published data only}*
Agnew J, Taaffe M, Darker C, O'Shea B, Clarke J. Delayed prescribing of antibiotics for respiratory tract infections: use of information leaflets. *Irish Medical Journal* 2013;**106**(8): 243–4.

Cates 1999 *{published data only}*
Cates C. An evidence based approach to reducing antibiotics use in children with acute otitis media: controlled before and after study. *BMJ* 1999;**318**:715–6.

De la Poza Abad 2013 *{published data only}*
De la Poza Abad M, Mas Dalmau G, Moreno Bakedano M, González González AI, Canellas Criado Y, Hernández Anadón S, et al. Rationale, design and organization of the delayed antibiotic prescription (DAP) trial: a randomized controlled trial of the efficacy and safety of delayed antibiotic prescribing strategies in the non-complicated acute respiratory tract infections in general practice. *BMC Family Practice* 2013;**14**(63):1–7. [DOI: 10.1186/1471-2296-14-63]

Fischer 2009 *{published data only}*
Fischer T, Singer A, Chale S. Observation option for acute otitis media in the emergency department. *Paediatric Emergency Care* 2009;**25**(9):575–8.

Little 2014 *{published data only}*
Little P, Moore M, Kelly J, Williamson I, Leydon G, McDermott L, et al. Delayed antibiotic prescribing strategies for respiratory tract infections in primary care: pragmatic, factorial, randomised controlled trial. *BMJ* 2014;**348**:g1606. [DOI: 10.1136/bmj.g1606]

Newson 2009 *{published data only}*
Newson L. Delayed prescribing. *Practice Nurse* 2009;**37**(2): 21.

Siegel 2003 *{published data only}*
Siegel R, Kiely M, Bien JP, Joseph EC, Davis JB, Mendel SG, et al. Treatment of otitis media with observation and a safety-net antibiotic prescription. *Pediatrics* 2003;**112**(3): 527–31.

Vouloumanou 2009 *{published data only}*
Vouloumanou E, Karageorgopoulos D, Kazanti M, Kapaskelis A, Falagas M. Antibiotics versus placebo or watchful waiting for acute otitis media: a meta-analysis of randomized controlled trials. *Journal of Antimicrobial Chemotherapy* 2009;**64**(1):16–24.

Worrall 2010 *{published data only}*
NCT02732847. Trial of Post-Dated Delayed Antibiotic Prescriptions [Post–Dated Versus Voluntary Delayed Antibiotic Prescriptions for Acute Respiratory Infections in Primary Care: A Randomized Trial]. clinicaltrials.gov/show/NCT02732847 27 May 2010.
* Worrall G, Kettle A, Graham W, Hutchinson J. Postdated versus usual delayed antibiotic prescriptions in primary care: Reduction in antibiotic use for acute respiratory infections?. *Canadian Family Physician* 2010;**56**(10):1032–6.

References to ongoing studies

NCT01800747 *{published data only}*
NCT01800747. Clinical Trial for the Assessment of Delayed Antibiotic Treatment in Pediatric (DAP-Pediatrics) [Clinical Trial for the Assessment of Delayed Antibiotic Treatment in the Non–complicated Acute Respiratory Tract Infections in Pediatric (Study DAP–Pediatrics)]. clinicaltrials.gov/ct2/show/record/NCT01800747 26 February 2013.

Additional references

AHRQ 2016
Agency for Healthcare Research and Quality. Improving antibiotic prescribing for uncomplicated acute respiratory tract infections. Rockville (MD): AHRQ; 2016. Comparative Effectiveness Review No. 163.

Arroll 2002b
Arroll B, Goodyear-Smith F, Thomas D, Kerse N. Delayed antibiotic prescriptions: what are the experiences and attitudes of physicians and patients?. *Journal of Family Practice* 2002;**51**(11):954–9.

Arroll 2003a
Arroll B, Kenealy T, Kerse N. Do delayed prescriptions reduce antibiotic use in respiratory tract infections? A systematic review. *British Journal of General Practice* 2003; **53**:871–7.

Arroll 2003b
Arroll B, Kenealy T, Goodyear-Smith F, Kerse N. Delayed prescriptions. *BMJ* 2003;**327**(7428):1361–2.

Arroll 2013
Arroll B, Kenealy T. Antibiotics for the common cold and acute purulent rhinitis. *Cochrane Database of Systematic Reviews* 2013, Issue 6. [DOI: 10.1002/14651858.CD000247.pub3]

Atkins 2004
Atkins D, Best D, Briss PA, Eccles M, Falck-Ytter Y, Flottorp S, et al. GRADE Working Group. Grading quality of evidence and strength of recommendations. *BMJ* 2004; **328**(7454):1490–4.

Butler 2001
Butler CC, Kinnersley P, Prout H, Rollnick S, Edwards A, Elwyn G. Antibiotics and shared decision-making in primary care. *Journal of Antimicrobial Chemotherapy* 2001; **48**(3):435–40.

CDC 2017
Centers for Disease Control and Prevention. Antibiotic/antimicrobial resistance. www.cdc.gov/drugresistance/ (accessed prior to 29 August 2017).

Cochrane 2017
The Cochrane Collaboration. Prioritization list project. community.cochrane.org/review-production/production-resources/prioritization-list-project (accessed prior to 29 August 2017).

Datta 2008
Datta M. Review: delayed or immediate prescriptions of antibiotics have similar clinical outcomes in respiratory infections. *Evidence-Based Medicine* 2008;**13**(2):42.

Dickersin 1994
Dickersin K, Scherer R, Lefebvre C. Identifying relevant studies for systematic reviews. *BMJ* 1994;**309**(6964): 1286–91.

Elliott 2014
Elliott JH, Turner T, Clavisi O, Thomas J, Higgins JP, Mavergames C, et al. Living systematic reviews: an emerging opportunity to narrow the evidence-practice gap. *PLoS Medicine* 2014;**11**:e1001603.

Everitt 2006
Everitt H, Little P, Smith P. A randomised controlled trial of management strategies for acute infective conjunctivitis in general practice. *BMJ* 2006;**333**(7563):321.

French 1950
French JRP. Field experiments: changing group productivity. In: Miller JG editor(s). *Experiments in Social Process: a Symposium on Social Psychology*. McGraw-Hill, 1950:82.

Goossens 2005
Goossens H, Ferech M, Vander Stichele R, Elseviers M. Outpatient antibiotic use in Europe and association with resistance: a cross-national database study. *Lancet* 2005;**365** (9459):579–87.

GRADEpro GDT 2014 [Computer program]
GRADE Working Group, McMaster University. GRADEpro GDT. Version (accessed 15 April 2017). Hamilton (ON): GRADE Working Group, McMaster University, 2014.

Higgins 2011
Higgins JPT. Chapter 8: Assessing risk of bias in included studies. In: Higgins JPT, Green S, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available at handbook.cochrane.org.

Hoffman 2017
Hoffman T, Oxman A, Ioannidis J, Moher D, Lasserson T, Tovey D, et al. Enhancing the usability of systematic reviews by improving the consideration and description of interventions. *BMJ* 2017;**358**:j2998.

Johnson 2007
Johnson NC, Holger JS. Pediatric acute otitis media: the case for delayed antibiotic treatment. *Journal of Emergency Medicine* 2007;**32**(3):279–84.

Kempf 2016
Kempf I, Jouy E, Chauvin C. Colistin use and colistin resistance in bacteria from animals. *International Journal of Antimicrobial Agents* 2016;**48**:598–606.

Kenealy 2013
Kenealy T, Arroll B. Antibiotics for the common cold and acute purulent rhinitis. *Cochrane Database of Systematic Reviews* 2013, Issue 6. [DOI: 10.1002/14651858.CD000247.pub3]

Kumar 2003
Kumar S, Little P, Britten N. Why do general practitioners prescribe antibiotics for sore throat?. *BMJ* 2003;**326**(7392): 138–43.

Legare 2007
Legare F, Labrecque M, Leblanc A, Thivierge R, Godin G, Laurier C, et al. Does training family physicians in shared decision making promote optimal use of antibiotics for acute respiratory infections? Study protocol of a pilot clustered randomised controlled trial. *BMC Family Practice* 2007;**8**:65.

Levitt 2011
Levitt SD, List JA. Was there really a Hawthorne effect at the Hawthorne plant? An analysis of the original illumination experiments. *American Economic Journal: Applied Economics* 2011;**3**(1):224–38.

Little 2005b
Little P. Delayed prescribing of antibiotics for upper respiratory tract infection. *BMJ* 2005;**331**(7512):301–2.

Little 2006
Little P, Moore M, Warner G, Dunleavy J, Williamson I. Longer term outcomes from a randomised trial of prescribing strategies in otitis media. *British Journal of General Practice* 2006;**56**(524):176–82.

Little 2017
Little P, Stuart B, Smith S, Thompson MJ, Knox K, van den Bruel A, et al. Antibiotic prescription strategies and adverse outcome for uncomplicated lower respiratory tract infections: prospective cough complication cohort (3C) study. *BMJ* 2017;**357**:j2418.

Macfarlane 1997
Macfarlane J, Holmes W, Macfarlane R, Britten N. Influence of patient's expectations on antibiotic management of acute lower respiratory tract illness in general practice: questionnaire study. *BMJ* 1997;**315**:1211–4.

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

Moore 2009
Moore M, Little P, Rumsby K, Kelly J, Watson L, Warner G, et al. Effect of antibiotic prescribing strategies and an information leaflet on longer-term reconsultation for acute lower respiratory tract infection. *British Journal of General Practice* 2009;**59**(567):728–34.

NICE 2016
National Institute for Health and Care Excellence. Self-limiting respiratory tract infections - antibiotic prescribing overview. London: NICE; 2016.

OMTG 2004
Otitis Media Treatment Guidelines. Diagnosis and management of acute otitis media. *Pediatrics* 2004;**113**(5): 1451–65.

RevMan 2014 [Computer program]
Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager 5. Version 5.3. Copenhagen: Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Sharland 2005
Sharland M, Kendall H, Yeates D, Randall A, Hughes G, Glasziou P, et al. Antibiotic prescribing in general practice and hospital admissions for peritonsillar abscess, mastoiditis and rheumatic fever in children: time trend analysis. *BMJ* 2005;**331**(7512):328–9.

Simmonds in press
Simmonds ME, Salanti G, McKenzie J, Elliott JE, on behalf of the Living Systematic Review Network. Living Systematic Reviews: 3. Statistical methods for updating meta-analyses. *Journal of Clinical Epidemiology* (in press).

Smith 2014
Smith SM, Fahey T, Smucny J, Becker LA. Antibiotics for acute bronchitis. *Cochrane Database of Systematic Reviews* 2014, Issue 3. [DOI: 10.1002/14651858.CD000245.pub2]

Spinks 2013
Spinks A, Glasziou PP, Del Mar C. Antibiotics for sore throat. *Cochrane Database of Systematic Reviews* 2013, Issue 11. [DOI: 10.1002/14651858.CD000023.pub3]

Sun 2012
Sun L, Klein E, Laxminarayan R. Seasonality and temporal correlation between community antibiotic use and resistance in the United States. *Clinical Infectious Diseases* 2012;**55**: 687–94.

Sung 2006
Sung L, Arroll J, Arroll B, Goodyear-Smith F, Kerse N, Norris P. Antibiotic use for upper respiratory tract infections before and after an education campaign as reported by general practitioners in New Zealand. *New Zealand Medical Journal* 2006;**119**(1233):U1956.

Synnot 2017
Synnot A, Turner T, Elliott JE, on behalf of the Living Systematic Review Network. Living systematic reviews - interim guidance for pilots (Version 0.3; 21 April 2017). community.cochrane.org/review-production/production-resources/living-systematic-reviews (accessed prior to 29 August 2017).

Tan 2008
Tan T, Little P, Stokes T. Antibiotic prescribing for self limiting respiratory tract infections in primary care: summary of NICE guidance. *BMJ* 2008;**337**:a437.

Van Zuijlen 2001
Van Zuijlen DA, Schilder AG, Van Balen FA, Hoes AQ. National differences in incidences of acute mastoiditis: relationship to prescribing patterns for acute otitis media. *Pediatric Infectious Disease* 2001;**20**:140–4.

Venekamp 2015
Venekamp RP, Sanders S, Glasziou PP, Del Mar CB, Rovers MM. Antibiotics for acute otitis media in children. *Cochrane Database of Systematic Reviews* 2015, Issue 6. [DOI: 10.1002/14651858.CD000219.pub3]

WHO 2014
World Health Organization. Antimicrobial resistance: Global report on surveillance 2014. Geneva: WHO; 2014.

World Bank 2017
World Bank. World Bank country and lending groups. World Bank (avialble at https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-country-and-lending-groups) 2017.

References to other published versions of this review

Spurling 2007

Spurling GKP, Del Mar CB, Dooley L, Foxlee R. Delayed antibiotics for symptoms and complications of respiratory infections. *Cochrane Database of Systematic Reviews* 2007, Issue 2. [DOI: 10.1002/14651858.CD004417.pub2]

Spurling 2010

Spurling GKP, Del Mar CB, Dooley L, Foxlee R. Delayed antibiotics for respiratory infections. *Cochrane Database of Systematic Reviews* 2010, Issue 1. [DOI: 10.1002/14651858.CD004417.pub2]

Spurling 2013

Spurling GKP, Del Mar CB, Dooley L, Foxlee R, Farley R. Delayed antibiotics for respiratory infections. *Cochrane Database of Systematic Reviews* 2013, Issue 4. [DOI: 10.1002/14651858.CD004417.pub4]

* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Arroll 2002a

Methods	Randomised controlled trial over 3 months
Participants	129 adults and children with the common cold presenting to primary care services in Auckland, New Zealand 62 participants were randomised to immediate antibiotic prescription, and 69 to *delayed* antibiotic prescription **Age:** the average age was 27.9 years (SD 3.1) in the immediate antibiotic group and 23.6 years (SD 2.7) in the *delayed* antibiotic group. **Gender:** immediate antibiotic group: 22 males out of 40; *delayed* antibiotic group: 26 males out of 41 **Exclusion criteria** included suspected streptococcal tonsillitis, sinusitis, bronchitis, pneumonia, lower respiratory signs, need for X-ray, history of rheumatic fever, serious illness, or any antibiotic treatment in the previous 2 weeks
Interventions	*Delayed* antibiotics (participants given script and instructed to fill within 72 hours) versus *immediate* antibiotics
Outcomes	**Primary outcomes:** participant diaries were used to measure fever, duration of fever, cough, duration of cough, pain, antibiotic use, and patient satisfaction **Secondary outcomes:** absence from school/work, diarrhoea, adverse effects of antibiotics, antibiotic use, and patient satisfaction
Notes	Funding source: Health Research Council

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer randomisation
Allocation concealment (selection bias)	Low risk	Opaque envelopes
Blinding (performance bias and detection bias) All outcomes	Low risk	Patient and care provider were blinded, but unsure regarding outcome assessor
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention-to-treat analysis was used and dropouts were reported. 62 out of 67 participants in the *delayed* antibiotic arm and 61 out of 62 participants in the immediate antibiotic arm completed the trial
Selective reporting (reporting bias)	Low risk	Prespecified outcomes were reported.

Arroll 2002a (*Continued*)

Other bias	Low risk	Funded by government grant

Chao 2008

Methods	Randomised controlled trial for 12 months
Participants	232 children with AOM presenting to 1 paediatric emergency department in an urban public hospital in the Bronx, New York, USA. Data were obtained from 206 participants, of which 100 were randomised to observation (*no* antibiotics) and 106 were randomised to *delayed* antibiotic prescription. **Age:** median age in the no antibiotic group was 5.0 years (IQR 3.7 to 6.7) and in the *delayed* antibiotic group was 3.7 years (IQR 2.8 to 5.8). **Gender:** 47 males (47%) in the no antibiotic group and 60 males (57%) in the *delayed* antibiotic group **Exclusion criteria**: children were excluded if they had a history of immunodeficiency, craniofacial abnormalities, were already taking antibiotics, had concurrent bacterial infection requiring antibiotic treatment, no telephone contact, AOM in last 30 days, pain did not settle with analgesia after 30 minutes, or 48 hours of otalgia and fever
Interventions	*No* antibiotics (observation) versus *delayed* antibiotics (observation plus prescription). Participants in the *delayed* antibiotic group were given a script, which they were instructed to fill if needed
Outcomes	**Primary outcomes:** data on fever, pain, antibiotic use, and patient satisfaction were collected by a research assistant during a phone call 7 to 10 days after the initial presentation **Secondary outcomes:** adverse events were collected by a research assistant during a phone call 7 to 10 days after the initial presentation
Notes	The funding source for this study was not described.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Random number table
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Outcome assessor blinded. Study authors did not indicate if participant and care provider were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data were described and ITT analysis applied. 232 participants were correctly enrolled, and 206 completed the final interview

Chao 2008 (*Continued*)

Selective reporting (reporting bias)	Low risk	Prespecified outcomes were reported.
Other bias	Unclear risk	Funding not described.

De la Poza Abad 2016

Methods	Randomised controlled trial over 2.5 years
Participants	405 adults with uncomplicated respiratory infections presenting to 23 primary healthcare centres in Spain. 398 participants were randomised, 198 to *delayed* antibiotics (100 to prescription collection strategy and 98 to patient-led prescription strategy), 101 to *immediate* antibiotics, and 99 to *no* antibiotics. **Age:** the average age of participants in the prescription collection *delayed* antibiotic strategy was 42 years (SD 17); the patient-led prescription *delayed* antibiotic strategy 45 years (SD 17); the immediate antibiotic group 48 years (SD 17); and the no antibiotic group 45 years (SD 16) **Gender:** there were 29 men (29%) in the prescription collection *delayed* antibiotics group; 33 men (34%) in the patient-led prescription *delayed* antibiotics group; 39 men (39%) in the immediate antibiotic group; and 35 men (35%) in the no antibiotic group **Exclusion criteria:** not reported
Interventions	*Delayed* antibiotics (patient-led prescription strategy) versus *delayed* antibiotics (prescription collection strategy) versus *immediate* antibiotics versus *no* antibiotics
Outcomes	**Primary outcomes:** duration of symptoms, severity of symptoms, antibiotic use, patient satisfaction **Secondary outcomes:** participants' beliefs about the effectiveness of antibiotics All outcomes were measured using a patient diary.
Notes	Grant funding came from a joint initiative of the Spanish federal government and the European Regional Development Fund. Study authors were approached for extra information and these data were obtained

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Participants were centrally randomised using an e-online platform
Allocation concealment (selection bias)	High risk	Not described
Blinding (performance bias and detection bias) All outcomes	High risk	No blinding undertaken.

De la Poza Abad 2016 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	405 participants were recruited and 398 included in the analysis; 3 lost to follow-up in *delayed* group, 4 lost to follow-up in the immediate/no prescription group. Intention-to-treat guided all analyses
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting
Other bias	Low risk	Funded by government body.

Dowell 2001

Methods	Randomised controlled trial over 1 year
Participants	191 adults and children presenting with cough to 22 general practices in Scotland 99 participants were randomised to *delayed* antibiotics, and 92 to *immediate* antibiotics. **Age:** the average age of participants in the *delayed* antibiotic group was 39.3 years, and in the immediate antibiotic group 43.8 years **Gender:** 43 of 99 participants in the *delayed* antibiotic group were men; 34 of 92 participants in the immediate antibiotic group were men **Exclusion criteria:** potential participants were excluded if the general practitioner would not consider offering antibiotics, or if the patient expressed a strong preference for antibiotics. Other exclusion criteria included people with chest signs, immunosuppression, pre-existing lung disease, diabetes, and patients who could not return to their general practice
Interventions	Participants were randomised to *delayed* antibiotics (script left at reception and participants instructed to pick up the script after 1 week of delay) or *immediate* antibiotics (antibiotic of general practitioner's choice).
Outcomes	Baseline data were collected by the general practitioner. The participants were also asked to fill out a diary at home for 14 days regarding their symptoms **Primary outcomes:** outcome measures included duration of cough, fever, breathlessness, runny nose, antibiotic use, and patient satisfaction
Notes	The study was funded by a grant from the Royal College of General Practitioners

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Random number table
Allocation concealment (selection bias)	Unclear risk	Numbered envelopes (opacity not mentioned)

Dowell 2001 (*Continued*)

Blinding (performance bias and detection bias) All outcomes	Unclear risk	Outcome assessor blinded. Blinding of participant and care provider not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropout numbers were described, and ITT analysis used. Of 191 participants, 148 returned questionnaires describing clinical outcomes and patient satisfaction
Selective reporting (reporting bias)	Low risk	Prespecified clinical outcomes were not published, but authors provided this information
Other bias	Low risk	Funded by Royal College of General Practitioners.

El-Daher 1991

Methods	Randomised controlled trial over 13 months
Participants	229 children with sore throat (suspected GABHS) presenting to the paediatric clinics of the University of Science and Technology in Jordan. Children were included if they had at least 3 of the 5 following signs of (1) fever greater than 38 °C, (2) tonsillar exudate/beefy red throat, (3) cervical lymph node tenderness, (4) sore throat associated with difficulty swallowing, and (5) systemic toxicity. The study enrolled 306 participants, but only randomised the 229 who were culture-positive **Age:** of the 111 participants randomised to the immediate antibiotic group, the average age was 7.8 years (SD 2.4); of the 118 participants randomised to the *delayed* antibiotic group, the average age was 8.3 years (SD 2.6) **Gender:** 60 of the 111 participants in the immediate antibiotic group were male; 66 of the 118 participants in the *delayed* antibiotic group were male **Exclusion criteria:** children were excluded if they had any of penicillin allergy, antibiotics in preceding 7 days, acute illness in preceding 7 days, GABHS infection in preceding month, and concurrent infection requiring treatment with an antibiotic that was not penicillin
Interventions	*Delayed* antibiotics (48-hour delay) versus *immediate* antibiotics for 10 days (penicillin V 50,000 IU/kg/day in 3 divided doses)
Outcomes	**Primary outcomes:** outcome measures included pain, malaise, vomiting, temperature **Secondary outcome:** infection recurrence
Notes	This study was supported by both Biochemie GmbH and Jordan University of Science and Technology. We approached the study authors for additional information, but did not receive a reply

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

El-Daher 1991 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	Method not described
Allocation concealment (selection bias)	High risk	Not described
Blinding (performance bias and detection bias) All outcomes	Low risk	Blinding of participant and care provider, but unsure about outcome assessor
Incomplete outcome data (attrition bias) All outcomes	High risk	Dropouts not described
Selective reporting (reporting bias)	Low risk	Prespecified outcomes reported
Other bias	High risk	Funded by Biochemie GmbH and Jordan University of Science and Technology

Gerber 1990

Methods	Randomised controlled trial over 6 months
Participants	113 adolescents and children with sore throat (suspected GABHS) presenting to a private paediatric office in Connecticut, USA **Age:** the average age of the 63 participants randomised to *delayed* antibiotics was 9.5 years; of the 50 participants randomised to *immediate* antibiotics it was 8.1 years. **Gender:** 30 of the 63 participants in the *delayed* antibiotics group were male; 29 of the 50 participants in the *immediate* antibiotics group were male. **Exclusion criteria:** hypersensitivity to penicillin, had received penicillin in the previous 72 hours, or had a negative throat culture
Interventions	Both groups received 250 mg of penicillin V 3 times a day for 10 days. Participants randomised to *delayed* antibiotics received their prescription 48 hours later than those randomised to *immediate* antibiotics.
Outcomes	**Primary outcomes:** symptoms were measured but not reported. **Secondary outcomes:** recurrence rate. Symptoms were measured but not reported.
Notes	Funding sources for this trial were not reported. We approached the authors for trial data, but did not receive a reply

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Random number table
Allocation concealment (selection bias)	High risk	No information

Gerber 1990 (*Continued*)

Blinding (performance bias and detection bias) All outcomes	High risk	No blinding described.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropouts were described. 63 out of 63 participants in the *delayed* antibiotic group returned for a follow-up visit after 4 days. 49 out of 50 participants in the immediate antibiotic group returned for follow-up visit at 4 days
Selective reporting (reporting bias)	Unclear risk	Clinical outcomes reported as 1 outcome.
Other bias	Unclear risk	Funding not described.

Little 1997

Methods	Open randomised controlled trial over 20 months
Participants	712 adults and children with sore throat presenting to 11 general practices in England, UK. Of these 712 participants, 235 were randomised to *delayed* antibiotics. **Age:** of the 235 participants randomised to *delayed* antibiotics, 181 were older than 12 years; of the 246 participants randomised to *immediate* antibiotics, 187 were older than 12 years; and of the 232 participants randomised to *no* antibiotics, 173 were older than 12 years. **Gender:** 82 of the 235 participants in the *delayed* antibiotics group were male; 95 of the 246 participants in the *immediate* antibiotics group were male; and 82 of the 232 participants in the *no* antibiotics group were male. **Exclusion criteria:** people were excluded if they had a sore throat that was clearly not a bacterial infection, e.g. due to drugs, aphthous ulcers, candidal infection. Other exclusion criteria included being very unwell, suspected or previous rheumatic fever, multiple (more than 5 per year) attacks of tonsillitis, quinsy, and pregnancy
Interventions	Participants in the *delayed* antibiotics group were instructed to pick up a script left at reception after 72 hours if needed. Participants in the *immediate* antibiotics group were immediately offered a script for antibiotics. The antibiotic prescription for both groups was penicillin V 250 mg 4 times a day for 10 days. For children aged 3 to 5 years, the dose was reduced to 125 mg. Participants who were penicillin allergic received a script for erythromycin with the same dosing regimen as for penicillin. Participants in the *no* antibiotics group were not offered antibiotics.
Outcomes	**Primary outcomes:** fever, cough, duration of pain, and duration of malaise. Antibiotic use and patient satisfaction were measured **Secondary outcomes:** absences from school, diarrhoea, stomachache, rash Outcomes were assessed using a patient diary and a follow-up telephone call from a research assistant

Little 1997 (*Continued*)

Notes	This study was supported by Wessex NHS regional research and development funds. We approached the authors for study data, which they provided

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation method not described.
Allocation concealment (selection bias)	Unclear risk	"Sealed envelopes", but no mention of opacity
Blinding (performance bias and detection bias) All outcomes	High risk	This study was described as an open randomised trial, so no blinding was used
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention-to-treat analysis conducted. In the *delayed* antibiotic group, 179 participants responded out of 235. In the immediate antibiotic group, 215 participants responded out of 246. In the no antibiotic group, 186 participants responded out of 231
Selective reporting (reporting bias)	Low risk	Outcomes were reported as indicated in the methods section.
Other bias	Low risk	Funded by government body

Little 2001

Methods	Pragmatic randomised controlled trial conducted over an unknown period of time
Participants	315 children aged 6 months to 10 years with AOM were recruited by 42 general practitioners in England, UK. 164 of the 315 children were randomised to *delayed* antibiotics. **Age:** of the 164 children in the *delayed* antibiotics group, 93 were older than 3 years of age; of the 151 children in the *immediate* antibiotics group, 93 were older than 3 years. **Gender:** not provided **Exclusion criteria:** children were excluded if they had a pink tympanic membrane only, and otoscopic appearances consistent with otitis media with effusion and chronic suppurative otitis media according to the treating general practitioner. Children were also excluded if they had a serious chronic disease, needed antibiotics for an ear infection in the preceding 2 weeks, had previous complications, or if the child was too unwell for a delay in antibiotics. Children were judged to be too unwell if they had a high fever, were floppy, drowsy, and/or not responding to antipyretics

Little 2001 (*Continued*)

Interventions	The parents of children in the *delayed* antibiotics group were advised to use the antibiotics script they had been given if their child had significant otalgia or fever after 72 hours, or if discharge lasted for 10 days or more. Alternatively, children were randomised to *immediate* antibiotics. The antibiotic prescription was amoxicillin syrup (125 mg in 5 mL) 3 times a day for 1 week in each group unless the child was penicillin allergic. The exact dosage depended on the age of the child. Children who were penicillin allergic were prescribed erythromycin (125 mg in 5 mL) 4 times a day for 1 week in a dose appropriate to their age
Outcomes	Outcomes were measured using a patient diary. **Primary outcomes:** fever, severity of pain, duration of malaise, antibiotic use, patient satisfaction, further earache at 3 and 12 months **Secondary outcomes:** absence from school, use of paracetamol
Notes	We approached the study authors for original study data, but they were unable to provide these data. This study was funded by the UK National Health Service

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "patients were randomised to a group"
Allocation concealment (selection bias)	Low risk	Quote: "doctor opened a sealed numbered opaque envelope"
Blinding (performance bias and detection bias) All outcomes	High risk	No blinding undertaken.
Incomplete outcome data (attrition bias) All outcomes	Low risk	A comparison of responders versus non-responders was undertaken. 150 of 164 participants in the *delayed* antibiotics group had outcome data analysed; 135 of 151 participants in the *immediate* antibiotics group had outcome data analysed.
Selective reporting (reporting bias)	Low risk	Prespecified outcomes were reported.
Other bias	Low risk	Funded by government body

Little 2005a

Methods	Randomised controlled trial over 5 years
Participants	807 adults and children aged 3 years and over with cough and at least 1 symptom or sign localising to the lower respiratory tract were included. Participants were recruited from 37 physicians in England. Of the 807 randomised participants, 272 were randomised to *delayed* antibiotics. **Age:** for the 272 participants randomised to *delayed* antibiotics, the average age was 38 years (SD 20); for the 262 participants randomised to *immediate* antibiotics, it was 40 years (SD 22); and for the 273 participants randomised to *no* antibiotics, it was 39 years (SD 20). **Gender:** not provided **Exclusion criteria:** potential participants were excluded if they were thought to have pneumonia based on focal chest signs, high fever, vomiting, or diarrhoea. People were also excluded if they had asthma, chronic or acute lung disease, cystic fibrosis, cardiovascular disease, major psychiatric illness, dementia, or previous complications from lower respiratory tract infection including a hospital admission for pneumonia
Interventions	Participants were randomised to *delayed* antibiotics (script left at reception and participants instructed to pick up the script after 14 days if required), *immediate* antibiotics, or *no* antibiotics. Participants in the antibiotic groups were prescribed 250 mg of amoxycillin 3 times a day for 10 days. This dosage was reduced to 125 mg for children aged less than 10 years. For participants who were penicillin allergic, erythromycin 250 mg 4 times a day was used
Outcomes	**Primary outcomes:** fever, cough, duration of cough, severity of cough, malaise, duration of malaise, antibiotic use, patient satisfaction **Secondary outcomes:** complications of disease, hospital admissions, diarrhoea, reconsultation in the 12 months following the index consultation, excluding the first month after the index consultation Outcomes were measured using a daily patient diary.
Notes	This study was funded by a grant from the UK's Medical Research Council. The study authors provided original study data, which we used in this review

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated random number tables and block randomisation (block size 6)
Allocation concealment (selection bias)	Low risk	Opaque, sealed envelopes
Blinding (performance bias and detection bias) All outcomes	High risk	Outcome assessor was blinded. Participant and care provider were not blinded

Little 2005a (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data were described, and ITT analysis used. Out of 272 participants randomised to *delayed* antibiotics, 214 were included in the data analysis. Out of 262 participants randomised to *immediate* antibiotics, 214 were included in the data analysis. Out of 273 participants randomised to *no* antibiotics, 212 were included in the data analysis.
Selective reporting (reporting bias)	Low risk	Prespecified outcomes were reported.
Other bias	Low risk	Funded by government body

Pichichero 1987

Methods	Open randomised controlled trial over 27 months
Participants	114 children with sore throat (suspected GABHS) were included who presented to 1 private paediatric practice in New York State, USA. Of these 114 children, 55 were randomised to *delayed* antibiotics and 59 were randomised to *immediate* antibiotics. **Age**: of the 55 children randomised to *delayed* antibiotics, the average age was 7.8 years (SD 2.3); of the 59 children randomised to *immediate* antibiotics, it was 7.5 years (SD 2.6). **Gender:** not reported **Exclusion criteria** included hypersensitivity to penicillin, receipt of antibiotics in preceding 7 days, acute illness in preceding 7 days, GABHS infection in the preceding month, and concurrent treatment with an antibiotic other than penicillin
Interventions	Children were randomised to *delayed* antibiotics (48-hour delay) versus *immediate* antibiotics. Children in each group received penicillin V 250 mg 3 times a day for 10 days
Outcomes	**Primary outcomes:** fever, duration of fever, malaise **Secondary outcomes:** reconsultation rates, vomiting Outcomes were measured using a symptom diary and reassessment at the paediatrician's office 3 days after child's initial enrolment
Notes	This study was funded by the Robert Wood Johnson Foundation, Eli Lilly and Company, and Elmwood Paediatric Research fund. We approached the authors for their study data, but they did not provide this information

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Table of random numbers

Pichichero 1987 (*Continued*)

Allocation concealment (selection bias)	High risk	Allocation concealment measures were not described.
Blinding (performance bias and detection bias) All outcomes	Low risk	Participant and doctor blinded, but there was no description of outcome assessor blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	No participants dropped out.
Selective reporting (reporting bias)	Low risk	Prespecified outcomes were reported.
Other bias	High risk	Funded by philanthropic organisation and Eli Lilly

Spiro 2006

Methods	Placebo and randomised controlled trial over 12 months
Participants	283 children aged 6 months to 12 years were recruited in an emergency department in Connecticut, USA. 138 of these 283 children were randomised to *delayed* antibiotics. **Age:** for the 138 children randomised to *delayed* antibiotics, the average age was 3.6 years; for the 145 children randomised to *immediate* antibiotics, it was 3.2 years. **Gender:** 79 of the 138 children in the *delayed* antibiotics group were male; 76 of the 145 children in the *immediate* antibiotics group were male. **Exclusion criteria** for this study included intercurrent bacterial infection, toxic appearance of child, patient hospitalisation, immunocompromise, child had been treated with antibiotics in the preceding 7 days, myringotomy tubes, current tympanic membrane perforation, uncertain medical access, uncertain telephone access, primary language of guardian other than English or Spanish
Interventions	Children were randomised to *delayed* antibiotics (advised to delay for 48 hours and the script was to expire after 72 hours) or *immediate* antibiotics. The clinician chose the antibiotic.
Outcomes	**Primary outcome measures:** fever, duration of fever, pain, duration of pain, antibiotic use **Secondary outcome measures:** adverse effects of antibiotics including vomiting, diarrhoea, and rash Outcomes were measured by telephone interview by a research assistant with caregivers of included children
Notes	This study was supported by funding from a grant from the US National Institutes of Health, a grant from the Yale University School of Medicine, and material support from Friends of Yale-New Haven Children's Hospital
Risk of bias	

Spiro 2006 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-assisted randomisation
Allocation concealment (selection bias)	Low risk	Sealed, opaque envelopes
Blinding (performance bias and detection bias) All outcomes	High risk	Study participants were not blinded, but outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Of the 138 participants randomised to *delayed* antibiotics, outcome data were reported for 132 participants. Of the 145 participants randomised to *immediate* antibiotics, outcome data were reported for 133 participants. Intention-to-treat analysis was conducted
Selective reporting (reporting bias)	Low risk	Prespecified outcomes were reported.
Other bias	Low risk	Funded by government body

AOM: acute otitis media
GABHS: group A beta-haemolytic streptococcus
IQR: interquartile range
ITT: intention-to-treat
SD: standard deviation

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

Study	Reason for exclusion
Agnew 2013	This study was interested in information leaflets rather than the treatment of respiratory tract infections with *delayed* antibiotics versus immediate or *no* antibiotics.
Cates 1999	Not a randomised controlled trial
De la Poza Abad 2013	Not a randomised controlled trial
Fischer 2009	Not a randomised controlled trial
Little 2014	Not a randomised controlled trial

(*Continued*)

Newson 2009	Not a randomised controlled trial
Siegel 2003	Not a randomised controlled trial
Vouloumanou 2009	Not a randomised controlled trial
Worrall 2010	This study was had two delayed antibiotic arms, not immediate versus delayed

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

NCT01800747

Trial name or title	Clinical Trial for the Assessment of delayed Antibiotic Treatment in Pediatric (DAP-Pediatrics) [Clinical Trial for the Assessment of delayed Antibiotic Treatment in the Non-complicated Acute Respiratory Tract Infections in Pediatric (Study DAP-Pediatrics)]. clinicaltrials.gov/ct2/show/record/NCT01800747 26 February 2013
Methods	Allocation: Randomized Intervention Model: Parallel Assignment Intervention Model Description: Antibiotic treatment versus *delayed* antibiotic treatmentMasking: None (Open Label) Primary Purpose: Treatment
Participants	Children (2 to 14 ages) with non-complicated acute respiratory tract infections, including pharyngotonsillitis, rhinosinusitis, acute bronchitis and acute media otitis. The doctors include children with these infections if they have reasonable doubts if they should treat with antibiotics
Interventions	Antibiotic prescription strategies
Outcomes	Duration and severity of symptoms [Time Frame: 30 days]
Starting date	June 2012
Contact information	Principal Investigator: Pablo Alonso Coello, PhD, Asociación Colaboración Cochrane Iberoamericana
Notes	

DATA AND ANALYSES

Comparison 1. Pain: delayed versus immediate antibiotics

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of participants with pain on Days 3 to 6	4		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 Pain severity on Day 3	2	327	Std. Mean Difference (IV, Fixed, 95% CI)	0.35 [0.13, 0.57]

Comparison 2. Malaise: delayed versus immediate antibiotics

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of people with malaise on Day 3	2		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 Malaise severity on Day 3	2	398	Std. Mean Difference (IV, Fixed, 95% CI)	0.29 [0.09, 0.48]

Comparison 3. Fever: delayed versus immediate antibiotics

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Fever on Days 3 to 6	2	394	Odds Ratio (M-H, Fixed, 95% CI)	0.86 [0.54, 1.38]
2 Fever severity on Day 3	3		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Comparison 4. Antibiotic use

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Antibiotic use: delayed versus immediate antibiotics	7	1963	Odds Ratio (M-H, Fixed, 95% CI)	0.04 [0.03, 0.05]
1.1 Antibiotic use: delayed (prescription at time of visit) versus immediate antibiotics	3	547	Odds Ratio (M-H, Fixed, 95% CI)	0.10 [0.06, 0.15]
1.2 Antibiotic use: delayed (prescription collection) versus immediate antibiotics	5	1416	Odds Ratio (M-H, Fixed, 95% CI)	0.02 [0.01, 0.03]