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Delayed antibiotics for symptoms and complications of respiratory infections [Review]

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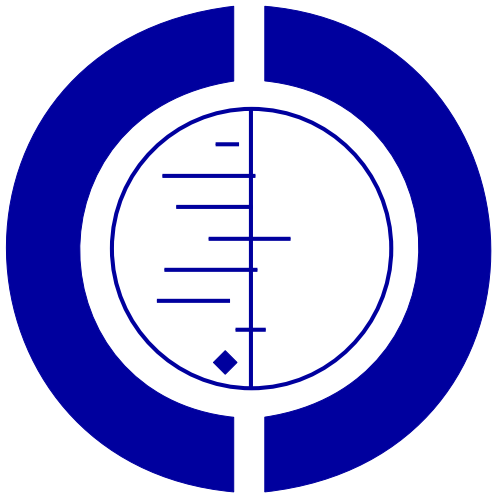

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ABSTRACT

Background
Providing patients with a prescription for antibiotics but suggesting delaying their use is a strategy that reduces antibiotic use. This review asks what effect this practice has on the clinical course of the illness.

Objectives
To evaluate the clinical effect of delayed antibiotic use in acute upper respiratory tract infections compared to immediate use of antibiotics.

Search strategy
The following electronic databases were searched: the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* Issue 1, 2004), MEDLINE (January 1966 to January Week 1 2004), EMBASE (1990 to September 2003) and Current Contents (1998 to 2003).

Selection criteria
Clinical outcomes measured included fever, cough, pain, malaise, complications of disease, adverse effects from antibiotics. Trial quality and data extraction were assessed independently by two reviewers blinded to author and journal for each study.

Data collection and analysis
Data were analysed and reported using Review Manager.

Main results
Seven randomised controlled trials (RCTs) were of high quality. Missing data and marked heterogeneity prevented meta-analysis. Three studies out of six reported fever, all for sore throat, showed more fever in the delayed antibiotic group. The remaining three showed no difference. There was no symptom differences for patients with cough or the common cold. Pain and malaise severity scores at day three significantly favoured the immediate antibiotic group in children with acute otitis media (Little 2001).

El-Daher 1991 showed reduced vomiting in children in the immediate antibiotic group with suspected streptococcal pharyngitis but there was no difference in children with sore throat in Little 1997. Little 1997 and Arroll 2002a showed no difference for the outcome of diarrhoea, while Little 2001 reported less diarrhoea in the delayed antibiotic group in children with otitis media.

Authors' conclusions
Delayed antibiotics have been used in an attempt to reduce the use of antibiotic prescriptions. For most outcomes there is no difference between immediate and delayed antibiotic groups. Three of the six studies, indicated that patients in the delayed antibiotic group had significantly more fever. Pain and malaise scores were worse for children with otitis media in the delayed antibiotic group. This price must be weighed up against the benefits of reduced antibiotic prescribing. Future RCTs of delaying antibiotics should fully report symptoms as well as changes of prescription rates.

PLAIN LANGUAGE SUMMARY

Previous studies have indicated that antibiotics have at best modest benefit for upper respiratory tract infections, which needs to be balanced against adverse effects and the risk of bacteria becoming resistant to antibiotics

Doctors prescribe delayed antibiotics to reduce the consumption of antibiotics while attempting to maintain patient satisfaction. This review looks at the effect of this strategy on the course of the illness in people with upper respiratory tract infections. It found that patients in three out of six studies, all with sore throat, had more fever if they delayed antibiotics. Additionally, children with a middle ear infection had more pain and malaise if they delayed antibiotics. For patients with cough or the common cold there was no difference between delayed and immediate antibiotic groups.

BACKGROUND

The use of antibiotics for upper respiratory tract infections is controversial. Although used this way for 60 years, empirical evidence suggests that antibiotics have only a modest benefit in acute otitis media (Glasziou 2004), pharyngitis (Del Mar 2004), and acute bronchitis (Smucny 2003), and no effect in the common cold (Arroll 2002a). Any benefits have to be weighed against common adverse reactions (including rash, abdominal pain, diarrhoea and vomiting), and cost (Berman 1997; Niemela 1999). Over-prescribing may contribute to community bacterial resistance to antibiotics (Arason 1996, Brook 1998; Verkatesum 1995).

There has been interest in strategies to reduce antibiotic prescribing for acute respiratory infections. One of these strategies is to advise patients to wait or "delay" and only fill the script if their symptoms persist or deteriorate. This strategy of delaying the use of prescribed antibiotics has been evaluated for cough, acute otitis media, pharyngitis and the common cold (Dowell 2001; Arroll 2002a; Little 1997; Little 2001). It is advocated as a means of demonstrating to patients that antibiotics are not always necessary, without making them feel under-serviced (Arroll 2002c). Such methods have been shown to reduce antibiotic prescribing in a systematic review by Arroll 2003. This review by Arroll 2003 showed that delayed antibiotic prescribing for respiratory tract infections had a clinically and statistically significant effect in reducing antibiotic prescribing in the five studies it looked at. The reduction in antibiotic use ranged from a RR 0.77 (95% CI 0.73 to 0.81) Dowell 2001 to RR 0.25 (95% CI 0.19 to 0.34) Little 1997.

A systematic review looking at the effect of delayed antibiotics on the symptoms and adverse effects of antibiotics in upper respiratory tract infections has not been done before. This review asks specifically what effect delayed antibiotics have on the clinical course of upper respiratory tract infections compared to immediate antibiotics.

OBJECTIVES

To evaluate the clinical effect of delayed antibiotic use in acute upper respiratory tract infections compared to immediate use of antibiotics.

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

Randomised controlled trials in which antibiotics are delayed in acute upper respiratory infections compared to antibiotics used immediately. Open randomised trials were accepted.

Types of participants

Patients of all ages defined as having acute otitis media, acute pharyngitis, sore throat, common cold, a viral upper respiratory tract infection, acute sinusitis, and acute bronchitis

Types of intervention

'Delayed antibiotic use' was defined as the use of or advice to use antibiotics more than 48 hours after the initial consultation.

'Immediate antibiotic use' is defined as the immediate use of a prescription of oral antibiotic given at the initial consultation.

Types of outcome measures

Primary clinical outcomes measured were: the presence or absence of fever, cough, pain, duration and severity of illness, complications of the disease, adverse effects from the antibiotics and length of absence from school or work.

Secondary clinical outcomes were re-consultation and other health seeking behaviours such as use of alternative therapies.

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

See: Acute Respiratory Infections Group methods used in reviews.

The following electronic databases were searched for reports of randomised controlled trials: the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* Issue 1,

2004), which includes the Acute Respiratory Infection Groups' specialised register; MEDLINE (January 1966 to January Week 1 2004); EMBASE (1990 to September 2003); and Current Contents 1998 to 2003).

MEDLINE and CENTRAL were searched using the following search strategy, in combination with the highly sensitive search strategy (Dickersin 1994):
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

EMBASE was searched using the following search strategy:
EMBASE (WebSpirs)
#1 explode 'respiratory-tract-infection' / all subheadings
#2 explode 'upper-respiratory-tract-infection' / all subheadings
#3 (respiratory tract infection* in ti) or (respiratory tract infection* in ab)
#4 explode 'otitis-media' / all subheadings
#5 (otitis media* in ti) or (otitis media* in ab)
#6 explode 'pharyngitis-' / all subheadings
#7 (pharyngitis in ti) or (pharyngitis in ab)
#8 explode 'tonsillitis-' / all subheadings
#9 (tonsillitis in ti) or (tonsillitis in ab)
#10 explode 'common-cold' / all subheadings
#11 (common cold in ti) or (common cold in ab)
#12 explode 'bronchitis-' / all subheadings
#13 (bronchitis in ti) or (bronchitis in ab)
#14 explode 'sinusitis-' / all subheadings
#15 (sinusitis in ti) or (sinusitis in ab)
#16 explode 'sore-throat' / all subheadings
#17 (sore throat in ti) or (sore throat in ab)
#18 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17
#19 explode 'antibiotic-agent' / all subheadings
#20 (antibiotic* in ti) or (antibiotic* in ab)
#21 #19 or #20
#22 delay* near prescri*
#23 #18 and #21 and #22

ISI Current Contents Connect (Web of Knowledge) was searched using the following search strategy:
#1 respiratory tract infection*
#2 otitis media
#3 pharyngitis
#4 tonsillitis
#5 common cold*
#6 bronchitis
#7 sinusitis
#8 sore throat
#9 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8
#10 (delay* prescri*)
#11 antibiotic*
#12 #9 AND #10 AND #11

The search was conducted by an expert librarian (RF) in conjunction with one reviewer (GS). Abstracts from the initial search results were scanned to identify trials that loosely meet the inclusion criteria. The references of all relevant retrieved trials were checked to identify the other articles.
The full text articles of the eight retrieved trials were then reviewed by two reviewers (RF and LD) and the inclusion criteria applied independently.

METHODS OF THE REVIEW

We used a modification of a published method to assess the methodological quality (Chalmers 1990). The items were assessed under the following headings:

Method of treatment assignment:
(1) Randomisation method described
(2) Treatment allocation concealed?

Comparability of intervention groups:
(3) Co-interventions avoided or comparable?
(4) Was the compliance measured in all groups?

Blinding:
(5) Was the care provider blinded to the intervention?
(6) Was the patient blinded to the intervention?
(7) Was the outcome assessor blinded to the intervention?

Outcomes:
(8) Were the outcome measures relevant?
(9) Was the withdrawal/ drop-out rate described and acceptable?
(10) Was the timing of the outcome assessment in both groups comparable?
(11) Intention-to-treat analysis performed?

Two reviewers (RF and LD) independently assessed the quality of all the study trials that met the inclusion criteria. Disputes were resolved by consensus of the two reviewers. Assessment was done blind (i.e. without the knowledge of the study results, nor the names of the authors, institutions, journal of publication).

Data extraction was performed independently by two reviewers (RF and LD) on the study trials to be included. Extraction was done blind without knowledge of authors, institutions, journal of publication. Additional data were extracted from graphs of the published articles of El-Daher 1991; Pichichero 1987 on fever severity and symptom scores.

DESCRIPTION OF STUDIES

Seven trials were eligible for inclusion according to the process outlined above. All are comparing immediate antibiotics with delayed antibiotics. Four trials investigated acute pharyngitis/sore throat; one dealt with the common cold; one with otitis media; and one with cough. 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) comparing delayed antibiotics and immediate antibiotics were conducted with a view to evaluating the use of delayed antibiotics to reduce the use of antibiotics for upper respiratory tract infections.

METHODOLOGICAL QUALITY

Studies were considered to be of high quality if they scored six or more out of 11 according to the scale outlined in methods of the review.

Six studies scored greater than six out of 11 by both reviewers and were included. Disagreement over one study was resolved by the two reviewers and was included in the study with a score of six (El-Daher 1991). All seven studies included in the trial had been appropriately randomised. Four studies had attempted to blind some or all aspects of the study i.e. the patients, the doctor and the outcome assessor.

In three studies (El-Daher 1991; Gerber 1990; Pichichero 1987), the aim of the study was to determine if delaying antibiotics prevented relapse of streptococcal pharyngitis. These studies included two arms which compared immediate and delayed antibiotics (48 hours). All patients were given tablets on day 1 to 10 but the patients in the delayed group had placebo tablets for the first two days which means that the patients and the care-providers could be blinded to their intervention group as in Pichichero 1987. In the study of Arroll 2002a patients were randomised and asked to open an envelope which contained one of two sets of instructions. This envelope was opened in front of a research assistant and not the doctor. The research assistant asked the patient not to tell them which set of instructions they received. Patients in this trial were also unaware of the nature of the other intervention arm of the trial. In this way the author attempted to blind both the caregiver and the patient.

In three studies an intention to treat analysis was included. All quality parameters assessed are outlined in Table 03.

RESULTS

Meta-analysis of results has not been included for three reasons. Firstly, data collected by some studies are not available and therefore the available data give an incomplete picture. Secondly, only a few forest plots have more than one study. Thirdly, most of the forest plots with more than one study have marked heterogeneity.

Forest plots without summary totals have been included to illustrated the pooled results available. Table 02 summarises the outcomes available for each study, including the percentage of scripts filled for each arm of the study.

Fever

Of the six studies which reported the outcome of fever, three favoured immediate antibiotics (El-Daher 1991; Little 1997; Pichichero 1987), three showed no difference (Arroll 2002a; Dowell 2001; Gerber 1990). In explaining the marked heterogeneity of results one notes that in the studies of El-Daher 1991 and Pichichero 1987 the temperature of the children was approximately two degrees higher than that of Arroll 2002a on day one. The children from El-Daher 1991 were from Jordan, a developing country, and may have been sicker than children in the other two trials. There were also different selection criteria in each trial. El-Daher 1991 and Pichichero 1987 yielded results favouring immediate antibiotics in children fitting criteria for streptococcal throat infections while Arroll 2002a found results with no difference in adults and children with the common cold on day 3. The study for sore throat in adults and children conducted by Little 1997 also reported less fever in the immediate antibiotics group on day three.

Cough

Only one study Arroll 2002a provided data for this outcome and no difference between the two groups was found. Dowell 2001 looked specifically at delayed versus immediate antibiotics in adults with cough and found there was no difference in symptom scores between the two groups.

Pain

Patients with pain on day 3 did not vary significantly different between delayed and immediate antibiotic groups in the studies of Little 2001, Little 1997 and Arroll 2002a. In the study by El-Daher 1991 patients were significantly more likely to have pain

on day 3 in the delayed antibiotic group than in the immediate antibiotic group (see Table 02). Pain scores were measured in two studies Little 2001 and Pichichero 1987 which favoured immediate antibiotics in Little 2001 but showed no significant difference in Pichichero 1987. Symptoms were measured on a three point Likert scale in Pichichero 1987 (absent, moderate and severe) and a 10 point scale in the study by Little 2001. In summary three studies appear to indicate that there is no difference while two indicate that the group taking delayed antibiotics have more pain on day 3 than the immediate antibiotic group and two did not report the outcome.

Malaise

Two studies did not find a difference for the outcome of malaise between the two groups Arroll 2002a and Little 1997, while two studies found significantly more malaise in the delayed antibiotic group El-Daher 1991 and Little 2001. There was significant heterogeneity in the results of these two studies which may be explained by differences in entry diagnoses, study population and amount of sickness. The Jordanian children with pharyngitis from the El-Daher 1991 study may have been sicker at baseline and responded to antibiotics more than the children with otitis media in the Little 2001 study. This is supported by the significantly higher fever found in the children in the El-Daher 1991 study compared to the children in the study by Little 2001. The adults with common cold in Arroll 2002a represent a different study population and diagnosis.

Other proxies for malaise outcomes reported by Little 2001included last day of crying which favoured the immediate antibiotic group by approximately 16 hours in children with acute otitis media (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).

Reconsultation rates

One study reported reconsultation rates (Pichichero 1987) and found no difference between delayed and immediate antibiotic groups (OR 0.83; 95% CI 0.30 to 2.29).

Adverse effects of antibiotics

Diarrhoea

Two studies showed no significant difference between the two groups for diarrhoea (Arroll 2002a; Little 1997). Little 2001 showed a significant reduction in diarrhoea in the delayed antibiotic group (see Table 02).

Vomiting,

El-Daher 1991 found significantly more vomiting in the delayed antibiotic group. Little 1997 found no difference between the two groups.

Rashes and stomach ache

There was no significant difference between the delayed and immediate antibiotic groups for rashes Little 1997; Little 2001 nor stomach ache Little 1997.

DISCUSSION

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. The remaining studies were conducted to determine if the strategy of delayed antibiotics reduces the number of prescriptions filled for upper respiratory tract infections (Arroll 2002a; Dowell 2001; Little 1997; Little 2001). There have been no randomised controlled trials where the primary aim was evaluation of symptoms for the interventions of delayed antibiotics and immediate antibiotics.

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 much appreciated raw data from some authors. However missing data (Table 01) have impacted on the results of this study and prevented us from presenting meta-analyses. We have tried to overcome this problem by presenting quantative and qualitative results of outcomes for all studies in Table 02. This missing data means that data presented in this review needs to be treated with caution.

Compliance and study design was variable among studies. Earlier studies (El-Daher 1991; Gerber 1990; Pichichero 1987) had rigid protocols with patients blinded to their intervention group with the use of placebo tablets for the first two days in the delayed group. There were no drop outs reported in the Pichichero 1987 and El-Daher 1991 studies with compliance being measured by urine detection of the antibiotic in the study by Pichichero 1987. Later studies conducted by Little 1997, Dowell 2001, Little 2001 and Arroll 2002a reflected the more realistic situation in primary care where the intervention groups consisted of advice to fill a script for antibiotics now or in three days (one week for Dowell 2001). Methods for delaying antibiotics varied in the four later studies. In Little 1997 and Little 2001 patients randomised to the delayed arm could collect a script for antibiotics from the surgery if they were not improving within three days and one week in the study of Dowell 2001. In Arroll 2002a, patients were actually given the script and instructed to fill it three days later if symptoms did not settle. In Arroll 2002a and Little 2001 there was the potential for the delayed script to be filled earlier than the three days advised and therefore impact on symptom scores. The percentage of scripts filled in each study for delayed and immediate groups is presented in Table 02.

It should be noted that Little 1997 and Little 2001 had outcomes favouring immediate antibiotics and had no blinding. However Gerber 1990 did not report blinding and there was no difference between the two groups. Trials which scored at least 1/3 for blinding and showed no difference between the immediate and delayed groups included Dowell 2001; Arroll 2002a and studies which scored at least 1/3 for blinding and showed results favouring immediate antibiotics include El-Daher 1991 and Pichichero 1987.

Symptoms

Fever

Of the three studies El-Daher 1991, Pichichero 1987 and Little 1997 giving results for fever favouring immediate antibiotics, the first two used a study population of children with objective criteria for streptococcal pharyngitis in a paediatric clinic while Little 1997 reported on children and adults with subjective sore throat and an abnormal physical sign in primary care. Of the two studies which showed no difference between the two groups for fever, Gerber 1990 included children with suspected streptococcal pharyngitis and Dowell 2001 included adults with cough. Arroll 2002a reported that for adults with the common cold their fever was slightly less on day 3 if they were in the delayed antibiotic group but was not statistically significant.

El-Daher 1991 showed the biggest difference in temperature of 0.90 (95% CI 0.5 to 1.3) favouring the immediate antibiotic group. This is a large, clinically significant effect. It is worth noting that this study was the only one performed in a developing country. This study was also of the lowest methodological quality but still scored 6/11 meriting inclusion Table 03.

Cough

Two studies both in primary care settings of good methodological quality examined cough and found no significant difference between the immediate and delayed antibiotic groups. Arroll 2002a looked at adults with the common cold and Dowell 2001 looked at adults with cough.

Pain and malaise

Patients with pain on day three favoured the immediate antibiotic group compared to the delayed antibiotics group in two trials (El-Daher 1991; Little 2001). In Little 2001 this translated into a reduced pain score on day 3 in the immediate antibiotic group. This represents a reduction of 0.75 (2.56 to 1.81) on a 10 point Likertcale (95% CI 0.26 to 1.24) for children with acute otitis media in the primary care setting. It is difficult to convert this measure into a clinically relevant outcome. However, a reduction of less than 10% on a 10 point scale is unlikely to be easily detected by patients.

Pichichero 1987 measured pain scores on day 3 for children with suspected streptococcal pharyngitis and found no statistically significant difference between the two groups.

The number of people with malaise on day 3 was also statistically significantly decreased in two trials in the immediate antibiotic group (El-Daher 1991; Little 2001). These results appear to be clinically significant with odds ratios greater than two (see Table 02).

In two high quality studies adults and children with the common cold (Arroll 2002a) and sore throat (Little 1997) in the primary care setting showed no difference in pain and malaise scores on day 3.

Other outcome measures in Little 2001 which may be used as proxies for malaise indicate that for the immediate antibiotic group crying is reduced by approximately 16 hours (0.69 days; 95% CI 0.31 to 1.07) and paracetamol use by half a spoon 0.59 (0.25 to 0.93) in children with otitis media compared to the delayed antibiotic group.

Adverse Events

There were few significant differences found in adverse event outcomes of antibiotics such as diarrhoea, vomiting, rash and stomach ache for the two intervention groups. Little 2001 found that diarrhoea was reduced in the delayed antibiotic group and El-Daher 1991 found that vomiting was reduced in the immediate antibiotic group. It is worth noting that adverse effects reported here may also actually be symptoms of the disease being studied.

Other Considerations

Other research has been interested in delayed antibiotics as a way of reducing the number of antibiotic prescriptions for upper respiratory infections given only modest evidence for the benefits of their use (Arroll 2002b; Del Mar 2004; Glasziou 2004; Smucny 2003) and potential harm from antibiotic resistance and adverse outcomes. This was examined in a systematic review by Arroll 2003 which reported that antibiotic use was significantly lower in the delayed groups versus the immediate antibiotic groups. The reduction in antibiotic use ranged from an RR 0.77 (95% CI 0.73 to 0.81) Dowell 2001to 0.25 (0.19 to 0.34) Little 1997. However the satisfaction of patients with a delayed prescription was less clear. This was not an outcome measure in this review but warrants consideration. The same review Arroll 2003 hypothesised that doctors may be concerned that if they don't prescribe antibiotics then patients would go to another doctor. This concern is supported by Little 2004 who found that perceived patient pressure was a significant factor in influencing doctors' decisions even if they did not think the intervention was needed.

The one study performed in a developing country context where the burden of disease is greatest, markedly favoured the immediate antibiotic group for reducing symptom scores El-Daher 1991. Here, the children enrolled in the study appear to have been sicker at baseline than patients enrolled in the other studies. This is illustrated in the L' Abbé plot (*see* Figure-01) for pain at day 3 (Figure-01)

Summary

It is plausible that antibiotics may reduce symptoms in children with sore throat and otitis media and this has been documented in

other Cochrane reviews (Del Mar 2004; Glasziou 2004). Children in these Cochrane reviews received the greatest benefit from antibiotic treatment at around day three and this was not significant by day seven. It follows that delaying antibiotics by three days as occurred in Little 2001 and El-Daher 1991 may result in more pain and malaise for the child than taking antibiotics immediately. These results for pain and malaise severity are most applicable to children in primary care with otitis media (Little 2001).

For many symptom outcomes there was no difference between immediate and delayed antibiotics in the seven studies included.

Results for pain and malaise in patients with sore throat/pharyngitis were not consistent with two studies showing no difference Little 1997 and Pichichero 1987 and one showing a large effect in favour of immediate antibiotics El-Daher 1991. Results for the common cold (Arroll 2002a) and cough (Dowell 2001) did not show any significant difference in symptom scores.

AUTHORS' CONCLUSIONS

Implications for practice

When considering treatment options for upper respiratory tract infections, the option of delayed antibiotics has been used in an attempt to reduce the use of antibiotic prescriptions. This review shows that for all symptom scores the evidence varies between trials. Most symptom outcomes show no difference between immediate and delayed antibiotic groups. Three of the six studies, all involving patients with sore throat, indicated that patients in the delayed antibiotic group had significantly more fever that their counterparts in the immediate antibiotic group. The other three showed no difference for the outcome of fever. There is evidence indicating that for children with otitis media, pain and malaise scores are worse in the delayed antibiotic group compared to the immediate antibiotic group. This price must be weighed up against the benefits of reduced antibiotic prescribing.

Implications for research

Future randomised controlled trials of delaying antibiotics as an intervention should fully report symptoms as well as changes of prescription rates.

POTENTIAL CONFLICT OF INTEREST

No known conflict of interest.

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Verkatesum P, Innes JA. Antibiotic resistance in common acute respiratory pathogens. *Thorax* 1995;**50**:481–3.

TABLES

Characteristics of included studies

Study	**Arroll 2002a**
Methods	Randomised controlled trial
Participants	Adults and children with the common cold
Interventions	Delayed antibiotics (72 hours) versus Immediate antibiotics
Outcomes	Fever, Duration of fever, Cough, Duration of cough, Pain, absence from school/work, diarrhoea
Notes	
Allocation concealment	A

Study	**Dowell 2001**
Methods	Randomised controlled trial
Participants	Adults and Children with cough

Characteristics of included studies (*Continued*)

Interventions	Delayed Antibiotics (1 week delay) versus Immediate antibiotics (antibiotic of Gp's choice)
Outcomes	Duration of cough
Notes	
Allocation concealment	B

Study	**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 50000iu/kg/day)
Outcomes	Pain, Malaise, Vomiting, Temperature
Notes	
Allocation concealment	B

Study	**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	
Allocation concealment	D

Study	**Little 1997**
Methods	Open Randomised controlled trial
Participants	Adults and Children with sore throat
Interventions	Delayed antibiotics (72 hours) 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	
Allocation concealment	A

Study	**Little 2001**
Methods	Pragmatic randomised controlled trial
Participants	Children aged 6 months to 10 years with otitis media
Interventions	Delayed antibiotics (72 hours) versus immediate antibiotics (Amoxycillin 250 mg tds for one week)
Outcomes	Fever, Severity of pain, Duration of Malaise, Absence from school, use of paracetamol
Notes	
Allocation concealment	B

Study	**Pichichero 1987**
Methods	Open randomised controlled trial
Participants	Children with sore throat (suspected Group A Beta Haemolytic Streptococcus)

Characteristics of included studies (*Continued*)

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	
Allocation concealment	D

Characteristics of excluded studies

Cates 1999	Non randomised trial

ADDITIONAL TABLES

Table 01. Results of data requests

Study	? Other studies	Raw data
Arroll 2002	Responded	Obtained
Dowell 2001	Responded	No response
El-Daher 1991	No response	No response
Gerber 1990	No response	No response
Little 1997	Responded	Unavailable
Little 2001	Responded	Obtained
Pichichero 1987	Responded	No response

Table 02. Summary of Outcomes

Study	Outcome	Favours	Result (with 95% CI)	Notes	Compliance	%Scripts Filled
Pichichero 1987 (pharyngitis)	Fever Severity on Day 3	Immediate Antibiotics	SMD 0.40 (0.05 to 0.75)		Immediate Group 100%	
	Malaise Severity on Day 3	No Difference	WMD 0.20 (-0.11 to 0.51)		Delayed Group 100%	
	Reconsultation rate	No Difference	OR 0.83 (0.30 to 2.29)			
	Pain Severity on Day 3	No Difference	WMD 0.30 (-0.15 to 0.75)			
Gerber 1990 (pharyngitis)	Recurrence rate	No Difference			Immediate Group 88%	
					Delayed Group 93%	
El Daher 1991 (pharyngitis)	Vomiting	Immediate Antibiotics	OR 25.00 (8.65 to 72.25)		Not Reported	
	Pain on Day 3	Immediate	OR 14.51 (7.14			

Table 02. Summary of Outcomes (*Continued*)

Study	Outcome	Favours	Result (with 95% CI)	Notes	Compliance	%Scripts Filled
		Antibiotics	to 29.50)			
	Malaise on Day 3	Immediate Antibiotics	OR 16.49 (5.68 to 47.83)			
	Fever Severity on Day 3	Immediate Antibiotics	WMD 0.90 (0.50 to 1.30)			
Little 1997 (sore throat)	Vomiting	No Difference	OR 0.99 (0.49 to 2.04)			Immediate Group 99%
	Diarrhoea	No Difference	OR 1.22 (0.66 to 2.26)			Delayed Group 31%
	Rash	No Difference	OR 0.93 (0.41 to 2.11)			
	Stomach Ache	No Difference	OR 0.82 (0.53 to 1.27)			
	Fever (>37.0 degrees)	Immediate Antibiotics				
	Sore throat	No Difference				
	Cough	No Difference				
	Malaise	No Difference				
	Analgesic Use	No Difference				
	Time Off Work	No Difference				
Dowell 2001 (cough)	Cough duration	No Difference				Immediate Group - not reported but all received a script at the first consultation
						Delayed Group 45%
Little 2001 (otitis media)	Diarrhoea	Delayed Antibiotics	OR 0.45 (0.22 to 0.91)			Immediate Group 98.5%
	Rash	No Difference	OR 1.21 (0.41 to 2.58)			Delayed Group 24%
	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 02. Summary of Outcomes (*Continued*)

Study	Outcome	Favours	Result (with 95% CI)	Notes	Compliance	%Scripts Filled
	Malaise Severity Day 3	Immediate Antibiotics	WMD 0.43 (0.11 to 0.75)			
	Malaise Severity on Day 7	No Difference	WMD 0.01 (-0.11 to 0.13)			
	Pain Severity on Day 3	Immediate Antibiotics	WMD 0.75 (0.26 to 1.24)			
	Pain severity on Day 7	No Difference	WMD 0.12 (-0.04 to 0.28)			
	Paracetamol consumption	Immediate antibiotics	WMD 0.59 (0.25 to 0.93)			
	Last Day of Crying	Immediate antibiotics	WMD 0.69 (0.31 to 1.07)			
Arroll 2002 (common cold)	Patients with Fever on Day 3	No Difference	OR 0.75 (0.22 to 2.6)			Immediate group 89% (95% CI; 76%-94%)
	Patients with Fever on Day 7	No Difference	OR 0.68 (0.15 to 3.17)			Delayed Group 48% (95% CI; 35%-60%)
	Patients with Diarrhoea	No Difference	OR 0.79 (0.53 to 1.19)			
	Patients with Pain on Day 3	No Difference	OR 1.47 (0.58 to 3.77)			
	Patients with Pain on Day 7	No Difference	OR 0.31 (0.03 to 3.03)			
	Patients with Cough on Day 3	No Difference	OR 0.90 (0.37 to 2.18)			
	Patients with Cough on Day 7	No Difference	OR 0.72 (0.32 to 1.58)			
	Fever Severity Day 3	No Difference	WMD -0.24 (-0.48 to 0.00)			
	Fever Severity on Day 7	Delayed Antibiotics	WMD -0.32 (-0.57 to -0.07)	Mean temperature for both <37 deg C		

Table 03. Quality of Included Studies

Study	Randomisation	Allocation concealed	Co-interventions	Compliance Measured	Blinding	Outcome measures	Intention to treat	Total /11
Pichichero 1987	Yes (1)	Unsure (0)	Unsure (0)	Yes (1)	Care Provider, Patient (2)	relevant (1)		7/11
					Unsure for outcome assessor (0)	withdrawals not reported (0)	yes (1)	
						Timing of outcome assessment comparable (1)		
Gerber 1990	Yes (1)	Yes (1)	avoided (1)	Yes (1)	No blinding (0/3)	relevant (1)	unsure (0)	7/11
						withdrawals reported (1)		
						Timing of outcome assessment comparable (1)		
El Daher 1991	Yes (1)	Unsure (0)	avoided (1)	Unsure (0)	Care Provider, Patient (2)	Relevant (1)		
					Unsure for outcome assessor (0)	With-drawals - unsure (0)	No (0)	6/11
						Timing of outcome assessment comparable (1)		
Little 1997	Yes (1)	Yes (1)	Unsure (0)	Yes (1)	No (0)	Relevant (1)	Yes (1)	7/11
						With-drawals reported (1)		
						Timing of outcome assessment comparable (1)		
Dowell 2001	Yes (1)	Unsure (0)	Unsure (0)	Yes (1)	Outcome assessor (1)	Relevant (1)	Unsure	6/11

Table 03. Quality of Included Studies (*Continued*)

Study	Randomisation	Allocation concealed	Co-interventions	Compliance Measured	Blinding	Outcome measures	Intention to treat	Total /11
					Not the care provider nor the patient (0)	With-drawals reported (1)		
						Timing of outcome assessment comparable (1)		
Little 2001	Yes (1)	Unsure (0)	Avoided (1)	Yes (1)	No (0)	Relevant (1)	Yes (1)	7/11
						With-drawals reported (1)		
						Timing of outcome assessment comparable (1)		
Arroll 2002	Yes (1)	Yes (1)	Unsure (0)	Unsure (0)	Care Provider, Patient (2)	Relevant (1)	Yes (1)	7/11
					Outcome assessor - unsure (0)	Withdrawal reported - unsure (0)		
						Timing of outcome assessment comparable (1)		

ANALYSES

Comparison 01. Fever

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Fever on day 3			Odds Ratio (Random) 95% CI	Totals not selected
02 Fever on day 7			Odds Ratio (Fixed) 95% CI	Totals not selected

Comparison 02. Adverse events

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Vomiting			Odds Ratio (Random) 95% CI	Totals not selected
02 Diarrhoea			Odds Ratio (Fixed) 95% CI	Totals not selected
03 Rash			Odds Ratio (Fixed) 95% CI	Totals not selected
04 Stomach ache			Odds Ratio (Fixed) 95% CI	Totals not selected
05 Reconsultation rate			Odds Ratio (Fixed) 95% CI	Totals not selected

Comparison 03. Pain

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Pain on day 3			Odds Ratio (Random) 95% CI	Totals not selected
02 Pain on day 7			Odds Ratio (Random) 95% CI	Totals not selected

Comparison 04. Malaise

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Malaise on day 3			Odds Ratio (Random) 95% CI	Totals not selected

Comparison 05. Cough

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Cough on day 3			Odds Ratio (Fixed) 95% CI	Totals not selected
02 Cough on day 7			Odds Ratio (Fixed) 95% CI	Totals not selected

Comparison 06. Malaise severity

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
04 Malaise severity day 3			Weighted Mean Difference (Random) 95% CI	Totals not selected
08 Malaise severity day 7			Weighted Mean Difference (Fixed) 95% CI	Totals not selected
09 Last day of crying			Weighted Mean Difference (Fixed) 95% CI	Totals not selected

Comparison 07. Pain severity

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
04 Pain severity day 3			Weighted Mean Difference (Fixed) 95% CI	Totals not selected
07 Pain severity day 7			Weighted Mean Difference (Fixed) 95% CI	Totals not selected

Comparison 08. Paracetamol consumption

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Spoons/day			Weighted Mean Difference (Fixed) 95% CI	Totals not selected

Comparison 09. Fever Severity

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Fever severity on day 3			Weighted Mean Difference (Random) 95% CI	Totals not selected
02 Fever severity on day 7			Weighted Mean Difference (Random) 95% CI	Totals not selected
03 Fever severity on day 1			Weighted Mean Difference (Random) 95% CI	Totals not selected

INDEX TERMS

Medical Subject Headings (MeSH)

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

MeSH check words

Humans

COVER SHEET

Title	Delayed antibiotics for symptoms and complications of respiratory infections
Authors	Spurling GKP, Del Mar CB, Dooley L, Foxlee R
Contribution of author(s)	Chris Del Mar (CDM) conceived the review. Geoff Spurling (GS) and Chris Del Mar designed the review. Ruth Foxlee (RF) and Geoff Spurling performed the literature search. Ruth Foxlee and Liz Dooley (LD) appraised the articles found and extracted data from these articles. Geoff Spurling entered data into RevMan with contributions from Liz Dooley, Ruth Foxlee and Chris Del Mar. Geoff Spurling secured funding for the review with the assistance of Chris Del Mar.
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Date new studies sought but none found	Information not supplied by author
Date new studies found but not yet included/excluded	Information not supplied by author
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Date authors' conclusions section amended	Information not supplied by author
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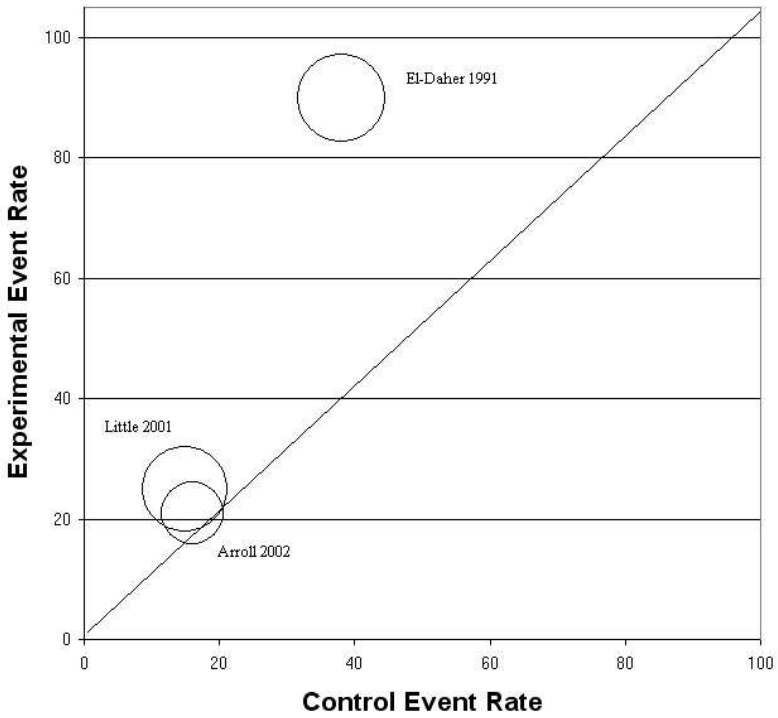
GRAPHS AND OTHER TABLES

Figure 01. Pain on day 3

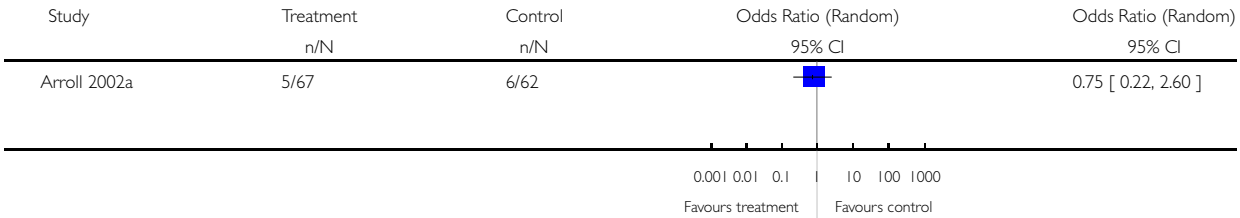


Analysis 01.01. Comparison 01 Fever, Outcome 01 Fever on day 3

Review: Delayed antibiotics for symptoms and complications of respiratory infections

Comparison: 01 Fever

Outcome: 01 Fever on day 3

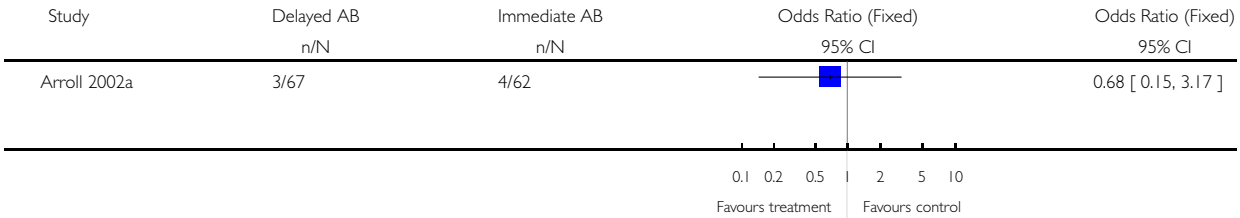


Analysis 01.02. Comparison 01 Fever, Outcome 02 Fever on day 7

Review: Delayed antibiotics for symptoms and complications of respiratory infections

Comparison: 01 Fever

Outcome: 02 Fever on day 7

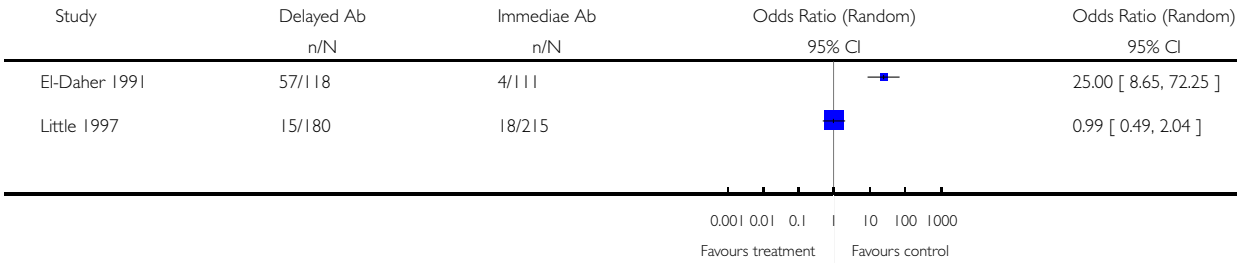


Analysis 02.01. Comparison 02 Adverse events, Outcome 01 Vomiting

Review: Delayed antibiotics for symptoms and complications of respiratory infections

Comparison: 02 Adverse events

Outcome: 01 Vomiting



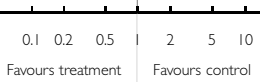
Analysis 02.02. Comparison 02 Adverse events, Outcome 02 Diarrhoea

Review: Delayed antibiotics for symptoms and complications of respiratory infections

Comparison: 02 Adverse events

Outcome: 02 Diarrhoea

Study	Delayed AB n/N	Immediate AB n/N	Odds Ratio (Fixed) 95% CI	Odds Ratio (Fixed) 95% CI
Arroll 2002a	11/67	12/62		0.82 [0.33, 2.02]
Little 1997	23/180	23/215		1.22 [0.66, 2.26]
Little 2001	14/150	25/135		0.45 [0.22, 0.91]

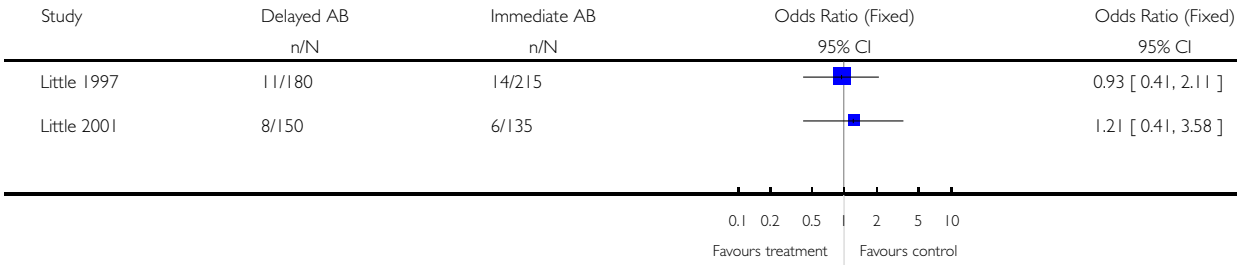


Analysis 02.03. Comparison 02 Adverse events, Outcome 03 Rash

Review: Delayed antibiotics for symptoms and complications of respiratory infections

Comparison: 02 Adverse events

Outcome: 03 Rash

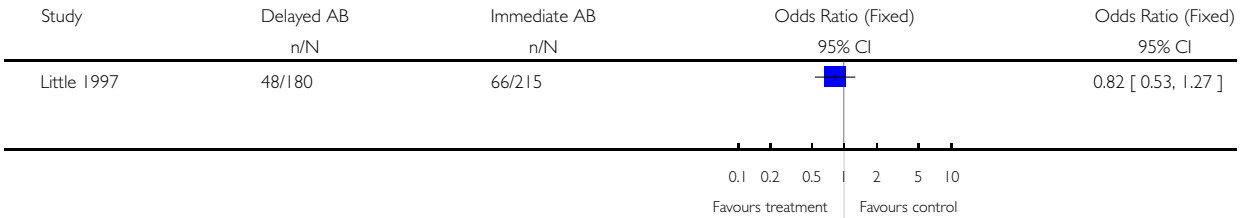


Analysis 02.04. Comparison 02 Adverse events, Outcome 04 Stomach ache

Review: Delayed antibiotics for symptoms and complications of respiratory infections

Comparison: 02 Adverse events

Outcome: 04 Stomach ache

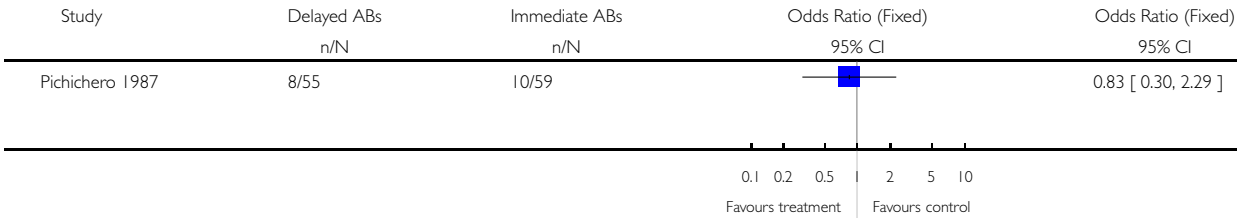


Analysis 02.05. Comparison 02 Adverse events, Outcome 05 Reconsultation rate

Review: Delayed antibiotics for symptoms and complications of respiratory infections

Comparison: 02 Adverse events

Outcome: 05 Reconsultation rate



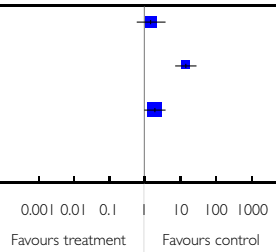
Analysis 03.01. Comparison 03 Pain, Outcome 01 Pain on day 3

Review: Delayed antibiotics for symptoms and complications of respiratory infections

Comparison: 03 Pain

Outcome: 01 Pain on day 3

Study	Delayed Abs n/N	Immediate Abs n/N	Odds Ratio (Random) 95% CI	Odds Ratio (Random) 95% CI
Arroll 2002a	13/61	9/58		1.47 [0.58, 3.77]
El-Daher 1991	106/118	42/111		14.51 [7.14, 29.50]
Little 2001	28/111	15/101		1.93 [0.96, 3.88]



Analysis 03.02. Comparison 03 Pain, Outcome 02 Pain on day 7

Review: Delayed antibiotics for symptoms and complications of respiratory infections

Comparison: 03 Pain

Outcome: 02 Pain on day 7

Analysis 04.01. Comparison 04 Malaise, Outcome 01 Malaise on day 3

Review: Delayed antibiotics for symptoms and complications of respiratory infections

Comparison: 04 Malaise

Outcome: 01 Malaise on day 3

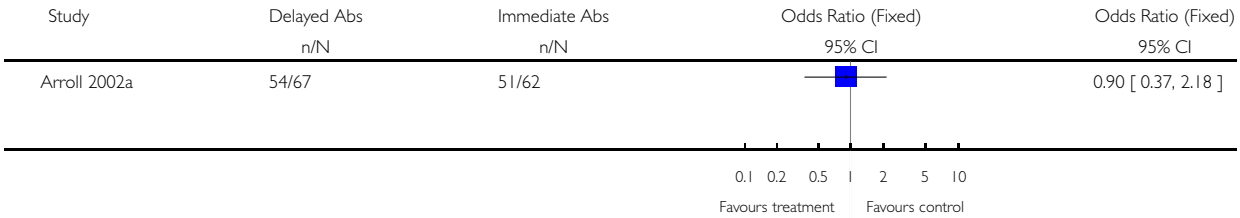
Study	Treatment n/N	Control n/N	Odds Ratio (Random) 95% CI	Odds Ratio (Random) 95% CI
El-Daher 1991	45/118	4/111		16.49 [5.68, 47.83]
Little 2001	45/150	19/135		2.62 [1.44, 4.76]

Analysis 05.01. Comparison 05 Cough, Outcome 01 Cough on day 3

Review: Delayed antibiotics for symptoms and complications of respiratory infections

Comparison: 05 Cough

Outcome: 01 Cough on day 3

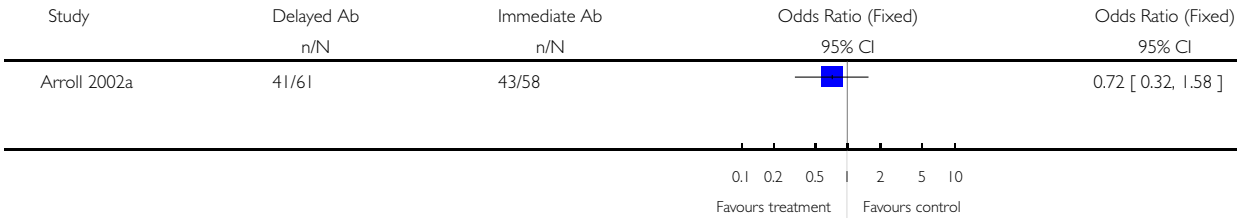


Analysis 05.02. Comparison 05 Cough, Outcome 02 Cough on day 7

Review: Delayed antibiotics for symptoms and complications of respiratory infections

Comparison: 05 Cough

Outcome: 02 Cough on day 7



Analysis 06.04. Comparison 06 Malaise severity, Outcome 04 Malaise severity day 3

Review: Delayed antibiotics for symptoms and complications of respiratory infections

Comparison: 06 Malaise severity

Outcome: 04 Malaise severity day 3

Study	Delayed Ab		Immediate Ab		Weighted Mean Difference (Random)	Weighted Mean Difference (Random)
	N	Mean(SD)	N	Mean(SD)	95% CI	95% CI
Little 2001	150	0.83 (1.69)	134	0.40 (0.97)		0.43 [0.11, 0.75]
Pichichero 1987	55	1.30 (1.00)	59	1.10 (0.67)		0.20 [-0.11, 0.51]

Analysis 06.08. Comparison 06 Malaise severity, Outcome 08 Malaise severity day 7

Review: Delayed antibiotics for symptoms and complications of respiratory infections

Comparison: 06 Malaise severity

Outcome: 08 Malaise severity day 7

Study	Delayed Ab		Immediate Ab		Weighted Mean Difference (Fixed)	Weighted Mean Difference (Fixed)
	N	Mean(SD)	N	Mean(SD)	95% CI	95% CI
Little 2001	150	0.10 (0.49)	134	0.09 (0.50)		0.01 [-0.11, 0.13]

Analysis 06.09. Comparison 06 Malaise severity, Outcome 09 Last day of crying

Review: Delayed antibiotics for symptoms and complications of respiratory infections

Comparison: 06 Malaise severity

Outcome: 09 Last day of crying

Study	Delayed Ab		Immediate Ab		Weighted Mean Difference (Fixed)	Weighted Mean Difference (Fixed)
	N	Mean(SD)	N	Mean(SD)	95% CI	95% CI
Little 2001	150	2.23 (2.00)	135	1.54 (1.22)		0.69 [0.31, 1.07]

Analysis 07.04. Comparison 07 Pain severity, Outcome 04 Pain severity day 3

Review: Delayed antibiotics for symptoms and complications of respiratory infections

Comparison: 07 Pain severity

Outcome: 04 Pain severity day 3

Study	Delayed Ab		Immediate Ab		Weighted Mean Difference (Fixed)	Weighted Mean Difference (Fixed)
	N	Mean(SD)	N	Mean(SD)	95% CI	95% CI
Little 2001	111	2.56 (2.14)	102	1.81 (1.44)		0.75 [0.26, 1.24]
Pichichero 1987	55	1.60 (1.38)	59	1.30 (1.00)		0.30 [-0.15, 0.75]

Analysis 07.07. Comparison 07 Pain severity, Outcome 07 Pain severity day 7

Review: Delayed antibiotics for symptoms and complications of respiratory infections

Comparison: 07 Pain severity

Outcome: 07 Pain severity day 7

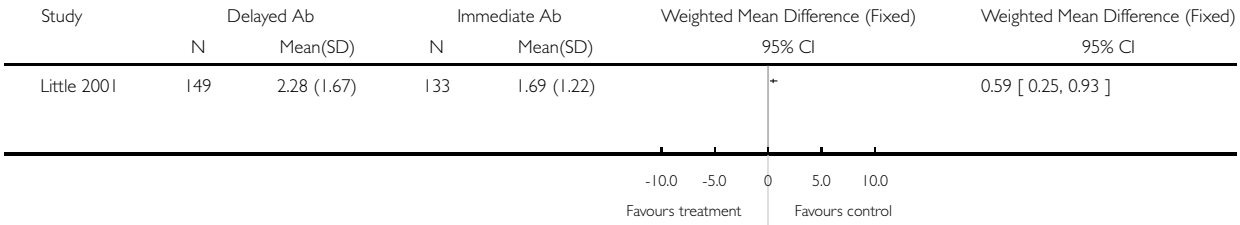
Study	Delayed Ab		Immediate Ab		Weighted Mean Difference (Fixed)	Weighted Mean Difference (Fixed)
	N	Mean(SD)	N	Mean(SD)	95% CI	95% CI
Little 2001	111	1.17 (0.75)	101	1.05 (0.38)		0.12 [-0.04, 0.28]

Analysis 08.01. Comparison 08 Paracetamol consumption, Outcome 01 Spoons/day

Review: Delayed antibiotics for symptoms and complications of respiratory infections

Comparison: 08 Paracetamol consumption

Outcome: 01 Spoons/day



Analysis 09.01. Comparison 09 Fever Severity, Outcome 01 Fever severity on day 3

Review: Delayed antibiotics for symptoms and complications of respiratory infections

Comparison: 09 Fever Severity

Outcome: 01 Fever severity on day 3

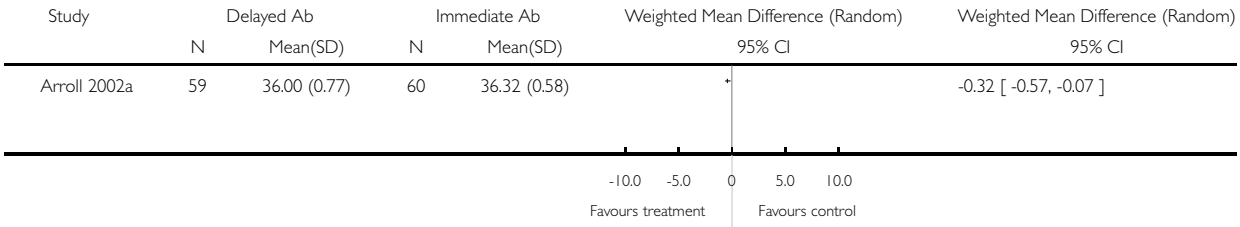
Study	Delayed Ab		Immediate Ab		Weighted Mean Difference (Random)	Weighted Mean Difference (Random)
	N	Mean(SD)	N	Mean(SD)	95% CI	95% CI
Arroll 2002a	61	36.15 (0.73)	58	36.39 (0.58)		-0.24 [-0.48, 0.00]
El-Daher 1991	118	38.00 (1.96)	111	37.10 (0.95)		0.90 [0.50, 1.30]
Pichichero 1987	55	37.20 (1.17)	59	36.80 (0.61)		0.40 [0.05, 0.75]

Analysis 09.02. Comparison 09 Fever Severity, Outcome 02 Fever severity on day 7

Review: Delayed antibiotics for symptoms and complications of respiratory infections

Comparison: 09 Fever Severity

Outcome: 02 Fever severity on day 7



Analysis 09.03. Comparison 09 Fever Severity, Outcome 03 Fever severity on day 1

Review: Delayed antibiotics for symptoms and complications of respiratory infections

Comparison: 09 Fever Severity

Outcome: 03 Fever severity on day 1

Study	Delayed Ab		Immediate Ab		Weighted Mean Difference (Random)	Weighted Mean Difference (Random)
	N	Mean(SD)	N	Mean(SD)	95% CI	95% CI
Arroll 2002a	67	36.74 (0.65)	61	36.87 (0.68)		-0.13 [-0.36, 0.10]
El-Daher 1991	118	38.70 (0.06)	111	38.80 (0.05)		-0.10 [-0.11, -0.09]
Pichichero 1987	55	38.20 (0.83)	59	38.10 (0.89)		0.10 [-0.22, 0.42]