Delayed antibiotics for respiratory infections (Review)

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[Intervention Review]

Delayed antibiotics for respiratory infections

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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.

Objectives

To evaluate clinical outcomes, adverse effects, antibiotic use and patient satisfaction associated with *delayed* antibiotic prescribing compared to *immediate* prescribing or *no* antibiotics for ARTIs.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2009, issue 1), which contains the Acute Respiratory Infections Group's Specialised Register; MEDLINE (January 1966 to March Week 3 2009), EMBASE (1990 to 2009 Week 12), CINAHL (1982 to March Week 4 2009); Current Contents (1998 to December 2007) and Science Citation Index (2007 to March 2009).

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

Data were collected and analysed by three review authors.

Main results

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 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 antibiotics compared to *immediate* antibiotics. A strategy of *no* antibiotics resulted in least antibiotic use.

Patient satisfaction favoured *immediate* antibiotics over *delayed* (OR 0.52; 95% 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.

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 the use of antibiotics is to prescribe *delayed*, (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).

While this review found 10 studies 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).

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) (Glasziou 2004), pharyngitis (Del Mar 2009), and acute bronchitis (Fahey 2004), and no effect in the common cold (Arroll 2005). 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).

How the intervention might work

A systematic review showed that using *delayed* antibiotics in ARTIs significantly reduces antibiotic prescribing. Arroll 2003 The reduction ranges from a RR 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 and patient satisfaction for the three prescribing strategies of *delayed* antibiotics, *immediate* antibiotics and *no* antibiotics.

OBJECTIVES

To evaluate the use of *delayed* antibiotics compared to *immediate* or *no* antibiotics as a prescribing strategy for ARTIs. We also evaluated the outcomes of antibiotic use, patient satisfaction 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 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 are available.

1. Clinical outcomes for sore throat, AOM, bronchitis (cough) and common cold. (We will include duration and severity measures the following symptoms; pain, malaise, fever, cough and rhinorrhea
2. Antibiotic use
3. Patient satisfaction (where patient satisfaction is measured on a five-point Likert scale. We defined satisfaction as including both satisfied and very satisfied.)

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

In this updated review we searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2009, issue 1), which includes the Acute Respiratory Infection Groups' Specialised Register; Ovid MEDLINE (January 1966 to March Week 3 2009); EMBASE (1990 to 2009 Week 12); and Current Contents (1998 to December 2007), Science Citation Index - Web of Science (January 2007 to March 2009); EBSCO CINAHL (1982 to March Week 4 2009).

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 no trial filters were applied. The MEDLINE search strategy was used to search CENTRAL and adapted to search Ovid EMBASE (see Appendix 1), ISI Science Citation Index(see Appendix 2) and EBSCO CINAHL (see Appendix 3).

MEDLINE (Ovid)

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

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

Searching other resources

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

Data collection and analysis

Selection of studies

Abstracts from the initial search results were scanned to identify trials that loosely met the inclusion criteria. The references of all relevant retrieved trials were checked to identify any other articles. The full text articles of the retrieved trials were then reviewed by three review authors (RF, LD and CDM) and the inclusion criteria applied independently.

In this updated review two review authors (LD, CDM) independently assessed the methodological quality of the new included study that met the inclusion criteria (Chao 2008).

Data extraction and management

In the initial publication of this review, three review authors (RF, LD and CDM) independently extracted data for each study trial to be included. Extraction was undertaken blinded. Additional data were extracted from graphs of the published articles of El-Daher 1991 and Pichichero 1987 on fever severity and symptom scores. In this updated review two review authors (LD, CDM) independently extracted data for the new included study.

Assessment of risk of bias in included studies

In the first publication of this review three review authors (RF, LD and CDM) independently assessed the quality of each of the study trials that met the inclusion criteria. Disagreements were resolved by consensus. Assessment was blinded (that is, without the knowledge of the study results, the names of the authors, institutions, or journal of publication).

The quality of each eligible RCT was rated according to the risk of bias tool available in RevMan 5 and criteria set out in the *Cochrane Handbook of Systematic Reviews of Interventions* (Higgins 2008). Methodological quality was assessed 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 new included trial for this review update. Any disagreement between the review authors was resolved by discussion.

Measures of treatment effect

Data were analysed using RevMan 5. Continuous data comparisons were expressed using mean differences where there was one study or standardised mean difference where more than one study used different measurement scales. Dichotomous data were expressed using odds ratios. Data were pooled into clinical outcomes where multiple trial results for the same clinical presentation existed and there was no heterogeneity.

Unit of analysis issues

The unit 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

Meta-analysis was not undertaken for most clinical outcomes owing to multiple analyses with only one or two study results. Results were pooled where satisfactorily low I^2 statistics and non-significant chi^2 test results were found. Meta-analysis was not undertaken for antibiotic use owing to heterogeneity of 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

Results were pooled where satisfactorily low I^2 statistics and non-significant chi^2 test results were found. Meta-analsysis was undertaken for the outcomes of fever for sore throat and patient satisfaction.

Subgroup analysis and investigation of heterogeneity

Heterogeneity was measured using $chi^2$and I^2 statistics and found to be significant for the outcomes related to antibiotic use. Heterogeneity was less likely to be important for the outcomes related to patient satisfaction.

RESULTS

Description of studies

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

Results of the search

Of the 167 RCTs identified by electronic searching, 23 were retrieved for more detailed evaluation. None of the remaining trials were excluded following quality appraisal. One new trial was included in this update (Chao 2008) such that 10 trials were eligible for inclusion. The 10 trials 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 arms of three trials.

Included studies

There was only one trial which compared *delayed* antibiotics with *none* (Chao 2008).

Nine 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 evaluating the use of *delayed* antibiotics to reduce the use of antibiotics for upper 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 study (Chao 2008) also asked patients in the *no* antibiotic arm to return if their symptoms had not resolved.

Excluded studies

Two trials were excluded. One because it used a before and after study design (Cates 1999) and one was 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.

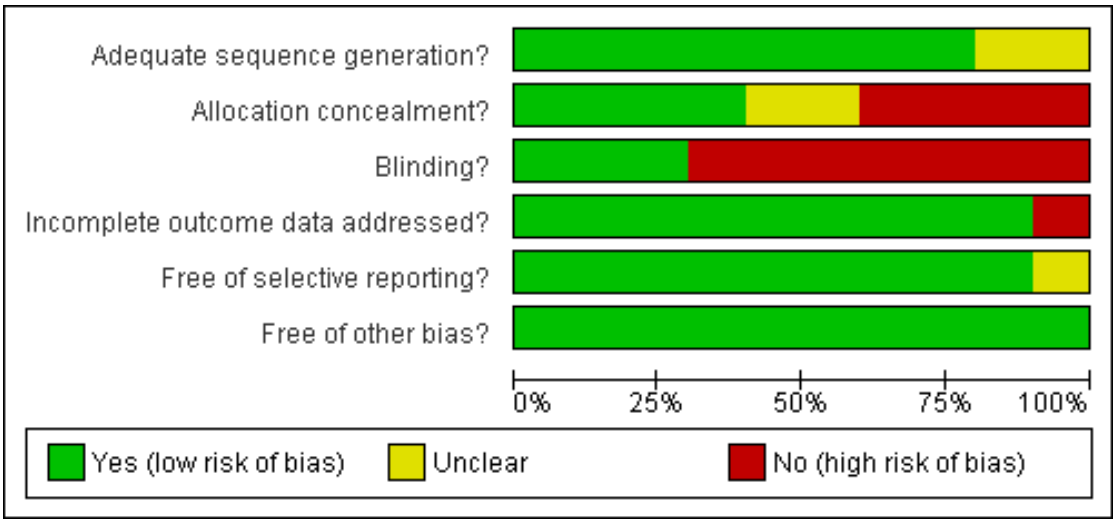
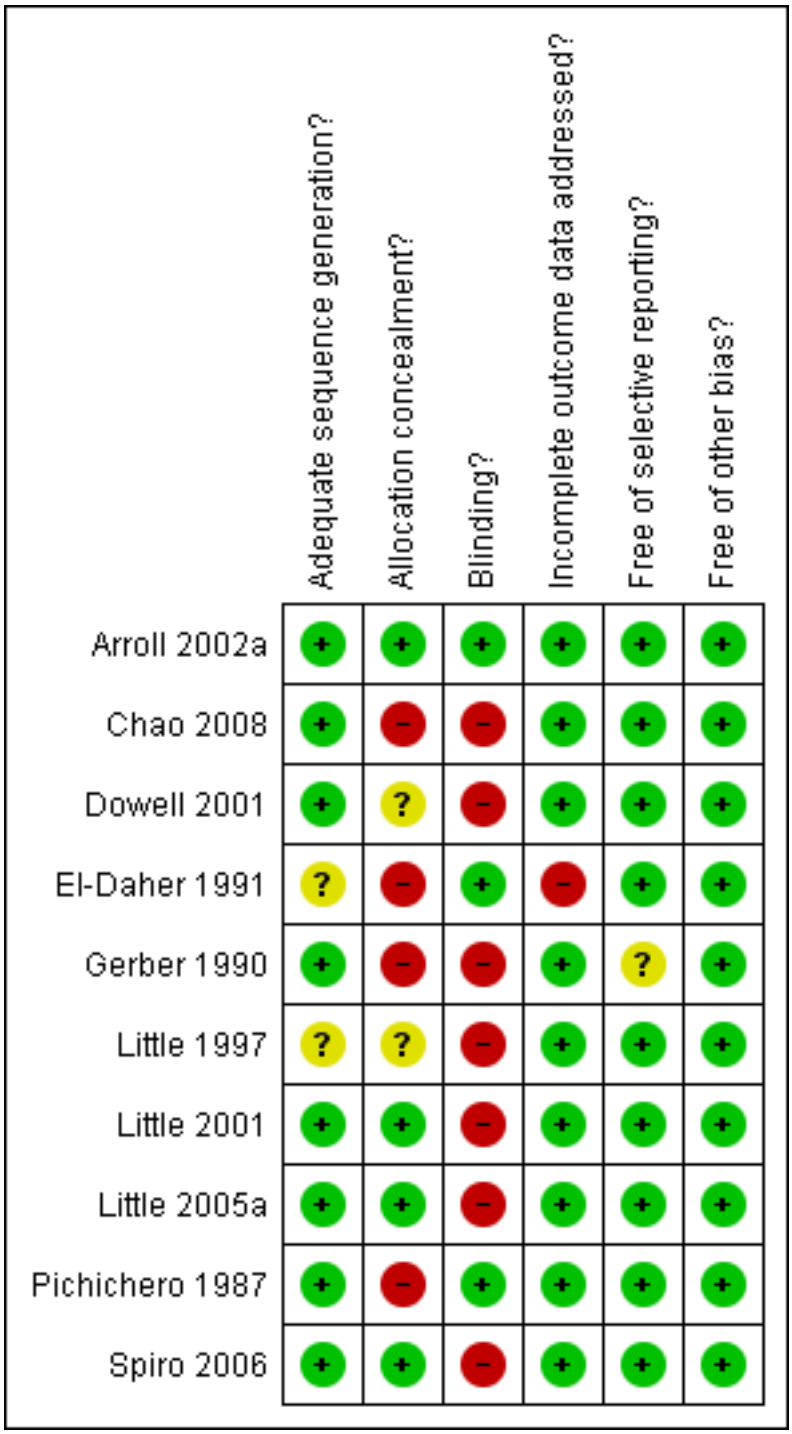


Figure 2. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.



Allocation

Eight included studies were adequately randomised using random number tables or computer generated randomisation. For two studies the method of randomisation was not described (Little 1997; El-Daher 1991). 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 mention of the outcome assessor (Arroll 2002a; El-Daher 1991; Pichichero 1987). Seven studies had 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 nor 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 3.

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. 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 OR 0.53 (95% 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.

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 ear ache and function from one trial (Little 2001) found no difference between *delayed* and *immediate* groups at three and 12 months for these two outcomes (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 represent 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 from 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 resulted in 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 (Analysis 13.1)

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

No antibiotics (Analysis 14.1)

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 less antibiotics were prescribed in the *no* antibiotic group (Analysis 14.1).

Overall, 65 patients filled scripts out of 466 participants (13.9%).

Patient satisfaction

See Table 1.

Delayed antibiotics versus *immediate* antibiotics (Analysis 15.1)

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 of 0.52 (95% CI: 0.35, 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 odds ratio 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 16.1)

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 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 between 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). 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 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 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.

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 RCTs is the main 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. Type I error is a concern when interpreting the results of this review, given the heterogeneity of results with multiple outcome measures. This is especially concerning for the comparisons for clinical outcomes between *delayed* and *immediate* antibiotic groups.

Agreements and disagreements with other studies or reviews

Some doctors use the *delay* strategy to reduce antibiotic use, empower patients, and save the patient time and money without jeopardizing the doctor-patient relationship (Arroll 2002b). 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 (Del Mar 2009; Glasziou 2004). 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).

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 at 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 is a dissociation 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 (Otitis Media Treatment Guidelines 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. 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

Immediate antibiotics is more likely to confer the modest benefits of antibiotics on clinical outcomes such as symptoms for AOM 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 antibiotics 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 RCTs 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 year of study]*

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	

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Table of random numbers
Allocation concealment?	No	D - Not used
Blinding? All outcomes	Yes	Patient and Doctor blinded but unsure re outcome assessor
Incomplete outcome data addressed? All outcomes	Yes	No drop outs
Free of selective reporting?	Yes	prespecified outcomes were reported
Free of other bias?	Yes	

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)
Outcomes	Malaise
Notes	

Risk of bias

Gerber 1990 (*Continued*)

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Random number table
Allocation concealment?	No	
Blinding? All outcomes	No	No blinding
Incomplete outcome data addressed? All outcomes	Yes	Drop outs described
Free of selective reporting?	Unclear	Clinical outcomes reported as one outcome
Free of other bias?	Yes	

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

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Method not described
Allocation concealment?	No	Not described
Blinding? All outcomes	Yes	Blinding of patient and care provider but unsure re outcome assessor
Incomplete outcome data addressed? All outcomes	No	Drop-outs not described
Free of selective reporting?	Yes	Prespecified outcomes reported
Free of other bias?	Yes	

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

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Randomisation method not described
Allocation concealment?	Unclear	"Sealed envelopes" no mention of opacity
Blinding? All outcomes	No	
Incomplete outcome data addressed? All outcomes	Yes	ITT analysis undertaken
Free of selective reporting?	Yes	
Free of other bias?	Yes	

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 one week of delay) versus *immediate* antibiotics (antibiotic of GP's choice)
Outcomes	Duration of cough, antibiotic use
Notes	

Risk of bias

Item	**Authors' judgement**	**Description**

Dowell 2001 (*Continued*)

Adequate sequence generation?	Yes	Random number table
Allocation concealment?	Unclear	Numbered envelopes (opacity not mentioned)
Blinding? All outcomes	No	Outcome Assessor blinded but not patient nor care provider
Incomplete outcome data addressed? All outcomes	Yes	Drop out numbers were described and intention to treat analysis used
Free of selective reporting?	Yes	Pre-specified clinical outcomes were not published but authors provided this information
Free of other bias?	Yes	

Little 2001

Methods	Pragmatic randomised controlled trial
Participants	Children aged 6 months to 10 years with AOM
Interventions	*Delayed* antibiotics (72 hours) versus *immediate* antibiotics (amoxicillin 250 mg tds for one week)
Outcomes	Fever, severity of pain, duration of malaise, absence from school, use of paracetamol, antibiotic use
Notes	

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Quote: "patients were randomised to a group"
Allocation concealment?	Yes	Quote: "doctor opened a sealed numbered opaque envelope
Blinding? All outcomes	No	No blinding undertaken
Incomplete outcome data addressed? All outcomes	Yes	A comparison of responders versus non-responders was undertaken
Free of selective reporting?	Yes	Pre-specified outcomes have been reported
Free of other bias?	Yes	

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

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Randomisation using Excel
Allocation concealment?	Yes	Yes - opaque envelopes
Blinding? All outcomes	Yes	Patient and care provider were blinded but unsure regarding outcome assessor
Incomplete outcome data addressed? All outcomes	Yes	ITT analysis used
Free of selective reporting?	Yes	Pre-specified outcomes were reported
Free of other bias?	Yes	

Little 2005a

Methods	Randomised controlled trial
Participants	Adults and children aged three years and over with cough and at least one 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
Notes	

Risk of bias

Item	**Authors' judgement**	**Description**

Little 2005a (*Continued*)

Adequate sequence generation?	Yes	Computer generated random number tables, and block randomization (block size 6)
Allocation concealment?	Yes	Opaque sealed envelopes
Blinding? All outcomes	No	Outcome assessor was blinded. Patient and care provider were not blinded
Incomplete outcome data addressed? All outcomes	Yes	Missing data were described and intention to treat analysis used
Free of selective reporting?	Yes	Pre-specified outcomes were reported
Free of other bias?	Yes	

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

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Computer assisted randomisation
Allocation concealment?	Yes	Sealed opaque envelopes
Blinding? All outcomes	No	Study participants were not blinded but outcome assessors were blinded
Incomplete outcome data addressed? All outcomes	Yes	More people in the wait and see prescription group stayed in the trial however this was acknowledges and addressed
Free of selective reporting?	Yes	Pre-specified outcomes were reported
Free of other bias?	Yes	

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	

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Random number table
Allocation concealment?	No	Not described
Blinding? All outcomes	No	Outcome Assessor blinded. Patient and care provider not blinded
Incomplete outcome data addressed? All outcomes	Yes	Missing data were described and ITT analysis applied
Free of selective reporting?	Yes	Pre-specified outcomes were reported
Free of other bias?	Yes	

tds: three times a day
qds: four times a day
iu: international units
ITT: intention-to-treat

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

Study	Reason for exclusion
Cates 1999	Non randomised trial. Before and after study
Siegel 2003	Non randomised 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: immediate versus delayed antibiotics	6		Odds Ratio (M-H, Random, 95% CI)	Totals not selected

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

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]

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 antibiotics versus no antibiotics	3	938	Odds Ratio (M-H, Random, 95% CI)	1.44 [0.99, 2.10]

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 Reconsultation rate	2	379	Odds Ratio (M-H, Fixed, 95% CI)	1.04 [0.55, 1.98]

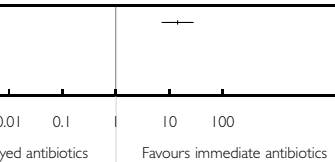
Analysis 1.1. Comparison 1 Sore throat - pain; Delayed versus Immediate Antibiotics, Outcome 1 Pain on Day 3.

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]



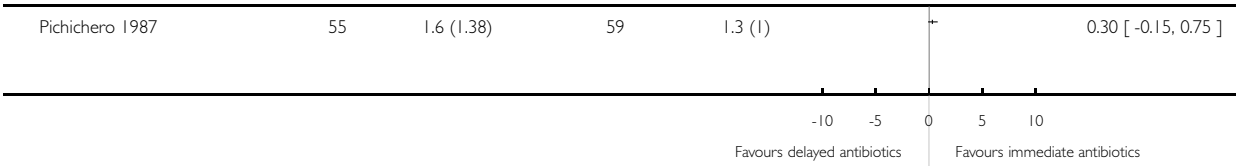
Analysis 1.2. Comparison 1 Sore throat - pain; Delayed versus Immediate Antibiotics, Outcome 2 Pain severity on Day 3.

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]



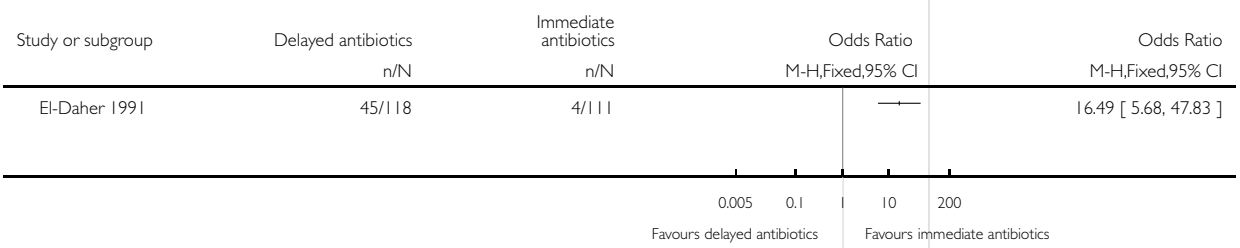
Analysis 2.1. Comparison 2 Sore throat - malaise; Delayed versus Immediate Antibiotics, Outcome 1 Malaise on Day 3.

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

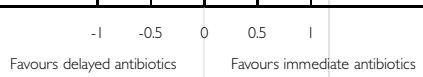
Outcome: 1 Fever severity on Day 3

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

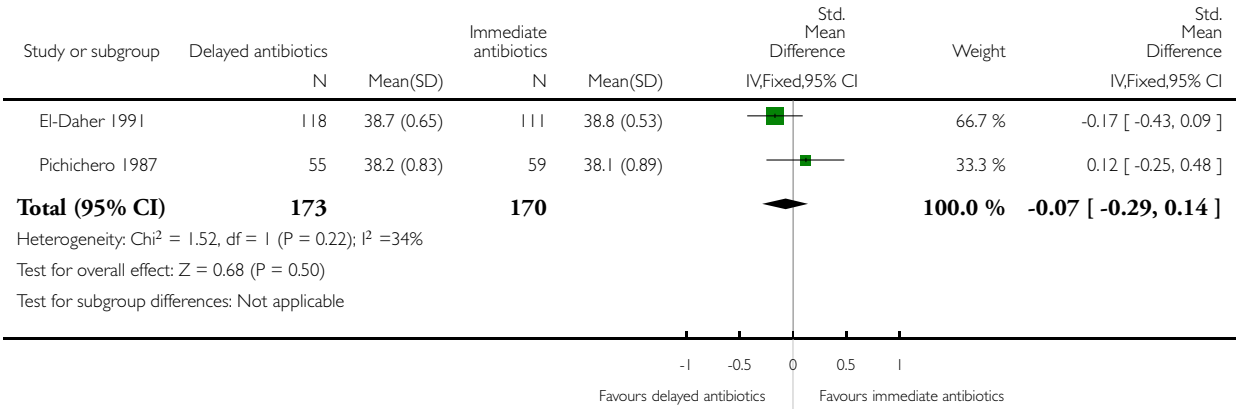


Analysis 3.2. Comparison 3 Sore throat - fever; Delayed versus Immediate Antibiotics, Outcome 2 Fever severity on Day 1.

Review: Delayed antibiotics for respiratory infections

Comparison: 3 Sore throat - fever; *Delayed* versus *Immediate* Antibiotics

Outcome: 2 Fever severity on Day 1

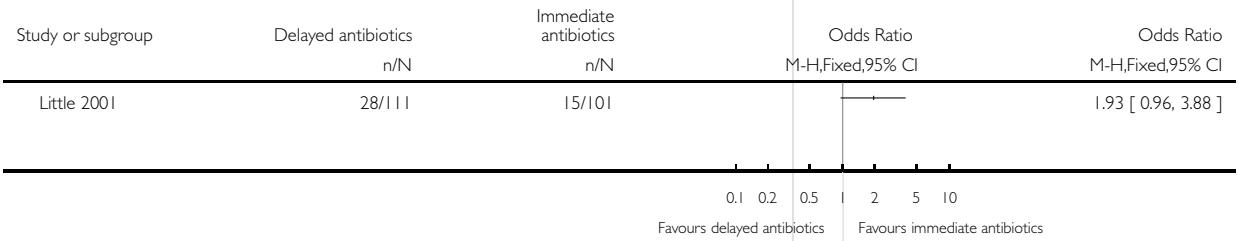


Analysis 4.1. Comparison 4 AOM - pain; Delayed versus Immediate Antibiotics, Outcome 1 Pain on Day 3.

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

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	85/132	89/133		0.89 [0.54, 1.48]

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

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	3/111	0/101		6.55 [0.33, 128.35]

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]

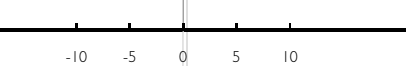
Analysis 4.5. Comparison 4 AOM - pain; Delayed versus Immediate Antibiotics, Outcome 5 Pain severity on Day 7.

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]

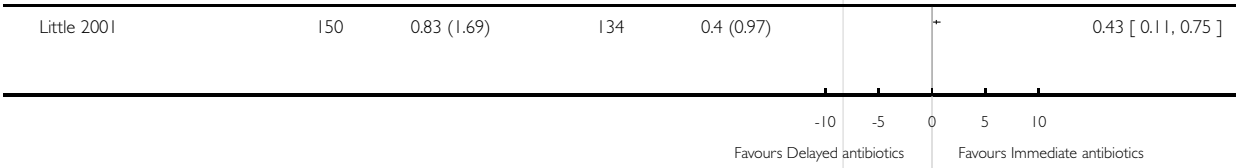
Analysis 5.2. Comparison 5 AOM - malaise; Delayed versus Immediate Antibiotics, Outcome 2 Malaise severity on Day 3.

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]

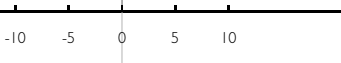
Analysis 6.1. Comparison 6 Supplementary medicine consumption; Delayed versus Immediate Antibiotics, Outcome 1 Spoons of paracetamol/day.

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]

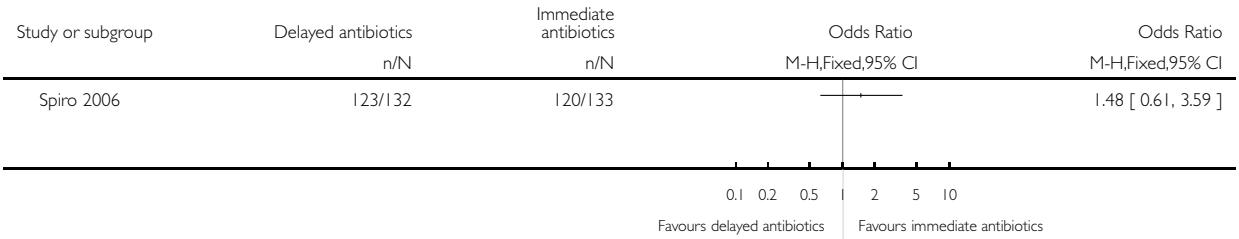


Analysis 6.2. Comparison 6 Supplementary medicine consumption; Delayed versus Immediate Antibiotics, Outcome 2 Use of paracetamol and ibuprofen.

Review: Delayed antibiotics for respiratory infections

Comparison: 6 Supplementary medicine consumption; *Delayed* versus *Immediate* Antibiotics

Outcome: 2 Use of paracetamol and ibuprofen

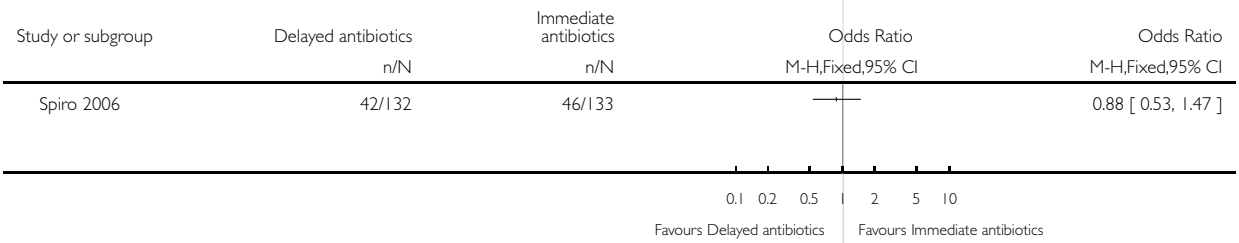


Analysis 7.1. Comparison 7 AOM - fever; Delayed versus Immediate Antibiotics, Outcome 1 Fever Days 4 to 6.

Review: Delayed antibiotics for respiratory infections

Comparison: 7 AOM - fever; *Delayed* versus *Immediate* Antibiotics

Outcome: 1 Fever Days 4 to 6

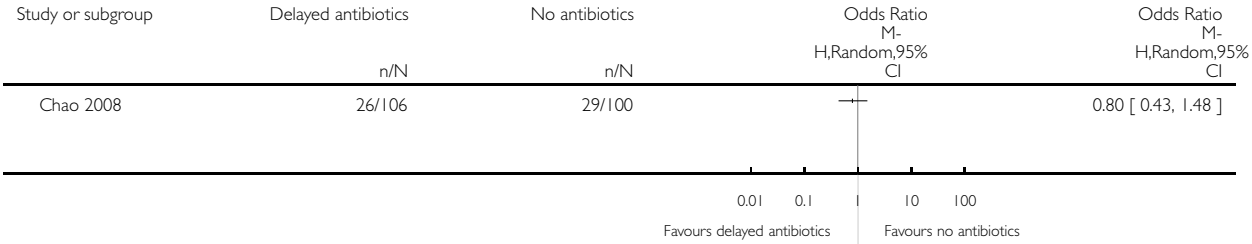


Analysis 8.1. Comparison 8 AOM - pain; Delayed versus No Antibiotics, Outcome 1 Otitis media pain on Day 3 delayed versus none.

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

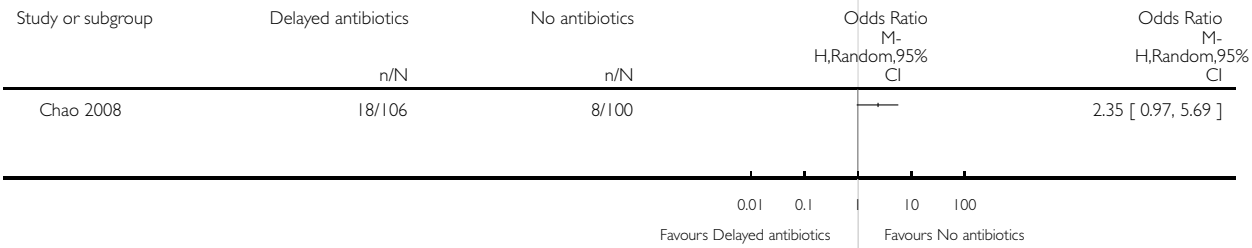


Analysis 9.1. Comparison 9 AOM - fever; Delayed versus No Antibiotics, Outcome 1 Otitis media number of patients with fever on Day 3 delayed versus none.

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



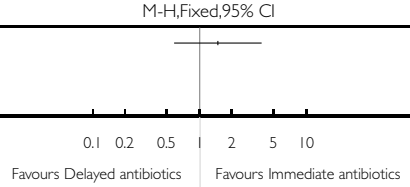
Analysis 10.1. Comparison 10 Common cold - pain; Delayed versus Immediate Antibiotics, Outcome 1 Pain on Day 3.

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]



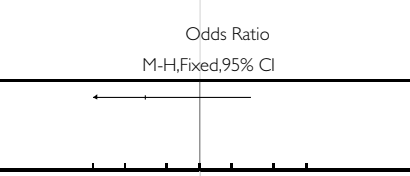
Analysis 10.2. Comparison 10 Common cold - pain; Delayed versus Immediate Antibiotics, Outcome 2 Pain on Day 7.

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]

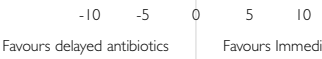
Analysis 11.5. Comparison 11 Common cold - fever; Delayed versus Immediate Antibiotics, Outcome 5 Fever severity on Day 7.

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: immediate versus delayed antibiotics.

Review: Delayed antibiotics for respiratory infections

Comparison: 13 Antibiotic use; *Delayed* versus *Immediate* Antibiotics

Outcome: 1 Antibiotic use: immediate versus delayed antibiotics

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
Arroll 2002a	32/67	55/67		0.20 [0.09, 0.44]
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]
Spiro 2006	50/132	116/133		0.09 [0.05, 0.17]

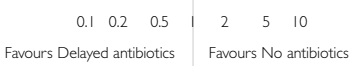
Analysis 14.1. Comparison 14 Antibiotic use; Delayed versus No Antibiotics, Outcome 1 Antibiotic use: delayed versus no antibiotics.

Review: Delayed antibiotics for respiratory infections

Comparison: 14 Antibiotic use; *Delayed* versus *No* Antibiotics

Outcome: 1 Antibiotic use: delayed versus no antibiotics

Study or subgroup	Delayed antibiotics n/N	No antibiotics n/N	Odds Ratio M-H,Random,95% CI	Odds Ratio M-H,Random,95% CI
Chao 2008	40/106	13/100		4.06 [2.01, 8.19]
Little 1997	55/176	23/184		3.18 [1.85, 5.46]
Little 2005a	39/197	29/182		1.30 [0.77, 2.21]



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

Study or subgroup	Delayed antibiotics n/N	Immediate antibiotics n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Arroll 2002a	64/67	58/62		6.3 %	1.47 [0.32, 6.85]
Dowell 2001	71/73	75/75		1.6 %	0.19 [0.01, 4.01]
Little 1997	165/177	202/211		18.1 %	0.61 [0.25, 1.49]
Little 2001	115/150	123/135		27.8 %	0.32 [0.16, 0.65]
Little 2005a	147/190	166/194		46.1 %	0.58 [0.34, 0.97]
Total (95% CI)	**657**	**677**		**100.0 %**	**0.52 [0.35, 0.76]**

Total events: 562 (Delayed antibiotics), 624 (Immediate antibiotics)

Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 4.28$, df = 4 (P = 0.37); $I^2 = 6\%$

Test for overall effect: Z = 3.31 (P = 0.00092)

Analysis 16.1. Comparison 16 Patient satisfaction; Delayed versus No Antibiotics, Outcome 1 Patient satisfaction: delayed antibiotics versus no antibiotics.

Review: Delayed antibiotics for respiratory infections

Comparison: 16 Patient satisfaction; *Delayed* versus *No* Antibiotics

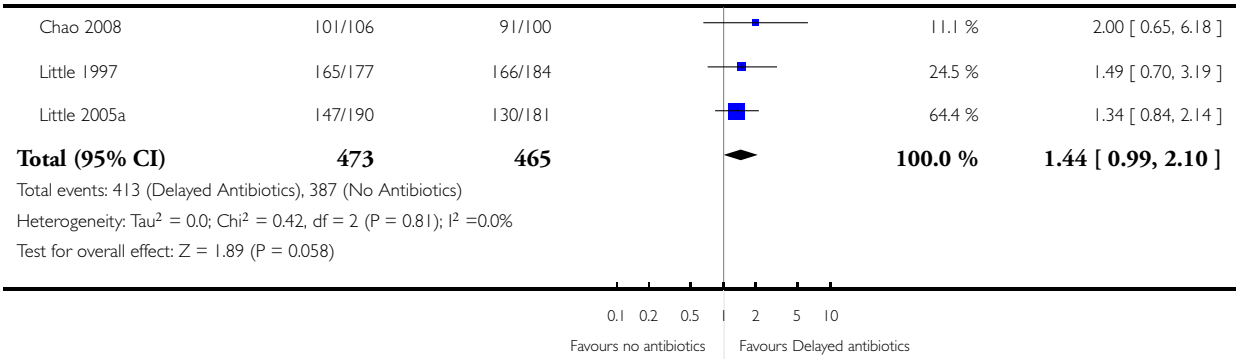
Outcome: 1 Patient satisfaction: delayed antibiotics versus no antibiotics

Study or subgroup	Delayed Antibiotics n/N	No Antibiotics n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Chao 2008	101/106	91/100		11.1 %	2.00 [0.65, 6.18]
Little 1997	165/177	166/184		24.5 %	1.49 [0.70, 3.19]
Little 2005a	147/190	130/181		64.4 %	1.34 [0.84, 2.14]
Total (95% CI)	**473**	**465**		**100.0 %**	**1.44 [0.99, 2.10]**

Total events: 413 (Delayed Antibiotics), 387 (No Antibiotics)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.42$, df = 2 (P = 0.81); $I^2 = 0.0\%$

Test for overall effect: Z = 1.89 (P = 0.058)



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]

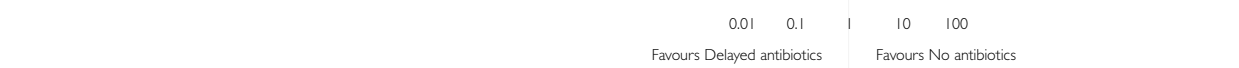
Analysis 18.1. Comparison 18 Adverse events: Delayed versus No Antibiotics, Outcome 1 Vomiting.

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]



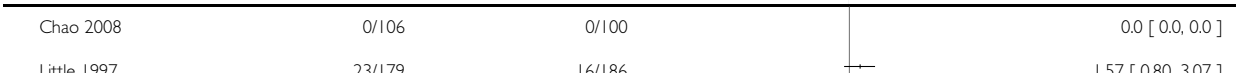
Analysis 18.2. Comparison 18 Adverse events: Delayed versus No Antibiotics, Outcome 2 Diarrhoea.

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		0.0 [0.0, 0.0]
Little 1997	23/179	16/186		1.57 [0.80, 3.07]



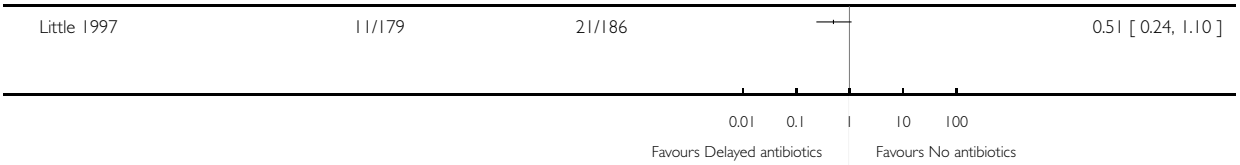
Analysis 18.3. Comparison 18 Adverse events: Delayed versus No Antibiotics, Outcome 3 Rash.

Review: Delayed antibiotics for respiratory infections

Comparison: 18 Adverse events: *Delayed* versus *No* Antibiotics

Outcome: 3 Rash

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	11/179	21/186		0.51 [0.24, 1.10]



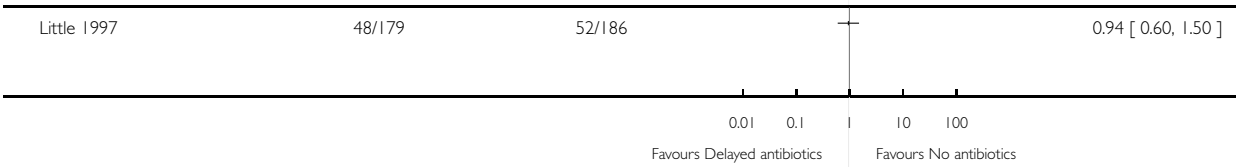
Analysis 18.4. Comparison 18 Adverse events: Delayed versus No Antibiotics, Outcome 4 Stomach ache.

Review: Delayed antibiotics for respiratory infections

Comparison: 18 Adverse events: *Delayed* versus *No* Antibiotics

Outcome: 4 Stomach ache

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	48/179	52/186		0.94 [0.60, 1.50]

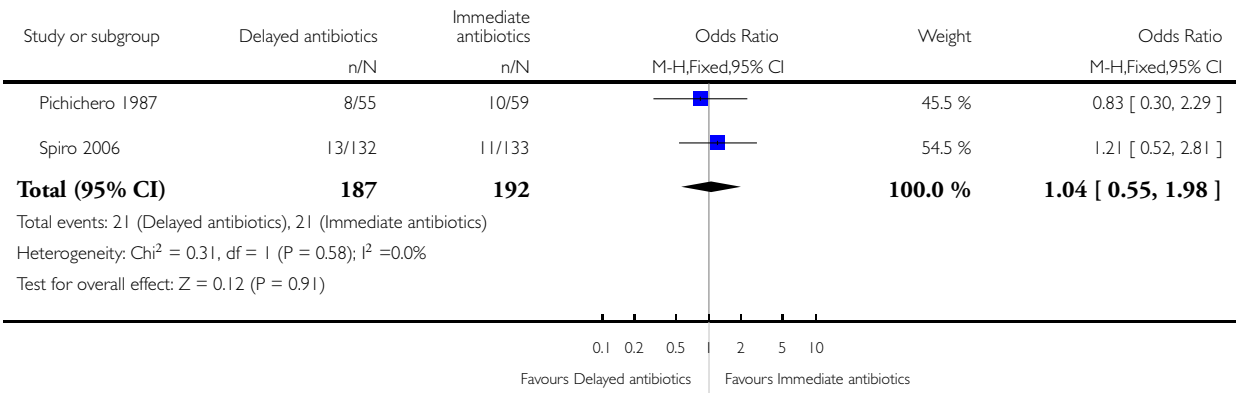


Analysis 19.1. Comparison 19 Re-consultation rate; Delayed versus Immediate Antibiotics, Outcome 1 Reconsultation rate.

Review: Delayed antibiotics for respiratory infections

Comparison: 19 Re-consultation rate; *Delayed* versus *Immediate* Antibiotics

Outcome: 1 Reconsultation rate



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		

Table 1. Summary of outcomes (*Continued*)

	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, 0.84]	
	Compliance			
Little 1997	Vomiting	No difference	OR 1.00 (0.49, 2.05)	
	Diarrhoea	No difference	OR 1.23 (0.67, 2.28)	
	Rash	No difference	OR 0.93 (0.41, 2.11)	
	Stomach ache	No difference	OR 0.82 (0.53, 1.27)	
	Fever (> 37.0 ºC)	*Immediate* antibiotics		
	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)	

Table 1. Summary of outcomes (*Continued*)

	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)	
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)	
	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)	

Table 1. Summary of outcomes (*Continued*)

	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 °C
	Antibiotic use			
	Sore throat			
Little 1997	Antibiotic use (none versus *delayed*)	*No* antibiotics (least antibiotic use)	OR 3.18 (1.85, 5.46)	
	Antibiotic use (*delayed* versus *immediate*)	*Delayed* antibiotics (less than *immediate*)	OR 0.00 (0.00, 0.02)	
	AOM			
Little 2001	Antibiotic use	*Delayed* antibiotics	OR 0.05 [0.02, 0.08]	
Spiro 2006	Antibiotic use	*Delayed* antibiotics	OR 0.09 [0.05, 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, 0.07)	
Little 2005	Antibiotic use (none versus *delayed*)	No difference	OR 1.30 (0.77, 2.21)	
Little 2005	Antibiotic use (*delayed* versus *immediate*)	*Delayed* antibiotics	OR 0.01 (0.00, 0.02)	
	Common Cold			
Arroll 2002	Antibiotic use	*Delayed* antibiotics	OR 0.20 (0.09, 0.44)	
	Patient satisfaction			
	Sore throat			
Little 1997	Patient satisfaction (none versus *delayed*)	No difference	OR 1.49 (0.70, 3.19)	

Table 1. Summary of outcomes (*Continued*)

	Patient satisfaction (*delayed* versus *immediate*)	No difference	OR 0.61 (0.25, 1.49)	
	AOM			
Little 2001	Patient satisfaction (*immediate* versus *delayed*)	*Immediate* antibiotics	OR 0.32 (0.16, 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, 4.01]	
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, 0.97)	
	Common cold			
Arroll 2002	Patient satisfaction	No difference	OR 1.47 (0.32, 6.85)	
	Secondary outcomes			
	Sore throat			
Pichichero 1987	Re-consultation rate	No difference	OR 0.83 (0.30 to 2.29)	
	AOM			
Spiro 2006	Reconsultation rate	No difference	OR 1.21 (0.52 to 2.81)	

APPENDICES

Appendix 1. Ovid EMBASE search strategy

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

Appendix 2. ISI Science Citation Index search strategy

ISI Current Contents Connect (Web of Knowledge)
#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*

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+")

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

WHAT'S NEW

Last assessed as up-to-date: 26 March 2009.

Date	Event	Description
9 December 2010	Amended	Contact details updated.

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 Feeback 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 the articles found in the first publication of this review and extracted data from these articles.

LD and CDM appraised the articles found in this updated review and extracted data.

GS 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)

Anti-Bacterial Agents [*administration & dosage]; Drug Administration Schedule; Drug Prescriptions; Fever [*drug therapy; etiology]; Otitis Media [drug therapy]; Pharyngitis [drug therapy]; Randomized Controlled Trials as Topic; Respiratory Tract Infections [complications; *drug therapy]

MeSH check words

Humans