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Delayed antibiotics for respiratory infections (Review)

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[Intervention Review]

Delayed antibiotics for respiratory infections

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

[1]Discipline of General Practice, University of Queensland, Herston, Australia. [2]Centre for Research in Evidence-Based Practice (CREBP), Bond University, Gold Coast, Australia. [3]Faculty of Health Sciences and Medicine, Bond University, Gold Coast, Australia. [4]Department of Health Sciences, University of York, York, UK

Contact address: Geoffrey KP Spurling, Discipline of General Practice, University of Queensland, Level 8, Health Sciences Building 16/910, Royal Brisbane and Women's Hospital, Herston, Queensland, 4029, Australia. g.spurling@uq.edu.au. geoffspurling@optusnet.com.au.

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ABSTRACT

Background

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

Objectives

To evaluate the use of *delayed* antibiotics compared to *immediate* or *no* antibiotics as a prescribing strategy for ARTIs. We evaluated clinical outcomes including duration and severity measures for pain, malaise, fever, cough and rhinorrhoea in sore throat, acute otitis media, bronchitis (cough) and the common cold. We also evaluated the outcomes of antibiotic use, patient satisfaction, antibiotic resistance and re-consultation rates and use of alternative therapies.

Search methods

We searched CENTRAL (*The Cochrane Library* 2013, Issue 2), which includes the Acute Respiratory Infection Group's Specialised Register; Ovid MEDLINE (January 1966 to February Week 3 2013); Ovid MEDLINE In-Process & Other Non-Indexed Citations (28 February 2013); EMBASE (1990 to 2013 Week 08); Science Citation Index - Web of Science (2007 to May 2012) and EBSCO CINAHL (1982 to 28 February 2013).

Selection criteria

Randomised controlled trials (RCTs) involving participants of all ages defined as having an ARTI, where *delayed* antibiotics were compared to antibiotics used *immediately* or *no* antibiotics.

Data collection and analysis

Three review authors independently extracted and collected data. Important adverse effects, including adverse effects of antibiotics and complications of disease, were included as secondary outcomes. We assessed the risk of bias of all included trials. We contacted trial authors to obtain missing information where available.

Main results

Ten studies, with a total of 3157 participants, were included in this review. Heterogeneity of the 10 included studies and their results generally precluded meta-analysis with patient satisfaction being an exception.

There was no difference between *delayed*, *immediate* and *no* prescribed antibiotics for the clinical outcomes evaluated in cough and common cold. In patients with acute otitis media (AOM) and sore throat *immediate* antibiotics were more effective than *delayed* for fever, pain and malaise in some studies. There were only minor differences in adverse effects with no significant difference in complication rates.

Delayed antibiotics resulted in a significant reduction in antibiotic use compared to *immediate* antibiotics. A strategy of *no* antibiotics resulted in least antibiotic use.

Patient satisfaction favoured *immediate* antibiotics over *delayed* (odds ratio (OR) 0.52; 95% confidence interval (CI) 0.35 to 0.76). *Delayed* and *no* antibiotics had similar satisfaction rates with both strategies achieving over 80% satisfaction (OR 1.44; 95% CI 0.99 to 2.10).

There was no difference in re-consultation rates for *immediate* and *delayed* groups.

None of the included studies evaluated antibiotic resistance.

Authors' conclusions

Most clinical outcomes show no difference between strategies. *Delay* slightly reduces patient satisfaction compared to *immediate* antibiotics (87% versus 92%) but not compared to *none* (87% versus 83%). In patients with respiratory infections where clinicians feel it is safe not to prescribe antibiotics *immediately*, *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.

PLAIN LANGUAGE SUMMARY

Delayed antibiotics for symptoms and complications of acute respiratory tract infections

Previous reviews indicate that antibiotics have, at best, only modest benefit for acute respiratory tract infections (ARTIs). These benefits need to be balanced against adverse effects, costs and the risk of bacteria becoming resistant to antibiotics. One way for doctors to reduce their use is to prescribe *delayed* antibiotics (meaning providing the prescription but advising the patient/carer to delay their use in the hope that symptoms resolve first). *Delayed* prescribing resulted in 32% of patients using antibiotics compared to 93% of patients in the *immediate* prescription group. However, *not* prescribing antibiotics at all results in the least antibiotic prescribing (14% of patients used antibiotics).

This review found 10 studies, involving 3157 participants, looking at prescribing strategies for respiratory infections. It was generally not possible to combine results from different studies because of incomplete information from some studies and the different types of patients in each study. There were only three trials comparing the strategies of *delayed* and *no* antibiotics.

For most symptoms like fever, pain and malaise, there was no difference between *immediate*, *delayed* and *no* antibiotics. The only differences were small and favoured *immediate* antibiotics for relieving pain and fever for sore throat and pain and malaise for middle ear infections. There was little difference in adverse effects of antibiotics for the three prescribing strategies and no significant difference in complication rates.

Patient satisfaction was slightly reduced in the *delayed* antibiotic group (87% satisfied) compared to the *immediate* antibiotic group (92% satisfied). Satisfaction rates were similar between *delayed* and *no* antibiotic groups (83% satisfied).

No included studies evaluated antibiotic resistance.

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, while maintaining similar patient satisfaction and symptom outcomes.

BACKGROUND

Description of the condition

The use of antibiotics for acute respiratory tract infections (ARTIs) is controversial. Empirical evidence suggests that antibiotics have only a modest benefit in acute otitis media (AOM) (Venekamp 2013), pharyngitis (Spinks 2011) and acute bronchitis (Smith 2011) and no effect in the common cold (Arroll 2010). Any benefits have to be weighed up against common adverse reactions (including rash, abdominal pain, diarrhoea and vomiting) and cost (Berman 1997; Niemela 1999). Over-prescribing may also contribute to community bacterial resistance to antibiotics (Arason 1996; Brook 1998; Verkatesum 1995).

Description of the intervention

There has been interest in strategies to reduce antibiotic prescribing for ARTIs. One of these strategies is to advise patients to 'delay' filling their script and only to fill it if their symptoms persist or deteriorate. *Delayed* antibiotics are 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 (with instructions not to use unless there is deterioration); and making the prescription available at the clinic reception (to be picked up in the event of deterioration).

How the intervention might work

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

A systematic review showed that using *delayed* antibiotics in ARTIs significantly reduces antibiotic prescribing (Arroll 2003a). The reduction ranges from a risk ratio (RR) of 0.77 (95% confidence interval (CI) 0.73 to 0.81) (Dowell 2001) to RR 0.25 (95% CI 0.19 to 0.34) (Little 1997).

Why it is important to do this review

The *delayed* antibiotic strategy has also been advocated more recently as a safety net for avoiding rare but important complications of initially uncomplicated ARTIs (Little 2005b). The same authors also advocated *delayed* antibiotics for reducing antibiotic use, allowing adequate control of symptoms, while providing high levels of patient satisfaction (Little 2005b).

This review asks specifically what effect *delayed* antibiotics have on clinical outcomes of ARTIs compared to *immediate* antibiotics and *no* antibiotics. This review also evaluates the available data on antibiotic use, patient satisfaction and antibiotic resistance for the three prescribing strategies of *delayed* antibiotics, *immediate* antibiotics and *no* antibiotics. This is an update of a Cochrane Review originally published in 2007 (Spurling 2007), with an updated version published in 2010 (Spurling 2010).

OBJECTIVES

To evaluate the use of *delayed* antibiotics compared to *immediate* or *no* antibiotics as a prescribing strategy for ARTIs. We aimed to evaluate clinical outcomes including duration and severity measures for pain, malaise, fever, cough and rhinorrhoea in sore throat, AOM, bronchitis (cough) and the common cold. We also aimed to evaluate the outcomes of antibiotic use, patient satisfaction, antibiotic resistance and re-consultation rates and use of alternative therapies.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) studying the treatment of ARTIs with *delayed* antibiotics versus *immediate* or *no* antibiotics. Open randomised trials were accepted.

Types of participants

Patients of all ages defined as having ARTIs.

Types of interventions

1. '*Delayed* antibiotic use' was 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' was defined as the immediate use of a prescription of oral antibiotics given at the initial consultation.
3. '*No* antibiotic use' was defined as no prescription of antibiotics at the initial consultation.

Types of outcome measures

Primary outcomes

We compared *delayed* antibiotics with *immediate* antibiotics and *delayed* antibiotics with *no* antibiotics where data were available.

1. Clinical outcomes for sore throat, AOM, 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 (where patient satisfaction is measured on a four to six-point Likert scale; we defined satisfaction as including both satisfied and very satisfied)
4. Antibiotic resistance

Secondary outcomes

1. Adverse effects of antibiotics
2. Complications of disease
3. Re-consultation
4. Use of alternative therapies

Search methods for identification of studies

Electronic searches

For this updated review we searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2013, Issue 2), which includes the Acute Respiratory Infection Group's Specialised Register; Ovid MEDLINE (January 1966 to February Week 3 2013); Ovid MEDLINE In-Process & Other Non-Indexed Citations (28 February 2013); EMBASE (1990 to 2013 Week 08); Science Citation Index - Web of Science (2007 to May 2012) and EBSCO CINAHL (1982 to 28 February 2013).

In the original version of this review MEDLINE was searched using the following keywords and MeSH terms in conjunction with the highly sensitive search strategy designed by The Cochrane Collaboration for identifying randomised controlled trials (Dickersin 1994). For this update we applied no trial filters. We used the MEDLINE search strategy to search CENTRAL (Appendix 1) and adapted this to search EMBASE (Appendix 2) and CINAHL (Appendix 3).

Ovid MEDLINE

1 exp Respiratory Tract Infections/ (114895)
2 (upper respiratory tract infection$ or urti).mp. (2482)
3 exp Otitis Media/ (8289)
4 otitis media.mp. (10100)
5 exp Pharyngitis/ (4870)
6 pharyngitis.mp. (3733)
7 exp Tonsillitis/ (2065)
8 tonsillitis.mp. (2423)
9 exp Common Cold/ (1492)
10 common cold.mp. (2207)
11 exp Bronchitis/ (8275)
12 bronchitis.mp. (8027)
13 exp Sinusitis/ (8071)
14 sinusitis.mp. (10465)
15 sore throat$.mp. (2080)
16 or/1-15 (133707)
17 exp Anti-Bacterial Agents/ (215537)
18 antibiotic$.mp. (127408)
19 or/17-18 (278179)
20 (delay$ adj15 prescri$).mp. (474)
21 and/16,19-20 (55)

There were no language or date of publication restrictions in any of the electronic database searches.

Searching other resources

We scanned abstracts from the search results to identify trials that loosely met the inclusion criteria. We checked references of all relevant retrieved trials to identify any other articles.

Data collection and analysis

Selection of studies

In the original publication of this review, we scanned abstracts from the initial search results to identify trials that loosely met the inclusion criteria. We checked references of all relevant retrieved trials to identify any other articles. Three review authors (RFo, LD, CDM) independently reviewed the full-text articles of the retrieved trials.

In the 2010 update, one further study was found to meet the inclusion criteria (Chao 2008) and two review authors (LD, CDM) independently assessed the methodological quality of the new included study that met the inclusion criteria at that time (Chao 2008).

Similarly, in this updated review (2013), three authors (RFo, GS, RFa) scanned abstracts from the updated searches to identify trials that met the inclusion criteria, checking the references of all retrieved trials to identify other articles. Three review authors (LD, CDM, RFa) independently reviewed the full-text articles of the retrieved trials and applied the inclusion criteria.

We identified two papers, Little 2006 and Moore 2009, as reporting longer-term outcomes from previously included studies (Little 2001; Little 2005a).

Data extraction and management

In the initial publication of this review, three review authors (RFo, LD and CDM) independently extracted data for each study trial

to be included. We extracted data in a blinded manner (that is, without the knowledge of the study results, the names of the authors, institutions or journal of publication). We extracted additional data from graphs of the published articles of El-Daher 1991 and Pichichero 1987 on fever severity and symptom scores.
In this most recent update (2013), two review authors (LD, CDM) independently extracted data from the two new included papers. We contacted the authors of Little 2006 to obtain original data for the outcomes of earache at three months and one year that had been reported as odds ratios (ORs) in the published trial. The complete data were unavailable and there was some inconsistency between what was provided and the published numbers. These results have been included in the text of this review, in the form of the published ORs.

Assessment of risk of bias in included studies

In the first publication of this review three review authors (RFo, LD, CDM) independently assessed the quality of each of the study trials that met the inclusion criteria. We resolved disagreements by consensus. Assessment was blinded (that is, without the knowledge of the study results, the names of the authors, institutions or journal of publication).
We rated the quality of each eligible RCT according to the 'Risk of bias' tool available in RevMan 5.2 and criteria set out in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We assessed methodological quality under the headings of allocation, blinding, incomplete outcome data, selective reporting and other potential sources of bias.
Two review authors (LD, CDM) independently assessed the methodological quality of the trial included in the 2010 update. We resolved disagreements by discussion.

Measures of treatment effect

We analysed data using RevMan 5.2. We expressed continuous data comparisons using mean differences (MD) where there was one study or standardised MD where more than one study used different measurement scales. We expressed dichotomous data using odds ratios (OR). We pooled data into clinical outcomes where multiple trial results for the same clinical presentation existed and there was no heterogeneity.

Unit of analysis issues

The units of analysis for each outcome are the individual research participants.

Dealing with missing data

Six studies included an intention-to-treat (ITT) analysis. Three other studies described their minimal drop-out rates. One study (El-Daher 1991) did not discuss the drop-out rate, though it was small.

Assessment of heterogeneity

We did not undertake a meta-analysis for most clinical outcomes owing to multiple analyses with only one or two study results. We pooled results where satisfactorily low I^2 statistic and non-significant Chi^2 test results were found. We did not undertake a meta-analysis for antibiotic use owing to the heterogeneity of the included study results, likely owing to different antibiotic indications for different clinical presentations.

Assessment of reporting biases

Two studies collected data on clinical outcomes yet did not report them in detail (Dowell 2001; Gerber 1990). In both cases, the studies reported that there was no difference between control and intervention groups.

Data synthesis

Most of the data in this review are reported as a narrative synthesis describing outcome measures. As indicated previously, we pooled results where satisfactorily low I^2 statistic and non-significant Chi^2 test results were found. We undertook a meta-analysis for the outcomes of fever for sore throat and patient satisfaction.

Subgroup analysis and investigation of heterogeneity

Subgroup analyses were considered for all outcomes and included year of publication, clinical presentation, differences in the intervention and risk of bias.
We describe in the results section the two subgroup analyses that showed differences in outcomes. We explored heterogeneity of antibiotic use in delayed antibiotic arms further with analysis of different methods of the delay strategy. We explored heterogeneity of patients satisfaction further with respect to blinding of outcome assessor and patient.

RESULTS

Description of studies

Results of the search

Searches conducted for this review have resulted in 244 articles being identified by electronic searching; 28 were retrieved for more detailed evaluation and 17 studies have been formally evaluated. Five studies were excluded and are described in the Excluded studies section. Two studies identified in this 2013 update reported longer-term outcomes from previously included studies (Little 2006; Moore 2009) and while their data have been added to this review, they are considered part of the original included studies.

Ten trials were eligible for inclusion. They included 1159 participants in their *delayed* antibiotic arm, with 1067 participants in the *immediate* antibiotic arm of nine trials and 465 participants in the *no* antibiotic arm of three trials.

In this most recent update (2013), following removal of duplicated studies, searches resulted in the identification of 77 articles (out of the 244 previously mentioned). Five articles were retrieved for further evaluation (out of 28). Three studies were excluded (out of a total of five) because they were not randomised. The remaining two reported longer-term outcomes from previously included studies (Little 2006; Moore 2009) and while their data have been added to this review, they are considered part of the original included studies. Therefore, there are no more included studies as a result of this 2013 update.

Included studies

Nine trials compared *immediate* antibiotics with delayed antibiotics. Four of these trials investigated acute pharyngitis/sore throat; two with AOM; two with cough and one dealt with the common cold. Early studies of sore throat (El-Daher 1991; Gerber 1990; Pichichero 1987) 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. Subsequent trials (Arroll 2002a; Dowell 2001; Little 1997; Little 2001; Spiro 2006) comparing delayed antibiotics and *immediate* antibiotics were conducted with a view to evaluate the use of *delayed* antibiotics to reduce the use of antibiotics for upper respiratory tract infections (RTIs).

Three studies compared the prescribing strategy of *no* antibiotics with *delayed* antibiotics (Chao 2008; Little 1997; Little 2005a). These three trials investigated the presentations of sore throat (Little 1997), cough (Little 2005a) and AOM (Chao 2008). This last trial (Chao 2008) also asked patients in the *no* antibiotic arm to return if their symptoms had not resolved.

Excluded studies

Since the first publication of this review, five trials have been excluded. One because it used a before-and-after study design (Cates 1999) and four because they were not randomised.

Risk of bias in included studies

Summaries of the bias in included studies are provided in Figure 1 and Figure 2.

Figure 1. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.

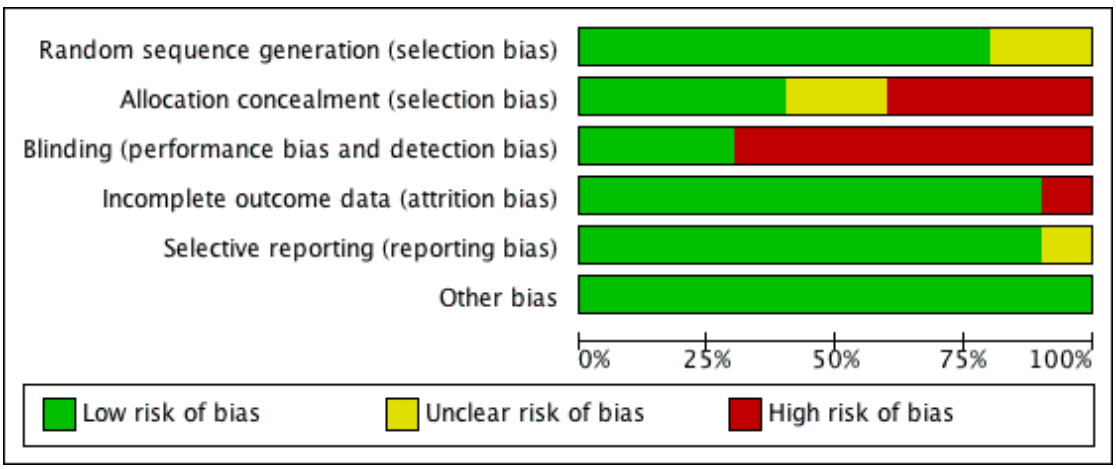
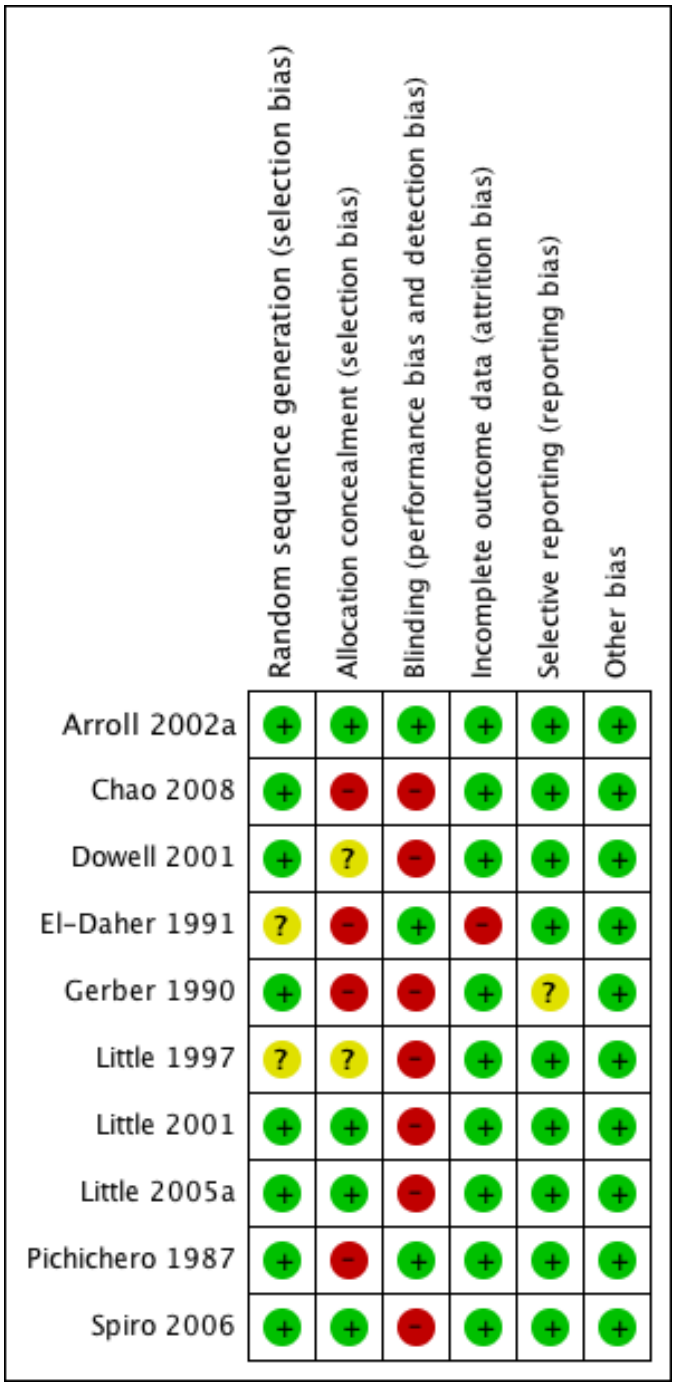


Figure 2. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.



Allocation

Eight included studies were adequately randomised using random number tables or computer-generated randomisation. In two studies the method of randomisation was not described (El-Daher 1991; Little 1997). Only four trials described adequate allocation concealment using opaque envelopes (Arroll 2002a; Little 2001; Little 2005a; Spiro 2006)

Blinding

Three studies attempted to blind the patient and the doctor without mentioning the outcome assessor (Arroll 2002a; El-Daher 1991; Pichichero 1987). In one study patients were told only that they would be given one of two sets of instructions about taking antibiotics for their colds. Participants read an information sheet and then completed a consent form. Thus, patients were blinded to what the other group would take (Arroll 2002a). Two studies used placebo tablets to blind patients (El-Daher 1991; Pichichero 1987). Seven studies attempted to blind some or all aspects of the study; that is, the patients, the doctor and the outcome assessor. For four studies (Chao 2008; Dowell 2001; Little 2005a; Spiro 2006), the outcomes assessor was blinded but not the patient or the care giver. For the remaining three studies no blinding was undertaken (Gerber 1990; Little 1997; Little 2001).

Incomplete outcome data

Only one trial (El-Daher 1991) had incomplete outcome data and did not adequately address it.

Selective reporting

Only one trial (Gerber 1990) reported collecting important information (in this case related to clinical outcomes) without fully reporting it.

Other potential sources of bias

No other sources of bias were identified.

Effects of interventions

For most outcomes meta-analyses were not possible: some studies did not describe their data in sufficient detail and others were too heterogeneous to safely allow meta-analysis. Therefore, few forest plots have more than one study. Table 1 summarises the statistical outcomes available for each study. However, for patient satisfaction, data were available and homogenous, so pooled results using a random-effects model are presented. For sore throat, two trials with minimal heterogeneity have been pooled for the outcome of fever severity on day three.

Results are outlined under the headings of clinical outcomes, antibiotic use and patient satisfaction in order to reflect the important clinical considerations relevant to the strategy of prescribing *delayed* antibiotics. The strategy of *delayed* antibiotics is compared to the strategies of *immediate* antibiotics and *no* antibiotics, depending on the available data. For each illness category there is at least one RCT (for example, common cold) with a maximum of four (sore throat). Given the low numbers of trials for each illness category, conclusions for illness categories need to be treated with caution. The multiplicity of comparisons for the clinical outcomes stratified by illness, makes a type I error more likely. However, clinical outcomes are stratified by illness owing to known differences in the effect of antibiotics on different types of respiratory infections. Antibiotic use and patient satisfaction data have been presented without this stratification as they are less likely to be affected by illness type and to show more clearly the effect of prescribing strategies.

Clinical outcomes

See Table 1.

Sore throat

Four included studies examined sore throat (El-Daher 1991; Gerber 1990; Little 1997; Pichichero 1987).

Delayed antibiotics versus immediate antibiotics

Pain was reduced on day three in the *immediate* antibiotic group compared to *delayed* antibiotics in one study (Analysis 1.1). Pain was not significantly different between *delayed* and *immediate* antibiotic groups in three studies (Gerber 1990; Little 1997; Pichichero 1987).

Malaise was reduced on day three in the *immediate* antibiotic group compared to *delayed* antibiotics in one study (Analysis 2.1) and no difference was found in the other study measuring this outcome (Analysis 2.2).

Fever severity on day three was reduced with *immediate* antibiotics compared to *delayed* antibiotics in two studies (pooled results odds ratio (OR) 0.53; 95% confidence interval (CI) 0.31 to 0.74) (Analysis 3.1). The number of days with fever was reduced in the *immediate* antibiotic group of Little 1997 and there was no difference found in the fourth study (Gerber 1990).

Delayed antibiotics versus no antibiotics

One study examining sore throat compared the prescribing strategy of *delayed* antibiotics with *no* antibiotics (Little 1997). This study found no difference in any clinical outcome between these two prescribing strategies.

Complications

Data on complications of sore throat such as rheumatic fever, post-streptococcal glomerulonephritis and peri-tonsillar abscess were not reported in any of the four studies looking at sore throat for the three prescribing strategies of *immediate*, *delayed* and *no* antibiotics.

Acute otitis media (AOM)

Three included trials examined AOM (Chao 2008; Little 2001; Spiro 2006).

Delayed antibiotics versus immediate antibiotics

Pain and malaise were greater using *delayed* antibiotics compared to *immediate* antibiotics in one study measuring these outcomes on day three (Analysis 4.1). One study examined clinical outcomes on days four to six and found no difference (Analysis 5.1).
Other proxies for malaise outcomes reported by Little 2001 included last day of crying, which favoured the *immediate* antibiotic group by approximately 16 hours in children with AOM (0.69 days; 95% CI 0.31 to 0.07). In the same study, just over half a spoon of paracetamol a day less was used in the *immediate* antibiotic group (0.59; 95% CI 0.25 to 0.93). On day one there were no significant differences between *immediate* and *delayed* antibiotic groups in symptom outcome measures and by day seven there was no difference between *immediate* and *delayed* antibiotic groups (Little 2001).
Further analysis of earache from one trial (Little 2001) found the *delayed* prescribing strategy did not significantly increase risk of earache at three months (OR 0.89; 95% CI 0.48 to 1.65) or one year (OR 1.03; 95% CI 0.60 to 1.78) (Little 2006).

Delayed antibiotics versus no antibiotics

Only one study compared *delayed* antibiotics with *no* antibiotics with no significant difference for pain or fever on day three (Analysis 8.1; Analysis 9.1). This trial also advised participants in the *no* antibiotic arm to re-present in two to three days if symptoms did not resolve.

Complications

Data on complications of AOM such as mastoiditis, rheumatic fever and post-streptococcal glomerulonephritis were not reported in any of the three studies looking at AOM for the prescribing strategies of *immediate* and *delayed* antibiotics. However, Spiro 2006 and Chao 2008 noted that there were no serious adverse events for participants in the study.

Bronchitis (cough)

Two studies examined the prescribing strategies of *immediate* versus *delayed* antibiotics for the clinical presentation of cough (Dowell 2001; Little 2005a) and neither found any difference in clinical outcomes, including fever and cough.

Complications

Little 2005a also looked at *delayed* antibiotics versus *no* antibiotics and found no difference in clinical outcomes between the two prescribing strategies. One patient in the *no* antibiotic group (out of 273) of this study developed pneumonia and recovered with antibiotics in hospital.
Dowell 2001 did not report on complications in the *immediate* and *delayed* antibiotic groups.

Common cold

One study looked at *immediate* antibiotics versus *delayed* antibiotics (Arroll 2002a) and found no difference between the two prescribing strategies for the clinical outcomes of fever, cough, pain and malaise (Analysis 10.1; Analysis 11.4; Analysis 12.1).

Antibiotic use

See Table 1.

Delayed antibiotics

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. Compliance in both *immediate* and *delayed* antibiotic groups was close to 100%. 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. 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 resulted in 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.
Overall, the seven trials post 1992 providing a *delayed* antibiotic arm found 295 prescriptions filled out of 923 participants (32.0%).

Immediate antibiotics

Six trials published post 1992 provided *immediate* antibiotic arms examining this outcome resulting in 790 participants filling prescriptions out of 847 participants (93.3%) (Analysis 13.1).

No antibiotics

Three studies compared *delayed* antibiotics with *no* antibiotics. Little 1997 found that there was less antibiotic use with the *no* antibiotic strategy compared to *delayed* antibiotics. Little 2005a found no differences. Chao 2008 is the most recent and only study conducted comparing *delayed* antibiotics only with *no* antibiotics and also found that fewer antibiotics were prescribed in the *no* antibiotic group (Analysis 15.1).
Overall, 65 patients filled scripts out of 466 participants (13.9%).

Patient satisfaction

See Table 1.

Delayed antibiotics versus immediate antibiotics

(Analysis 16.1)
Patient satisfaction has been measured in five out of seven studies evaluating the prescribing strategy of *delayed* antibiotics since 1992 (Arroll 2002a; Dowell 2001; Little 1997; Little 2001; Little 2005a). Two of these studies indicated that study participants were more satisfied with the strategy of *immediate* antibiotics than *delayed* antibiotics (Little 2001; Little 2005a). There was no difference found in the other three studies (Arroll 2002a; Dowell 2001; Little 1997). The pooled result for this outcome with these five studies was an odds ratio (OR) of 0.52 (95% CI 0.35 to 0.76) favouring *immediate* antibiotics. Fixed- and random-effects analyses gave similar results. A breakdown of the trials by blinding gave two trials (Dowell 2001; Little 2005a) which blinded the outcome assessor and one blinded the patient and the doctor (Arroll 2002a) to give an odds ratio for all three studies of 0.62 (95% CI 0.38 to 1.01). The two completely unblinded trials (Little 1997; Little 2001) give an OR of 0.42 (95% CI 0.22 to 0.78). Overall 92% of the participants in the immediate antibiotics arms were satisfied versus 87% in the delayed arms.

Delayed antibiotics versus no antibiotics

(Analysis 17.1)
Three studies examined patient satisfaction comparing the prescribing strategies of *delayed* antibiotics and *no* antibiotics (Chao 2008; Little 1997; Little 2005a). While there was no difference in patient satisfaction for any of these studies, the pooled result for these three studies was an odds ratio of 1.44 (95% CI 0.99 to 2.10) showing no statistically significant difference. Fixed- and random-effects analyses gave similar results. A breakdown of the trials by blinding gave two trials (Chao 2008; Little 2005a) which blinded the outcome assessor to give an odds ratio for these two trials of 1.42 (95% CI 0.92 to 2.19). The one completely unblinded trial (Little 1997) gave an odds ratio of 1.49 (95% CI 0.70 to 3.19). In the *delayed* antibiotic arm 413 of the participants were satisfied or very satisfied out of 473 participants (87.3%) compared to 387 out of 465 participants in the *no* antibiotics group (83.2%).

Adverse effects of antibiotics

Adverse effects are considered under different clinical headings owing to differences in antibiotic prescribing recommendations for each condition. This is likely to have contributed to the heterogeneity evident in the forest plots for these outcomes preventing pooling of results. Adverse results are presented graphically for *delayed* versus *immediate* antibiotics (Analysis 17.1; Analysis 17.2; Analysis 17.3; Analysis 18.4) and *delayed* versus *no* antibiotics (Analysis 18.1; Analysis 18.2; Analysis 18.3; Analysis 18.4).

Sore throat

Delayed antibiotics versus immediate antibiotics

One study (Little 1997) found no difference for diarrhoea, vomiting, rash and stomach ache. El-Daher 1991 found more vomiting in the *delayed* group compared to the *immediate* antibiotics.

Delayed antibiotics versus no antibiotics

One study (Little 1997) found no difference for diarrhoea, vomiting, rash and stomach ache.

AOM

Delayed antibiotics versus immediate antibiotics

Little 2001 and Spiro 2006 found reduced diarrhoea in the *delayed* antibiotic group. Spiro 2006 did not find any difference between *delayed* and *immediate* antibiotics for vomiting and Little 2001 found no difference for the outcome of rash.

Delayed antibiotics versus no antibiotics

There were no adverse events in either group reported by Chao 2008.

Bronchitis (cough)

Delayed antibiotics versus immediate antibiotics

Little 2005a found no difference for adverse effects.

Delayed antibiotics versus no antibiotics

Little 2005a found no difference for adverse effects.

Common cold

Delayed antibiotics versus immediate antibiotics

There was no significant difference between the groups for diarrhoea, a potential adverse effect of antibiotics (Arroll 2002a).

Re-consultation rates

Re-consultation rates were the same between *delayed* and *immediate* antibiotic groups in two studies (Analysis 19.1). Subsequent consultation rates in the 12 months (excluding the first month) were also the same 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 *delayed* antibiotics (Little 1997).

DISCUSSION

Summary of main results

Small differences were found between prescribing strategies for clinical outcomes with *immediate* antibiotics most likely to show benefit over *delayed* antibiotics in participants with sore throat and acute otitis media (AOM). All strategies appear to have similar safety with no advantage found for *delayed* antibiotics over *no* antibiotics for disease complications. *Delay* and *no* antibiotic strategies dramatically reduce the use of antibiotics for acute respiratory tract infections (ARTIs) compared to *immediate* antibiotics. The least antibiotic use was in the *no* antibiotic group followed by *delay* and then *immediate.* The number needed to treat to prevent one antibiotic prescription using the delay strategy is 1.6 compared to *immediate* antibiotics. The number needed to treat to prevent one antibiotic prescription using a *no* antibiotic strategy compared to *delay* is 5.6. Patient satisfaction was highest in the *immediate* antibiotic group with 92.2% being satisfied or very satisfied with the consultation. The *delay* and *no* groups had similar quite high satisfaction rates at 87.3% and 83.2%, respectively. These high satisfaction results may reflect patient involvement in studies where their treating physicians are more thorough in their explanations than usual (Hawthorne effect) (French 1950; Levitt 2011). Results for satisfaction may not be as high in routine general practice.

Overall completeness and applicability of evidence

Studies comparing *delayed* and *immediate* antibiotics have been performed for two different motives. The studies of Pichichero 1987, Gerber 1990 and El-Daher 1991 were concerned that *immediate* antibiotics for streptococcal pharyngitis might impair the body's immune response and predispose the patient to a relapse of pharyngitis. These studies are useful for determining the effect of *delayed* versus *immediate* antibiotics on the clinical course of suspected streptococcal pharyngitis. Six of the remaining studies were conducted to determine if the strategy of *delayed* antibiotics reduces the number of prescriptions filled for upper ARTIs (Arroll 2002a; Dowell 2001; Little 1997; Little 2001) while maintaining patient safety and satisfaction. The most recent study may indicate evolution in prescribing habits as it was the first to drop the *immediate* antibiotic arm (Chao 2008).

Useful data were collected for many symptom outcomes in all studies but were not always reported in a way that could be analysed. This problem was partially overcome by obtaining raw data from some trial authors. The seven studies conducted after 1992 all reported useful data on antibiotic use and six on patient satisfaction.

There are only three trials comparing *delayed* antibiotics with *no* antibiotics.

Quality of the evidence

All but one trial (El-Daher 1991) were adequately randomised and accounted for incomplete data. El-Daher 1991 did find large differences for clinical outcomes for sore throat in favour of *immediate* antibiotics compared to *delayed* antibiotics.

This intervention does not lend itself to blinding. However, three trials attempted to blind patients and doctors (Arroll 2002a; El-Daher 1991; Pichichero 1987). For four studies (Chao 2008; Dowell 2001; Little 2005a; Spiro 2006), the outcomes assessor was blinded but not the patient nor the care giver.

Otherwise, studies were well reported and appeared to be high quality.

Potential biases in the review process

Heterogeneity of randomised controlled trials (RCTs) is one limitation of this review. Heterogeneity may have resulted from variable clinical presentations, differences in delay method, differences in antibiotic use and quality of included studies. Potential for type I error is another limitation of this review given the large number of reported 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 in our review might have been anticipated. Systematic reviews on antibiotics for sore throat and AOM found that their time of greatest benefit for symptoms is apparent at days three or four after treatment has started (Spinks 2011; Venekamp 2013). Thus delaying antibiotics by 48 hours or more would 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.

The greatest difference in clinical outcomes was found in the only trial of *delayed* antibiotics conducted in a low socio-economic environment, favouring *immediate* antibiotics over *delay* (El-Daher 1991). This trial was also the least methodologically sound but it highlighted that concerns expressed about *delayed* antibiotics for children, the elderly (Datta 2008) and those with language or cultural difficulties (Johnson 2007) may also need to be extended to low socio-economic populations.

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

A recent randomised controlled trial published in 2010 (Worrall 2010) comparing *delayed* prescriptions dated either the day of the office visit or two days later, but not comparing with either *immediate* or *no* antibiotics, demonstrated no significant difference between the two groups in terms of antibiotic use.

RCTs comparing *delayed* with *no* antibiotics (concluding that they were both equally acceptable alternatives to *immediate* antibiotics as a means of reducing antibiotic prescriptions) (Little 2001; Little 2005a) led to recommending *delayed* instead of *no* antibiotics to address concerns about risks of complications (Little 2005b). Doctors worried about the risk of serious infective complications consequent to adopting a *no* antibiotic rather than *delayed* strategy might take comfort from a UK observational study showing that reduced prescribing resulted in no increase in admissions to hospital for peri-tonsillar 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). Thirty-five per cent of parents in the AOM trials (Chao 2008; Little 2001; Spiro 2006) used their *delayed* script suggesting that the number of *delayed* scripts required to prevent one case of mastoiditis would be significantly higher than 2500. 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). This review did not find any significant difference for complication rates between prescribing strategies.

There is little controversy within published guidelines that *immediate* antibiotics are recommended for patients who appear to be seriously unwell, fit multiple criteria indicating bacterial tonsillitis, are under six months of age with AOM, have bilateral AOM or have AOM with otorrhoea (Tan 2008). American guidelines also recommend *immediate* antibiotics for children under 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. It seems clear that *no* antibiotics will result in least antibiotic use and therefore less antibiotic resistance. Concerns about patient and doctor satisfaction with *no* antibiotics appear to be driving the use of a *delayed* strategy. Some doctors use the *delay* strategy to reduce antibiotic use, empower patients and save the patient time and money without jeopardising the doctor-patient relationship (Arroll 2002b). A qualitative study conducted in 2002 (Arroll 2002b) found that while some patients appreciated the option of controlling the decision as to whether and when to take antibiotics, others expected "the physician to decide". Concern was expressed by one physician that patients might view delayed prescribing as physician incompetence, substantiated by comments from some patients. Shared decision-making (Butler 2001; Legare 2007) and education campaigns for doctors (Sung 2006) have been proposed as ways of helping doctors and patients avoid unnecessary antibiotic use. One suggestion is that *delayed* antibiotics may in time become redundant as doctors and their patients gain more reassurance in the safety of not using antibiotics (Arroll 2003b).

AUTHORS' CONCLUSIONS

Implications for practice

A strategy of *immediate* antibiotics is more likely to confer the modest benefits of antibiotics on clinical outcomes such as symptoms for acute otitis media and sore throat than *delayed* antibiotics. There were no differences in complication rates between *immediate* and *delayed* antibiotics nor between *delayed* and *no* antibiotics.

Immediate antibiotics had slightly higher levels of patient satisfaction than *delayed* antibiotics, which reached statistical significance but is of marginal clinical significance (92% versus 87%). Patient satisfaction was similarly high in the *delayed* and *no* antibiotic groups with a trend towards delayed antibiotics that was neither statistically nor clinically significant (87% versus 83%). *Delayed* antibiotic prescribing strategies achieved lower rates of antibiotic use compared to *immediate* antibiotics (32% versus 93%). *No* antibiotics achieved lower rates of antibiotic use compared to *delayed* antibiotics (13% versus 32%).

Delayed antibiotics for respiratory infections is a strategy which reduces antibiotic use compared to *immediate* antibiotics but has not been shown by this review to be different to *no* antibiotics in terms of symptom control and disease complications. In patients with respiratory infections where clinicians feel it is safe not to prescribe antibiotics *immediate*ly, *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.

Implications for research

Further research into antibiotic prescribing strategies for respiratory infections may best be focused on identifying patient groups at high risk of disease complications, enhancing doctors' communication with patients to maintain satisfaction and ways of reducing doctors' anxieties about not prescribing antibiotics for respiratory 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.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Arroll 2002a

Methods	Randomised controlled trial
Participants	Adults and children with the common cold
Interventions	*Delayed* antibiotics (patients given script and instructed to fill within 72 hours) versus *immediate* antibiotics
Outcomes	Fever, duration of fever, cough, duration of cough, pain, absence from school/work, diarrhoea, antibiotic use
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomisation using Excel
Allocation concealment (selection bias)	Low risk	Yes - 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 used
Selective reporting (reporting bias)	Low risk	Pre-specified outcomes were reported
Other bias	Low risk	No information

Chao 2008

Methods	Randomised controlled trial
Participants	Children with AOM
Interventions	*No* antibiotics (observation) versus *delayed* antibiotics (observation plus prescription) - patients given script and instructed to fill the script if required
Outcomes	Fever, pain, antibiotic use, patient satisfaction, adverse events
Notes	

Chao 2008 (*Continued*)

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	Not described
Blinding (performance bias and detection bias) All outcomes	High risk	Outcome assessor blinded. Patient and care provider not blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data were described and ITT analysis applied
Selective reporting (reporting bias)	Low risk	Pre-specified outcomes were reported
Other bias	Low risk	No Information

Dowell 2001

Methods	Randomised controlled trial
Participants	Adults and children with cough
Interventions	*Delayed* antibiotics (script left at reception and patients instructed to pick up the script after 1 week of delay) versus *immediate* antibiotics (antibiotic of GP's choice)
Outcomes	Duration of cough, antibiotic use
Notes	

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	High risk	Outcome assessor blinded but not patient nor care provider
Incomplete outcome data (attrition bias) All outcomes	Low risk	Drop-out numbers were described and intention-to-treat analysis used

Dowell 2001 (*Continued*)

Selective reporting (reporting bias)	Low risk	Pre-specified clinical outcomes were not published but authors provided this information
Other bias	Low risk	No Information

El-Daher 1991

Methods	Randomised controlled trial
Participants	Children with sore throat (suspected group A beta haemolytic Streptococcus)
Interventions	*Delayed* antibiotics (48 hours) versus *immediate* antibiotics (penicillin V 50,000 IU/kg/day)
Outcomes	Pain, malaise, vomiting, temperature
Notes	

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 patient and care provider but unsure about outcome assessor
Incomplete outcome data (attrition bias) All outcomes	High risk	Drop-outs not described
Selective reporting (reporting bias)	Low risk	Pre-specified outcomes reported
Other bias	Low risk	No Information

Gerber 1990

Methods	Randomised controlled trial
Participants	Adults and children with sore throat (suspected group A beta haemolytic Streptococcus)
Interventions	*Delayed* antibiotics (48 hours) versus *immediate* antibiotics (penicillin V, 250 mg qds for 10 days)

Gerber 1990 (*Continued*)

Outcomes	Malaise	
Notes		
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
Incomplete outcome data (attrition bias) All outcomes	Low risk	Drop outs described
Selective reporting (reporting bias)	Unclear risk	Clinical outcomes reported as one outcome
Other bias	Low risk	No Information

Little 1997

Methods	Open randomised controlled trial	
Participants	Adults and children with sore throat	
Interventions	*Delayed* antibiotics (script left at reception and patients instructed to pick it up 72 hours later if required) versus *immediate* antibiotics versus *no* antibiotics (penicillin V 250 mg qds in both groups)	
Outcomes	Fever, cough, duration of pain, duration of malaise, absence from school, diarrhoea and rash	
Notes		
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"; no mention of opacity

Little 1997 (*Continued*)

Blinding (performance bias and detection bias) All outcomes	High risk	No Information
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis undertaken
Selective reporting (reporting bias)	Low risk	No Information
Other bias	Low risk	No Information

Little 2001

Methods	Pragmatic randomised controlled trial
Participants	Children aged 6 months to 10 years with AOM
Interventions	*Delayed* antibiotics (72 hours, parents were advised to use antibiotics if their child had significant otalgia or fever after 72 hours, or if discharge lasted for 10 days or more) versus *immediate* antibiotics (amoxicillin 250 mg tds for 1 week)
Outcomes	Fever, severity of pain, duration of malaise, absence from school, use of paracetamol, antibiotic use, further earache at 3 and 12 months
Notes	

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
Selective reporting (reporting bias)	Low risk	Pre-specified outcomes have been reported
Other bias	Low risk	No Information

Little 2005a

Methods	Randomised controlled trial
Participants	Adults and children aged 3 years and over with cough and at least 1 symptom or sign localising to the lower respiratory tract
Interventions	*Delayed* antibiotics (script left at reception and patients instructed to pick up the script after 14 days if required) versus *immediate* antibiotics versus *no* antibiotics
Outcomes	Fever, cough, duration of cough, severity of cough, malaise, duration of malaise, complications of disease, hospital admissions, diarrhoea, antibiotic use, re-consultation in the 12 months following the index consultation, excluding the first month after the index consultation
Notes	

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. Patient and care provider were not blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing data were described and intention-to-treat analysis used
Selective reporting (reporting bias)	Low risk	Pre-specified outcomes were reported
Other bias	Low risk	No Information

Pichichero 1987

Methods	Open randomised controlled trial
Participants	Children with sore throat (suspected group A beta haemolytic Streptococcus)
Interventions	*Delayed* antibiotics (48 hours) versus *immediate* antibiotics (penicillin 250 mg tds for 10 days)
Outcomes	Fever, duration of fever, malaise, re-consultation rates, vomiting
Notes	

Pichichero 1987 (*Continued*)

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	Not used
Blinding (performance bias and detection bias) All outcomes	Low risk	Patient and doctor blinded but unsure about outcome assessor
Incomplete outcome data (attrition bias) All outcomes	Low risk	No drop-outs
Selective reporting (reporting bias)	Low risk	Pre-specified outcomes were reported
Other bias	Low risk	No Information

Spiro 2006

Methods	Placebo and randomised controlled trial
Participants	Children aged 6 months to 12 years
Interventions	*Delayed* antibiotics (patients given a script which was to expire after 72 hours) versus *immediate* antibiotics
Outcomes	Fever, duration of fever, pain, duration of pain, vomiting, diarrhoea, rash, antibiotic use
Notes	

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	More people in the wait and see prescription group stayed in the trial, however this was acknowledged and addressed
Selective reporting (reporting bias)	Low risk	Pre-specified outcomes were reported
Other bias	Low risk	No Information

AOM: acute otitis media
ITT: intention-to-treat
IU: international units
qds: four times a day
tds: three times a day

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

Study	Reason for exclusion
Cates 1999	Not a randomised controlled trial
Fischer 2009	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

DATA AND ANALYSES

Comparison 1. Sore throat - pain; delayed versus immediate antibiotics

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain on day 3	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 Pain severity on day 3	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Comparison 2. Sore throat - malaise; delayed versus immediate antibiotics

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Malaise on day 3	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 Malaise severity	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Comparison 3. Sore throat - fever; delayed versus immediate antibiotics

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Fever severity on day 3	2	343	Std. Mean Difference (IV, Fixed, 95% CI)	0.53 [0.31, 0.74]
2 Fever severity on day 1	2	343	Std. Mean Difference (IV, Fixed, 95% CI)	-0.07 [-0.29, 0.14]

Comparison 4. AOM - pain; delayed versus immediate antibiotics

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain on day 3	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 Pain on days 4 to 6	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
3 Pain on day 7	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
4 Pain severity on day 3	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
5 Pain severity on day 7	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Comparison 5. AOM - malaise; delayed versus immediate antibiotics

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Malaise on day 3	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 Malaise severity on day 3	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3 Malaise severity on day 7	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Comparison 6. Supplementary medicine consumption; delayed versus immediate antibiotics

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Spoons of paracetamol/day	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2 Use of paracetamol and ibuprofen	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected

Comparison 7. AOM - fever; delayed versus immediate antibiotics

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Fever Days 4 to 6	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected

Comparison 8. AOM - pain; delayed versus no antibiotics

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Otitis media pain on Day 3 delayed versus none	1		Odds Ratio (M-H, Random, 95% CI)	Totals not selected

Comparison 9. AOM - fever; delayed versus no antibiotics

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Otitis media number of patients with fever on day 3 delayed versus none	1		Odds Ratio (M-H, Random, 95% CI)	Totals not selected

Comparison 10. Common cold - pain; delayed versus immediate antibiotics

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain on day 3	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 Pain on day 7	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected

Comparison 11. Common cold - fever; delayed versus immediate antibiotics

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Fever on day 3	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 Fever on day 7	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
3 Fever severity on day 1	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4 Fever severity on day 3	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
5 Fever severity on day 7	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Comparison 12. Common cold - cough; delayed versus immediate antibiotics

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Cough on day 3	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 Cough on day 7	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected

Comparison 13. Antibiotic use: delayed versus immediate antibiotics

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Antibiotic use: delayed versus immediate antibiotics	6		Odds Ratio (M-H, Random, 95% CI)	Totals not selected
1.1 Antibiotic use: delayed (prescription at time of visit) versus immediate antibiotics	2		Odds Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.2 Antibiotic use: delayed (return for prescription) versus immediate antibiotics	4		Odds Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Comparison 14. Antibiotic use: delayed versus no antibiotics

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Antibiotic use: delayed versus no antibiotics	3		Odds Ratio (M-H, Random, 95% CI)	Totals not selected
1.1 Antibiotic use: delayed (prescription at time of visit) versus no antibiotics	1		Odds Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.2 Antibiotic use: delayed (return for prescription) versus no antibiotics	2		Odds Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Comparison 15. Patient satisfaction: delayed versus immediate antibiotics

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Patient satisfaction: delayed versus immediate antibiotics	5	1334	Odds Ratio (M-H, Random, 95% CI)	0.52 [0.35, 0.76]
1.1 Patient satisfaction: delayed (prescription at time of consult) versus immediate antibiotics	1	129	Odds Ratio (M-H, Random, 95% CI)	1.47 [0.32, 6.85]
1.2 Patient satisfaction: delayed (return for prescription) versus immediate antibiotics	4	1205	Odds Ratio (M-H, Random, 95% CI)	0.48 [0.33, 0.71]

Comparison 16. Patient satisfaction: delayed versus no antibiotics

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Patient satisfaction: delayed versus no antibiotics	3	938	Odds Ratio (M-H, Random, 95% CI)	1.44 [0.99, 2.10]
1.1 Patient satisfaction: delayed (prescription provided at visit) versus no antibiotics	1	206	Odds Ratio (M-H, Random, 95% CI)	2.00 [0.65, 6.18]
1.2 Patient satisfaction: delayed (return for prescription) versus no antibiotics	2	732	Odds Ratio (M-H, Random, 95% CI)	1.38 [0.93, 2.06]

Comparison 17. Adverse events: delayed versus immediate antibiotics

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Vomiting	3		Odds Ratio (M-H, Random, 95% CI)	Totals not selected
2 Diarrhoea	4		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
3 Rash	2		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
4 Stomach ache	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected

Comparison 18. Adverse events: delayed versus no antibiotics

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Vomiting	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 Diarrhoea	2		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
3 Rash	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
4 Stomach ache	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected

Comparison 19. Re-consultation rate; delayed versus immediate antibiotics

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Re-consultation rate	2	379	Odds Ratio (M-H, Fixed, 95% CI)	1.04 [0.55, 1.98]

Comparison 20. Subsequent consultation rates in the 12 months following the index consultation (excluding first month following consultation); delayed versus immediate antibiotics

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Re-consultation in the 12 months following the index consultation (excluding the first month following the index consultation)	1		Rate Ratio (Fixed, 95% CI)	Totals not selected

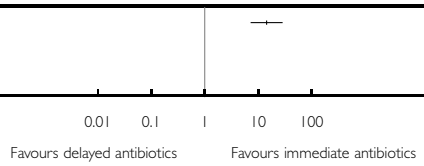
Analysis 1.1. Comparison 1 Sore throat - pain; delayed versus immediate antibiotics, Outcome 1 Pain on day 3.

Review: Delayed antibiotics for respiratory infections

Comparison: 1 Sore throat - pain; delayed versus immediate antibiotics

Outcome: 1 Pain on day 3

Study or subgroup	Delayed antibiotics n/N	Immediate antibiotics n/N	Odds Ratio M-H,Fixed,95% CI	Odds Ratio M-H,Fixed,95% CI
El-Daher 1991	106/118	42/111		14.51 [7.14, 29.50]



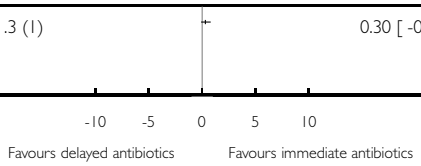
Analysis 1.2. Comparison 1 Sore throat - pain; delayed versus immediate antibiotics, Outcome 2 Pain severity on day 3.

Review: Delayed antibiotics for respiratory infections

Comparison: 1 Sore throat - pain; delayed versus immediate antibiotics

Outcome: 2 Pain severity on day 3

Study or subgroup	Delayed antibiotics		Immediate antibiotics		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI	IV,Fixed,95% CI
Pichichero 1987	55	1.6 (1.38)	59	1.3 (1)		0.30 [-0.15, 0.75]



Analysis 2.1. Comparison 2 Sore throat - malaise; delayed versus immediate antibiotics, Outcome 1 Malaise on day 3.

Review: Delayed antibiotics for respiratory infections

Comparison: 2 Sore throat - malaise; delayed versus immediate antibiotics

Outcome: 1 Malaise on day 3

Study or subgroup	Delayed antibiotics	Immediate antibiotics	Odds Ratio	Odds Ratio
	n/N	n/N	M-H,Fixed,95% CI	M-H,Fixed,95% CI
El-Daher 1991	45/118	4/111		16.49 [5.68, 47.83]

Analysis 2.2. Comparison 2 Sore throat - malaise; delayed versus immediate antibiotics, Outcome 2 Malaise severity.

Review: Delayed antibiotics for respiratory infections

Comparison: 2 Sore throat - malaise; delayed versus immediate antibiotics

Outcome: 2 Malaise severity

Study or subgroup	Delayed antibiotics		Immediate antibiotics		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI	IV,Fixed,95% CI
Pichichero 1987	55	1.3 (1)	59	1.1 (0.67)		0.20 [-0.11, 0.51]

Analysis 3.1. Comparison 3 Sore throat - fever; delayed versus immediate antibiotics, Outcome 1 Fever severity on day 3.

Review: Delayed antibiotics for respiratory infections

Comparison: 3 Sore throat - fever; delayed versus immediate antibiotics

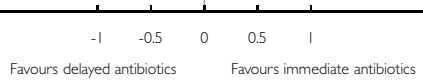
Outcome: 1 Fever severity on day 3

Study or subgroup	Delayed antibiotics		Immediate antibiotics		Std. Mean Difference	Weight	Std. Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI		IV,Fixed,95% CI
El-Daher 1991	118	38 (1.96)	111	37.1 (0.95)		66.4 %	0.58 [0.31, 0.84]
Pichichero 1987	55	37.2 (1.17)	59	36.8 (0.61)		33.6 %	0.43 [0.06, 0.80]
Total (95% CI)	**173**		**170**			**100.0 %**	**0.53 [0.31, 0.74]**

Heterogeneity: $Chi^2 = 0.40$, df = 1 (P = 0.53); $I^2 = 0.0\%$

Test for overall effect: Z = 4.80 (P < 0.00001)

Test for subgroup differences: Not applicable

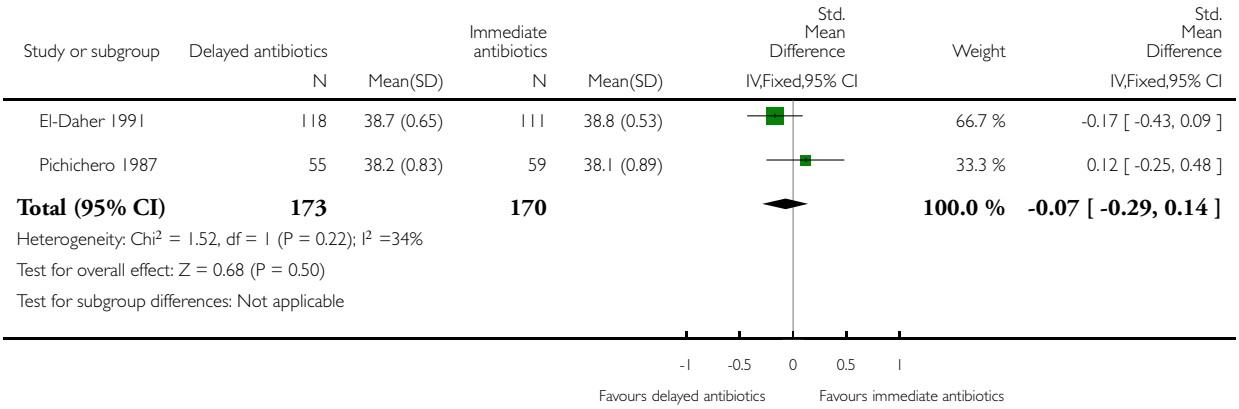


Analysis 3.2. Comparison 3 Sore throat - fever; delayed versus immediate antibiotics, Outcome 2 Fever severity on day 1.

Review: Delayed antibiotics for respiratory infections

Comparison: 3 Sore throat - fever; delayed versus immediate antibiotics

Outcome: 2 Fever severity on day 1

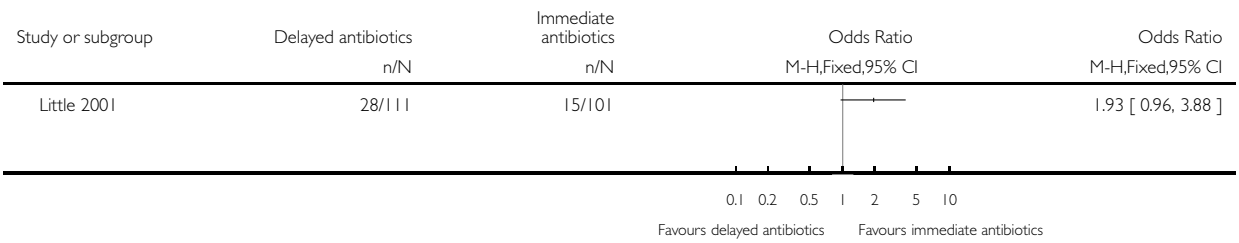


Analysis 4.1. Comparison 4 AOM - pain; delayed versus immediate antibiotics, Outcome 1 Pain on day 3.

Review: Delayed antibiotics for respiratory infections

Comparison: 4 AOM - pain; delayed versus immediate antibiotics

Outcome: 1 Pain on day 3

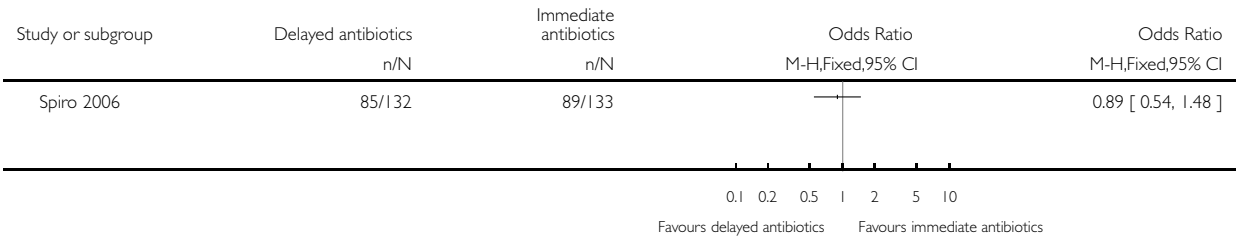


Analysis 4.2. Comparison 4 AOM - pain; delayed versus immediate antibiotics, Outcome 2 Pain on days 4 to 6.

Review: Delayed antibiotics for respiratory infections

Comparison: 4 AOM - pain; delayed versus immediate antibiotics

Outcome: 2 Pain on days 4 to 6

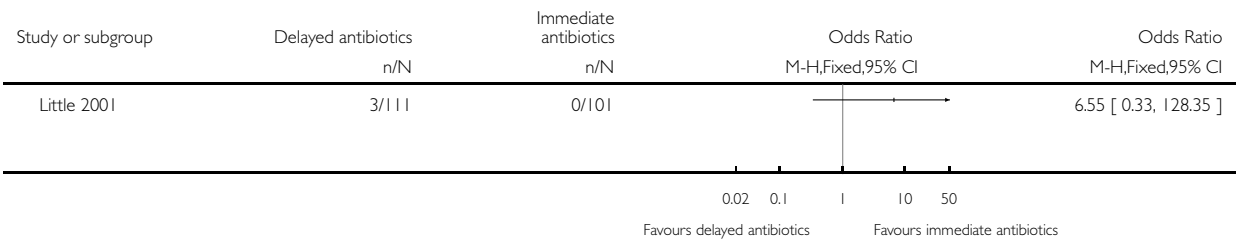


Analysis 4.3. Comparison 4 AOM - pain; delayed versus immediate antibiotics, Outcome 3 Pain on day 7.

Review: Delayed antibiotics for respiratory infections

Comparison: 4 AOM - pain; delayed versus immediate antibiotics

Outcome: 3 Pain on day 7



Analysis 4.4. Comparison 4 AOM - pain; delayed versus immediate antibiotics, Outcome 4 Pain severity on day 3.

Review: Delayed antibiotics for respiratory infections

Comparison: 4 AOM - pain; delayed versus immediate antibiotics

Outcome: 4 Pain severity on day 3

Study or subgroup	Delayed antibiotics		Immediate antibiotics		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI	IV,Fixed,95% CI
Little 2001	111	2.56 (2.14)	102	1.81 (1.44)		0.75 [0.26, 1.24]

Analysis 4.5. Comparison 4 AOM - pain; delayed versus immediate antibiotics, Outcome 5 Pain severity on day 7.

Review: Delayed antibiotics for respiratory infections

Comparison: 4 AOM - pain; delayed versus immediate antibiotics

Outcome: 5 Pain severity on day 7

Study or subgroup	Delayed antibiotics		Immediate antibiotics		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI	IV,Fixed,95% CI
Little 2001	111	1.17 (0.75)	101	1.05 (0.38)		0.12 [-0.04, 0.28]

Analysis 5.1. Comparison 5 AOM - malaise; delayed versus immediate antibiotics, Outcome 1 Malaise on day 3.

Review: Delayed antibiotics for respiratory infections

Comparison: 5 AOM - malaise; delayed versus immediate antibiotics

Outcome: 1 Malaise on day 3

Study or subgroup	Delayed antibiotics n/N	Immediate antibiotics n/N	Odds Ratio M-H,Fixed,95% CI	Odds Ratio M-H,Fixed,95% CI
Little 2001	45/150	19/135		2.62 [1.44, 4.76]

Analysis 5.2. Comparison 5 AOM - malaise; delayed versus immediate antibiotics, Outcome 2 Malaise severity on day 3.

Review: Delayed antibiotics for respiratory infections

Comparison: 5 AOM - malaise; delayed versus immediate antibiotics

Outcome: 2 Malaise severity on day 3

Study or subgroup	Delayed antibiotics N	Mean(SD)	Immediate antibiotics N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
Little 2001	150	0.83 (1.69)	134	0.4 (0.97)		0.43 [0.11, 0.75]

Analysis 5.3. Comparison 5 AOM - malaise; delayed versus immediate antibiotics, Outcome 3 Malaise severity on day 7.

Review: Delayed antibiotics for respiratory infections

Comparison: 5 AOM - malaise; delayed versus immediate antibiotics

Outcome: 3 Malaise severity on day 7

Study or subgroup	Delayed antibiotics		Immediate antibiotics		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI	IV,Fixed,95% CI
Little 2001	150	2.23 (2)	135	1.54 (1.22)		0.69 [0.31, 1.07]

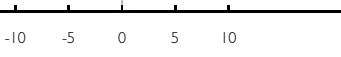
Analysis 6.1. Comparison 6 Supplementary medicine consumption; delayed versus immediate antibiotics, Outcome 1 Spoons of paracetamol/day.

Review: Delayed antibiotics for respiratory infections

Comparison: 6 Supplementary medicine consumption; delayed versus immediate antibiotics

Outcome: 1 Spoons of paracetamol/day

Study or subgroup	Delayed antibiotics		Immediate antibiotics		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI	IV,Fixed,95% CI
Little 2001	149	2.28 (1.67)	133	1.69 (1.22)		0.59 [0.25, 0.93]



Analysis 6.2. Comparison 6 Supplementary medicine consumption; delayed versus immediate antibiotics, Outcome 2 Use of paracetamol and ibuprofen.

Review: Delayed antibiotics for respiratory infections

Comparison: 6 Supplementary medicine consumption; delayed versus immediate antibiotics

Outcome: 2 Use of paracetamol and ibuprofen

Study or subgroup	Delayed antibiotics n/N	Immediate antibiotics n/N	Odds Ratio M-H,Fixed,95% CI	Odds Ratio M-H,Fixed,95% CI
Spiro 2006	123/132	120/133		1.48 [0.61, 3.59]

Analysis 7.1. Comparison 7 AOM - fever; delayed versus immediate antibiotics, Outcome 1 Fever Days 4 to 6.

Review: Delayed antibiotics for respiratory infections

Comparison: 7 AOM - fever; delayed versus immediate antibiotics

Outcome: 1 Fever Days 4 to 6

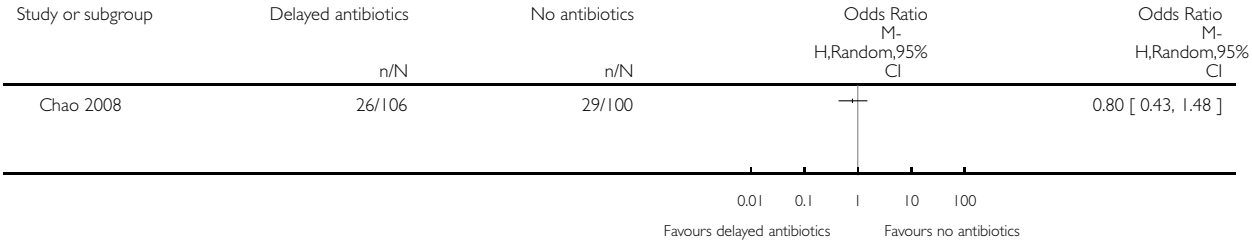
Study or subgroup	Delayed antibiotics n/N	Immediate antibiotics n/N	Odds Ratio M-H,Fixed,95% CI	Odds Ratio M-H,Fixed,95% CI
Spiro 2006	42/132	46/133		0.88 [0.53, 1.47]

Analysis 8.1. Comparison 8 AOM - pain; delayed versus no antibiotics, Outcome 1 Otitis media pain on Day 3 delayed versus none.

Review: Delayed antibiotics for respiratory infections

Comparison: 8 AOM - pain; delayed versus no antibiotics

Outcome: 1 Otitis media pain on Day 3 delayed versus none

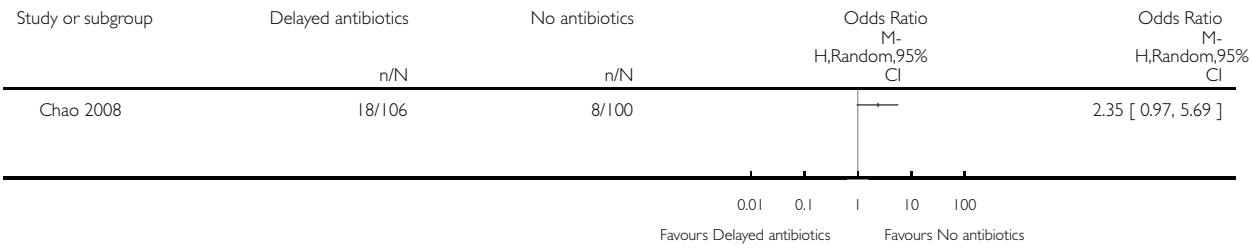


Analysis 9.1. Comparison 9 AOM - fever; delayed versus no antibiotics, Outcome 1 Otitis media number of patients with fever on day 3 delayed versus none.

Review: Delayed antibiotics for respiratory infections

Comparison: 9 AOM - fever; delayed versus no antibiotics

Outcome: 1 Otitis media number of patients with fever on day 3 delayed versus none



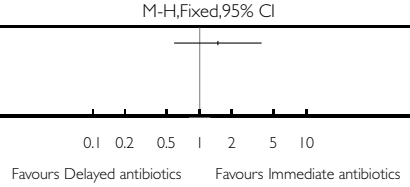
Analysis 10.1. Comparison 10 Common cold - pain; delayed versus immediate antibiotics, Outcome 1 Pain on day 3.

Review: Delayed antibiotics for respiratory infections

Comparison: 10 Common cold - pain; delayed versus immediate antibiotics

Outcome: 1 Pain on day 3

Study or subgroup	Delayed antibiotics n/N	Immediate antibiotics n/N	Odds Ratio M-H,Fixed,95% CI	Odds Ratio M-H,Fixed,95% CI
Arroll 2002a	13/61	9/58		1.47 [0.58, 3.77]



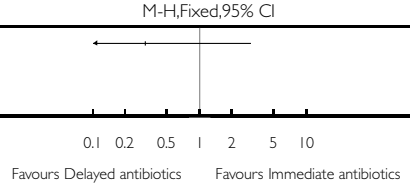
Analysis 10.2. Comparison 10 Common cold - pain; delayed versus immediate antibiotics, Outcome 2 Pain on day 7.

Review: Delayed antibiotics for respiratory infections

Comparison: 10 Common cold - pain; delayed versus immediate antibiotics

Outcome: 2 Pain on day 7

Study or subgroup	Delayed antibiotics n/N	Immediate antibiotics n/N	Odds Ratio M-H,Fixed,95% CI	Odds Ratio M-H,Fixed,95% CI
Arroll 2002a	1/61	3/58		0.31 [0.03, 3.03]



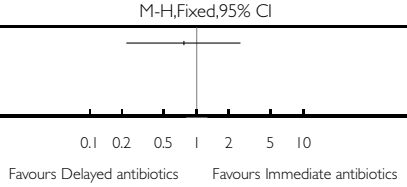
Analysis 11.1. Comparison 11 Common cold - fever; delayed versus immediate antibiotics, Outcome 1 Fever on day 3.

Review: Delayed antibiotics for respiratory infections

Comparison: 11 Common cold - fever; delayed versus immediate antibiotics

Outcome: 1 Fever on day 3

Study or subgroup	Delayed antibiotics n/N	Immediate antibiotics n/N	Odds Ratio M-H,Fixed,95% CI	Odds Ratio M-H,Fixed,95% CI
Arroll 2002a	5/67	6/62		0.75 [0.22, 2.60]



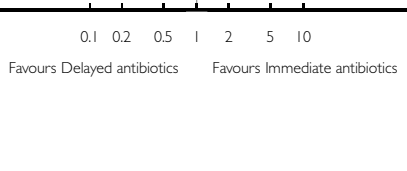
Analysis 11.2. Comparison 11 Common cold - fever; delayed versus immediate antibiotics, Outcome 2 Fever on day 7.

Review: Delayed antibiotics for respiratory infections

Comparison: 11 Common cold - fever; delayed versus immediate antibiotics

Outcome: 2 Fever on day 7

Study or subgroup	Delayed antibiotics n/N	Immediate antibiotics n/N	Odds Ratio M-H,Fixed,95% CI	Odds Ratio M-H,Fixed,95% CI
Arroll 2002a	3/67	4/62		0.68 [0.15, 3.17]



Analysis 11.3. Comparison 11 Common cold - fever; delayed versus immediate antibiotics, Outcome 3 Fever severity on day 1.

Review: Delayed antibiotics for respiratory infections

Comparison: 11 Common cold - fever; delayed versus immediate antibiotics

Outcome: 3 Fever severity on day 1

Study or subgroup	Delayed antibiotics		Immediate antibiotics		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI	IV,Fixed,95% CI
Arroll 2002a	67	36.74 (0.65)	61	36.87 (0.68)		-0.13 [-0.36, 0.10]

Analysis 11.4. Comparison 11 Common cold - fever; delayed versus immediate antibiotics, Outcome 4 Fever severity on day 3.

Review: Delayed antibiotics for respiratory infections

Comparison: 11 Common cold - fever; delayed versus immediate antibiotics

Outcome: 4 Fever severity on day 3

Study or subgroup	Delayed antibiotics		Immediate antibiotics		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI	IV,Fixed,95% CI
Arroll 2002a	61	36.15 (0.73)	58	36.39 (0.58)		-0.24 [-0.48, 0.00]

Analysis 11.5. Comparison 11 Common cold - fever; delayed versus immediate antibiotics, Outcome 5 Fever severity on day 7.

Review: Delayed antibiotics for respiratory infections

Comparison: 11 Common cold - fever; delayed versus immediate antibiotics

Outcome: 5 Fever severity on day 7

Study or subgroup	Delayed antibiotics		Immediate antibiotics		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI	IV,Fixed,95% CI
Arroll 2002a	59	36 (0.77)	60	36.32 (0.58)		-0.32 [-0.57, -0.07]

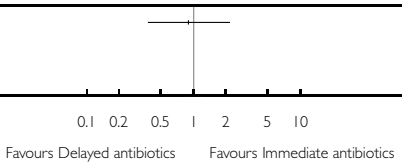
Analysis 12.1. Comparison 12 Common cold - cough; delayed versus immediate antibiotics, Outcome 1 Cough on day 3.

Review: Delayed antibiotics for respiratory infections

Comparison: 12 Common cold - cough; delayed versus immediate antibiotics

Outcome: 1 Cough on day 3

Study or subgroup	Delayed antibiotics	Immediate antibiotics	Odds Ratio	Odds Ratio
	n/N	n/N	M-H,Fixed,95% CI	M-H,Fixed,95% CI
Arroll 2002a	54/67	51/62		0.90 [0.37, 2.18]



Analysis 12.2. Comparison 12 Common cold - cough; delayed versus immediate antibiotics, Outcome 2 Cough on day 7.

Review: Delayed antibiotics for respiratory infections

Comparison: 12 Common cold - cough; delayed versus immediate antibiotics

Outcome: 2 Cough on day 7

Study or subgroup	Delayed antibiotics n/N	Immediate antibiotics n/N	Odds Ratio M-H,Fixed,95% CI	Odds Ratio M-H,Fixed,95% CI
Arroll 2002a	41/61	43/58		0.72 [0.32, 1.58]

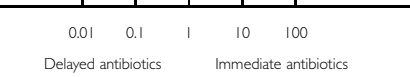
Analysis 13.1. Comparison 13 Antibiotic use: delayed versus immediate antibiotics, Outcome 1 Antibiotic use: delayed versus immediate antibiotics.

Review: Delayed antibiotics for respiratory infections

Comparison: 13 Antibiotic use: delayed versus immediate antibiotics

Outcome: 1 Antibiotic use: delayed versus immediate antibiotics

Study or subgroup	Delayed n/N	Immediate n/N	Odds Ratio M-H,Random,95% CI	Odds Ratio M-H,Random,95% CI
1 Antibiotic use: delayed (prescription at time of visit) versus immediate antibiotics				
Arroll 2002a	32/67	55/67		0.20 [0.09, 0.44]
Spiro 2006	50/132	116/133		0.09 [0.05, 0.17]
2 Antibiotic use: delayed (return for prescription) versus immediate antibiotics				
Dowell 2001	43/95	92/92		0.00 [0.00, 0.07]
Little 1997	55/176	210/211		0.00 [0.00, 0.02]
Little 2001	36/150	132/151		0.05 [0.02, 0.08]
Little 2005a	39/197	185/193		0.01 [0.00, 0.02]

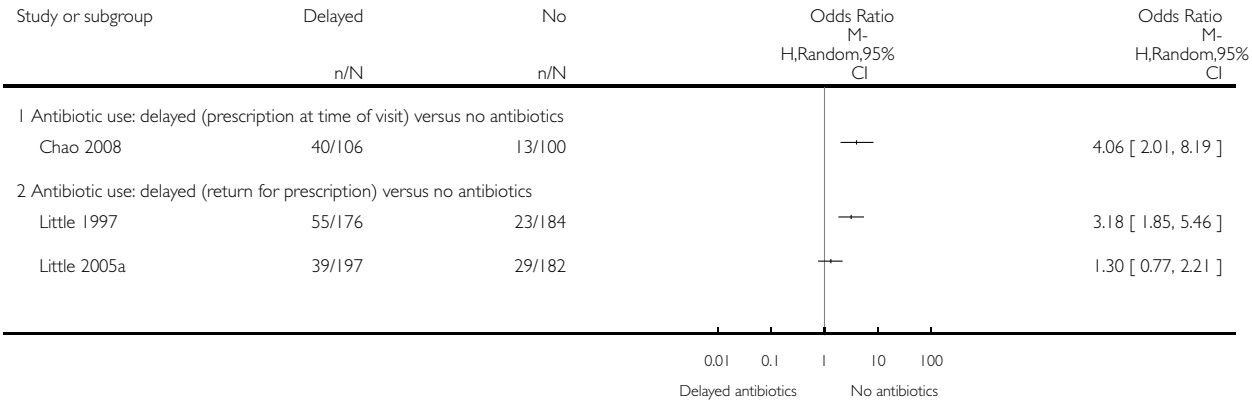


Analysis 14.1. Comparison 14 Antibiotic use: delayed versus no antibiotics, Outcome 1 Antibiotic use: delayed versus no antibiotics.

Review: Delayed antibiotics for respiratory infections

Comparison: 14 Antibiotic use: delayed versus no antibiotics

Outcome: 1 Antibiotic use: delayed versus no antibiotics

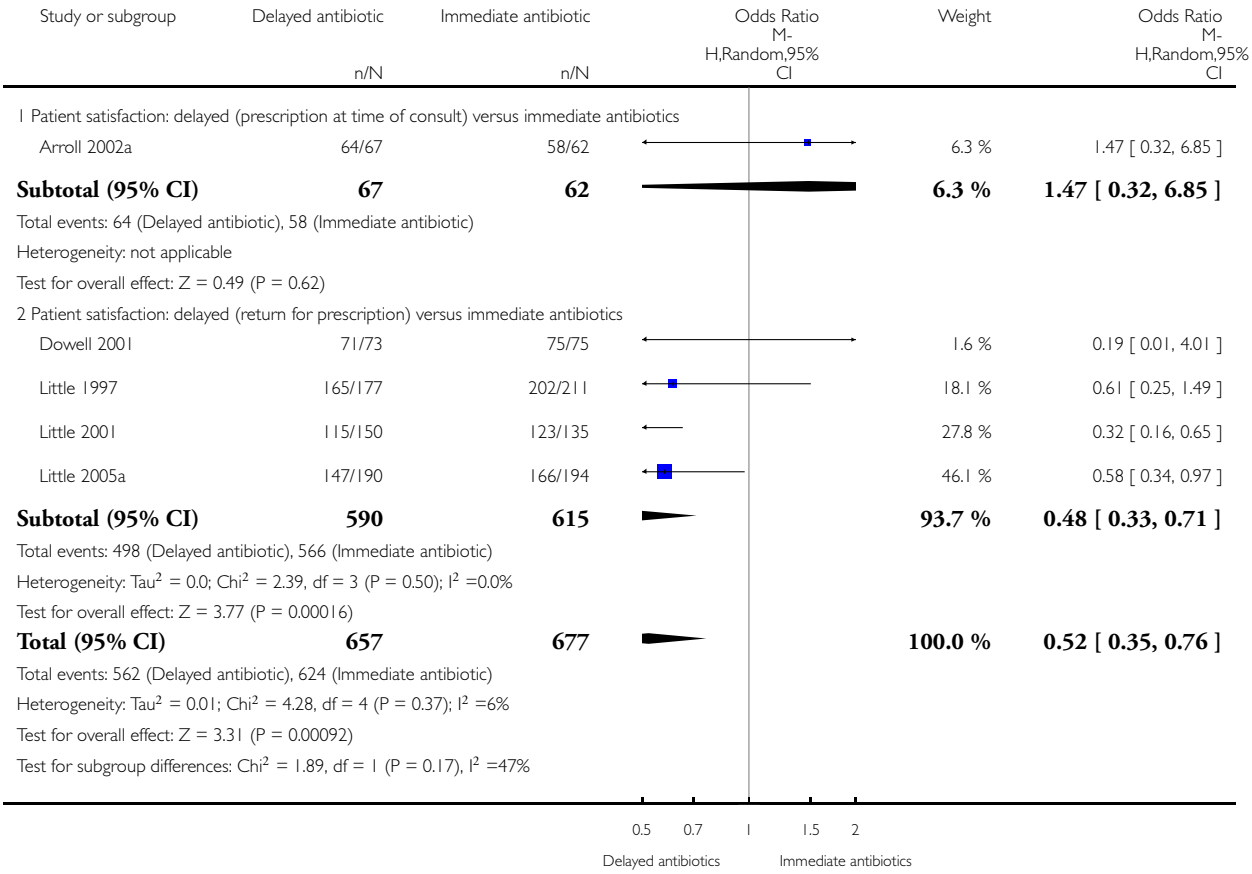


Analysis 15.1. Comparison 15 Patient satisfaction: delayed versus immediate antibiotics, Outcome 1 Patient satisfaction: delayed versus immediate antibiotics.

Review: Delayed antibiotics for respiratory infections

Comparison: 15 Patient satisfaction: delayed versus immediate antibiotics

Outcome: 1 Patient satisfaction: delayed versus immediate antibiotics

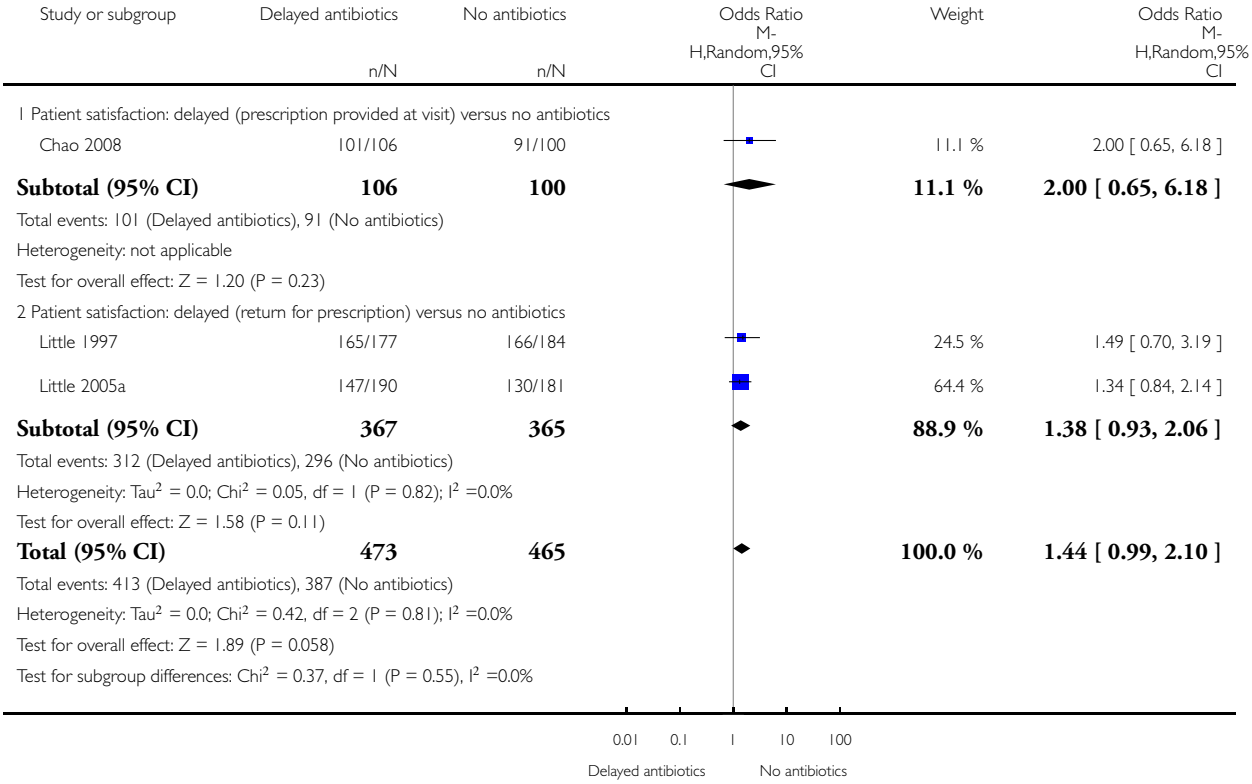


Analysis 16.1. Comparison 16 Patient satisfaction: delayed versus no antibiotics, Outcome 1 Patient satisfaction: delayed versus no antibiotics.

Review: Delayed antibiotics for respiratory infections

Comparison: 16 Patient satisfaction: delayed versus no antibiotics

Outcome: 1 Patient satisfaction: delayed versus no antibiotics



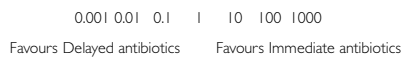
Analysis 17.1. Comparison 17 Adverse events: delayed versus immediate antibiotics, Outcome 1 Vomiting.

Review: Delayed antibiotics for respiratory infections

Comparison: 17 Adverse events: delayed versus immediate antibiotics

Outcome: 1 Vomiting

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



Analysis 17.2. Comparison 17 Adverse events: delayed versus immediate antibiotics, Outcome 2 Diarrhoea.

Review: Delayed antibiotics for respiratory infections

Comparison: 17 Adverse events: delayed versus immediate antibiotics

Outcome: 2 Diarrhoea

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

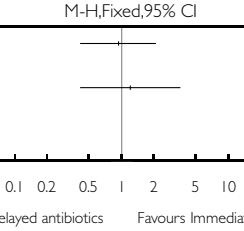
Analysis 17.3. Comparison 17 Adverse events: delayed versus immediate antibiotics, Outcome 3 Rash.

Review: Delayed antibiotics for respiratory infections

Comparison: 17 Adverse events: delayed versus immediate antibiotics

Outcome: 3 Rash

Study or subgroup	Delayed antibiotics n/N	Immediate antibiotics n/N	Odds Ratio M-H,Fixed,95% CI	Odds Ratio M-H,Fixed,95% CI
Little 1997	11/180	14/215		0.93 [0.41, 2.11]
Little 2001	8/150	6/135		1.21 [0.41, 3.58]



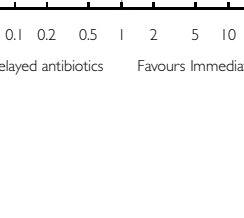
Analysis 17.4. Comparison 17 Adverse events: delayed versus immediate antibiotics, Outcome 4 Stomach ache.

Review: Delayed antibiotics for respiratory infections

Comparison: 17 Adverse events: delayed versus immediate antibiotics

Outcome: 4 Stomach ache

Study or subgroup	Delayed antibiotics n/N	Immediate antibiotics n/N	Odds Ratio M-H,Fixed,95% CI	Odds Ratio M-H,Fixed,95% CI
Little 1997	48/180	66/215		0.82 [0.53, 1.27]



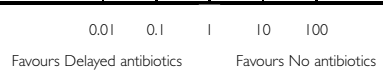
Analysis 18.1. Comparison 18 Adverse events: delayed versus no antibiotics, Outcome 1 Vomiting.

Review: Delayed antibiotics for respiratory infections

Comparison: 18 Adverse events: delayed versus no antibiotics

Outcome: 1 Vomiting

Study or subgroup	Delayed antibiotics n/N	No antibiotics n/N	Odds Ratio M-H,Fixed,95% CI	Odds Ratio M-H,Fixed,95% CI
Little 1997	15/179	22/186		0.68 [0.34, 1.36]



Analysis 18.2. Comparison 18 Adverse events: delayed versus no antibiotics, Outcome 2 Diarrhoea.

Review: Delayed antibiotics for respiratory infections

Comparison: 18 Adverse events: delayed versus no antibiotics

Outcome: 2 Diarrhoea

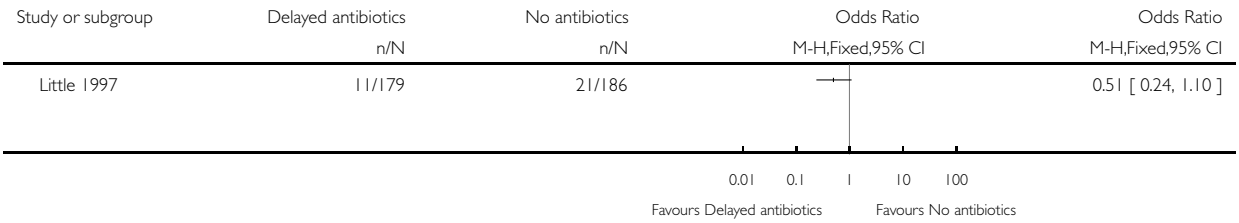
Study or subgroup	Delayed antibiotics n/N	No antibiotics n/N	Odds Ratio M-H,Fixed,95% CI	Odds Ratio M-H,Fixed,95% CI
Chao 2008	0/106	0/100		Not estimable
Little 1997	23/179	16/186		1.57 [0.80, 3.07]

Analysis 18.3. Comparison 18 Adverse events: delayed versus no antibiotics, Outcome 3 Rash.

Review: Delayed antibiotics for respiratory infections

Comparison: 18 Adverse events: delayed versus no antibiotics

Outcome: 3 Rash

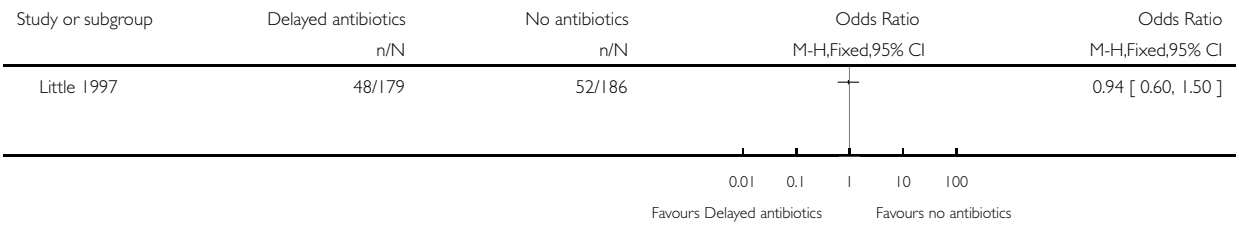


Analysis 18.4. Comparison 18 Adverse events: delayed versus no antibiotics, Outcome 4 Stomach ache.

Review: Delayed antibiotics for respiratory infections

Comparison: 18 Adverse events: delayed versus no antibiotics

Outcome: 4 Stomach ache



Analysis 19.1. Comparison 19 Re-consultation rate; delayed versus immediate antibiotics, Outcome 1 Re-consultation rate.

Review: Delayed antibiotics for respiratory infections

Comparison: 19 Re-consultation rate; delayed versus immediate antibiotics

Outcome: 1 Re-consultation rate

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

Total events: 21 (Delayed antibiotics), 21 (Immediate antibiotics)

Heterogeneity: $Chi^2 = 0.31$, df = 1 (P = 0.58); $I^2 = 0.0\%$

Test for overall effect: Z = 0.12 (P = 0.91)

Test for subgroup differences: Not applicable

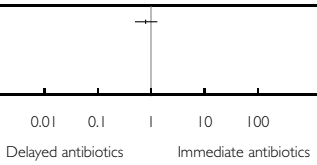
Analysis 20.1. Comparison 20 Subsequent consultation rates in the 12 months following the index consultation (excluding first month following consultation); delayed versus immediate antibiotics, Outcome 1 Re-consultation in the 12 months following the index consultation (excluding the first month following the index consultation).

Review: Delayed antibiotics for respiratory infections

Comparison: 20 Subsequent consultation rates in the 12 months following the index consultation (excluding first month following consultation); delayed versus immediate antibiotics

Outcome: 1 Re-consultation in the 12 months following the index consultation (excluding the first month following the index consultation)

Study or subgroup	log [Rate Ratio] (SE)	Rate Ratio IV,Fixed,95% CI	Rate Ratio IV,Fixed,95% CI
Little 2005a	-0.21 (0.24)		0.81 [0.51, 1.30]



ADDITIONAL TABLES

Table 1. Summary of outcomes

Study	Outcome	Favours	Result (with 95% CI)	Notes
	Sore throat			
	Outcomes in this table are the result of a comparison between *delayed* and *immediate* antibiotics unless otherwise specified			
Pichichero 1987	Fever severity on day 3		SMD 0.40 (0.05 to 0.75)	
	Malaise severity on day 3	No difference	MD 0.20 (-0.11 to 0.51)	
	Pain severity on day 3	No difference	MD 0.30 (-0.15 to 0.75)	
	Compliance	No difference	100% in both groups	
Gerber 1990	Recurrence rate	No difference		
	Compliance	*Delayed* antibiotics	88% in *immediate* group and 93% in the *delayed* group	
El Daher 1991	Vomiting	*Immediate* antibiotics	OR 25.00 (8.65 to 72.25)	
	Pain on day 3	*Immediate* antibiotics	OR 14.51 (7.14 to 29.50)	
	Malaise on day 3	*Immediate* antibiotics	OR 16.49 (5.68 to 47.83)	
	Fever severity on day 3	*Immediate* antibiotics	SMD 0.58 (0.31 to 0.84)	
	Compliance			
Little 1997	Vomiting	No difference	OR 1.00 (0.49 to 2.05)	
	Diarrhoea	No difference	OR 1.23 (0.67 to 2.28)	
	Rash	No difference	OR 0.93 (0.41 to 2.11)	
	Stomach ache	No difference	OR 0.82 (0.53 to 1.27)	
	Fever (> 37.0 °C)	*Immediate* antibiotics		

Table 1. Summary of outcomes (*Continued*)

	Sore throat	No difference		
	Cough	No difference		
	Malaise	No difference		
	Analgesic use	No difference		
	Time off work	No difference		
	AOM			
Little 2001	Diarrhoea	*Delayed* antibiotics	OR 0.45 (0.22 to 0.91)	
	Rash	No difference	OR 1.21 (0.41 to 2.58)	
	Patients with pain on day 3	No difference	OR 1.93 (0.96 to 3.88)	
	Patients with pain on day 7	No difference	OR 6.55 (0.33 to 128. 35)	
	Patients with malaise on day 3	*Immediate* antibiotics	OR 2.62 (1.44 to 4.76)	
	Malaise severity day 3	*Immediate* antibiotics	MD 0.43 (0.11 to 0.75)	
	Malaise severity on day 7	No difference	MD 0.01 (-0.11 to 0.13)	
	Pain severity on day 3	*Immediate* antibiotics	MD 0.75 (0.26 to 1.24)	
	Pain severity on day 7	No difference	MD 0.12 (-0.04 to 0.28)	
	Paracetamol consumption	*Immediate* antibiotics	MD 0.59 (0.25 to 0.93)	
	Last day of crying	*Immediate* antibiotics	MD 0.69 (0.31 to 1.07)	
Little 2001 (published in Little 2006)	Episodes of earache in the 3 months since randomisation	No difference	OR 0.89 (0.48 to 1.65)	
	Episodes of earache over 1 year	No difference	OR 1.03 (0.6 to 1.78)	
Spiro 2006	Fever day 4 to 6	No difference	OR 0.88 (0.53 to 1.47)	
	Vomiting	No difference	OR 1.01 (0.47 to 2.16)	

Table 1. Summary of outcomes (*Continued*)

	Diarrhoea	*Delayed* antibiotics	OR 0.27 (0.13 to 0.58)	
Chao 2008	Fever day 3	No difference	OR 1.45 (0.50 to 4.24)	
	Pain day 3	No difference	OR 0.64 (0.29 to 1.38)	
	Cough			
Dowell 2001	Clinical outcomes	No difference		
Little 2005a	All clinical outcomes	No difference		
	Common cold			
Arroll 2002	Patients with fever on day 3	No difference	OR 0.75 (0.22 to 2.6)	
	Patients with fever on day 7	No difference	OR 0.68 (0.15 to 3.17)	
	Patients with diarrhoea	No difference	OR 0.79 (0.53 to 1.19)	
	Patients with pain on day 3	No difference	OR 1.47 (0.58 to 3.77)	
	Patients with pain on day 7	No difference	OR 0.31 (0.03 to 3.03)	
	Patients with cough on day 3	No difference	OR 0.90 (0.37 to 2.18)	
	Patients with cough on day 7	No difference	OR 0.72 (0.32 to 1.58)	
	Fever severity day 3	No difference	MD -0.24 (-0.48 to 0. 00)	
	Fever severity on day 7	*Delayed* antibiotics	MD -0.32 (-0.57 to -0. 07)	Mean temperature for both < 37 ºC
	Antibiotic use			
	Sore throat			
Little 1997	Antibiotic use (none versus *delayed*)	*No* antibiotics (least antibiotic use)	OR 3.18 (1.85 to 5.46)	

Table 1. Summary of outcomes (*Continued*)

	Antibiotic use (*delayed* versus *immediate*)	*Delayed* antibiotics (less than *immediate*)	OR 0.00 (0.00 to 0.02)	
	AOM			
Little 2001	Antibiotic use	*Delayed* antibiotics	OR 0.05 (0.02 to 0.08)	
Spiro 2006	Antibiotic use	*Delayed* antibiotics	OR 0.09 (0.05 to 0.17)	
Chao 2008	Antibiotic use	*No* antibiotics	OR 4.06 (2.01 to 8.19)	
	Cough			
Dowell 2001	Antibiotic use	*Delayed* antibiotics	OR 0.00 (0.00 to 0.07)	
Little 2005	Antibiotic use (none versus *delayed*)	No difference	OR 1.30 (0.77 to 2.21)	
Little 2005	Antibiotic use (*delayed* versus *immediate*)	*Delayed* antibiotics	OR 0.01 (0.00 to 0.02)	
	Common cold			
Arroll 2002	Antibiotic use	*Delayed* antibiotics	OR 0.20 (0.09 to 0.44)	
	Patient satisfaction			
	Sore throat			
Little 1997	Patient satisfaction (none versus *delayed*)	No difference	OR 1.49 (0.70 to 3.19)	
	Patient satisfaction (*delayed* versus *immediate*)	No difference	OR 0.61 (0.25 to 1.49)	
	AOM			
Little 2001	Patient satisfaction (*immediate* versus *delayed*)	*Immediate* antibiotics	OR 0.32 (0.16 to 0.65)	
Chao 2008	Patient satisfaction (*delayed* versus none)	No difference	OR 2.00 (0.65 to 6.18)	
	Cough			
Dowell 2001	Patient satisfaction	*Immediate* antibiotics	OR 0.19 (0.01 to 4.01)	

Table 1. Summary of outcomes (*Continued*)

Little 2005	Patient satisfaction (none versus *delayed*)	No difference	OR 1.34 (0.84 to 2.14)	
Little 2005	Patient satisfaction (*delayed* versus *immediate*)	*Immediate* antibiotics	OR 0.58 (0.34 to 0.97)	
	Common cold			
Arroll 2002	Patient satisfaction	No difference	OR 1.47 (0.32 to 6.85)	
	Secondary outcomes			
	Sore throat			
Pichichero 1987	Re-consultation rate	No difference	OR 0.83 (0.30 to 2.29)	
	AOM			
Spiro 2006	Re-consultation rate	No difference	OR 1.21 (0.52 to 2.81)	
	LRTI			
Little 2005a (published in Moore 2009)	Re-consultation in the year following the index consultation (excluding the first month after consultation)	No difference	IRR 0.81 (0.51 to 1.28)	

AOM: acute otitis media
CI: confidence interval
IRR: incident rate ratio
LRTI: lower respiratory tract infection
MD: mean difference
OR: odds ratio
SMD: standardised mean difference

APPENDICES

Appendix 1. Ovid EMBASE search strategy

1 exp Respiratory Tract Infection/ (172448)
2 exp Upper Respiratory Tract Infection/ (22007)
3 (upper respiratory tract infection$ or urti).mp. (14226)
4 exp Otitis Media/ (15047)
5 otitis media.mp. (16846)
6 exp Pharyngitis/ (13679)
7 pharyngitis.mp. (9017)
8 exp Tonsillitis/ (5085)
9 tonsillitis.mp. (4596)
10 exp Common Cold/ (4421)
11 common cold.mp. (5401)
12 exp Bronchitis/ (24102)
13 bronchitis.mp. (17391)
14 exp Sinusitis/ (19381)
15 sinusitis.mp. (18397)
16 sore throat$.mp. (8421)
17 or/1-16 (234854)
18 exp Antibiotic Agent/ (544500)
19 antibiotic$.mp. (328859)
20 or/18-19 (628363)
21 (delay$ adj15 prescri$).mp. (841)
22 17 and 20 and 21 (102)

Appendix 2. CENTRAL search strategy

#1 MeSH descriptor: [Respiratory Tract Infections] explode all trees 9072
#2 (upper next respiratory next tract infection*) or URTI 1061
#3 MeSH descriptor: [Otitis Media] explode all trees 1009
#4 otitis next media 1926
#5 MeSH descriptor: [Pharyngitis] explode all trees 841
#6 pharyngitis 1237
#7 MeSH descriptor: [Tonsillitis] explode all trees 322
#8 tonsillitis 651
#9 MeSH descriptor: [Common Cold] explode all trees 375
#10 common next cold* 729
#11 MeSH descriptor: [Bronchitis] explode all trees 1416
#12 bronchitis 2754
#13 MeSH descriptor: [Sinusitis] explode all trees 626
#14 sinusitis 1362
#15 sore next throat* 826
#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 14213
#17 MeSH descriptor: [Anti-Bacterial Agents] explode all trees 8199
#18 antibiotic* 15634
#19 #17 or #18 19843
#20 delay* near/15 prescri* 87
#21 #16 and #19 and #20 28

Appendix 3. EBSCO CINAHL search strategy

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+")

Appendix 4. ISI Current Contents Connect search strategy

#14 #13 AND #12 AND #9
#13 TS=antibiotic*
#12 #11 OR #10
#11 TS=immediate*
#10 TS=delay*
#9 #8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1
#8 TS=sore throat
#7 TS=sinusitis
#6 TS=bronchitis
#5 TS=common cold*
#4 TS=tonsillitis
#3 TS=pharyngitis
#2 TS=otitis media
#1 TS=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.
Theses 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 recent 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

Contributors

Jas Janjuha, Occupation Pharmacist

WHAT'S NEW

Last assessed as up-to-date: 28 February 2013.

Date	Event	Description
28 February 2013	New search has been performed	The searches have been updated. Two new papers (Little 2006; Moore 2009) were included. They 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. Three new trials were excluded (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.

HISTORY

Protocol first published: Issue 4, 2003

Review first published: Issue 4, 2004

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

CONTRIBUTIONS OF AUTHORS

Chris Del Mar (CDM) conceived the review.

Geoff Spurling (GS) and CDM designed the review.

Ruth Foxlee (RF) and GS performed the literature searches.

RF, Liz Dooley (LD) and CDM appraised articles and extracted data from these articles.

GS and Rebecca Farley (RFa) entered data into RevMan with contributions from LD, RF and CDM.

GS secured funding for the review with the assistance of CDM.

DECLARATIONS OF INTEREST

No known conflict of interest.

SOURCES OF SUPPORT

Internal sources

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

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

External sources

- General Practice Education and Training, Australia.

INDEX TERMS

Medical Subject Headings (MeSH)

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

MeSH check words

Humans