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Immediate versus delayed versus no antibiotics for respiratory infections (Review)

Spurling GKP, Dooley L, Clark J, Askew DA

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[Intervention Review]

Immediate versus delayed versus no antibiotics for respiratory infections

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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 proposed strategy to reduce antibiotic prescribing is to provide prescriptions, but to advise delay in antibiotic use with the expectation that symptoms will resolve first. This is an update of a Cochrane Review originally published in 2007, and updated in 2010, 2013 and 2017.

Objectives

To evaluate the effects on duration and/or severity of clinical outcomes (pain, malaise, fever, cough and rhinorrhoea), antibiotic use, antibiotic resistance and patient satisfaction of advising a *delayed* prescription of antibiotics in respiratory tract infections.

Search methods

From May 2017 until 20 August 2022, this was a living systematic review with monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase, CINAHL and Web of Science. We also searched the WHO International Clinical Trials Registry Platform (ICTRP) and ClinicalTrials.gov on 20 August 2022. Due to the abundance of evidence supporting the review's key findings, it ceased being a living systematic review on 21 August 2022.

Selection criteria

Randomised controlled trials involving participants of all ages with an RTI, where *delayed* antibiotics were compared to *immediate* 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.

Main results

For this 2022 update, we added one new trial enrolling 448 children (436 analysed) with uncomplicated acute RTIs. Overall, this review includes 12 studies with a total of 3968 participants, of which data from 3750 are available for analysis. These 12 studies involved acute RTIs 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 (two studies). Six studies involved only children, two only adults and four included both adults and children. Six studies were conducted in primary care, four in paediatric clinics and two in emergency departments.

Studies were well reported and appeared to provide moderate-certainty evidence. Randomisation was not adequately described in two trials. Four trials blinded the outcome assessor, and three included blinding of participants and doctors. We conducted meta-analyses for pain, malaise, fever, adverse effects, antibiotic use and patient satisfaction.

Cough (four studies): we found no differences amongst *delayed*, *immediate* and *no* prescribed antibiotics for clinical outcomes in any of the four studies.

Sore throat (six studies): for the outcome of fever with sore throat, four of the six studies favoured *immediate* antibiotics, and two found no difference. For the outcome of pain related to sore throat, two studies favoured *immediate* antibiotics, and four found no difference. Two studies compared *delayed* antibiotics with *no* antibiotic for sore throat, and found no difference in clinical outcomes.

Acute otitis media (four studies): two studies compared *immediate* with *delayed* antibiotics - one found no difference for fever, and the other favoured *immediate* antibiotics for pain and malaise severity on Day 3. Two studies compared *delayed* with *no* antibiotics: one found no difference for pain and fever severity on Day 3, and the other found no difference for the number of children with fever on Day 3.

Common cold (two studies): neither study found differences for clinical outcomes between *delayed* and *immediate* antibiotic groups. One study found *delayed* antibiotics were probably favoured over *no* antibiotics for pain, fever and cough duration (moderate-certainty evidence).

Adverse effects: there were either no differences for adverse effects or results may have favoured *delayed* over *immediate* antibiotics with no significant differences in complication rates (low-certainty evidence).

Antibiotic use: *delayed* antibiotics probably resulted in a reduction in antibiotic use compared to *immediate* antibiotics (odds ratio (OR) 0.03, 95% confidence interval (CI) 0.01 to 0.07; 8 studies, 2257 participants; moderate-certainty evidence). However, a *delayed* antibiotic was probably more likely to result in reported antibiotic use than *no* antibiotics (OR 2.52, 95% CI 1.69 to 3.75; 5 studies, 1529 participants; moderate-certainty evidence).

Patient satisfaction: patient satisfaction probably favoured *delayed* over *no* antibiotics (OR 1.45, 1.08 to 1.96; 5 studies, 1523 participants; moderate-certainty evidence). There was probably no difference in patient satisfaction between *delayed* and *immediate* antibiotics (OR 0.77, 95% CI 0.45 to 1.29; 7 studies, 1927 participants; moderate-certainty evidence).

No studies evaluated antibiotic resistance. Reconsultation rates and use of alternative medicines were similar for *delayed, immediate* and *no* antibiotic strategies. In one of the four studies reporting use of alternative medicines, less paracetamol was used in the immediate group compared to the delayed group.

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 (30% versus 93%). The strategy of *no* antibiotics further reduced antibiotic use compared to *delaying* prescription for antibiotics (13% versus 27%).

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 RTIs, *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 *delayed* antibiotics. Where clinicians are not confident in not prescribing antibiotics, *delayed* antibiotics may be an acceptable compromise in place of *immediate* prescribing to significantly reduce unnecessary antibiotic use for RTIs, while maintaining patient safety and satisfaction levels.

Further research into antibiotic prescribing strategies for RTIs may best be focused on identifying patient groups at high risk of disease complications, enhancing doctors' communication with patients to maintain satisfaction, ways of increasing doctors' confidence to not prescribe antibiotics for RTIs, and policy measures to reduce unnecessary antibiotic prescribing for RTIs.

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 including sore throat, middle ear infection, cough (bronchitis) and the common cold?

Background

Using 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 use is to provide an antibiotic prescription, but with advice to delay filling the prescription. The prescriber assesses that antibiotics are not immediately required, expecting that symptoms will resolve without antibiotics.

We searched for studies that compared *delayed* antibiotics with *immediate* or *no* antibiotics for respiratory tract infections, 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 previously updated in 2010, 2013 and 2017.

Search date

The evidence is current to 20 August 2022.

Study characteristics

We included 12 trials with a total of 3968 participants, of which data from 3750 were available for evaluation of prescribing strategies for people with a variety of respiratory tract infections. Eleven of these studies compared strategies of *delaying* antibiotics with *immediate* antibiotics. Five studies compared *delayed* antibiotics with *no* antibiotics. Of the 12 studies, six included only children (1569 participants), two included only adults (589 participants), and four included children and adults (1596 participants). The new study included in this update enrolled 448 participants, and 436 were analysed following application of exclusion criteria.

Study funding sources

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

Key results

Antibiotic use was greatest in the *immediate* antibiotic group (93%), followed by *delayed* antibiotics (29%) and *no* antibiotics (13%).

Patient satisfaction was similar for people who trialled *delayed* antibiotics (88% satisfied) compared to *immediate* antibiotics (90% satisfied), but was greater than *no* antibiotics (86% versus 81% satisfied).

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.

In the first month after the initial consultation, two studies indicated that participants were no more likely to come back and see the doctor in either the *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 the *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

Our confidence in the evidence is only moderate because of concerns that people in the studies were not randomly placed into the different treatment groups. This means that differences between the groups could be due to differences between people rather than between the treatments. It is also possible that people in the studies were aware of which treatment they were getting. Not all of the studies provided data about everything that we were interested in.

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 but may result in lower patient satisfaction. Using a *delayed* antibiotic strategy will still result in a significant reduction in antibiotic use compared to the use of *immediate* antibiotics.

Summary of findings 1. Summary of findings table - 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	11 studies contributed data to this comparison of measured clinical outcomes. Cough or common cold (5 studies): no evidence of difference for clinical outcomes, except for 1 study finding fever severity at day 7 favoured delayed antibiotics. Sore throat (pharyngitis) (6 studies): no evidence of difference for most clinical outcomes. Acute otitis media (3 studies): 2 studies reported evidence favouring immediate antibiotics for malaise and pain severity on Day 3. The other study found no evidence of difference in clinical outcomes. Acute otitis media and sore throat: results favoured immediate antibiotics over delayed antibiotics for reducing pain and malaise severity on Day 3. Acute otitis media and common cold: no evidence of differences in the number of participants with fever on Days 3 to 6.			2748 (11 RCTs)	⊕⊕⊕⊖ Moderate[a]	
Duration of clinical outcomes (pain, malaise, fever)	3 studies contributed data to this comparison of duration of clinical outcomes. Pain: 3 studies measured duration of pain associated with pharyngitis (sore throat) and found no evidence of difference. 1 study measured duration of pain associated with acute otitis media and found no difference. Malaise: 2 studies measured duration of malaise. 2 studies found no evidence of difference between delayed (prescription at time of visit) and immediate antibiotics for duration of malaise. 1 study found results favoured immediate antibiotics over delayed (prescription collection). Fever: 3 studies measured duration of fever. 2 found no evidence of difference in duration of fever, and the other found results favoured immediate antibiotics (P = 0.04).			1077 (3 RCTs)	⊕⊕⊕⊖ Moderate[a]	

Antibiotic use: delayed (all strategies) versus immediate antibiotics	934 per 1000	**299 per 1000** (125 to 499)	**OR 0.03** (0.01 to 0.07)	2257 (8 RCTs)	⊕⊕⊕⊖ Moderate[a]
Patient satisfaction: delayed (all strategies) versus immediate antibiotics	904 per 1000	**879 per 1000** (809 to 924)	**OR 0.77** (0.45 to 1.29)	1927 (7 RCTs)	⊕⊕⊕⊖ Moderate[a]
Reconsultation rate: delayed (all strategies) versus immediate antibiotics	93 per 1000	**96 per 1000** (63 to 143)	**OR 1.04** (0.66 to 1.63)	972 (4 RCTs)	⊕⊕⊕⊖ Moderate[a]
Adverse effects of antibiotics assessed with: diarrhoea, vomiting, rash follow-up: range 1 days to 7 days	Diarrhoea: 4 studies assessed diarrhoea. Results favoured delayed antibiotics in 2 studies, and there was no evidence of difference in the other 2. Vomiting: 3 studies assessed vomiting. There was no evidence of difference in 2 studies, and results favoured immediate antibiotics in the third. Rash: 2 studies assessed rash. There was no evidence of difference in these 2 studies.			1302 (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; **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.

See interactive version of this table: https://gdt.gradepro.org/presentations/#/isof/isof_question_revman_web_438787660910747115.

[a] Downgraded 1 level because more than half of the studies were not adequately blinded and did not report allocation concealment.
[b] Downgraded 1 level because results were inconsistent (I2 = 93% for vomiting, I2 = 72% for diarrhoea, I2 = 0% for rash).

Summary of findings 2. Summary of findings table - 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, paediatric outpatients
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: pain, malaise, fever follow-up: range 1 days to 7 days	5 studies measured clinical outcomes for this comparison. 3 studies recruited participants with sore throat (pharyngitis), 2 studies recruited participants with acute otitis media and 2 studies recruited participants with cough (bronchitis); for these studies there was no evidence of differences found. 1 study recruited participants with the common cold and results favoured delayed antibiotics (prescription at time of visit) for duration of pain and fever, and delayed antibiotics (prescription collection) for duration of fever and cough.			1685 (5 RCTs)	⊕⊕⊕⊖ Moderate[a]	
Duration of clinical outcomes (pain, malaise, fever)	2 studies measured duration of clinical outcomes and contributed to this comparison. Pain: 2 studies measured duration of pain associated with sore throat (pharyngitis) and found no evidence of difference. 1 study measured duration of pain associated with acute otitis media and found no evidence of difference. Malaise: 2 studies measured duration of malaise. Results favoured delayed over no antibiotics for duration of malaise when the prescription was collected (prescription collection) (1 study), but no difference in duration of malaise between delayed and no antibiotics when the prescription was given at the time of visit. Fever: 2 studies measured duration of fever. 1 study found no evidence of difference in duration of fever associated with pharyngitis, and the other study found results favoured delayed over no antibiotics.			585 (2 RCTs)	⊕⊕⊕⊖ Moderate[a]	
Antibiotic use: delayed (all strategies) versus no antibiotics	133 per 1000	**279 per 1000** (206 to 365)	**OR 2.52** (1.69 to 3.75)	1529 (5 RCTs)	⊕⊕⊕⊖ Moderate[a]	
Patient satisfaction: delayed (prescription collec-	841 per 1000	**885 per 1000** (851 to 912)	**OR 1.45** (1.08 to 1.96)	1523 (5 RCTs)	⊕⊕⊕⊖ Moderate[a]	

tion) versus no antibiotics					
Reconsultation rate: delayed (all strategies) versus no antibiotics	96 per 1000	**81 per 1000** (46 to 139)	**OR 0.83** (0.46 to 1.52)	584 (2 RCTs)	⊕⊕⊕⊖ Moderate[a]
Adverse effects of antibiotics (diarrhoea, vomiting, rash): delayed versus no antibiotics follow-up: range 1 days to 7 days	2 studies measured adverse effects: 1 recruited participants with sore throat and 1 with acute otitis media. Neither study found any difference in adverse effects.			674 (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; **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.

See interactive version of this table: https://gdt.gradepro.org/presentations/#/isof/isof_question_revman_web_439286631830684374.

[a] Downgraded 1 level because more than half of the studies were not adequately blinded and did not report allocation concealment.

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, more than 2.8 million people acquire infections with antibiotic-resistant bacteria, causing more than 35,000 deaths (CDC 2022). 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 used in medicine continue to be prescribed in primary care and mainly for people with RTIs (Goossens 2005; Llor 2014; 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 antibiotic prescriptions, and to only fill a prescription 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 at the time of consultation (with instructions not to redeem it unless there is deterioration in illness), and making the prescription available at the clinic (to be picked up in the event of illness deterioration).

How the intervention might work

Delaying antibiotics may provide a feeling of safety for both patient and clinician should the 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. It also empowers patients by giving them control over whether they fill the prescription or not, and enables them to consult less frequently in the future (Little 2014).

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; Spurling 2017).

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 (updated in 2018) 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; McDonagh 2018). AHRQ 2016 also highlighted the need for further research reporting on resistance.

OBJECTIVES

To evaluate the effects on duration and/or severity of clinical outcomes (pain, malaise, fever, cough and rhinorrhoea), antibiotic use, antibiotic resistance and patient satisfaction of advising a *delayed* prescription of antibiotics in respiratory tract infections.

METHODS

Criteria for considering studies for this review

Types of studies

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

Types of participants

We included adults and children diagnosed with RTIs.

Types of interventions

We included trials that investigated use of the following.

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

Types of outcome measures

Primary outcomes

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

1. Clinical outcomes for sore throat, acute otitis media, bronchitis (cough) and common cold (we included duration and severity

measures for the following symptoms: pain, malaise, fever, cough and rhinorrhoea).
2. Antibiotic use.
3. Patient satisfaction (measured on a four- to six-point Likert scale; we defined satisfaction as including moderately satisfied, very satisfied and extremely satisfied).
4. Antibiotic resistance.

Secondary outcomes

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

Search methods for identification of studies

Electronic searches

For the period from 12 August 2017 until 10 August 2022, this was a living review and therefore the searches were conducted monthly. For this 2022 update, searches of the Cochrane Central Register of Controlled Trials (CENTRAL) (the Cochrane Library); MEDLINE (via Ovid); Embase (via Elsevier); CINAHL (via EBSCO) and Web of Science Core Collection (via Clarivate) were searched on 20 August 2022. We also searched the WHO International Clinical Trials Registry Platform (ICTRP) and ClinicalTrials.gov from 12 August 2017 to 20 August 2022.

The search strings used both keywords and MeSH terms and were designed by an experienced Cochrane Information Specialist. Search strings 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.

Data collection and analysis

Selection of studies

For this 2022 update, two review authors (GS, JC) independently screened titles and abstracts of the studies identified since the previous update. We retrieved full-text reports of potentially eligible studies, and two review authors (GS, JC) independently identified studies for inclusion. We resolved any disagreements through discussion. 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. 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.

For this 2022 update, two review authors (DA, GS) extracted outcome data. We resolved disagreements by discussion. One review author (DA) transferred data into RevMan Web, and double-checked the accuracy with the study reports. We noted in the Characteristics of included studies table if outcome data were not reported in a usable way.

Assessment of risk of bias in included studies

For this 2022 update, two review authors (DA, GS) conducted the risk of bias assessment of the newly included studies using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We resolved any disagreements by discussion. 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 risk. We summarised the risk of bias judgements across different studies for each of the domains listed. We considered blinding separately for different key outcomes where necessary. Where information on risk of bias related to unpublished data or correspondence with a trialist, we noted this in risk of bias tables. When considering treatment effects, we took into account the risk of bias for studies that contributed to that outcome.

Assessment of bias in conducting the systematic review

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

Measures of treatment effect

For this 2022 update, we entered outcome data into data tables in RevMan Web to calculate the treatment effects (RevMan Web 2019). 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 contacted 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 explored the impact of including such studies in the overall assessment of results by a sensitivity analysis.

Where possible, if numerical outcome data were missing, such as standard deviations or correlation coefficients, and they were not obtainable from the study authors, we calculated 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 amongst 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. Due to heterogeneity across studies, we repeated all analyses using the random-effects model only.

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 investigated the comparison of *delayed* antibiotics versus *immediate* antibiotics and included clinical outcomes, duration of clinical outcomes, antibiotics use, patient satisfaction, reconsultation rates and adverse effects of antibiotics (Summary of findings 1). The second table investigated the comparison of *delayed* antibiotics versus *no* antibiotics and included clinical outcomes, duration of clinical outcomes, antibiotics use, patient satisfaction, reconsultation rates and adverse effects of antibiotics (Summary of findings 2). We used the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the certainty of the body of evidence as it relates to the studies that contributed 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 downgrade or upgrade the certainty of evidence using footnotes, and made comments to aid the reader's understanding of the review where necessary.

RESULTS

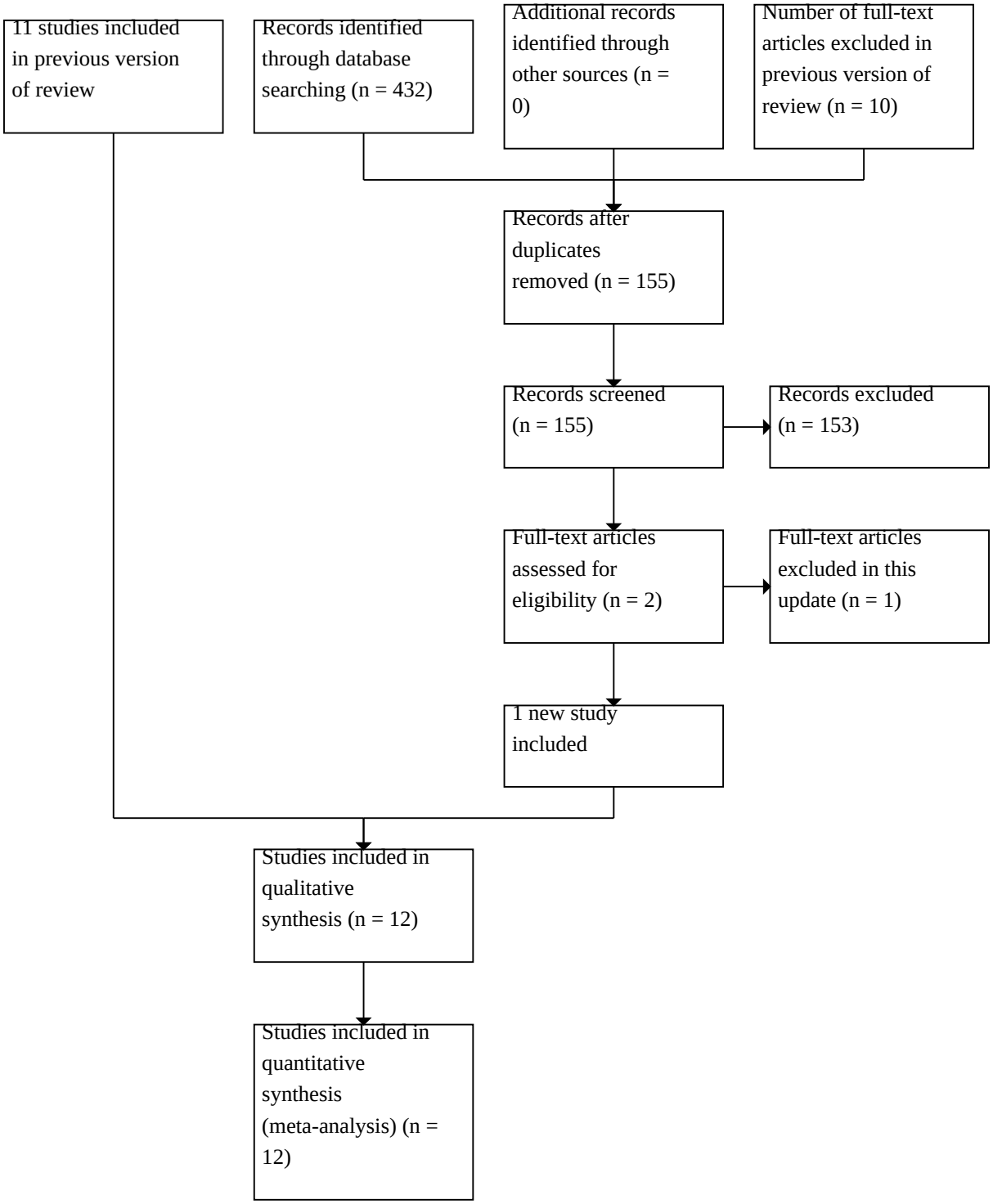
Description of studies

See Table 1 and the Characteristics of excluded studies table.

Results of the search

For this 2022 update, we added one new trial involving 448 children with uncomplicated acute respiratory infections. Overall, we identified 432 records in database searching, and 155 records remained after duplicates were removed. We removed 153 records that were clearly not relevant based on title alone, leaving two records. We retrieved two full-text reports, and, of these, one study met our inclusion criteria. This record plus the 11 studies identified before 2022 means we have 12 included studies for this review (Figure 1).

Figure 1. Study flow diagram.



Included studies

For this 2022 update, we added one new trial enrolling 448 children (436 analysed) with uncomplicated acute respiratory infections. In total, the review includes 12 trials involving a total of 3968 participants, of whom data from 3750 were available for analysis. Eleven trials compared *immediate* provision of antibiotics with *delayed* antibiotics; four also included a *no* antibiotics group. One trial compared *delayed* antibiotics with *no* antibiotics. Two trials tested the intervention on a number of acute upper RTIs, four trials limited participation to people with sore throat (pharyngitis), two trials only included people with acute otitis media (AOM), two only included people with cough (bronchitis) and one included people with the common cold.

Two different strategies for provision of *delayed* antibiotics were used - antibiotic prescription given to the patient at the consultation (prescription at time of visit) and antibiotic prescription available for collection from the clinic reception three days after the first consultation (prescription collection). Five trials compared *delayed* antibiotics (prescription at time of visit) to *immediate* antibiotics (Arroll 2002a; El-Daher 1991; Gerber 1990; Pichichero 1987; Spiro 2006); two trials compared *delayed* antibiotics (prescription collection) to *immediate* antibiotics (Dowell 2001; Little 2001); two trials compared *delayed* antibiotics (prescription collection) to *immediate* antibiotics and *no* antibiotics (Little 1997; Little 2005a); one trial compared *delayed* antibiotics (prescription at time of visit) to *immediate* antibiotics and *no* antibiotics (Mas-Dalmau 2021); and one trial compared *delayed* antibiotics (prescription at time of visit) to *delayed* antibiotics (prescription collection), *immediate* antibiotics and *no* antibiotics (De la Poza Abad 2016). One trial compared *delayed* antibiotics (prescription at time of visit) to *no* antibiotics (Chao 2008).

Of the 12 included trials, 1673 participants were randomised to receive *delayed* antibiotics. In 11 of these trials, 1427 participants were randomised to receive *immediate* antibiotics, and in five trials, 861 participants were randomised to receive *no* antibiotics. Five studies compared the prescribing strategy of *no* antibiotics with *delayed* antibiotics (Chao 2008; De la Poza Abad 2016; Little 1997; Little 2005a; Mas-Dalmau 2021). These five trials investigated the presentations of pharyngitis/sore throat (De la Poza Abad 2016; Little 1997; Mas-Dalmau 2021), bronchitis (cough) (De la Poza Abad 2016; Little 2005a; Mas-Dalmau 2021), AOM (Chao 2008; Mas-Dalmau 2021), and the common cold/rhinosinusitis (De la Poza Abad 2016). Please see Table 1 for the characteristics of included studies.

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 evaluating 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; Mas-Dalmau 2021; Spiro 2006).

Population

Of the 12 included studies, six included only children (Chao 2008 - aged 2 to 12 years; El-Daher 1991 - 4 to 14 years; Little 2001 - 6 months to 10 years; Mas-Dalmau 2021 - 2 to 14 years; Pichichero 1987 - 4 to 18 years; Spiro 2006 - 6 months to 12 years), two included only adults (De la Poza Abad 2016; Dowell 2001), and four included both adults and children (Arroll 2002a - any age; Gerber 1990 - 2 to 22 years; Little 1997 - ≥ 4 years; Little 2005a - ≥ 3 years). Please see Table 1 for more details of the populations involved in each trial.

Setting

Of the 12 included studies, seven were conducted in primary care (Arroll 2002a; De la Poza Abad 2016; Dowell 2001; Little 1997; Little 2001; Little 2005a; Mas-Dalmau 2021), three in paediatric clinics (El-Daher 1991; Gerber 1990; Pichichero 1987), and two in emergency departments (Chao 2008; Spiro 2006). All primary care-based studies, except for the study by Arroll 2002a, were multisite. The studies in paediatric clinics and emergency departments were all single-site studies. Individual randomisation was used in each study.

Excluded studies

One study has been excluded since the last update because it was not a RCT (Ghebrehewet 2020).

Previously, 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 seven studies were not RCTs (Cates 1999; De la Poza Abad 2013; Fischer 2009; Little 2014; Newson 2009; Siegel 2003; Vouloumanou 2009).

Risk of bias in included studies

Overall, we assessed the included studies as at low risk of bias. Studies were most likely to be assessed as at unclear or moderate risk of bias for the domains of allocation concealment and blinding. Almost all studies showed a low risk of bias for all other domains. We assessed randomisation of studies as low risk for all the included studies except for two, for which the randomisation was unclear. We assessed allocation concealment as low risk of bias for five 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, unclear in two studies and high risk of bias for the remaining seven studies. For incomplete data, we assessed 11 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 two studies. We detected no other biases apart from bias associated with funding source. Two studies were funded by pharmaceutical companies and we assessed them 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 eight studies were funded by state institutions or a specialist college and we assessed them 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.

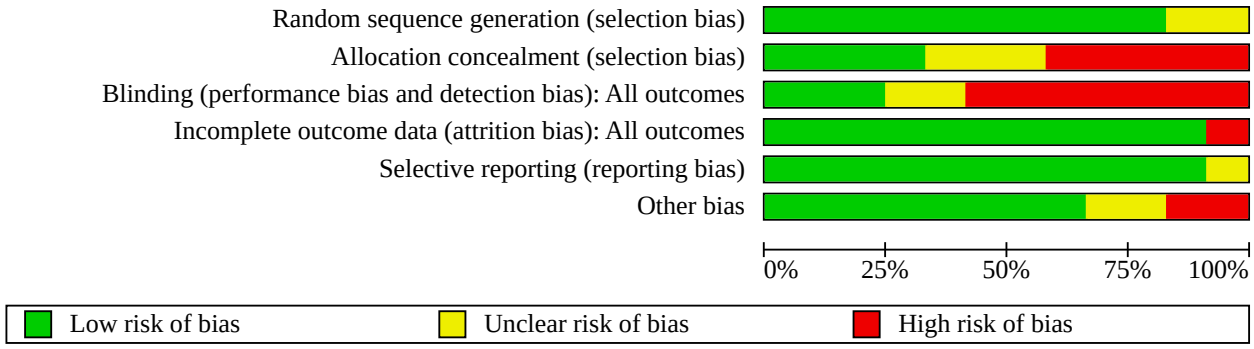
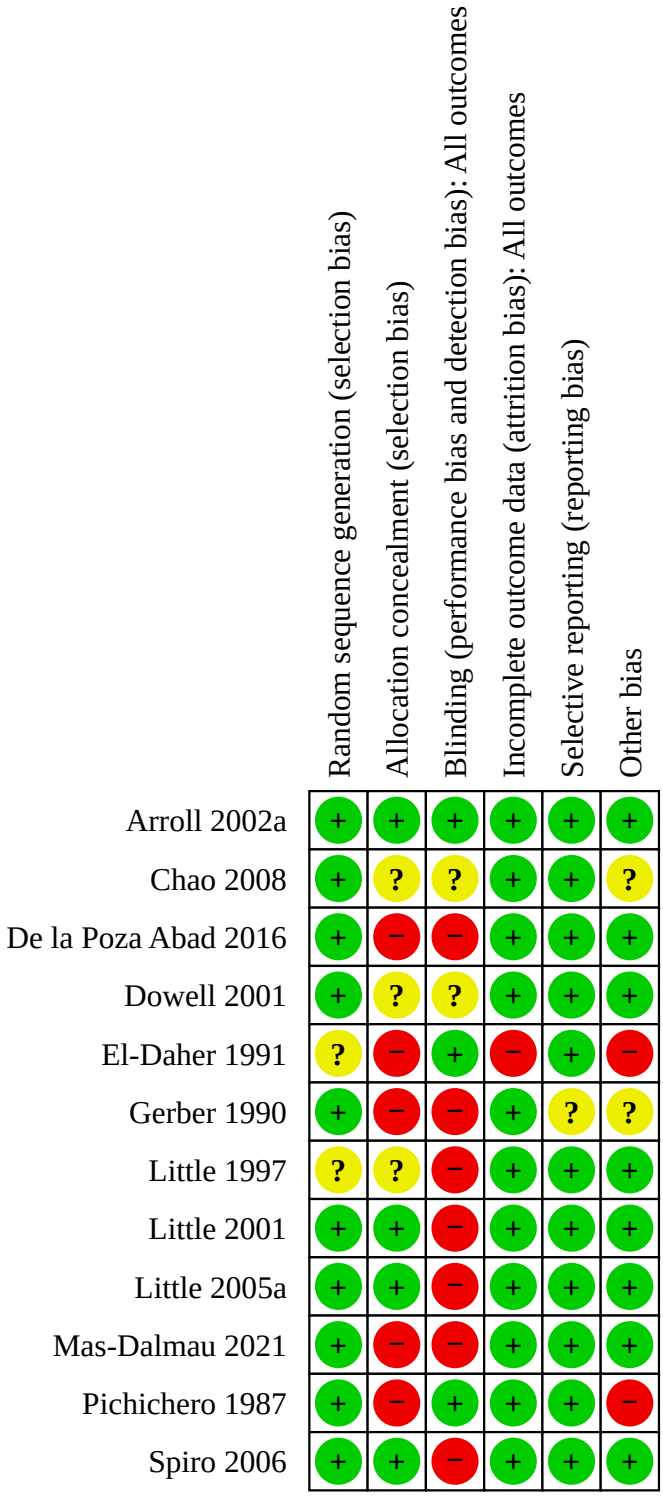


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Ten studies reported using random number tables or computer-generated randomisation and we assessed them as at low risk of bias. Two studies did not describe randomisation methods and we assessed them as at unclear risk of bias (El-Daher 1991; Little 1997). Four trials described adequate allocation concealment using opaque envelopes and we assessed them 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 outcome 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 five studies (De la Poza Abad 2016; Gerber 1990; Little 1997; Little 2001; Mas-Dalmau 2021).

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 we assessed it as at unclear risk of bias. We assessed all the other studies as at low risk of bias because they reported on their predetermined outcome measures.

Other potential sources of bias

Seven 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; Mas-Dalmau 2021; Spiro 2006). One study received funding from their relevant specialist college (Dowell 2001). We assessed these eight 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** Summary of findings table - Delayed antibiotics compared to immediate antibiotics for respiratory infections; **Summary of findings 2** Summary of findings table - Delayed antibiotics compared to no antibiotics for respiratory infections

For this update, we included one new study. Our conclusions remain unchanged from previous versions.

We assessed the effects of interventions using all 12 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 respiratory tract infections (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; duration: Analysis 1.3, Analysis 1.4), malaise (Days 3 to 6: Analysis 2.1, Analysis 2.2; duration: Analysis 2.3, Analysis 2.4) and fever (Days 3 to 6: Analysis 3.1, Analysis 3.2; duration: Analysis 3.3, Analysis 3.4), 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.

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; Analysis 6.4; Analysis 6.5; Analysis 6.6) and reconsultation (Analysis 7.1; Analysis 7.2) 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 *delayed* antibiotics (prescription at time of visit compared with prescription collection). 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. Six studies included only child participants (Chao 2008; El-Daher 1991; Little 2001; Mas-Dalmau 2021; 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. Two studies involving only children measured patient satisfaction for *delayed* antibiotics versus *immediate* antibiotics (Little 2001; Mas-Dalmau 2021), and two studies involving only children measured patient satisfaction for *delayed* antibiotics versus *no* antibiotics (Chao 2008; Mas-Dalmau 2021). 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 and Table 2 for *delayed* versus *immediate* antibiotics, and Summary of findings 2 and Table 3 for *delayed* versus *no* antibiotics.

Sore throat (pharyngitis)

Six studies recruited participants with sore throats (De la Poza Abad 2016; El-Daher 1991; Gerber 1990; Little 1997; Mas-Dalmau 2021; Pichichero 1987).

Delayed antibiotics versus *immediate* antibiotics

Pain associated with sore throat was examined by all six studies (N = 2004) (De la Poza Abad 2016; El-Daher 1991; Gerber 1990; Little 1997; Mas-Dalmau 2021; Pichichero 1987).

Severity of pain on Day 3 was not significantly different for *delayed* and *immediate* antibiotic groups in three studies (N = 941) (Gerber 1990; Little 1997; Pichichero 1987), but was reported by a higher proportion of participants in the *delayed* antibiotic group (N = 118) compared to the *immediate* antibiotic group (N = 111) in a fourth study (El-Daher 1991), with an odds ratio (OR) of 14.51 (95% confidence interval (CI) 7.14 to 29.50) (Table 2).

Duration of pain was not significantly different for *delayed* and *immediate* antibiotics in two studies (N = 834) (De la Poza Abad 2016; Mas-Dalmau 2021). De la Poza Abad 2016 tested two different strategies for *delayed* antibiotics - a script at the time of consultation and prescription collection - there was no significant difference in duration of pain for either *delayed* strategies compared with *immediate* antibiotics (Table 2).

Malaise associated with sore throat was examined by two studies (N = 343) (El-Daher 1991; Pichichero 1987).

Severity of malaise on Day 3 was not significantly different for *delayed* and *immediate* antibiotic groups in one study (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), OR 16.49, 95% CI 5.68 to 47.83 (Table 2) (El-Daher 1991).

Duration of malaise was not investigated.

Fever (> 37.0 °C) associated with sore throat was examined by five studies (N = 1568) (De la Poza Abad 2016; El-Daher 1991; Gerber 1990; Little 1997; Pichichero 1987).

Severity of fever on Day 3 was higher for participants in the *delayed* antibiotic group than in the *immediate* antibiotic group in two studies (N = 343), with a pooled mean difference (MD) of 0.64 °C (95% CI 0.15 to 1.13) (El-Daher 1991; Pichichero 1987)

Duration of fever was longer for participants in the *delayed* antibiotic group (N = 238) than for participants in the *immediate* antibiotic group in one study (N = 246) (P = 0.04) (Little 1997), but was not significantly different in two other studies (N = 834) (De la Poza Abad 2016) (Table 2).

Two studies did not report either severity or duration of fever in a way that could be readily compared with other studies (Gerber 1990; Little 1997).

Delayed antibiotics versus *no* antibiotics

Three studies that recruited participants with sore throat compared the prescribing strategy of *delayed* antibiotics with *no* antibiotics (N = 1548) (De la Poza Abad 2016; Little 1997; Mas-Dalmau 2021). These studies found no evidence of difference in severity or duration of pain, malaise or fever 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 six studies evaluating sore throat for the three prescribing strategies of *immediate*, *delayed* and *no* antibiotics.

Acute otitis media

Four studies recruited participants with acute otitis media (AOM) (N = 1222) (Chao 2008; Little 2001; Mas-Dalmau 2021; Spiro 2006).

Delayed antibiotics versus *immediate* antibiotics

Pain associated with AOM was examined by three studies (N = 1016) (Little 2001; Mas-Dalmau 2021; Spiro 2006).

Severity of pain on Day 3 was greater for participants in the *delayed* antibiotics group compared to the *immediate* antibiotics group in one study (N = 315) (Little 2001), but no evidence of difference was found on Days 4 to 6 in another study (N = 265) (Table 2) (Spiro 2006). 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).

Duration of pain was examined in one study (N = 436) (Mas-Dalmau 2021). There was no evidence of difference in duration of earache between *delayed* or *immediate* antibiotic groups (Table 2).

Malaise associated with AOM was examined by one study (N = 315) (Little 2001).

Severity of malaise on Day 3 was greater in participants in the *delayed* antibiotics group compared to the *immediate* antibiotics group (Table 2) (Little 2001).

Duration of malaise was not investigated by any of the included studies.

Fever associated with AOM was examined by one study (N = 265) (Spiro 2006).

Severity of fever on Days 4 to 6 was no different between *delayed* or *immediate* antibiotic groups (Table 2) (Spiro 2006).

Duration of fever was not investigated by any of the included studies.

Delayed antibiotics versus *no* antibiotics

Two studies compared *delayed* antibiotics with *no* antibiotics (N = 642) (Chao 2008; Mas-Dalmau 2021). In one study, no significant difference was detected for the outcomes of pain or fever for participants in *delayed* antibiotic and *no* 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). Analysis comparing duration of earache was not available in the other study (Mas-Dalmau 2021).

Complications

Data on complications of AOM such as mastoiditis (pain, soreness, redness or tenderness behind the ear), rheumatic fever and poststreptococcal glomerulonephritis were not reported in any of the four 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 = 471).

Bronchitis (cough)

Four studies recruited participants with bronchitis (cough) (N = 1665) (De la Poza Abad 2016; Dowell 2001; Little 2005a; Mas-Dalmau 2021).

Delayed antibiotics versus *immediate* antibiotics

Four studies examined the prescribing strategies of *immediate* versus *delayed* antibiotics for the clinical presentation of cough (N = 1665) (De la Poza Abad 2016; Dowell 2001; Little 2005a; Mas-Dalmau 2021). None of the studies found any difference in clinical outcomes including pain, fever and cough (Table 2).

Delayed antibiotics versus *no* antibiotics

De la Poza Abad 2016, Little 2005a and Mas-Dalmau 2021 (N = 1474) 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 of one study (N = 640) developed pneumonia and recovered with antibiotics in hospital (Little 2005a). Another study (N = 398) reported that there was no evidence of differences in complication rates between the *delayed* and *immediate* antibiotic groups (De la Poza Abad 2016). The other two studies (N = 627) did not report on complications in the *immediate* and *delayed* antibiotic groups (Dowell 2001; Mas-Dalmau 2021).

Common cold

Two studies recruited participants with the common cold (N = 527) (Arroll 2002a; De la Poza Abad 2016).

Delayed antibiotics versus immediate antibiotics

Neither study found any evidence of difference between *delayed* antibiotics and *immediate* antibiotics for fever, cough, pain, malaise and rhinorrhoea (runny nose) associated with the common cold, except for the outcome of fever severity on Day 7, which favoured *delayed* antibiotics (N = 527) (Arroll 2002a; De la Poza Abad 2016) (Table 2).

Delayed antibiotics versus no antibiotics

De la Poza Abad 2016 (N = 398) compared *delayed* antibiotics with *no* antibiotics and found a reduction in pain duration with one *delayed* antibiotic strategy (prescription at the time of visit) and reductions in fever and cough duration for both *delayed* strategies (prescription at the time of visit 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* or *no* antibiotics)

The following section only reports outcomes from the meta-analyses conducted where results were sufficiently homogenous. Results from individual studies are presented above.

For the comparison of *delayed* versus *immediate* antibiotics, we pooled results for the outcomes of number of participants with pain (Days 3 to 6), pain severity (Day 3), duration of pain, malaise (Day 3), malaise severity (Day 3), malaise duration, number of participants with fever (Days 3 to 6), fever severity (Day 3) and fever duration.

For the comparison of *delayed* versus *no* antibiotics, we pooled results for the clinical outcomes of duration of pain and duration of malaise.

Pain

Number of participants with pain on Days 3 to 6: there is no evidence of difference between *delayed* (prescription at time of visit) and *immediate* antibiotics (Analysis 1.1) (Arroll 2002a; El-Daher 1991; Spiro 2006).

Severity of pain on Day 3: the results favour *immediate* antibiotics over *delayed* antibiotics (MD 0.51, 95% CI 0.07 to 0.95; Analysis 1.2) (Little 2001; Pichichero 1987)

Duration of pain associated with pharyngitis: there is no evidence of difference between *delayed* (prescription at time of visit) and *immediate* antibiotics (MD 0.21, 95% CI -0.75 to 1.18; Analysis 1.3), or *no* antibiotics (MD -0.85, 95% CI -1.80 to 0.11; Analysis 1.4) (De la Poza Abad 2016; Mas-Dalmau 2021).

Malaise

Number of participants with malaise on Days 3 to 6: there is no evidence of difference between *delayed* and *immediate* antibiotics (Analysis 2.1) (El-Daher 1991; Little 2001).

Severity of malaise on Day 3: the results favour *immediate* antibiotics over *no* antibiotics (MD 0.29, 95% CI 0.15 to 0.43; Analysis 2.2) (Little 2001; Pichichero 1987).

Duration of malaise: there is no evidence of difference between *delayed* antibiotics (prescription at time of the visit) and *immediate* antibiotics (Analysis 2.3) or *no* antibiotics (Analysis 2.4) (De la Poza Abad 2016; Mas-Dalmau 2021).

Fever

Number of participants with fever on Days 3 to 6: there is no evidence of difference between *delayed* and *immediate* antibiotics (OR 0.86, 95% CI 0.54 to 1.38; Analysis 3.1) (Arroll 2002a; Spiro 2006).

Severity of fever on Day 3: there is no evidence of difference between *delayed* and *immediate* antibiotics (MD 0.34, 95% CI -0.33 to 1.01; Analysis 3.2) (Arroll 2002a; El-Daher 1991; Pichichero 1987).

Duration of fever (De la Poza Abad 2016; Mas-Dalmau 2021): there is no evidence of difference between *delayed* and *immediate* antibiotics (Analysis 3.3).

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 (N = 456) (El-Daher 1991; Gerber 1990; Pichichero 1987). Antibiotic use in both *immediate* and *delayed* antibiotic groups was close to 100% as per the study design.

Eight of the included studies published after 1992 (N = 3088) investigated if *delayed* antibiotics reduced antibiotic use for respiratory infections compared to *immediate* antibiotics (Arroll 2002a; De la Poza Abad 2016; Dowell 2001; Little 1997; Little 2001; Little 2005a; Mas-Dalmau 2021; Spiro 2006). In the *delayed* antibiotics group, 30.6% (344/1161) of prescriptions were filled compared with 93.4% (1024/1096) of prescriptions issued in the *immediate* antibiotics group. Meta-analysis shows that antibiotic use was significantly reduced in the *delayed* antibiotic group compared to the *immediate* antibiotic group (OR 0.03, 95% CI 0.01 to 0.07; Analysis 4.1).

Two different strategies for *delaying* use of antibiotics were employed in the eight studies published after 1992: 1) keeping the delayed script at the health service reception to be collected later if symptoms did not resolve in a set number of days (prescription collection; and 2) issuing the script to patients at the consultation with instructions to only fill the script if symptoms did not resolve in a set number of days (prescription at time of visit).

Five studies compared the *delaying* strategy of prescription collection with *immediate antibiotics* (N = 2258) (De la Poza Abad 2016; Dowell 2001; Little 1997; Little 2001; Little 2005a), and four compared the delaying strategy of prescription at time of visit with immediate antibiotics (N = 1228) (Arroll 2002a; De la Poza Abad 2016; Mas-Dalmau 2021; Spiro 2006). De la Poza Abad 2016 was specifically designed to determine the relative efficacy and safety of both *delayed* strategies (prescription collection and prescription at time of visit).

Both *delaying* strategies resulted in significantly reduced use of antibiotics compared with *immediate* antibiotics (Analysis 4.1). In the prescription collection group, antibiotics were used in 27% of cases (196/718) and 34% of cases (151/443) in the prescription at time of visit group.

Delayed antibiotics versus *no* antibiotics

Five studies compared *delayed* antibiotics with *no* antibiotics (N = 2394) (Chao 2008; De la Poza Abad 2016; Little 1997; Little 2005a; Mas-Dalmau 2021). Pooled results of these studies showed that antibiotic prescriptions were filled by 94 out of 706 participants (13.3%) in the *no* antibiotic arms compared with 226 out of 823 participants (27.5%) in the *delayed* antibiotics arms (OR 2.52, 95% CI 1.69 to 3.75; Analysis 4.2). This evidence is of moderate certainty according to GRADE assessment (Summary of findings 2).

3. Patient satisfaction

Delayed antibiotics versus immediate antibiotics

Seven studies compared patient satisfaction with *delayed* antibiotics versus *immediate* antibiotics (N = 2823) (Arroll 2002a; De la Poza Abad 2016; Dowell 2001; Little 1997; Little 2001; Little 2005a; Mas-Dalmau 2021). Pooling the results from these studies shows that a slightly higher proportion of participants in the *immediate* antibiotics arms were satisfied or very satisfied compared with 87% of participants in the *delayed* antibiotics arms. This difference was not statistically significant (OR 0.77, 95% CI 0.45 to 1.29; 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 = 960) (Arroll 2002a; Dowell 2001; Little 2005a). Similarly, the four studies without any blinding (N = 1863) found an OR for this outcome of 0.82 (95% CI 0.38 to 1.76) (De la Poza Abad 2016; Little 1997; Little 2001; Mas-Dalmau 2021). Of the two studies that involved only child participants, one found in favour of *immediate* antibiotics, with an OR of 0.32 (95% CI 0.16 to 0.65) (Little 2001), while the second found no evidence of a difference in satisfaction between *delayed* and *immediate* antibiotics, with an OR of 1.70 (95% CI 0.77 to 3.74) (Mas-Dalmau 2021). These results are based on moderate-certainty evidence according to GRADE assessment (Summary of findings 1).

Delayed antibiotics versus no antibiotics

Five studies compared patient satisfaction with *delayed* antibiotics versus *no* antibiotics (N = 2394) (Chao 2008; De la Poza Abad 2016; Little 1997; Little 2005a; Mas-Dalmau 2021). Pooling the results from these studies shows that 88% of participants in the *delayed* antibiotic group were satisfied or very satisfied compared with 84% in the *no* antibiotics group (OR 1.45, 95% CI 1.08 to 1.96; Analysis 5.2). 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 = 846) (Chao 2008; Little 2005a). Similarly, the three unblinded trials found an OR of 1.48 (95% CI 0.98 to 2.25) (N = 1548) (De la Poza Abad 2016; Little 1997; Mas-Dalmau 2021). The two studies that involved only child participants found no evidence of difference, with an OR of 1.47 (95% CI 0.75 to 2.88) (Chao 2008; Mas-Dalmau 2021). 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

Eight studies reported on the adverse effects of antibiotics (N = 2934) (Arroll 2002a; Chao 2008; El-Daher 1991; Little 1997; Little 2001; Little 2005a; Mas-Dalmau 2021; 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). Gastrointestinal adverse events were reported in one study with results favouring *delayed* antibiotics and *no* antibiotics over *immediate* antibiotics (P = 0.037) (Mas-Dalmau 2021). Overall results for adverse effects comparing *delayed* and *immediate* antibiotics are presented for the outcomes of vomiting (N = 907) (Analysis 6.1) (El-Daher 1991; Little 1997; Spiro 2006), diarrhoea (N = 1068) (Arroll 2002a; Little 1997; Little 2001; Spiro 2006) (Analysis 6.3) and rash (N = 665) (Little 1997; Little 2001) (Analysis 6.5). Results favoured *delayed* antibiotics over *immediate* antibiotics for diarrhoea, but there was no evidence of difference between *delayed* or *immediate* antibiotics for vomiting or rash. The evidence presented below is of low certainty 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 stomach ache 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 = 714) found no evidence of difference for the outcomes of vomiting in participants with sore throat (OR 0.64, 95% CI 0.32 to 1.26). Little 1997 also found no evidence of difference for the outcome of diarrhoea (OR 1.43, 95% CI 0.74 to 2.78). In the study Chao 2008 (N = 206) in children with AOM there were no reports of diarrhoea in either the *delayed* or *no* antibiotics groups. Little 1997 found no evidence of difference for the outcome of rash between *delayed* antibiotics and *no* antibiotics (OR 0.48, 95% CI 0.23 to 1.02). These results were based on moderate-certainty evidence according to GRADE assessment (Summary of findings 2).

2. Complications of disease

There was no significant difference in complication rates between the three prescribing strategies. Six studies reported on complications or serious adverse effects (N = 2074) (Arroll 2002a; Chao 2008; De la Poza Abad 2016; Little 2005a; Mas-Dalmau 2021; Spiro 2006). More details of disease complications are reported above under the clinical outcomes for each disease category.

3. Reconsultation rates

Reconsultation rates were similar between *delayed* and *immediate* antibiotic groups in four studies (N = 1213) (De la Poza Abad 2016; Mas-Dalmau 2021; Pichichero 1987; Spiro 2006). Pooling resulted in an OR of 1.04 (95% CI 0.66 to 1.63; Analysis 7.1). Reconsultation rates were similar between *delayed* and *no* antibiotics in two studies (N = 834) (De la Poza Abad 2016; Mas-Dalmau 2021). Pooling resulted in an OR of 0.83 (95% CI 0.46 to 1.52). 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

Four studies reported on use of other medicines (N = 1730) (Little 1997; Little 2001; Mas-Dalmau 2021; 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 the *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 that 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). Mas-Dalmau 2021 reported that non-antibiotic use was similar in the *delayed* and *no* antibiotic arms, and both were higher than in the *immediate* antibiotic arm.

DISCUSSION

Summary of main results

The strategy of delayed antibiotics resulted in an important reduction in antibiotic use compared with immediate prescription, without significantly reducing participant satisfaction. The least antibiotic use was in the *no* antibiotic group, followed by *delayed* and then *immediate* antibiotic groups. The highest level of participant satisfaction was in the *immediate* antibiotics group, followed by the *delayed* antibiotics group, with the least satisfaction in the *no* antibiotics group. 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).

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. Results favoured *immediate* antibiotics over *delayed* antibiotics for severity of pain and malaise on Day 3 (participants presented with otitis media and sore throat), and duration of malaise. Results favoured *delayed* antibiotics over *no* antibiotics for duration of fever. There was no evidence of difference between *delayed* and *immediate* antibiotics in the number of participants with fever on Days 3 to 6 (participants presented with the common cold and otitis media), in the duration of pain associated with

pharyngitis and otitis media, or the duration of fever associated with pharyngitis.

All strategies appear to have similar safety with no advantage for *delayed* antibiotics over either *no* antibiotics or *immediate* antibiotics for disease complications.

Overall completeness and applicability of evidence

Importantly, this review has demonstrated that antibiotic use is decreased by delayed antibiotics without any significant decrease in patient satisfaction.

Incorporated into this review were data on antibiotic use from the eight studies conducted after 1992 comparing *delayed* and *immediate* antibiotics (Arroll 2002a; De la Poza Abad 2016; Dowell 2001; Little 1997; Little 2001; Little 2005a; Mas-Dalmau 2021; Spiro 2006), and data on patient satisfaction from seven studies (Arroll 2002a; De la Poza Abad 2016; Dowell 2001; Little 1997; Little 2001; Little 2005a; Mas-Dalmau 2021). The study De la Poza Abad 2016 further aimed to explore the relative efficacy and safety of two *delayed* prescribing strategies.

Five trials compared *delayed* antibiotics with *no* antibiotics.

The review has included any RCT comparing *delayed* antibiotics with *immediate* and/or no antibiotics for treatment of respiratory tract infections. Consequently, the review includes different RTIs, different antibiotic regimens and different symptom outcomes. This diversity was also reflected in the ways the data were reported, limiting the extent to which we could compare data across studies or employ meta-analyses. This problem was partially overcome by obtaining raw data from some trial authors.

Studies comparing *delayed* and *immediate* antibiotics have been performed with two different motives. Prior to 1992, the studies 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.

There were no data on levels of antibiotic resistance.

Certainty of the evidence

All but one trial (El-Daher 1991) was 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 outcome 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 assessment 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; Summary of findings 2).

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 have 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 the 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 2021). 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 2021). 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 ear discharge (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 *delayed* 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 about 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: 26.7 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 antibiotic prescribing for RTIs and thereby reduce antibiotic resistance.

AUTHORS' CONCLUSIONS

Implications for practice

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. 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.

A *delayed* antibiotics strategy results in more antibiotic use than *no* antibiotics, but also greater patient satisfaction compared to *no* antibiotics, and minimal differences for symptom control and complications compared with *no* antibiotics.

A strategy of *immediate* antibiotics is more likely to confer the modest benefits of antibiotics on some clinical outcomes such as symptoms for acute otitis media and sore throat than *delayed* antibiotics. There was no evidence of differences in complication rates between *immediate* and *delayed* antibiotics or between *delayed* and *no* antibiotics.

In patients with respiratory infections where clinicians, informed by relevant guidelines, feel it is safe, *no* antibiotics with advice to return if symptoms do not resolve will result 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 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

While we are confident that delayed antibiotics reduces rates of antibiotic use in respiratory tract infections, there remain some unanswered questions requiring further research. For example, which patient groups are at highest risk of disease complications and therefore may require immediate antibiotics, how to enhance 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. Strategies to ensure the results of this research are incorporated into policy also need to be identified.

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- Sign-off Editors (final editorial decision): Mark Jones (Bond University, Australia); Mieke van Driel (The University of Queensland, Australia).
- Managing Editor (provided editorial guidance to authors, edited the review, selected peer reviewers, collated peer reviewer comments): Naomi Dayan (Herlev Hospital, Denmark).
- Contact Editor (provided valuable comments during the process of updating this review and recommended an editorial decision): Tom Fahey (Royal College of Surgeons, Ireland).
- Copy Editor (copy editing and production): Jenny Bellorini (Cochrane Central Production Service).

Peer reviewers who provided comments and recommended an editorial decision:

- Peer reviewer: Siri Aas Smedemark (Geriatric Research Unit, Odense University Hospital, Odense, Denmark & Department of Clinical Research, University of Southern Denmark, Odense, Denmark).
- Methods reviewer: Dr Peter Knapp (University of York, UK).
- Methods reviewer: Emma Axon (Cochrane Central Executive Team).
- Statistical Editor (provided comments): Ravi Shankar (Department of Statistics, Manipal University, India).
- Consumer reviewer: Janet Wale (independent consumer advocate).
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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

Arroll 2002a *(Continued)*

	62 participants were randomised to *immediate* antibiotic prescription, and 67 to *delayed* (prescription at time of visit) antibiotic prescription **Age:** the average age was 27.9 years (SD 3.1) in the immediate antibiotic group and 23.6 years (SD 2.7) in the *delayed* antibiotic group **Sex:***immediate* antibiotic group: 22 males, 40 females; *delayed* (prescription at time of visit) 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 of New Zealand

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	ITT 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 *no* antibiotics and 106 were randomised to *delayed* antibiotic prescription.

Chao 2008 *(Continued)*

	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 **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. 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.

De la Poza Abad 2016 *(Continued)*

	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 **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

Dowell 2001 *(Continued)*

	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.
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)

El-Daher 1991 *(Continued)*

	Sex:*delayed* antibiotic group: 66 male, 52 female; *immediate* antibiotic group: 60 male, 51 female **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 **Sex:***delayed* antibiotics group: 30 males, 33 females; *immediate* antibiotics: 29 males, 21 females **Exclusion criteria:** hypersensitivity to penicillin, had received penicillin in the previous 72 hours, or had a negative throat culture

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 aged ≥ 4 years 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 **Sex:** *delayed* antibiotics group: 82 males, 153 females; *immediate* antibiotics group: 95 males, 151 females; *no* antibiotics group: 82 males, 150 females **Exclusion criteria:** people were excluded if they had a sore throat that was clearly not a bacterial infection, e.g. due to drugs, aphthous ulcers, candidal infection. Other exclusion criteria included being very unwell, suspected or previous rheumatic fever, multiple (more than 5 per year) attacks of tonsillitis, quinsy and pregnancy.
Interventions	Participants in the *delayed* antibiotics group were instructed to pick up a script left at reception after 72 hours if needed. Participants in the *immediate* antibiotics group were immediately offered a script for antibiotics. The antibiotic prescription for both groups was penicillin V 250 mg 4 times a day for 10

Little 1997 *(Continued)*

	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, stomach ache, 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 **Sex:** 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

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.

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). **Sex:** 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

Mas-Dalmau 2021 *(Continued)*

Methods	Randomised controlled trial
Participants	436 children aged 2 to 14 years with uncomplicated respiratory infections (pharyngitis, rhinosinusitis, acute bronchitis, acute otitis media) who attended, with their parent(s), 39 primary care paediatrician'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), in the *immediate antibiotic* group was 6.4 years (SD 3.1) and in the *no* antibiotic group was 6.1 years (SD 6.1) **Sex:** *delayed* antibiotic group: 78 males, 68 females; *immediate antibiotic* group: 69 males, 79 females; *no* antibiotic group: 63 males, 79 females **Exclusion criteria:** *acute otitis media*: 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 otorrhoea (ear discharge); previous complications (septic complications, hearing disturbances); antibiotic intake in 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, tachypnoea, vomiting, severe diarrhoea); high fever (axillary temperature > 38.5 °C); vomiting and/or severe diarrhoea; bronchial asthma; other acute or chronic lung diseases including cystic fibrosis; active heart disease; psychiatric diagnoses; antibiotic intake in the previous 2 weeks; and using C-reactive protein quick tests during the visit.
Interventions	*Delayed* antibiotic prescription, *immediate* antibiotic prescription, *no* antibiotic prescription
Outcomes	**Primary outcome:** severity and duration of acute respiratory tract infection (pharyngitis, rhinosinusitis, acute bronchitis or acute otitis media) symptoms over 30 days **Secondary outcomes**: antibiotic use over 30 days, parental satisfaction and beliefs regarding antibiotic efficacy, and additional unscheduled visits to primary care over 30 days
Notes	The study was funded by the Instituto de Salud Carlos III

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was stratified by pathology and in blocks. The nature of the blocks was not described.
Allocation concealment (selection bias)	High risk	Children, parents and health professionals were not blinded
Blinding (performance bias and detection bias) All outcomes	High risk	Children, parents and health professionals were not blinded

Mas-Dalmau 2021 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	436 participants were recruited and included in the analysis. 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

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) **Sex:** not reported **Exclusion criteria** included hypersensitivity to penicillin, receipt of antibiotics in preceding 7 days, acute illness in preceding 7 days, GABHS infection in the preceding month and concurrent treatment with an antibiotic other than penicillin
Interventions	Children were randomised to *delayed* antibiotics (48-hour delay) versus *immediate* antibiotics. Children in each group received penicillin V 250 mg 3 times a day for 10 days.
Outcomes	**Primary outcomes:** fever, duration of fever, malaise **Secondary outcomes:** reconsultation rates, vomiting Outcomes were measured using a symptom diary and reassessment at the paediatrician's office 3 days after child's initial enrolment
Notes	This study was funded by the Robert Wood Johnson Foundation, Eli Lilly and Company, and Elmwood Paediatric Research fund. We approached the authors for their study data, but they did not provide this information.

Risk of bias

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

Pichichero 1987 *(Continued)*

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 **Sex:***delayed* antibiotics group: 79 males, 59 females; *immediate* antibiotics group: 76 males, 69 females **Exclusion criteria** for this study included intercurrent bacterial infection, toxic appearance of child, patient hospitalisation, immunocompromise, child had been treated with antibiotics in the preceding 7 days, myringotomy tubes, current tympanic membrane perforation, uncertain medical access, uncertain telephone access, primary language of guardian other than English or Spanish
Interventions	Children were randomised to *delayed* antibiotics (advised to delay for 48 hours and the script was to expire after 72 hours) or *immediate* antibiotics. The clinician chose the antibiotic.
Outcomes	**Primary outcome measures:** fever, duration of fever, pain, duration of pain, antibiotic use **Secondary outcome measures:** adverse effects of antibiotics including vomiting, diarrhoea and rash Outcomes were measured by telephone interview by a research assistant with the caregivers of the 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.

Spiro 2006 *(Continued)*

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. ITT analysis was conducted.
Selective reporting (reporting bias)	Low risk	Prespecified outcomes were reported.
Other bias	Low risk	Funded by government body

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

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

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

DATA AND ANALYSES

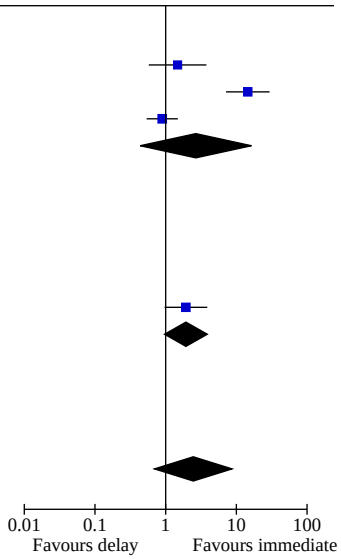
Comparison 1. Pain

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: delayed versus immediate antibiotics	4	825	Odds Ratio (M-H, Random, 95% CI)	2.46 [0.70, 8.69]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1.1 Delayed (prescription at time of visit) versus immediate antibiotics	3	613	Odds Ratio (M-H, Random, 95% CI)	2.67 [0.44, 16.35]
1.1.2 Delayed (prescription collection) versus immediate antibiotics	1	212	Odds Ratio (M-H, Random, 95% CI)	1.93 [0.96, 3.88]
1.2 Pain severity on day 3: delayed versus immediate antibiotics	2	327	Mean Difference (IV, Random, 95% CI)	0.51 [0.07, 0.95]
1.3 Duration of pain: delayed versus immediate antibiotics (days)	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.3.1 Pharyngitis: delayed (prescription at time of visit) versus immediate antibiotics	2	493	Mean Difference (IV, Random, 95% CI)	0.21 [-0.75, 1.18]
1.3.2 Pharyngitis: delayed (prescription collection) versus immediate antibiotics	1	201	Mean Difference (IV, Random, 95% CI)	1.10 [-0.20, 2.40]
1.3.3 Acute otitis media: delayed (prescription at time of visit) versus immediate antibiotics	1	294	Mean Difference (IV, Random, 95% CI)	-0.70 [-1.76, 0.36]
1.4 Duration of pain: delayed versus no antibiotics (days)	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.4.1 Pharyngitis pain: delayed (prescription at time of visit) versus no antibiotics	2	485	Mean Difference (IV, Random, 95% CI)	-0.85 [-1.80, 0.11]
1.4.2 Pharyngitis pain: delayed (prescription collection) versus no antibiotics	1	199	Mean Difference (IV, Random, 95% CI)	-1.10 [-2.65, 0.45]
1.4.3 Acute otitis media pain: delayed (prescription at time of visit) versus no antibiotics	1	288	Mean Difference (IV, Random, 95% CI)	-0.80 [-2.01, 0.41]

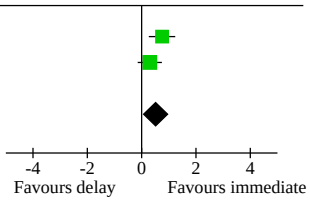
Analysis 1.1. Comparison 1: Pain, Outcome 1: Number of participants with pain on days 3 to 6: delayed versus immediate antibiotics

Study or Subgroup	Delayed antibiotics Events	Total	Immediate antibiotics Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
1.1.1 Delayed (prescription at time of visit) versus immediate antibiotics						
Arroll 2002a	13	61	9	58	23.7%	1.47 [0.58 , 3.77]
El-Daher 1991	106	118	42	111	25.1%	14.51 [7.14 , 29.50]
Spiro 2006	85	132	89	133	26.1%	0.89 [0.54 , 1.48]
Subtotal (95% CI)		**311**		**302**	**74.8%**	**2.67 [0.44 , 16.35]**
Total events:	204		140			
Heterogeneity: Tau² = 2.42; Chi² = 40.24, df = 2 (P < 0.00001); I² = 95%						
Test for overall effect: Z = 1.06 (P = 0.29)						
1.1.2 Delayed (prescription collection) versus immediate antibiotics						
Little 2001	28	111	15	101	25.2%	1.93 [0.96 , 3.88]
Subtotal (95% CI)		**111**		**101**	**25.2%**	**1.93 [0.96 , 3.88]**
Total events:	28		15			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.86 (P = 0.06)						
Total (95% CI)		**422**		**403**	**100.0%**	**2.46 [0.70 , 8.69]**
Total events:	232		155			
Heterogeneity: Tau² = 1.53; Chi² = 40.26, df = 3 (P < 0.00001); I² = 93%						
Test for overall effect: Z = 1.40 (P = 0.16)						
Test for subgroup differences: Chi² = 0.11, df = 1 (P = 0.75), I² = 0%						



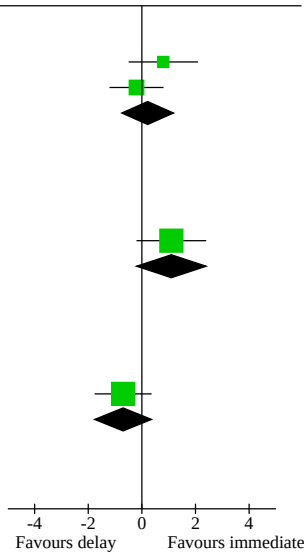
Analysis 1.2. Comparison 1: Pain, Outcome 2: Pain severity on day 3: delayed versus immediate antibiotics

Study or Subgroup	Delayed antibiotics Mean	SD	Total	Immediate antibiotics Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Little 2001	2.56	2.14	111	1.81	1.44	102	47.5%	0.75 [0.26 , 1.24]
Pichichero 1987	1.6	1.38	55	1.3	1	59	52.5%	0.30 [-0.15 , 0.75]
Total (95% CI)			**166**			**161**	**100.0%**	**0.51 [0.07 , 0.95]**
Heterogeneity: Tau² = 0.04; Chi² = 1.79, df = 1 (P = 0.18); I² = 44%								
Test for overall effect: Z = 2.29 (P = 0.02)								
Test for subgroup differences: Not applicable								



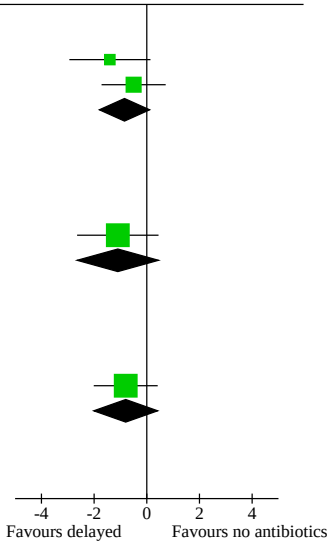
Analysis 1.3. Comparison 1: Pain, Outcome 3: Duration of pain: delayed versus immediate antibiotics (days)

Study or Subgroup	Delayed antibiotics Mean	SD	Total	Immediate antibiotics Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.3.1 Pharyngitis: delayed (prescription at time of visit) versus immediate antibiotics								
De la Poza Abad 2016	6.7	4.6	98	5.9	4.7	101	41.5%	0.80 [-0.49 , 2.09]
Mas-Dalmau 2021	5	4.1	146	5.2	4.7	148	58.5%	-0.20 [-1.21 , 0.81]
Subtotal (95% CI)			**244**			**249**	**100.0%**	**0.21 [-0.75 , 1.18]**
Heterogeneity: Tau² = 0.15; Chi² = 1.43, df = 1 (P = 0.23); I² = 30%								
Test for overall effect: Z = 0.44 (P = 0.66)								
1.3.2 Pharyngitis: delayed (prescription collection) versus immediate antibiotics								
De la Poza Abad 2016	7	4.7	100	5.9	4.7	101	100.0%	1.10 [-0.20 , 2.40]
Subtotal (95% CI)			**100**			**101**	**100.0%**	**1.10 [-0.20 , 2.40]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.66 (P = 0.10)								
1.3.3 Acute otitis media: delayed (prescription at time of visit) versus immediate antibiotics								
Mas-Dalmau 2021	4.4	3.9	146	5.1	5.3	148	100.0%	-0.70 [-1.76 , 0.36]
Subtotal (95% CI)			**146**			**148**	**100.0%**	**-0.70 [-1.76 , 0.36]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.29 (P = 0.20)								
Test for subgroup differences: Chi² = 0.00, df = 2 (P < 0.00001), I² = 0%								



Analysis 1.4. Comparison 1: Pain, Outcome 4: Duration of pain: delayed versus no antibiotics (days)

Study or Subgroup	Delayed antibiotics Mean	SD	Total	No antibiotics Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.4.1 Pharyngitis pain: delayed (prescription at time of visit) versus no antibiotics								
De la Poza Abad 2016	6.7	4.6	98	8.1	6.3	99	38.5%	-1.40 [-2.94 , 0.14]
Mas-Dalmau 2021	5	4.1	146	5.5	6.2	142	61.5%	-0.50 [-1.72 , 0.72]
Subtotal (95% CI)			**244**			**241**	**100.0%**	**-0.85 [-1.80 , 0.11]**
Heterogeneity: Tau² = 0.00; Chi² = 0.81, df = 1 (P = 0.37); I² = 0%								
Test for overall effect: Z = 1.74 (P = 0.08)								
1.4.2 Pharyngitis pain: delayed (prescription collection) versus no antibiotics								
De la Poza Abad 2016	7	4.7	100	8.1	6.3	99	100.0%	-1.10 [-2.65 , 0.45]
Subtotal (95% CI)			**100**			**99**	**100.0%**	**-1.10 [-2.65 , 0.45]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.39 (P = 0.16)								
1.4.3 Acute otitis media pain: delayed (prescription at time of visit) versus no antibiotics								
Mas-Dalmau 2021	4.4	3.9	146	5.2	6.3	142	100.0%	-0.80 [-2.01 , 0.41]
Subtotal (95% CI)			**146**			**142**	**100.0%**	**-0.80 [-2.01 , 0.41]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.29 (P = 0.20)								
Test for subgroup differences: Chi² = 0.00, df = 2 (P < 0.00001), I² = 0%								



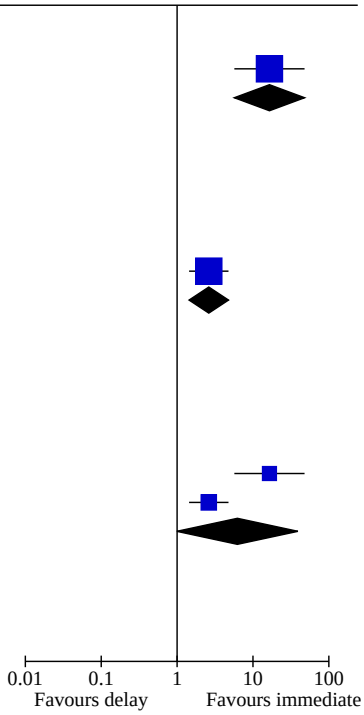
Comparison 2. Malaise

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Number of participants with malaise on days 3 to 6: delayed versus immediate antibiotics	2		Odds Ratio (M-H, Random, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1.1 Delayed (prescription at time of visit) versus immediate antibiotics	1	229	Odds Ratio (M-H, Random, 95% CI)	16.49 [5.68, 47.83]
2.1.2 Delayed (prescription collection) versus immediate antibiotics	1	285	Odds Ratio (M-H, Random, 95% CI)	2.62 [1.44, 4.76]
2.1.3 Delayed (all strategies) versus immediate antibiotics	2	514	Odds Ratio (M-H, Random, 95% CI)	6.23 [0.99, 39.09]
2.2 Malaise severity on day 3: delayed versus immediate antibiotics	2	796	Std. Mean Difference (IV, Random, 95% CI)	0.29 [0.15, 0.43]
2.2.1 Delayed (prescription at time of visit) versus immediate antibiotics	1	114	Std. Mean Difference (IV, Random, 95% CI)	0.24 [-0.13, 0.60]
2.2.2 Delayed (prescription collection) versus immediate antibiotics	1	284	Std. Mean Difference (IV, Random, 95% CI)	0.31 [0.07, 0.54]
2.2.3 Delayed (both strategies) versus immediate antibiotics	2	398	Std. Mean Difference (IV, Random, 95% CI)	0.29 [0.09, 0.48]
2.3 Duration of malaise: delayed versus immediate antibiotics	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
2.3.1 Delayed (prescription at time of visit) versus immediate antibiotics	2	493	Mean Difference (IV, Random, 95% CI)	0.38 [-0.56, 1.32]
2.3.2 Delayed (prescription collection) versus immediate antibiotics	1	201	Mean Difference (IV, Random, 95% CI)	2.00 [0.23, 3.77]
2.4 Duration of malaise: delayed versus no antibiotics	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
2.4.1 Delayed (prescription at time of visit) versus no antibiotics	2	485	Mean Difference (IV, Random, 95% CI)	-1.09 [-3.12, 0.95]
2.4.2 Delayed (prescription collection) versus no antibiotics	1	199	Mean Difference (IV, Random, 95% CI)	-1.50 [-3.46, 0.46]

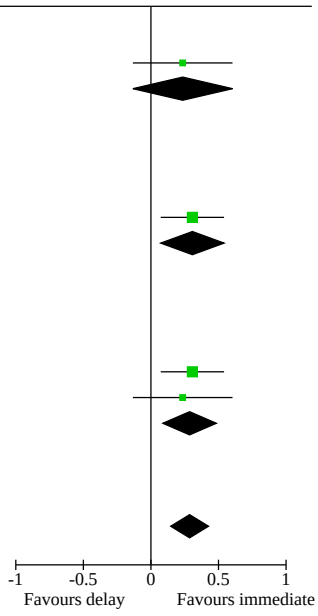
Analysis 2.1. Comparison 2: Malaise, Outcome 1: Number of participants with malaise on days 3 to 6: delayed versus immediate antibiotics

Study or Subgroup	Delay Events	Delay Total	Immediate Events	Immediate Total	Weight	Odds Ratio M-H, Random, 95% CI
2.1.1 Delayed (prescription at time of visit) versus immediate antibiotics						
El-Daher 1991	45	118	4	111	100.0%	16.49 [5.68 , 47.83]
Subtotal (95% CI)		**118**		**111**	**100.0%**	**16.49 [5.68 , 47.83]**
Total events:	45		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 5.16 (P < 0.00001)						
2.1.2 Delayed (prescription collection) versus immediate antibiotics						
Little 2001	45	150	19	135	100.0%	2.62 [1.44 , 4.76]
Subtotal (95% CI)		**150**		**135**	**100.0%**	**2.62 [1.44 , 4.76]**
Total events:	45		19			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.15 (P = 0.002)						
2.1.3 Delayed (all strategies) versus immediate antibiotics						
El-Daher 1991	45	118	4	111	47.1%	16.49 [5.68 , 47.83]
Little 2001	45	150	19	135	52.9%	2.62 [1.44 , 4.76]
Subtotal (95% CI)		**268**		**246**	**100.0%**	**6.23 [0.99 , 39.09]**
Total events:	90		23			
Heterogeneity: Tau² = 1.57; Chi² = 9.07, df = 1 (P = 0.003); I² = 89%						
Test for overall effect: Z = 1.95 (P = 0.05)						

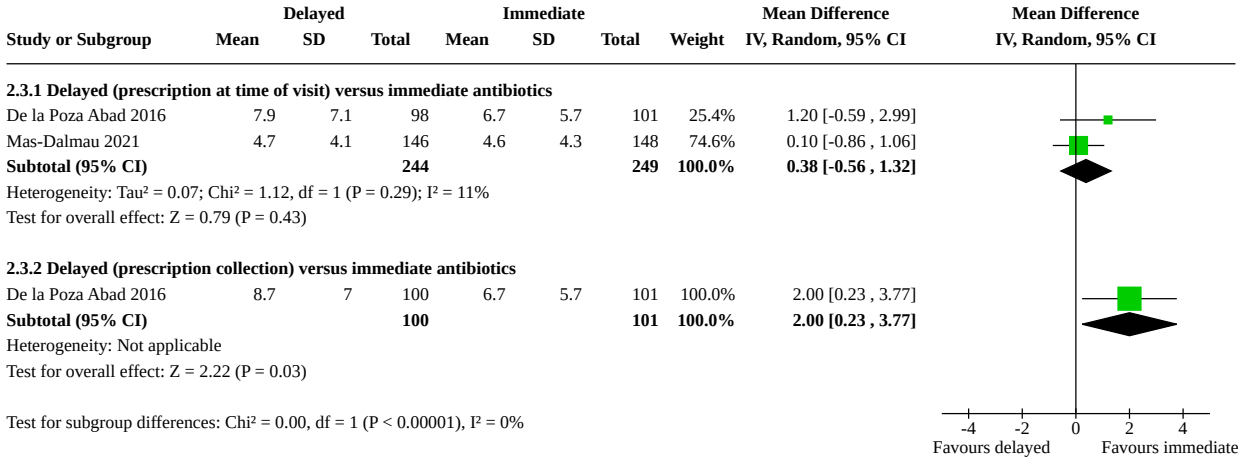


Analysis 2.2. Comparison 2: Malaise, Outcome 2: Malaise severity on day 3: delayed versus immediate antibiotics

Study or Subgroup	Delay Mean	Delay SD	Delay Total	Immediate Mean	Immediate SD	Immediate Total	Weight	Std. Mean Difference IV, Random, 95% CI
2.2.1 Delayed (prescription at time of visit) versus immediate antibiotics								
Pichichero 1987	1.3	1	55	1.1	0.67	59	14.4%	0.24 [-0.13 , 0.60]
Subtotal (95% CI)			**55**			**59**	**14.4%**	**0.24 [-0.13 , 0.60]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.25 (P = 0.21)								
2.2.2 Delayed (prescription collection) versus immediate antibiotics								
Little 2001	0.83	1.69	150	0.4	0.97	134	35.6%	0.31 [0.07 , 0.54]
Subtotal (95% CI)			**150**			**134**	**35.6%**	**0.31 [0.07 , 0.54]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.57 (P = 0.01)								
2.2.3 Delayed (both strategies) versus immediate antibiotics								
Little 2001	0.83	1.69	150	0.4	0.97	134	35.6%	0.31 [0.07 , 0.54]
Pichichero 1987	1.3	1	55	1.1	0.67	59	14.4%	0.24 [-0.13 , 0.60]
Subtotal (95% CI)			**205**			**193**	**50.0%**	**0.29 [0.09 , 0.48]**
Heterogeneity: Tau² = 0.00; Chi² = 0.10, df = 1 (P = 0.75); I² = 0%								
Test for overall effect: Z = 2.84 (P = 0.005)								
Total (95% CI)			**410**			**386**	**100.0%**	**0.29 [0.15 , 0.43]**
Heterogeneity: Tau² = 0.00; Chi² = 0.21, df = 3 (P = 0.98); I² = 0%								
Test for overall effect: Z = 4.01 (P < 0.0001)								
Test for subgroup differences: Chi² = 0.10, df = 2 (P = 0.95), I² = 0%								

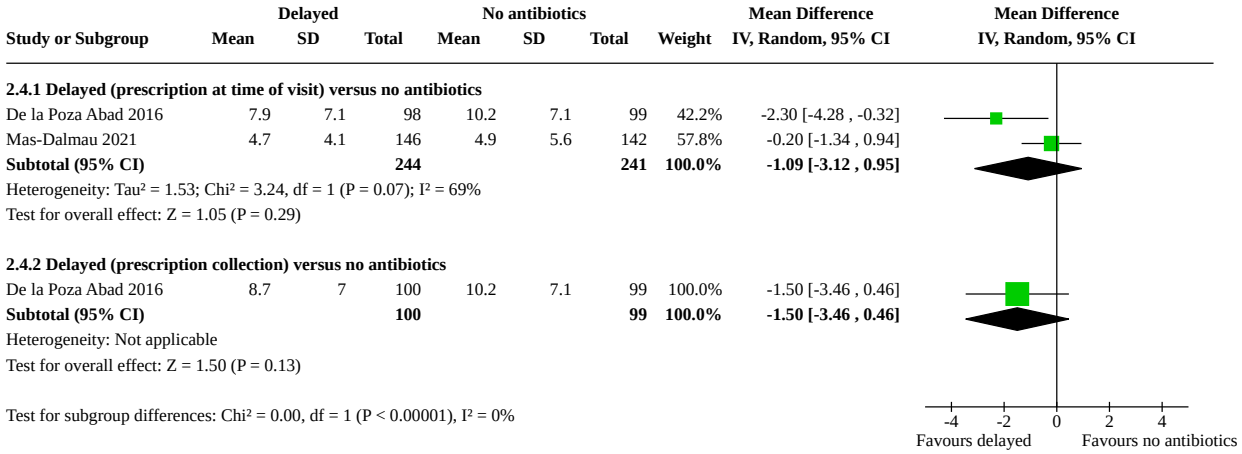


Analysis 2.3. Comparison 2: Malaise, Outcome 3: Duration of malaise: delayed versus immediate antibiotics



Study or Subgroup	Delayed Mean	Delayed SD	Delayed Total	Immediate Mean	Immediate SD	Immediate Total	Weight	Mean Difference IV, Random, 95% CI
2.3.1 Delayed (prescription at time of visit) versus immediate antibiotics								
De la Poza Abad 2016	7.9	7.1	98	6.7	5.7	101	25.4%	1.20 [-0.59 , 2.99]
Mas-Dalmau 2021	4.7	4.1	146	4.6	4.3	148	74.6%	0.10 [-0.86 , 1.06]
Subtotal (95% CI)			**244**			**249**	**100.0%**	**0.38 [-0.56 , 1.32]**
Heterogeneity: Tau² = 0.07; Chi² = 1.12, df = 1 (P = 0.29); I² = 11%								
Test for overall effect: Z = 0.79 (P = 0.43)								
2.3.2 Delayed (prescription collection) versus immediate antibiotics								
De la Poza Abad 2016	8.7	7	100	6.7	5.7	101	100.0%	2.00 [0.23 , 3.77]
Subtotal (95% CI)			**100**			**101**	**100.0%**	**2.00 [0.23 , 3.77]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.22 (P = 0.03)								
Test for subgroup differences: Chi² = 0.00, df = 1 (P < 0.00001), I² = 0%								

Analysis 2.4. Comparison 2: Malaise, Outcome 4: Duration of malaise: delayed versus no antibiotics



Study or Subgroup	Delayed Mean	Delayed SD	Delayed Total	No antibiotics Mean	No antibiotics SD	No antibiotics Total	Weight	Mean Difference IV, Random, 95% CI
2.4.1 Delayed (prescription at time of visit) versus no antibiotics								
De la Poza Abad 2016	7.9	7.1	98	10.2	7.1	99	42.2%	-2.30 [-4.28 , -0.32]
Mas-Dalmau 2021	4.7	4.1	146	4.9	5.6	142	57.8%	-0.20 [-1.34 , 0.94]
Subtotal (95% CI)			**244**			**241**	**100.0%**	**-1.09 [-3.12 , 0.95]**
Heterogeneity: Tau² = 1.53; Chi² = 3.24, df = 1 (P = 0.07); I² = 69%								
Test for overall effect: Z = 1.05 (P = 0.29)								
2.4.2 Delayed (prescription collection) versus no antibiotics								
De la Poza Abad 2016	8.7	7	100	10.2	7.1	99	100.0%	-1.50 [-3.46 , 0.46]
Subtotal (95% CI)			**100**			**99**	**100.0%**	**-1.50 [-3.46 , 0.46]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.50 (P = 0.13)								
Test for subgroup differences: Chi² = 0.00, df = 1 (P < 0.00001), I² = 0%								

Comparison 3. Fever

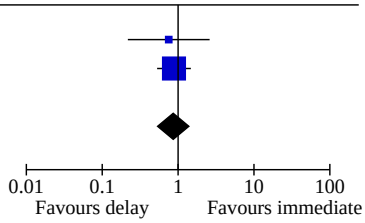
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Number of participants with fever on days 3 to 6: delayed (prescription at time of visit) versus immediate antibiotics	2	394	Odds Ratio (M-H, Random, 95% CI)	0.86 [0.54, 1.38]
3.2 Fever severity on day 3: delayed (prescription at time of visit) versus immediate antibiotic	3	462	Mean Difference (IV, Random, 95% CI)	0.34 [-0.33, 1.01]
3.3 Duration of fever: delayed versus immediate antibiotics	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
3.3.1 Delayed (prescription at time of visit) versus immediate antibiotics	1	199	Mean Difference (IV, Random, 95% CI)	0.10 [-1.00, 1.20]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.3.2 Delayed (prescription collection) versus immediate antibiotics	1	201	Mean Difference (IV, Random, 95% CI)	0.10 [-0.93, 1.13]
3.3.3 Pharyngitis: Delayed (prescription at time of visit) versus immediate antibiotics	1	294	Mean Difference (IV, Random, 95% CI)	0.40 [-0.51, 1.31]
3.4 Duration of fever: delayed versus no antibiotics	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
3.4.1 Delayed (prescription at time of visit) versus no antibiotics	1	197	Mean Difference (IV, Random, 95% CI)	-1.60 [-3.04, -0.16]
3.4.2 Delayed (prescription collection) versus no antibiotics	1	199	Mean Difference (IV, Random, 95% CI)	-1.60 [-2.99, -0.21]
3.4.3 Pharyngitis: delayed (prescription at time of visit) versus no antibiotics	1	288	Mean Difference (IV, Random, 95% CI)	-0.20 [-1.41, 1.01]

Analysis 3.1. Comparison 3: Fever, Outcome 1: Number of participants with fever on days 3 to 6: delayed (prescription at time of visit) versus immediate antibiotics

Study or Subgroup	Delay Events	Delay Total	Immediate Events	Immediate Total	Weight	Odds Ratio M-H, Random, 95% CI
Arroll 2002a	5	67	6	62	14.5%	0.75 [0.22 , 2.60]
Spiro 2006	42	132	46	133	85.5%	0.88 [0.53 , 1.47]
Total (95% CI)		**199**		**195**	**100.0%**	**0.86 [0.54 , 1.38]**
Total events:	47		52			

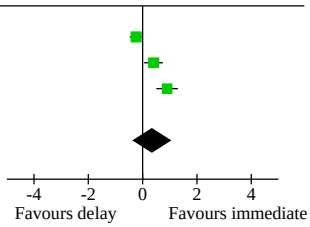
Heterogeneity: Tau² = 0.00; Chi² = 0.05, df = 1 (P = 0.82); I² = 0%
Test for overall effect: Z = 0.61 (P = 0.54)
Test for subgroup differences: Not applicable



Analysis 3.2. Comparison 3: Fever, Outcome 2: Fever severity on day 3: delayed (prescription at time of visit) versus immediate antibiotic

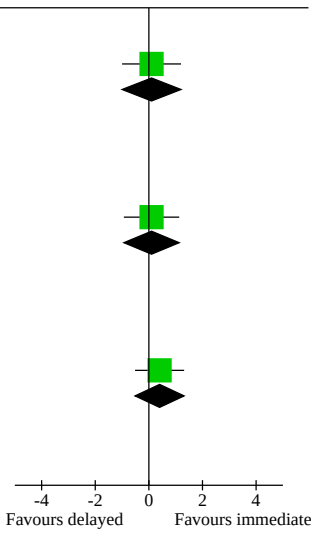
Study or Subgroup	Delayed Mean	Delayed SD	Delayed Total	Immediate Mean	Immediate SD	Immediate Total	Weight	Mean Difference IV, Random, 95% CI
Arroll 2002a	36.15	0.73	61	36.39	0.58	58	34.7%	-0.24 [-0.48 , -0.00]
Pichichero 1987	37.2	1.17	55	36.8	0.61	59	33.1%	0.40 [0.05 , 0.75]
El-Daher 1991	38	1.96	118	37.1	0.95	111	32.2%	0.90 [0.50 , 1.30]
Total (95% CI)			**234**			**228**	**100.0%**	**0.34 [-0.33 , 1.01]**

Heterogeneity: Tau² = 0.33; Chi² = 26.29, df = 2 (P < 0.00001); I² = 92%
Test for overall effect: Z = 0.99 (P = 0.32)
Test for subgroup differences: Not applicable



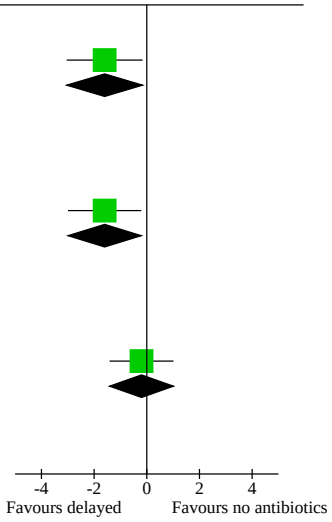
Analysis 3.3. Comparison 3: Fever, Outcome 3: Duration of fever: delayed versus immediate antibiotics

Study or Subgroup	Delayed Mean	Delayed SD	Delayed Total	Immediate Mean	Immediate SD	Immediate Total	Weight	Mean Difference IV, Random, 95% CI
3.3.1 Delayed (prescription at time of visit) versus immediate antibiotics								
De la Poza Abad 2016	3.8	3.7	98	3.7	4.2	101	100.0%	0.10 [-1.00 , 1.20]
Subtotal (95% CI)			**98**			**101**	**100.0%**	**0.10 [-1.00 , 1.20]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.18 (P = 0.86)								
3.3.2 Delayed (prescription collection) versus immediate antibiotics								
De la Poza Abad 2016	3.8	3.2	100	3.7	4.2	101	100.0%	0.10 [-0.93 , 1.13]
Subtotal (95% CI)			**100**			**101**	**100.0%**	**0.10 [-0.93 , 1.13]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.19 (P = 0.85)								
3.3.3 Pharyngitis: Delayed (prescription at time of visit) versus immediate antibiotics								
Mas-Dalmau 2021	4	5.2	146	3.6	2.2	148	100.0%	0.40 [-0.51 , 1.31]
Subtotal (95% CI)			**146**			**148**	**100.0%**	**0.40 [-0.51 , 1.31]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.86 (P = 0.39)								



Analysis 3.4. Comparison 3: Fever, Outcome 4: Duration of fever: delayed versus no antibiotics

Study or Subgroup	Delayed Mean	Delayed SD	Delayed Total	No antibiotics Mean	No antibiotics SD	No antibiotics Total	Weight	Mean Difference IV, Random, 95% CI
3.4.1 Delayed (prescription at time of visit) versus no antibiotics								
De la Poza Abad 2016	3.8	3.7	98	5.4	6.3	99	100.0%	-1.60 [-3.04 , -0.16]
Subtotal (95% CI)			**98**			**99**	**100.0%**	**-1.60 [-3.04 , -0.16]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.18 (P = 0.03)								
3.4.2 Delayed (prescription collection) versus no antibiotics								
De la Poza Abad 2016	3.8	3.2	100	5.4	6.3	99	100.0%	-1.60 [-2.99 , -0.21]
Subtotal (95% CI)			**100**			**99**	**100.0%**	**-1.60 [-2.99 , -0.21]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.26 (P = 0.02)								
3.4.3 Pharyngitis: delayed (prescription at time of visit) versus no antibiotics								
Mas-Dalmau 2021	4	5.2	146	4.2	5.3	142	100.0%	-0.20 [-1.41 , 1.01]
Subtotal (95% CI)			**146**			**142**	**100.0%**	**-0.20 [-1.41 , 1.01]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.32 (P = 0.75)								

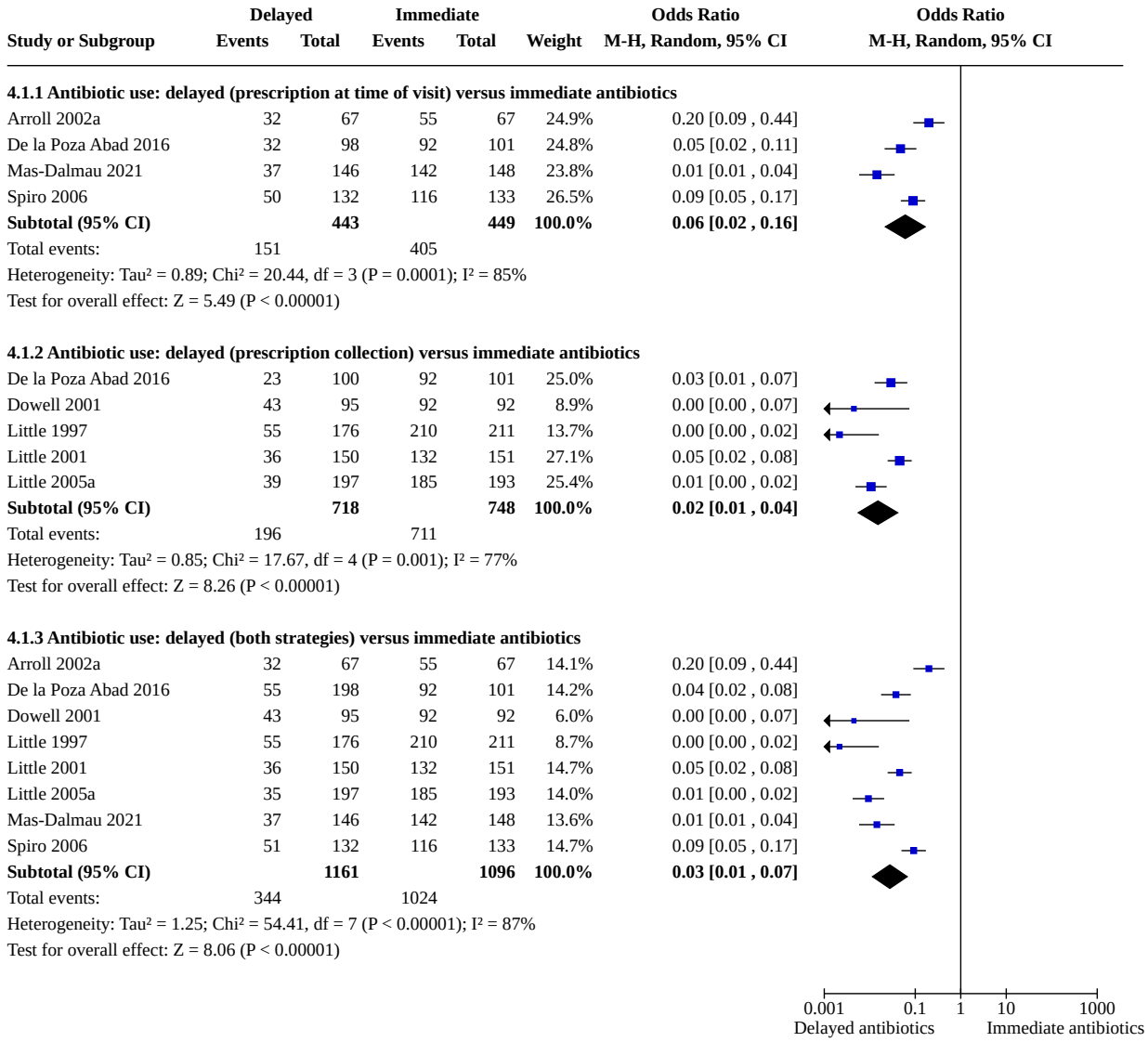


Comparison 4. Antibiotic use

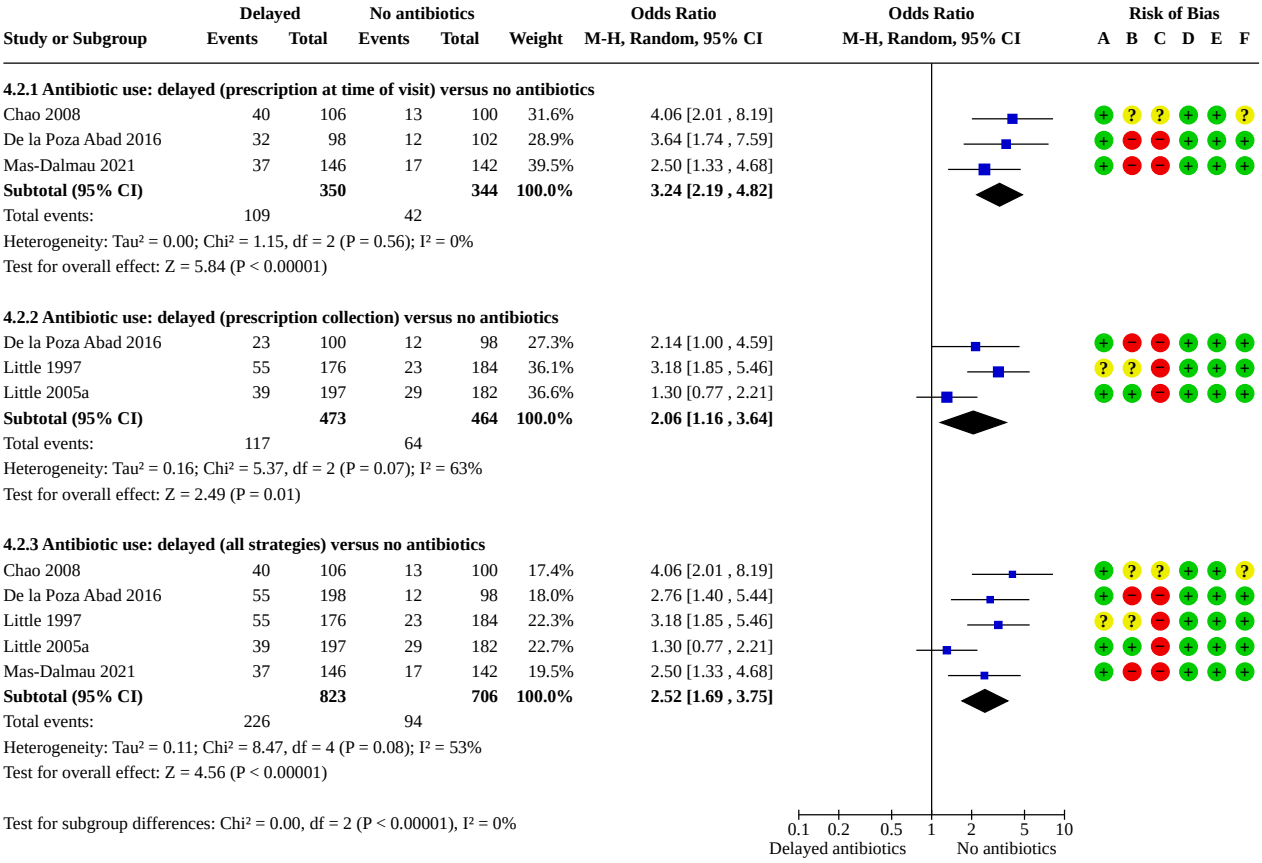
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Antibiotic use: delayed versus immediate antibiotics	8		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
4.1.1 Antibiotic use: delayed (prescription at time of visit) versus immediate antibiotics	4	892	Odds Ratio (M-H, Random, 95% CI)	0.06 [0.02, 0.16]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1.2 Antibiotic use: delayed (prescription collection) versus immediate antibiotics	5	1466	Odds Ratio (M-H, Random, 95% CI)	0.02 [0.01, 0.04]
4.1.3 Antibiotic use: delayed (both strategies) versus immediate antibiotics	8	2257	Odds Ratio (M-H, Random, 95% CI)	0.03 [0.01, 0.07]
4.2 Antibiotic use: delayed versus no antibiotics	5		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
4.2.1 Antibiotic use: delayed (prescription at time of visit) versus no antibiotics	3	694	Odds Ratio (M-H, Random, 95% CI)	3.24 [2.19, 4.82]
4.2.2 Antibiotic use: delayed (prescription collection) versus no antibiotics	3	937	Odds Ratio (M-H, Random, 95% CI)	2.06 [1.16, 3.64]
4.2.3 Antibiotic use: delayed (all strategies) versus no antibiotics	5	1529	Odds Ratio (M-H, Random, 95% CI)	2.52 [1.69, 3.75]

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



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



Risk of bias legend

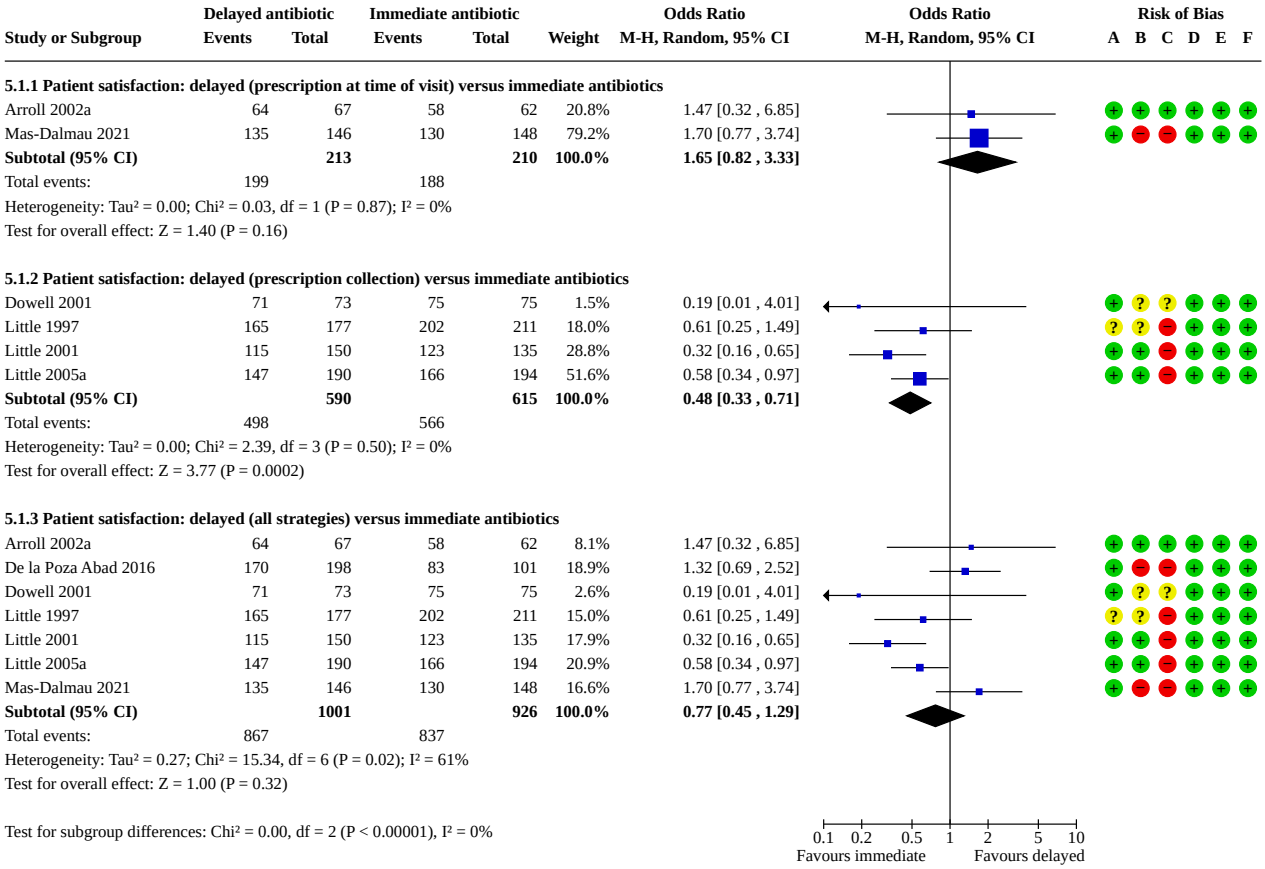
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding (performance bias and detection bias)
(D) Incomplete outcome data (attrition bias)
(E) Selective reporting (reporting bias)
(F) Other bias

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		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
5.1.1 Patient satisfaction: delayed (prescription at time of visit) versus immediate antibiotics	2	423	Odds Ratio (M-H, Random, 95% CI)	1.65 [0.82, 3.33]
5.1.2 Patient satisfaction: delayed (prescription collection) versus immediate antibiotics	4	1205	Odds Ratio (M-H, Random, 95% CI)	0.48 [0.33, 0.71]
5.1.3 Patient satisfaction: delayed (all strategies) versus immediate antibiotics	7	1927	Odds Ratio (M-H, Random, 95% CI)	0.77 [0.45, 1.29]

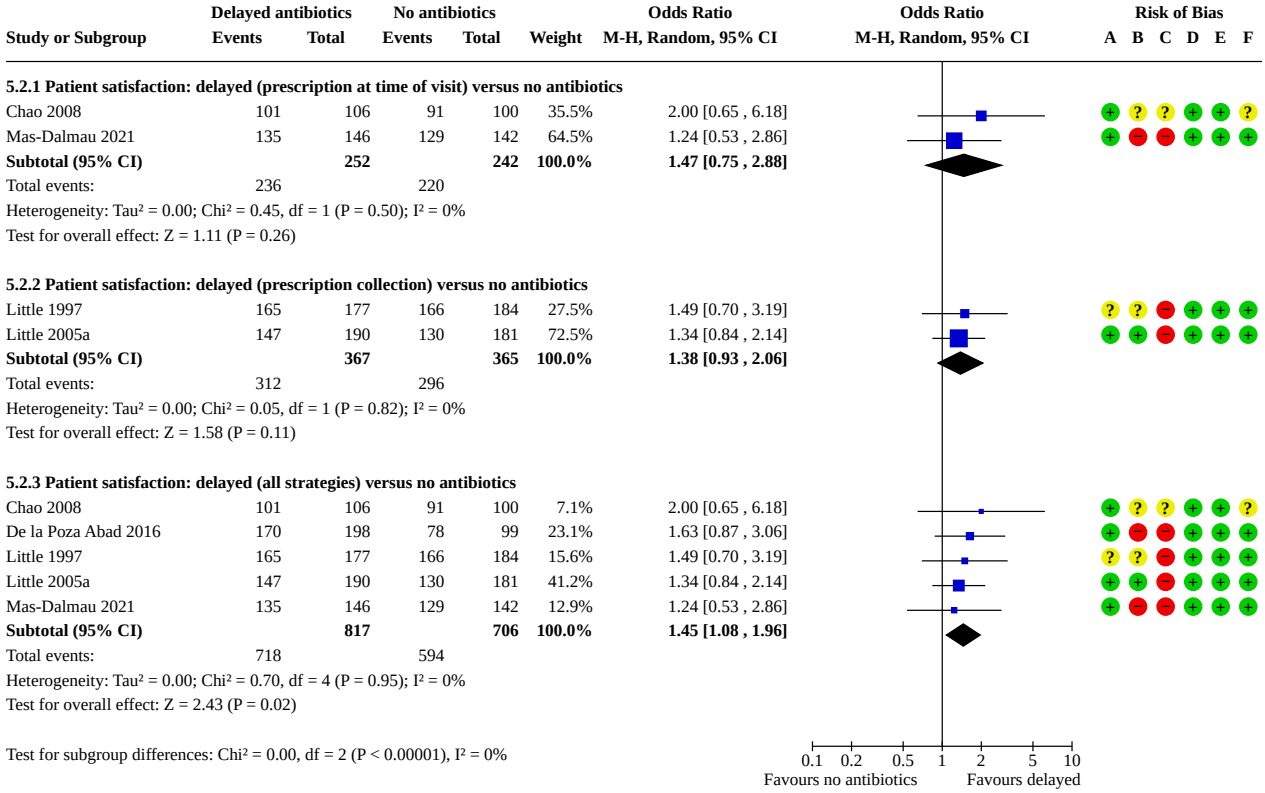
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.2 Patient satisfaction: delayed versus no antibiotics	5		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
5.2.1 Patient satisfaction: delayed (prescription at time of visit) versus no antibiotics	2	494	Odds Ratio (M-H, Random, 95% CI)	1.47 [0.75, 2.88]
5.2.2 Patient satisfaction: delayed (prescription collection) versus no antibiotics	2	732	Odds Ratio (M-H, Random, 95% CI)	1.38 [0.93, 2.06]
5.2.3 Patient satisfaction: delayed (all strategies) versus no antibiotics	5	1523	Odds Ratio (M-H, Random, 95% CI)	1.45 [1.08, 1.96]

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



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding (performance bias and detection bias)
(D) Incomplete outcome data (attrition bias)
(E) Selective reporting (reporting bias)
(F) Other bias

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



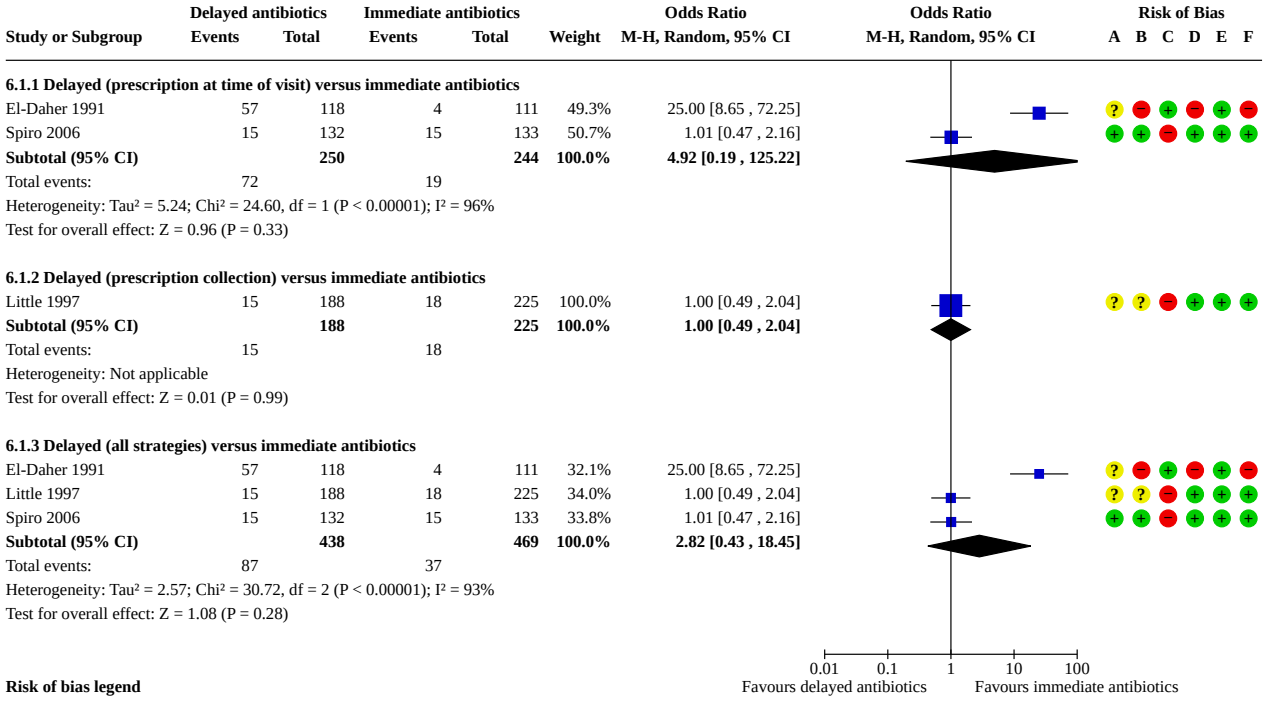
Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding (performance bias and detection bias)
(D) Incomplete outcome data (attrition bias)
(E) Selective reporting (reporting bias)
(F) Other bias

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)	Subtotals only
6.1.1 Delayed (prescription at time of visit) versus immediate antibiotics	2	494	Odds Ratio (M-H, Random, 95% CI)	4.92 [0.19, 125.22]
6.1.2 Delayed (prescription collection) versus immediate antibiotics	1	413	Odds Ratio (M-H, Random, 95% CI)	1.00 [0.49, 2.04]
6.1.3 Delayed (all strategies) versus immediate antibiotics	3	907	Odds Ratio (M-H, Random, 95% CI)	2.82 [0.43, 18.45]
6.2 Vomiting: delayed (prescription collection) versus no antibiotics	1		Odds Ratio (M-H, Random, 95% CI)	Totals not selected
6.3 Diarrhoea: delayed versus immediate antibiotics	4		Odds Ratio (M-H, Random, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.3.1 Delayed (prescription at time of visit) versus immediate antibiotics	2	394	Odds Ratio (M-H, Random, 95% CI)	0.46 [0.15, 1.36]
6.3.2 Delayed (prescription collection) versus immediate antibiotics	2	674	Odds Ratio (M-H, Random, 95% CI)	0.72 [0.26, 2.03]
6.3.3 Delayed (all strategies) versus immediate antibiotics	4	1068	Odds Ratio (M-H, Random, 95% CI)	0.58 [0.29, 1.17]
6.4 Diarrhoea: delayed (prescription collection) versus no antibiotics	1	468	Odds Ratio (M-H, Random, 95% CI)	1.43 [0.74, 2.78]
6.5 Rash: delayed (prescription collection) versus immediate antibiotics	2	665	Odds Ratio (M-H, Random, 95% CI)	0.96 [0.50, 1.85]
6.6 Rash: delayed (prescription collection) versus no antibiotics	1		Odds Ratio (M-H, Random, 95% CI)	Totals not selected

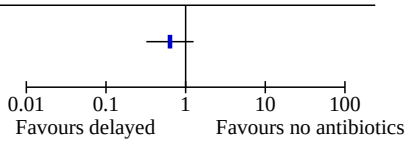
Analysis 6.1. Comparison 6: Adverse events, Outcome 1: Vomiting: delayed versus immediate antibiotics



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding (performance bias and detection bias)
(D) Incomplete outcome data (attrition bias)
(E) Selective reporting (reporting bias)
(F) Other bias

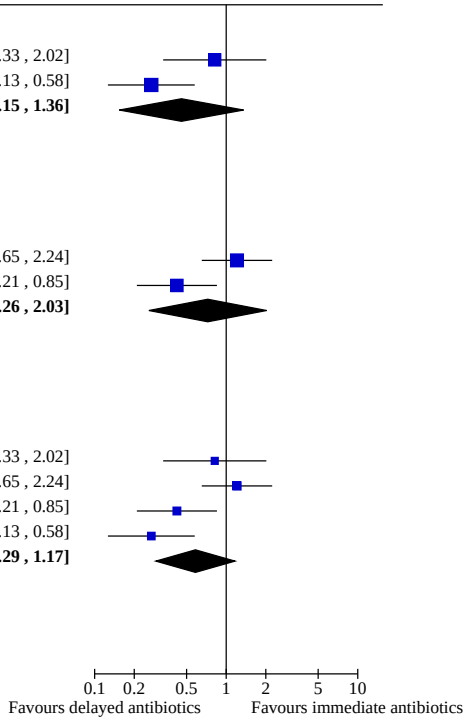
Analysis 6.2. Comparison 6: Adverse events, Outcome 2: Vomiting: delayed (prescription collection) versus no antibiotics

Study or Subgroup	Delayed Events	Delayed Total	No antibiotics Events	No antibiotics Total	Odds Ratio M-H, Random, 95% CI
Little 1997	15	238	22	230	0.64 [0.32 , 1.26]



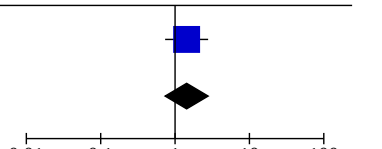
Analysis 6.3. Comparison 6: Adverse events, Outcome 3: Diarrhoea: delayed versus immediate antibiotics

Study or Subgroup	Delayed antibiotics Events	Delayed antibiotics Total	Immediate antibiotics Events	Immediate antibiotics Total	Weight	Odds Ratio M-H, Random, 95% CI
6.3.1 Delayed (prescription at time of visit) versus immediate antibiotics						
Arroll 2002a	11	67	12	62	47.5%	0.82 [0.33 , 2.02]
Spiro 2006	10	132	31	133	52.5%	0.27 [0.13 , 0.58]
Subtotal (95% CI)		**199**		**195**	**100.0%**	**0.46 [0.15 , 1.36]**
Total events:	21		43			
Heterogeneity: Tau² = 0.44; Chi² = 3.41, df = 1 (P = 0.06); I² = 71%						
Test for overall effect: Z = 1.41 (P = 0.16)						
6.3.2 Delayed (prescription collection) versus immediate antibiotics						
Little 1997	23	177	23	209	51.3%	1.21 [0.65 , 2.24]
Little 2001	14	156	25	132	48.7%	0.42 [0.21 , 0.85]
Subtotal (95% CI)		**333**		**341**	**100.0%**	**0.72 [0.26 , 2.03]**
Total events:	37		48			
Heterogeneity: Tau² = 0.44; Chi² = 4.88, df = 1 (P = 0.03); I² = 80%						
Test for overall effect: Z = 0.61 (P = 0.54)						
6.3.3 Delayed (all strategies) versus immediate antibiotics						
Arroll 2002a	11	67	12	62	22.0%	0.82 [0.33 , 2.02]
Little 1997	23	177	23	209	27.5%	1.21 [0.65 , 2.24]
Little 2001	14	156	25	132	25.8%	0.42 [0.21 , 0.85]
Spiro 2006	10	132	31	133	24.7%	0.27 [0.13 , 0.58]
Subtotal (95% CI)		**532**		**536**	**100.0%**	**0.58 [0.29 , 1.17]**
Total events:	58		91			
Heterogeneity: Tau² = 0.36; Chi² = 10.64, df = 3 (P = 0.01); I² = 72%						
Test for overall effect: Z = 1.52 (P = 0.13)						



Analysis 6.4. Comparison 6: Adverse events, Outcome 4: Diarrhoea: delayed (prescription collection) versus no antibiotics

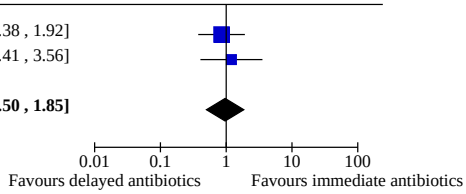
Study or Subgroup	Delayed Events	Delayed Total	No antibiotics Events	No antibiotics Total	Weight	Odds Ratio M-H, Random, 95% CI
Little 1997	23	238	16	230	100.0%	1.43 [0.74 , 2.78]
Total (95% CI)		**238**		**230**	**100.0%**	**1.43 [0.74 , 2.78]**
Total events:	23		16			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.06 (P = 0.29)						
Test for subgroup differences: Not applicable						



Analysis 6.5. Comparison 6: Adverse events, Outcome 5: Rash: delayed (prescription collection) versus immediate antibiotics

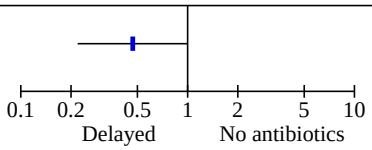
Study or Subgroup	Delayed antibiotics Events	Total	Immediate antibiotics Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Little 1997	11	183	14	200	63.9%	0.85 [0.38 , 1.92]
Little 2001	8	149	6	133	36.1%	1.20 [0.41 , 3.56]
Total (95% CI)		**332**		**333**	**100.0%**	**0.96 [0.50 , 1.85]**
Total events:	19		20			

Heterogeneity: Tau² = 0.00; Chi² = 0.25, df = 1 (P = 0.62); I² = 0%
Test for overall effect: Z = 0.11 (P = 0.91)
Test for subgroup differences: Not applicable



Analysis 6.6. Comparison 6: Adverse events, Outcome 6: Rash: delayed (prescription collection) versus no antibiotics

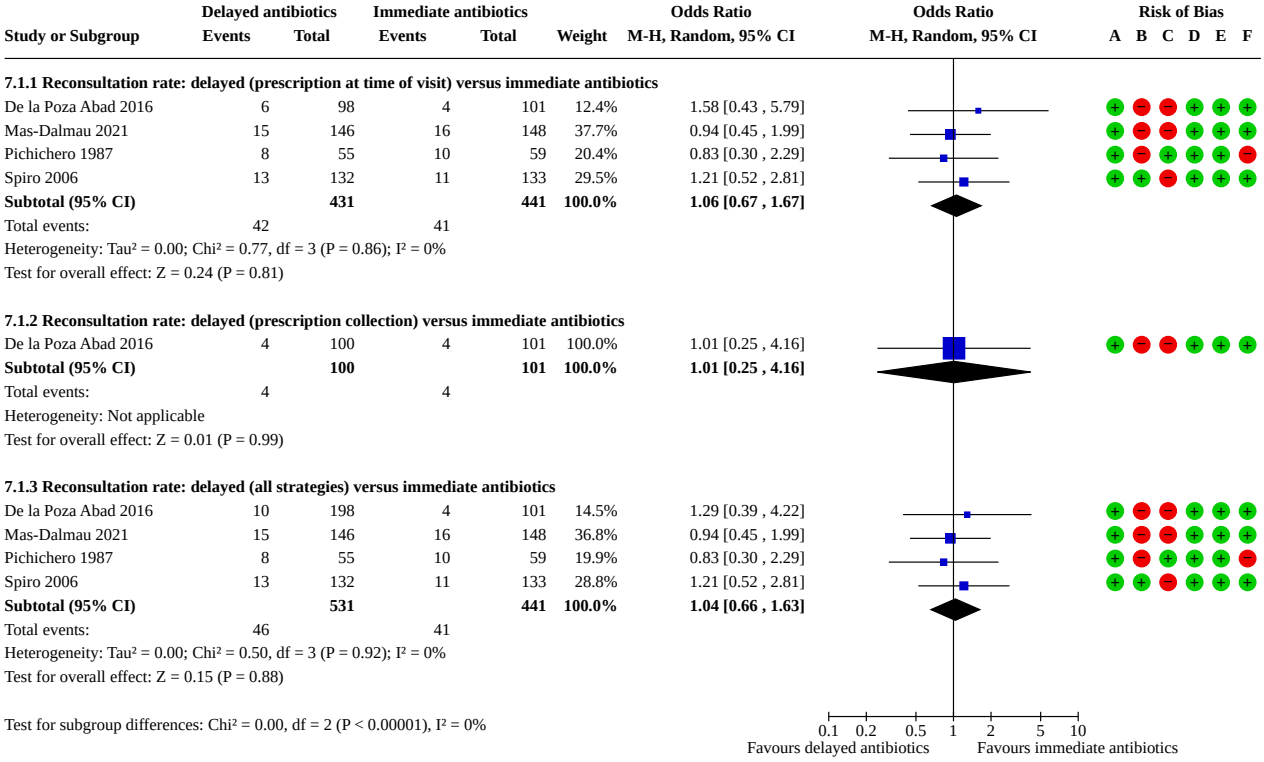
Study or Subgroup	Delayed Events	Total	No antibiotics Events	Total	Odds Ratio M-H, Random, 95% CI
Little 1997	11	183	21	175	0.47 [0.22 , 1.00]



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	4		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
7.1.1 Reconsultation rate: delayed (prescription at time of visit) versus immediate antibiotics	4	872	Odds Ratio (M-H, Random, 95% CI)	1.06 [0.67, 1.67]
7.1.2 Reconsultation rate: delayed (prescription collection) versus immediate antibiotics	1	201	Odds Ratio (M-H, Random, 95% CI)	1.01 [0.25, 4.16]
7.1.3 Reconsultation rate: delayed (all strategies) versus immediate antibiotics	4	972	Odds Ratio (M-H, Random, 95% CI)	1.04 [0.66, 1.63]
7.2 Reconsultation rate: delayed versus no antibiotics	2		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
7.2.1 Reconsultation rate: delayed (prescription at time of visit) versus no antibiotics	2	484	Odds Ratio (M-H, Random, 95% CI)	0.88 [0.47, 1.65]
7.2.2 Reconsultation rate: delayed (prescription collection) versus no antibiotics	1	198	Odds Ratio (M-H, Random, 95% CI)	0.64 [0.17, 2.34]
7.2.3 Reconsultation rate: delayed (all strategies) versus no antibiotics	2	584	Odds Ratio (M-H, Random, 95% CI)	0.83 [0.46, 1.52]

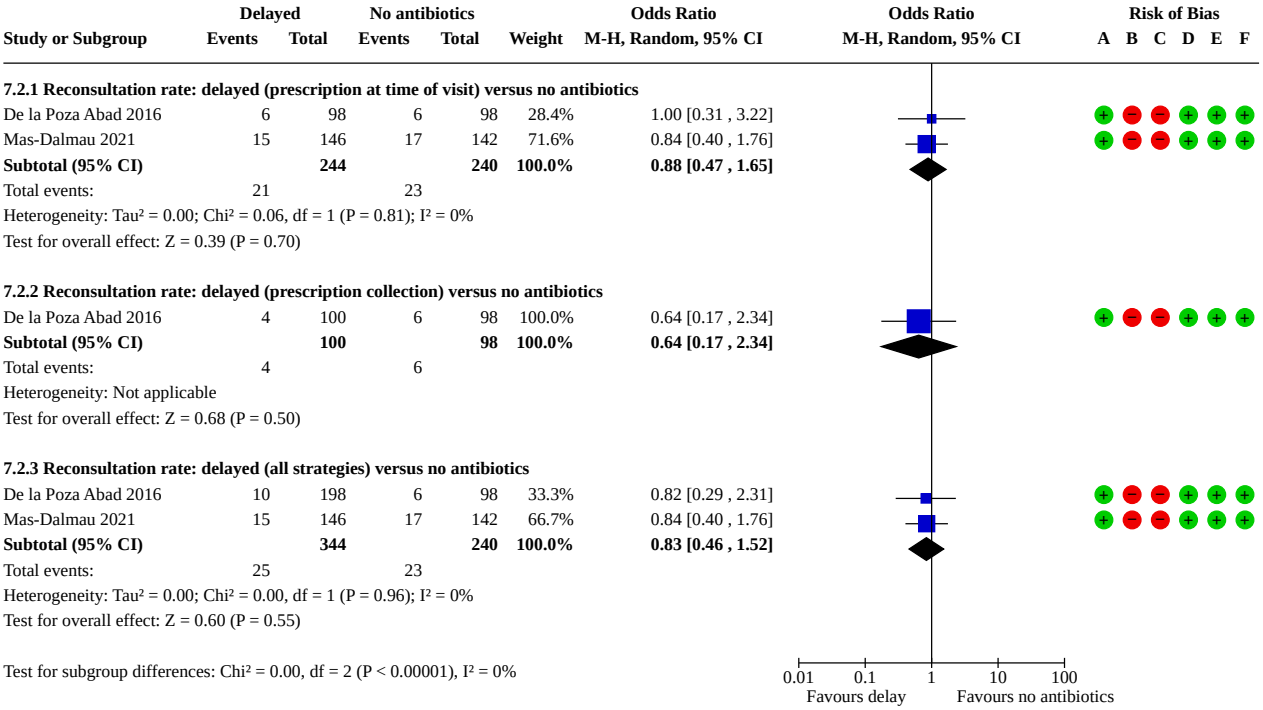
Analysis 7.1. Comparison 7: Reconsultation rate, Outcome 1: Reconsultation rate: delayed versus immediate antibiotics



Study or Subgroup	Delayed antibiotics Events	Total	Immediate antibiotics Events	Total	Weight	Odds Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F
7.1.1 Reconsultation rate: delayed (prescription at time of visit) versus immediate antibiotics							
De la Poza Abad 2016	6	98	4	101	12.4%	1.58 [0.43 , 5.79]	
Mas-Dalmau 2021	15	146	16	148	37.7%	0.94 [0.45 , 1.99]	
Pichichero 1987	8	55	10	59	20.4%	0.83 [0.30 , 2.29]	
Spiro 2006	13	132	11	133	29.5%	1.21 [0.52 , 2.81]	
Subtotal (95% CI)		**431**		**441**	**100.0%**	**1.06 [0.67 , 1.67]**	
Total events:	42		41				
Heterogeneity: Tau² = 0.00; Chi² = 0.77, df = 3 (P = 0.86); I² = 0%							
Test for overall effect: Z = 0.24 (P = 0.81)							
7.1.2 Reconsultation rate: delayed (prescription collection) versus immediate antibiotics							
De la Poza Abad 2016	4	100	4	101	100.0%	1.01 [0.25 , 4.16]	
Subtotal (95% CI)		**100**		**101**	**100.0%**	**1.01 [0.25 , 4.16]**	
Total events:	4		4				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.01 (P = 0.99)							
7.1.3 Reconsultation rate: delayed (all strategies) versus immediate antibiotics							
De la Poza Abad 2016	10	198	4	101	14.5%	1.29 [0.39 , 4.22]	
Mas-Dalmau 2021	15	146	16	148	36.8%	0.94 [0.45 , 1.99]	
Pichichero 1987	8	55	10	59	19.9%	0.83 [0.30 , 2.29]	
Spiro 2006	13	132	11	133	28.8%	1.21 [0.52 , 2.81]	
Subtotal (95% CI)		**531**		**441**	**100.0%**	**1.04 [0.66 , 1.63]**	
Total events:	46		41				
Heterogeneity: Tau² = 0.00; Chi² = 0.50, df = 3 (P = 0.92); I² = 0%							
Test for overall effect: Z = 0.15 (P = 0.88)							
Test for subgroup differences: Chi² = 0.00, df = 2 (P < 0.00001), I² = 0%							

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding (performance bias and detection bias)
(D) Incomplete outcome data (attrition bias)
(E) Selective reporting (reporting bias)
(F) Other bias

Analysis 7.2. Comparison 7: Reconsultation rate, Outcome 2: Reconsultation rate: delayed versus no antibiotics



Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding (performance bias and detection bias)
(D) Incomplete outcome data (attrition bias)
(E) Selective reporting (reporting bias)
(F) Other bias

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 complementary 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 respira-	Adults	Symptom duration and severity, antibiotic use,	Physician structured script and patient information sheet about self-limiting nat-	GPs	4 groups of antibiotic prescription use:	23 primary care centres in 4	Once, at index consultation; *delayed*	All advised to return if no improvement or	None reported	None	None

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

	tory infection		patient satisfaction, patients' beliefs in antibiotic effectiveness, reconsultation rates, adverse effects	ural history of respiratory infection, pros and cons of antibiotics used with patients. Antibiotic prescription as indicated		1) *Immediate* 2) *Delayed*, patient-led prescription 3) *Delayed*, prescription collection 4) *None* *Delayed* = 3 days	regions in Spain	prescription collection group could collect after 3 days if needed	worsening after 5 days (sore throat (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

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

Gerber 1990	GABHS pharyngitis (sore throat)	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 (sore throat)	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	42 GPs	*Immediate*: usual care *Delayed*: wait 3 days to	General practices in Scotland, UK	At index consultation; *delayed* prescription group	Antipyretics were allowed	None reported	Patient diary	No

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

			paracetamol consumption	prescription, and then only if necessary GP used standardised advice sheets specific to each group		collect prescription		asked to 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, leaflet 6) *Immediate* antibiotics, 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
Mas-Dalmau 2021	Acute uncomplicated respira-	Children (2 to 14 years)	Symptom duration and severity, antibi-	Physician structured script and patient information sheet about	Primary care paediatricians	3 groups of antibiotic pre-	39 primary care cen-	At index consultation; delayed	Children in delayed group advised to	None reported	None reported	None reported

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

	tory infection		otic use, parental satisfaction, unscheduled visits, adverse effects	self-limiting natural history of respiratory infection, adverse effects, marginal benefits of antibiotics with parents Antibiotic prescription as indicated		scription use: 1) *Immediate* 2) *Delayed*, patient-led prescription 3) *None* *Delayed* = 4 days for acute otitis media; 7 days for pharyngitis (sore throat); 15 days for rhinosinusitis; 20 days for acute bronchitis	tres in Spain	asked to wait 4 days for acute otitis media; 7 days for pharyngitis (sore throat); 15 days for rhinosinusitis; 20 days for acute bronchitis (cough)	return if parents felt it necessary or if the child felt worse after taking the antibiotics. Children in the immediate or no antibiotics advised to return if did not feel better after 4, 7, 15, or 20 days for acute otitis media, pharyngitis (sore throat), rhinosinusitis, or acute bronchitis (cough) respectively; or if the child had a fever, or felt much worse.			
Pichichero 1987	Sore throat (presumed GABHS pharyngitis)	Children (4 to 18 years)	Symptomatic response, recurrent infections	Drugs supplied directly to patients Usual care 10-day course penicillin V *Delayed* group provided with place-	Study nurse	*Immediate*: usual care *Delayed*: placebo for 3 days then penicillin	Primary care paediatric practice in the USA	At index consultation	Antibiotic (tablet or suspension) Antipyretics were allowed	None reported	Check drug bottles at 3 days and 3 weeks Test urine at	Confirmed in 98% cases (drug bottles); no ABs used in placebo group

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

				bo for first 3 days, then penicillin							3 days for antibiotic	
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

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

Study	Outcome	Delay	Immediate	Favours	Result (95% CI)
Sore throat (pharyngitis)					
Pichichero 1987	Fever severity on Day 3	37.2 °C (SD 1.2, n = 55)	36.8 °C (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)
	Stomach ache	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

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

	Time off work	Unavailable	Unavailable	No difference	Data not available
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)	No difference	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)
Mas-Dalmau 2021	Headache duration	5.5 days (SD 7.0, n = 146)	5.8 days (SD 8.7, n = 148)	No difference	P = 0.867
	Headache severity[a]	3 (IQR 2 to 3)	2 (IQR 1 to 4)	Unavailable	Unavailable
	Sore throat duration	5.0 days (SD 4.1, n = 146)	5.2 days (SD 4.7, n = 148)	No difference	P = 0.824
	Sore throat severity[a]	3 (IQR 2 to 5)	3 (IQR 2 to 3)	Unavailable	Unavailable
	Difficulty swallowing duration	4.7 days (SD 3.8, n = 146)	4.9 days (SD 4.8, n = 148)	No difference	P = 0.812
	Difficulty swallowing severity[a]	3 (IQR 2 to 4)	2 (IQR 2 to 3)	No difference	Unavailable
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)

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

	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)
	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)
Mas-Dalmau 2021	Earache duration	4.4 days (SD 3.9, n = 146)	5.1 days (SD 5.3, n = 148)	No difference	P = 0.239
	Earache severity[a]	2 (IQR 1 to 3)	2 (IQR 1 to 3)	Unavailable	Unavailable
Cough (bronchitis)					
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)

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

	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)
Mas-Dalmau 2021	Cough duration	9.5 days (SD 7.1, n = 146)	7.9 days (SD 4.4, n = 148)	No difference	P = 0.295
	Cough severity[a]	3 (IQR 2 to 3)	2 (IQR 2 to 3)	Unavailable	Unavailable
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)
	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)

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

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
IQR: interquartile range
MD: mean difference
OR: odds ratio
SD: standard deviation
SMD: standardised mean difference
[a]Mas-Dalmau 2021 symptom severity scored on Likert scale from 0 (no problem) to 6 (as bad as it could be) and reported as median (interquartile range (IQR)).

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

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

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

Mas-Dalmau 2021	Headache duration	5.5 days (SD 7.0, n = 146)	3.3 days (SD 3.0, n = 142)	Unavailable	Unavailable
	Headache severity[a]	2 (IQR 2 to 3)	3 (IQR 2 to 4)	Unavailable	Unavailable
	Sore throat duration	5.0 days (SD 4.1, n = 146)	5.5 days (SD 6.2, n = 142)	Unavailable	Unavailable
	Sore throat severity[a]	3 (IQR 2 to 5)	3 (IQR 2 to 4)	Unavailable	Unavailable
	Difficulty swallowing duration	4.7 days (SD 3.8, n = 146)	5.0 days (SD 5.2, n = 142)	Unavailable	Unavailable
	Difficulty swallowing severity[a]	3 (IQR 2 to 4)	2 (IQR 2 to 4)	Unavailable	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)
Mas-Dalmau 2021	Earache duration	4.4 days (SD 3.9, n = 146)	5.2 days (SD 6.3, n = 142)	Unavailable	Unavailable
	Earache severity[a]	2 (IQR 1 to 3)	2 (IQR 2 to 3)	Unavailable	Unavailable
Cough (bronchitis)					
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)
Mas-Dalmau 2021	Cough duration	9.5 (SD 7.1, n = 146)	8.0 (SD 6.6, n = 142)	Unavailable	Unavailable
	Cough severity[a]	3 (IQR = 2-3)	2 (IQR = 1-3)	Unavailable	Unavailable

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
IQR: interquartile range
MD: mean difference
OR: odds ratio
SD: standard deviation
[a]Mas-Dalmau 2021 symptom severity scored on Likert scale from 0 (no problem) to 6 (as bad as it could be) and reported as median (interquartile range (IQR)).

APPENDICES

Appendix 1. CENTRAL, MEDLINE, Embase, CINAHL and Web of Science search strategies

Cochrane Central Register of Controlled Trials (CENTRAL)

#1 [mh “Respiratory Tract Infections”]
#2 ((upper next respiratory next tract infection*) or URTI):ti,ab,kw
#3 [mh “Otitis Media”]
#4 (otitis next media):ti,ab,kw
#5 [mh Pharyngitis]
#6 pharyngitis:ti,ab,kw
#7 [mh Tonsillitis]
#8 tonsillitis:ti,ab,kw
#9 [mh “Common Cold”]
#10 (common next cold*):ti,ab,kw
#11 [mh Bronchitis]
#12 bronchitis:ti,ab,kw

#13 [mh Sinusitis]
#14 sinusitis:ti,ab,kw
#15 (sore next throat*):ti,ab,kw
#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
#17 [mh “Anti-Bacterial Agents”]
#18 antibiotic*:ti,ab,kw
#19 #17 or #18
#20 (delay* near/15 prescri*):ti,ab,kw
#21 #16 and #19 and #20

MEDLINE (via Ovid)

1. exp Respiratory Tract Infections/
2. (upper respiratory tract infection$ or urti).mp.
3. exp Otitis Media/
4. otitis media.mp.
5. exp Pharyngitis/
6. pharyngitis.mp.
7. exp Tonsillitis/
8. tonsillitis.mp.
9. exp Common Cold/
10. common cold.mp.
11. exp Bronchitis/
12. bronchitis.mp.
13. exp Sinusitis/
14. sinusitis.mp.
15. sore throat$.mp.
16. or/1-15
17. exp Anti-Bacterial Agents/
18. antibiotic$.mp.
19. or/17-18
20. (delay$ adj15 prescri$).mp.
21. 16 and 19 and 20

Embase (via Elsevier)
#22. #17 AND #20 AND #21
#21. (delay* NEAR/15 prescri*):ti,ab,de,tn
#20. #18 OR #19
#19. 'antibiotic':ti,ab,de,tn OR 'antibiotics':ti,ab,de,tn
#18. 'antibiotic agent'/exp
#17. #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 OR #16
#16. 'sore throat':ti,ab,de,tn OR 'sore throats':ti,ab,de,tn
#15. sinusitis:ti,ab,de,tn
#14. 'sinusitis'/exp
#13. bronchitis:ti,ab,de,tn
#12. 'bronchitis'/exp
#11. 'common cold':ti,ab,de,tn
#10. 'common cold'/exp
#9. tonsillitis:ti,ab,de,tn
#8. 'tonsillitis'/exp
#7. pharyngitis:ti,ab,de,tn
#6. 'pharyngitis'/exp
#5. 'otitis media':ti,ab,de,tn
#4. 'otitis media'/exp
#3. 'upper respiratory tract infection':ti,ab,de,tn OR 'upper respiratory tract infections':ti,ab,de,tn OR urti:ti,ab,de,tn
#2. 'upper respiratory tract infection'/exp
#1. 'respiratory tract infection'/exp

CINAHL Plus (via EBSCO)
S15 S10 and S13 and S14
S14 TI delay* N15 prescri* or AB delay* N15 prescri*
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, 9 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
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, 18 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 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 October 2022	New search has been performed	We updated the search on 20 August 2022 and included one new trial with 448 children (436 analysed) (Mas-Dalmau 2021). We excluded one new trial (Ghebrehewet 2020).
4 October 2022	New citation required but conclusions have not changed	Our conclusions remain unchanged.

HISTORY

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

Date	Event	Description
10 August 2022	Amended	Moved out of living mode.
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-

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.

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

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.

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

CONTRIBUTIONS OF AUTHORS

Geoffrey Spurling (GS) designed the review, performed literature searches, edited and entered data into Review Manager 5, and secured funding for previous versions of this review. Independently screened titles and abstracts of the studies identified, extracted outcome data and approved the final version of this 2022 update.
Liz Dooley (LD) appraised articles, extracted data and entered data into Review Manager 5 for previous versions of this review. Edited and approved the final version of this 2022 update.
Justin Clark (JC) designed and ran the monthly updated search strategies, independently screened titles and abstracts of the studies identified, extracted outcome data and approved the final version of this 2022 update.
Deborah Askew (DA) entered data into RevMan Web for this update, edited and approved the final version of the 2022 update.

DECLARATIONS OF INTEREST

Geoffrey KP Spurling has declared that they have no conflict of interest.
Liz Dooley has declared that they have no conflict of interest.
Deborah A Askew has declared that they have no conflict of interest.
Justin Clark has declared that he has no conflict of interest.

SOURCES OF SUPPORT

Internal sources

- Bond University, Gold Coast, Australia

  For providing the infrastructure that allowed the updates of this review to be conducted.
- 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

- No sources of support provided

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In the 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.

In this 2022 update, we expanded the outcomes to include duration of symptoms, as these outcomes are very important to clinicians and patients. This update includes summary of findings tables, which were not specified in the protocol (Spurling 2003). We also changed the title from 'Delayed antibiotic prescriptions for respiratory infections' to 'Immediate versus delayed versus no antibiotics for respiratory infections'.

INDEX TERMS

Medical Subject Headings (MeSH)

Anti-Bacterial Agents [adverse effects]; *Common Cold [complications] [drug therapy]; Cough [drug therapy]; Fever [drug therapy] [etiology]; *Otitis Media [drug therapy]; Pain [drug therapy]; *Pharyngitis [drug therapy]; *Respiratory Tract Infections [drug therapy]

MeSH check words

Adult; Child; Humans