Cochrane Library

**Cochrane** Database of Systematic Reviews

# Paracetamol (acetaminophen) or non-steroidal anti-inflammatory drugs, alone or combined, for pain relief in acute otitis media in children (Review)

de Sévaux JL, Damoiseaux RAMJ, van de Pol AC, Lutje V, Hay AD, Little P, Schilder AGM, Venekamp RP

de Sévaux JL.H., Damoiseaux RAMJ, van de Pol AC, Lutje V, Hay AD, Little P, Schilder AGM, Venekamp RP.
Paracetamol (acetaminophen) or non-steroidal anti-inflammatory drugs, alone or combined, for pain relief in acute otitis media in children.
*Cochrane Database of Systematic Reviews* 2023, Issue 8. Art. No.: CD011534.
DOI: 10.1002/14651858.CD011534.pub3.

**www.cochranelibrary.com**




WILEY

# TABLE OF CONTENTS

[Intervention Review]

# Paracetamol (acetaminophen) or non-steroidal anti-inflammatory drugs, alone or combined, for pain relief in acute otitis media in children

Joline L.H. de Sévaux[1], Roger AMJ Damoiseaux[1], Alma C van de Pol[1], Vittoria Lutje[2], Alastair D Hay[3], Paul Little[4], Anne GM Schilder[1,5,6], Roderick P Venekamp[1]

[1]Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht University, Utrecht, Netherlands. [2]Cochrane Infectious Diseases group, Liverpool School of Tropical Medicine, Liverpool, UK. [3]Centre for Academic Primary Care, Bristol Medical School: Population Health Sciences, University of Bristol, Bristol, UK. [4]Primary Care Research Centre, Primary Care Population Sciences and Medical Education Unit, Faculty of Medicine, University of Southampton, Aldermoor Health Centre, Southampton, UK. [5]National Institute for Health Research University College London Hospitals Biomedical Research Centre , London, UK. [6]evidENT, Ear Institute, University College London, London, UK

**Contact:** Roger AMJ Damoiseaux, r.a.m.j.damoiseaux@umcutrecht.nl.

**Editorial group:** Cochrane Acute Respiratory Infections Group.
**Publication status and date:** New search for studies and content updated (no change to conclusions), published in Issue 8, 2023.

**Citation:** de Sévaux JL.H., Damoiseaux RAMJ, van de Pol AC, Lutje V, Hay AD, Little P, Schilder AGM, Venekamp RP. Paracetamol (acetaminophen) or non-steroidal anti-inflammatory drugs, alone or combined, for pain relief in acute otitis media in children. *Cochrane Database of Systematic Reviews* 2023, Issue 8. Art. No.: CD011534. DOI: 10.1002/14651858.CD011534.pub3.



## ABSTRACT

### Background

Acute otitis media (AOM) is one of the most common childhood infectious diseases. Pain is the key symptom of AOM and central to children's and parents' experience of the illness. Because antibiotics provide only marginal benefits, analgesic treatment including paracetamol (acetaminophen) and non-steroidal anti-inflammatory drugs (NSAIDs) is regarded as the cornerstone of AOM management. This is an update of a review first published in 2016.

### Objectives

Our primary objective was to assess the effectiveness of paracetamol (acetaminophen) or NSAIDs, alone or combined, compared with placebo or no treatment in relieving pain in children with AOM. Our secondary objective was to assess the effectiveness of NSAIDs as compared with paracetamol in children with AOM.

### Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL), Issue 5, April 2023; MEDLINE (Ovid, from 1946 to May 2023), Embase (from 1947 to May 2023), CINAHL (from 1981 to May 2023), LILACS (from 1982 to May 2023), and Web of Science Core Collection (from 1955 to May 2023). We searched the WHO ICTRP and ClinicalTrials.gov for completed and ongoing trials (23 May 2023).

### Selection criteria

We included randomised controlled trials comparing the effectiveness of paracetamol or NSAIDs, alone or combined, for pain relief in non-hospitalised children aged six months to 16 years with AOM. We also included trials of paracetamol or NSAIDs, alone or combined, for children with fever or upper respiratory tract infections if we were able to extract subgroup data on pain relief in children with AOM either directly or after obtaining additional data from study authors. We extracted and summarised data for the following comparisons: paracetamol versus placebo, NSAIDs versus placebo, NSAIDs versus paracetamol, and NSAIDs plus paracetamol versus paracetamol alone.

**Data collection and analysis**

We used standard methodological procedures expected by Cochrane. We rated the overall certainty of evidence for each outcome of interest using the GRADE approach.

**Main results**

We included four trials (411 children) which were assessed at low to high risk of bias.

**Paracetamol versus placebo**

Data from one trial (148 children) informed this comparison. Paracetamol may be more effective than placebo in relieving pain at 48 hours (proportion of children with pain 10% versus 25%, risk ratio (RR) 0.38, 95% confidence interval (CI) 0.17 to 0.85; number needed to treat for an additional beneficial outcome (NNTB) 7; low-certainty evidence). The evidence is very uncertain about the effects of paracetamol on fever at 48 hours (RR 1.03, 95% CI 0.07 to 16.12; very low-certainty evidence) and adverse events (RR 1.03, 95% CI 0.21 to 4.93; very low-certainty evidence). No data were available for our other outcomes of interest.

**NSAIDs versus placebo**

Data from one trial (146 children) informed this comparison. Ibuprofen may be more effective than placebo in relieving pain at 48 hours (proportion of children with pain 7% versus 25%, RR 0.28, 95% CI 0.11 to 0.70; NNTB 6; low-certainty evidence). The evidence is very uncertain about the effect of ibuprofen on fever at 48 hours (RR 1.06, 95% CI 0.07 to 16.57; very low-certainty evidence) and adverse events (RR 1.76, 95% CI 0.44 to 7.10; very low-certainty evidence). No data were available for our other outcomes of interest.

**NSAIDs versus paracetamol**

Data from four trials (411 children) informed this comparison. The evidence is very uncertain about the effect of ibuprofen versus paracetamol in relieving ear pain at 24 hours (RR 0.83, 95% CI 0.59 to 1.18; 2 RCTs, 39 children; very low-certainty evidence); 48 to 72 hours (RR 0.91, 95% CI 0.54 to 1.54; 3 RCTs, 183 children; low-certainty evidence); and four to seven days (RR 0.74, 95% CI 0.17 to 3.23; 2 RCTs, 38 children; very low-certainty evidence).

The evidence is very uncertain about the effect of ibuprofen versus paracetamol on mean pain score at 24 hours (0.29 lower, 95% CI 0.79 lower to 0.20 higher; 3 RCTs, 111 children; very low-certainty evidence); 48 to 72 hours (0.25 lower, 95% CI 0.66 lower to 0.16 higher; 3 RCTs, 108 children; very low-certainty evidence); and four to seven days (0.30 higher, 95% CI 1.78 lower to 2.38 higher; 2 RCTs, 31 children; very low-certainty evidence).

The evidence is very uncertain about the effect of ibuprofen versus paracetamol in resolving fever at 24 hours (RR 0.69, 95% CI 0.24 to 2.00; 2 RCTs, 39 children; very low-certainty evidence); 48 to 72 hours (RR 1.18, 95% CI 0.31 to 4.44; 3 RCTs, 182 children; low-certainty evidence); and four to seven days (RR 2.75, 95% CI 0.12 to 60.70; 2 RCTs, 39 children; very low-certainty evidence).

The evidence is very uncertain about the effect of ibuprofen versus paracetamol on adverse events (RR 1.71, 95% CI 0.43 to 6.90; 3 RCTs, 281 children; very low-certainty evidence); reconsultations (RR 1.13, 95% CI 0.92 to 1.40; 1 RCT, 53 children; very low-certainty evidence); and delayed antibiotic prescriptions (RR 1.32, 95% CI 0.74 to 2.35; 1 RCT, 53 children; very low-certainty evidence).

No data were available on time to resolution of pain.

**NSAIDs plus paracetamol versus paracetamol alone**

Data on the effectiveness of ibuprofen plus paracetamol versus paracetamol alone came from two trials that provided crude subgroup data for 71 children with AOM. The small sample provided imprecise effect estimates, therefore we were unable to draw any firm conclusions (very low-certainty evidence).

**Authors' conclusions**

Despite explicit guideline recommendations on the use of analgesics in children with AOM, the current evidence on the effectiveness of paracetamol or NSAIDs, alone or combined, in children with AOM is limited. Paracetamol and ibuprofen as monotherapies may be more effective than placebo in relieving short-term ear pain in children with AOM. The evidence is very uncertain for the effect of ibuprofen versus paracetamol on relieving short-term ear pain in children with AOM, as well as for the effectiveness of ibuprofen plus paracetamol versus paracetamol alone, thereby preventing any firm conclusions. Further research is needed to provide insights into the role of ibuprofen as adjunct to paracetamol, and other analgesics such as anaesthetic eardrops, for children with AOM.

## PLAIN LANGUAGE SUMMARY

### Drugs to relieve pain for children with acute middle ear infection

**Key messages**

- The current evidence on the effectiveness of painkillers, alone or together, in relieving ear pain in children with acute middle ear infection (acute otitis media (AOM)) is limited.

- Both paracetamol (acetaminophen) and ibuprofen as standalone treatments may be more effective than placebo in relieving short-term ear pain in children with AOM. We are uncertain if there is a difference in effect between ibuprofen and paracetamol and between ibuprofen plus paracetamol and paracetamol alone, thereby preventing any firm conclusions.

- Further research is needed into the role of ibuprofen as an add-on treatment to paracetamol, as well as on other pain relievers such as analgesic eardrops, for children with AOM.

**What is AOM?**

AOM, or acute middle ear infection, is one of the most common childhood infections and is usually preceded by a viral upper respiratory tract infection. Ear pain is the key symptom and central to children's and parents' experience of the illness.

**What did we want to find out?**

We wanted to find out if painkillers are effective for relieving ear pain in children with AOM and which drugs, alone or together, provide the most effective pain relief.

**What did we do?**

We searched for studies that looked at the effectiveness of paracetamol (acetaminophen) or non-steroidal anti-inflammatory drugs (NSAIDs such as ibuprofen), alone or combined, compared with placebo (dummy treatment) or no treatment in relieving pain in non-hospitalised children aged six months to 16 years with AOM. We also wanted to evaluate the effectiveness of NSAIDs as compared with paracetamol in these children. We compared and summarised the results of these studies, and rated our confidence in the evidence based on factors such as study methods and effect sizes.

**What did we find?**

Very limited information was available to assess how useful painkillers are for relieving ear pain in children with AOM. One trial compared paracetamol versus placebo (148 children) and NSAIDs versus placebo (146 children). We found that when used alone, paracetamol and ibuprofen may be more effective than placebo in relieving ear pain at 48 hours (25% of children receiving placebo had pain at 48 hours versus 10% in the paracetamol and 7% in the ibuprofen group). Four trials (411 children) compared ibuprofen versus paracetamol in children with AOM. The evidence is very uncertain about the effect of ibuprofen versus paracetamol in relieving short-term ear pain in children with AOM. The evidence is very uncertain about the effects of paracetamol and ibuprofen on adverse events.

The very limited number of participants prevented us from drawing any firm conclusions on the effects of ibuprofen plus paracetamol versus paracetamol alone.

**What are the limitations of the evidence?**

Due to such issues as study limitations and questions about the applicability of the evidence, we have low confidence in the evidence for all comparisons.

**How up-to-date is this evidence?**

The evidence in this review is current to 23 May 2023.

## SUMMARY OF FINDINGS

### Summary of findings 1. Paracetamol versus placebo for acute otitis media in children

**Paracetamol versus placebo for acute otitis media in children**

**Patients:** children with acute otitis media
**Setting:** outpatients in 4 centres
**Intervention:** paracetamol
**Control:** placebo

| Outcomes | Anticipated absolute effects* (95% CI) | | Relative effect (95% CI) | No. of participants (studies) | Certainty of the evidence (GRADE) | Comments |
|---|---|---|---|---|---|---|
| | Risk with placebo | Risk with paracetamol | | | | |
| **Pain at various time points** | | | | | | |
| 24 hours | No data available | | - | - | - | |
| 48 to 72 hours (48 hours) | Study population | | RR 0.38 (0.17 to 0.85) | 148 (1 RCT) | ⊕⊕⊖⊖ **Low**[a] | NNTB based on the study population risk was 1/(253 to 96)*1000 = 7. |
| | 253 per 1000 | 96 per 1000 (43 to 215) | | | | |
| 4 to 7 days | No data available | | - | - | - | |
| **Adverse events** Follow-up: after 48 hours of treatment, or not specified | Study population | | RR 1.03 (0.21 to 4.93) | 148 (1 RCT) | ⊕⊖⊖⊖ **Very low**[b] | |
| | 40 per 1000 | 41 per 1000 (8 to 197) | | | | |
| **Mean time to resolution of pain** | No data available | | - | - | - | |
| **Mean pain score at various time points** | No data available | | - | - | - | |
| **Fever at various time points** Rectal temperature ≥ 38.5 °C | | | | | | |
| 24 hours | No data available | | - | - | - | |
| 48 to 72 hours (48 hours) | Study population | | RR 1.03 (0.07 to 16.12) | 148 (1 RCT) | ⊕⊖⊖⊖ **Very low**[c] | |

| | | | | | |
|---|---|---|---|---|---|
| | 13 per 1000 | 14 per 1000 (1 to 215) | | | |
| 4 to 7 days | No data available | | - | - | - |
| **Reconsultations** | No data available | | - | - | - |
| **Delayed antibiotic prescriptions** | No data available | | - | - | - |

*__The risk in the intervention group__ (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

**CI:** confidence interval; **NNTB:** number needed to treat for an additional beneficial outcome; **RCT:** randomised controlled trial; **RR:** risk ratio

**GRADE Working Group grades of evidence**
**High certainty:** We are very confident that the true effect lies close to that of the estimate of the effect.
**Moderate certainty:** We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
**Low certainty:** Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
**Very low certainty:** We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]We downgraded the evidence from high to low certainty due to study limitations and questions about the applicability of evidence.
[b]We downgraded the evidence from high to very low certainty due to study limitations and imprecise effect estimate (small sample size and infrequent occurrence of the outcome).
[c]We downgraded the evidence from high to very low certainty due to study limitations, imprecise effect estimate (infrequent occurrence of the outcome), and questions about the applicability of evidence.

### Summary of findings 2. NSAIDs versus placebo for acute otitis media in children

**NSAIDs versus placebo for acute otitis media in children**

**Patients:** children with acute otitis media
**Setting:** outpatients in 4 centres
**Intervention:** ibuprofen
**Control:** placebo

| Outcomes | Anticipated absolute effects* (95% CI) | | Relative effect (95% CI) | No. of participants (studies) | Certainty of the evidence (GRADE) | Comments |
|---|---|---|---|---|---|---|
| | Risk with placebo | Risk with ibuprofen | | | | |
| **Pain at various time points** | | | | | | |
| 24 hours | No data available | | - | - | - | |

| | | | | | | |
|---|---|---|---|---|---|---|
| 48 to 72 hours (48 hours) | Study population | | RR 0.28 (0.11 to 0.70) | 146 (1 RCT) | ⊕⊕⊖⊖ **Low**[a] | NNTB based on the study population risk was 1/(253 to 71)*1000 = 6. |
| | 253 per 1000 | 71 per 1000 (28 to 177) | | | | |
| 4 to 7 days | No data available | | - | - | - | |
| **Adverse events** Follow-up: after 48 hours of treatment, or not specified | Study population | | RR 1.76 (0.44 to 7.10) | 146 (1 RCT) | ⊕⊖⊖⊖ **Very low**[b] | |
| | 40 per 1000 | 70 per 1000 (18 to 284) | | | | |
| **Mean time to resolution of pain** | No data available | | - | - | - | |
| **Mean pain score at various time points** | No data available | | - | - | - | |
| **Fever at various time points** Rectal temperature ≥ 38.5 °C | | | | | | |
| 24 hours | No data available | | - | - | - | |
| 48 to 72 hours (48 hours) | Study population | | RR 1.06 (0.07 to 16.57) | 146 (1 RCT) | ⊕⊖⊖⊖ **Very low**[c] | |
| | 13 per 1000 | 14 per 1000 (1 to 221) | | | | |
| 4 to 7 days | No data available | | - | - | - | |
| **Reconsultations** | No data available | | - | - | - | |
| **Delayed antibiotic prescriptions** | No data available | | - | - | - | |

*__The risk in the intervention group__ (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

**CI:** confidence interval; **NNTB:** number needed to treat for an additional beneficial outcome; **NSAID:** non-steroidal anti-inflammatory drug; **RCT:** randomised controlled trial; **RR:** risk ratio

**GRADE Working Group grades of evidence**
**High certainty:** We are very confident that the true effect lies close to that of the estimate of the effect.
**Moderate certainty:** We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
**Low certainty:** Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

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

[a]We downgraded the evidence from high to low certainty due to study limitations and questions about the applicability of evidence.
[b]We downgraded the evidence from high to very low certainty due to study limitations and imprecise effect estimate (small sample size and infrequent occurrence of the outcome).
[c]We downgraded the evidence from high to very low certainty due to study limitations, imprecise effect estimate (infrequent occurrence of the outcome), and questions about the applicability of evidence.

### Summary of findings 3. NSAIDs versus paracetamol for acute otitis media in children

**NSAIDs versus paracetamol for acute otitis media in children**

**Patients:** children with acute otitis media
**Setting:** community, primary care, secondary care
**Intervention:** ibuprofen
**Control:** paracetamol

| Outcomes | Anticipated absolute effects* (95% CI) | | Relative effect (95% CI) | No. of participants (studies) | Certainty of the evidence (GRADE) |
|---|---|---|---|---|---|
| | Risk with paracetamol | Risk with ibuprofen | | | |
| **Pain at various time points** | | | | | |
| 24 hours | Study population | | RR 0.83 (0.59 to 1.18) | 39 (2 RCTs) | ⊕⊖⊖⊖ **Very low[a]** |
| | 778 per 1000 | 646 per 1000 (459 to 918) | | | |
| 48 to 72 hours | Study population | | RR 0.91 (0.54 to 1.54) | 183 (3 RCTs) | ⊕⊕⊖⊖ **Low[b]** |
| | 178 per 1000 | 162 per 1000 (96 to 274) | | | |
| 4 to 7 days | Study population | | RR 0.74 (0.17 to 3.23) | 38 (2 RCTs) | ⊕⊖⊖⊖ **Very low[a]** |
| | 188 per 1000 | 139 per 1000 (32 to 606) | | | |
| **Adverse events** Follow-up: after 48 hours of treatment, or not specified | Study population | | RR 1.71 (0.43 to 6.90) | 281 (3 RCTs) | ⊕⊖⊖⊖ **Very low[c]** |
| | 30 per 1000 | 51 per 1000 (13 to 207) | | | |

| | | | | | |
|---|---|---|---|---|---|
| **Mean time to resolution of pain** | No data available | | - | - | - |
| **Mean pain score at various time points**** | | | | | |
| 24 hours | The mean pain score with paracetamol was on average 0.29 lower (0.79 lower to 0.20 higher). | The mean pain score with ibuprofen ranged from 2.5 to 3.97. | - | 111<br>(3 RCTs) | ⊕⊖⊖⊖<br>**Verylow**[a] |
| 48 to 72 hours | The mean pain score with paracetamol was on average 0.25 lower (0.66 lower to 0.16 higher). | The mean pain score with ibuprofen ranged from 1.6 to 2.95. | - | 108<br>(3 RCTs) | ⊕⊖⊖⊖<br>**Verylow**[a] |
| 4 to 7 days | The mean pain score with paracetamol was on average 0.30 higher (1.78 lower to 2.38 higher). | The mean pain score with ibuprofen ranged from 1 to 2.2. | - | 31<br>(2 RCTs) | ⊕⊖⊖⊖<br>**Verylow**[a] |
| **Fever at various time points**<br>Rectal temperature ≤ 38.5 °C or < 37.2 °C or parent-reported fever | | | | | |
| 24 hours | Study population | | RR 0.69<br>(0.24 to 2.00) | 39<br>(2 RCTs) | ⊕⊖⊖⊖<br>**Verylow**[a] |
| | 294 per 1000 | 203 per 1000<br>(71 to 588) | | | |
| 48 to 72 hours | Study population | | RR 1.18<br>(0.31 to 4.44) | 182<br>(3 RCTs) | ⊕⊕⊖⊖<br>**Low**[b] |
| | 33 per 1000 | 39 per 1000<br>(10 to 148) | | | |
| 4 to 7 days | Study population | | RR 2.75<br>(0.12 to 60.70) | 39<br>(2 RCTs) | ⊕⊖⊖⊖<br>**Verylow**[a] |
| | 0 per 1000 | 0 per 1000<br>(0 to 0) | | | |
| **Reconsultations** | Study population | | RR 1.13<br>(0.92 to 1.40) | 53<br>(1 RCT) | ⊕⊖⊖⊖<br>**Verylow**[a] |
| | 815 per 1000 | 921 per 1000<br>(750 to 1000) | | | |
| **Delayed antibiotic prescriptions** | Study population | | RR 1.32<br>(0.74 to 2.35) | 53<br>(1 RCT) | ⊕⊖⊖⊖<br>**Verylow**[a] |
| | 407 per 1000 | 538 per 1000<br>(301 to 957) | | | |

*__The risk in the intervention group__ (and its 95% CI) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

**Hay 2009 assessed fever-associated discomfort using a validated comfort scale (no comfort; not quite normal; some pain/distress; crying/very distressed), whereas Little 2013 assessed ear pain using a validated symptom score (ranging from 0 to 6, with 0 = no problem and 6 = as bad as it could be), and Kara 2022 assessed ear pain by rating five behaviours (Face, Legs, Activity, Consolability, and Cry (FLACC)) on a scale of 0 to 2, resulting in a maximum score of 10.

**CI:** confidence interval; **NNTB:** number needed to treat for an additional beneficial outcome; **NSAID:** non-steroidal anti-inflammatory drug; **RCT:** randomised controlled trial; **RR:** risk ratio

---

**GRADE Working Group grades of evidence**
**High certainty:** We are very confident that the true effect lies close to that of the estimate of the effect.
**Moderate certainty:** We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
**Low certainty:** Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
**Very low certainty:** We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

---

[a]We downgraded the evidence from high to very low certainty due to study limitations and imprecise effect estimate (very small sample size).
[b]We downgraded the evidence from high to low certainty due to study limitations and questions about the applicability of evidence.
[c]We downgraded the evidence from high to very low certainty due to study limitations and imprecise effect estimate (small sample size and infrequent occurrence of the outcome).

# BACKGROUND

## Description of the condition

Acute otitis media (AOM) is one of the most common childhood infectious diseases, with an estimated incidence of approximately 300 physician-diagnosed AOM episodes per 1000 person-years in children aged up to two years (Liese 2014). By three years of age, over 80% of all children have experienced at least one AOM episode (Teele 1989). Moreover, AOM is an important cause of antibiotic prescriptions in children (Ashworth 2005; Grijalva 2009). Although severe complications of AOM, such as acute mastoiditis, meningitis, and intracranial abscess, are rare in high-income countries, AOM significantly impairs quality of life for children and their parents and carers. AOM is associated with substantial healthcare resource use and lost workdays for parents and carers (Greenberg 2003; Tong 2018).

AOM is defined by the presence of middle ear effusion together with acute onset of signs and symptoms of middle ear inflammation (Bluestone 2007; Lieberthal 2013). Cardinal signs of AOM are bulging of the eardrum or new onset of ear discharge not due to acute otitis externa; typical AOM symptoms include ear pain and general symptoms of illness such as fever, irritability, and problems feeding and sleeping (Lieberthal 2013). Ear pain due to infection of the middle ear and pressure behind the eardrum is a major symptom of AOM (Lieberthal 2013). Pain is central to children's and parents' experience of the illness (Barber 2014; Schechter 2003). Antibiotics provide only marginal benefits (Rovers 2006; Venekamp 2015), and analgesic treatment, including paracetamol (acetaminophen) and non-steroidal anti-inflammatory drugs (NSAIDs), is regarded as the cornerstone of AOM management in children (Lieberthal 2013), although it does not address the underlying disease course.

## Description of the intervention

The exact mechanism of paracetamol action is not fully understood, but has been assumed to act as a selective inhibitor of cyclooxygenase (COX)-1 and COX-2 in the central nervous system (Bruno 2014). Unlike NSAIDs, paracetamol does not prevent prostaglandin synthesis by competitive binding to the COX enzyme, but modulates the COX pathway through its ability to reduce COX activity (Bruno 2014). Although paracetamol might have some peripheral effects, its main action appears to be located centrally by inhibiting prostaglandin synthesis in the brain (Marzuillo 2014). Due to its minor peripheral effects, paracetamol lacks significant anti-inflammatory activity (van den Anker 2013). When administered as an oral suspension, the peak plasma concentration of paracetamol is reached in around 30 minutes; for oral tablets and suppositories this is approximately 30 to 45 minutes and two to four hours, respectively (Marzuillo 2014). The recommended dose of paracetamol for children is 10 to 15 mg/kg per dose, every four to six hours orally (van den Anker 2013).

In contrast to paracetamol, NSAIDs have both central and peripheral effects and can be divided in traditional and selective COX-2 inhibitors (Bruno 2014). COX-2 inhibition leads to reduced release of pyrogenic molecules in the inflamed cells (mainly prostaglandin E2) causing the anti-inflammatory and analgesic effects of NSAIDs (Bruno 2014; Rainsford 2009), whilst COX-1 inhibition is mainly responsible for gastrointestinal adverse effects (Bruno 2014). Gastrointestinal adverse effects such as peptic ulcers or bleeding are caused by a dual effect of NSAIDs on the gastrointestinal tract: the prostaglandin biosynthesis and maintenance of gastric mucosal integrity (Bruno 2014). Ibuprofen, a non-selective COX inhibitor, is the most commonly used NSAID in children, with a recommended dose of 5 to 10 mg/kg per dose every six to eight hours orally, to a maximum dose of 500 mg per day (van den Anker 2013). The relatively low incidence of serious gastrointestinal adverse effects associated with ibuprofen, as compared with other NSAIDs, is thought to be the result of its relatively short half-life (Rainsford 2009). However, ibuprofen, like other NSAIDs, is associated with rare but serious adverse drug reactions of the skin (Stevens-Johnson syndrome), renal (papillary necrosis), and cardiovascular systems (Rainsford 2009). Furthermore, both ibuprofen and paracetamol have been associated with an increased risk of inducing bronchospasm or asthma in children (Beasley 2008; Rainsford 2009; Sordillo 2015). A meta-analysis found no difference in the odds of developing asthma or presenting an exacerbation of asthma in children who received paracetamol compared to ibuprofen (Sherbash 2020). Compared with paracetamol, ibuprofen has a longer duration of action, and as such, has the advantage of less frequent dosing (every six to eight hours versus every four hours for paracetamol) (van den Anker 2013).

## How the intervention might work

Because pain is a major symptom of AOM in children, current guidance explicitly recommends analgesic treatment, irrespective of antibiotics use (Lieberthal 2013). In daily practice, paracetamol and NSAIDs (ibuprofen) are widely used for relieving pain and fever in children. Paracetamol is generally considered to be well tolerated and safe with only few adverse effects, such as rash and other allergic reactions, when used at therapeutic dosages (Marzuillo 2014; Southey 2009). However, paracetamol has the potential for hepatotoxicity following overdose (Marzuillo 2014). In general, the safety profile of ibuprofen is considered to be comparable with paracetamol when both drugs are used at the recommended doses and in the absence of specific contraindications (children with gastrointestinal bleeding or ulcers, congenital heart disease, severe kidney and liver disease, concurrent use of anticoagulant and steroid drugs, and in children aged less than six months) (Southey 2009; van den Anker 2013).

## Why it is important to do this review

Whilst the effectiveness of analgesic eardrops in children with AOM has been reviewed (Foxlee 2006), this has not been done for paracetamol or NSAIDs, whether alone or combined. Previous Cochrane Reviews on paracetamol or NSAIDs (or both) focused either on children with fever due to infectious diseases (Meremikwu 2005; Wong 2013), or included both children and adults with the common cold (Kim 2013). As such, these reviews did not include randomised controlled trials on paracetamol or NSAIDs (or both) for relieving symptoms in childhood AOM. Since AOM is a specific clinical entity with a high incidence and substantial societal impact, a comprehensive literature search and systematic review was warranted to assess 1) the effectiveness of paracetamol or NSAIDs, alone or combined, compared with placebo or no treatment in relieving pain in children with AOM; and 2) whether the effects of NSAIDs and paracetamol differ in terms of relieving pain in children with AOM.

## OBJECTIVES

Our primary objective was to assess the effectiveness of paracetamol (acetaminophen) or NSAIDs, alone or combined, compared with placebo or no treatment in relieving pain in children with AOM. Our secondary objective was to assess the effectiveness of NSAIDs as compared with paracetamol in children with AOM.

## METHODS

### Criteria for considering studies for this review

#### Types of studies

Randomised controlled trials (RCTs) assessing the effectiveness of paracetamol or NSAIDs, alone or combined, in relieving pain in children with AOM.

We also included trials of paracetamol or NSAIDs, alone or combined, for children with fever or upper respiratory tract infections (URTIs) if we could extract subgroup data on pain relief (including discomfort, distress and/or irritability) in children with AOM (irrespective of the number of eligible children) either directly or upon request from the original trial authors.

We intended to include trials reporting concurrent therapy (e.g. co-treatment with oral or topical antibiotics) if we could make direct comparison between the intervention and control group (e.g. paracetamol with concurrent antibiotic therapy versus placebo with concurrent antibiotic therapy) and if participants in each arm were not treated differently. We defined 'not treated differently' as a maximum of 10% difference in the proportion of children who received the concurrent therapy in the intervention and control groups.

#### Types of participants

We included children aged from six months to 16 years with AOM irrespective of the diagnostic criteria used. We excluded studies on children with grommets (ventilation tubes or tympanostomy tubes) in place and those in which children were hospitalised (see Differences between protocol and review).

#### Types of interventions

We included trials of paracetamol and NSAIDs administered orally or rectally. We excluded trials of paracetamol or NSAIDs administered parenterally (intravenous administration).

We extracted and summarised data for the following comparisons: paracetamol versus placebo, NSAIDs versus placebo, NSAIDs versus paracetamol, NSAIDs plus paracetamol versus paracetamol alone.

#### Types of outcome measures

We analysed primary and secondary outcomes, but they were not used as a basis for study inclusion or exclusion.

##### *Primary outcomes*

1. Proportion of children with pain (yes/no) as rated by parents or carers or children themselves at various time points after study participation (24 hours, 48 to 72 hours, 4 to 7 days).
2. Adverse events likely to be related to the use of paracetamol or NSAIDs (or both), such as kidney failure or dysfunction, liver failure or dysfunction, gastrointestinal complaints or bleeding, and hypersensitivity reactions such as erythema, urticaria (hives, skin itching), or anaphylactic shock.

##### *Secondary outcomes*

1. Proportion of children with at most mild pain (defined as pain less than or equal to 3/10 on a 0-to-10 numerical pain rating scale or less than or equal to 30 mm on a 0-to-100-millimetre visual analogue scale) as rated by parents, carers, or patients at various time points (24 hours, 48 to 72 hours, 4 to 7 days).
2. Mean time to resolution of pain.
3. Mean pain score at various time points (24 hours, 48 to 72 hours, 4 to 7 days) using validated pain scores.
4. Disease-specific quality of life as measured by a validated instrument (e.g. AOM Severity of Symptoms Scale (SOS) survey, Otitis Media-6 (OM-6) questionnaire).
5. Mean time to resolution of fever.
6. Proportion of children with fever at various time points (24 hours, 48 to 72 hours, 4 to 7 days).
7. Proportion of children with reconsultations at various time points.
8. Proportion of children with (delayed) antibiotic prescriptions at various time points.
9. Total days lost from nursery or school for children because of AOM.
10. Total days lost from work or education for parents and carers because of their child's AOM.
11. Serious complications related to AOM such as acute mastoiditis and meningitis.

### Search methods for identification of studies

We conducted systematic searches for RCTs and controlled clinical trials. There were no language, publication year, or publication status restrictions. We searched up to 23 May 2023.

#### Electronic searches

We searched the Cochrane Central Register of Controlled Trials (CENTRAL), Issue 5, April 2023, which contains the Cochrane Acute Respiratory Infections Group Specialised Register (Appendix 1), MEDLINE (1946 to 23 May 2023) (Appendix 2), Embase (1947 to 23 May 2023) (Appendix 3), CINAHL (Cumulative Index to Nursing and Allied Health Literature) (1981 to 23 May 2023) (Appendix 4), LILACS (Latin American and Caribbean Health Science Information database) (1982 to 23 May 2023) (Appendix 5), and Web of Science Core Collection (1955 to 23 May 2023) (Appendix 6). We used the Cochrane Highly Sensitive Search Strategy for identifying randomised trials in MEDLINE: sensitivity- and precision-maximising version (2008 revision); Ovid format and adapted the search strategy for Embase, CINAHL, LILACS, and Web of Science searches.

#### Searching other resources

We searched the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (trialsearch.who.int/) and ClinicalTrials.gov (clinicaltrials.gov/) for completed and ongoing trials on 23 May 2023. We scanned the reference lists of identified publications for additional trials and contacted trial authors as necessary. We also searched MEDLINE, Trip medical database, and the Cochrane Library to retrieve any published systematic

reviews relevant to this review and scanned the citations of identified reviews for additional trials. Furthermore, we searched the extended abstracts published in the Proceedings from the International Symposia on Recent Advances in Otitis Media (grey literature) for any additional trials.

## Data collection and analysis

### Selection of studies

After de-duplication using EndNote software (EndNote 2013), two review authors (JLHdS, RPV for the 2023 update) independently screened the titles and abstracts and scanned citations of potentially relevant reviews retrieved from database searches using Rayyan software (Rayyan 2016). The same review authors independently reviewed the full texts of potentially relevant studies for inclusion in the review. We resolved any disagreements by discussion. We recorded the selection process in sufficient detail to complete a study flow diagram (Figure 1) and a Characteristics of excluded studies table.

**Figure 1. Study flow diagram.**

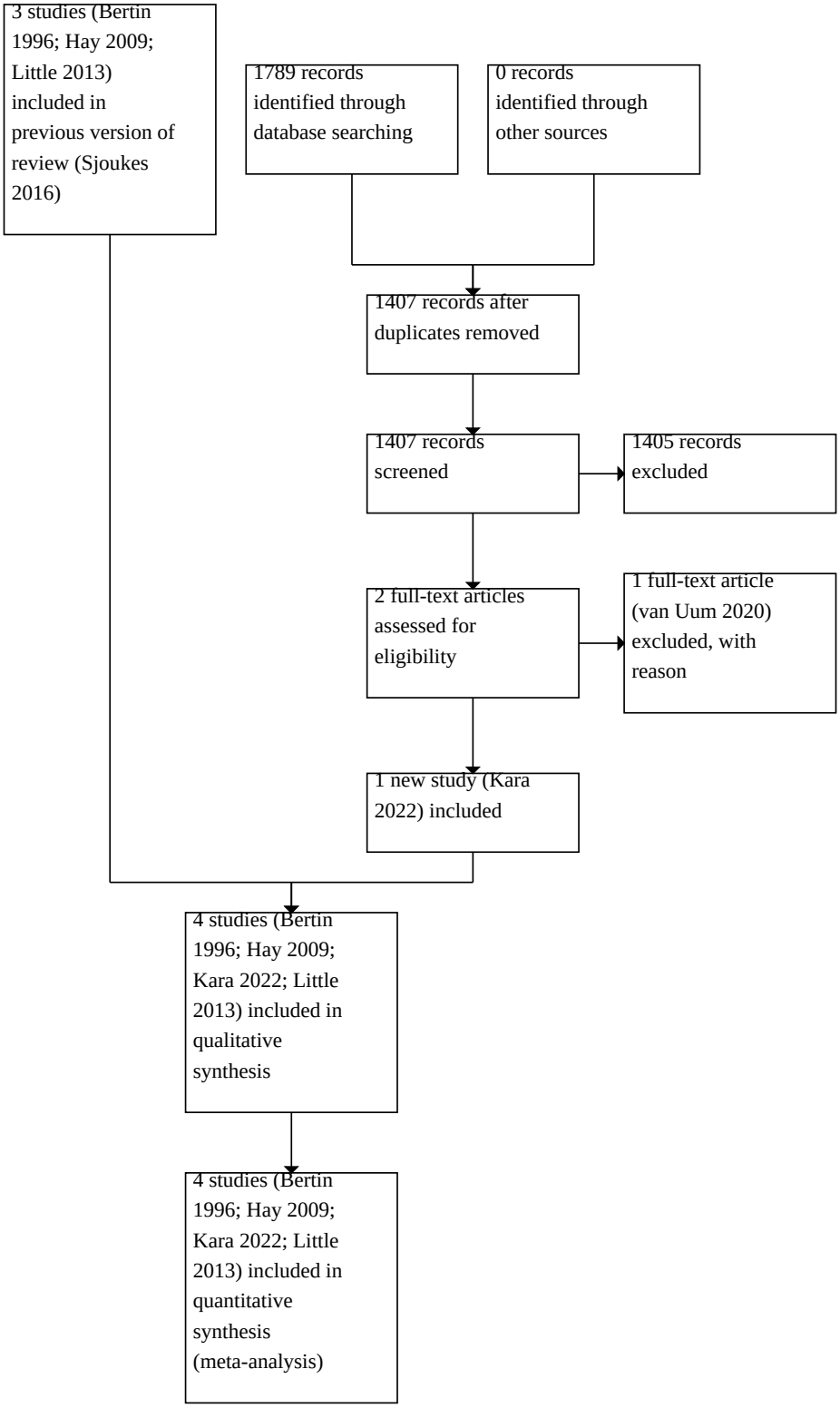


**Figure 1. (Continued)**

### Data extraction and management

Two review authors (JLHdS, RPV for the 2023 update) independently extracted data from the included studies using standardised data extraction forms. We extracted the following information from each trial.

1. Study characteristics: setting, design, method of data analysis.
2. Participants: study population, number of participants in each group, participant characteristics including age, gender, ethnicity.
3. Interventions: type of intervention used including timing and dosage and route of administration.
4. Outcomes: primary and secondary outcomes recorded, time points.

We resolved any disagreements by discussion.

### Assessment of risk of bias in included studies

Two review authors (JLHdS, RPV for the 2023 update) independently assessed the methodological quality of the included trials. We resolved any disagreements by discussion. We assessed risk of bias using the risk of bias tool as described in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We judged the following domains as at low, high, or unclear risk of bias.

1. Sequence generation (selection bias)
2. Allocation concealment (selection bias)
3. Blinding of participants and personnel (performance bias)
4. Blinding of outcome assessment (detection bias)
5. Incomplete outcome data (attrition bias)
6. Selective outcome reporting (reporting bias)
7. Other sources of bias

### Measures of treatment effect

We expressed dichotomous outcomes as risk ratios (RRs) with accompanying 95% confidence intervals (CIs) and calculated the number needed to treat for an additional beneficial outcome (NNTB). We expressed continuous outcome variables either as mean differences (MDs) if reported on the same scale or standardised mean differences (SMD) if different continuous scales were used, with accompanying 95% CIs.

### Unit of analysis issues

We did not identify any studies with non-standard designs, such as cross-over or cluster-randomised trials.

### Dealing with missing data

In the case of missing data, we contacted corresponding authors of the included trials to provide additional information. In primary analyses, we analysed available data according to the intention-to-treat (ITT) principle, that is we analysed all participants in the groups to which they had originally been allocated. For dichotomous outcomes, we proposed to assess the impact of incomplete data reporting by performing scenario analyses (best- and worst-case scenarios). For mean ear pain score at various time points, we proposed to assess the impact of missing outcome data by using the baseline-observation-carried-forward approach (Moore 2012).

### Assessment of heterogeneity

We considered both clinical and statistical heterogeneity. We assessed the level of clinical diversity amongst trials by reviewing the included studies for potential differences in study populations, interventions, and outcomes measured. We assessed statistical heterogeneity for each outcome by visual inspection of forest plots and using the $Chi^2$ test, with a significance level set at $P < 0.10$, and the $I^2$ statistic (Higgins 2021): $I^2$ values of 40% to 60% may represent moderate heterogeneity, 50% to 90% may represent substantial heterogeneity, and 75% to 100% represent considerable heterogeneity (Higgins 2021).

Where there was substantial statistical heterogeneity, we proposed to carry out prespecified subgroup analyses and sensitivity analyses based on risk of bias (see Subgroup analysis and investigation of heterogeneity; Sensitivity analysis). If these analyses did not completely resolve statistical heterogeneity, we employed a random-effects (DerSimonian and Laird) model to provide a more conservative effect estimate (DerSimonian 1986).

### Assessment of reporting biases

We searched the internet and ClinicalTrials.gov (clinicaltrials.gov/) for relevant study protocols to determine if all outcomes listed in the study protocols had been published and if all reported outcomes were predefined. We intended to assess reporting biases by using funnel plots if there were at least 10 trials included in the meta-analysis (Higgins 2021).

### Data synthesis

We primarily performed available-case analyses, so using data for every participant for whom the outcome was obtained, according to the ITT principle.

For both primary and secondary dichotomous outcomes measured at various time points, we primarily performed a meta-analysis using a wide window of one to seven days. In secondary analyses, we used the specific time point reported in most studies. We performed statistical analyses using Review Manager Web software (RevMan Web 2022).

For the comparison of NSAIDs plus background therapy (paracetamol) versus background therapy only, we performed a meta-analysis of studies comparing NSAIDs plus background therapy versus background therapy only.

For dichotomous data, we calculated RR with 95% CIs using the Mantel-Haenszel method with a fixed-effect model if appropriate, or the random-effects (DerSimonian and Laird) model where unexplained heterogeneity was found (see Assessment of

heterogeneity) (DerSimonian 1986). We also calculated the NNTB or number needed to treat for an additional harmful outcome (NNTH) based on the average risks of the control groups in the included studies (study population) (Higgins 2021).

If we deemed meta-analysis inappropriate for a given outcome, we presented descriptive statistics only.

### Subgroup analysis and investigation of heterogeneity

We planned to investigate heterogeneity by conducting subgroup analysis for the following categories if sufficient data (at least 10 studies) were available.

1. Age (up to two years versus two years and older), since previous evidence indicates that age might be an important effect modifier.
2. Route of administration of analgesics (oral versus rectal), since the effect of the interventions may differ between routes of administration.
3. Concurrent therapy (concurrent antibiotic therapy versus no concurrent antibiotic therapy), since concurrent therapy may alter the effects of the interventions.
4. Definition of AOM (AOM diagnosis based solely on symptoms versus AOM diagnosis based on symptoms and bulging of the eardrum or new onset of ear discharge not due to acute otitis externa), since the certainty of diagnosis may impact the effectiveness of the interventions.

### Sensitivity analysis

We intended to undertake sensitivity analysis to explore whether key methodological factors affected the main result; to make informal comparisons between the different ways of estimating the effect under different assumptions; and to assess the impact of incomplete data reporting by performing scenario analyses at various time points. However, we were unable to conduct these analyses because of the small number of outcomes reported by the few included studies, and the relatively low number of missing data for our predefined outcomes in the few included studies.

### Summary of findings and assessment of the certainty of the evidence

Two review authors (JLHdS, RPV for the 2023 update) independently assessed the certainty of evidence. We resolved any disagreements by discussion. We used the GRADE approach to rate the overall certainty of evidence for any of the outcomes of interest reported in the included trials (Atkins 2004). There are four possible ratings: high, moderate, low, and very low. The GRADE approach rates evidence from RCTs that do not have serious limitations as high certainty. However, several factors can lead to the downgrading of the evidence. The degree of downgrading is determined by the seriousness of the following factors: study limitations, consistency of effect, imprecision, indirectness, and publication bias, to assess the certainty of a body of evidence as it relates to the studies that contribute data to the meta-analyses for the prespecified outcomes. We used the methods and recommendations described in Chapter 14 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2021), employing GRADEpro GDT software (GRADEpro GDT). We justified all decisions to downgrade the certainty of the evidence using footnotes, and made comments to aid the reader's understanding of the review where necessary.

Summary of findings tables are provided for the main comparisons of interest: paracetamol versus placebo (Summary of findings 1), NSAIDs versus placebo (Summary of findings 2), and NSAIDs versus paracetamol (Summary of findings 3), including what we considered to be the seven most important outcomes, as follows.

1. Proportion of children with pain (yes/no) at various time points (24 hours, 48 to 72 hours, 4 to 7 days).
2. Adverse events.
3. Mean time to resolution of pain.
4. Mean pain score at various time points (24 hours, 48 to 72 hours, 4 to 7 days) using validated pain scores.
5. Proportion of children with fever at various time points (24 hours, 48 to 72 hours, 4 to 7 days).
6. Proportion of children with reconsultations at various time points.
7. Proportion of children with (delayed) antibiotic prescriptions at various time points.

We did not create a summary of findings table for our fourth comparison, NSAIDs plus paracetamol versus paracetamol alone, given the very limited amount of data available for analysis.

## RESULTS

### Description of studies

See Characteristics of included studies and Characteristics of excluded studies.

### Results of the search

This review is an update of a Cochrane Review published in 2016 (Sjoukes 2016). In the 2016 review, our electronic database searches identified a total of 1869 records. Following removal of duplicates, we assessed 1573 unique articles. We identified 24 potentially eligible articles based on title and abstract screening. After reviewing full-text reports, we excluded 22 articles: three were non-randomised studies (Campos 1992; Schuetz 2014; Siegel 2003); five included only adults (Azuma 2010; Eccles 2006; Motoichi 1997; Nouri 1984; Ryan 1987); two did not include children with AOM (Caretti 1986; Lozano Gonzalez 1989); one included hospitalised children (Polidori 1993); and 11 did not include relevant interventions and comparators (see also Excluded studies) (Cappella 1993; Dasgupta 2002; Fort 2000; Kim 2013; Metta 2000; Milvio 1984; Passali 2001; Siquet 1983; Stipon 1983; Weippl 1985; Yoon 2008). We therefore included two studies identified from our electronic database searches in the original review (Bertin 1996; Little 2013). Little 2013 did not report subgroup data for children with AOM in the trial publication; data were provided by the first author of this trial (Paul Little).

After reviewing the reference lists of relevant systematic reviews, we identified three additional potentially relevant articles (Hay 2009; McIntyre 1996; Sarrell 2006). We excluded one study because it included hospitalised children (McIntyre 1996). Since neither Hay 2009 nor Sarrell 2006 reported subgroup data for children with AOM, we contacted the lead trial authors. We did not succeed in obtaining additional data in relation to Sarrell 2006, but relevant data were provided by the first author (Alastair Hay) for Hay 2009. Adding this study to the two studies retrieved from our electronic database searches led to a total of three included studies (Bertin 1996; Hay 2009; Little 2013).

For the current update, our searches of the electronic databases (August 2016 to May 2023) retrieved 1789 records. After de-duplication, we screened the titles and abstracts of 1407 unique records and identified two additional potentially eligible articles. We excluded one article based on full-text review that included an intervention that was not suitable for inclusion in the review (van Uum 2020). We therefore included one additional study in this update (Figure 1) (Kara 2022). Kara 2022 reported median pain scores, but mean pain scores and standard deviations were provided by the first author of this trial (Ateş Kara).

We identified no additional relevant trials or completed studies after searching the WHO ICTRP and ClinicalTrials.gov trial registries for completed and ongoing trials.

### Included studies

We included four studies that presented data for a total of 411 children with AOM (Bertin 1996; Hay 2009; Kara 2022; Little 2013). Methods, participants, interventions, and outcomes of the included studies are described in the Characteristics of included studies table.

#### *Design*

Two trials applied a three-arm, parallel group, double-blind design (Bertin 1996; Hay 2009); one was a four-arm, parallel-group, open-label design (Kara 2022); and one was a 3 x 2 x 2 factorial, open-label design (Little 2013).

#### *Participants and settings*

In Bertin 1996, all 219 children aged from one year to seven years were diagnosed with AOM. Hay 2009 included 156 febrile children aged from six months to six years, of whom 26 were diagnosed with AOM; Little 2013 included 889 children aged three years and over with respiratory tract infections, of whom 82 had AOM. We therefore included data from 327 children. Kara 2022 included 184 children with AOM, of whom 84 received either paracetamol or ibuprofen without analgesic ear drops and were eligible for inclusion in the review.

AOM diagnosis was based on the aspect of the eardrum in Bertin 1996 and based on the American Academy of Pediatrics Guideline 2013 criteria in Kara 2022 (Lieberthal 2013), whereas AOM was diagnosed either by the general practitioner or research nurse without further specification of diagnostic criteria in Hay 2009 and Little 2013.

Little 2013 was performed in a primary care setting; Hay 2009 in the community and primary and secondary care settings; and in Bertin 1996 (all children were seen as outpatients in four centres without further specification) and Kara 2022 (all children were seen in 15 centres in Turkey without further specification) the setting was unclear.

#### *Interventions and comparators*

Bertin 1996 compared paracetamol (10 mg/kg three times daily) versus NSAIDs (ibuprofen 10 mg/kg three times daily) versus placebo. Hay 2009, a three-arm, parallel-group trial, compared paracetamol (15 mg/kg orally, maximum of four doses in 24 hours) versus NSAIDs (ibuprofen 10 mg/kg, maximum of three doses in 24 hours) versus NSAID plus paracetamol. Little 2013 applied a 3 x 2 x 2 factorial design and compared paracetamol versus NSAIDs (ibuprofen) versus NSAIDs (ibuprofen) plus paracetamol. Children in Little 2013 were randomised to one of the three treatment groups, but also to one of two dosing regimens (regularly or as required) and one of two steam inhalation therapy groups (steam versus no steam). Doses of paracetamol and ibuprofen used in this trial were the maximum recommended by the British National Formulary (which varies by age) (www.bnf.org/products/bnf-online/). Kara 2022, a four-arm, parallel-group trial, compared paracetamol (10 mg/kg four times daily) only versus paracetamol (10 mg/kg four times daily) with topical anaesthetic 1% lidocaine (four drops to each ear topically, three times daily) versus ibuprofen (7.5 mg/kg three times daily) only versus ibuprofen (7.5 mg/kg three times daily) with topical anaesthetic 1% lidocaine (four drops to each ear topically, three times daily).

Bertin 1996 prescribed concurrent antibiotic therapy (cefaclor 15 mg to 30 mg/kg twice daily for seven days). Furthermore, children with fever > 39 °C could be given paracetamol (30 mg to 60 mg) in addition to the studied treatments in Bertin 1996. In Kara 2022, the choice of concurrent antibiotic treatment or a watchful-waiting approach was at the discretion of the treating physician.

#### *Outcomes*

Relevant data derived from at least one trial could be extracted for all outcomes, except for the secondary outcomes days lost from nursery or school for children because of AOM and days lost from work or education for parents and carers because of their child's AOM.

In Bertin 1996, ear pain was reported as a dichotomous outcome (yes versus no). Hay 2009 assessed fever-associated discomfort using a validated comfort scale (no comfort; not quite normal; some pain/distress; crying/very distressed), whereas Little 2013 assessed ear pain using a validated symptom score (ranging from 0 to 6 with 0 = no problem and 6 = as bad as it could be), and Kara 2022 assessed ear pain score using the Face, Legs, Activity, Cry, and Consolability (FLACC) scale. The FLACC scale measures pain intensity by rating five behaviours (face, legs, activity, consolability, and cry) on a scale of 0 to 2, resulting in a maximum score of 10.

#### *Funding sources*

In Bertin 1996, study medications were supplied by a pharmaceutical company (Ethypharm); no further details were provided about the role of this company in the design, conduct, analysis, or reporting of the trial. Two other trials were funded by governmental (non-commercial) grants (Hay 2009; Little 2013). In Hay 2009, study medications were purchased from and provided by two companies (Pfizer and DHP Investigational Medicinal Products); these companies had no role in the design, conduct, analysis, or reporting of the trial. No information about funding sources was provided in Kara 2022.

### Excluded studies

We excluded 25 studies:

1. three were non-randomised studies (Campos 1992; Schuetz 2014; Siegel 2003);
2. five included only adults (Azuma 2010; Eccles 2006; Motoichi 1997; Nouri 1984; Ryan 1987);
3. two did not include children with AOM (Caretti 1986; Lozano Gonzalez 1989);

4. two included hospitalised children (McIntyre 1996; Polidori 1993);
5. 12 did not include relevant interventions and comparators (Cappella 1993; Dasgupta 2002; Fort 2000; Kim 2013; Metta 2000; Milvio 1984; Passali 2001; Siquet 1983; Stipon 1983; van Uum 2020; Weippl 1985; Yoon 2008); and
6. one did not report crude subgroup data of children with AOM, and we were unsuccessful in obtaining additional data from the authors (Sarrell 2006).

### Risk of bias in included studies

The included studies were assessed at low to high risk of bias. Details of the risk of bias assessment are summarised in Figure 2 and Figure 3.

**Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.**

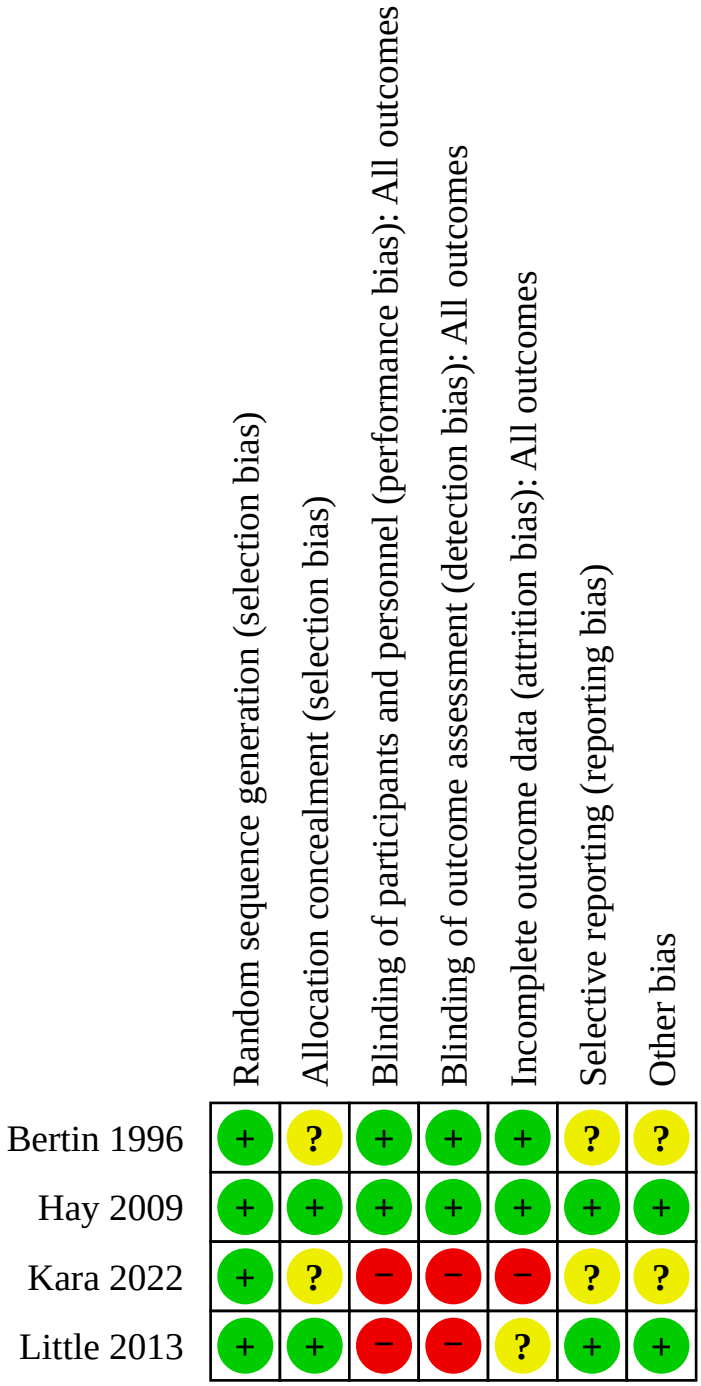
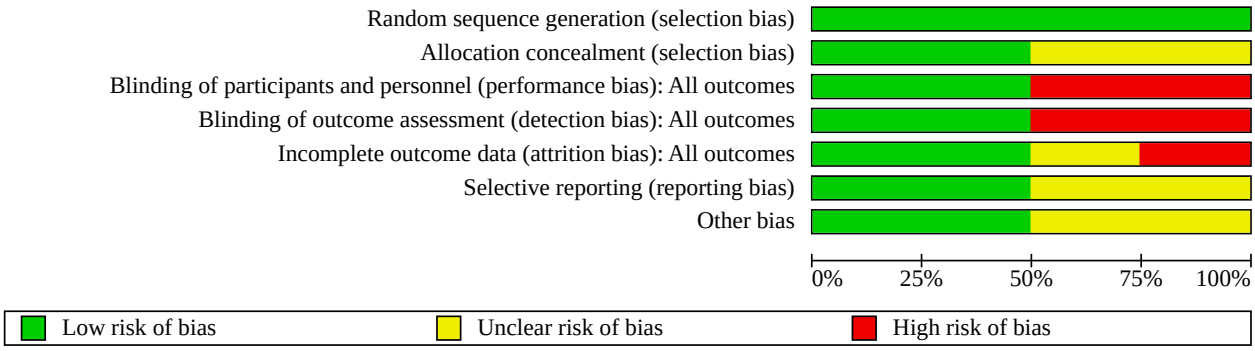


**Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.**




### Allocation

We judged random sequence generation to be adequate in all four trials. Concealment of allocation was adequately described in Hay 2009 and Little 2013, but was unclear in Bertin 1996 and Kara 2022.

### Blinding

The risk of bias for blinding of participants and personnel and outcome assessors (performance and detection bias) was low in Bertin 1996 and Hay 2009 and high in Little 2013 and Kara 2022.

### Incomplete outcome data

Risk of attrition bias was low in Bertin 1996 and Hay 2009, unclear in Little 2013, and high in Kara 2022.

### Selective reporting

Risk of reporting bias was low in Hay 2009 and Little 2013. We could not retrieve the trial protocols for Bertin 1996 and Kara 2022 and were therefore unable to determine the risk of reporting bias.

### Other potential sources of bias

Risk of other potential sources of bias was low in Hay 2009 and Little 2013 and unclear in Bertin 1996 and Kara 2022.

## Effects of interventions

See: **Summary of findings 1** Paracetamol versus placebo for acute otitis media in children; **Summary of findings 2** NSAIDs versus placebo for acute otitis media in children; **Summary of findings 3** NSAIDs versus paracetamol for acute otitis media in children

### Comparison: paracetamol versus placebo

#### *Primary outcomes*

##### 1. Proportion of children with pain at 48 hours

We included data from one trial for this outcome (148 randomised children, 148 (100%) included in analysis) (Bertin 1996). Paracetamol as monotherapy may be more effective than placebo in relieving pain at 48 hours (10% versus 25%; risk ratio (RR) 0.38, 95% confidence interval (CI) 0.17 to 0.85; number needed to treat for an additional beneficial outcome (NNTB) 7; Analysis 1.1).

##### Certainty of evidence

The evidence for this outcome was of low certainty, downgraded due to study limitations and questions about the applicability of evidence. All children received concurrent antibiotic therapy, and those with fever > 39 °C could be given paracetamol (30 mg to 60 mg) in addition to the studied treatments. This may have substantially influenced trial findings.

##### 2. Adverse events likely to be related to the use of paracetamol

We included data from one trial for this outcome (148 randomised children, 148 (100%) included in analysis) (Bertin 1996). Adverse events were reported infrequently. The evidence is very uncertain about the effect of paracetamol on adverse events (4% versus 4%; RR 1.03, 95% CI 0.21 to 4.93; Analysis 1.2).

##### Certainty of evidence

The evidence for this outcome was of very low certainty, downgraded due to study limitations and imprecise effect estimate (small sample size and infrequent occurrence of the outcome).

##### Other prespecified primary outcomes

None of the other prespecified time points for the primary outcome 'proportion of children with pain (yes/no) as rated by parents or carers or children themselves at various time points after study participation' were reported for the comparison paracetamol versus placebo.

#### *Secondary outcomes*

##### 6. Proportion of children with fever at 48 hours

We included data from one trial for this outcome (148 randomised children, 148 (100%) included in analysis) (Bertin 1996). The evidence is very uncertain about the effect of paracetamol on fever at 48 hours (1% versus 1%; RR 1.03, 95% CI 0.07 to 16.12; Analysis 1.3).

##### Certainty of evidence

The evidence for this outcome was of very low certainty, downgraded due to study limitations, imprecise effect estimate (infrequent occurrence of the outcome), and questions about the applicability of evidence. All children received concurrent antibiotic therapy, and those with fever > 39 °C could be given paracetamol

(30 mg to 60 mg) in addition to the studied treatments. This may have substantially influenced trial findings.

#### Other prespecified secondary outcomes

None of the other prespecified secondary outcomes were reported for the comparison paracetamol versus placebo.

### Comparison: NSAIDs (ibuprofen) versus placebo

#### *Primary outcomes*

##### 1. Proportion of children with pain at 48 hours

We included data from one trial for this outcome (146 randomised children, 146 (100%) included in analysis) (Bertin 1996). Ibuprofen may be more effective than placebo in relieving pain at 48 hours (7% versus 25%; RR 0.28, 95% CI 0.11 to 0.70; NNTB 6; Analysis 2.1).

##### Certainty of evidence

The evidence for this outcome was of low certainty, downgraded due to study limitations and questions about the applicability of evidence. All children received concurrent antibiotic therapy, and those with fever > 39 °C could be given paracetamol (30 mg to 60 mg) in addition to the studied treatments. This may have substantially influenced trial findings.

##### 2. Adverse events likely to be related to the use of NSAIDs (ibuprofen)

We included data from one trial for this outcome (146 randomised children, 146 (100%) included in analysis) (Bertin 1996). Adverse events were reported infrequently. The evidence is very uncertain about the effect of ibuprofen on adverse events (7% versus 4%; RR 1.76, 95% CI 0.44 to 7.10; Analysis 2.2).

##### Certainty of evidence

The evidence for this outcome was of very low certainty, downgraded due to study limitations and imprecise effect estimate (small sample size and infrequent occurrence of the outcome).

#### Other prespecified primary outcomes

None of the other prespecified time points for the primary outcome 'proportion of children with pain (yes/no) as rated by parents or carers or children themselves at various time points after study participation' were reported for the comparison NSAIDs (ibuprofen) versus placebo.

#### *Secondary outcomes*

##### 6. Proportion of children with fever at 48 hours

We included data from one trial for this outcome (146 randomised children, 146 (100%) included in analysis) (Bertin 1996). The evidence is very uncertain about the effect of ibuprofen on fever at 48 hours (1% versus 1%; RR 1.06, 95% CI 0.07 to 16.57; Analysis 2.3).

##### Certainty of evidence

The evidence for this outcome was of very low certainty, downgraded due to study limitations, imprecise effect estimate (infrequent occurrence of the outcome), and questions about the applicability of evidence. All children received concurrent antibiotic therapy, and those with fever > 39 °C could be given paracetamol (30 mg to 60 mg) in addition to the studied treatments. This may have substantially influenced trial findings.

#### Other prespecified secondary outcomes

None of the other prespecified secondary outcomes were reported for the comparison NSAIDs (ibuprofen) versus placebo.

### Comparison: NSAIDs (ibuprofen) versus paracetamol

#### *Primary outcomes*

##### 1. Proportion of children with pain at various time points

###### 24 hours

We pooled data from two trials for this outcome (71 randomised children, 39 (55%) included in analysis) (Hay 2009; Little 2013). The evidence is very uncertain about the effect of ibuprofen verus paracetamol in relieving pain at 24 hours (57% versus 78%; RR 0.83, 95% CI 0.59 to 1.18; $I^2$ = 0%; fixed-effect model; Analysis 3.1). We deemed subgroup and sensitivity analyses not to be useful because of the low number of trials and included children.

##### Certainty of evidence

The evidence for this outcome was of very low certainty, downgraded due to study limitations and imprecise effect estimate (very small sample size).

###### 48 to 72 hours

We pooled data from three trials for this outcome (215 randomised children, 183 (85%) included in analysis) (Bertin 1996; Hay 2009; Little 2013). The evidence is uncertain about the effect of ibuprofen versus paracetamol in relieving pain at 48 to 72 hours (17% versus 18%; RR 0.91, 95% CI 0.54 to 1.54; $I^2$ = 0%; fixed-effect model; Analysis 3.2). We deemed subgroup and sensitivity analyses not to be useful because of the low number of trials.

##### Certainty of evidence

The evidence for this outcome was of low certainty, downgraded due to study limitations and questions about the applicability of evidence. All children in Bertin 1996 received concurrent antibiotic therapy, and those with fever > 39 °C could be given paracetamol (30 mg to 60 mg) in addition to the studied treatments. This may have substantially influenced trial findings.

###### Four to seven days

We pooled data from two trials for this outcome (71 randomised children, 38 (54%) included in analysis) (Hay 2009; Little 2013). The evidence is very uncertain about the effect of ibuprofen versus paracetamol in relieving pain at four to seven days (14% versus 19%; RR 0.74, 95% CI 0.17 to 3.23; $I^2$ = 36%; fixed-effect model; Analysis 3.3). We deemed subgroup and sensitivity analyses not to be useful because of the low number of trials and included children.

##### Certainty of evidence

The evidence for this outcome was of very low certainty, downgraded due to study limitations and imprecise effect estimate (very small sample size).

##### 2. Adverse events likely to be related to the use of paracetamol or NSAIDs (ibuprofen)

We pooled data from three trials for this outcome (281 randomised children, 281 (100%) included in analysis) (Bertin 1996; Kara 2022; Little 2013). Adverse events were reported infrequently. The evidence is very uncertain about the effect of ibuprofen versus placebo on adverse events (4% versus 2%; RR 1.71, 0.43 to 6.90; $I^2$

= not available; random-effects model; Analysis 3.4). We deemed subgroup and sensitivity analyses not to be useful because of the low number of trials.

#### Certainty of evidence

The evidence for this outcome was of very low certainty, downgraded due to study limitations and imprecise effect estimate (small sample size and infrequent occurrence of the outcome).

### *Secondary outcomes*

#### 1. Proportion of children with at most mild pain at various time points

#### 24 hours

We pooled data from two trials for this outcome (71 randomised children, 39 (55%) included in analysis) (Hay 2009; Little 2013). The evidence is very uncertain about the effect of ibuprofen versus paracetamol in terms of the proportion of children with mild pain at 24 hours (18% versus 18%; RR 1.08, 95% CI 0.31 to 3.73; $I^2$ = 0%; fixed-effect model; Analysis 3.5). We deemed subgroup and sensitivity analyses not to be useful because of the low number of trials and included children.

#### Certainty of evidence

The evidence for this outcome was of very low certainty, downgraded due to study limitations and imprecise effect estimate (very small sample size).

#### 48 to 72 hours

We pooled data from two trials for this outcome (71 randomised children, 39 (55%) included in analysis) (Hay 2009; Little 2013). The evidence is very uncertain about the effect of ibuprofen versus paracetamol in terms of the proportion of children with mild pain at 48 to 72 hours (36% versus 29%; RR 1.35, 95% CI 0.62 to 2.91; $I^2$ = 0%; fixed-effect model; Analysis 3.6). We deemed subgroup and sensitivity analyses not to be useful because of the low number of trials and included children.

#### Certainty of evidence

The evidence for this outcome was of very low certainty, downgraded due to study limitations and imprecise effect estimate (very small sample size).

#### Four to seven days

We included data from two trials for this outcome (71 randomised children, 39 (55%) included in analysis) (Hay 2009; Little 2013). The evidence is very uncertain about the effect of ibuprofen versus paracetamol in terms of the proportion of children with mild pain at four to seven days (23% versus 29%). Data did not enable pooling of trial results; the summary statistic relates only to Little 2013 (RR 0.91, 95% CI 0.37 to 2.23; Analysis 3.7). We deemed subgroup and sensitivity analyses not to be useful because of the low number of trials and included children.

#### Certainty of evidence

The evidence for this outcome was of very low certainty, downgraded due to study limitations and imprecise effect estimate (very small sample size).

#### 2. Mean time to resolution of pain

None of the included trials reported this prespecified secondary outcome.

#### 3. Mean pain score at various time points

#### 24 hours

We pooled data from three trials for this outcome (155 randomised children, 111 (72%) included in analysis) (Hay 2009; Kara 2022; Little 2013). The evidence is very uncertain about the effect of ibuprofen versus paracetamol in terms of the mean pain score at 24 hours (0.29 lower, 95% CI 0.79 lower to 0.20 higher; $I^2$ = 12%; fixed-effect model; Analysis 3.8). We deemed subgroup and sensitivity analyses not to be useful because of the low number of trials and included children.

#### Certainty of evidence

The evidence for this outcome was of very low certainty, downgraded due to study limitations and imprecise effect estimate (very small sample size).

#### 48 to 72 hours

We pooled data from three trials for this outcome (155 randomised children, 108 (70%) included in analysis) (Hay 2009; Kara 2022; Little 2013). The evidence is very uncertain about the effect of ibuprofen versus paracetamol in terms of the mean pain score at 48 to 72 hours (0.25 lower, 95% CI 0.66 lower to 0.16 higher; $I^2$ = 0%; fixed-effect model; Analysis 3.9). We deemed subgroup and sensitivity analyses not to be useful because of the low number of trials and included children.

#### Certainty of evidence

The evidence for this outcome was of very low certainty, downgraded due to study limitations and imprecise effect estimate (very small sample size).

#### Four to seven days

We included data from two trials (71 randomised children, 31 (44%) included in analysis) (Hay 2009; Little 2013). The evidence is very uncertain about the effect of ibuprofen versus paracetamol in terms of the mean pain score at four to seven days (0.30 higher, 95% CI 1.78 lower to 2.38 higher). Data did not enable pooling of trial results; the summary statistic relates only to Little 2013 (mean difference (MD) −0.30, 95% CI −2.38 to 1.78; Analysis 3.10). We deemed subgroup and sensitivity analyses not to be useful because of the low number of trials and included children.

#### Certainty of evidence

The evidence for this outcome was of very low certainty, downgraded due to study limitations and imprecise effect estimate (very small sample size).

#### 4. Disease-specific quality of life as measured by a validated instrument

None of the included trials reported this prespecified secondary outcome.

#### 5. Mean time to resolution of fever

None of the included trials reported this prespecified secondary outcome.

#### 6. Proportion of children with fever at various time points

##### 24 hours

We pooled data from two trials for this outcome (71 randomised children, 39 (55%) included in analysis) (Hay 2009; Little 2013). The evidence is very uncertain about the effect of ibuprofen versus paracetamol in terms of the proportion of children with fever at 24 hours (18% versus 29%; RR 0.69, 95% CI 0.24 to 2.00; $I^2$ = 0%; fixed-effect model; Analysis 3.11). We deemed subgroup and sensitivity analyses not to be useful because of the low number of trials and included children.

##### Certainty of evidence

The evidence for this outcome was of very low certainty, downgraded due to study limitations and imprecise effect estimate (very small sample size).

##### 48 to 72 hours

We pooled data from three trials for this outcome (215 randomised children, 182 (85%) included in analysis) (Bertin 1996; Hay 2009; Little 2013). The evidence is uncertain about the effect of ibuprofen versus paracetamol in terms of the proportion of children with fever at 48 to 72 hours (4% versus 3%; RR 1.18, 95% CI 0.31 to 4.44; $I^2$ = 0%; fixed-effect model; Analysis 3.12). We deemed subgroup and sensitivity analyses not to be useful because of the low number of trials.

##### Certainty of evidence

The evidence for this outcome was of low certainty, downgraded due to study limitations and questions about the applicability of evidence. All children in Bertin 1996 received concurrent antibiotic therapy, and those with fever > 39 °C could be given paracetamol (30 mg to 60 mg) in addition to the studied treatments. This may have substantially influenced trial findings.

##### Four to seven days

We included data from two trials (71 randomised children, 39 (55%) included in analysis) (Hay 2009; Little 2013). The evidence is very uncertain about the effect of ibuprofen versus paracetamol in terms of the proportion of children with fever at four to seven days (5% versus 0%). Data did not enable pooling of trial results; the summary statistic relates only to Little 2013 (RR 2.75, 95% CI 0.12 to 60.70; Analysis 3.13). We deemed subgroup and sensitivity analyses not to be useful because of the low number of trials and included children.

##### Certainty of evidence

The evidence for this outcome was of very low certainty, downgraded due to study limitations and imprecise effect estimate (very small sample size).

#### 7. Proportion of children with reconsultations

We included data from one trial for this outcome (53 randomised children, 53 (100%) included in analysis) (Little 2013). The evidence is very uncertain about the effect of ibuprofen versus paracetamol in terms of the proportion of children with reconsultations at day 28 (92% versus 81%; RR 1.13, 95% CI 0.92 to 1.40; Analysis 3.14).

##### Certainty of evidence

The evidence for this outcome was of very low certainty, downgraded due to study limitations and imprecise effect estimate (very small sample size).

#### 8. Proportion of children with (delayed) antibiotic prescriptions

We included data from one trial for this outcome (53 randomised children, 53 (100%) included in analysis) (Little 2013). The evidence is very uncertain about the effect of ibuprofen versus paracetamol in terms of the proportion of children with delayed antibiotics (54% versus 41%; RR 1.32, 95% CI 0.74 to 2.35; Analysis 3.15).

##### Certainty of evidence

The evidence for this outcome was of very low certainty, downgraded due to study limitations and imprecise effect estimate (very small sample size).

#### 9. Total days lost from nursery or school for children because of AOM

None of the included trials reported this prespecified secondary outcome.

#### 10. Total days lost from work or education for parents and carers because of their child's AOM

None of the included trials reported this prespecified secondary outcome.

#### 11. Serious complications

We pooled data from two trials for this outcome (71 randomised children, 71 (100%) included in analysis) (Hay 2009; Little 2013). No serious complications related to AOM were reported in either trial. We deemed subgroup and sensitivity analyses not to be useful because of the low number of trials and included children.

##### Certainty of evidence

The evidence for this outcome was of very low certainty, downgraded due to study limitations and imprecise effect estimate (small sample size and infrequent occurrence of the outcome).

### Comparison: NSAIDs (ibuprofen) and paracetamol versus paracetamol

#### *Primary outcomes*

#### 1. Proportion of children with pain at various time points

##### 24 hours

We pooled data from two trials for this outcome (71 randomised children, 41 (58%) included in analysis) (Hay 2009; Little 2013). The evidence is very uncertain about the effects of ibuprofen and paracetamol versus paracetamol alone in terms of the proportion of children with pain at 24 hours (79% versus 71%; RR 1.07, 95% CI 0.78 to 1.47; $I^2$ = 0%; fixed-effect model; Analysis 4.1). We deemed subgroup and sensitivity analyses not to be useful because of the low number of trials and included children.

##### Certainty of evidence

The evidence for this outcome was of very low certainty, downgraded due to study limitations and imprecise effect estimate (very small sample size).

#### 48 to 72 hours

We pooled data from two trials for this outcome (71 randomised children, 41 (58%) included in analysis) (Hay 2009; Little 2013). The evidence is very uncertain about the effects of ibuprofen and paracetamol versus paracetamol alone in terms of the proportion of children with pain at 48 to 72 hours (42% versus 53%; RR 0.71, 95% CI 0.42 to 1.20; $I^2$ = 0%; fixed-effect model; Analysis 4.2). We deemed subgroup and sensitivity analyses not to be useful because of the low number of trials and included children.

#### Certainty of evidence

The evidence for this outcome was of very low certainty, downgraded due to study limitations and imprecise effect estimate (very small sample size).

#### Four to seven days

We pooled data from two trials for this outcome (71 randomised children, 41 (58%) included in analysis) (Hay 2009; Little 2013). The evidence is very uncertain about the effects of ibuprofen and paracetamol versus paracetamol alone in terms of the proportion of children with pain at four to seven days (33% versus 18%; RR 1.65, 95% CI 0.58 to 4.72; $I^2$ = 0%; fixed-effect model; Analysis 4.3). We deemed subgroup and sensitivity analyses not to be useful because of the low number of trials and included children.

#### Certainty of evidence

The evidence for this outcome was of very low certainty, downgraded due to study limitations and imprecise effect estimate (very small sample size).

### 2. Adverse events likely to be related to the use NSAIDs (ibuprofen) and paracetamol or paracetamol alone

We included data from one trial (56 randomised children, 56 (100%) included in analysis) (Little 2013). No adverse events were reported in this trial (Analysis 4.4).

#### Certainty of evidence

The evidence for this outcome was of very low certainty, downgraded due to study limitations and imprecise effect estimate (very small sample size and infrequent occurrence of the outcome).

## *Secondary outcomes*

### 1. Proportion of children with at most mild pain at various time points

#### 24 hours

We included data from two trials (71 randomised children, 41 (58%) included in analysis) (Hay 2009; Little 2013). The evidence is very uncertain about the effects of ibuprofen and paracetamol versus paracetamol alone in terms of the proportion of children with at most mild pain at 24 hours (4% versus 18%). Data did not enable pooling of the trial results; the summary statistic relates only to Little 2013 (RR 0.21, 95% CI 0.02 to 1.74; Analysis 4.5). We deemed subgroup and sensitivity analyses not to be useful because of the low number of trials and included children.

#### Certainty of evidence

The evidence for this outcome was of very low certainty, downgraded due to study limitations and imprecise effect estimate (very small sample size).

#### 48 to 72 hours

We included data from two trials(71 randomised children, 41 (58%) included in analysis) (Hay 2009; Little 2013). The evidence is very uncertain about the effects of ibuprofen and paracetamol versus paracetamol alone in terms of the proportion of children with at most mild pain (21% versus 29%). Data did not enable pooling of trial results; the summary statistic relates only to Little 2013 (RR 0.63, 95% CI 0.24 to 1.62; Analysis 4.6). We deemed subgroup and sensitivity analyses not to be useful because of the low number of trials and included children.

#### Certainty of evidence

The evidence for this outcome was of very low certainty, downgraded due to study limitations and imprecise effect estimate (very small sample size).

#### Four to seven days

We included data from two trials (71 randomised children, 41 (58%) included in analysis) (Hay 2009; Little 2013). The evidence is very uncertain about the effects of ibuprofen and paracetamol versus paracetamol alone in terms of the proportion of children with at most mild pain at four to seven days (17% versus 29%). Data did not enable pooling of trial results; the summary statistic relates only to Little 2013 (RR 0.50, 95% CI 0.17 to 1.43; Analysis 4.7). We deemed subgroup and sensitivity analyses not to be useful because of the low number of trials and included children.

#### Certainty of evidence

The evidence for this outcome was of very low certainty, downgraded due to study limitations and imprecise effect estimate (very small sample size).

### 2. Mean time to resolution of pain

None of the included trials reported this prespecified secondary outcome.

### 3. Mean pain score at various time points

#### 24 hours

We pooled data from two trials for this outcome (71 randomised children, 40 (56%) included in analysis) (Hay 2009; Little 2013). The evidence is very uncertain about the effects of ibuprofen and paracetamol versus paracetamol alone on mean pain scores at 24 hours (MD 0.32, 95% CI −0.59 to 1.23; $I^2$ = 61%; random-effects model; Analysis 4.8). We deemed subgroup and sensitivity analyses not to be useful because of the low number of trials and included children.

#### Certainty of evidence

The evidence for this outcome was of very low certainty, downgraded due to study limitations and imprecise effect estimate (very small sample size).

#### 48 to 72 hours

We included data from two trials (71 randomised children, 40 (56%) included in analysis) (Hay 2009; Little 2013). The evidence is very uncertain about the effects of ibuprofen and paracetamol versus paracetamol alone on mean pain scores at 48 to 72 hours. Data did not enable pooling of trial results; the summary statistic relates only to Little 2013 (MD 0.60, 95% CI −0.77 to 1.97; Analysis 4.9). We

deemed subgroup and sensitivity analyses not to be useful because of the low number of trials and included children.

#### Certainty of evidence

The evidence for this outcome was of very low certainty, downgraded due to study limitations and imprecise effect estimate (very small sample size).

#### Four to seven days

We included data from two trials (71 randomised children, 33 (46%) included in analysis) (Hay 2009; Little 2013). The evidence is very uncertain about the effects of ibuprofen and paracetamol versus paracetamol alone on mean pain scores at four to seven days. Data did not enable pooling of trial results; the summary statistic relates only to Little 2013 (MD 0.70, 95% CI −1.01 to 2.41; Analysis 4.10). We deemed subgroup and sensitivity analyses not to be useful because of the low number of trials and included children.

#### Certainty of evidence

The evidence for this outcome was of very low certainty, downgraded due to study limitations and imprecise effect estimate (very small sample size).

### 4. Disease-specific quality of life as measured by a validated instrument

None of the included trials reported this prespecified secondary outcome.

### 5. Mean time to resolution of fever

None of the included trials reported this prespecified secondary outcome.

### 6. Proportion of children with fever at various time points

#### 24 hours

We pooled data from two trials for this outcome (71 randomised children, 41 (58%) included in analysis) (Hay 2009; Little 2013). The evidence is very uncertain about the effects of ibuprofen and paracetamol versus paracetamol alone in terms of the proportion of children with fever at 24 hours (50% versus 29%; RR 1.48, 95% CI 0.73 to 2.99; $I^2$ = 0%; fixed-effect model; Analysis 4.11). We deemed subgroup and sensitivity analyses not to be useful because of the low number of trials and included children.

#### Certainty of evidence

The evidence for this outcome was of very low certainty, downgraded due to study limitations and imprecise effect estimate (very small sample size).

#### 48 to 72 hours

We pooled data from two trials for this outcome (71 randomised children, 41 (58%) included in analysis) (Hay 2009; Little 2013). The evidence is very uncertain about the effects of ibuprofen and paracetamol versus paracetamol alone in terms of the proportion of children with fever at 48 to 72 hours (29% versus 12%; RR 2.13, 95% CI 0.60 to 7.60; $I^2$ = 4%; fixed-effect model; Analysis 4.12). We deemed subgroup and sensitivity analyses not to be useful because of the low number of trials.

#### Certainty of evidence

The evidence for this outcome was of very low certainty, downgraded due to study limitations and imprecise effect estimate (very small sample size).

#### Four to seven days

We pooled data from two trials for this outcome (71 randomised children, 41 (58%) included in analysis) (Hay 2009; Little 2013). No participant in either group had fever at four to seven days (Analysis 4.13). We deemed subgroup and sensitivity analyses not to be useful because of the low number of trials and included children.

#### Certainty of evidence

The evidence for this outcome was of very low certainty, downgraded due to study limitations and imprecise effect estimate (very small sample size).

### 7. Proportion of children with reconsultations

We included data from one trial (56 randomised children, 56 (100%) included in analysis) (Little 2013). The evidence is very uncertain about the effects of ibuprofen and paracetamol versus paracetamol alone in terms of the proportion of children with reconsultations at day 28 (66% versus 81%; RR 0.80, 95% CI 0.58 to 1.11; Analysis 4.14).

#### Certainty of evidence

The evidence for this outcome was of very low certainty, downgraded due to study limitations and imprecise effect estimate (very small sample size).

### 8. Proportion of children with (delayed) antibiotic prescriptions

We included data from one trial (56 randomised children, 56 (100%) included in analysis) (Little 2013). The evidence is very uncertain about the effects of ibuprofen and paracetamol versus paracetamol alone in terms of the proportion of children with delayed antibiotics (52% versus 41%; RR 1.27, 95% CI 0.71 to 2.26; Analysis 4.15).

#### Certainty of evidence

The evidence for this outcome was of very low certainty, downgraded due to study limitations and imprecise effect estimate (very small sample size).

### 9. Total days lost from nursery or school for children because of AOM

None of the included trials reported this prespecified secondary outcome.

### 10. Total days lost from work or education for parents and carers because of their child's AOM

None of the included trials reported this prespecified secondary outcome.

### 11. Serious complications

We pooled data from two trials for this outcome (71 randomised children, 71 (100%) included in analysis) (Hay 2009; Little 2013). No serious complications related to AOM were reported in either trial (Analysis 4.16). We deemed subgroup and sensitivity analyses not to be useful because of the low number of trials and included children.

**Certainty of evidence**

The evidence for this outcome was of very low certainty, downgraded due to study limitations and imprecise effect estimate (very small sample size and infrequent occurrence of the outcome).

# DISCUSSION

## Summary of main results

The current evidence on the effectiveness of paracetamol or NSAIDs, alone or combined, in relieving pain in children with AOM is limited.

We included four RCTs (411 children) with low to high risk of bias. One RCT compared paracetamol versus ibuprofen versus placebo in 219 children with AOM. In this trial, children received concurrent antibiotic therapy, and those with fever > 39 °C could receive paracetamol (30 mg to 60 mg) in addition to the studied treatments. The authors of two RCTs comparing paracetamol versus ibuprofen versus paracetamol and ibuprofen in children with fever and patients with respiratory tract infections provided crude subgroup data on children with AOM (26 and 82 children, respectively). The authors of one RCT comparing paracetamol versus ibuprofen with/without analgesic ear drops in children with AOM provided mean pain scores of 84 children for the comparison of paracetamol (alone) versus ibuprofen (alone).

Paracetamol and ibuprofen as monotherapies may be more effective than placebo in relieving pain at 48 hours (paracetamol versus placebo: proportion of children with pain 10% versus 25%; RR 0.38, 95% CI 0.17 to 0.85; NNTB 7; low-certainty evidence; ibuprofen versus placebo: proportion of children with pain 7% versus 25%; RR 0.28, 95% CI 0.11 to 0.70; NNTB 6; low-certainty evidence).

Adverse events occurred infrequently, and limited data were available for analysis. The evidence for the effects of paracetamol and ibuprofen, alone or combined, on adverse events is very uncertain.

The evidence for the effect of ibuprofen versus paracetamol on relieving short-term ear pain in children with AOM is very uncertain.

We could not draw any firm conclusions about the effectiveness of ibuprofen plus paracetamol versus paracetamol alone in relieving ear pain in children with AOM mainly because of the very limited amount of data available for analysis.

## Overall completeness and applicability of evidence

We included one trial comparing the effectiveness of paracetamol, ibuprofen, and placebo in children with AOM as diagnosed by otoscopy (Bertin 1996). However, all trial participants received co-treatment with antibiotics (cefaclor 15 to 30 mg/kg twice daily for seven days), which is no longer routinely recommended for use in the management of children with AOM. In another trial which compared paracetamol and ibuprofen with/without analgesic eardrops in children with AOM, the choice of concurrent antibiotic treatment or watchful waiting was at the discretion of the treating physician; oral antibiotics were prescribed in 82% of children (Kara 2022). Although oral antibiotics have only marginal beneficial effect in relieving ear pain in children with AOM (Venekamp 2015), co-treatment with antibiotics may potentially have influenced the trial findings.

We included subgroup data from children with fever and patients with respiratory tract infections from the other two trials (Hay 2009; Little 2013). In these trials, AOM was diagnosed either by the general practitioner or research nurse without further specification of diagnostic criteria applied.

Furthermore, the dosage of paracetamol used in the double-blind randomised trial comparing paracetamol versus ibuprofen versus placebo was relatively low (10 mg/kg three times daily) (Bertin 1996). This may have underestimated the effect of paracetamol in this trial. In the same trial (Bertin 1996), children with fever > 39 °C could be given paracetamol (30 mg to 60 mg) in addition to the studied treatments, which may have substantially influenced trial findings. As such, the overall degree of completeness and applicability of the evidence is low.

## Certainty of the evidence

For the comparisons paracetamol versus placebo and ibuprofen versus placebo, the certainty of the evidence was low for the primary outcome evaluating effectiveness and very low for adverse events and secondary effectiveness outcomes.

For the comparison ibuprofen versus paracetamol, the certainty of the evidence varied from low to very low for the primary outcome evaluating effectiveness and was mostly very low for adverse events and secondary effectiveness outcomes.

For the comparison ibuprofen plus paracetamol versus paracetamol alone, the certainty of evidence for all outcomes was very low.

## Potential biases in the review process

We used a broad search strategy (not only including otitis media but also upper respiratory tract infection as search terms) without language or publication restrictions. For feasibility purposes we did not include fever in our search strategy, but we systematically screened the reference lists of all relevant reviews on the effectiveness of paracetamol or NSAIDs, or both, for children with fever including relevant Cochrane Reviews (Meremikwu 2005; Wong 2013). In the 2016 version of our review (Sjoukes 2016), we found three potentially relevant trials that were not retrieved by our database searches (Hay 2009; McIntyre 1996; Sarrell 2006). In addition, we searched the WHO ICTRP and ClinicalTrials.gov for completed and ongoing trials. We therefore feel confident that our review includes all relevant completed and ongoing trials.

We were unable to retrieve AOM subgroup data from one potentially relevant trial (Sarrell 2006). However, it is unlikely that these subgroup data would have a major impact on our review findings.

## Agreements and disagreements with other studies or reviews

No previous review has been undertaken to assess the effectiveness of paracetamol or NSAIDs, alone or combined, in children with AOM. Previous Cochrane Reviews on paracetamol or NSAIDs (or both) focused either on children with fever due to infectious diseases (Meremikwu 2005; Wong 2013), or included both children and adults with the common cold (Kim 2013). For children with fever, the reviews found only a few trials comparing paracetamol against placebo (Meremikwu 2005), showing some evidence that both alternating and combined antipyretic therapy may be more

effective at reducing temperatures than monotherapy alone, and inconclusive evidence for measures of child discomfort (Wong 2013). For the common cold, the review concluded that "NSAIDs are somewhat effective in relieving discomfort caused by a cold, but there is no clear evidence of their effect in easing respiratory symptoms" (Kim 2013).

## AUTHORS' CONCLUSIONS

### Implications for practice

The current evidence on the effectiveness of paracetamol or non-steroidal anti-inflammatory drugs (NSAIDs), alone or combined, in relieving pain in children with acute otitis media (AOM) is limited.

Data from one trial indicated that paracetamol and ibuprofen as monotherapies may be more effective than placebo in relieving ear pain at 48 hours in children with AOM. However, we assessed the certainty of evidence as low due to study limitations and questions about the applicability of evidence.

Low- to very low-certainty evidence suggested no difference between ibuprofen and paracetamol in relieving short-term ear pain in children with AOM. However, these findings should be interpreted cautiously given that study limitations, very small sample size, and questions about applicability of evidence substantially affected our confidence in the results.

The currently available evidence on the effectiveness of ibuprofen plus paracetamol versus paracetamol alone is insufficient to draw any firm conclusions.

### Implications for research

Despite explicit guideline recommendations on the use of analgesics in children with AOM (Lieberthal 2013), analgesics are infrequently recommended to parents of children with AOM in daily practice (Pulkki 2006). Moreover, semi-structured interviews with Australian parents of children who had recently visited their general practitioner with AOM revealed that parents considered analgesics insufficient as standalone treatment (Hansen 2015). Increasing parental knowledge and physicians' adherence to guidelines on the use of analgesics in childhood AOM seems warranted since suboptimal management of ear pain may lead to unnecessary discomfort of the child, sleepless nights, and days off work for parents, and preventable doctor reconsultations because of persisting AOM symptoms. Randomised controlled trials assessing the effectiveness of interventions aimed at both physicians and parents involved in the care of children with AOM are needed to evaluate whether optimised pain management provides any benefit over care as usual in relieving AOM symptoms and reducing reconsultations and (delayed) antibiotic prescriptions.

Further randomised controlled trials are also needed to assess the effectiveness of ibuprofen as adjunct to paracetamol versus paracetamol alone and to establish whether other analgesics such as anaesthetic eardrops are beneficial in relieving ear pain in children with AOM.

## ACKNOWLEDGEMENTS

We gratefully thank Alies Sjoukes who contributed to the review first published in 2016 (Sjoukes 2016).

The following people conducted the editorial process for this 2023 update.

- Sign-off Editor (final editorial decision): Mark Jones (Bond University, Australia) and Mieke van Driel (The University of Queensland, Australia).
- Managing Editor (provided editorial guidance to authors, edited the review, selected peer reviewers, collated peer-reviewer comments): Liz Dooley (Bond University, Australia).
- Contact Editor (assessed peer-review comments and recommended an editorial decision): Tom Fahey, Department of General Practice, Royal College of Surgeons in Ireland, Dublin, Ireland.
- Statistical Editor (provided comments): Menelaos Konstantinidis, Li Ka Shing Knowledge Institute, St Michael's Hospital, Unity Health Toronto, Canada.
- Copy Editor (copy-editing and production): Lisa Winer, Cochrane Central Production Service.

Peer reviewers (provided comments and recommended an editorial decision):

- Clinical/content review: Sebastian Straube, BM BCh, MA (Oxon), DPhil, Professor, Division of Preventive Medicine, Department of Medicine, University of Alberta, Canada.
- Consumer review: Sallie Bernard, parent. Janet Wale, independent consumer advocate.
- Search review: Justin Clark (Bond University, Australia); Yuan Chi peer reviewed search methods.

# REFERENCES

## References to studies included in this review

**Bertin 1996** *{published data only}*

Bertin L, Pons G, d'Athis P, Duhamel JF, Maudelonde C, Lasfargues G. A randomized, double-blind, multicentre controlled trial of ibuprofen versus acetaminophen and placebo for symptoms of acute otitis media in children. *Fundamental & Clinical Pharmacology* 1996;**10**(4):387-92.

**Hay 2009** *{published data only}*

* Hay AD, Redmond NM, Costelloe C, Montgomery AA, Fletcher M, Hollinghurst S, et al. Paracetamol and ibuprofen for the treatment of fever in children: the PITCH randomised controlled trial. *Health Technology Assessment* 2009;**13**(27):iii-iv, ix-x, 1-163.

Hollinghurst S, Redmond N, Costelloe C, Montgomery A, Fletcher M, Peters TJ, et al. Paracetamol plus ibuprofen for the treatment of fever in children (PITCH): economic evaluation of a randomised controlled trial. *BMJ* 2008;**337**:a1490.

**Kara 2022** *{published data only}*

Kara A, Büyükcam A, Sütçü M, Sali E, Bozdemir ŞE, Kara M, et al. The effectiveness of topical 1% lidocaine with systemic oral analgesics for ear pain with acute otitis media. *International Journal of Pediatric Otorhinolaryngology* 2022;**156**:111116.

**Little 2013** *{published data only}*

Little P, Moore M, Kelly J, Williamson I, Leydon G, McDermott L, et al. Ibuprofen, paracetamol, and steam for patients with respiratory tract infections in primary care: pragmatic randomised factorial trial. *BMJ* 2013;**347**:f6041.

## References to studies excluded from this review

**Azuma 2010** *{published data only}*

Azuma A, Kudoh S, Nakashima M, Nagatake T. A double-blind study of zaltoprofen for the treatment of upper respiratory tract infection. *Pharmacology* 2010;**85**(1):41-7.

**Campos 1992** *{published data only}*

Campos L, Díaz Gómez M, Ondiviela R, Masorra F. Naproxen sodium in the treatment of otitis. *Atencion Primaria* 1992;**9**(6):314, 316-7.

**Cappella 1993** *{published data only}*

Cappella L, Guerra A, Laudizi L, Cavazzuti GB. Efficacy and tolerability of nimesulide and lysine-acetylsalicylate in the treatment of paediatric acute upper respiratory tract inflammation. *Drugs* 1993;**46**(Suppl 1):222-5.

**Caretti 1986** *{published data only}*

Caretti JP. Single-blind study of an anti-inflammatory agent v. paracetamol in acute infections of the oral cavity and upper respiratory tract. *Clinical Trials Journal* 1986;**23**(6):372-81.

**Dasgupta 2002** *{published data only}*

Dasgupta KS, Deshpande AS, Vedi JN, Patel S. Evaluation of efficacy of nizer versus nimesulide tablets in otitis media. *Journal of the Indian Medical Association* 2002;**100**(10):619.

**Eccles 2006** *{published data only}*

Eccles R, Jawad M, Jawad S, Ridge D, North M, Jones E, et al. Efficacy of a paracetamol-pseudoephedrine combination for treatment of nasal congestion and pain-related symptoms in upper respiratory tract infection. *Current Medical Research and Opinion* 2006;**22**(12):2411-8.

**Fort 2000** *{published data only}*

Fort G. Analgesia in otorhinolaryngological diseases: Lysine clonixinate versus ibuprofen. *Prensa Medica Argentina* 2000;**87**(4):409-18.

**Kim 2013** *{published data only}*

Kim CK, Callaway Z, Choung JT, Yu JH, Shim KS, Kwon EM. Dexibuprofen for fever in children with upper respiratory tract infection. *Pediatrics International* 2013;**55**(4):443-9.

**Lozano Gonzalez 1989** *{published data only}*

Lozano Gonzalez CH, Flores Tamez ME. Clinical assessment of the antipyretic and analgesic effectiveness, as well as the rectal tolerance, of a new association: Naproxen sodium + paracetamol, compared to paracetamol alone, in the treatment of respiratory tract infections. *Compendium de Investigaciones Clinicas Latinoamericanas* 1989;**9**(1):27-31.

**McIntyre 1996** *{published data only}*

McIntyre J, Hull D. Comparing efficacy and tolerability of ibuprofen and paracetamol in fever. *Archives of Disease in Childhood* 1996;**74**(2):164.

**Metta 2000** *{published data only}*

Metta H, Haidar N, Mendoza JJ, Webb E, Azcarate V, Rocatti C, et al. Lysine clonixinate vs. ibuprofen in otorhinolaryngology. *Prensa Médica Argentina* 2000;**87**(9):906-18.

**Milvio 1984** *{published data only}*

Milvio C. Nimesulide for the treatment of painful inflammatory process in the ear, nose and throat areas: a double-blind controlled study with benzydamine. *Journal of International Medical Research* 1984;**12**(6):327-32.

**Motoichi 1997** *{published data only}*

Motoichi T, Takashi F, Junzaburo K, Riichiro M, Shyoji K, Takuzo S. Phase III study of anti-inflammatory agent, 2-phenyl-5-benzothiazoleacetic acid (K-308) – a double blind controlled trial on acute upper respiratory infections. *Rinsho Hyoka (Clinical Evaluation)* 1997;**5**(1):7-21.

**Nouri 1984** *{published data only}*

Nouri ME. Nimesulide for treatment of acute inflammation of the upper respiratory tract. *Clinical Therapeutics* 1984;**6**(2):142-50.

**Passali 2001** *{published data only}*

Passali D, Balli R, Scotti A, Oldani V. Controlled, double-blind, randomized comparison of nimesulide β-cyclodextrin and morniflumate in acute otitis. *Current Therapeutic Research* 2001;**62**(2):153-66.

**Polidori 1993** *{published data only}*

Polidori G, Titti G, Pieragostini P, Comito A, Scaricabarozzi I. A comparison of nimesulide and paracetamol in the treatment of fever due to inflammatory diseases of the upper respiratory tract in children. *Drugs* 1993;**46**(Suppl 1):231-3.

**Ryan 1987** *{published data only}*

Ryan PB, Rush DR, Nicholas TA, Graham DG. A double-blind comparison of fenoprofen calcium, acetaminophen, and placebo in the palliative treatment of common nonbacterial upper respiratory infections. *Current Therapeutic Research* 1987;**41**(1):17-23.

**Sarrell 2006** *{published data only}*

Sarrell EM, Wielunsky E, Cohen HA. Antipyretic treatment in young children with fever: acetaminophen, ibuprofen, or both alternating in a randomized, double-blind study. *Archives of Pediatrics and Adolescent Medicine* 2006;**160**(2):197-202.

**Schuetz 2014** *{published data only}*

Schuetz P. Randomised controlled trial: Neither ibuprofen nor steam improves symptom control compared with paracetamol in patients with acute respiratory tract infections in primary care. *Evidence-Based Medicine* 2014;**19**(3):102.

**Siegel 2003** *{published data only}*

Siegel RM, Kiely M, Bien JP, Joseph EC, Davis JB, Mendel SG. Treatment of otitis media with observation and a safety-net antibiotic prescription. *Pediatrics* 2003;**112**(3 Pt 1):527-31.

**Siquet 1983** *{published data only}*

Siquet J. Fentiazac suspension in the treatment of acute inflammation of the upper respiratory tract in children. *Clinical Trials Journal* 1983;**20**(6):305-12.

**Stipon 1983** *{published data only}*

Stipon JP, Le Bihan Y, de Rotalier P. Evaluation of the analgesic effect of UP 341-01 in patients presenting with acute pain in ORL. *Semaine des Hopitaux* 1983;**59**(39):2735-8.

**van Uum 2020** *{published data only}*

van Uum RT, Venekamp RP, Zuithoff NP, Sjoukes A, van de Pol AC, Schilder AG, et al. Improving pain management in childhood acute otitis media in general practice: a cluster randomised controlled trial of a GP-targeted educational intervention. *British Journal of General Practice* 2020;**70**(699):e684-95.

**Weippl 1985** *{published data only}*

Weippl G, Michos N, Stocker H. Clinical experience and results of treatment with suprofen in pediatrics. 4th communication: Assessment of pain in babies and infants/Analgesic effect of suprofen syrup in otitis media. *Arzneimittel-Forschung* 1985;**35**(11):1732-4.

**Yoon 2008** *{published data only}*

Yoon JS, Jeong DC, Oh JW, Lee KY, Lee HS, Koh YY, et al. The effects and safety of dexibuprofen compared with ibuprofen in febrile children caused by upper respiratory tract infection. *British Journal of Clinical Pharmacology* 2008;**66**(6):854-60.

## Additional references

**Ashworth 2005**

Ashworth M, Charlton J, Ballard K, Latinovic R, Gulliford M. Variations in antibiotic prescribing and consultation rates for acute respiratory infection in UK general practices 1995-2000. *British Journal of General Practice* 2005;**55**(517):603-8.

**Atkins 2004**

Atkins D, Best D, Briss PA, Eccles M, Falck-Ytter Y, Flottorp S, et al, GRADE Working Group. Grading quality of evidence and strength of recommendations. *BMJ* 2004;**328**(7454):1490.

**Barber 2014**

Barber C, Ille S, Vergison A, Coates H. Acute otitis media in young children – what do parents say? *International Journal of Pediatric Otorhinolaryngology* 2014;**78**(2):300-6.

**Beasley 2008**

Beasley R, Clayton T, Crane J, von Mutius E, Lai CK, Montefort S, et al. Association between paracetamol use in infancy and childhood, and risk of asthma, rhinoconjunctivitis, and eczema in children aged 6-7 years: analysis from Phase Three of the ISAAC programme. *Lancet* 2008;**372**(9643):1039-48.

**Bluestone 2007**

Bluestone C, Klein J. Definitions, terminology, and classification. In: Bluestone CD, Klein JO, editors(s). Otitis Media in Infants and Children. 4th edition. Hamilton, Canada: BC Decker, 2007:1-19.

**Bruno 2014**

Bruno A, Tacconelli S, Patrignani P. Variability in the response to non-steroidal anti-inflammatory drugs: mechanisms and perspectives. *Basic and Clinical Pharmacology and Toxicology* 2014;**114**(1):56-63.

**DerSimonian 1986**

DerSimonian R, Laird N. Meta-analysis in clinical trials. *Controlled Clinical Trials* 1986;**7**(3):177-88.

**EndNote 2013 [Computer program]**

EndNote. Philadelphia, PA: Clarivate, 2013.

**Foxlee 2006**

Foxlee R, Johansson A, Wejfalk J, Dawkins J, Dooley L, Del Mar C. Topical analgesia for acute otitis media. *Cochrane Database of Systematic Reviews* 2006, Issue 3. Art. No: CD005657. [DOI: 10.1002/14651858.CD005657]

**GRADEpro GDT [Computer program]**

GRADEpro GDT. Version accessed 19 August 2016. Hamilton, ON: McMaster University (developed by Evidence Prime). Available at gradepro.org.

**Greenberg 2003**

Greenberg D, Bilenko N, Liss Z, Shagan T, Zamir O, Dagan R. The burden of acute otitis media on the patient and the family. *European Journal of Pediatrics* 2003;**162**(9):576-81.

**Grijalva 2009**

Grijalva CG, Nuorti JP, Griffin MR. Antibiotic prescription rates for acute respiratory tract infections in US ambulatory settings. *JAMA* 2009;**302**(7):758-66.

**Hansen 2015**

Hansen MP, Howlett J, Del Mar C, Hoffmann TC. Parents' beliefs and knowledge about the management of acute otitis media: a qualitative study. *BMC Family Practice* 2015;**16**:82.

**Hay 2019**

Hay AD, Downing H, Francis NA, Young GJ, Clement C, Harris SD, et al. Anaesthetic-analgesic ear drops to reduce antibiotic consumption in children with acute otitis media: the CEDAR RCT. *Health Technology Assessment* 2019;**23**(34):1-48.

**Higgins 2011**

Higgins JP, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from training.cochrane.org/handbook/archive/v5.1/.

**Higgins 2021**

Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 6.2 (updated February 2021). Cochrane, 2021. Available from training.cochrane.org/handbook/archive/v6.2.

**Kim 2013**

Kim SY, Chang YJ, Cho HM, Hwang YW, Moon YS. Non-steroidal anti-inflammatory drugs for the common cold. *Cochrane Database of Systematic Reviews* 2013, Issue 6. Art. No: CD006362. [DOI: 10.1002/14651858.CD006362.pub3]

**Lieberthal 2013**

Lieberthal AS, Carroll AE, Chonmaitree T, Ganiats TG, Hoberman A, Jackson MA, et al. The diagnosis and management of acute otitis media. *Pediatrics* 2013;**131**(3):e964-e99.

**Liese 2014**

Liese JG, Silfverdal SA, Ciaquinto C, Carmona A, Larcombe JH, Garcia-Sicilia J, et al. Incidence and clinical presentation of acute otitis media in children aged < 6 years in European medical practices. *Epidemiology and Infection* 2014;**142**(8):1778-88.

**Marzuillo 2014**

Marzuillo P, Guarino S, Barbi E. Paracetamol: a focus for the general pediatrician. *European Journal of Pediatrics* 2014;**173**(4):415-25.

**Meremikwu 2005**

Meremikwu M, Marson AG. Paracetamol versus placebo or physical methods for treating fever in children. *Cochrane Database of Systematic Reviews* 2005, Issue 1. Art. No: CD003676. [DOI: 10.1002/14651858.CD003676]

**Moore 2012**

Moore RA, Straube S, Eccleston C, Derry S, Aldington D, Wiffen P, et al. Estimate at your peril: imputation methods for patient withdrawal can bias efficacy outcomes in chronic pain trials using responder analyses. *Pain* 2012;**153**(2):265-8.

**Pulkki 2006**

Pulkki J, Huikko S, Rautakorpi U-M, Honkanen P, Klaukka T, Mäkelä M, et al. Management of pain in acute otitis media in Finnish primary care. *Scandinavian Journal of Infectious Diseases* 2006;**38**(4):265-7.

**Rainsford 2009**

Rainsford KD. Ibuprofen: pharmacology, efficacy and safety. *Inflammopharmacology* 2009;**17**(6):275-342.

**Rayyan 2016 [Computer program]**

Rayyan – a web and mobile app for systematic reviews. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A, 2016. [DOI: 10.1186/s13643-016-0384-4]

**RevMan Web 2022 [Computer program]**

Review Manager Web (RevMan Web). Version 4.22.0. The Cochrane Collaboration, 2022. Available at revman.cochrane.org.

**Rovers 2006**

Rovers MM, Glasziou P, Appelman CL, Burke P, McCormick DP, Damoiseaux RA, et al. Antibiotics for acute otitis media: a meta-analysis with individual patient data. *Lancet* 2006;**368**(9545):1429-35.

**Schechter 2003**

Schechter NL. Management of common pain problems in the primary care pediatric setting. In: Schechter NL, Berde CB, Yaster M, editors(s). Pain in Infants and Adolescents. 2nd edition. Philadelphia, PA: Lippincott Williams & Wilkins, 2003:693-706.

**Sherbash 2020**

Sherbash M, Furuya-Kanamori L, Nader JD, Thalib L. Risk of wheezing and asthma exacerbation in children treated with paracetamol versus ibuprofen: a systematic review and meta-analysis of randomised controlled trials. *BMC Pulmonary Medicine* 2020;**20**(1):72. [DOI: 10.1186/s12890-020-1102-5]

**Sordillo 2015**

Sordillo JE, Scirica CV, Rifas-Shiman SL, Gillman MW, Bunyavanich S, Camargo CA Jr, et al. Prenatal and infant exposure to acetaminophen and ibuprofen and the risk for wheeze and asthma in children. *Journal of Allergy and Clinical Immunology* 2015;**135**(2):441-8. [DOI: 10.1016/j.jaci.2014.07.065]

**Southey 2009**

Southey ER, Soares-Weiser K, Kleijnen J. Systematic review and meta-analysis of the clinical safety and tolerability of

ibuprofen compared with paracetamol in paediatric pain and fever. *Current Medical Research and Opinion* 2009;**25**(9):2207-22.

**Teele 1989**

Teele DW, Klein JO, Rosner B. Epidemiology of otitis media during the first seven years of life in children in greater Boston: a prospective, cohort study. *Journal of Infectious Diseases* 1989;**160**(1):83-94.

**Tong 2018**

Tong S, Amand C, Kieffer A, Kyaw MH. Trends in healthcare utilization and costs associated with acute otitis media in the United States during 2008-2014. *BMC Health Services Research* 2018;**18**(1):318.

**van den Anker 2013**

van den Anker JN. Optimising the management of fever and pain in children. *International Journal of Clinical Practice* 2013;**178**(Suppl):26-32.

**Venekamp 2015**

Venekamp RP, Sanders SL, Glasziou PP, Del Mar CB, Rovers MM. Antibiotics for acute otitis media in children. *Cochrane Database of Systematic Reviews* 2015, Issue 6. Art. No: CD000219. [DOI: 10.1002/14651858.CD000219.pub4]

**Wong 2013**

Wong T, Stang AS, Ganshorn H, Hartling L, Maconochie IK, Thomsen AM, et al. Combined and alternating paracetamol and ibuprofen therapy for febrile children. *Cochrane Database of Systematic Reviews* 2013, Issue 10. Art. No: CD009572. [DOI: 10.1002/14651858.CD009572.pub2]

### References to other published versions of this review

**Sjoukes 2015**

Sjoukes A, Venekamp RP, van de Pol AC, Schilder AGM, Damoiseaux RAMJ. Paracetamol (acetaminophen) or non-steroidal anti-inflammatory drugs, alone or combined for pain relief in acute otitis media in children. *Cochrane Database of Systematic Reviews* 2015, Issue 2. Art. No: CD011534. [DOI: 10.1002/14651858.CD011534]

**Sjoukes 2016**

Sjoukes A, Venekamp RP, van de Pol AC, Hay AD, Little P, Schilder AGM, et al. Paracetamol (acetaminophen) or non-steroidal anti-inflammatory drugs, alone or combined, for pain relief in acute otitis media in children. *Cochrane Database of Systematic Reviews* 2016, Issue 12. Art. No: CD011534. [DOI: 10.1002/14651858.CD011534]

* Indicates the major publication for the study

## CHARACTERISTICS OF STUDIES

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

**Bertin 1996**

| ***Study characteristics*** | |
|---|---|
| Methods | **Allocation:** randomised<br><br>**Design:** 3-arm, parallel group, double-blind design |
| Participants | **Number:** 219 children (219 included in analysis)<br><br>**Age:** 1 year to 6.75 years<br><br>**Gender:** 96 female (44%), 123 male (56%)<br><br>**Setting:** children seen as outpatients in 4 centres<br><br>**Inclusion criteria:** the diagnosis of AOM was based on the aspect of the tympanic membrane using a semi-quantitative scale ("tympanic score") from 0 to 6. The tympanic score had to be ≥ 3 for at least 1 ear for children to be eligible.<br><br>**Exclusion criteria:** cardiac, hepatic, or renal disorders; gastroduodenal disease; known hypersensitivity to NSAIDs and penicillins or receiving antibiotic, analgesic, diuretic, or anti-inflammatory drugs within 1 week before the study. Children with AOM requiring myringotomy or with chronic otitis were not eligible. |
| Interventions | **Intervention group 1:** NSAIDs (ibuprofen) 10 mg/kg orally, 3 times daily, for 48 hours. N = 71<br><br>**Intervention group 2**: PCM 10 mg/kg orally, 3 times daily, for 48 hours. N = 73<br><br>**Comparator group**: placebo orally, 3 times daily, for 48 hours. N = 75 |

**Bertin 1996** *(Continued)*

| | |
|---|---|
| | **Use of additional interventions:** all children received antibiotics (cefaclor 15 to 30 mg/kg orally, 2 times daily, for 7 days). In case of fever ≥ 39 °C, children could be given PCM (30 to 60 mg/kg/day) in addition to the studied treatment. In case of fever ≥ 39 °C, external cooling techniques (e.g. sponging) were allowed. |
| Outcomes | **Primary outcome:** aspect of the tympanic membrane, as described using tympanic score<br><br>**Secondary outcomes:** ear pain, rectal temperature, quality of life (based on appetite, sleep, and playing activity), tolerance<br><br>**Outcome assessment:**<br><br>Evaluation of ear pain: dichotomous (0 (no pain); 1 (pain in the ear))<br><br>Fever (rectal temperature): 0 (< 37 °C), 1 (37.1 °C to 38.4 °C), 2 (> 38.5 °C)<br><br>Tolerance: presence or absence of nausea, vomiting, abdominal pain, and cutaneous rash |
| Funding sources | All treatments were supplied by Ethypharm. |
| Declaration of interest | No information provided. |
| Notes | **Participants lost to follow-up total:** according to tables, no children were lost to follow-up<br><br>PCM was prescribed 10 mg/kg, 3 times daily, which today would be considered a suboptimal dosage. |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Patients were randomised using a computer-generated list |
| Allocation concealment (selection bias) | Unclear risk | Method not described |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Quote: "Participants were given ibuprofen microgranules (in packets of 100 or 200 mg), or identically looking acetaminophen and placebo microgranules." |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Double-blind; subjective outcomes relevant for this review were assessed by parents/children. Blinding of participants was adequate |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | Loss to follow-up has not been explicitly described. However, following information provided in the tables, no children were lost to follow-up |
| Selective reporting (reporting bias) | Unclear risk | No protocol available; insufficient information to permit a judgement of low or high risk. Both positive and negative outcomes, however, have been reported in the paper |
| Other bias | Unclear risk | Baseline characteristics: balanced<br>All children were included in analysis; unclear whether ITT analysis was performed<br>Formal sample size calculations were performed<br>Compliance of treatment: no information provided |

**Hay 2009**

| ***Study characteristics*** | |
|---|---|
| Methods | **Allocation:** randomised<br><br>**Design:** 3-arm, parallel group, double-blind design |
| Participants | **Number:** 156 children, 26 children diagnosed with AOM<br><br>**Age:** 0.5 to 6 years<br><br>**Gender:** 68 female (44%), 88 male (56%)<br><br>**Setting:** community, primary care (including out-of-hours services) and secondary care (emergency department of a children's hospital)<br><br>**Inclusion criteria:** children aged between 6 months and 6 years with fever ≥ 37.8 °C and ≤ 41 °C due to an illness that could be managed at home<br><br>**Exclusion criteria:** previous participation in the PITCH trial or in another drug trial in the previous 30 days; weight 7 kg or less; illness requiring hospital admission; epilepsy or other chronic neurological disease; allergy or intolerance to the study medication; known study medicine contraindication; skin conditions precluding the use of adhesive tape; peptic ulceration or bleeding; known diagnosis of or any ongoing investigating into suspected cardiac, pulmonary, liver, or kidney disease; and parents/legal guardians who could not read or write English |
| Interventions | **Intervention group 1:** NSAIDs (ibuprofen) 10 mg/kg orally, repeated every 6 to 8 hours (maximum 3 doses in 24 hours), for 48 hours. N = 11/52 diagnosed with AOM<br><br>**Intervention group 2**: PCM 15 mg/kg orally repeated every 4 to 6 hours (maximum 4 doses in 24 hours), for 48 hours. N = 7/52 diagnosed with AOM<br><br>**Comparator group:** PCM + NSAIDs combined. Ibuprofen 10 mg/kg orally, repeated every 6 to 8 hours, and PCM 15 mg/kg orally repeated every 4 to 6 hours, for 48 hours. N = 8/52 diagnosed with AOM<br><br>**Use of additional interventions:** all children received a standardised advice sheet regarding fever in children, with the advice to: 1) use the study medicine as instructed; 2) keep the child lightly dressed in a room with normal temperature; and 3) give cool drinks |
| Outcomes | **Primary outcomes:** time without fever within the first 4 hours and the proportion of children scoring no fever-associated discomfort at 48 hours<br><br>**Secondary outcomes:** time until first fever clearance, time without fever within the first 24 hours, activity, appetite, sleep, adverse effects, and costs (including lost days of work for parents and day care/school for children)<br><br>**Outcome assessment:**<br><br>Time without fever: number of minutes in the first 24 hours using a continuous axillary thermometer. Temperature was also assessed using an axillary digital thermometer at 4, 16, 24, 48 hours at day 5.<br><br>Fever-associated discomfort at 48 hours: validated comfort scale (no comfort; not quite normal; some pain/distress; crying/very distressed) completed by parents in a symptom diary at 0, 2, 4, 16, 24, 32, 40, and 48 hours and day 5<br><br>Time until first fever clearance: time in minutes until the temperature first fell below the fever threshold of 37.2 °C using a continuous axillary thermometer<br><br>Adverse effects: measured at 24 hours, 48 hours, and day 5<br><br>Lost days of work for parents and day care/school for children: a research nurse visited the child at baseline, 24 hours, and 48 hours, and performed a telephone call at day 5 |

**Hay 2009** *(Continued)*

| | |
|---|---|
| | The number of children treated with antibiotics was recorded.<br><br>The number of return visits was recorded as part of the economic evaluation. |
| Funding sources | The study was funded by the National Institute for Health and Care Research Health Technology Assessment programme. The active drugs and matched placebos were purchased from and provided by Pfizer and DHP Investigational Medicinal Products. |
| Declaration of interest | Quote: "The views and opinions expressed in the paper did not necessarily reflect those of the NIHR HTA, NCCRCD, or Department of Health." Pfizer and DHP Investigational Medicinal Products had no role in the design, conduct, analysis, or reporting of the trial. |
| Notes | **Participants lost to follow-up total**: 3/156 (2%) for time without fever within the first 4 hours and 0/156 for fever-associated discomfort at 48 hours<br><br>Lost to follow-up NSAID group: 1/52 (2%) children. No reasons provided.<br><br>Lost to follow-up PCM group: 0/52 children<br><br>Lost to follow-up NSAID + PCM group: 2/52 children (4%). No reasons provided.<br><br>The diagnosis of AOM was made by the GP. No further details were provided regarding diagnostic criteria. |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Quotes: "The randomisation sequence was generated via a remote, automated telephone service provided by the Health Services Research Unit at the University of Aberdeen." "Eligible children were randomised with a block size of six and stratified according to five minimisation variables, ..." |
| Allocation concealment (selection bias) | Low risk | Quote: "The study medicines were provided by Pfizer Ltd and sent to DHP Ltd, a manufacturer of clinical trials medicines. DHP was aware of the randomisation procedure and the company was asked to supply the study medicines to the trial fully concealed." |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Quotes: "Study medicines were provided in a white cardboard pack containing the two bottles, one of paracetamol/placebo and one of ibuprofen/placebo suspensions. The identity of the next treatment allocation was concealed from research nurses by the fact that they carried at least one unopened box of six medicine packs during any randomisation visit." "After inputting participant information required for randomisation, the research nurses were informed which pack to give to the child." |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Quote: "The parents, principal investigator, trial co-ordinator, research nurses and project administrator were all blinded to the study medicines allocated to randomised children throughout the recruitment and analysis periods." |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | For discomfort there was no lost to follow-up, whereas 3 children (2%) were lost to follow-up for time without fever |
| Selective reporting (reporting bias) | Low risk | All outcomes have been described according to the protocol |
| Other bias | Low risk | Baseline characteristics: balanced<br>ITT analysis performed |

**Hay 2009** *(Continued)*

| | |
|---|---|
| | Formal sample size calculations were performed. However they did not achieve their original sample size (831 children)<br>Compliance of treatment: Quote: "First, in the first 24 hours, parents administered the minimum intended doses of paracetamol or placebo (four doses) to 42% to 65% of children and of ibuprofen or placebo (three doses) to 71% to 75% of children. This suggests that three times daily dosing is superior or more likely to be adhered to than four times daily dosing and may have contributed towards greater ibuprofen efficacy." |

**Kara 2022**

| ***Study characteristics*** | |
|---|---|
| Methods | **Allocation:** randomised<br>**Design:** open-label |
| Participants | **Number:** 220 children (184 included in analysis)<br>**Age:** 1 year to 5 years<br>**Gender:** male-to-female ratio: 1:6<br>**Setting:** 15 centres in Turkey<br>**Inclusion criteria:** children diagnosed with bilateral AOM with otalgia were enrolled in the study. AOM diagnosis was based on the American Academy of Pediatrics Guideline 2013 criteria.<br>**Exclusion criteria:** known allergy to lidocaine, PCM, or ibuprofen; presence of patient's symptoms more than 48 h before evaluation; receipt of any kind of ear drops or analgesic within the 24 h preceding hospital admission; presence of otorrhoea, ear drum perforation, or ventilation tubes; any known underlying disease, including epilepsy, immunodeficiency, liver, heart, or kidney disease; otologic or craniofacial malformations; any concurrent disease, including infection and complications from otitis before; and an inability to use the pain scale |
| Interventions | **Intervention group 1:** oral ibuprofen alone (7.5 mg/kg, 3 times daily)<br>**Intervention group 2:** oral paracetamol alone (10 mg/kg, 4 times daily)<br>**Intervention group 3:** oral ibuprofen (7.5 mg/kg, 3 times daily) with 1% lidocaine topical anaesthetic (4 drops to each ear topically, 3 times daily, concurrent with systemic analgesic)<br>**Intervention group 4:** oral paracetamol (10 mg/kg, 4 times daily) with 1% lidocaine topical anaesthetic (4 drops to each ear topically, 4 times daily, concurrent with systemic analgesic) |
| Outcomes | **Primary outcomes:** patient-measured pain scores amongst the 4 groups at T0, T10, T20, and T45 min after receiving topical 1% lidocaine and/or oral PCM/ibuprofen at hospital admission, and at day 1 and day 2 at home<br>**Secondary outcomes:** reduction of patient-measured pain scores by 25% and 50% between T0 and T10 min, side effects<br>**Outcome assessment:** the ear pain score was evaluated with the Face, Legs, Activity, Cry, and Consolability (FLACC) scale. Designed to assess postoperative pain in young children aged 2 months to 7 years, the FLACC scale scores pain intensity by rating five behaviours (face, legs, activity, consolability, and cry) on a scale of 0 to 2, resulting in a maximum score of 10. |
| Funding sources | N/A |

**Kara 2022** *(Continued)*

| | |
|---|---|
| Declaration of interest | N/A |
| Notes | **Participants lost to follow-up:** due to 36 participants' non-compliance (discontinuing the treatment and not completing the pain diary), an equal number of children is not included in each group after randomisation<br><br>Lost to follow-up group 1: 12/55 children<br><br>Lost to follow-up group 2: 14/55 children<br><br>Lost to follow-up group 3: 0/55 children<br><br>Lost to follow-up group 4: 10/55 children |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Quote: ''On enrollment, the children were assigned by computer-numbered randomization.'' |
| Allocation concealment (selection bias) | Unclear risk | Method not described |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | Not blinded |
| Blinding of outcome assessment (detection bias)<br>All outcomes | High risk | Not blinded |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | Reasons for missing outcome data (especially discontinuing the treatment) are likely to be related to the outcome. Quote: ''Due to 36 patients' incompatibility (discontinuing the treatment and not completing the pain diary), an equal number of patients were not included in each group after randomization.''<br><br>Also, there is an imbalance in numbers of drop outs between the groups<br><br>Drop outs group 1: 12/55 (22%)<br><br>Drop outs group 2: 14/55 (25%)<br><br>Drop outs group 3: 0/55 (0%)<br><br>Drop outs group 4: 10/55 (18%) |
| Selective reporting (reporting bias) | Unclear risk | No protocol available; insufficient information to permit a judgement of low or high risk. |
| Other bias | Unclear risk | Baseline characteristics: no baseline characteristics table available. Quote: ''There were no statistically significant differences in the distribution of age (p = 0.241), gender (p = 0.935), and antibiotic use (p = 0.501) among the four groups.''<br><br>Unclear whether ITT analysis was performed<br><br>No formal sample size calculations were performed |

**Kara 2022** *(Continued)*

| | |
|---|---|
| | Compliance of treatment: no information provided |

**Little 2013**

| ***Study characteristics*** | |
|---|---|
| Methods | **Allocation:** randomised<br><br>**Design:** parallel, open 3 x 2 x 2 factorial trial |
| Participants | **Number:** 889 participants, 82 diagnosed with AOM<br><br>**Age:** 3 years and older<br><br>**Gender:** 540 female (61%), 349 male (39%)<br><br>**Setting:** participants presented to a GP or nurse in primary care (in total 53 GPs and practice nurses in 25 practices)<br><br>**Inclusion criteria:** people aged 3 years and older presenting to a GP or nurse in primary care with a respiratory tract infection diagnosed by the health professional<br><br>**Exclusion criteria:** asthma (unless it was not sensitive to ibuprofen or aspirin); peptic ulcer; hypersensitivity to analgesics; inability to complete outcomes; conditions requiring hospital admission; immunodeficiency; pregnancy; and breastfeeding |
| Interventions | **Intervention group 1:** NSAIDs (ibuprofen). N = 26/290 diagnosed with AOM<br><br>**Intervention group 2**: PCM. N = 27/302 diagnosed with AOM<br><br>**Comparator group**: PCM + NSAIDs (ibuprofen) alternating. N = 29/254 diagnosed with AOM<br><br>The doses of PCM and ibuprofen used in this trial were the maximum recommended by the British National Formulary (which varies by age).<br><br>**Use of additional interventions:** participants were not only randomised to the 3 drug groups, but also to 2 dosing groups and 2 steam groups. The dosing groups were advised to either use drugs regularly 4 times a day for at least 3 days or to take drugs as required. The steam groups were advised to either inhale with steam for at least 15 minutes (5 minutes, 3 times a day) or not to inhale with steam. |
| Outcomes | **Primary outcome:** symptom control<br><br>**Secondary outcomes:** side effects (rash, diarrhoea, vomiting, abdominal pain), temperature, antibiotic use, return visits<br><br>**Outcome assessment:**<br><br>Symptom control: mean symptom severity at the end of each day, averaged over days 2 to 4 of a 2-week symptom diary using a format for rating symptoms (0 = no problem, 6 = as bad as it could be)<br><br>Side effects: such as vomiting, diarrhoea, rash, or abdominal pain, reported in a 2-week symptom diary<br><br>Temperature: mean morning and evening temperature reading with Tempadot thermometers (orally where possible), averaged over days 2 to 4<br><br>Antibiotic use: documented in the diary. Randomisation was stratified by antibiotic prescription strategy (immediate versus delayed).<br><br>Return visit: a return with a symptom or diagnosis of respiratory tract infection recorded with a structured pro forma by a member of the research team. Complications were defined as a new consultation documented in the notes within 28 days. |

**Little 2013** *(Continued)*

| | |
|---|---|
| Funding sources | The study was funded by the National Institute for Health Research Programme Grants for Applied Research programme. |
| Declaration of interest | All authors declared none. |
| Notes | **Participants lost to follow-up total:** 138/889 (16%) for symptom severity<br>Participants lost to follow-up NSAID group: 43/297 (15%)<br>Participants lost to follow-up PCM group: 51/305 (17%)<br>Participants lost to follow-up NSAID + PCM group: 49/287 (15%)<br>The diagnosis of AOM was made by the GP or research nurse. No further details were provided regarding diagnostic criteria.<br>There was no advice regarding the dose of PCM and ibuprofen. |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Quotes: "A statistician independent of the study team coordinated the randomisation, .." "Patients were randomised to one of 12 advice groups"...", with computer generated random number tables to determine one of 12 advice slips contained in sealed numbered envelopes." |
| Allocation concealment (selection bias) | Low risk | Quote: "..the clinician took the next pack off the shelf that contained pre-randomised advice sheets". As described above the advice slips were contained in sealed numbered envelopes |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | Not blinded |
| Blinding of outcome assessment (detection bias)<br>All outcomes | High risk | Not blinded |
| Incomplete outcome data (attrition bias)<br>All outcomes | Unclear risk | 138/889 (16%) for symptom severity;<br>Quote: "The characteristics of patients in whom the primary outcome was not documented were similar to those followed up ..." |
| Selective reporting (reporting bias) | Low risk | All outcomes have been described according to the protocol |
| Other bias | Low risk | Baseline characteristics: balanced<br>ITT analysis with complete data (no imputation of missing data)<br>Formal sample size calculations were performed<br>Compliance of treatment: Quote: "From the main diary data for paracetamol use, patients took a mean of 4.2 doses a day for the first three days in the paracetamol group, 3.5 in the combined group, and 0.4 in the ibuprofen group. For ibuprofen, patients took a mean of 0.3 doses in the paracetamol group, 2.9 in the ibuprofen group, and 2.7 in the combined group. Steam inhalation was reported a mean of 1.6 times a day in the steam group for days two and three and 0.1 times in the no steam group. Advice to use analgesic regularly compared with as required made little difference to the amount of analgesia used |

| | |
|---|---|
| **Little 2013** *(Continued)* | for either paracetamol (2.8 doses v 2.4 doses) or ibuprofen (2.0 doses v 1.9 doses)." |

AOM: acute otitis media
GP: general practitioner
N/A: not available
NSAID: non-steroidal anti-inflammatory drug
PCM: paracetamol
ITT: intention-to-treat

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

| Study | Reason for exclusion |
|---|---|
| Azuma 2010 | Participants: adults only (no children included) |
| Campos 1992 | Allocation: non-randomised study |
| Cappella 1993 | Interventions: trial comparing nimesulide (NSAID) versus lysine-acetyl salicylate |
| Caretti 1986 | Participants: study did not include children with AOM (only tonsillitis and pharyngitis) |
| Dasgupta 2002 | Interventions: trial comparing nizer (NSAID) versus nimesulide (NSAID) |
| Eccles 2006 | Participants: adults only (no children included) |
| Fort 2000 | Interventions: trial comparing ibuprofen (NSAID) versus lysine clonixinate (NSAID) |
| Kim 2013 | Interventions: trial comparing dexibuprofen (NSAID) 3.5 or 7 mg/kg versus ibuprofen 5 or 10 mg/kg (NSAID) |
| Lozano Gonzalez 1989 | Participants: study did not include children with AOM (only tonsillitis, pharyngitis, tracheitis, bronchitis, and pneumonia) |
| McIntyre 1996 | Participants: trial included hospitalised children |
| Metta 2000 | Interventions: trial comparing ibuprofen (NSAID) versus lysine clonixinate (NSAID) |
| Milvio 1984 | Interventions: trial comparing nimesulide (NSAID) versus benzydamine (NSAID) |
| Motoichi 1997 | Participants: adults only (no children included) |
| Nouri 1984 | Participants: adults only (no children included) |
| Passali 2001 | Interventions: trial comparing nimesulide (NSAID) versus morniflumate (NSAID) |
| Polidori 1993 | Participants: trial included both outpatient and hospitalised children |
| Ryan 1987 | Participants: adults only (no children included) |
| Sarrell 2006 | Other: we were not able to obtain the crude subgroup data of children with AOM from this trial |
| Schuetz 2014 | Allocation: non-randomised study |
| Siegel 2003 | Allocation: non-randomised study |

| Study | Reason for exclusion |
|---|---|
| Siquet 1983 | Interventions: trial comparing fentiazac (NSAID) versus ibuprofen (NSAID) |
| Stipon 1983 | Interventions: trial comparing an intravenous injection of UP 341.01 (bio-precursor of paracetamol) 1 g versus 2 g |
| van Uum 2020 | Interventions: trial comparing the effectiveness of a GP-targeted educational intervention aimed at improving pain management for AOM versus usual care |
| Weippl 1985 | Interventions: trial comparing suprofen (NSAID) versus lidocaine + phenazone ear drops |
| Yoon 2008 | Interventions: trial comparing dexibuprofen (NSAID) 5 or 7 mg/kg versus 10 mg ibuprofen (NSAID) |

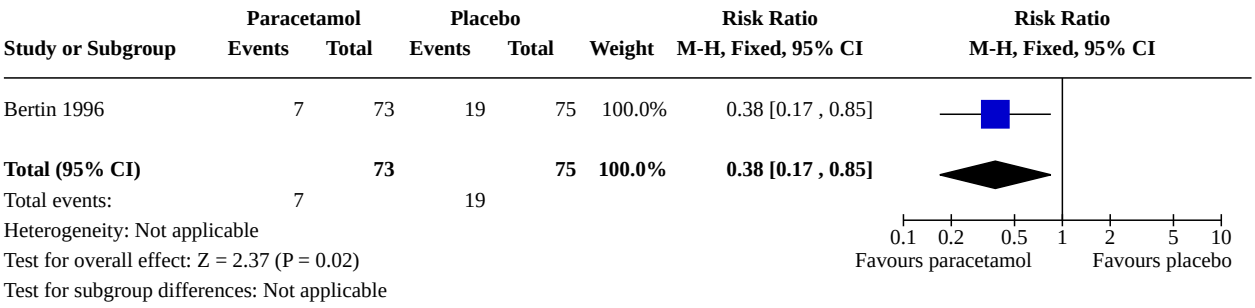
AOM: acute otitis media
GP: general practitioner
NSAID: non-steroidal anti-inflammatory drug

## DATA AND ANALYSES

### Comparison 1. Paracetamol versus placebo

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1.1 Pain at 48 hours | 1 | 148 | Risk Ratio (M-H, Fixed, 95% CI) | 0.38 [0.17, 0.85] |
| 1.2 Adverse events | 1 | 148 | Risk Ratio (M-H, Fixed, 95% CI) | 1.03 [0.21, 4.93] |
| 1.3 Fever at 48 hours | 1 | 148 | Risk Ratio (M-H, Fixed, 95% CI) | 1.03 [0.07, 16.12] |

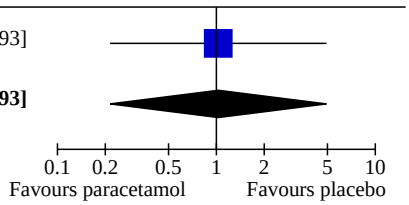
### Analysis 1.1. Comparison 1: Paracetamol versus placebo, Outcome 1: Pain at 48 hours



### Analysis 1.2. Comparison 1: Paracetamol versus placebo, Outcome 2: Adverse events

| Study or Subgroup | Paracetamol Events | Paracetamol Total | Placebo Events | Placebo Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Bertin 1996 | 3 | 73 | 3 | 75 | 100.0% | 1.03 [0.21 , 4.93] |
| **Total (95% CI)** | | **73** | | **75** | **100.0%** | **1.03 [0.21 , 4.93]** |
| Total events: | 3 | | 3 | | | |

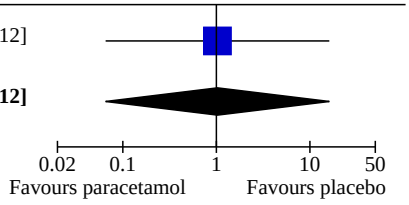
Heterogeneity: Not applicable
Test for overall effect: Z = 0.03 (P = 0.97)
Test for subgroup differences: Not applicable




### Analysis 1.3. Comparison 1: Paracetamol versus placebo, Outcome 3: Fever at 48 hours

| Study or Subgroup | Paracetamol Events | Paracetamol Total | Control Events | Control Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Bertin 1996 | 1 | 73 | 1 | 75 | 100.0% | 1.03 [0.07 , 16.12] |
| **Total (95% CI)** | | **73** | | **75** | **100.0%** | **1.03 [0.07 , 16.12]** |
| Total events: | 1 | | 1 | | | |

Heterogeneity: Not applicable
Test for overall effect: Z = 0.02 (P = 0.98)
Test for subgroup differences: Not applicable



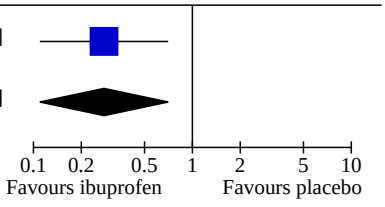

## Comparison 2. NSAIDs versus placebo

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 2.1 Pain at 48 hours | 1 | 146 | Risk Ratio (M-H, Fixed, 95% CI) | 0.28 [0.11, 0.70] |
| 2.2 Adverse events | 1 | 146 | Risk Ratio (M-H, Fixed, 95% CI) | 1.76 [0.44, 7.10] |
| 2.3 Fever at 48 hours | 1 | 146 | Risk Ratio (M-H, Fixed, 95% CI) | 1.06 [0.07, 16.57] |

### Analysis 2.1. Comparison 2: NSAIDs versus placebo, Outcome 1: Pain at 48 hours

| Study or Subgroup | Ibuprofen Events | Ibuprofen Total | Placebo Events | Placebo Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Bertin 1996 | 5 | 71 | 19 | 75 | 100.0% | 0.28 [0.11 , 0.70] |
| **Total (95% CI)** | | **71** | | **75** | **100.0%** | **0.28 [0.11 , 0.70]** |
| Total events: | 5 | | 19 | | | |

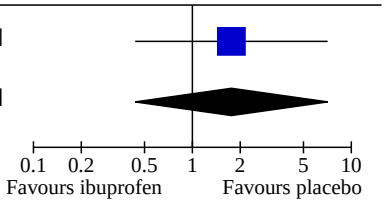
Heterogeneity: Not applicable
Test for overall effect: Z = 2.70 (P = 0.007)
Test for subgroup differences: Not applicable



### Analysis 2.2. Comparison 2: NSAIDs versus placebo, Outcome 2: Adverse events

| Study or Subgroup | Ibuprofen Events | Ibuprofen Total | Placebo Events | Placebo Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Bertin 1996 | 5 | 71 | 3 | 75 | 100.0% | 1.76 [0.44 , 7.10] |
| **Total (95% CI)** | | **71** | | **75** | **100.0%** | **1.76 [0.44 , 7.10]** |
| Total events: | 5 | | 3 | | | |

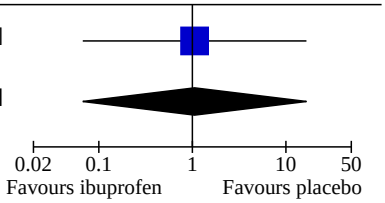
Heterogeneity: Not applicable
Test for overall effect: Z = 0.80 (P = 0.43)
Test for subgroup differences: Not applicable




### Analysis 2.3. Comparison 2: NSAIDs versus placebo, Outcome 3: Fever at 48 hours

| Study or Subgroup | Ibuprofen Events | Ibuprofen Total | Placebo Events | Placebo Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Bertin 1996 | 1 | 71 | 1 | 75 | 100.0% | 1.06 [0.07 , 16.57] |
| **Total (95% CI)** | | **71** | | **75** | **100.0%** | **1.06 [0.07 , 16.57]** |
| Total events: | 1 | | 1 | | | |

Heterogeneity: Not applicable
Test for overall effect: Z = 0.04 (P = 0.97)
Test for subgroup differences: Not applicable




## Comparison 3. NSAIDs versus paracetamol

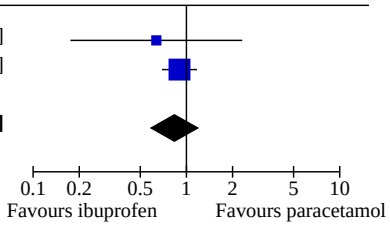
| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 3.1 Pain at 24 hours | 2 | 39 | Risk Ratio (M-H, Fixed, 95% CI) | 0.83 [0.59, 1.18] |
| 3.2 Pain at 48 to 72 hours | 3 | 183 | Risk Ratio (M-H, Fixed, 95% CI) | 0.91 [0.54, 1.54] |
| 3.3 Pain at 4 to 7 days | 2 | 38 | Risk Ratio (M-H, Fixed, 95% CI) | 0.74 [0.17, 3.23] |
| 3.4 Adverse events | 3 | 281 | Risk Ratio (M-H, Random, 95% CI) | 1.71 [0.43, 6.90] |
| 3.5 Mild pain at 24 hours | 2 | 39 | Risk Ratio (M-H, Fixed, 95% CI) | 1.08 [0.31, 3.73] |
| 3.6 Mild pain at 48 to 72 hours | 2 | 39 | Risk Ratio (M-H, Fixed, 95% CI) | 1.35 [0.62, 2.91] |
| 3.7 Mild pain at 4 to 7 days | 2 | 39 | Risk Ratio (M-H, Fixed, 95% CI) | 0.91 [0.37, 2.23] |
| 3.8 Mean pain score at 24 hours | 3 | 111 | Mean Difference (IV, Fixed, 95% CI) | 0.29 [-0.20, 0.79] |
| 3.9 Mean pain score at 48 to 72 hours | 3 | 108 | Mean Difference (IV, Fixed, 95% CI) | 0.25 [-0.16, 0.66] |
| 3.10 Mean pain score at 4 to 7 days | 2 | 31 | Mean Difference (IV, Fixed, 95% CI) | -0.30 [-2.38, 1.78] |

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 3.11 Fever at 24 hours | 2 | 39 | Risk Ratio (M-H, Fixed, 95% CI) | 0.69 [0.24, 2.00] |
| 3.12 Fever at 48 to 72 hours | 3 | 182 | Risk Ratio (M-H, Fixed, 95% CI) | 1.18 [0.31, 4.44] |
| 3.13 Fever at 4 to 7 days | 2 | 39 | Risk Ratio (M-H, Fixed, 95% CI) | 2.75 [0.12, 60.70] |
| 3.14 Reconsultations | 1 | 53 | Risk Ratio (M-H, Fixed, 95% CI) | 1.13 [0.92, 1.40] |
| 3.15 Delayed antibiotic prescriptions | 1 | 53 | Risk Ratio (M-H, Fixed, 95% CI) | 1.32 [0.74, 2.35] |

### Analysis 3.1. Comparison 3: NSAIDs versus paracetamol, Outcome 1: Pain at 24 hours

| Study or Subgroup | Ibuprofen Events | Ibuprofen Total | Paracetamol Events | Paracetamol Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Hay 2009 | 3 | 11 | 3 | 7 | 25.0% | 0.64 [0.18 , 2.31] |
| Little 2013 | 9 | 10 | 11 | 11 | 75.0% | 0.90 [0.69 , 1.17] |
| **Total (95% CI)** | | **21** | | **18** | **100.0%** | **0.83 [0.59 , 1.18]** |
| Total events: | 12 | | 14 | | | |

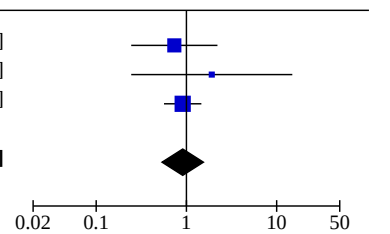
Heterogeneity: Chi² = 0.49, df = 1 (P = 0.48); I² = 0%
Test for overall effect: Z = 1.02 (P = 0.31)
Test for subgroup differences: Not applicable




### Analysis 3.2. Comparison 3: NSAIDs versus paracetamol, Outcome 2: Pain at 48 to 72 hours

| Study or Subgroup | Ibuprofen Events | Ibuprofen Total | Paracetamol Events | Paracetamol Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Bertin 1996 | 5 | 71 | 7 | 73 | 41.8% | 0.73 [0.24 , 2.21] |
| Hay 2009 | 3 | 11 | 1 | 7 | 7.4% | 1.91 [0.24 , 14.91] |
| Little 2013 | 8 | 11 | 8 | 10 | 50.8% | 0.91 [0.56 , 1.46] |
| **Total (95% CI)** | | **93** | | **90** | **100.0%** | **0.91 [0.54 , 1.54]** |
| Total events: | 16 | | 16 | | | |

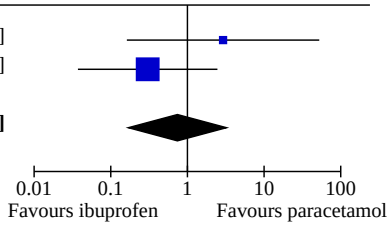
Heterogeneity: Chi² = 0.65, df = 2 (P = 0.72); I² = 0%
Test for overall effect: Z = 0.35 (P = 0.73)
Test for subgroup differences: Not applicable



### Analysis 3.3. Comparison 3: NSAIDs versus paracetamol, Outcome 3: Pain at 4 to 7 days

| Study or Subgroup | Ibuprofen Events | Ibuprofen Total | Paracetamol Events | Paracetamol Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Hay 2009 | 2 | 11 | 0 | 6 | 16.7% | 2.92 [0.16 , 52.47] |
| Little 2013 | 1 | 11 | 3 | 10 | 83.3% | 0.30 [0.04 , 2.46] |
| **Total (95% CI)** | | **22** | | **16** | **100.0%** | **0.74 [0.17 , 3.23]** |
| Total events: | 3 | | 3 | | | |

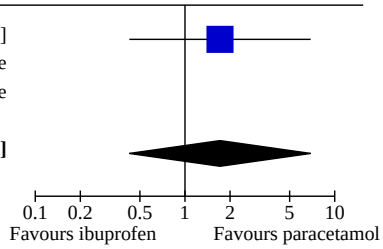
Heterogeneity: Chi² = 1.56, df = 1 (P = 0.21); I² = 36%
Test for overall effect: Z = 0.40 (P = 0.69)
Test for subgroup differences: Not applicable




### Analysis 3.4. Comparison 3: NSAIDs versus paracetamol, Outcome 4: Adverse events

| Study or Subgroup | Ibuprofen Events | Ibuprofen Total | Paracetamol Events | Paracetamol Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| Bertin 1996 | 5 | 71 | 3 | 73 | 100.0% | 1.71 [0.43 , 6.90] |
| Kara 2022 | 0 | 43 | 0 | 41 | | Not estimable |
| Little 2013 | 0 | 26 | 0 | 27 | | Not estimable |
| **Total (95% CI)** | | **140** | | **141** | **100.0%** | **1.71 [0.43 , 6.90]** |
| Total events: | 5 | | 3 | | | |

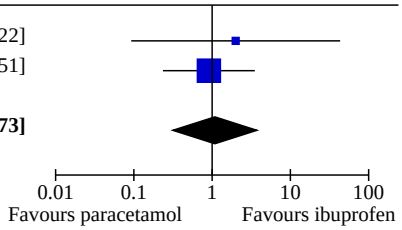
Heterogeneity: Not applicable
Test for overall effect: Z = 0.76 (P = 0.45)
Test for subgroup differences: Not applicable




### Analysis 3.5. Comparison 3: NSAIDs versus paracetamol, Outcome 5: Mild pain at 24 hours

| Study or Subgroup | Ibuprofen Events | Ibuprofen Total | Paracetamol Events | Paracetamol Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Hay 2009 | 1 | 11 | 0 | 7 | 16.0% | 2.00 [0.09 , 43.22] |
| Little 2013 | 3 | 11 | 3 | 10 | 84.0% | 0.91 [0.24 , 3.51] |
| **Total (95% CI)** | | **22** | | **17** | **100.0%** | **1.08 [0.31 , 3.73]** |
| Total events: | 4 | | 3 | | | |

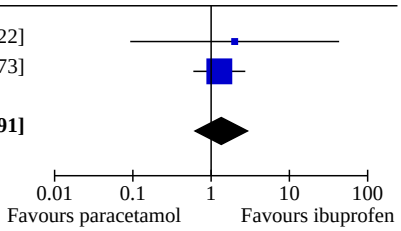
Heterogeneity: Chi² = 0.22, df = 1 (P = 0.64); I² = 0%
Test for overall effect: Z = 0.13 (P = 0.90)
Test for subgroup differences: Not applicable



### Analysis 3.6. Comparison 3: NSAIDs versus paracetamol, Outcome 6: Mild pain at 48 to 72 hours

| Study or Subgroup | Ibuprofen Events | Ibuprofen Total | Paracetamol Events | Paracetamol Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Hay 2009 | 1 | 11 | 0 | 7 | 10.3% | 2.00 [0.09 , 43.22] |
| Little 2013 | 7 | 11 | 5 | 10 | 89.7% | 1.27 [0.59 , 2.73] |
| **Total (95% CI)** | | **22** | | **17** | **100.0%** | **1.35 [0.62 , 2.91]** |
| Total events: | 8 | | 5 | | | |

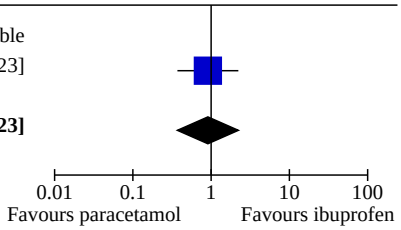
Heterogeneity: Chi² = 0.08, df = 1 (P = 0.77); I² = 0%
Test for overall effect: Z = 0.76 (P = 0.45)
Test for subgroup differences: Not applicable




### Analysis 3.7. Comparison 3: NSAIDs versus paracetamol, Outcome 7: Mild pain at 4 to 7 days

| Study or Subgroup | Ibuprofen Events | Ibuprofen Total | Paracetamol Events | Paracetamol Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Hay 2009 | 0 | 11 | 0 | 7 | | Not estimable |
| Little 2013 | 5 | 11 | 5 | 10 | 100.0% | 0.91 [0.37 , 2.23] |
| **Total (95% CI)** | | **22** | | **17** | **100.0%** | **0.91 [0.37 , 2.23]** |
| Total events: | 5 | | 5 | | | |

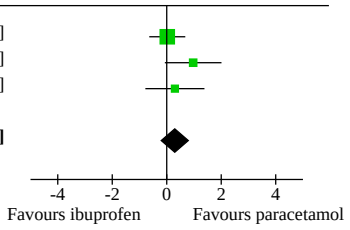
Heterogeneity: Not applicable
Test for overall effect: Z = 0.21 (P = 0.83)
Test for subgroup differences: Not applicable




### Analysis 3.8. Comparison 3: NSAIDs versus paracetamol, Outcome 8: Mean pain score at 24 hours

| Study or Subgroup | Ibuprofen Mean | Ibuprofen SD | Ibuprofen Total | Paracetamol Mean | Paracetamol SD | Paracetamol Total | Weight | Mean Difference IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Hay 2009 | 2.45 | 0.9 | 11 | 2.43 | 0.53 | 7 | 56.3% | 0.02 [-0.64 , 0.68] |
| Kara 2022 | 3.97 | 2.22 | 38 | 3 | 2.27 | 34 | 22.8% | 0.97 [-0.07 , 2.01] |
| Little 2013 | 3.9 | 1.1 | 11 | 3.6 | 1.4 | 10 | 20.9% | 0.30 [-0.78 , 1.38] |
| **Total (95% CI)** | | | **60** | | | **51** | **100.0%** | **0.29 [-0.20 , 0.79]** |

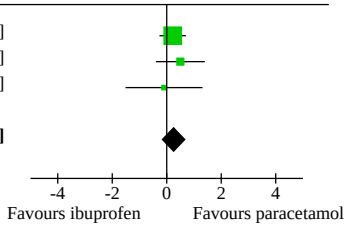
Heterogeneity: Chi² = 2.28, df = 2 (P = 0.32); I² = 12%
Test for overall effect: Z = 1.17 (P = 0.24)
Test for subgroup differences: Not applicable




### Analysis 3.9. Comparison 3: NSAIDs versus paracetamol, Outcome 9: Mean pain score at 48 to 72 hours

| Study or Subgroup | Ibuprofen Mean | Ibuprofen SD | Ibuprofen Total | Paracetamol Mean | Paracetamol SD | Paracetamol Total | Weight | Mean Difference IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Hay 2009 | 2.36 | 0.67 | 11 | 2.14 | 0.38 | 7 | 70.9% | 0.22 [-0.27 , 0.71] |
| Kara 2022 | 2.95 | 1.8 | 35 | 2.45 | 2 | 34 | 20.7% | 0.50 [-0.40 , 1.40] |
| Little 2013 | 1.6 | 1.8 | 11 | 1.7 | 1.5 | 10 | 8.4% | -0.10 [-1.51 , 1.31] |
| **Total (95% CI)** | | | **57** | | | **51** | **100.0%** | **0.25 [-0.16 , 0.66]** |

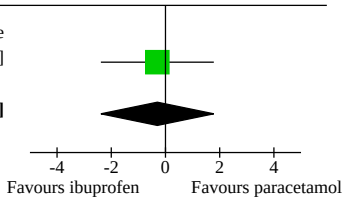
Heterogeneity: Chi² = 0.55, df = 2 (P = 0.76); I² = 0%
Test for overall effect: Z = 1.20 (P = 0.23)
Test for subgroup differences: Not applicable



### Analysis 3.10. Comparison 3: NSAIDs versus paracetamol, Outcome 10: Mean pain score at 4 to 7 days

| Study or Subgroup | Ibuprofen Mean | SD | Total | Paracetamol Mean | SD | Total | Weight | Mean Difference IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Hay 2009 | 2.18 | 0.4 | 11 | 2 | 0 | 7 | | Not estimable |
| Little 2013 | 1 | 2 | 6 | 1.3 | 1.8 | 7 | 100.0% | -0.30 [-2.38 , 1.78] |
| **Total (95% CI)** | | | **17** | | | **14** | **100.0%** | **-0.30 [-2.38 , 1.78]** |

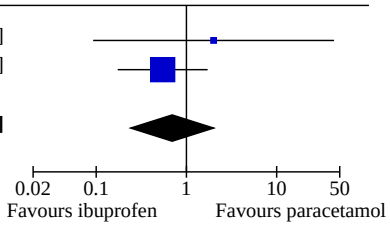
Heterogeneity: Not applicable
Test for overall effect: Z = 0.28 (P = 0.78)
Test for subgroup differences: Not applicable




### Analysis 3.11. Comparison 3: NSAIDs versus paracetamol, Outcome 11: Fever at 24 hours

| Study or Subgroup | Ibuprofen Events | Total | Paracetamol Events | Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Hay 2009 | 1 | 11 | 0 | 7 | 10.3% | 2.00 [0.09 , 43.22] |
| Little 2013 | 3 | 11 | 5 | 10 | 89.7% | 0.55 [0.17 , 1.72] |
| **Total (95% CI)** | | **22** | | **17** | **100.0%** | **0.69 [0.24 , 2.00]** |
| Total events: | 4 | | 5 | | | |

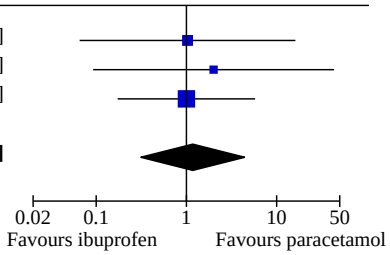
Heterogeneity: Chi² = 0.63, df = 1 (P = 0.43); I² = 0%
Test for overall effect: Z = 0.67 (P = 0.50)
Test for subgroup differences: Not applicable




### Analysis 3.12. Comparison 3: NSAIDs versus paracetamol, Outcome 12: Fever at 48 to 72 hours

| Study or Subgroup | Ibuprofen Events | Total | Paracetamol Events | Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Bertin 1996 | 1 | 71 | 1 | 73 | 27.5% | 1.03 [0.07 , 16.12] |
| Hay 2009 | 1 | 11 | 0 | 7 | 16.7% | 2.00 [0.09 , 43.22] |
| Little 2013 | 2 | 10 | 2 | 10 | 55.8% | 1.00 [0.17 , 5.77] |
| **Total (95% CI)** | | **92** | | **90** | **100.0%** | **1.18 [0.31 , 4.44]** |
| Total events: | 4 | | 3 | | | |

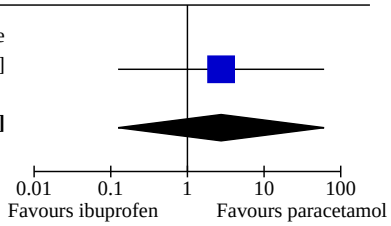
Heterogeneity: Chi² = 0.16, df = 2 (P = 0.92); I² = 0%
Test for overall effect: Z = 0.24 (P = 0.81)
Test for subgroup differences: Not applicable



### Analysis 3.13. Comparison 3: NSAIDs versus paracetamol, Outcome 13: Fever at 4 to 7 days

| Study or Subgroup | Ibuprofen Events | Ibuprofen Total | Paracetamol Events | Paracetamol Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Hay 2009 | 0 | 11 | 0 | 7 | | Not estimable |
| Little 2013 | 1 | 11 | 0 | 10 | 100.0% | 2.75 [0.12 , 60.70] |
| **Total (95% CI)** | | **22** | | **17** | **100.0%** | **2.75 [0.12 , 60.70]** |
| Total events: | 1 | | 0 | | | |

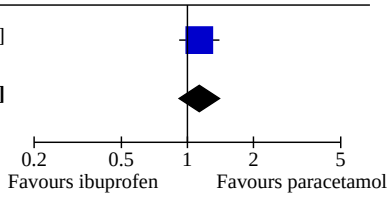
Heterogeneity: Not applicable
Test for overall effect: Z = 0.64 (P = 0.52)
Test for subgroup differences: Not applicable




### Analysis 3.14. Comparison 3: NSAIDs versus paracetamol, Outcome 14: Reconsultations

| Study or Subgroup | Ibuprofen Events | Ibuprofen Total | Paracetamol Events | Paracetamol Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Little 2013 | 24 | 26 | 22 | 27 | 100.0% | 1.13 [0.92 , 1.40] |
| **Total (95% CI)** | | **26** | | **27** | **100.0%** | **1.13 [0.92 , 1.40]** |
| Total events: | 24 | | 22 | | | |

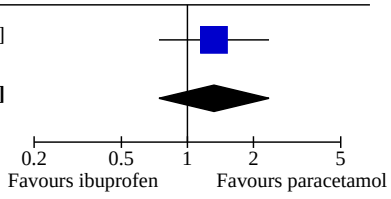
Heterogeneity: Not applicable
Test for overall effect: Z = 1.16 (P = 0.25)
Test for subgroup differences: Not applicable




### Analysis 3.15. Comparison 3: NSAIDs versus paracetamol, Outcome 15: Delayed antibiotic prescriptions

| Study or Subgroup | Ibuprofen Events | Ibuprofen Total | Paracetamol Events | Paracetamol Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Little 2013 | 14 | 26 | 11 | 27 | 100.0% | 1.32 [0.74 , 2.35] |
| **Total (95% CI)** | | **26** | | **27** | **100.0%** | **1.32 [0.74 , 2.35]** |
| Total events: | 14 | | 11 | | | |

Heterogeneity: Not applicable
Test for overall effect: Z = 0.95 (P = 0.34)
Test for subgroup differences: Not applicable

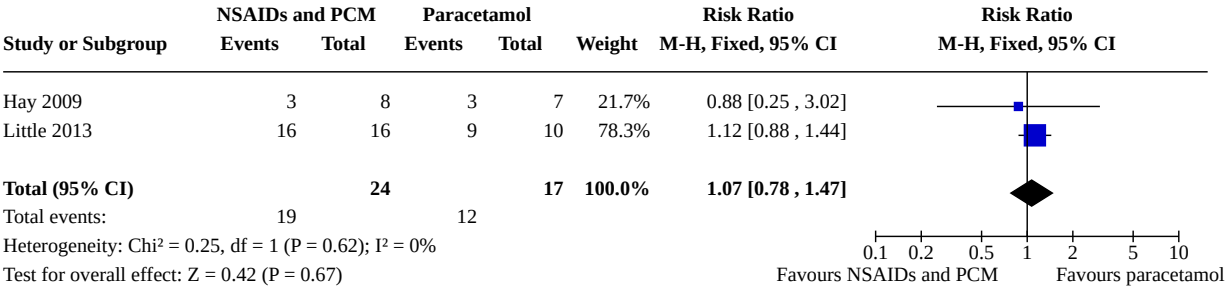



## Comparison 4. NSAIDs + paracetamol versus paracetamol

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 4.1 Pain at 24 hours | 2 | 41 | Risk Ratio (M-H, Fixed, 95% CI) | 1.07 [0.78, 1.47] |
| 4.2 Pain at 48 to 72 hours | 2 | 41 | Risk Ratio (M-H, Fixed, 95% CI) | 0.71 [0.42, 1.20] |
| 4.3 Pain at 4 to 7 days | 2 | 41 | Risk Ratio (M-H, Fixed, 95% CI) | 1.65 [0.58, 4.72] |
| 4.4 Adverse events | 1 | 0 | Risk Ratio (M-H, Fixed, 95% CI) | Not estimable |
| 4.5 Mild pain at 24 hours | 2 | 41 | Risk Ratio (M-H, Fixed, 95% CI) | 0.21 [0.02, 1.74] |

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 4.6 Mild pain at 48 to 72 hours | 2 | 41 | Risk Ratio (M-H, Fixed, 95% CI) | 0.62 [0.24, 1.62] |
| 4.7 Mild pain at 4 to 7 days | 2 | 41 | Risk Ratio (M-H, Fixed, 95% CI) | 0.50 [0.17, 1.43] |
| 4.8 Mean pain at 24 hours | 2 | 40 | Mean Difference (IV, Random, 95% CI) | 0.32 [-0.59, 1.23] |
| 4.9 Mean pain at 48 to 72 hours | 2 | 40 | Mean Difference (IV, Fixed, 95% CI) | 0.60 [-0.77, 1.97] |
| 4.10 Mean pain at 4 to 7 days | 2 | 33 | Mean Difference (IV, Fixed, 95% CI) | 0.70 [-1.01, 2.41] |
| 4.11 Fever at 24 hours | 2 | 41 | Risk Ratio (M-H, Fixed, 95% CI) | 1.48 [0.73, 2.99] |
| 4.12 Fever at 48 to 72 hours | 2 | 41 | Risk Ratio (M-H, Fixed, 95% CI) | 2.13 [0.60, 7.60] |
| 4.13 Fever at 4 to 7 days | 2 | 0 | Risk Ratio (M-H, Fixed, 95% CI) | Not estimable |
| 4.14 Reconsultations | 1 | 56 | Risk Ratio (M-H, Fixed, 95% CI) | 0.80 [0.58, 1.11] |
| 4.15 Delayed antibiotic prescriptions | 1 | 56 | Risk Ratio (M-H, Fixed, 95% CI) | 1.27 [0.71, 2.26] |
| 4.16 Serious complications | 2 | 0 | Risk Ratio (M-H, Fixed, 95% CI) | Not estimable |

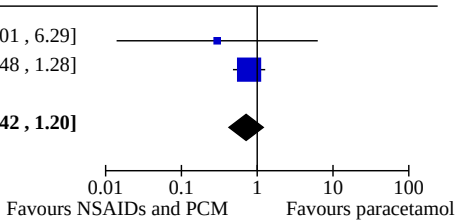
**Analysis 4.1. Comparison 4: NSAIDs + paracetamol versus paracetamol, Outcome 1: Pain at 24 hours**



### Analysis 4.2. Comparison 4: NSAIDs + paracetamol versus paracetamol, Outcome 2: Pain at 48 to 72 hours

| Study or Subgroup | NSAIDs and PCM Events | Total | Paracetamol Events | Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Hay 2009 | 0 | 8 | 1 | 7 | 13.9% | 0.30 [0.01 , 6.29] |
| Little 2013 | 10 | 16 | 8 | 10 | 86.1% | 0.78 [0.48 , 1.28] |
| **Total (95% CI)** | | **24** | | **17** | **100.0%** | **0.71 [0.42 , 1.20]** |
| Total events: | 10 | | 9 | | | |

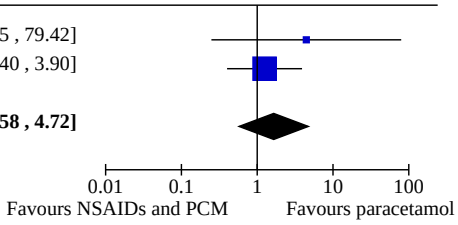
Heterogeneity: Chi² = 0.45, df = 1 (P = 0.50); I² = 0%
Test for overall effect: Z = 1.27 (P = 0.20)
Test for subgroup differences: Not applicable




### Analysis 4.3. Comparison 4: NSAIDs + paracetamol versus paracetamol, Outcome 3: Pain at 4 to 7 days

| Study or Subgroup | NSAIDs and PCM Events | Total | Paracetamol Events | Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Hay 2009 | 2 | 8 | 0 | 7 | 12.5% | 4.44 [0.25 , 79.42] |
| Little 2013 | 6 | 16 | 3 | 10 | 87.5% | 1.25 [0.40 , 3.90] |
| **Total (95% CI)** | | **24** | | **17** | **100.0%** | **1.65 [0.58 , 4.72]** |
| Total events: | 8 | | 3 | | | |

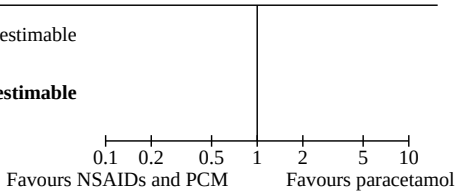
Heterogeneity: Chi² = 0.68, df = 1 (P = 0.41); I² = 0%
Test for overall effect: Z = 0.94 (P = 0.35)
Test for subgroup differences: Not applicable




### Analysis 4.4. Comparison 4: NSAIDs + paracetamol versus paracetamol, Outcome 4: Adverse events

| Study or Subgroup | NSAIDs and PCM Events | Total | Paracetamol Events | Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Little 2013 | 0 | 29 | 0 | 27 | | Not estimable |
| **Total (95% CI)** | | **0** | | **0** | | **Not estimable** |
| Total events: | 0 | | 0 | | | |

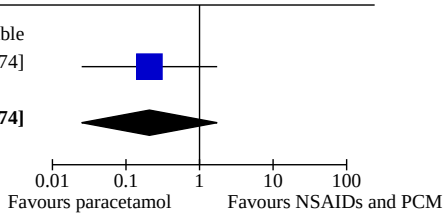
Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable




### Analysis 4.5. Comparison 4: NSAIDs + paracetamol versus paracetamol, Outcome 5: Mild pain at 24 hours

| Study or Subgroup | NSAIDs and PCM Events | Total | Paracetamol Events | Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Hay 2009 | 0 | 8 | 0 | 7 | | Not estimable |
| Little 2013 | 1 | 16 | 3 | 10 | 100.0% | 0.21 [0.02 , 1.74] |
| **Total (95% CI)** | | **24** | | **17** | **100.0%** | **0.21 [0.02 , 1.74]** |
| Total events: | 1 | | 3 | | | |

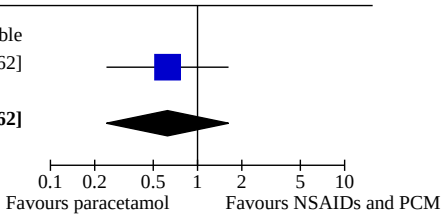
Heterogeneity: Not applicable
Test for overall effect: Z = 1.45 (P = 0.15)
Test for subgroup differences: Not applicable



### Analysis 4.6. Comparison 4: NSAIDs + paracetamol versus paracetamol, Outcome 6: Mild pain at 48 to 72 hours

| Study or Subgroup | NSAIDs and PCM Events | Total | Paracetamol Events | Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Hay 2009 | 0 | 8 | 0 | 7 | | Not estimable |
| Little 2013 | 5 | 16 | 5 | 10 | 100.0% | 0.63 [0.24 , 1.62] |
| **Total (95% CI)** | | **24** | | **17** | **100.0%** | **0.63 [0.24 , 1.62]** |
| Total events: | 5 | | 5 | | | |

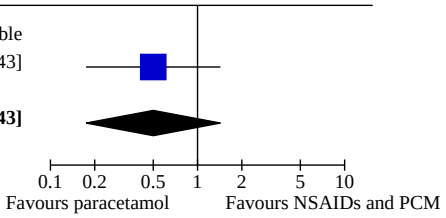
Heterogeneity: Not applicable
Test for overall effect: Z = 0.96 (P = 0.33)
Test for subgroup differences: Not applicable




### Analysis 4.7. Comparison 4: NSAIDs + paracetamol versus paracetamol, Outcome 7: Mild pain at 4 to 7 days

| Study or Subgroup | NSAIDs and PCM Events | Total | Paracetamol Events | Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Hay 2009 | 0 | 8 | 0 | 7 | | Not estimable |
| Little 2013 | 4 | 16 | 5 | 10 | 100.0% | 0.50 [0.17 , 1.43] |
| **Total (95% CI)** | | **24** | | **17** | **100.0%** | **0.50 [0.17 , 1.43]** |
| Total events: | 4 | | 5 | | | |

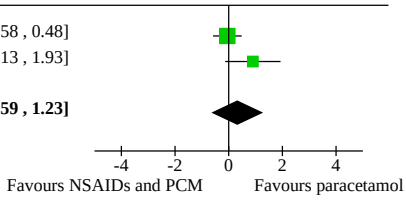
Heterogeneity: Not applicable
Test for overall effect: Z = 1.29 (P = 0.20)
Test for subgroup differences: Not applicable




### Analysis 4.8. Comparison 4: NSAIDs + paracetamol versus paracetamol, Outcome 8: Mean pain at 24 hours

| Study or Subgroup | NSAIDs and PCM Mean | SD | Total | Paracetamol Mean | SD | Total | Weight | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Hay 2009 | 2.38 | 0.52 | 8 | 2.43 | 0.53 | 7 | 61.2% | -0.05 [-0.58 , 0.48] |
| Little 2013 | 4.5 | 1.1 | 15 | 3.6 | 1.4 | 10 | 38.8% | 0.90 [-0.13 , 1.93] |
| **Total (95% CI)** | | | **23** | | | **17** | **100.0%** | **0.32 [-0.59 , 1.23]** |

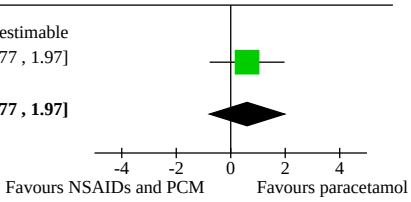
Heterogeneity: Tau² = 0.28; Chi² = 2.57, df = 1 (P = 0.11); I² = 61%
Test for overall effect: Z = 0.69 (P = 0.49)
Test for subgroup differences: Not applicable




### Analysis 4.9. Comparison 4: NSAIDs + paracetamol versus paracetamol, Outcome 9: Mean pain at 48 to 72 hours

| Study or Subgroup | NSAIDs and PCM Mean | SD | Total | Paracetamol Mean | SD | Total | Weight | Mean Difference IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Hay 2009 | 2 | 0 | 8 | 2.14 | 0.38 | 7 | | Not estimable |
| Little 2013 | 2.3 | 2 | 15 | 1.7 | 1.5 | 10 | 100.0% | 0.60 [-0.77 , 1.97] |
| **Total (95% CI)** | | | **23** | | | **17** | **100.0%** | **0.60 [-0.77 , 1.97]** |

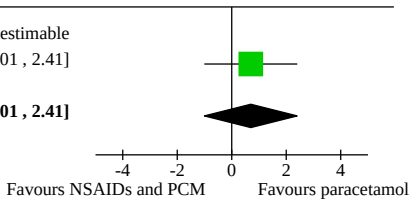
Heterogeneity: Not applicable
Test for overall effect: Z = 0.86 (P = 0.39)
Test for subgroup differences: Not applicable



### Analysis 4.10. Comparison 4: NSAIDs + paracetamol versus paracetamol, Outcome 10: Mean pain at 4 to 7 days

| Study or Subgroup | NSAIDs and PCM Mean | SD | Total | Paracetamol Mean | SD | Total | Weight | Mean Difference IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Hay 2009 | 2.25 | 0.46 | 8 | 2 | 0 | 7 | | Not estimable |
| Little 2013 | 2 | 1.8 | 11 | 1.3 | 1.8 | 7 | 100.0% | 0.70 [-1.01 , 2.41] |
| **Total (95% CI)** | | | **19** | | | **14** | **100.0%** | **0.70 [-1.01 , 2.41]** |

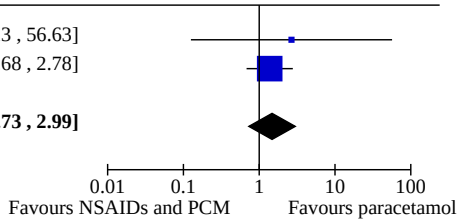
Heterogeneity: Not applicable
Test for overall effect: Z = 0.80 (P = 0.42)
Test for subgroup differences: Not applicable




### Analysis 4.11. Comparison 4: NSAIDs + paracetamol versus paracetamol, Outcome 11: Fever at 24 hours

| Study or Subgroup | NSAIDs and PCM Events | Total | Paracetamol Events | Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Hay 2009 | 1 | 8 | 0 | 7 | 7.9% | 2.67 [0.13 , 56.63] |
| Little 2013 | 11 | 16 | 5 | 10 | 92.1% | 1.38 [0.68 , 2.78] |
| **Total (95% CI)** | | **24** | | **17** | **100.0%** | **1.48 [0.73 , 2.99]** |
| Total events: | 12 | | 5 | | | |

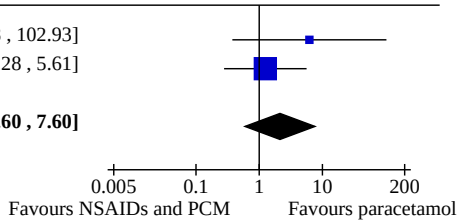
Heterogeneity: Chi² = 0.18, df = 1 (P = 0.67); I² = 0%
Test for overall effect: Z = 1.09 (P = 0.28)
Test for subgroup differences: Not applicable




### Analysis 4.12. Comparison 4: NSAIDs + paracetamol versus paracetamol, Outcome 12: Fever at 48 to 72 hours

| Study or Subgroup | NSAIDs and PCM Events | Total | Paracetamol Events | Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Hay 2009 | 3 | 8 | 0 | 7 | 17.7% | 6.22 [0.38 , 102.93] |
| Little 2013 | 4 | 16 | 2 | 10 | 82.3% | 1.25 [0.28 , 5.61] |
| **Total (95% CI)** | | **24** | | **17** | **100.0%** | **2.13 [0.60 , 7.60]** |
| Total events: | 7 | | 2 | | | |

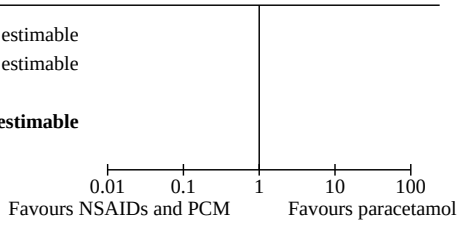
Heterogeneity: Chi² = 1.04, df = 1 (P = 0.31); I² = 4%
Test for overall effect: Z = 1.17 (P = 0.24)
Test for subgroup differences: Not applicable




### Analysis 4.13. Comparison 4: NSAIDs + paracetamol versus paracetamol, Outcome 13: Fever at 4 to 7 days

| Study or Subgroup | NSAIDs and PCM Events | Total | Paracetamol Events | Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Hay 2009 | 0 | 8 | 0 | 7 | | Not estimable |
| Little 2013 | 0 | 16 | 0 | 10 | | Not estimable |
| **Total (95% CI)** | | **0** | | **0** | | **Not estimable** |
| Total events: | 0 | | 0 | | | |

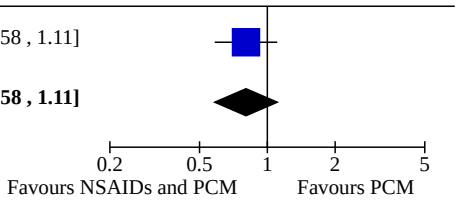
Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable



### Analysis 4.14. Comparison 4: NSAIDs + paracetamol versus paracetamol, Outcome 14: Reconsultations

| Study or Subgroup | NSAIDs and PCM Events | Total | Paracetamol Events | Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Little 2013 | 19 | 29 | 22 | 27 | 100.0% | 0.80 [0.58 , 1.11] |
| **Total (95% CI)** | | **29** | | **27** | **100.0%** | **0.80 [0.58 , 1.11]** |
| Total events: | 19 | | 22 | | | |

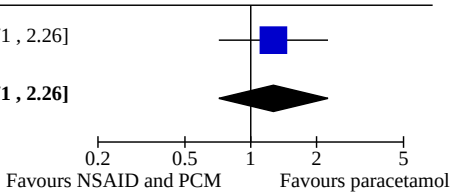
Heterogeneity: Not applicable
Test for overall effect: Z = 1.34 (P = 0.18)
Test for subgroup differences: Not applicable




### Analysis 4.15. Comparison 4: NSAIDs + paracetamol versus paracetamol, Outcome 15: Delayed antibiotic prescriptions

| Study or Subgroup | NSAID and PCM Events | Total | Paracetamol Events | Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Little 2013 | 15 | 29 | 11 | 27 | 100.0% | 1.27 [0.71 , 2.26] |
| **Total (95% CI)** | | **29** | | **27** | **100.0%** | **1.27 [0.71 , 2.26]** |
| Total events: | 15 | | 11 | | | |

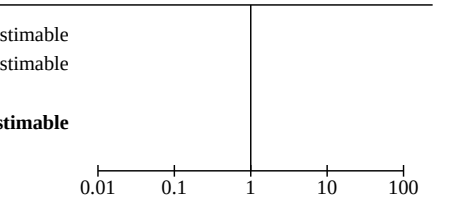
Heterogeneity: Not applicable
Test for overall effect: Z = 0.81 (P = 0.42)
Test for subgroup differences: Not applicable




### Analysis 4.16. Comparison 4: NSAIDs + paracetamol versus paracetamol, Outcome 16: Serious complications

| Study or Subgroup | NSAID and PCM Events | Total | Paracetamol Events | Total | Weight | Risk Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Hay 2009 | 0 | 8 | 0 | 7 | | Not estimable |
| Little 2013 | 0 | 29 | 0 | 27 | | Not estimable |
| **Total (95% CI)** | | **0** | | **0** | | **Not estimable** |
| Total events: | 0 | | 0 | | | |

Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable




## APPENDICES

### Appendix 1. CENTRAL search strategy

#1 [mh “otitis media”] OR otitis media OR aom OR ome OR (middle AND ear AND (effusion OR inflammation* OR infection*)) OR glue ear

#2 [mh “respiratory tract infection”] OR respiratory infection* OR (acute OR upper) respiratory AND (symptom* OR illness* OR infection* OR inflammation*)

#3 #1 OR #2

#4 [mh acetaminophen] OR paracetamol OR acetaminophen OR acetaminophen OR tylenol OR [mh “Anti-Inflammatory Agents, Non-Steroidal”] OR (nonsteroidal OR 'non steroidal' AND (antiinflammatory OR 'anti inflammatory')) OR nsaid OR nsaids

#5 [mh pain] OR [mh “Pain Management”] OR Pain OR Pains OR Ache OR Aches OR analgesia

#6 #3 AND #4 AND #5

## Appendix 2. MEDLINE (Ovid) search strategy

1 exp Otitis Media/ OR otitis media OR aom OR ome OR (middle ear adj2 (effusion OR inflam* OR infection OR infections)) OR glue ear

2 exp Respiratory Tract Infections/ OR (respiratory adj2 infection*) OR ((acute or upper) adj2 respiratory adj2 (symptom* or illness* or infect* or inflam*))

3 1 OR 2

4 exp Acetaminophen/ OR paracetamol OR acetaminophen OR acetaminophen OR tylenol OR exp Anti-Inflammatory Agents, Non-Steroidal/ OR ((nonsteroid* or non-steroid*) adj1 (antiinflam* or anti-inflam*)) OR nsaid or nsaids

5 exp Pain/ OR exp Pain Management/ OR Pain OR Pains OR Ache OR Aches OR Analgesia

6 ((randomized controlled trial or controlled clinical trial).pt. or randomized.ab. or randomised.ab. or placebo.ab. or drug therapy.fs. or randomly.ab. or trial.ab. or groups.ab.) not (exp animals/ not humans.sh.)

7 3 AND 4 AND 5 AND 6

## Appendix 3. Embase search strategy

#1 'otitis media'/exp OR otitis media OR aom OR ome OR (middle AND ear AND (effusion OR inflammation* OR infection*)) OR glue ear

#2 'respiratory tract infection'/exp OR respiratory infection* OR (acute OR upper) respiratory AND (symptom* OR illness* OR infection* OR inflammation*)

#3 #1 OR #2

#4 'paracetamol'/exp OR paracetamol OR acetaminophen OR acetaminophen OR tylenol OR 'nonsteroid antiinflammatory agent'/exp OR (nonsteroidal OR 'non steroidal' AND (antiinflammatory OR 'anti inflammatory')) OR nsaid OR nsaids

#5 'pain'/exp OR 'analgesia'/exp OR Pain OR Pains OR Ache OR Aches OR analgesia

#6 random* OR factorial OR crossover OR placebo OR blind OR blinded OR assign OR assigned OR allocate OR allocated OR 'crossover procedure'/exp OR 'double-blind procedure'/exp OR 'randomized controlled trial'/exp OR 'single-blind procedure'/exp

#7 #3 AND #4 AND #5 AND #6

## Appendix 4. CINAHL search strategy

S1 (MH "Otitis Media+") OR otitis media OR aom OR ome OR (middle ear (effusion OR inflammation* OR infection*)) OR glue ear

S2 (MH "Respiratory Tract Infections+") OR respiratory infection* OR (acute OR upper) respiratory (symptom* OR illness* OR infection* OR inflammation*)

S3 S1 OR S2

S4 (MH "Acetaminophen") OR paracetamol OR acetaminophen OR acetaminophen OR tylenol OR (MH "Antiinflammatory Agents, Non-Steroidal+") OR (nonsteroid* OR non-steroid*) (antiinflam* or anti-inflam*) OR nsaid OR nsaids

S5 (MH "Pain+") OR (MH "Analgesia+") OR Pain OR Pains OR Ache OR Aches OR Analgesia

S6 (MH "Clinical Trials+") OR random* OR factorial OR crossover OR placebo OR blind OR blinded OR assign OR assigned OR allocate OR allocated OR trial OR trials OR groups

S7 S3 AND S4 AND S5 AND S6

## Appendix 5. LILACS search strategy

(tw:(Otitis media OR aom OR ome OR (middle ear (effusion OR inflammation* OR infection*)) OR glue ear OR Respiratory infection* OR (acute OR upper) respiratory (symptom* OR illness* OR infection* OR inflammation*)))

AND

(tw:(Paracetamol OR acetaminophen OR acetaminophen OR tylenol OR (nonsteroid* OR non-steroid*) (antiinflam* or anti-inflam*) OR nsaid OR nsaids))

AND

(tw:(Pain OR Pains OR Ache OR Aches OR Analgesia))

AND

(tw:(random* OR factorial OR crossover OR placebo OR blind OR blinded OR assign OR assigned OR allocate OR allocated OR trial OR trials OR groups))

### Appendix 6. Web of Science search strategy

#1 **TOPIC:** (Otitis media OR aom OR ome OR (middle ear (effusion OR inflammation* OR infection*)) OR glue ear) *OR***TOPIC:** (Respiratory infection* OR (acute OR upper) respiratory (symptom* OR illness* OR infection* OR inflammation*))

#2 **TOPIC:** (Paracetamol OR acetaminophen OR acetaminophen OR tylenol OR (nonsteroid* OR non-steroid*) (antiinflam* or anti-inflam*) OR nsaid OR nsaids) *AND***TOPIC:** (Pain OR Pains OR Ache OR Aches OR Analgesia) *AND***TOPIC:** (random* OR factorial OR crossover OR placebo OR blind OR blinded OR assign OR assigned OR allocate OR allocated OR trial OR trials OR groups)

#3 #2 AND #1

## WHAT'S NEW

| Date | Event | Description |
|---|---|---|
| 18 August 2023 | New citation required but conclusions have not changed | Our conclusions remain unchanged. |
| 18 August 2023 | New search has been performed | Two new review authors joined the team. We updated the searches 23 May 2023 and included one new trial (Kara 2022; 84 participants) in this update. We excluded one new trial (van Uum 2020) as it did not include interventions and comparators relevant for this review. We did not identify any relevant ongoing studies. |

## HISTORY

Protocol first published: Issue 2, 2015
Review first published: Issue 12, 2016

## CONTRIBUTIONS OF AUTHORS

Drafting of protocol: AS, RPV, ACvdP, AGMS, RAMJD
Screening search results: JLHdS, RPV
Extracting data: JLHdS, RPV
Assessing risk of bias: JLHdS, RPV
Entering data into Review Manager Web: JLHdS, RPV
Carrying out analysis: JLHdS, RPV
Interpreting the analysis: all authors
Writing the review: all authors
General advice on the review: all authors

## DECLARATIONS OF INTEREST

Joline LH de Sévaux (JLHdS) is an investigator of the OPTIMA study, a pragmatic trial on the effectiveness of analgesic ear drops for children with acute otitis media in primary care, which is funded by a research grant from The Netherlands Organisation for Health Research and Development (grant no. 10060011910003).

Roger AMJ Damoiseaux (RAMJ) is an Editor of the Cochrane Acute Respiratory Infections Group. Roger is an investigator of the OPTIMA study, a pragmatic trial on the effectiveness of analgesic ear drops for children with acute otitis media in primary care, which is funded by a research grant from The Netherlands Organisation for Health Research and Development (grant no. 10060011910003), and was an investigator of the PIM-POM study, a cluster-randomised clinical trial to optimise pain management in children with acute otitis media, which is funded by a research grant from The Netherlands Organisation for Health Research and Development/SBOH no. 80-83910-98-13006 (van Uum 2020).

Alma C van de Pol (ACvdP) was an investigator of the PIM-POM study, a cluster-randomised clinical trial to optimise pain management in children with acute otitis media, which is funded by a research grant from The Netherlands Organisation for Health Research and Development/SBOH no. 80-83910-98-13006 (van Uum 2020).

Vittoria Lutje (VL): has declared that they have no conflict of interest.

Alastair D Hay (ADH) is funded by National Institute for Health and Care Research (NIHR) Research Professorship (NIHR-RP-02-12-012); is an investigator of the OPTIMA study, a pragmatic trial on the effectiveness of analgesic ear drops for children with acute otitis media in primary care, which is funded by a research grant from The Netherlands Organisation for Health Research and Development (grant no. 10060011910003); and was principal investigator of the UK primary care-based randomised controlled trial comparing the clinical- and cost-effectiveness of anaesthetic (benzocaine-phenazone) eardrops versus placebo drops and no drops in children aged 12 months to 10 years with acute otitis media (Hay 2019).

Paul Little (PL) is an Editor of the Cochrane Acute Respiratory Infections Group and an investigator of the OPTIMA study, a pragmatic trial on the effectiveness of analgesic ear drops for children with acute otitis media in primary care, which is funded by a research grant from The Netherlands Organisation for Health Research and Development (grant no. 10060011910003). He was an investigator of the UK primary care-based randomised controlled trial comparing the clinical- and cost-effectiveness of anaesthetic (benzocaine-phenazone) eardrops versus placebo drops and no drops in children aged 12 months to 10 years with acute otitis media (Hay 2019).

Anne GM Schilder (AGMS) is Joint Co-ordinating Editor of Cochrane ENT. Her team, evidENT, at the Ear Institute, University College London, is supported by a National Institute for Health and Care Research (NIHR) Research Professorship award. Anne is an investigator of the OPTIMA study, a pragmatic trial on the effectiveness of analgesic ear drops for children with acute otitis media in primary care, which is funded by a research grant from The Netherlands Organisation for Health Research and Development (grant no. 10060011910003), and was an investigator of the PIM-POM study, a cluster-randomised clinical trial to optimise pain management in children with acute otitis media, which is funded by a research grant from The Netherlands Organisation for Health Research and Development/SBOH no. 80-83910-98-13006 (van Uum 2020).

Roderick P Venekamp (RPV) is an Editor of the Cochrane Acute Respiratory Infections and ENT Groups. Roderick is an investigator of the OPTIMA study, a pragmatic trial on the effectiveness of analgesic ear drops for children with acute otitis media in primary care, which is funded by a research grant from The Netherlands Organisation for Health Research and Development (grant no. 10060011910003), and was an investigator of the PIM-POM study, a cluster-randomised clinical trial to optimise pain management in children with acute otitis media, which is funded by a research grant from The Netherlands Organisation for Health Research and Development/SBOH no. 80-83910-98-13006 (van Uum 2020).

## SOURCES OF SUPPORT

### Internal sources

- No sources of support provided

### External sources

- The Netherlands Organisation for Health Research and Development (ZonMw), Netherlands

  At the time of publication of the previous version of this review (Sjoukes 2016), the authors received a grant from The Netherlands Organisation for Health Research and Development (ZonMw) to conduct a pragmatic, cluster-randomised clinical trial on pain management for children with acute otitis media in primary care. Whilst conducting the review update, the authors received a grant from ZonMw to conduct a pragmatic trial on the effectiveness of analgesic ear drops for children with acute otitis media in primary care (grant no. 10060011910003).
- NIHR Research Professorship Award, UK

  Professor Anne Schilder received an NIHR Research Professorship Award in 2012.

## DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We excluded studies that focused on hospitalised children because we aimed to summarise evidence on analgesics for children with acute otitis media applicable to everyday clinical practice. Hospitalisation secondary to acute otitis media is now rare in high-income countries,

and any evidence on this study population is not easily transferable to everyday clinical practice. This was not specifically mentioned in our published protocol (Sjoukes 2015).

## INDEX TERMS

### Medical Subject Headings (MeSH)

Acetaminophen [*therapeutic use]; Acute Disease; Analgesics, Non-Narcotic [*therapeutic use]; Anti-Bacterial Agents [therapeutic use]; Anti-Inflammatory Agents, Non-Steroidal [therapeutic use]; Drug Therapy, Combination; Fever [drug therapy]; Ibuprofen [therapeutic use]; Otitis Media [*complications]; Pain [*drug therapy] [etiology]; Randomized Controlled Trials as Topic

### MeSH check words

Child; Child, Preschool; Humans