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Spurling GKP, Del Mar CB, Dooley L, Clark J, Askew DA

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

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TABLE OF CONTENTS

ABSTRACT 1
PLAIN LANGUAGE SUMMARY 2
SUMMARY OF FINDINGS 4
BACKGROUND 7
OBJECTIVES 7
METHODS 7
RESULTS 9
Figure 1. 10
Figure 2. 11
Figure 3. 12
DISCUSSION 17
AUTHORS' CONCLUSIONS 19
ACKNOWLEDGEMENTS 19
REFERENCES 20
CHARACTERISTICS OF STUDIES 23
DATA AND ANALYSES 36
Analysis 1.1. Comparison 1: Pain: delayed versus immediate antibiotics, Outcome 1: Number of participants with pain on Days 3 to 6 37
Analysis 1.2. Comparison 1: Pain: delayed versus immediate antibiotics, Outcome 2: Pain severity on Day 3 37
Analysis 1.3. Comparison 1: Pain: delayed versus immediate antibiotics, Outcome 3: Duration of malaise 38
Analysis 1.4. Comparison 1: Pain: delayed versus immediate antibiotics, Outcome 4: Duration of pain symptoms 38
Analysis 2.1. Comparison 2: Malaise: delayed versus immediate antibiotics, Outcome 1: Number of people with malaise on Day 3 38
Analysis 2.2. Comparison 2: Malaise: delayed versus immediate antibiotics, Outcome 2: Malaise severity on Day 3 39
Analysis 3.1. Comparison 3: Fever: delayed versus immediate antibiotics, Outcome 1: Fever on Days 3 to 6 39
Analysis 3.2. Comparison 3: Fever: delayed versus immediate antibiotics, Outcome 2: Fever severity on Day 3 39
Analysis 4.1. Comparison 4: Antibiotic use, Outcome 1: Antibiotic use: delayed versus immediate antibiotics 40
Analysis 4.2. Comparison 4: Antibiotic use, Outcome 2: Antibiotic use: delayed versus no antibiotics 41
Analysis 5.1. Comparison 5: Patient satisfaction, Outcome 1: Patient satisfaction: delayed versus immediate antibiotics 42
Analysis 5.2. Comparison 5: Patient satisfaction, Outcome 2: Patient satisfaction: delayed versus no antibiotics 42
Analysis 6.1. Comparison 6: Adverse events, Outcome 1: Vomiting: delayed versus immediate antibiotics 43
Analysis 6.2. Comparison 6: Adverse events, Outcome 2: Diarrhoea: delayed versus immediate antibiotics 43
Analysis 6.3. Comparison 6: Adverse events, Outcome 3: Rash: delayed versus immediate antibiotics 43
Analysis 7.1. Comparison 7: Reconsultation rate, Outcome 1: Reconsultation rate: delayed versus immediate antibiotics 44
ADDITIONAL TABLES 45
APPENDICES 55
FEEDBACK 57
WHAT'S NEW 59
HISTORY 59
CONTRIBUTIONS OF AUTHORS 63
DECLARATIONS OF INTEREST 63
SOURCES OF SUPPORT 63
DIFFERENCES BETWEEN PROTOCOL AND REVIEW 63
INDEX TERMS 63

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[Intervention Review]

Delayed antibiotic prescriptions for respiratory infections

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Editorial group: Cochrane Acute Respiratory Infections Group.
Publication status and date: Edited (no change to conclusions), published in Issue 8, 2022.

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

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ABSTRACT

Background

Concerns exist regarding antibiotic prescribing for respiratory tract infections (RTIs) owing to adverse reactions, cost, and antibacterial resistance. One strategy to reduce antibiotic prescribing is to provide prescriptions, but advise delay in antibiotic use with the expectation that symptoms will resolve first. This is an update of a Cochrane Review published in 2007, and updated in 2010 and 2013. This is was previously a living systematic review. Searches were run and screened monthly since May 2017.

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 (405 participants) with uncomplicated acute respiratory infection. We included 11 studies (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.

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Studies were well reported, and appeared to be of moderate certainty evidence. 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 certainty evidence for all clinical outcomes).

There were either no differences for adverse effects or results favoured *delayed* antibiotics over *immediate* antibiotics (low certainty evidence) 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 certainty evidence).

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 certainty evidence).

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 certainty 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 certainty 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.

Editor note: This was previously a living systematic review. Searches were run and screened monthly since May 2017. The review authors have decided to cease maintaining this review in living systematic mode as a reasonable level of certainty has been reached in the existing evidence.

PLAIN LANGUAGE SUMMARY

Delayed antibiotic prescriptions for respiratory tract infections

Review question

Does *delaying* antibiotic prescription compared to *immediate* prescription or *no* antibiotics decrease the number of antibiotics taken for people with respiratory tract infections (RTIs) including sore throat, middle ear infection, cough (bronchitis), and the common cold?

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.

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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 first published in 2007 and updated in 2010, 2013, and 2017.

Search date

Evidence is current to 25th May 2017.

Study characteristics

We included 12 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.

Study funding sources

Two studies were funded by pharmaceutical companies, two studies did not describe the funding sources, and the remaining seven studies were funded by state institutions or specialist college.

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.

Certainty of the evidence

Overall, the certainty 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 was previously a living systematic review. Searches were run and screened monthly since May 2017. The review authors have decided to cease maintaining this review in living systematic mode as a reasonable level of certainty has been reached in the existing evidence.

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SUMMARY OF FINDINGS

Summary of findings 1. Delayed antibiotics compared to immediate antibiotics for respiratory infections

***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)	Certainty 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[a]	
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[a]	
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[a]	
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[a]	

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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[a,b]

*__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 certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: 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 certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

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

Summary of findings 2. Delayed antibiotics compared to No antibiotics for respiratory infections

***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)	Certainty of the evidence (GRADE)	Comments
	Risk with *no* antibiotics	Risk with *delayed* antibiotics				
Clinical outcomes (clinical outcomes) assessed with: pain, fever, cough, nasal mucosity,	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 com-		-	955 (4 RCTs)	⊕⊕⊕⊖ MODERATE[a]	

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follow-up: range 1 days to 16 days	mon cold, and found results favouring *delayed* antibiotics for pain, fever, and cough duration, but no evidence of difference for nasal mucosity				
Antibiotic use: *delayed* versus *no* antibiotics	137 per 1000	287 per 1000 (201 to 392)	OR 2.55 (1.59 to 4.08)	1241 (4 RCTs)	⊕⊕⊕⊖ MODERATE[a]
Patient satisfaction: *delayed* versus *no* antibiotics	824 per 1000	875 per 1000 (835 to 906)	OR 1.49 (1.08 to 2.06)	1235 (4 RCTs)	⊕⊕⊕⊖ MODERATE[a]
Adverse effects of antibiotics (adverse effects) assessed with: vomiting, diarrhoea, rash, follow-up: range 1 days to 7 days	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[a]

*__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 certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: 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 certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

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

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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.

This was previously a living systematic review. Searches were run and screened monthly since May 2017. The review authors have decided to cease maintaining this review in living systematic mode as a reasonable level of certainty has been reached in the existing evidence.

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

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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 1.

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.

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. This was previously a living systematic review. Searches were run and screened monthly since May 2017. The review authors have decided to cease maintaining this review in living systematic mode as a reasonable level of certainty has been reached in the existing evidence.

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. We resolved any disagreements 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.

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

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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.

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.

Summary of findings and assessment of the certainty of the evidence

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 1). 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 certainty 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). We justified all decisions to down- or upgrade the certainty 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.

RESULTS

Description of studies

See Characteristics of included studies and Characteristics of excluded studies tables.

Results of the search

We identified 432 records in database searching, and 155 records remained after duplicates were removed. We removed 134 records that were clearly not relevant based on title alone, leaving 21 records. We retrieved 21 full-text reports, and of these 11 met our inclusion criteria (Figure 1).

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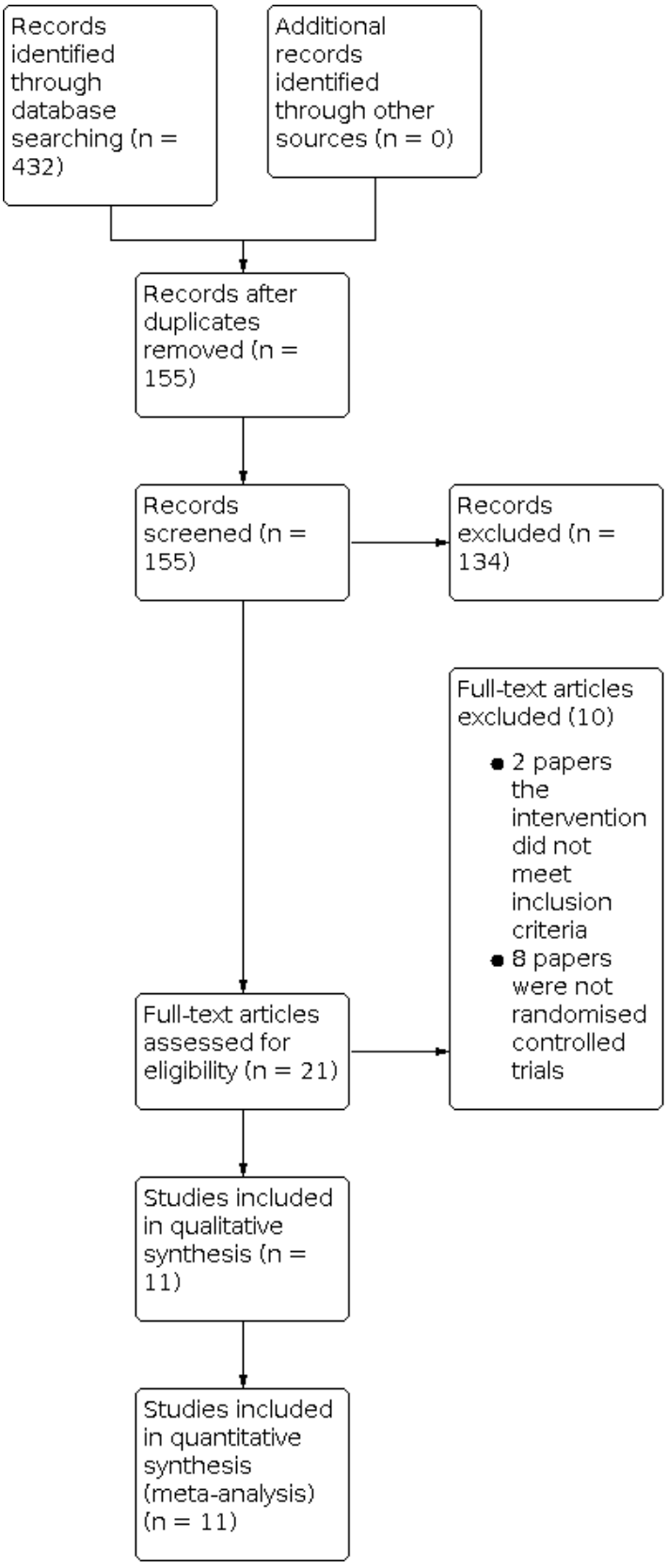
Figure 1. Study flow diagram.



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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 study because it investigated information leaflets rather than prescribing strategies (Agnew 2013). We excluded a total of 10 studies; the other eight studies were not RCTs (Cates 1999; De la Poza Abad 2013; Fischer 2009; Ghebrehewet 2020; 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. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

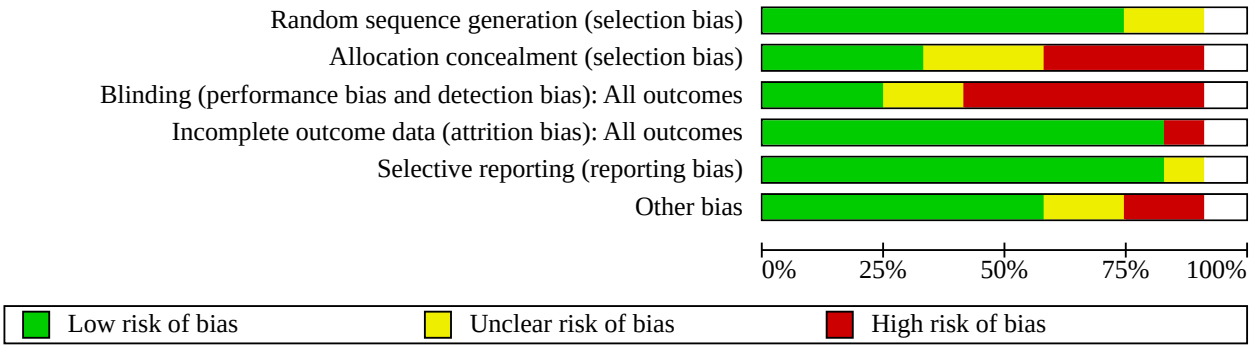

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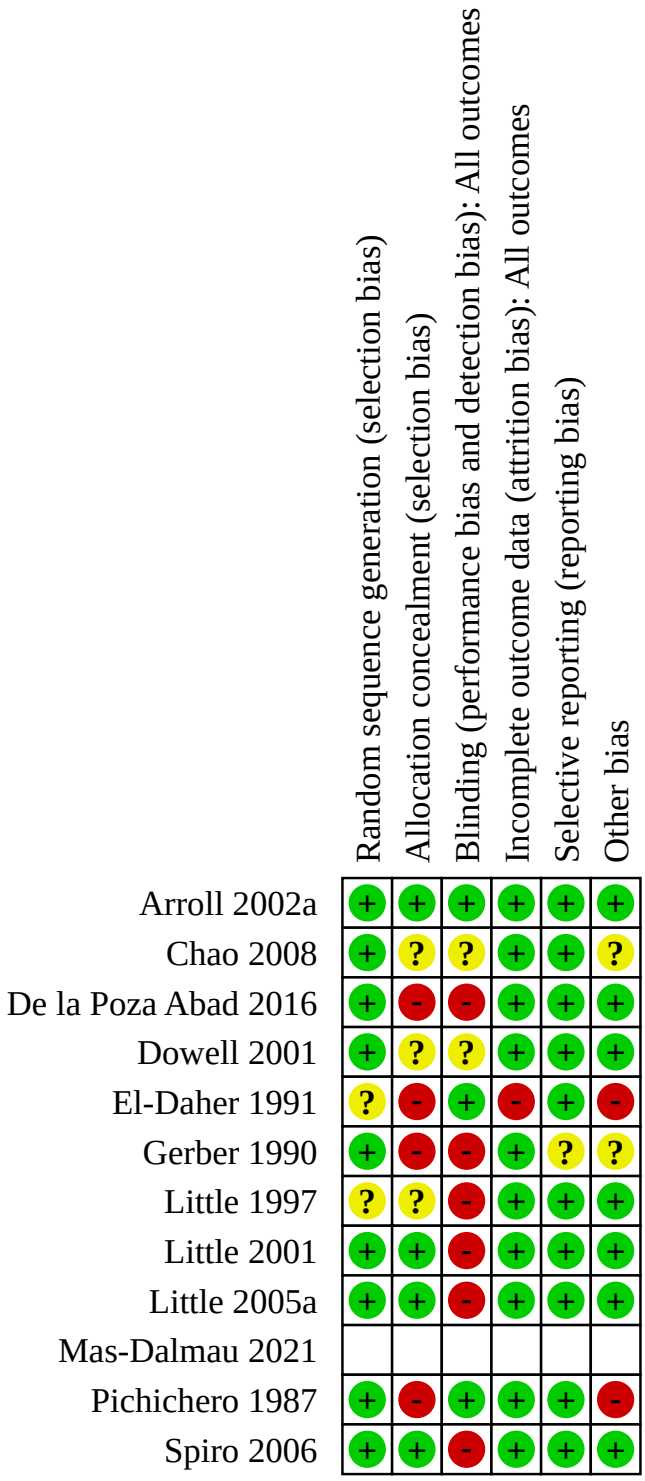
Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



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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 1** 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 (Hoffmann 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

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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 certainty evidence according to GRADE assessment, and are summarised in Summary of findings 1 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).

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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 certainty according to GRADE assessment (Summary of findings 1).

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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 certainty 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 certainty evidence according to GRADE assessment (Summary of findings 1).

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 certainty 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 certainty 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 1).

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 certainty evidence according to GRADE assessment (Summary of findings 2).

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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 certainty evidence according to GRADE assessment (Summary of findings 1).

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).

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 1; Summary of findings 2). GRADE assessments of clinical outcome data and reconsultation rates were moderate (Summary of findings 1, 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 1).

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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 certainty 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). However, an even larger cohort study (1.82 million participants) recruited people with a diagnosis of upper respiratory tract infection, and compared hospitalisation (primary outcome) rates for both delayed and immediate antibiotics (van Staa 2020). Participants who had a delay in antibiotic prescription experienced a 52% increased risk of hospitalisation (adjusted hazard ratio 1.52, 95% confidence interval (CI) 1.43 to 1.62) which was equivalent to a number needed to harm of 1357 compared to immediate antibiotics. This non-randomised cohort study is important owing to its large size and statistical power. However, the authors only collected data on actual delay of antibiotic prescription, so it is not known as to what extent the results reflect delayed antibiotics as a clinical prescribing strategy. Nevertheless, it does raise concerns about the small increased risks of hospitalisation associated with delayed antibiotics (van Staa 2020). 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.

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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 certainty 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 certainty evidence according to GRADE assessment). *Delayed* antibiotics had higher levels of patient satisfaction than *no* antibiotics (87% versus 82% - moderate certainty evidence according to GRADE assessment). *Delayed* antibiotic prescribing strategies achieved markedly lower rates of antibiotic use compared to *immediate* antibiotics (31% versus 93% - moderate certainty 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 certainty 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. We also thank Libby Gibson for her assistance formatting the TIDieR (Template for Intervention Description and Replication) table.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Arroll 2002a

Study characteristics	
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

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Arroll 2002a *(Continued)*

	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. **Sex:***immediate* antibiotic group: 22 males, 40 females; *delayed* antibiotic group: 26 males, 41 females **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.
Other bias	Low risk	Funded by government grant

Chao 2008

Study characteristics	
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 whom 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). **Sex:** *no* antibiotic group: 47 males, 53 females; *delayed* antibiotic group: 60 males, 46 females

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Chao 2008 *(Continued)*

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

De la Poza Abad 2016

Study characteristics	
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). **Sex:***delayed* antibiotics (prescription collection) group: 29 males, 71 females; *delayed* antibiotics (patient-led prescription) group: 33 males, 65 females; *immediate* antibiotic group: 39 males, 61 females; *no* antibiotic group: 35 males, 64 females

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De la Poza Abad 2016 *(Continued)*

	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.
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

Study characteristics

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. **Sex:** *delayed* antibiotic group: 43 males, 56 females; *immediate* antibiotic group: 34 male, 58 female **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.

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Dowell 2001 *(Continued)*

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)
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

Study characteristics

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

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El-Daher 1991 *(Continued)*

	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
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

Study characteristics

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

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Gerber 1990 *(Continued)*

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
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

Study characteristics

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

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Little 1997 *(Continued)*

	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.
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

Study characteristics

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

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Little 2001 *(Continued)*

	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.
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

Study characteristics

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.

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Little 2005a *(Continued)*

	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.
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

Mas-Dalmau 2021

Study characteristics

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Mas-Dalmau 2021 *(Continued)*

Methods	Randomised controlled trial
Participants	436 children aged 2 to 14 years with uncomplicated respiratory infections (pharyngititis, rhinosinusitis, acute bronchitis, acute otitis media) who attended, with their parent(s), 39 primary care pediatrician's offices in Spain 146 children were randomised to *delayed* antibiotics, 148 to *immediate* antibiotics and 142 to *no* antibiotics. **Age:** the mean age of participants in the *delayed* antibiotic group was 6.4 years (SD 3.2); the *immediate* antibotic group was 6.4 years (SD 3.1); and the *no* antibiotic group was 6.1 years (SD 6.1). **Sex:** 68 of the 146 children in the *delayed* antibiotic group were female; 79 of the 148 children in the *immediate* antibotic group were female; and 79 of the 142 children in the *no* antibiotic group were female. **Exclusion criteria:** AOM: otoscopy with isolated tympanum erythema plus isolated crying, history of fever (low likelihood of otitis diagnosis); history suggestive of serous otitis or chronic suppurative otitis media; serious chronic disease, such as cystic fibrosis or valve heart disease; high fever with crying and severe earache; bilateral involvement; purulent otorrhea; previous complications (septic complications, hearing disturbances); antibiotic intake the previous 2 weeks; symptoms lasting ≥ 4 days; and poor general health status (high fever, hypotonic, somnolence, no response to antipyretic). Rhinosinusitis: clinical presentation for < 1 week, antibiotic intake in the previous 2 weeks, and using C-reactive protein quick tests during the visits. Pharyngitis: other causes of sore throat such as ulcers, aphthous ulcer, or thrush; no presence or presence of 1 or 4 Centor criteria, antibiotic intake in the previous 2 weeks, a history of rheumatic fever, a history of peritonsillar abscess, recurrent pharyngotonsillitis (> 5 episodes in the previous year), and using quick antigenic techniques during the visit. Acute bronchitis: children < 3 years old; suspected pneumonia (crepitant, tubular breath sound, unilateral asymmetric hypophonesis, tachypnea, vomiting, severe diarrhea); high fever (axillary temperature > 38.5°C); vomiting and/or severe diarrhea; bronchial asthma; other acute or chronic lung diseases including cystic frosis; active heart disease; psychiatric diagnoses; antibiotic intake in the previous 2 weeks; and using C-reactive protein quick tests during the visit.
Interventions	*Delayed* antibiotics prescription (*immediate* antibiotic *prescription*, no antibiotic prescription)
Outcomes	
Notes	

Pichichero 1987

Study characteristics	
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

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Pichichero 1987 *(Continued)*

	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
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

Study characteristics

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

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Spiro 2006 *(Continued)*

	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

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

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Study	Reason for exclusion
Fischer 2009	Not a randomised controlled trial
Ghebrehewet 2020	Not a randomised controlled trial
Little 2014	Not a randomised controlled trial
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

Study name	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: randomised 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

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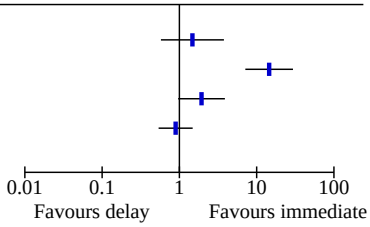
Comparison 1. Pain: delayed versus immediate antibiotics

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Number of participants with pain on Days 3 to 6	4		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.2 Pain severity on Day 3	2	327	Std. Mean Difference (IV, Fixed, 95% CI)	0.35 [0.13, 0.57]
1.3 Duration of malaise	1	294	Mean Difference (IV, Random, 95% CI)	0.10 [-0.86, 1.06]
1.4 Duration of pain symptoms	1	588	Mean Difference (IV, Random, 95% CI)	-0.44 [-1.17, 0.29]
1.4.1 Pharyngitis	1	294	Mean Difference (IV, Random, 95% CI)	-0.20 [-1.21, 0.81]
1.4.2 Acute otitis media	1	294	Mean Difference (IV, Random, 95% CI)	-0.70 [-1.76, 0.36]

Analysis 1.1. Comparison 1: Pain: delayed versus immediate antibiotics, Outcome 1: Number of participants with pain on Days 3 to 6

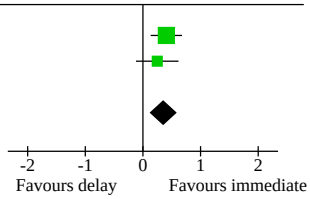
Study or Subgroup	Delayed antibiotics Events	Total	Immediate antibiotics Events	Total	Odds Ratio M-H, Fixed, 95% CI
Arroll 2002a	13	61	9	58	1.47 [0.58 , 3.77]
El-Daher 1991	106	118	42	111	14.51 [7.14 , 29.50]
Little 2001	28	111	15	101	1.93 [0.96 , 3.88]
Spiro 2006	85	132	89	133	0.89 [0.54 , 1.48]



Analysis 1.2. Comparison 1: Pain: delayed versus immediate antibiotics, Outcome 2: Pain severity on Day 3

Study or Subgroup	Delayed antibiotics Mean	SD	Total	Immediate antibiotics Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Little 2001	2.56	2.14	111	1.81	1.44	102	64.8%	0.41 [0.13 , 0.68]
Pichichero 1987	1.6	1.38	55	1.3	1	59	35.2%	0.25 [-0.12 , 0.62]
Total (95% CI)			**166**			**161**	**100.0%**	**0.35 [0.13 , 0.57]**

Heterogeneity: Chi² = 0.46, df = 1 (P = 0.50); I² = 0%
Test for overall effect: Z = 3.15 (P = 0.002)
Test for subgroup differences: Not applicable



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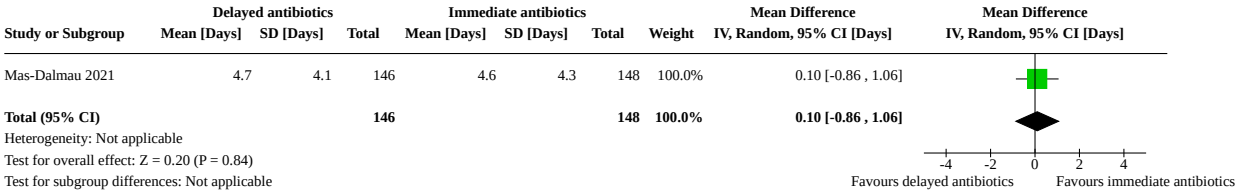
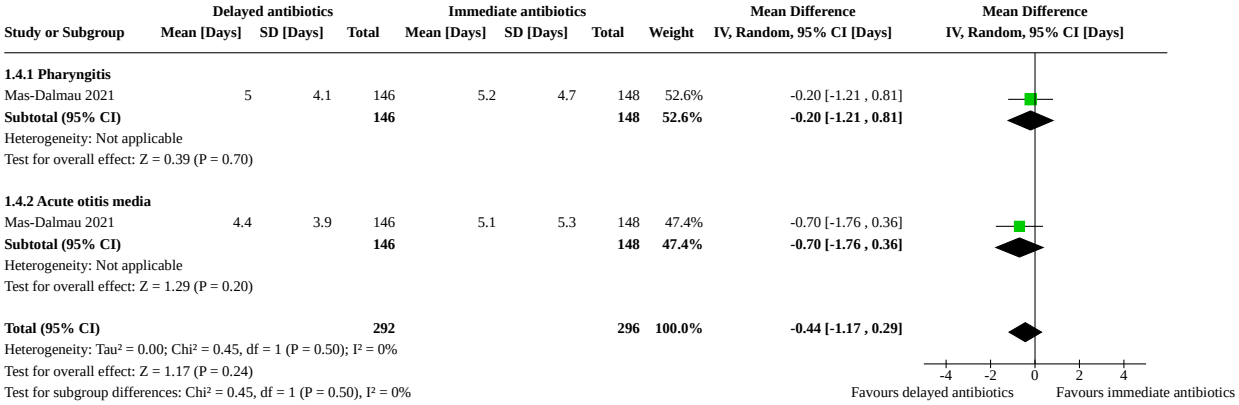
Analysis 1.3. Comparison 1: Pain: delayed versus immediate antibiotics, Outcome 3: Duration of malaise



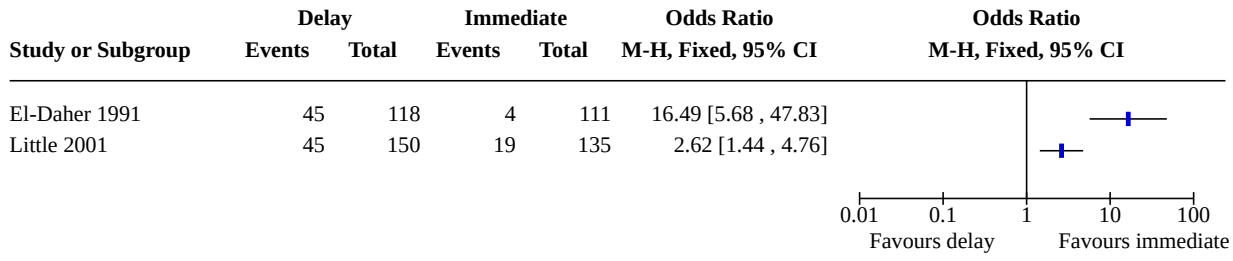
Analysis 1.4. Comparison 1: Pain: delayed versus immediate antibiotics, Outcome 4: Duration of pain symptoms



Comparison 2. Malaise: delayed versus immediate antibiotics

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

Analysis 2.1. Comparison 2: Malaise: delayed versus immediate antibiotics, Outcome 1: Number of people with malaise on Day 3



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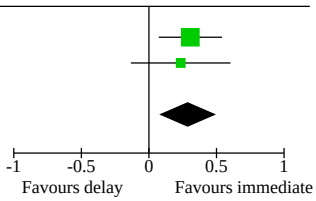
Analysis 2.2. Comparison 2: Malaise: delayed versus immediate antibiotics, Outcome 2: Malaise severity on Day 3

Study or Subgroup	Delay Mean	Delay SD	Delay Total	Immediate Mean	Immediate SD	Immediate Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Little 2001	0.83	1.69	150	0.4	0.97	134	71.2%	0.31 [0.07 , 0.54]
Pichichero 1987	1.3	1	55	1.1	0.67	59	28.8%	0.24 [-0.13 , 0.60]
Total (95% CI)			**205**			**193**	**100.0%**	**0.29 [0.09 , 0.48]**

Heterogeneity: Chi² = 0.10, df = 1 (P = 0.75); I² = 0%
Test for overall effect: Z = 2.84 (P = 0.005)
Test for subgroup differences: Not applicable



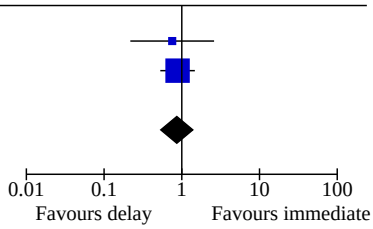
Comparison 3. Fever: delayed versus immediate antibiotics

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

Analysis 3.1. Comparison 3: Fever: delayed versus immediate antibiotics, Outcome 1: Fever on Days 3 to 6

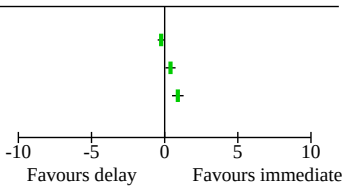
Study or Subgroup	Delay Events	Delay Total	Immediate Events	Immediate Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Arroll 2002a	5	67	6	62	15.6%	0.75 [0.22 , 2.60]
Spiro 2006	42	132	46	133	84.4%	0.88 [0.53 , 1.47]
Total (95% CI)		**199**		**195**	**100.0%**	**0.86 [0.54 , 1.38]**
Total events:	47		52			

Heterogeneity: Chi² = 0.05, df = 1 (P = 0.82); I² = 0%
Test for overall effect: Z = 0.61 (P = 0.54)
Test for subgroup differences: Not applicable



Analysis 3.2. Comparison 3: Fever: delayed versus immediate antibiotics, Outcome 2: Fever severity on Day 3

Study or Subgroup	Delay Mean	Delay SD	Delay Total	Immediate Mean	Immediate SD	Immediate Total	Mean Difference IV, Fixed, 95% CI
Arroll 2002a	36.15	0.73	61	36.39	0.58	58	-0.24 [-0.48 , -0.00]
Pichichero 1987	37.2	1.17	55	36.8	0.61	59	0.40 [0.05 , 0.75]
El-Daher 1991	38	1.96	118	37.1	0.95	111	0.90 [0.50 , 1.30]



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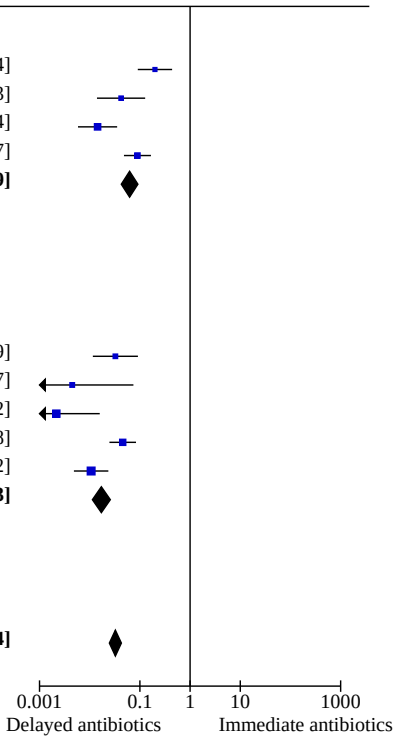
Comparison 4. Antibiotic use

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Antibiotic use: delayed versus immediate antibiotics	8	2257	Odds Ratio (M-H, Fixed, 95% CI)	0.03 [0.02, 0.04]
4.1.1 Antibiotic use: delayed (prescription at time of visit) versus immediate antibiotics	4	841	Odds Ratio (M-H, Fixed, 95% CI)	0.06 [0.04, 0.09]
4.1.2 Antibiotic use: delayed (prescription collection) versus immediate antibiotics	5	1416	Odds Ratio (M-H, Fixed, 95% CI)	0.02 [0.01, 0.03]
4.2 Antibiotic use: delayed versus no antibiotics	4	1241	Odds Ratio (M-H, Random, 95% CI)	2.55 [1.59, 4.08]
4.2.1 Antibiotic use: delayed (prescription at time of visit) versus no antibiotics	2	353	Odds Ratio (M-H, Random, 95% CI)	3.84 [2.18, 6.76]
4.2.2 Antibiotic use: delayed (prescription collection) versus no antibiotics	3	888	Odds Ratio (M-H, Random, 95% CI)	2.05 [1.11, 3.80]

Analysis 4.1. Comparison 4: Antibiotic use, Outcome 1: Antibiotic use: delayed versus immediate antibiotics

Study or Subgroup	Delayed Events	Delayed Total	Immediate Events	Immediate Total	Weight	Odds Ratio M-H, Fixed, 95% CI
4.1.1 Antibiotic use: delayed (prescription at time of visit) versus immediate antibiotics						
Arroll 2002a	32	67	55	67	4.0%	0.20 [0.09 , 0.44]
De la Poza Abad 2016	32	98	46	50	5.6%	0.04 [0.01 , 0.13]
Mas-Dalmau 2021	37	146	142	148	14.5%	0.01 [0.01 , 0.04]
Spiro 2006	50	132	116	133	9.9%	0.09 [0.05 , 0.17]
Subtotal (95% CI)		**443**		**398**	**34.0%**	**0.06 [0.04 , 0.09]**
Total events:	151		359			
Heterogeneity: Chi² = 20.45, df = 3 (P = 0.0001); I² = 85%						
Test for overall effect: Z = 14.31 (P < 0.00001)						
4.1.2 Antibiotic use: delayed (prescription collection) versus immediate antibiotics						
De la Poza Abad 2016	23	100	46	51	6.5%	0.03 [0.01 , 0.09]
Dowell 2001	43	95	92	92	7.1%	0.00 [0.00 , 0.07]
Little 1997	55	176	210	211	18.1%	0.00 [0.00 , 0.02]
Little 2001	36	150	132	151	13.8%	0.05 [0.02 , 0.08]
Little 2005a	39	197	185	193	20.6%	0.01 [0.00 , 0.02]
Subtotal (95% CI)		**718**		**698**	**66.0%**	**0.02 [0.01 , 0.03]**
Total events:	196		665			
Heterogeneity: Chi² = 17.77, df = 4 (P = 0.001); I² = 77%						
Test for overall effect: Z = 19.46 (P < 0.00001)						
Total (95% CI)		**1161**		**1096**	**100.0%**	**0.03 [0.02 , 0.04]**
Total events:	347		1024			
Heterogeneity: Chi² = 51.94, df = 8 (P < 0.00001); I² = 85%						
Test for overall effect: Z = 24.42 (P < 0.00001)						
Test for subgroup differences: Chi² = 20.63, df = 1 (P < 0.00001), I² = 95.2%						



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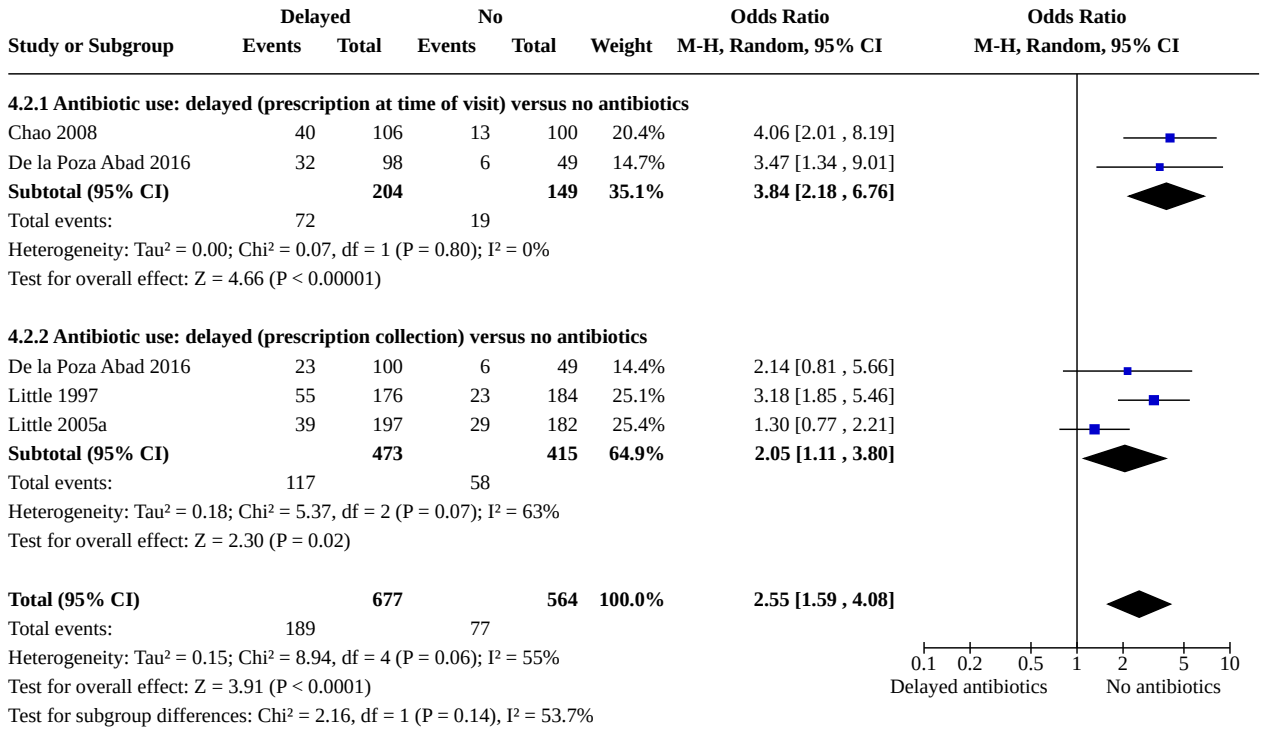
Analysis 4.2. Comparison 4: Antibiotic use, Outcome 2: Antibiotic use: delayed versus no antibiotics



Comparison 5. Patient satisfaction

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 Patient satisfaction: delayed versus immediate antibiotics	7	1927	Odds Ratio (M-H, Random, 95% CI)	0.77 [0.45, 1.29]
5.2 Patient satisfaction: delayed versus no antibiotics	4	1235	Odds Ratio (M-H, Random, 95% CI)	1.49 [1.08, 2.06]

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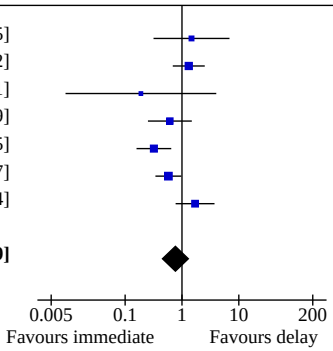
Analysis 5.1. Comparison 5: Patient satisfaction, Outcome 1: Patient satisfaction: delayed versus immediate antibiotics

Study or Subgroup	Delayed antibiotic Events	Total	Immediate antibiotic Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Arroll 2002a	64	67	58	62	8.1%	1.47 [0.32 , 6.85]
De la Poza Abad 2016	170	198	83	101	18.9%	1.32 [0.69 , 2.52]
Dowell 2001	71	73	75	75	2.6%	0.19 [0.01 , 4.01]
Little 1997	165	177	202	211	15.0%	0.61 [0.25 , 1.49]
Little 2001	115	150	123	135	17.9%	0.32 [0.16 , 0.65]
Little 2005a	147	190	166	194	20.9%	0.58 [0.34 , 0.97]
Mas-Dalmau 2021	135	146	130	148	16.6%	1.70 [0.77 , 3.74]
Total (95% CI)		**1001**		**926**	**100.0%**	**0.77 [0.45 , 1.29]**
Total events:	867		837			

Odds Ratio M-H, Random, 95% CI

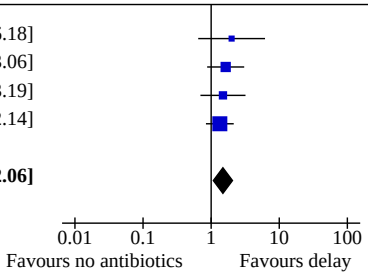


Heterogeneity: Tau² = 0.27; Chi² = 15.34, df = 6 (P = 0.02); I² = 61%
Test for overall effect: Z = 1.00 (P = 0.32)
Test for subgroup differences: Not applicable

Analysis 5.2. Comparison 5: Patient satisfaction, Outcome 2: Patient satisfaction: delayed versus no antibiotics

Study or Subgroup	Delayed antibiotics Events	Total	No antibiotics Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Chao 2008	101	106	91	100	8.2%	2.00 [0.65 , 6.18]
De la Poza Abad 2016	170	198	78	99	26.6%	1.63 [0.87 , 3.06]
Little 1997	165	177	166	184	18.0%	1.49 [0.70 , 3.19]
Little 2005a	147	190	130	181	47.3%	1.34 [0.84 , 2.14]
Total (95% CI)		**671**		**564**	**100.0%**	**1.49 [1.08 , 2.06]**
Total events:	583		465			

Odds Ratio M-H, Random, 95% CI



Heterogeneity: Tau² = 0.00; Chi² = 0.54, df = 3 (P = 0.91); I² = 0%
Test for overall effect: Z = 2.41 (P = 0.02)
Test for subgroup differences: Not applicable

Comparison 6. Adverse events

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.1 Vomiting: delayed versus immediate antibiotics	3		Odds Ratio (M-H, Random, 95% CI)	Totals not selected
6.2 Diarrhoea: delayed versus immediate antibiotics	4		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
6.3 Rash: delayed versus immediate antibiotics	2	680	Odds Ratio (M-H, Fixed, 95% CI)	1.03 [0.54, 1.97]

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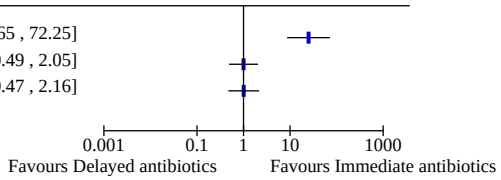
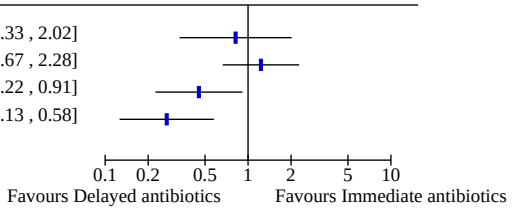
Analysis 6.1. Comparison 6: Adverse events, Outcome 1: Vomiting: delayed versus immediate antibiotics

Study or Subgroup	Delayed antibiotics Events	Total	Immediate antibiotics Events	Total	Odds Ratio M-H, Random, 95% CI
El-Daher 1991	57	118	4	111	25.00 [8.65 , 72.25]
Little 1997	15	179	18	215	1.00 [0.49 , 2.05]
Spiro 2006	15	132	15	133	1.01 [0.47 , 2.16]



Analysis 6.2. Comparison 6: Adverse events, Outcome 2: Diarrhoea: delayed versus immediate antibiotics

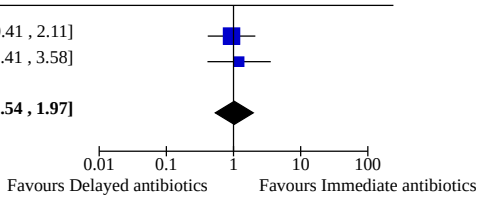
Study or Subgroup	Delayed antibiotics Events	Total	Immediate antibiotics Events	Total	Odds Ratio M-H, Fixed, 95% CI
Arroll 2002a	11	67	12	62	0.82 [0.33 , 2.02]
Little 1997	23	179	23	215	1.23 [0.67 , 2.28]
Little 2001	14	150	25	135	0.45 [0.22 , 0.91]
Spiro 2006	10	132	31	133	0.27 [0.13 , 0.58]



Analysis 6.3. Comparison 6: Adverse events, Outcome 3: Rash: delayed versus immediate antibiotics

Study or Subgroup	Delayed antibiotics Events	Total	Immediate antibiotics Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Little 1997	11	180	14	215	66.7%	0.93 [0.41 , 2.11]
Little 2001	8	150	6	135	33.3%	1.21 [0.41 , 3.58]
Total (95% CI)		**330**		**350**	**100.0%**	**1.03 [0.54 , 1.97]**
Total events:	19		20			

Heterogeneity: Chi² = 0.14, df = 1 (P = 0.71); I² = 0%
Test for overall effect: Z = 0.08 (P = 0.94)
Test for subgroup differences: Not applicable



Comparison 7. Reconsultation rate

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.1 Reconsultation rate: delayed versus immediate antibiotics	2	379	Odds Ratio (M-H, Fixed, 95% CI)	1.04 [0.55, 1.98]

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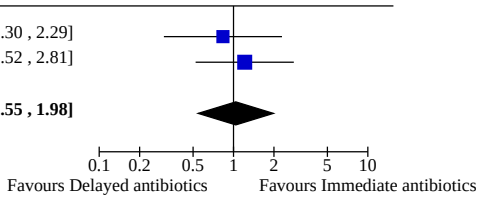
Analysis 7.1. Comparison 7: Reconsultation rate, Outcome 1: Reconsultation rate: delayed versus immediate antibiotics

Study or Subgroup	Delayed antibiotics Events	Total	Immediate antibiotics Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Pichichero 1987	8	55	10	59	45.5%	0.83 [0.30 , 2.29]
Spiro 2006	13	132	11	133	54.5%	1.21 [0.52 , 2.81]
Total (95% CI)		**187**		**192**	**100.0%**	**1.04 [0.55 , 1.98]**
Total events:	21		21			

Heterogeneity: Chi² = 0.31, df = 1 (P = 0.58); I² = 0%
Test for overall effect: Z = 0.12 (P = 0.91)
Test for subgroup differences: Not applicable



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ADDITIONAL TABLES

Table 1. TIDieR (Template for Intervention Description and Replication) table

Author Year	Disease	Participants	Trial outcomes	Materials and procedures for clinicians delivering intervention	Clinicians delivering intervention	How intervention was delivered to participants	Where intervention was delivered	When and how much	Tailoring	Modified during trial?	Checks of fidelity?	Fidelity
Arroll 2002a	Common cold	Any age	Antibiotic use, satisfaction, and symptoms of *delayed* prescribing	Antibiotic prescription (deemed appropriate by treating GP). Procedure not detailed	15 GPs	*Delayed*: to fill prescription after 3 days if symptoms not improved Immediate: usual care	1 general practice, New Zealand	Once, at index consultation; *delayed* group asked to wait 3 days	Participants advised to return to GP if symptoms worsened.	None reported	Not detailed	-
Chao 2008	Acute otitis media	Children (2 to 12 years)	Antibiotic use	2 forms of discharge instruction sheet provided by clinicians to patients: 1) completion of all: when to return for medical care (after 2 to 3 days); how to use complimentary symptom drugs 2) comparison: as above + prescription to fill if still unwell at 2 to 3 days	14 emergency department physicians	Not detailed	Emergency department of an urban public hospital in the USA	Once, at index consultation	Provided with complimentary optional ibuprofen or paracetamol +/- benzocaine otic drops at index consultation	None reported	None	None
De la Poza Abad 2016	Acute uncomplicated respiratory infection	Adults	Symptom duration and severity, antibiotic use,	Physician structured script and patient information sheet about self limiting natural history of respiratory infection, pros and cons of an-	GPs	4 groups of antibiotic prescription use:	23 primary care centres in 4 regions in Spain	Once, at index consultation; *delayed* prescrip-	All advised to return if no improvement or worsen-	None reported	None	None

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Table 1. TIDieR (Template for Intervention Description and Replication) table *(Continued)*

			patient satisfaction, patients' beliefs in antibiotic effectiveness	tibiotics used with patients. Antibiotic prescription as indicated		1) immediate; 2) *delayed*, patient-led prescription; 3) *delayed*, prescription collection; 4) none. *Delayed* = 3 days		tion collection group could collect after 3 days if needed	ing after 5 days (pharyngitis) or 10 days (other infections). Central phone follow-up if symptoms persisted			
Dowell 2001	Acute uncomplicated cough	Adults (> 16 years)	Symptom duration, prescription uptake, patient satisfaction, patient enablement subsequent consultation rates	Antibiotic prescription of GP's choice provided or lodged at reception.	48 GPs	Immediate: usual care *delayed*: collect prescription after 1 week if required (within 2 weeks)	22 general practices in Scotland, UK	Once, at index consultation; *delayed* prescription group asked to wait 1 week	Nil	None reported	Date scripts collected by *delayed* group	35% (12/34) waited 7 days as asked; mean wait 6 days (range 1 to 10).
El-Daher 1991	GABHS	Children (4 to 14 years)	Signs and symptoms, antibody titre, subsequent episodes	Immediate group: supplied with 2 days of penicillin, then 8 days of penicillin on Day 3. *delayed* group: supplied with 2 days of placebo, then 10 days of penicillin on Day 3	Physician	Immediate: 2 days penicillin, then 8 days penicillin *delayed*: 2 days placebo, then 10 days penicillin	Paediatric clinics at Jordan University of Science and Technology, Jordan	At index consultation, then re-examined on Day 3	Paracetamol as needed	None reported	None reported	None reported

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Table 1. TIDieR (Template for Intervention Description and Replication) table *(Continued)*

Gerber 1990	GABHS pharyngitis	Children / adolescents (2 to 22 years)	Positive follow-up throat cultures, recurrences, symptomatic recurrences, or new acquisitions	Immediate group: supplied with 10-day course of dose appropriate penicillin V. *Delayed* group: instructed to wait 48 hours before commencing 10-day course of penicillin. Telephone follow-up 24 hours later in both groups and next 24 hours for *delayed* group to advise commencement	Not reported (implied treating physicians)	Immediate: usual care *delayed*: wait 48 hours before commencing penicillin	1 private paediatric practice in the USA	At index consultation and telephone follow-up 24 and 48 hours afterwards	Further 10-day courses of penicillin if further GABHS pharyngitis	None reported	Urine sample at Day 9, mailed after drying for analysis	No report of urine sample compliance results
Little 1997	Sore throat	≥ 4 years	Duration of symptoms, satisfaction and compliance with and perceived efficacy of antibiotics, time off school or work	Immediate group given 10-day prescription of dose appropriate penicillin V. *Delayed* group offered antibiotics but could collect prescription if symptoms not settled within 3 days. GP standard advice sheets provided to participants	25 GPs	3 groups of antibiotic prescriptions: 1) immediate: usual care; 2) *no* antibiotics; 3) *delayed*: to collect within 3 days.	11 general practices, England, UK	At index consultation; *delayed* prescription group within 3 days	Erythromycin if sensitive to penicillin. Analgesics or antipyretics allowed.	None reported	GP documented prescription on sheet. Patient daily diary until symptom-free and medication finished	GPs' compliance: immediate: 99%; no ABs: 2%; *delayed*: 5% left with script AB use: immediate: 99%; no: 13%; *delayed*: 31%
Little 2001	Acute otitis media	Children (0.5 to 10 years)	Symptom resolution, absence from school or nursery,	Immediate group prescribed amoxicillin. *Delayed* group asked to delay 3 days before using prescrip-	42 GPs	Immediate: usual care *delayed*: wait 3 days to collect	General practices in Scotland, UK	At index consultation; *delayed* prescription group asked to	Antipyretics were allowed.	None reported	Patient diary	No

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Table 1. TIDieR (Template for Intervention Description and Replication) table *(Continued)*

			paracetamol consumption	tion, and then only if necessary. GP used standardised advice sheets specific to each group		prescription		wait 3 days				
Little 2005a	Acute uncomplicated lower respiratory tract infection	≥ 3 years	Symptom duration and severity, antibiotic use, satisfaction, belief in antibiotics	Immediate group: prescription for 10 days amoxicillin. *Delayed* group: prescription written and left at reception for patient to retrieve if wanted (but advised to wait 14 days). Leaflet groups: 1-page information leaflet covering natural history of illness, when to seek further help. All groups: statement about analgesics, natural history of illness, and prescribing strategy read out by physicians	37 GPs	6 groups (factorial): 1) *no* antibiotics, no leaflet; 2) *delayed* antibiotics, no leaflet; 3) immediate antibiotics, no leaflet; 4) *no* antibiotics, leaflet; 5) *delayed* antibiotics and leaflet; 6) immediate antibiotics and leaflet. Delay = 14 days	General practices, England, UK	At index consultation; 14 days for *delayed* prescription group	Erythromycin if allergic to penicillin. Antipyretics allowed.	None reported	Reported antibiotic use in diary	96% immediate group; 20% *delayed* group; 16% no ABs group
Pichichero 1987	Sore throat (presumed GABHS)	Children (4 to 18 years)	Symptomatic response,	Drugs supplied directly to patients. Usual care 10-day course penicillin V.	Study nurse	Immediate: usual care	Primary care paediatric practice	At index consultation	Antibiotic (tablet or suspension).	None reported	Check drug bottles at 3 days and 3	Confirmed in 98% cases (drug bottles);

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Table 1. TIDieR (Template for Intervention Description and Replication) table *(Continued)*

			recurrent infections	*Delayed* group provided with placebo for first 3 days, then penicillin		*delayed*: placebo for 3 days then penicillin	in the USA		Antipyretics were allowed		weeks. Test urine at 3 days for antibiotic	no ABs used in placebo group
Spiro 2006	Acute otitis media	Children (0.5 to 12 years)	Antibiotic use, clinical symptoms, adverse outcomes, days off school or work, unscheduled medical visits, parents' comfort with management	Provision of written prescription for antibiotics valid for 3 days. Wait-and-see prescription group given written and verbal instructions to only fill prescription if no improvement or worsening 2 days after emergency room visit	Emergency department clinicians	Immediate: usual care Wait-and-see prescription: wait 2 days	Paediatric emergency department in the USA	At index consultation and within 3 days if prescription filled	Ibuprofen and otic drops as needed. Primary care contact if worsening	None reported	Verification of filling of prescription by phone call to designated pharmacies for 28% of the sample	All instances of no filling of prescription confirmed by pharmacies, and 90% confirmation of parent report of prescription filled

ABs: antibiotics
GABHS: group A beta-haemolytic streptococcus
GP: general practitioner

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Table 2. Summary of clinical outcomes: delayed versus immediate antibiotics

Study	Outcome	Delay	Immediate	Favours	Result (95% CI)
Sore throat					
Pichichero 1987	Fever severity on Day 3	37.2 (SD 1.2, n = 55)	36.8 (SD 0.6, n = 59)	Immediate antibiotics	MD 0.40 (95% CI 0.05 to 0.75)
	Malaise severity on Day 3	1.3 (SD 1.0, n = 55)	1.1 (SD 0.7, n = 59)	No difference	MD 0.20 (95% CI -0.11 to 0.51)
	Pain severity on Day 3	1.6 (SD 1.4, n = 55)	1.3 (SD 1.3, n = 59)	No difference	MD 0.30 (95% CI -0.15 to 0.75)
	Compliance	55/55	59/59	No difference	100% in both groups
Gerber 1990	Recurrence rate	-	-	No difference	Data not available
	Compliance	44/50	59/63	*Delayed* antibiotics	88% in immediate group and 93% in *delayed* group
El-Daher 1991	Vomiting	57/118	4/111	Immediate antibiotics	OR 25.00 (95% CI 8.65 to 72.25)
	Pain on Day 3	106/118	42/111	Immediate antibiotics	OR 14.51 (95% CI 7.14 to 29.50)
	Malaise on Day 3	45/118	4/111	Immediate antibiotics	OR 16.49 (95% CI 5.68 to 47.83)
	Fever severity on Day 3	38.0 °C (SD 2.0, n = 118)	37.1 °C (SD 1.0, n = 111)	Immediate antibiotics	SMD 0.58 (95% CI 0.31 to 0.84)
Little 1997	Vomiting	15/179	18/215	No difference	OR 1.00 (95% CI 0.49 to 2.05)
	Diarrhoea	23/179	23/215	No difference	OR 1.23 (95% CI 0.67 to 2.28)
	Rash	11/180	14/215	No difference	OR 0.93 (95% CI 0.41 to 2.11)
	Stomachache	48/180	66/215	No difference	OR 0.82 (95% CI 0.53 to 1.27)
	Fever (> 37.0 °C)	Unavailable	Unavailable	Immediate antibiotics	Data not available
	Pain	Unavailable	Unavailable	No difference	Data not available
	Cough	Unavailable	Unavailable	No difference	Data not available
	Malaise	Unavailable	Unavailable	No difference	Data not available
	Analgesic use	Unavailable	Unavailable	No difference	Data not available
	Time off work	Unavailable	Unavailable	No difference	Data not available

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Table 2. Summary of clinical outcomes: delayed versus immediate antibiotics *(Continued)*

De la Poza Abad 2016	Pain duration (*delayed* prescription at time of visit)	5.7 days (SD 5.1, n = 45)	4.4 days (SD 2.4, n = 47)	No difference	MD 1.30 (95% CI -0.34 to 2.94)
	Pain duration (*delayed* prescription requiring collection)	7.4 days (SD 6.3, n = 46)	4.4 days (SD 2.4, n = 47)	Immediate antibiotics	MD 3.00 (95% CI -1.03 to 4.95)
	Fever duration (*delayed* prescription at time of visit)	3.1 days (SD 1.8, n = 45)	2.9 days (SD 1.7, n = 47)	No difference	MD -0.20 (95% CI -0.52 to 0.92)
	Fever duration (*delayed* prescription requiring collection)	3.4 days (SD 2.4, n = 46)	2.9 days (SD 1.7, n = 47)	No difference	MD 0.50 (95% CI -0.35 to 1.35)
	Cough duration (*delayed* prescription at time of visit)	8.1 days (SD 5.9, n = 45)	8.1 days (SD 5.7, n = 47)	No difference	MD -2.50 (95% CI -5.52 to 0.52)
	Cough duration (*delayed* prescription requiring collection)	8.2 days (SD 6.9, n = 46)	8.1 days (SD 5.7, n = 47)	No difference	MD -2.40 (95% CI -5.59 to 0.79)
	Nasal mucosity duration (*delayed* prescription at time of visit)	7.2 days (SD 4.3, n = 45)	5.4 days (SD 3.9, n = 47)	Immediate antibiotics	MD -1.80 (95% CI 0.12 to 3.48)
	Nasal mucosity duration (*delayed* prescription requiring collection)	9.7 days (SD 8.3, n = 46)	8.9 days (SD 6.5, n = 46)	Immediate antibiotics	MD 4.30 (95% CI 1.65 to 6.95)
Acute otitis media					
Little 2001	Diarrhoea	14/150	25/135	*Delayed* antibiotics	OR 0.45 (95% CI 0.22 to 0.91)
	Rash	8/150	6/135	No difference	OR 1.21 (95% CI 0.41 to 2.58)
	Participants with pain on Day 3	28/111	15/101	No difference	OR 1.93 (95% CI 0.96 to 3.88)
	Participants with pain on Day 7	3/111	0/101	No difference	OR 6.55 (95% CI 0.33 to 128.35)
	Participants with malaise on Day 3	45/150	19/135	Immediate antibiotics	OR 2.62 (95% CI 1.44 to 4.76)
	Malaise severity Day 3	0.8 (SD 1.7, n = 150)	0.4 (SD 1.0, n = 134)	Immediate antibiotics	MD 0.43 (95% CI 0.11 to 0.75)
	Malaise severity on Day 7	2.2 (SD 2.0, n = 150)	1.5 (SD 1.2, n = 135)	No difference	MD 0.01 (95% CI -0.11 to 0.13)
	Pain severity on Day 3	2.6 (SD 2.1, n = 111)	1.8 (SD 1.4, n = 102)	Immediate antibiotics	MD 0.75 (95% CI 0.26 to 1.24)
	Pain severity on Day 7	1.17 (SD 0.75, n = 111)	1.05 (SD 0.38, n = 101)	No difference	MD 0.12 (95% CI -0.04 to 0.28)
	Paracetamol consumption	2.3 spoons	1.7 spoons	Immediate antibiotics	MD 0.59 (95% CI 0.25 to 0.93)

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Table 2. Summary of clinical outcomes: delayed versus immediate antibiotics *(Continued)*

	Last day of crying	2.2 days	1.5 days	Immediate antibiotics	MD 0.69 (95% CI 0.31 to 1.07)
Little 2006	Episodes of earache in the 3 months since randomisation	Unavailable	Unavailable	No difference	OR 0.89 (95% CI 0.48 to 1.65)
	Episodes of earache over 1 year	Unavailable	Unavailable	No difference	OR 1.03 (95% CI 0.60 to 1.78)
Spiro 2006	Pain day 4 to 6	85/132	89/133	No difference	OR 0.89 (95% CI 0.54 to 1.48)
	Fever day 4 to 6	42/132	46/133	No difference	OR 0.88 (95% CI 0.53 to 1.47)
	Vomiting	15/132	15/133	No difference	OR 1.01 (95% CI 0.47 to 2.16)
	Diarrhoea	10/132	31/133	*Delayed* antibiotics	OR 0.27 (95% CI 0.13 to 0.58)
Cough					
Dowell 2001	Clinical outcomes	Unavailable	Unavailable	No difference	Data not available
Little 2005a	Clinical outcomes	Unavailable	Unavailable	No difference	Data not available
De la Poza Abad 2016	Pain duration (*delayed* prescription at time of visit)	11.0 days (SD 8.0, n = 32)	10.5 days (SD 8.0, n = 32)	No difference	MD 0.50 (95% CI -0.34 to 4.42)
	Pain duration (*delayed* prescription requiring collection)	8.9 days (SD 6.9, n = 32)	10.5 days (SD 8.0, n = 32)	No difference	MD -1.60 (95% CI -5.26 to 2.06)
	Fever duration (*delayed* prescription at time of visit)	5.6 days (SD 5.9, n = 32)	4.1 days (SD 5.7, n = 32)	No difference	MD 1.50 (95% CI -1.34 to 4.34)
	Fever duration (*delayed* prescription requiring collection)	4.7 days (SD 4.6, n = 32)	4.1 days (SD 5.7, n = 32)	No difference	MD 0.60 (95% CI -1.94 to 3.14)
	Cough duration (*delayed* prescription at time of visit)	15.6 days (SD 8.8, n = 32)	13.0 days (SD 7.0, n = 32)	No difference	MD 2.60 (95% CI -1.30 to 6.50)
	Cough duration (*delayed* prescription requiring collection)	12 days (SD 5.6, n = 32)	13.0 days (SD 7.0, n = 32)	No difference	MD -1.00 (95% CI -4.11 to 2.11)
Common cold					
Arroll 2002a	Participants with fever on Day 3	5/67	6/62	No difference	OR 0.75 (95% CI 0.22 to 2.6)
	Participants with fever on Day 7	3/67	4/62	No difference	OR 0.68 (95% CI 0.15 to 3.17)
	Participants with diarrhoea	11/67	12/62	No difference	OR 0.79 (95% CI 0.53 to 1.19)

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Table 2. Summary of clinical outcomes: delayed versus immediate antibiotics *(Continued)*

	Participants with pain on Day 3	13/61	9/58	No difference	OR 1.47 (95% CI 0.58 to 3.77)
	Participants with pain on Day 7	1/61	3/58	No difference	OR 0.31 (95% CI 0.03 to 3.03)
	Participants with cough on Day 3	54/67	51/62	No difference	OR 0.90 (95% CI 0.37 to 2.18)
	Participants with cough on Day 7	41/61	43/58	No difference	OR 0.72 (95% CI 0.32 to 1.58)
	Fever severity on Day 3	36.2 °C (SD 0.7, n = 61)	36.4 °C (SD 0.6, n = 58)	No difference	MD -0.24 (95% CI -0.48 to 0.00)
	Fever severity on Day 7	36.0 °C (SD 0.8, n = 59)	36.3 °C (SD 0.6, n = 60)	*Delayed* antibiotics	MD -0.32 (95% CI -0.57 to -0.07)
De la Poza Abad 2016	Pain duration (*delayed* prescription at time of visit)	8.4 days (SD 8.2, n = 29)	6.7 days (SD 4.5, n = 20)	No difference	MD 1.70 (95% CI -1.88 to 5.28)
	Pain duration (*delayed* prescription requiring collection)	10.1 days (SD 7.5, n = 20)	6.7 days (SD 4.5, n = 20)	No difference	MD 3.40 (95% CI -0.43 to 7.23)
	Fever duration (*delayed* prescription at time of visit)	3.0 days (SD 1.2, n = 29)	5.3 days (SD 6.2, n = 20)	No difference	MD -2.30 (95% CI -5.05 to 0.45)
	Fever duration (*delayed* prescription requiring collection)	4.2 days (SD 3.0, n = 20)	5.3 days (SD 6.2, n = 20)	No difference	MD -1.10 (95% CI -4.12 to 1.92)
	Cough duration (*delayed* prescription at time of visit)	8.3 days (SD 5.2, n = 29)	7.6 days (SD 5.6, n = 20)	No difference	MD -0.70 (95% CI -2.40 to 3.80)
	Cough duration (*delayed* prescription requiring collection)	6.4 days (SD 4.6, n = 20)	7.6 days (SD 5.6, n = 20)	No difference	MD -1.20 (95% CI -4.38 to 1.98)
	Nasal mucosity duration (*delayed* prescription at time of visit)	15.2 days (SD 9.7, n = 29)	13.0 days (SD 8.8, n = 20)	No difference	MD 2.20 (95% CI -3.03 to 7.43)
	Nasal mucosity duration (*delayed* prescription requiring collection)	10.7 days (SD 7.2, n = 20)	13.0 days (SD 8.8, n = 20)	No difference	MD -2.30 (95% CI -7.28 to 2.68)

CI: confidence interval
MD: mean difference
OR: odds ratio
SD: standard deviation
SMD: standardised mean difference

Table 3. Summary of clinical outcomes: delayed versus no antibiotics

Study	Outcome	*Delay*	*No* antibiotics	Favours	Result (with 95% CI)
Sore throat					

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Table 3. Summary of clinical outcomes: delayed versus no antibiotics *(Continued)*

De la Poza Abad 2016	Pain duration (*delayed* prescription at time of visit)	5.7 days (SD 5.1, n = 45)	7.8 days (SD 6.0, n = 46)	No difference	MD -2.10 (95% CI -4.39 to 0.19)
	Pain duration (*delayed* prescription requiring collection)	7.4 days (SD 6.3, n = 46)	7.8 days (SD 6.0, n = 46)	No difference	MD -0.40 (95% CI -2.91 to 2.11)
	Fever duration (*delayed* prescription at time of visit)	3.1 days (SD 1.8, n = 45)	3.2 days (SD 2.5, n = 46)	No difference	MD 0.10 (95% CI 0.99 to 0.79)
	Fever duration (*delayed* prescription requiring collection)	3.4 days (SD 2.4, n = 46)	3.2 days (SD 2.5, n = 46)	No difference	MD 0.20 (95% CI -0.80 to 1.20)
	Cough duration (*delayed* prescription at time of visit)	8.1 days (SD 5.9, n = 45)	10.6 days (SD 8.6, n = 46)	No difference	MD 0.0 (95% CI -2.37 to 2.37)
	Cough duration (*delayed* prescription requiring collection)	8.2 days (SD 6.9, n = 46)	10.6 days (SD 8.6, n = 46)	No difference	MD 0.10 (95% CI -2.48 to 2.68)
	Nasal mucosity duration (*delayed* prescription at time of visit)	7.2 days (SD 4.3, n = 45)	8.9 days (SD 6.5, n = 45)	No difference	MD -1.70 (95% CI -3.96 to 0.56)
	Nasal mucosity duration (*delayed* prescription requiring collection)	9.7 days (SD 8.3, n = 46)	8.9 days (SD 6.5, n = 46)	No difference	MD 0.80 (95% CI -2.25 to 3.85)
Little 2005a	Clinical outcomes	Unavailable	Unavailable	No difference	Unavailable
Acute otitis media					
Chao 2008	Fever day 3	18/106	8/100	No difference	OR 1.45 (95% CI 0.50 to 4.24)
	Pain day 3	26/106	29/100	No difference	OR 0.64 (95% CI 0.29 to 1.38)
Cough					
De la Poza Abad 2016	Pain duration (*delayed* prescription at time of visit versus *no* antibiotics)	11 days (SD 8.0, n = 32)	12.2 days (SD 8.0, n = 32)	No difference	MD -1.20 (95% CI -5.07 to 2.67)
	Pain duration (*delayed* prescription requiring collection versus *no* antibiotics)	8.9 days (SD 6.9, n = 32)	12.2 days (SD 7.8, n = 32)	No difference	MD -3.30 (95% CI -6.91 to 0.31)
	Fever duration (*delayed* prescription at time of visit versus *no* antibiotics)	5.6 days (SD 5.9, n = 32	7.2 days (SD 7.9, n = 32)	No difference	MD -1.60 (95% CI -8.82 to 5.62)
	Fever duration (*delayed* prescription requiring collection versus *no* antibiotics)	4.7 days (SD 4.6, n = 32)	7.2 days (SD 7.9, n = 32)	No difference	MD -2.50 (95% CI -5.67 to 0.67)
	Cough duration (*delayed* prescription at time of visit versus *no* antibiotics)	15.6 days (SD 8.8, n = 32)	15.1 days (SD 7.6, n = 32)	No difference	MD -0.50 (95% CI -3.53 to 4.53)
	Cough duration (*delayed* prescription requiring collection versus *no* antibiotics)	12.0 days (SD 5.6, n = 32)	15.1 days (SD 7.6, n = 32)	No difference	MD -3.10 (95% CI -6.37 to 0.17)

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Table 3. Summary of clinical outcomes: delayed versus no antibiotics *(Continued)*

Common cold

De la Poza Abad 2016	Pain duration (*delayed* prescription at time of visit versus *no* antibiotics)	8.4 days (SD 8.2, n = 29)	13.7 days (SD 6.7, n = 19)	*Delayed* antibiotics	MD -5.30 (95% CI -9.54 to -1.06)
	Pain duration (*delayed* prescription requiring collection versus *no* antibiotics)	10.1 days (SD 7.5, n = 20)	13.7 days (SD 6.7, n = 19)	No difference	MD -3.60 (95% CI -8.06 to 0.86)
	Fever duration (*delayed* prescription at time of visit versus *no* antibiotics)	3.0 days (SD 1.2, n = 29)	9.0 days (SD 8.9, n = 19)	*Delayed* antibiotics	MD -6.00 (95% CI -10.03 to -1.97)
	Fever duration (*delayed* prescription requiring collection versus *no* antibiotics)	4.2 days (SD 3, n = 20)	9.0 days (SD 8.9, n = 19)	*Delayed* antibiotics	MD -4.80 (95% CI -9.01 to -0.59)
	Cough duration (*delayed* prescription at time of visit versus *no* antibiotics)	8.3 days (SD 5.2, n = 29)	11.7 days (SD 6.4, n = 19)	No difference	MD -3.40 (95% CI -6.84 to 0.04)
	Cough duration (*delayed* prescription requiring collection versus *no* antibiotics)	6.4 days (SD 4.6, n = 20)	11.7 days (SD 6.4, n = 19)	*Delayed* antibiotics	MD -5.30 (95% CI -8.81 to -1.79)
	Nasal mucosity duration (*delayed* prescription at time of visit versus *no* antibiotics)	15.2 days (SD 9.7, n = 29)	15.2 days (SD 7.5, n = 19)	No difference	MD -0.0 (95% CI -4.88 to 4.88)
	Nasal mucosity (*delayed* prescription requiring collection versus *no* antibiotics)	10.7 days (SD 7.2, n = 20)	15.2 days (SD 7.5, n = 19)	No difference	MD -4.50 (95% CI -9.12 to 0.12)

CI: confidence interval
MD: mean difference
OR: odds ratio
SD: standard deviation

APPENDICES

Appendix 1. CENTRAL, MEDLINE, Embase, CINAHL, and Web of Science search strategies (May 2017)

Cochrane Central Register of Controlled Trials (CENTRAL)

#1 MeSH descriptor: [Respiratory Tract Infections] explode all trees 11364
#2 ((upper next respiratory next tract next infection*) or URTI):ti,ab,kw 3288
#3 MeSH descriptor: [Otitis Media] explode all trees 1142
#4 (otitis next media):ti,ab,kw 2330
#5 MeSH descriptor: [Pharyngitis] explode all trees 1044
#6 pharyngitis:ti,ab,kw 1936
#7 MeSH descriptor: [Tonsillitis] explode all trees 379
#8 tonsillitis:ti,ab,kw 841
#9 MeSH descriptor: [Common Cold] explode all trees 427
#10 (common next cold*):ti,ab,kw 1011
#11 MeSH descriptor: [Bronchitis] explode all trees 1552
#12 bronchitis:ti,ab,kw 3462
#13 MeSH descriptor: [Sinusitis] explode all trees 880
#14 sinusitis:ti,ab,kw 2268
#15 (sore next throat*):ti,ab,kw 1761

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#16 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 21200
#17 MeSH descriptor: [Anti-Bacterial Agents] explode all trees 10749
#18 antibiotic*:ti,ab,kw 21099
#19 #17 or #18 26699
#20 (delay* near/15 prescri*):ti,ab,kw 117
#21 #16 and #19 and #20 34

Ovid MEDLINE

1 exp Respiratory Tract Infections/ (333159)
2 (upper respiratory tract infection$ or urti).mp. (5051)
3 exp Otitis Media/ (24227)
4 otitis media.mp. (28308)
5 exp Pharyngitis/ (14945)
6 pharyngitis.mp. (9818)
7 exp Tonsillitis/ (7710)
8 tonsillitis.mp. (8717)
9 exp Common Cold/ (4111)
10 common cold.mp. (5606)
11 exp Bronchitis/ (28759)
12 bronchitis.mp. (31223)
13 exp Sinusitis/ (19143)
14 sinusitis.mp. (24467)
15 sore throat$.mp. (4552)
16 or/1-15 (381421)
17 exp Anti-Bacterial Agents/ (642079)
18 antibiotic$.mp. (317830)
19 or/17-18 (782421)
20 (delay$ adj15 prescri$).mp. (947)
21 16 and 19 and 20 (100)
22 (2013* or 2014* or 2015* or 2016* or 2017*).ed. (4463544)
23 21 and 22 (37)

Ovid Embase

1 exp Respiratory Tract Infection/ (386692)
2 exp Upper Respiratory Tract Infection/ (42709)
3 (upper respiratory tract infection$ or urti).mp. (26164)
4 exp Otitis Media/ (35233)
5 otitis media.mp. (38904)
6 exp Pharyngitis/ (27035)
7 pharyngitis.mp. (18176)
8 exp Tonsillitis/ (14789)
9 tonsillitis.mp. (14114)
10 exp Common Cold/ (8474)
11 common cold.mp. (10180)
12 exp Bronchitis/ (63141)
13 bronchitis.mp. (53196)
14 exp Sinusitis/ (39583)
15 sinusitis.mp. (37060)
16 sore throat$.mp. (15576)
17 or/1-16 (536945)
18 exp antibiotic agent/ (1228358)
19 antibiotic$.mp. (674521)
20 or/18-19 (1398274)
21 (delay$ adj15 prescri$).mp. (1402)
22 17 and 20 and 21 (144)
23 (2013* or 2014* or 2015* or 2016* or 2017*).em. (31737001)
24 22 and 23 (136)

EBSCO CINAHL Plus

S15 S10 and S13 and S14
S14 TI delay* N15 prescri* or AB delay* N15 prescri*

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S13 S11 or S12
S12 TI antibiotic* or AB antibiotic*
S11 (MH "Antibiotics+")
S10 S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9
S9 TI (otitis media or pharyngitis or tonsillitis or common cold* or bronchitis or sinusitis or sore throat*) or AB (otitis media or pharyngitis or tonsillitis or common cold* or bronchitis or sinusitis or sore throat*)
S8 (MH "Sinusitis+")
S7 (MH "Bronchitis+")
S6 (MH "Common Cold")
S5 (MH "Tonsillitis+")
S4 (MH "Pharyngitis")
S3 (MH "Otitis Media+")
S2 TI (upper respiratory tract infection* or urti) or AB (upper respiratory tract infection* or urti)
S1 (MH "Respiratory Tract Infections+")

Web of Science
#15#14 AND #11 AND #10
#14#13 OR #12
#13TS=prescri*
#12TS=delay*
#11TS=antibiotic*
#10#9 OR #8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1
#9TS="sore throat*"
#8TS=sinusitis
#7TS=bronchitis
#6TS="common cold"
#5TS=tonsillitis
#4TS=pharyngitis
#3TS="otitis media"
#2TS=urti
#1TS="Respiratory Tract Infection*"

F E E D B A C K

Feedback: Analysis 15.01 Comparison 15 may have some errors, June 2008

Summary

Feedback: Analysis 15.01 Comparison 15 Patient satisfaction immediate versus *delayed* antibiotics, Outcome 01 Patient satisfaction: immediate versus *delayed* antibiotics may have some errors.

We think that the extracted data has been entered under the wrong headings, i.e. for Little 1997, it reports that 165/177 were satisfied with *delayed* antibiotics but the RevMan forest plot has 165/177 under the immediate antibiotics.

Data extracted from one article (Dowell 2001) may have been entered incorrectly, i.e. the percentage has been entered into RevMan directly rather than as the actual number. In other words, for Dowell 2001, the paper reports 100% (73% very satisfied and 27% moderately satisfied), whereas the forest plot has reported the 73% as 73/75. This is a double query? see below for issue of inconsistent grouping of satisfaction scores.

Suggest that the data extracted for Dowell 2001 should be consistent with the logic used for Arroll 2002 in their results for the same outcome. We think that possibly the forest plot analysis should be conducted with the figures below. We have looked at all the original papers.

Arroll 2002a
64/67* *delayed* Antibiotics
58/62* Immediate Antibiotics
Dowell 2001
71/73# *delayed* Antibiotics
75/75# Immediate Antibiotics
Little 1997
165/177 *delayed* Antibiotics
202/211 Immediate Antibiotics
Little 2001
115/150 *delayed* Antibiotics

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123/135 Immediate Antibiotics
Little 2005a
147/190 *delayed* Antibiotics
166/194 Immediate Antibiotics
Arroll et al noted that for these results, groups responding 1 and 2 have been combined and groups 3 and 4 have been combined where: 1= very satisfied; 2= moderately satisfied; 3 = slightly satisfied; 4 = not at all satisfied.
Using similar logic as Arroll et al, results for groups responding ?very satisfied? and ?moderately satisfied? have been combined, as have ? not very satisfied? and ?not at all satisfied? to get the figures in the table above for Dowell 2001. (Note: in the review table, the figures were extracted directly from the?very satisfied? column only, where they were presented as a percentage without then recalculating them as a whole figure).
We don't think these possible errors effect the overall conclusions made by the authors in the review.
Submitter agrees with default conflict of interest statement:
I certify that I have no affiliations with or involvement in any organisation or entity with a financial interest in the subject matter of my feedback.

Reply

We thank those who have given feedback on this review. We greatly appreciate the work you have done to uncover these errors and the opportunity you have given us to correct them. We agree with all the feedback you have submitted and have made corrections to analysis 15 comparison 15.1, analysis 16 comparison 16.1, analysis 13 comparison 13.1 (antibiotic use *delayed* versus immediate), analysis 14 comparison 14.1 (antibiotic use *delayed* versus none) and analysis 3 comparison 3.1 (fever severity on day 3). We have also added an analysis 17: adverse events *delayed* versus no antibiotics.

These changes have not fundamentally changed the results of the review. However the text and outcome tables have been amended to reflect changes made.

Geoff Spurling, Chris Del Mar, Liz Dooley
Feedback reply added 25 June 2008

Contributors

Dianne Lowe, Rebecca Ryan
Feedback comment added 16 June 2008

It would be interesting to explore the comparative evidence base for the most effective method of delayed prescription, March 2009

Summary

Feedback: It would be interesting to explore the comparative evidence base for the most effective method of "*delayed* prescription" e.g.:
1. Script dated today given to patient
2. Script dated 2-3 days from now - given to patient
3. Script held at practice
Submitter agrees with default conflict of interest statement:
I certify that I have no affiliations with or involvement in any organization or entity with a financial interest in the subject matter of my feedback.

Reply

We thank you for your feedback on this review. We agree that it would be interesting to explore the comparative evidence base for the most effective method of *delayed* prescription. Subgroups highlighting the method of *delayed* prescribing have been added for the outcomes antibiotic use and patient satisfaction. Unfortunately, there was great heterogeneity in the methods of *delayed* prescribing that makes combining studies difficult. Methods of *delayed* prescribing ranged from issuing a prescription at the time of the initial consults with instruction to delay, to holding the *delayed* prescription at reception to be picked up if symptoms hadn't improved after a specified period of time. The recommended periods of delay ranged from three to fourteen days.

The three studies included in this systematic review published prior to 1992 examined the concern that immediate antibiotics for streptococcal pharyngitis might impair the body's immune response and predispose the patient to a relapse of pharyngitis. Six of the included studies published after 1992 were conducted to evaluate the role of *delayed* antibiotics as a way of reducing antibiotic use for respiratory infections compared to immediate antibiotics. While all six 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 contributed to the marked heterogeneity of this result. Of the seven studies published after 1991, four had the *delayed* script kept at reception to be picked up (Dowell 2001; Little 1997; Little 2001; Little 2005a) and in three, the script was issued to patients with instructions to delay (Arroll 2002a; Chao 2008; Spiro 2006). For the *delayed* arms of the four studies where the script was

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left at reception, antibiotics were used in 28% of cases (173/618) compared with antibiotics being used in 40% of cases (122/305) where antibiotics were issued to patients with instructions to delay.

None of the included studies specifically addressed whether or not prescriptions had been post-dated. However, a randomised controlled trial published in 2010, (Worrall 2010) comparing *delayed* prescriptions dated either the day of the office visit or 2 days later, but not comparing with either immediate or no antibiotics, demonstrated no significant difference between the two groups in terms of antibiotic use.

Geoff Spurling, Chris Del Mar, Liz Dooley, Rebecca Farley
Feedback reply added 25 March 2012

An RCT published in 2016 explored the comparative evidence base for four different methods of *delayed* prescribing. The trial compared patients randomised to either re-contact for a prescription, post-dated prescription, collection of the prescription or patient led (the patient was given the prescription. This study did not compare *delayed* versus immediate or *no antibiotics* and consequently did not meet the inclusion criteria for this review.

Contributors

Jas Janjuha, Occupation Pharmacist

WHAT'S NEW

Date	Event	Description
4 August 2022	Amended	This was previously a living systematic review. Searches were run and screened monthly since May 2017. The review authors have decided to cease maintaining this review in living systematic mode, as a reasonable level of certainty has been reached in the existing evidence.

HISTORY

Protocol first published: Issue 4, 2003
Review first published: Issue 4, 2004

Date	Event	Description
10 May 2022	Amended	This is a living systematic review. Searches are run and screened monthly. Last search date 10 May 2022. One new study identified in April 2021, but is unlikely to have an important impact on review findings and will be integrated later. Another trial was identified in December 2021, and is being considered for inclusion. It is a small trial, and also unlikely to impact review findings. The review conclusions can be considered up to date.
11 April 2022	Amended	This is a living systematic review. Searches are run and screened monthly. Last search date 12 April 2022. One new study identified in April 2021, but is unlikely to have an important impact on review findings and will be integrated later. Another trial was identified in December 2021, and is being considered for inclusion. It is a small trial, and also unlikely to impact review findings. The review conclusions can be considered up to date.
10 February 2022	Amended	This is a living systematic review. Searches are run and screened monthly. Last search date 10 February 2022. One new study identified in April 2021, but is unlikely to have an important impact on review findings and will be integrated later. Another trial was identified in December 2021, and is being considered for inclu-

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Date	Event	Description
		sion. It is a small trial, and also unlikely to impact review findings. The review conclusions can be considered up to date.
17 January 2022	Amended	This is a living systematic review. Searches are run and screened monthly. Last search date 17 January 2022. One new study identified in April 2021, but is unlikely to have an important impact on review findings and will be integrated later. Another trial was identified in December 2021, and is being considered for inclusion. It is a small trial, and also unlikely to impact review findings. The review conclusions can be considered up to date.
12 November 2021	Amended	This is a living systematic review. Searches are run and screened monthly. Last search date 12 November 2021. One new study identified in April 2021, but is unlikely to have an important impact on review findings and will be integrated later. The review conclusions can be considered up to date.
12 October 2021	Amended	This is a living systematic review. Searches are run and screened monthly. Last search date 12 October 2021. One new study identified in April 2021, but is unlikely to have an important impact on review findings and will be integrated later. The review conclusions can be considered up to date.
13 September 2021	Amended	This is a living systematic review. Searches are run and screened monthly. Last search date 13 September 2021. One new study identified in April 2021, but is unlikely to have an important impact on review findings and will be integrated later. The review conclusions can be considered up to date.
12 July 2021	Amended	This is a living systematic review. Searches are run and screened monthly. Last search date 12 July 2021. One new study identified in April 2021, but is unlikely to have an important impact on review findings and will be integrated later. The review conclusions can be considered up to date.
10 June 2021	Amended	This is a living systematic review. Searches are run and screened monthly. Last search date 10 June 2021. One new study identified in April 2021, but is unlikely to have an important impact on review findings and will be integrated later. The review conclusions can be considered up to date.
10 April 2021	Amended	This is a living systematic review. Searches are run and screened monthly. Last search date 10 April 2021. One new study identified but is unlikely to have an important impact on review findings and will be integrated later. The review conclusions can be considered up to date.
10 February 2021	Amended	This is a living systematic review. Searches are run and screened monthly. Last search date 10 February, 2021. Results of all new studies identified have been incorporated. The conclusions of this Cochrane Review are therefore considered up to date.
12 January 2021	Amended	This is a living systematic review. Searches are run and screened monthly. Last search date 12 January, 2021. Results of all new studies identified have been incorporated. The conclusions of this Cochrane Review are therefore considered up to date.

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Date	Event	Description
10 November 2020	Amended	This is a living systematic review. Searches are run and screened monthly. Last search date 10 November, 2020. Results of all new studies identified have been incorporated. The conclusions of this Cochrane Review are therefore considered up to date.
12 October 2020	Amended	This is a living systematic review. Searches are run and screened monthly. Last search date 12 October, 2020. Results of all new studies identified have been incorporated. The conclusions of this Cochrane Review are therefore considered up to date.
21 September 2020	Amended	This is a living systematic review. Searches are run and screened monthly. Last search date 21 September, 2020. Results of all new studies identified have been incorporated. The conclusions of this Cochrane Review are therefore considered up to date.
12 August 2020	Amended	This is a living systematic review. Searches are run and screened monthly. Last search date 12 August, 2020. Results of all new studies identified have been incorporated. The conclusions of this Cochrane Review are therefore considered up to date.
10 June 2020	Amended	This is a living systematic review. Searches are run and screened monthly. Last search date 10 June, 2020. Results of all new studies identified have been incorporated. The conclusions of this Cochrane Review are therefore considered up to date.
11 May 2020	Amended	This is a living systematic review. Searches are run and screened monthly. Last search date 11 May, 2020. Results of all new studies identified have been incorporated. The conclusions of this Cochrane Review are therefore considered up to date.
15 April 2020	Amended	This is a living systematic review. Searches are run and screened monthly. Last search date 15 April, 2020. Results of all new studies identified have been incorporated. The conclusions of this Cochrane Review are therefore considered up to date.
11 March 2020	Amended	This is a living systematic review. Searches are run and screened monthly. Last search date 11 March, 2020. Results of all new studies identified have been incorporated. The conclusions of this Cochrane Review are therefore considered up to date.
10 February 2020	Amended	This is a living systematic review. Searches are run and screened monthly. Last search date 10 February, 2020. Results of all new studies identified have been incorporated. The conclusions of this Cochrane Review are therefore considered up to date.
13 January 2020	Amended	This is a living systematic review. Searches are run and screened monthly. Last search date 13 January, 2020. Results of all new studies identified have been incorporated. The conclusions of this Cochrane Review are therefore considered up to date.
10 December 2019	Amended	This is a living systematic review. Searches are run and screened monthly. Last search date 11 November, 2019. Results of all new studies identified have been incorporated. The conclusions of this Cochrane Review are therefore considered up to date.
10 December 2019	Amended	This is a living systematic review. Searches are run and screened monthly. Last search date 10 December, 2019. Results of all new

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Date	Event	Description
		studies identified have been incorporated. The conclusions of this Cochrane Review are therefore considered up to date.
10 October 2019	Amended	This is a living systematic review. Searches are run and screened monthly. Last search date 10 October, 2019. Results of all new studies identified have been incorporated. The conclusions of this Cochrane Review are therefore considered up to date.
12 September 2019	Amended	This is a living systematic review. Searches are run and screened monthly. Last search date 11 September, 2019. Results of all new studies identified have been incorporated. The conclusions of this Cochrane Review are therefore considered up to date.
12 August 2019	Amended	This is a living systematic review. Searches are run and screened monthly. Last search date 12 August, 2019. Results of all new studies identified have been incorporated. The conclusions of this Cochrane Review are therefore considered up to date.
25 May 2017	New search has been performed	We updated the searches and included one new trial, De la Poza Abad 2016, and excluded four new trials (Agnew 2013; De la Poza Abad 2013; Little 2014; Worrall 2010).
25 May 2017	New citation required and conclusions have changed	Patient satisfaction favoured *delayed* over *no antibiotics* (odds ratio 1.49, 95% confidence interval 1.08 to 2.06). When doctors feel it is safe not to prescribe antibiotics immediately, prescribing none with advice to return if symptoms do not resolve, rather than delaying them, will result in lower subsequent antibiotic use. However, patient satisfaction may be greater when a *delayed* prescribing strategy is used; this will still result in a significant reduction in antibiotic use compared to an *immediate* prescribing strategy. *No* antibiotics resulted in the least antibiotic prescribing.
28 February 2013	New search has been performed	We have updated the searches. We included two new papers (Little 2006; Moore 2009), which reported longer-term outcomes of two previously included studies (Little 2001; Little 2005a), including impact of delayed antibiotic prescribing on earache recurrence and subsequent consultation rates in the 12 months following the initial consultation. We excluded three new trials (Fischer 2009; Newson 2009; Vouloumanou 2009). Our conclusions remain unchanged.
28 February 2013	New citation required but conclusions have not changed	A new author joined the team to update the review.
5 August 2010	Amended	Contact details updated.
27 March 2009	New search has been performed	Searches conducted. This 2009 update contains one new study, Chao 2008, and Feedback on a comment submitted via the Cochrane Library.
16 June 2008	Feedback has been incorporated	Feedback comment added.
16 June 2008	Amended	Converted to new review format.
21 January 2007	New search has been performed	Searches conducted.

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Date	Event	Description
9 January 2004	New search has been performed	Searches conducted.

CONTRIBUTIONS OF AUTHORS

- Chris Del Mar (CDM) conceived the review.
- Geoffrey Spurling (GS) and CDM designed the review.
- Ruth Foxlee (RFo) and GS performed the literature searches.
- RFo, Liz Dooley (LD), and CDM appraised articles and extracted data.
- GS and Rebecca Farley entered data into Review Manager 5 with contributions from LD, RFo, and CDM.
- GS secured funding for the review with the assistance of CDM.

DECLARATIONS OF INTEREST

Geoffrey KP Spurling
Chris B Del Mar
Liz Dooley has declared that they have no conflict of interest.
Ruth Foxlee
Rebecca Farley
Deborah A Askew
Justin Clark

SOURCES OF SUPPORT

Internal sources

- Bond University, Gold Coast, Australia
- The Discipline of General Practice at the University of Queensland, Australia

  For providing the infrastructure that allowed the first publication of this review to be conducted.

External sources

- General Practice Education and Training, Australia

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In this 2017 update we expanded the Objectives to include the remaining primary outcomes, that is antibiotic use, patient satisfaction, and antibiotic resistance, as these outcomes are very important for clinicians. This 2017 update includes summary of findings tables which were not specified in the protocol.

This was previously a living systematic review. Searches were run and screened monthly since May 2017. The review authors have decided to cease maintaining this review in living systematic mode as a reasonable level of certainty has been reached in the existing evidence. This review has now transitioned out of living mode to a standard review.

INDEX TERMS

Medical Subject Headings (MeSH)

Acute Disease; Anti-Bacterial Agents [*administration & dosage]; Common Cold [drug therapy]; Cough [drug therapy]; Drug Administration Schedule; *Drug Prescriptions; Fever [*drug therapy] [etiology]; Otitis Media [drug therapy]; Pain [drug therapy]; Patient Satisfaction; Pharyngitis [drug therapy]; Randomized Controlled Trials as Topic; Respiratory Tract Infections [complications] [*drug therapy]; Time Factors

MeSH check words

Adult; Child; Humans

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