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Review article

The effectiveness of homeopathy in relieving symptoms and reducing antibiotic use in patients with otitis media: A systematic review and meta-analysis

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ABSTRACT

Aim: This systematic review of clinical trial evidence aims to determine whether homeopathy can effectively relieve symptoms and reduce antibiotic use in patients diagnosed with otitis media (OM).

Methods: Seven databases and four trial registries were searched. Eligible studies included randomised- and non-randomised-controlled-trials in patients diagnosed with OM. Studies on Individualised- and non-Individualised-Homeopathy (IH, non-IH) were included, and controls were inactive and/or active treatment. Primary outcomes were clinical-improvement and antibiotic-use. Data extraction, Risk of Bias and certainty of evidence (GRADE) were performed using established methodology.

Results: Nine studies (IH = 4, non-IH = 5) comprising seven Randomised Clinical Trials (RCTs) and two non-RCTs (nRCTS) compared homeopathy with placebo (n = 2) or standard care (n = 7). 4/7 included RCTs reported statistically significant individual outcomes at relevant time points (symptom score, MEE, and antibiotic use) favouring homeopathy. However, heterogeneity of study designs, homeopathic interventions and outcome measures hindered the pooling of data for most outcomes, except for antibiotic use (non-IH). Add-on non-IH reduced filled antibiotic prescriptions by 46 % (RR = 0.54 [95%CI: 0.28, 1.06], P = 0.07, I^2 = 12 %), but this did not reach statistical significance. Most studies demonstrated that the homeopathy group had less adverse events than the control group.

Conclusions: The evidence base for the effectiveness of homeopathy and OM treatment is modest in study number, size, and risk of bias assessment. Individual RCTs report positive effects on clinical improvement and/or antibiotic use at relevant time points with homeopathy with no safety issues. Due to heterogeneity, the current evidence is insufficient to satisfactorily answer whether homeopathy is effective for clinical improvement and reducing antibiotic use in patients

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with OM. A Core Outcome Set for OM for future research is warranted to improve the potential for meta-analyses and strengthen the evidence base.

1. Introduction

Eighty percent of health service antibiotics are prescribed for common primary care infections [1], making it one of the most important contributors to the development of Antimicrobial Resistance (AMR) [2]. Reducing the use of antibiotics in primary care and controlling the development of AMR are global priorities.

Otitis media (OM) represents a broad spectrum of diseases, including acute otitis media (AOM) and otitis media with effusion (OME; 'glue ear'). Approximately 80 % of children will have at least one episode of AOM, and between 80 % and 90 % will have at least one episode of OME before school age [1,3].

AOM causes pain and distress to the child and parents; it frequently results in health service consultations and is the most common infection for which a child is Fig 3 and 4 given antibiotics in the UK [4]. The level of antibiotic prescribing is not surprising given the distress and associated parental concern, but it is unnecessary and contrary to clinical guidelines. Most children and young people get better within three days without antibiotics [5]. General practitioner's (GP) perception of a patient's Fig 5 and 6 wish for antibiotics and an inability to effectively negotiate or explain appropriate use of antibiotics is still one of the most important determinants of inappropriate antibiotic prescribing, besides a direct request for an antibiotic by a patient [6].

Effective and safe non-antibiotic treatment as a substitute treatment or as part of a delayed prescription strategy may reduce antibiotic prescription and use. This could meet doctors' and patients' desire for treatment and symptom relief and lead to reducing AMR.Fig 7

Previous studies have demonstrated the benefits of Traditional, Complementary and Integrative Health (TCIH) strategies in reducing overall healthcare costs [7,8], antibiotic prescription rates [9] and antibiotic use [10–12]. Homeopathy, a TCIH approach, is a system of medicine based on the principle that "like cures like" whereby a substance which can cause Fig 8 and 9 symptoms when given in large doses to healthy individuals can be used in small doses to treat patients with similar symptoms [13]. Homeopathy can be categorised into two main treatment approaches: individualised (IH) and non-individualised (non-IH). IH involves a personalised prescription, selected according to the patient's specific presenting symptoms, usually following a consultation with a qualified practitioner. In non-individualised homeopathy the choice of homeopathic medicine is determined by the clinical diagnosis, based on the causative agent or common symptoms of the condition being treated, rather than a patient's specific presenting symptoms. Reasons for using homeopathy include the perception that it is, safer, natural, and more affordable than conventional drugs [14].

Whilst homeopathic treatment is widely used for respiratory tract infections and OM [11,15], the effectiveness of homeopathy in OM remains unclear. This systematic review of clinical trial evidence aims to determine whether homeopathy can effectively relieve symptoms and reduce antibiotic use in patients clinically diagnosed with OM.

2. Methods

2.1. Research objectives

The main research objectives of the systematic review are.

1. To assess the effect of homeopathy on clinical improvement (symptoms and signs).
2. To assess the effect of homeopathy on antibiotic use.

This systematic review followed the Cochrane Handbook for Systematic Reviews of Interventions [16], and additional expert advice was sought to further guide methodological decisions (see acknowledgements). It is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) [17]. The study protocol was prospectively registered in the PROSPERO database (CRD42022367188).

2.2. Search

A search strategy was developed using keywords for the electronic databases according to their specific subject headings or structure (see Appendix 1).

The following databases and trial registers were searched for relevant trials and reviews (to check on primary studies) from their inception to 27.11.23.

Databases: The-Cochrane-Database, The-Cochrane-Central-Register-of-Controlled-Trials (CENTRAL) in The Cochrane Library, MEDLINE-(from-1946), EMBASE-(from-1974), AMED (Allied-and-Complementary-Medicine-Database) (from 1985) via OVID, CINAHL via EBSCO (Cumulative-Index-to-Nursing-and-Allied-Health-Literature, from 1981), CORE-Hom, CAM-QUEST.

Trials registers: The-US-National-Institutes-of Health Ongoing Trials Register (www.clinicaltrials.gov); World Health Organization International Clinical Trials Registry platform (https://www.isrctn.com/); The-EU-Clinical-Trials-Registry (www.clinicaltrialsregister.eu); International-Traditional-Medicine Clinical-Trial-Registry www.ccebtcm.org.cn).

We applied no restrictions on language or publication date.

2.3. Searching other resources

Reference lists of all identified Randomised Clinical Trials (RCTs) and relevant reviews were checked for further relevant trials, and we performed forward reference searching using Google Scholar and Scopus. We contacted investigators who have previously conducted RCTs and/or nRCTs on homeopathic interventions to obtain information about ongoing studies pertinent to the review.

2.4. Eligibility criteria

The inclusion criteria followed the PICO framework.

2.5. Reference management and study selection

An endnote file (EndNote X9.3.3) of all references was produced, and duplicates were removed. These references underwent a two-stage process of screening using the above eligibility criteria. Two reviewers (RP, EvdW) independently screened the titles and abstracts of the searched studies and performed study selection. At both stages of screening, disagreement resolved via discussion or by consulting a third reviewer (AH). The article selection process is presented in a PRISMA flow diagram [21]. When the reported data were insufficient or unambiguous, the authors contacted the corresponding author to request additional information or clarification (see Appendix 6).

2.6. Data extraction

Two researchers independently extracted the data using a custom-designed extraction form. An external reviewer (PH) checked the data extraction accuracy. Any disagreement between the authors was resolved by a discussion with a third reviewer. Data on study design, participant, intervention and methodological characteristics and outcomes were extracted (if available/reported) (Appendix 7).

2.7. Data synthesis

Both RCTs and nRCTs are presented narratively, guided by the Synthesis Without Meta-analysis (SWiM) protocol [19], which complements PRISMA. Meta-analyses were performed on the highest level of available evidence available only (RCTs), using Review Manager Version 5.4.

2.8. Measurement of the treatment effect and assessment of statistical heterogeneity

Dichotomous outcomes were expressed as risk ratios (RR), continuous outcomes were expressed as mean differences (MD). Pooled risk ratios (RRs) and 95 % CIs were calculated for dichotomous outcomes using the Mantel-Haenszel method for random-effects meta-analysis. The I^2 statistic was calculated to quantify and interpret statistical heterogeneity [20,21].

2.9. Dealing with missing data

Where reporting of data was incomplete or missing, investigators were contacted to verify key study characteristics and obtain missing numerical outcome data where possible (see Appendix 6). We used intention-to-treat (ITT) data where possible.

2.10. Subgroup analysis, sensitivity analyse and publication bias

Due to an insufficient number of studies and variety in study comparators and outcomes, we were unable to perform our pre-specified subgroup or sensitivity analyses to investigate the presence of clinical heterogeneity.

2.11. Risk of bias assessment

The Cochrane ROB 2.0 tool [22] was used to assess the risk of bias (RoB) of RCTs, and the ROBINS-I tool [23] was used for nRCTs by 1 reviewer (RP) and independently checked by 2 other reviewers (AH, EVDW). Additional checks were performed by an additional researcher (NML). All domains of the two RoB assessment tools, as prescribed by the Cochrane Handbook for Systematic Reviews of Interventions, have been included in our analysis [16]. ROB assessment was completed on our primary outcomes only.

2.12. Summary of findings and assessment of certainty of evidence

The strength of the overall body of evidence for our primary outcomes was assessed using the GRADE (Grading of Recommendations, Assessment, Development, and Evaluations) software system [24]. The summary of findings table presents both the

comparison of homeopathy versus placebo, and homeopathy versus standard care. GRADE was only completed on RCT data, and following the GRADE handbook recommendations [25], even when there was only one study available for a particular outcome.

3. Results

3.1. Search results

The initial search yielded 527 potentially relevant papers (PRISMA diagram-Appendix 2). Handsearching retrieved an additional seven papers. Once screened, 83 papers were shortlisted, and full-text copies were retrieved. From these papers, nine studies were eligible for inclusion [26–34]. For five studies reported in multiple publications, we used the main publication and used information from linked publications when needed (see Appendix 3 for excluded studies and Appendix 4 for linked studies) (see Table 1).

All studies were published between 1997 and 2016 in peer-reviewed journals except one [30]. They were conducted in the USA (n = 3), the UK, Germany, India, Spain and Italy (n = 1 each). Sample sizes ranged from 33 to 390. One study was translated from Italian to English [30] using Deepl translate [35] and was checked by an Italian native speaker. A summary of the interventions and main results are shown in Table 1 and 2. The full characteristics of included studies and further details of the results can be found in the Appendix (Appendix 11 and 12).

We identified four studies that used IH and five that used non-IH. Seven studies were RCTs, and 2 studies were n-RCTs. Six studies [26,28,29,32–34] presented with AOM and the remaining three presented with OME [27,30,31]. Two were placebo-controlled [28,31] and seven were compared to standard care. We also identified two other studies close to being published. One RCT from India (Varanasi et al., 2023 [unpublished]) and one nRCT from Germany (Hukle et al., [unpublished]) (see Appendix 8 for further information).

The presented data below is grouped by type of homeopathy (IH/non-IH), outcome (clinical improvement/antibiotic use), and whether the condition was AOM or OME. The wide range of terms used to express the outcomes within the individual-included studies belonging to our primary outcomes have been listed below.

3.1.1. Clinical improvement outcomes

3.1.1.1. Symptoms & signs.

- Parental diary symptom scores
- Improvement in AOM symptoms
- Pain rating scale for pain intensity to assess presence/absence of typical clinical symptoms
- Ear-Treatment-Group-5-Scale (ETG-5) scores
- “Cured” score (Acute-Otitis-Media-Severity-of-Symptoms (AOM-SOS) combined with tympanogram data)

Table 1
Inclusion criteria.

Participants	Participants with clinically diagnosed and symptomatic OM (AOM/OME), being of any age, ethnicity, and gender.
Intervention	Studies comparing Individualised Homeopathy (IH) or Non-Individualised Homeopathy (non-IH), with no limitation on potency, dosage, or duration of treatment. We defined ‘Homeopathic products’ as those administered orally as pills, tablets or liquids and are available ‘over the counter’ or as individualised prescriptions after consultation with a practitioner.
Comparator	Controls could be either inactive treatment (placebo, no treatment) and/or active treatment (e.g., standard care, antibiotics, analgesics).
Outcomes	Self-reported measures and objectively measured outcomes.
	Primary outcomes
	Clinical improvement (symptoms and signs)*
	Antibiotic use*
	Secondary outcomes
	Antibiotic prescribing
	Hearing loss
	Recurrence
	Health service and medication use
	Quality of life
	Re-consultation
	Adverse events (Type, frequency, and severity of adverse events and complications)
Study type	Randomised controlled trials (RCTs), controlled trials and non-randomised controlled trials (nRCTs), including individual or cluster level allocation.
	As only a small number of randomised trials are likely to be available, nRCTs will be included to provide complementary information. nRCT results will be discussed in the context of their limitations but will not be included in meta- analyses [18].

* As defined by individual studies.

Table 2
Summary of main results for primary outcomes.

First author, Date, Country, Setting	Study design	Type of OM	No of participants randomised (analysed)	Intervention, Comparator	Primary outcome (P-value)* Green: favours intervention (P<0.05) Red: favours comparator (P>0.05) *Original P-values extracted from studies
INDIVIDUALISED HOMEOPATHY					
Friese et al., 1997[26] Germany 1 homeopathic practice 5 conventional ENT practices	Non-randomised controlled study	AOM	131 children I=103 (99, 98): C=28 (28, 27)	I: Individualised homeopathic single remedy C: Nasal drops, antibiotics, secretolytics or antipyrectics or combination (SC)	**1) Clinical improvement** duration of pain (P=0.12) duration of therapy (P=0.0001) disease progression - % noticeable improvement (P value NR) tympanogram after 2 weeks *normal* (P value NR) *restricted* (P value NR) *flat* (P value NR) **2) Antibiotic use** Participants switched groups to either receive or not receive antibiotics (P value NR)
Harrison et al., 1999[27] UK Isle of Wight- Department of Community Paediatrics (St. Mary's NHS Trust). Swindon – St. Margaret's Hospital.	RCT Non-blind, pilot	OME	33 children I=17 (17) C=16 (16)	I: individualised homeopathy C: "watch and wait" with auto inflation of ears and some antibiotic prescribing (SC)	**1) Clinical symptoms** **Tympanogram after 12 months:** Normal/fluid/flat combined (P=0.015) More participants in H group had normal tympanogram. **2) Course of antibiotics** "1 or more" or "none received" difference between proportions (P=0.16)
Jacobs et al., 2001[28] USA Private paediatric practice in Seattle	RCT placebo-controlled, pilot	AOM	75 children I=36 (36) C=39 (39)	I:Individualised homeopathy C:placebo	**1) Clinical Improvement** **Symptom scores (diaries)** symptom scores at 24 and 64 hrs (I=P <0.05, C=NR) **Treatment failure** day 5 (P=0.39) 2 weeks (P=0.17) 6 weeks (P=0.13) **Presence of middle ear effusion (MEE)** 2 weeks (P=0.83) 6 weeks (P=0.30)
Sinha et al., 2012[29] India General Paediatric clinic at the Regional Research Institute of Homeopathy, Jaipur,	RCT ,parallel group Pilot study (incorrectly stated as placebo - controlled in the abstract)	AOM	80 children I=40 (40) C=41 (40)	I: individualised homeopathy C: conventional treatment (analgesics, antipyretics and anti-inflammatory drugs) with observation option	**1) Clinical Improvement** **-Improvement status** day 3 (P=0.000) (we could not replicate this result in our plot (p=0.17)) day 7 (P=0.36) day 10 (P=0.14) day 21 (P=0.20) **-Symptom change** within group results (Control: no patients with symptoms 'At end)'. Reported P values unclear and same as Tympanic membrane examination **-Tympanic membrane examination** Reported P values unclear and same as Symptom change **2) Antibiotic use** Lack of clarity on AB data
NON-INDIVIDUALISED HOMEOPATHY					
Arrighi, 2003 Italy[30] Free Choice Pediatrics	RCT (author correspondence)	OME	157 children I=81 C=76	I: homotoxicology protocol C: standard allopathic protocol (SC)	**1)Clinical Improvement** **-No of episodes of OME after 180 days** 0 episodes (P value NR but reached significance) 1-5 episodes (P value NR but NS) >5 episodes (P value NR but reached significance) **MEE (otoscopy) after 90 days** No improvement (P value NR but NS) >30% improvement (P value NR but NS) With normalised findings (P value NR but NS) **- MEE (otoscopy) after 180 days** No reduction (P value NR but reached significance) >30% effusion (P value NR, significance influenced by other 2 groups) No effusion (P value NR) but reached significance) **-Tympanometry after 90 days** No improvement (P value NR) >30% improvement (P value NR) With normalised findings (P value NR) **Tympanometry after 180 days** No improvement (P value NR) ->30% improvement (P value NR) With normalised findings (P value NR) **Audiometry after 90 days** -No improvement (P value NR) ->30% hearing function (P value NR) -with normalized findings (P value NR) **Audiometry after 180 days** -No improvement (P value NR but reached significance) ->30% hearing function (P value NR, significance influenced by other 2 groups) -with normalized findings (P value NR but reached significance)
Pedrero-Escalas et al., 2016[31] Spain Department of Otorhinolaryngology and	RCT double blind, placebo-control	OME	96 children I=46(42) C=50 (44)	I= Aerosol therapy + Homeopathic treatment A or B C= aerosol therapy +placebo treatment	**1) Clinical Improvement** Recovery (P=0.631)

Head-Neck Surgery at Toledo Hospital Complex					
Taylor & Jacobs 2011[32] USA University of Washington Medical Center Pediatric Care Centre	RCT	AOM	120 children I=59 (56) C=60 (57)	I=Hyland ear drops + standard therapy C=standard therapy (SC)	**1)Clinical Improvement** **-Ear treatment Group-5 scores**, *All assessments were lower in H group (1 to 10) but just 2 were significant* *Assessment 2* (P=0.04) *Assessment 3* (P=0.003) Improvement in AOM symptoms after 70-82% of doses of ear drops, but only 48-55% of the time when the drops were given for non-AOM symptoms. **-Functional status (FSIIR scores)** Similar between groups (P=0.97) **2) Antibiotic Use** prescriptions filled (P=0.17)
Taylor & Jacobs 2014[33] USA University of Washington Medical Center Roosevelt Pediatric Care Center or practices that are members of the Puget Sound Pediatric Research Network	RCT	AOM	210 children I=105(104) C=105(102)	I=Hyland ear drops + standard therapy C=standard therapy	**1)Clinical Improvement** **-Ear treatment Group-5 scores** *Day 5 to 7* (P=0.14) Lower scores in Control group *Day 12 to 15* (P=0.87) No difference after adjusting for BL values **-Other symptoms (parent reports)** Vomit (P=0.83) Rash (P=0.03) Diarrhoea (P=0.86) "Hyper" behaviour (P=0.37) Headache (P=0.95) Lethargy (P=0.22) Any additional symptom – lower in H group (P=0.31) **2)Use of antibiotics (within 15 days of diagnosis)** Filled original antibiotic prescription (P=0.032) Filled original prescription or additional prescription (P=0.034) Filled prescription 7 days after diagnosis (P=0.062)
Wustrow et al., 2004[34] Germany 16 alternative centres and 13 conventional centres.	Non-randomised parallel group study	AOM	390 children I=194(192) C=196 (193)	*Otowen* (mother tinctures + homeopathy) + SC if needed C=SC	**1)Clinical Improvement** Clinical symptom score- baseline only Time to recovery within 14 days (P=0.34) Earache SPID pain resolutions (P value NR) **2) Antibiotics usage** Antibiotic use (P<0.001)

KEY: AOM-acute otitis media; C-control; I- intervention; SPID – sum of pain intensity differences; OME – otitis media with effusion; RCT – randomised controlled trial; BL – baseline; SC - standard care.

- Pain duration/pain resolution episodes of ear infection
- Sum-of-pain-intensity differences (SPID)
- Improvement status
- Recovery rate (by pneumatic otoscopy (PNO)
- Rate of recovery defined as duration of illness or time to recovery in days
- Treatment failure
- Presence-of-middle-ear-effusion (MEE) by Tympanometry and/or Pneumatic otoscopy (PNO)

3.1.2. Antbiotic use outcomes

- Antibiotic use (actual consumption)
- (Filled) antibiotic prescriptions

As some of the included studies use (filled) antibiotic prescriptions as a proxy measure for antibiotic use, our outcome of antibiotic use includes both actual use and (filled) antibiotic prescriptions.

3.2. Individualised homeopathy (IH)

Four studies used IH, three RCTs and one nRCT, of which one RCT was placebo-controlled [28]. For clinical improvement, 2 studies [28,29] used composite measures (A) and 4 studies [26–29] used individual symptoms and signs (B). A small number of drop-outs occurred in all studies, but this was similar between groups. ITT analysis was used to impute results, except in Friese et al., [26].

1) Clinical Improvement

3.2.1. Composite measures (2 RCTs)

i) "Cure"

Sinha et al. [29],[AOM], compared homeopathy to conventional medicine (including analgesics, antipyretics, and anti-inflammatory drugs) with an observation period of 3 days before antibiotics were prescribed for AOM. Patients were considered 'Cured' when the total scores (Acute-Otitis-Media-Severity of-Symptoms-Score-(AOM-SOS)- + -Tympanic-Membrane-Examination-Scale) became zero. The percentage of patients experiencing cure at first follow-up (day 3) was higher in the homeopathy group (n = 4) compared to the control group (n = 1). The study authors report this as statistically significant based on a Student T-test ($P < 0.05$), but our plot shows wide confidence intervals crossing the line of no-effect. There was no treatment difference at the three later time points either (Day 7, 10, 21) (see Plot 1). The overall RoB had "some concerns" for this outcome due to blinding issues and the lack of a predefined analysis plan (Table 3). The certainty of evidence (GRADE) was low for this outcome (Table 5).

In this plot, we have reversed the data to the number of "uncured" cases to ensure the consistency of the plots in our review.

ii) Symptom Relief

Jacobs et al. [28],[AOM] compared homeopathy to placebo and used the symptom scores from parental diaries. The homeopathy group showed a decreased symptom score at all time points ($P < 0.05$ after 24 and 64 h of treatment). The data has not been plotted as no standard deviations (SD) have been provided in the paper, only P-values. As we were not pooling data, we did not impute the SD. The overall RoB was "low" for this outcome (Table 3). The certainty of evidence (GRADE) was moderate for this outcome.

iii) Treatment failure

Jacobs et al. [28],[AOM] defined treatment failure as "ear pain and/or a fever of greater than 38.0 [degrees]C orally at any time after the first 48 h of treatment; or severe ear pain (crying from pain) Table 4and/or a fever of greater than 39.0[degrees]C orally after the first 24 h". There were fewer treatment failures in the homeopathy group, but the confidence intervals crossed the line of no-effect at all time points (see Plot 2). The overall RoB was "low" for this outcome (Table 3). The certainty of evidence (GRADE) was moderate (Table 5).

3.2.2. Individual symptoms and signs

i) Pain (2 RCTs; 1 nRCT)

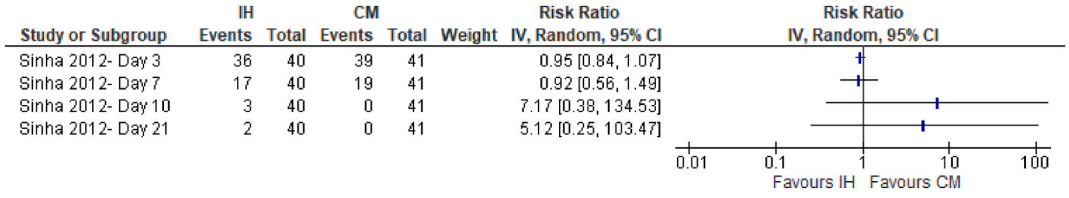
Pain was reported in 2 RCTs (Sinha et al. [29],[AOM] and Jacobs et al. [28],[AOM] but as Sinha et al. [29], already included this symptom under "cure" and Jacobs et al. [28], under "treatment failure', pain has not been separately reported here.

Friese et al. [26],[AOM]assessed pain duration and demonstrated a lower number of days of pain in the homeopathy group compared to the control [median (IQR): I = 2(1–3): C = 3(1–4), P = 0.12]. The overall RoB was "serious" for this outcome (Table 3) using the ROBINS-I scale.

ii) Presence of Middle Ear Effusion (MEE) (2 RCTs, 1nRCT)

The RCT by Harrison et al. [27],[OME] compared homeopathy to standard care including a watch and wait period (WW) with potential antibiotic prescribing. They demonstrated, using tympanometry, that IH improved MEE at 12 months (RR = 0.34 [95% CI:0.14, 0.86], P = 0.02), (see Plot 3a) but the outcome was assessed as high RoB. This study was compromised by the possibility that the randomisation process was unconcealed. The certainty of evidence (GRADE) was low for this outcome.

Whereas the RCT by Jacobs et al. [28],[AOM] comparing IH versus placebo showed, using pneumatic otoscopy, a direction of effect favouring the placebo group at 6 weeks, although not reaching significance (RR = 1.35 [95%CI:0.84, 2.18], P = 0.30) (see Plot 3b). The overall RoB was "low" for this outcome (Table 3). The certainty of evidence (GRADE) was moderate (Table 5).



Plot 1. Cure*

* The patients were considered "cured" when the total scores (AOM-Severity of symptoms scores + Tympanic Membrane Examination Scale) became zero.

H vs. Conventional Medicine (CM) plus an observation option with possible antibiotics after day 3.

Table 3
Risk of bias for Clinical improvement and Antibiotic use.

PART 1: Risk of bias for Clinical improvement and Antibiotic use (RCTs - RoB 2.0)						
1.Clinical improvement						
A.Composite measures						
Study	**D1**	**D2**	**D3**	**D4**	**D5**	**OVERALL**
Sinha 2011[29] (Cure)	Low	Some concerns	Low	Low	Low	**Some concerns**
Jacobs 2001[28] (Symptom relief)	Low	Low	Low	Low	Low	**Low**
Jacobs 2001[28] (Treatment failure)	Low	Low	Low	Low	Low	**Low**
B. Individual symptoms and signs						
Harrison 1999[27] (MEE)	High	Some concerns	Low	Low	Some concerns	**High**
Jacobs 2001[28] (MEE)	Low	Low	Low	Low	Low	**Low**
2. Antibiotic use						
Harrison 1999[27]	High	Some concerns	Low	Low	Some concerns	**High**
Domain 1: Bias arising from randomisation process **Domain 2:**Bias due to deviations from intended interventions **Domain 3 :** Bias due to missing outcome data **Domain 4**: Bias in the measurement of the outcome **Domain 5**: Bias in the selection of the reported result. **Range of outcomes:** Low-Some concerns-High.						
PART 2: Risk of bias for Clinical improvement and Antibiotic use (nRCTs - ROBINS-I)						
1. Clinical improvement						
B. Individual symptoms and signs						
Study	**D1**	**D2**	**D3**	**D4**	**D5**	**D6**	**D7**	**OVERALL**
Friese 1997[26] (Pain duration)	Moderate	Low	Low	Serious	Moderate	Moderate	Low	**Serious**
2. Antibiotic use								
Friese 1997[26]	Moderate	Low	Low	Serious	Moderate	Moderate	Low	**Serious**
D1: Bias due to confounding **D2:** Bias in selection of participants into the study **D3**: Bias in classification of interventions **D4:** Bias due to deviations from intended interventions **D5**: Bias due to missing data **D6:** Bias in measurement of outcomes **D7**: Bias in selection of the reported result. **Range of outcomes:** Low-Moderate-Serious-Critical.								

In a nRCT, Friese et al. [26],[AOM] showed changes in the tympanogram assessment after 2 weeks in both groups, with the prevalence of an abnormal tympanogram (defined as "restricted" and "flat") remaining higher in the control group (I = 17/73 vs C = 7/19). The overall RoB was "serious" for this outcome (Table 4) using the ROBINS-I scale.

2. Antibiotic use (2 RCTs, 1nRCT)

In the RCT by Harrison et al. [27],[OME], the percentage of patients on antibiotics after the initial visit was lower after 12 months in the homeopathy group (5/17 39 %) than in the WW group (9/16 (56 %): RR = 0.52 [95%CI: 0.22, 1.23], P = 0.14) (see Plot 4). The overall RoB was "high" for this outcome (Table 3), due to deviations from the intended intervention. The certainty of evidence (GRADE) was low (Table 5).

In the RCT by Sinha et al. [29],[AOM] the requirement for antibiotics was reported: 0/40 (0 %) of children in the homeopathy group required antibiotics and 39/40 (98 %) of children in the conventional treatment group. Just like the Cochrane Reviewers [36] we contacted the author of Sinha et al. [29], to clarify concerns regarding the antibiotic commencement at the three-day mark for the homeopathy group, but we did not receive a response. Given this lack of clarity, it was impossible to include this as a quantitative outcome in our analyses. For this outcome, RoB was not assessed and the study has not been included in the GRADE assessment.

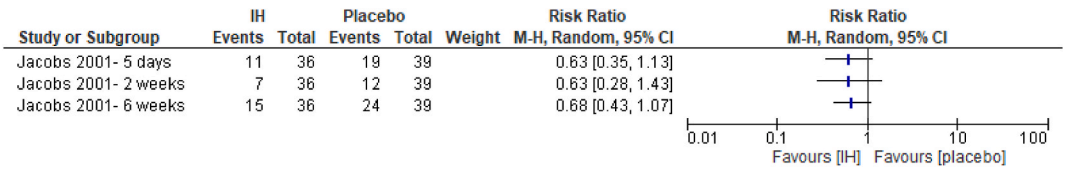
In the nRCT by Friese et al. [26],[AOM], comparing IH to conventional therapy including nasal drops, antibiotics, secretolytics and/or antipyretics, the authors reported that 95 % of the patients with AOM could be treated without antibiotics. Five patients from the homeopathy group changed to the control group and received antibiotics; however, no further information on these 5 participants was provided. The overall RoB was "serious" for this outcome, using the ROBINS-I scale (Table 3).

3.3. Non-individualised homeopathy (non-IH)

Five studies used non-IH, four RCTs and one nRCT of which one was placebo-controlled. For Clinical improvement, 3 studies used composite measures (A) [32–34] and 4 studies used individual symptoms and signs (B) [30–32,34]. A small number of drop-outs occurred in all studies, but this was similar between groups. No ITT analysis was conducted.

Table 4
Risk of bias for Clinical improvement and Antibiotic use.

PART 1: Risk of bias for Clinical improvement and Antibiotic use (RCTs - RoB 2.0)						
1. Clinical Improvement						
A. Composite measures						
Study	**D1**	**D2**	**D3**	**D4**	**D5**	**OVERALL**
Taylor 2011[32] (ETG-5 scale)	Low	Some concerns	Low	High	Low	**High**
Taylor 2014[33] (ETG-5 Scale)	Low	Some concerns	Low	High	Low	**High**
B. Individual symptoms and signs						
Arrighi 2003[30] (MEE)	Some concerns	Some concerns	Low	Low	Some concerns	**High**
Pedrero-Escalas 2016[31] (MEE)	Some concerns	Low	Some concerns	Low	Low	**Some concerns**
Taylor 2011[32] (Symptom severity (AOM-FS))	Low	Some concerns	Low	High	Low	**High**
2. Antibiotic use (filled AB prescription)						
Taylor 2011[32]	Low	Some concerns	Low	Some concerns	Low	**Some concerns**
Taylor 2014[33]	Low	Some concerns	Low	Some concerns	Low	**Some concerns**
Domain 1: Bias arising from randomisation process **Domain 2**:Bias due to deviations from intended interventions **Domain 3** : Bias due to missing outcome data. **Domain 4:** Bias in the measurement of the outcome **Domain 5:** Bias in the selection of the reported result. **Range of outcomes:** Low-Some concerns-High.						
PART 2: Risk of bias for for Clinical improvement and Antibiotic use (nRCTs - ROBINS-I)						
1. Clinical Improvement						
A. Composite measures						
Study	**D1**	**D2**	**D3**	**D4**	**D5**	**D6**	**D7**	**OVERALL**
Friese 1997[26] (MEE)	Moderate	Low	Low	Serious	Moderate	Moderate	Low	**Serious**
Wustrow 2004[34] (% recovered)	Moderate	Low	Low	Low	Moderate	moderate	Low	**Moderate**
B. Individual symptoms and signs								
Wustrow 2004[34] (pain)	Moderate	Low	Low	Low	Moderate	Moderate	Low	**Moderate**
2. Antibiotic use								
Wustrow 2004[34]	Moderate	Low	Low	Low	Moderate	Moderate	Low	**Moderate**
D1: Bias due to confounding **D2:** Bias in selection of participants into the study **D3:** Bias in classification of interventions **D4**: Bias due to deviations from intended interventions **D5**: Bias due to missing dataD6: Bias in measurement of outcomes **D7**: Bias in selection of the reported result. **Range of outcomes:** Low-Moderate-Serious-Critical.								



Plot 2. Treatment failure*
*Ear pain and/or fever of greater than 38 C orally at any time after the first 48 h of treatment; or severe ear pain (crying from pain and/or a fever of 30 C orally after the first 24 h.
IH vs. Placebo.

1. Clinical Improvement

3.3.1. Composite measures (2 RCTs, 1 nRCT)

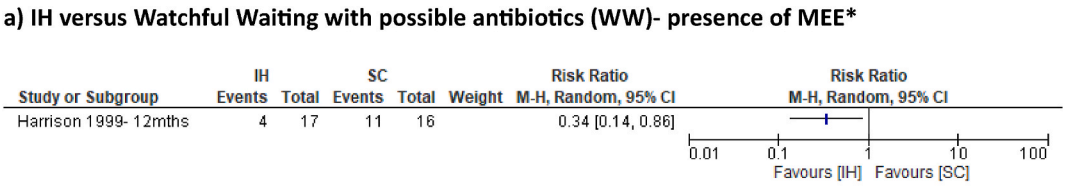
i) ETG-5 scores

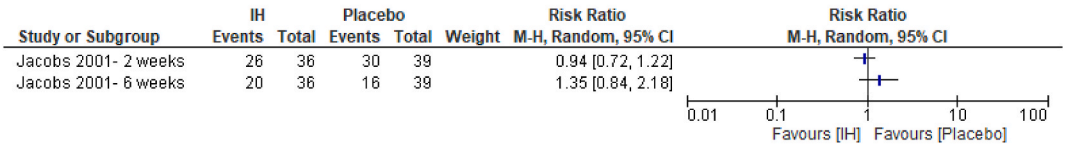
In the RCT by Taylor et al. [32],[AOM] comparing standard care plus homeopathy versus standard care alone, investigators used the Ear-Treatment-Group-5-Scale (ETG-5) [37] to assess symptoms twice daily for the first 5 days after enrolment. ETG-5 scores were lower at each assessment in children randomly assigned to the standard care plus homeopathic eardrop group. Differences were

Table 5
GRADE Summary of findings.

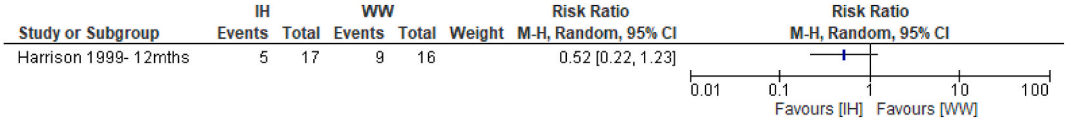
Outcomes	Number of studies	Impact	Certainty of evidence	Comments
INDIVIDUALISED HOMEOPATHY				
Homeopathy versus standard care				
"Cure" assessed using AOM-SOS	Sinha, 2012 [23] [AOM]	H was superior to control in day 3 following treatment but did not reach significance. There was no treatment difference at the 3 later time points (Day 7, 10, 21).	⨁⨁◯◯ LOW	**Risk of bias:** "some concerns" for this outcome due to blinding issues and lack of predefined analysis plan **Imprecision**: small number of events
Presence of Middle Ear Effusion (MEE)	Harrison, 1999 [27] [OME]	Demonstrated, using tympanometry, that H improved MEE at 12 months (RR = 0.34 [95%CI:0.14, 0.86]) P = 0.02	⨁⨁◯◯ LOW	**Risk of bias:** high RoB due to deviations from intended intervention and issues with randomisation concealment. **Imprecision:** small number of events
Antibiotic use	Harrison, 1999 [27] [OME]	Percentage of patients receiving an antibiotic prescription after the initial visit was lower after 12 months in the H group than in the WW group (RR = 0.52 [95%CI: 0.22, 1.23]), P = 0.14	⨁⨁◯◯ LOW	**Risk of bias:** high due to deviations from intended intervention and issues with randomisation concealment. **Imprecision**: small number of events
Homeopathy versus placebo				
Symptom Relief - symptom scores from parental diaries	Jacobs, 2001 [28] [AOM]	H group showed a decreased symptom score at all time points (P < 0.05 after 24 and 64 h of treatment).	⨁⨁⨁◯ MODERATE	**Imprecision**: small number of events
Treatment failure	Jacobs, 2001 [28] [AOM]	Fewer treatment failures in the H group, but did not reach significance.	⨁⨁⨁◯ MODERATE	**Imprecision:** small number of events
Presence of Middle Ear Effusion (MEE)	Jacobs, 2001 [28] [AOM]	Using pneumatic otoscopy, a direction of effect favouring the placebo group at 6 weeks was reported but did not reach significance (RR = 1.35 (95%CI: 0.84 to 2.18), P = 0.30).	⨁⨁⨁◯ MODERATE	**Imprecision**: small number of events
NON-INDIVIDUALISED HOMEOPATHY				
Homeopathy versus placebo				
Presence of Middle ear effusion (MEE)	Pedrero-Escalas, 2016 [31] [OME]	Plot shows the non-recovered numbers in both groups with no significant effect demonstrated (RR = 0.92 [95%CI: 0.54 to 1.56], P = 0.74).	⨁⨁◯◯ LOW	**Risk of bias**: some concerns due to baseline differences **Imprecision**: small number of events and includes null effect AND appreciable benefit or harm
Homeopathy versus standard care				
Symptom scores ETG-5	Taylor, 2011 [32] Taylor, 2014 [33] [AOM]	Taylor 2011 ETG-5 scores were lower at each assessment for H group, the 2nd and 3rd assessment were significantly lower (P = 0.04, P = 0.003) Taylor 2014 more impact (but not significant) from the standard care at week 1 (P = 0.14), but no difference at 2 weeks.	⨁⨁◯◯ LOW	**Risk of bias**: high due to lack of blinding and subjective nature of the scales completed by parents. **Imprecision**: large sample size but includes null effect AND appreciable benefit or harm
Symptom severity (FACES scale)	Taylor, 2011 [32] [AOM]	Demonstrated no difference between groups on the severity of symptoms as assessed by the FACES scale at any of the 10 assessments.	⨁⨁◯◯ LOW	**Risk of bias**: high due to lack of blinding and subjective nature of the FACES scale completed by parents. I**mprecision**: large sample size but includes null effect AND appreciable benefit or harm
Presence of Middle ear effusion (MEE)	Arrighi, 2003 [30] [OME]	The number of children with any effusion remaining resulted in a significant reduction of effusion in the homeopathy group after 6 months (RR = 0.66, [95% CI: 0.56 to 0.78], P < 0.00001)	⨁⨁◯◯ LOW	**Risk of bias**: high, issues with randomisation/allocation concealment and blinding **Imprecision**: small number of events
Antibiotic use day 7	Taylor, 2011 [32], Taylor, 2014 [33] [AOM]	At day 7, H reduced the number of filled prescriptions by 46 % (RR = 0.54 [0.28, 1.06], P = 0.07)	⨁◯◯◯ VERY LOW	**Risk of bias:** some concerns mainly due to lack of blinding and bias in measuring the outcome. **Inconsistency:** variation in effect size **Imprecision: s**mall number of events
Antibiotic use day 12–15	Taylor, 2014 [33] [AOM]	H reduced the number of filled prescriptions by 35 % compared to standard care (RR = 0.65 [95%CI:0.44, 0.97], P = 0.03	⨁⨁◯◯ LOW	**Risk of bias:** some concerns mainly due to lack of blinding and bias in measuring the outcome. **Imprecision:** small number of events

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.





Plot 3. Middle Ear Effusion (MEE)
*flat/fluid data combined as "abnormal".
** using a protocol for diagnosis of MEE by pneumatic otoscopy where a score of 10 or more in one or both ears indicates that MEE is present.
a) IH versus Watchful Waiting with possible antibiotics (WW)- presence of MEE*
b) IH vs. Placebo – presence of MEE**.



Plot 4. Course of antibiotics
IH vs. Watch and Wait with possible antibiotics (WW).

statistically significant at the 2nd and 3rd assessments (P = 0.04 and P = 0.003, respectively). The data has not been plotted as only standard errors were provided in a graph and therefore preciseness was lacking for calculating standard deviations. As only one other study [33] had useable data it was not possible to estimate a mean SD.

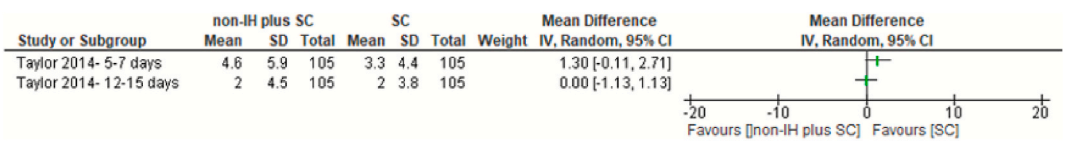
In contrast, in the RCT by Taylor et al. [33],[AOM], also comparing standard care plus homeopathy versus standard care alone, it was demonstrated that the control group (standard care with delayed antibiotic prescription) lowered the mean symptom score more than the standard care plus homeopathy group after 5–7 days (P = 0.14), but this difference was no longer present between groups at the 12–15-day assessment (see Plot 5).

The overall RoB for this outcome was "high" in both studies (Table 4) due to the lack of blinding and the subjective nature of the scales completed by parents. The certainty of evidence (GRADE) was low for this outcome (Table 5).

ii) Clinical symptom score (1 nRCT)

In the nRCT by Wustrow et al. [34],[AOM] comparing the homeopathic product *Otowen* to standard care, investigators reported a clinical symptom score, calculated using the following measures: fever (2), irritability (2), unusual crying or screaming (1), lack of drive (1), loss of appetite (1), unusual sleep behaviour (1). The mean (sd) baseline score was 5.6 (2.2) in the homeopathy group and 6.6 (2.1) in the control group (90%CI: 0.43–0.53). Clinical symptom scores were measured at baseline, follow-up and final assessment, but data were provided for baseline only; therefore, no RoB assessment could be conducted.

iii) Recovery rate (1 nRCT)



Plot 5. Ear treatment Group 5 (ETG-5) Scale.
Standard care (with (delayed) AB prescription) plus non-IH versus standard care (with (delayed) AB prescription).

Wustrow et al. [34],[AOM] also measured recovery rate as the duration of illness or time to recovery in days (up to 14 days). The study authors demonstrated no between-group difference (p = 0.34). When adjusted for baseline symptom scores, the OR for recovery did not reach the threshold for significance in the intention-to-treat sample. The overall RoB for this outcome was "moderate", using the ROBINS-I scale (Table 5).

3.3.2. Individual symptoms and signs

i) Symptom severity (1 RCT)

Taylor et al. [32], used the Acute Otitis Media-Faces (AOM-FS) scale. Although AOM-FS mean scores (no SDs given) tended to be lower in children who received the homeopathic ear drops in addition to standard care (SC) than in those who were randomised to SC alone, no significant differences were noted at any of the 10 assessments. The overall RoB for this outcome was "high" (Table 4) due to the lack of blinding and the subjective nature of the FACE scale completed by parents. The certainty of evidence (GRADE) was low for this outcome (Table 5).

ii) Pain (1 nRCT)

Wustrow et al. [34],[AOM] reported on pain resolution using the Sum of pain intensity differences (SPID). Homeopathy treatment was slightly inferior when adjusted for baseline otoscopy and symptom scores but slightly superior when adjusted for higher baseline pain scores [I = −5.2(2.5): C = −5.8(2.4), OR = 1.15]. This outcome was rated at "moderate" RoB using the ROBINS-I scale (Table 4).

ii) Presence of middle ear effusion (MEE) (2 RCTs)

In the RCT by Pedrero-Escalas et al. [31],[OME], comparing Aerosol therapy plus homeopathic treatment versus Aerosol therapy plus placebo treatment. The authors defined the presence of MEE as "recovery" (see footnote). After 3 months, 56 % of the intervention group vs. 50 % of the placebo group had recovered. Our plot shows the non-recovered numbers in both groups with no significant effect demonstrated (RR = 0.92 [95%CI: 0.54 to 1.56], P = 0.74) (see Plot 6). Despite being the only non-IH study that was placebo-controlled and reported on allocation concealment, there were still "some concerns" regarding RoB (Table 4) due to baseline differences in "the number of AOM in the previous year "and "school absenteeism for otological causes." The certainty of evidence (GRADE) was low for this outcome (Table 5).

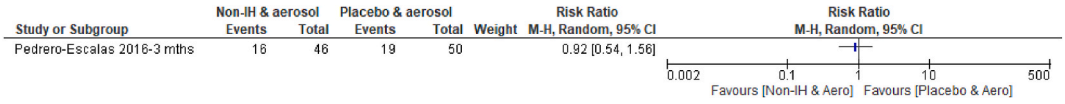
In this plot, we have reversed the data to the number of "non-recovered" cases to ensure the consistency of the plots in our review.

In the RCT by Arrighi [30],[OME], comparing homeopathy to standard care. They presented both the absence and presence of MEE. They demonstrated that the homeopathy group had a lower percentage of children with no reduction compared to standard care after 6 months (7.4 % versus 15.8 %). They also demonstrated less presence of MEE overall in the homeopathy group. We have combined the number of children with any effusion remaining, resulting in a significant reduction of effusion in the homeopathy group after 6 months (RR = 0.66, [95%CI: 0.56 to 0.78], P < 0.00001) (see Plot 7). This outcome was rated as having a high RoB (Table 4). We contacted the author who confirmed randomisation as this was not clearly stated in the paper. The certainty of evidence (GRADE) was low for this outcome (Table 5).

2. Antibiotic use (2 RCTs, 1 nRCT)

In the RCT by Taylor et al. [32],[AOM] investigators compared SC (including immediate or delayed AB prescription) plus non-IH to SC (including immediate or delayed AB prescription) alone. They used a sub-group of 30/90 patients who received a delayed antibiotic prescription. Whereas in the RCT by Taylor et al. [33],[AOM] SC only included the option for a delayed antibiotic prescription.

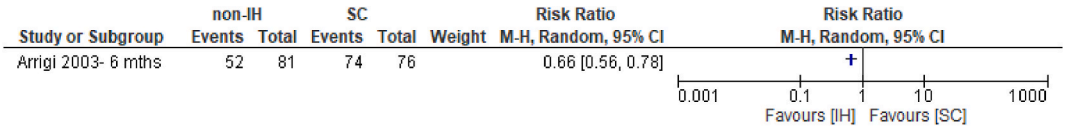
Results of both studies were pooled for filled antibiotic prescriptions for up to 7 days. Our analysis showed that the homeopathic add-on intervention reduced the number of filled prescriptions by 46 % (RR = 0.54 [95%CI: 0.28, 1.06], P = 0.07) (see Plot 8) but did not reach statistical significance. Heterogeneity (I^2 = 12 %) is considered as not important [21]. For both studies, the RoB for this outcome was assessed as having "some concerns" (Table 4), mainly due to a lack of blinding and potential bias in measuring the outcome using a proxy measure for antibiotic use. There is very low certainty of evidence (GRADE) on antibiotic use for up to 7 days (Table 5).



Plot 6. Middle Ear Effusion (MEE) – Recovery*

*Recovery is defined as when, after 3 months of treatment, the pneumatic otoscopy changed from negative in the first visit to positive in the third visit.

Aerosol therapy plus non-IH vs Aerosol therapy plus placebo.



Plot 7. Middle Ear Effusion (MEE)*
* Remaining MEE at 6 months.
Non-IH vs. Standard Care (SC).

Plot 8. Filled antibiotic prescription for up to 7 days.
NB: Taylor et al. (2011) reported on 30 participants with delayed prescriptions, but no details on the distribution of groups were given; therefore, the number of participants quoted in the results was used. Taylor et al., 2014 measure antibiotic follow-up at 5–7 days but report data for up to 7 days.
SC with delayed antibiotic prescription plus non-IH vs. SC alone
i) Up to ≤7 days.

Taylor et al. [33],[AOM] also reported on antibiotic prescriptions at 12–15 days. They demonstrated that homeopathy significantly reduced the number of filled prescriptions by 35 % for up to 15 days compared to standard care (RR = 0.65 [95%CI:0.44, 0.97], P = 0.03 (see Plot 9). The RoB for this outcome was assessed as having "some concerns" (Table 4), mainly due to a lack of blinding and bias in measuring the outcome. The certainty of evidence (GRADE) was low for this outcome (Table 5).

The nRCT by Wustrow et al. [34],[AOM] demonstrated that the control group used more antibiotics than the homeopathy group [I=(14.4 %):C(80.5 %), P < 0.001]. This study has issues with patients switching groups post-baseline. The overall RoB was "moderate" for this outcome (Table 4), when using the ROBINS-I scale.

3.4. Secondary outcomes

Secondary outcomes of interest were antibiotic prescription, hearing loss, recurrence, health service and medication use, quality of life, re-consultation, and adverse events. Due to the reporting of the individual studies on antibiotic prescription as a proxy measure for antibiotic use, it has been reported as part of the primary outcome "antibiotic use". The short-term secondary outcome "adverse events" has been reported below; the other longer-term secondary outcomes are in Appendix 10.

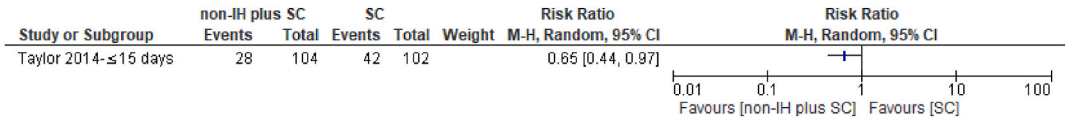
3.4.1. Adverse events (4 RCTS, 2 nRCTS)

Six studies reported adverse events (AEs) (see Appendix 9) [26,28,31–34]. Most studies demonstrated that the control group had more AEs, although none were serious, ranging from stomach upsets, vomiting, rash, diarrhoea, 'hyper' behaviour, headache, and lethargy. One non-IH (Pedrero-Escalas et al. [31],[OME]) RCT demonstrated that the number of upper respiratory tract infection (URTI) was much higher in the control group (P = 0.009). Another nRCT (Wustrow et al. [34],[AOM]) on non-IH reported that one child in the control group developed exanthema after amoxicillin, but after switching to the homeopathy group this AE was resolved.

4. Discussion

4.1. Summary of the main results

The evidence base for the effectiveness of homeopathy and OM treatment is modest in study number, size, and risk of bias. The overall heterogeneity of the study designs (comparison, follow-up periods), homeopathic intervention (individualised prescriptions and various non-individualised preparations), populations (AOM and OME) and the range of outcome measures applied preclude meta-analyses for most outcomes, except for antibiotic use in non-IH. Analysis of the pooled data from two studies showed that the homeopathic add-on intervention (non-IH) reduced the number of filled antibiotic prescriptions by 46 % (up to seven days), but this effect did not reach statistical significance.



Plot 9. Filled antibiotic prescription for up to 15 days.
NB: Taylor et al., 2014 measures antibiotic follow-up at 12–15 days but reports data for up to 15 days.
SC with delayed antibiotic prescription plus non-IH vs. SC with delayed antibiotic prescription
Time scale ≤15 days.

Four of the seven included RCTs reported statistically significant individual outcomes at relevant timepoints (symptom score, MEE, and antibiotic use) favouring the effectiveness of homeopathy compared to standard care or placebo [27,30,32,33]. However, the assessed risk of bias and low certainty of evidence requires a cautious interpretation of the results. Most studies demonstrated that the homeopathy group had less AEs than the control group, although none were serious.

4.2. Deviations from the protocol

There are four protocol deviations to be noted: 1) Inclusion of AOM- and OME-studies due to the inter-relation of these conditions; 2) renaming of the primary outcome "Symptom Relief" into "Clinical improvement"(including symptoms and signs) due to the variation in composite and single symptom scores used in the individual nRCTs; 3) Inclusion of (filled) antibiotic prescriptions in the outcome antibiotic use as some of the included studies used (filled) antibiotic prescriptions as a proxy-measure to measure antibiotic use; 4) addition of GRADE assessments for our primary outcomes.

4.3. Strengths and limitations of the review process

A major strength of the review is that it summarises the collective evidence on homeopathy for OM, providing an evidence base and risk of bias assessment for IH and non-IH separately. The systematic review and analysis were conducted using robust established methodology and for non-IH, only studies testing the same intervention were pooled per outcome.

Due to the variation in comparators and the lack of standardisation of outcome assessment amongst the included studies, we could only perform one meta-analysis. Rigorous GRADE assessments could only be completed for non-IH studies on the one meta-analysis on Antibiotic use and on the outcome "ETG-5 score" reported by two (un-pooled) studies. All other GRADE assessments were based on single study, un-pooled data, which limits the GRADE assessment.

We did not proceed to sensitivity analyses for our primary outcomes with high clinical and statistical heterogeneity because the data were only from a very limited number of studies. We were limited by the poor quality of the reporting in several studies and could not replicate a significant finding in one study (Sinha et al., 2012). Despite several attempts to contact authors for additional information (see Appendix 6), few responded. However, our review process revealed that there are potential to-be-published studies which will increase the number of RCTs in OM and might make future pooling of data and/or sensitivity analyses possible (Varanasi et al., 2023; Hukle et al., [both unpublished]) (see Appendix 8).

4.4. Strengths and limitations of the included studies

There were no causal safety issues in any of the studies, and drop-out rates were generally low, suggesting homeopathic treatment is acceptable and well-tolerated. There was marked clinical heterogeneity for intervention and comparator, with variations in their components, duration, and mode of administration; for example, some studies allowed conventional treatments alongside homeopathy, whereas others included homeopathy exclusively. Two studies were placebo-controlled, whereas others compared homeopathy with standard care. Treatment period ranged from a few days to several weeks. The timing of follow-up assessments was not always clearly defined or consistent between studies, ranging from two weeks to 12 months. This lack of uniformity likely caused reporting rates to differ between studies. Moreover, some outcomes were inconsistently reported (means and SDs, or medians and IQR) and in one case [32], no variance data (SD) was provided and so this could not be incorporated into our plots. Most studies were pilot studies and therefore not appropriately powered; only one [33] conducted a power calculation confirming the results are suitably powered, but has "some concerns" in its RoB assessment. Further variability was introduced due to unclear definitions of some secondary outcomes and definition differences between studies. Seven of the nine studies reported on their funding body. The majority were funded by a funder with interest in TCIH (including homeopathy).

4.5. Agreements and disagreements with previous research

Our findings align with the results of a literature review [38] on complementary and alternative medicine (CAM) for paediatric OM reporting that, compared to conventional treatment, homeopathy may yield faster symptom improvement with less analgesic and antibiotic use and may be less expensive. Three of the studies [28,29,31] included in our review are also included in the Cochrane review on homeopathic medicinal products for preventing and treating acute respiratory tract infections (RTIs) in children [36]. Like us, the Cochrane reviewers were limited in their data analyses due to a lack of standardisation of outcomes and assessed the certainty of the evidence per study outcome as low for most outcomes.

An interesting finding of another Cochrane review [39] is that RTI antibiotic use is lower when doctors feel it is safe not to prescribe antibiotics immediately, but advise *no* antibiotics combined with the request to return if symptoms do not resolve, rather than *delayed* antibiotics. Conversely, patient satisfaction is found to be greater when a *delayed* prescribing strategy is used. Our review indicates that homeopathy is safe and acceptable to be used in addition to standard care as a strategy to reduce antibiotic consumption, including an immediate or delayed antibiotic prescription. Combining delayed antibiotics with homeopathic treatment for symptom relief meets doctors' and patients' expectations for symptom relief and reduced antibiotic use, as shown in two RCTs [32,33]. The decision of immediate, delayed or no antibiotic treatment should be considered individually by a trained medical practitioner following clinical guidelines as severe cases of OM with complications or those that fail to improve with observation or CAM (after 48–72 h) should be treated with antibiotics and, in some cases, surgical intervention [40].

Although bacterial pathogens can only be isolated from the middle-ear fluid (MEF) in approximately 30 % of AOM cases, it is generally considered a bacterial infection and therefore patients' demand for antibiotics is high [41]. GPs' and parents' mutual understanding of the perception of a patient's wish for antibiotics might help GPs explain the appropriate use of antibiotics.

4.6. Future research

Minor self-limiting infections form most of the cases in which antibiotics are prescribed inappropriately [42]. It seems an appropriate way forward to promote self-management of these infections by providing evidence-based information on TCIH treatment options to help relieve symptoms and reduce the need to consult a doctor (which is the main risk factor for getting antibiotics). Promoting self-management should be combined with alerting people on possible risks requiring consultation. Future studies testing 'self-managed homeopathy' in patients with mild to moderate AOM should be considered. Although current strategies focus on reduction in antibiotic use, there is a lack of evidence regarding how far prescribing can be safely reduced. Future studies investigating reduced antibiotic use should therefore also incorporate health and adverse-events outcomes.

The heterogeneity of outcomes measured and reported in homeopathy research in OM hinders data pooling and evidence accumulation in most outcomes (except antibiotic use in non-IH). Consistency of outcome measures to aid replication and help pool data in future meta-analyses would be beneficial. It is therefore necessary to identify and validate a Core Outcome Set (COS) for Otitis Media – standardising what, how, and when to measure – to improve reporting in future homeopathy studies.

There is a general need for large, well-designed RCTs testing the effectiveness of homeopathy (both IH/non-IH) in primary care infection, specifically with 1) blinding, and where possible with the same blinded outcome assessor, 2) data presented using ITT analysis and 3) inclusion of adverse events as an outcome. Further, future homeopathy trials could employ digital technology to monitor adherence and include aspects of implementation and scaling up of the interventions within the health system.

5. Conclusions

The heterogeneity of the study designs, preparations, populations, and various outcome measures applied hindered the data pooling for most outcomes. Therefore, the current evidence is insufficient to satisfactorily answer our research question of whether homeopathy is effective for clinical improvement and reducing antibiotic use in patients with OM. Individual RCTs report positive effects on individual outcomes at relevant time points in favour of homeopathy compared to placebo or standard care. To strengthen the evidence base for the effectiveness of homeopathy on symptom control and reduction of antibiotic use in patients with OM, future studies using a Core Outcome Set for OM are warranted to improve the gathering of combined evidence for future research and practice.

CRediT authorship contribution statement

Rachel Perry: Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Data curation. **Alyson L. Huntley:** Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Data curation. **Nai Ming Lai:** Writing – review & editing, Methodology, Conceptualization. **Michael Teut:** Writing – review & editing, Conceptualization. **David D. Martin:** Writing – review & editing, Conceptualization. **Esther T. van der Werf:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Ethical approval

Due to the nature of the study (systematic review), no ethical approval has been gained.

Author Disclosure statement

The authors declare no conflict of interest.

Data Availability

The data is included in the article and in the supplementary material.

Funding information

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

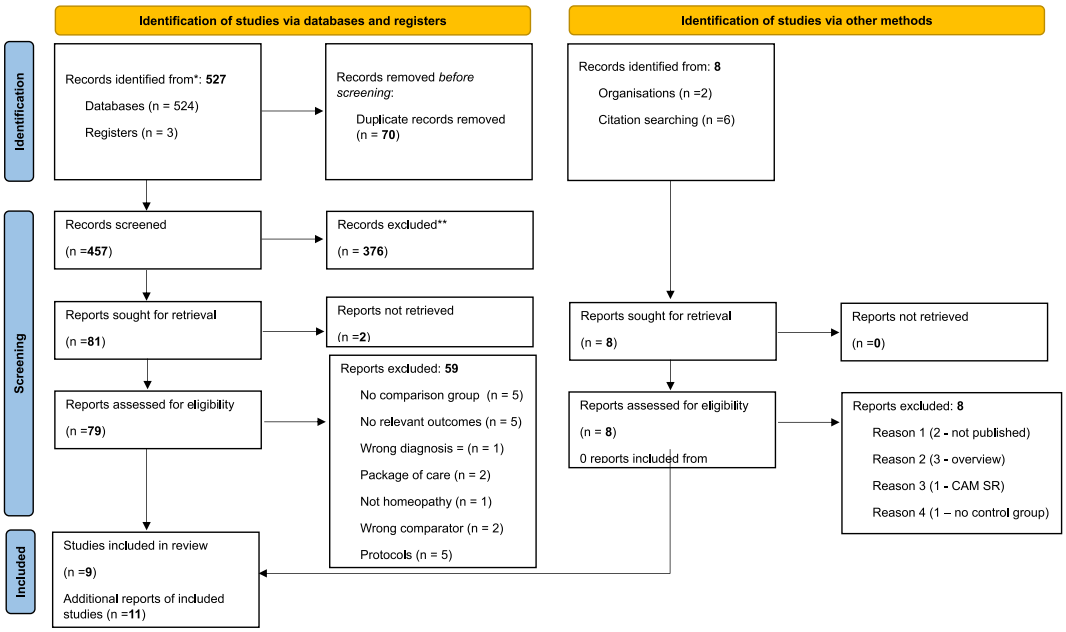
Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e39174.

Appendix 1

Search MEDLINE

1. exp Earache/
2. exp Otitis Media/
3. earache*.tw.
4. (ear* adj2 (ache* or infect* or inflamm*)).tw.
5. (otitis adj2 media*).tw.
6. (middle adj2 ear).tw.
7. otalgia.tw.
8. 1 or 2 or 3 or 4 or 5 or 6 or 7
9. homeopathy.tw.
10. homeop*.tw.
11. homeopathic.tw.
12. homoeopathy.tw.
13. homoeopathic.tw.
14. homoeop*.tw.
15. homoop*.tw.
16. exp Homeopathy/
17. exp Complementary Therapies/
18. exp Holistic Health/
19. exp Materia Medica/

20. (materia medica or nosode*).tw.
21. (dilut* adj2 (very or ultra* or high or serial* or substance* or agent*)).tw.
22. (potentis* or potentiz*).tw.
23. (pulsatilla or chamom* or sulphur or sulphur or calcarea or belladonna or lycopodium or hepar).tw.
24. exp Formulary, Homeopathic/
25. exp Pharmacopoeia, Homeopathic/
26. 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25
27. 8 and 26
28. exp Clinical Trials as Topic/or exp Randomized Controlled Trials as Topic/
29. random.ti,ab.
30. ((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.)
31. RCT.ti,ab.
32. 28 or 29 or 30 or 31
33. 27 and 32



Appendix 2. PRISMA 2020 flow diagram.

Appendix 3

Excluded studies table with reasons

	1st Author	Date	Reason for exclusion
Database search			
1)	Anonymous	2003	Editorial on guidelines
2)	Barnett	2000	no comparison group
3)	Basu	2015	their outcome (measure) appears to be 'improvement' OR ineligible comparator
4)	D'Souza	2012	no relevant outcomes
5)	Dhooge	2005	Commentary/guideline
6)	Ernst	2005	letter/reply to study of Hamre
7)	Fisher	2001	commentary on Jacobs 2001
8)	Frei	2001	no comparison group
9)	Gilbey	2012	commentary on Taylor 2011
10)	Grimaldi-Bensouda	2014	can't extract AOM data specifically

(*continued on next page*)

Appendix 3 (*continued*)

	1st Author	Date	Reason for exclusion
11)	Haidvogl	2007	because ear pain prevalence is only given at day 0, and there is no break-down afterwards, so no relevant extractable data.
12)	Heger	2000	Linked to Haidvogl 2007
13)	Hamre	2005a	anthropomorphic medicine package of care + no separate group
14)	Hamre	2005b	letter reply to Ernst 2005 critique
15)	Hamre	2014	anthropomorphic medicine package of care + no separate group
16)	Hamre	2016	secondary analysis of Hamre 2014
17)	Heynen	1969	no data/control
18)	Jacobs	2012	editorial
19)	Kemper	2002	*Otikon* is a herbal ear drop not homeopathic
20)	Malerba	2005	No comparison group
21)	Melnyk	2007	editorial
22)	Mossinger	1985	no comparison group
23)	Mossinger	1995b	re-analysis of Mossinger 1985
24)	Oppermann	2010	wrong comparison groups/diagnosis
25)	Riley	2001	ear pain outcome data is not separated, and clinical improvement is only given overall. No relevant outcome data.
26)	Rose	2013	commentary on Sinha 2012
27)	Steinsbekk	2004	comparing parents and homeopaths choice of prescription - no relevant outcome data.
28)	Steinsbekk	2005	no relevant outcome data.
29)	Walach	2001	commentary on Jacobs 2001
Handsearching			
30)	Bell	2013	Overview
31)	Marchisio	2011	Review
32)	Saha	2015	No comparison group
33)	de Lange de Klerk	1994	wrote to authors - no subgroup data
34)	Zulkiflee	2013	Overview
35)	Browns	1935	Overview
36)	Varanasi		Not yet published
37)	Hucke		Not yet published

Reviews (25) have not been listed here.
Protocols (n = 5) listed in table (Appendix 5).

Appendix 4
Table of linked studies

Friese 1997a	
1	Friese 1994a: The homeopathic therapy of acute otitis media in children
2	Freise 1994b: Ergebnisse vergleichender Untersuchungen bei homöopathischer und konventioneller Behandlung der Otitis Media im Rahmen einer Dissertation
3	Friese 1996a: Otitis media in children. A comparison of conventional and homeopathic drugs
4	Friese 1996b: Acute otitis media in children Comparison between conventional and homeopathic therapy
5	Friese 1997b: Acute otitis media in children: a comparison of conventional and homeopathic treatment
7	Kruse 1998: Otitis Media bei Kindern
Jacobs 2001a	
8	Jacobs 2001b: Homeopathic treatment of acute otitis media: Hoping for the best
Taylor 2011a	
9	Taylor 2011b: Homeopathic ear drops as an adjunct to standard therapy in children with acute otitis media
Both Taylor 2011a, Taylor 2014	
10	Taylor 2016: Homeopathic treatment of respiratory illnesses in children: Results from two randomized trials
Wustrow 2004	
11	Wustrow 2004b: Alternative versus conventional treatment strategy in uncomplicated acute otitis media in children: a prospective, open, controlled parallel-group comparison
12	Wustrow 2005: Naturopathic therapy for acute otitis media an alternative to primary antibiotic use

Appendix 5

Clinical trials registries (using terms: homeopathy and otitis media)

The US National Institutes of Health Ongoing Trials Register (www.clinicaltrials.gov)	
NCT01003210	Taylor Homeopathic Ear Drops for Otitis Media Study – now published and included in the paper
NCT00622518	Taylor Ear Drops for Children With Otitis Media – now published and included in the paper
World Health Organization International Clinical Trials Registry platform https://www.isrctn.com/	
ISRCTN11416813 https://doi.org/10.1186/ISRCTN11416813	Pedrero-Escalas: Effectiveness of homeopathic treatment (Agraphis nutans 5CH, Thuya occidentalis 5CH, Kalium muriaticum 9CH and Arsenicum iodatum 9CH), as an adjuvant in secretory otitis (SO) in childhood
The EU Clinical Trials Registry (www.clinicaltrialsregister.eu**).**	
0 trials identified	
International Traditional Medicine Clinical Trial Registry (ccebtcm.org.cn)	
0 trials identified	

Appendix 6

Contact with authors for additional information/missing data

Author	Contact details	Date	Request	Response
De Lange- de Klerk	De Lange- de Klerk	January 12, 2023	Written via ResearchGate to access data	no subgroup data
Sinha	Dr. Deepti Singh Research Officer (Homeopathy)/Scientist	April 28, 2023	Contacted co-author to explain: Table Check data on Antibiotics	2 authors have been contacted by the contact research team; no response
Taylor	Taylor	January 19, 2023	Contacted author for: Standard deviation	No response
Taylor	Jacobs	January 19, 2023	Contacted author for: Standard deviation	Referred to Dr Taylor: no response
Arrighi	Arrighi	April 25, 2023	Contacted author to confirm: Randomised/non-randomised	Response: randomised trial

Appendix 7

Data extracted

1. General study information: full citation, publication status, declaration of interest, and funding sources.
2. Methodological characteristics: overall study design, cluster vs. individual randomisation, type of trial, total number of participants in each group, and follow-up duration.
3. Participant characteristics: diagnostic criteria used or method of diagnosis, sex, group demographics and setting.
4. Intervention characteristics: type of homeopathy, homeopathic product, potency, dose, frequency, route and duration of administration, number of participants lost to follow-up in each group.
5. Outcome data: time point and unit of measurement, and results for each outcome.

Appendix 8

Studies to be published

Author, country, study type, condition	Intervention/control/population	Results
Varanasi et al. India RCT AOM	Comparing homeopathy (H-group) and Allopathy (A-group) for AOM and its recurrence in 222 children (aged 0–12 years).	There was a reduction of scores in H-group compared to A-group at day 3 (P = 0.0001), at day 7 (P = 0.0001) and at day 10 (P = 0.0001) favouring homeopathy. Clinical failure by day 3 was observed in 11 % (H-group) vs 24 % (A-group) (P = 0.03). None of the children in the H group required antibiotics whereas 14 children in A-group required them.
Hucke et al. Germany Observational study OM	Children, aged 6 months to 12 years, who had uncomplicated otitis media were treated with the homeopathic medicine *Otofren*® alone (or as an adjunct to conventional therapy) versus just conventional treatment (antibiotics and analgesics).	The findings indicate that *Otofren*® is suitable as an alternative or adjunct to conventional treatment. There were no obvious disadvantages compared to conventional treatment. Both groups demonstrated rapid alleviation and resolution of disease symptoms, with patients in the *Otofren*® group taking antibiotics less frequently overall. Treatment with *Otofren*® also led to a high level of satisfaction among both physicians and parents.

Appendix 9

Adverse events

Individualised homeopathy v placebo control	
Jacobs et al., 2001 (AOM) RCT	The authors reported there were no AEs reported in either group
Individualised homeopathy v conventional therapy	
Friese et al., 1997 (OME) nRCT	**Serious AEs:** none reported in either group. **Non-serious AEs** H group – no AEs; C group -diarrhoea and stomach-aches occurred (number NR)
Non-individualised homeopathy v placebo control	
Pedrero-Escalas et al., 2016 (OME) RCT	Adverse events in 3 months of treatment were evenly distributed except for URIs. URTI I = 3:C = 13, p = 0.009 GI I = 5:C = 3, p = 0.475 LRTI I = 2:C = 1, p = 1.0 UTI I = 0:C = 1, p = 1.0 Fever without focus I = 1:C = 0, p = 0.483 Agitation I = 0:C = 1, p = 1.0 Vomits I = 0:C = 1, p = 1.0
Non-individualised homeopathy v conventional therapy	
Taylor et al., 2011 (AOM) RCT	Adverse events- data on the occurrence of 'other symptoms' were the main assessment of adverse events related to treatment. Vomiting I = 5 (11 %); C = 10 (20 %) Rash I = 3 (7 %); C = 5 (10 %) Diarrhoea I = 3 (7 %); C = 12 (24 %) 'Hyper' behaviour I = 3 (7 %); C = 11 (22 %) Headache I = 7(16 %); C = 6 (12 %) Lethargy I = 13 (30 %); C = 15 (30 %) Other symptoms I = 19 (43 %); C = 22 (44 %)
Taylor et al., 2014 (AOM) RCT	At the 5- to 7-day and 12- to 15-day telephone follow-up, no serious adverse events were reported in either group.
Wustrow et al., 2004 (AOM) nRCT	One child in the control group developed exanthema after amoxicillin but switched treatment arm and this was resolved.

Key AE-adverse event; AOM-acute otitis media; OME – otitis media with effusion; UTRI – upper respiratory tract infection; GI - LTRI – lower respiratory tract infection; UTI- urinary tract infection. RCT -randomised controlled trial – nRCT – non-randomised controlled trial; NR-not reported; H-homeopathy group; C-control group.

Appendix 10

Secondary Outcomes

Outcome	Summary of results
Recurrence	One non-IH RCT (Pedrero-Escalas et al., 2016 [OME]) and one IH nRCT (Friese et al., 1997 [AOM]) demonstrated recurrence was lower in the homeopathy group compared to the control but did not reach significance P = 0.53 and P = 0.39 respectively.
Hearing loss (audiometric measures)	One IH RCT (Harrison et al., 1999 [OME]) reported a higher percentage of hearing loss in the homeopathy group than control (P < 0.2) after 12 months but it is important to note that there were higher levels (P = 0.03) of hearing loss in the homeopathy group at baseline. One non-IH RCT (Arrighi et al., 2003[OME]) reported hearing function by both audiometry and tympanometry after 90 & 180 days. The percentage of patients in the "normalized function" category were higher in the homeopathy group than in the control group after both 90 and 180 days. A non-IH nRCT (Friese et al., 1997[AOM]) tested hearing loss with an audiogram after 2 weeks and found similar results between groups (no p-value provided).
Health service and medication use	***Analgesic usage*** One IH RCT (Jacobs et al., 2001 [AOM) and one non-IH n-RCT (Wustrow et al., 2004 [AOM]) reported lower analgesic usage in the homeopathy group compared to control. One non-IH nRCT (Friese et al., 1997 [AOM]) reported that no analgesics were used in the homeopathy group but did not report numbers for the control group.
Quality of Life (QoL)	No studies reported on QoL
Re-consultation	***Referral to specialists*** One IH RCT (Harrison et al., 1999 [OME]) reported that the homeopathy group had lower rates of referral to a specialist to receive myringotomy/grommets (I = 17.6 % versus 31.3 %) and to a speech therapist (I = 0 % vs C = 6 %) than the control group. In contrast, the non-IH RCT (Arrighi et al., 2003 [OME]) had a higher number of patients in the homeopathy group who were referred for adenoidectomy surgery after one year.

TABLE 11
Characteristics of studies

ID	1st Author, year and country, study design	Aim: Total (n) Intervention (n) Control (n) No. analysed (An) if reported Total number of withdrawals	Patient population inclusion/exclusion criteria	Demographics (mean(SD) or n (%) unless otherwise stated)	Intervention	Comparator	Setting; Training levels of individuals who delivered the intervention	Delayed antibiotics strategy	Only outcome measures of interest reported (with measurement tools)	Adherence	Funding; conflicts of interest, ethics and registration
INDIVIDUALISED HOMEOPATHY											
1	Friese et al., 1997 Germany Open, non-randomised, controlled Study **AOM**	Aim: to test how the results of homeopathic treatment compare with those of conventional therapy. 131 children I = 103(99, 98): C = 28 (28, 27) I = 5 switched to antibiotics C = 1 switched to homeopathy	**Inclusion** Aged 6 mths to 11 yrs with parental consent, and at least 2 signs of AOM: Obligatory typical tympanon, earaches, reduced hearing, fever, reduced general feeling, typical history, no previous treatment. **Exclusion** Severe concomitant disease (immune deficiency). Long term use of steroids and other immune suppressors, antibiotics as prophylaxis, first contact in emergency service, living more than 30k from practice.	**Age yrs, median (IQR)** I = 5 (4–6):C = 6 (4–8) **Sex M (%)** I = 63.1:C = 50 **Previous OM occurrence median (IQR)** I = 2(1–6):C = 2(1–6) **Previous adenectomy (%)** I = 15.5: C = 32.1	Individualised homeopathic single remedy (*Aconitum 30c*, *Apis 6x, Belladonna 30c, Capsicum 6x, Chamomilla 3x, Kalium bich 4x, Lachesis 12x, Lycopodium 6x*, *Mercurius sol 12x, Okoubaka 3x, Pulsatilla 2x, Silicea 6x*). Dosage depended on acuteness but mostly every 2 h or 3 times per day. No additional medication given.	Nasal drops, antibiotics (dosed by weight), secretolytics or antipyrectics or a combination of the 4.	1 homeopathic practice and 5 conventional ENT practices situated in the outskirts of Stuttgart; 1 homeopath, 4 conventional ENT practitioners.	No	Regular follow ups after 2 wks post OM termination were conducted for up to 1 yr -Duration of pain, -Duration of therapy -No. of recurrences after 1 yr -Clear subjective improvement after 3 h (protocol) -No of analgesics -Post treatment tymphany and audiometry after 2 weeks	Not assessed	**Funding:** Karl and Veronika Carstens-Stiftung in the Stifterverband für die deutsche Wissenschaft, Essen. **CoI:** NR
2	Harrison et al., 1999 UK RCT, non-blind, parallel group Pilot study **OME**	Aim: whether homeopathic treatment of children suffering from glue ear is more effective than standard GP care at producing a return to normal hearing (a hearing loss of <20 dB) within 12 months. 33 children from 2 sites I = 17 (17) C = 16 (16) I = 2 did not report all data but missing results included	**Inclusion** OME and positive diagnosis of OM by GP. Hearing loss 20 dbHL>20dBHL; an abnormal tympanogram and age range 18 mths to 8 yrs **Exclusion** A congenital abnormality affecting ears or throat, Downs syndrome or other substantial abnormalities, a history of surgical interventions, or tympanic membrane disease.	**Age yrs, range** <2 to 9 **Sex** NR **Initial hearing loss** **20–30 dB** I= I (5.8 %): C = 7 (43.7 %) **30–40 dB** I = 6 (35.2 %): C = 5 (31.3 %) **>40 dB** I = I0 (58.8 %): C = 4 (25 %)	Individualised homeopathic treatments comprised an initial consultation lasting 1–1.5 h in addition to FUs at mthly intervals. The practitioners used classical homeopathy (constitutional and acute prescribing). Patients were free to see their GPs as normal.	A 'watch and wait' policy with autoinflation of ears, and in some cases, a course of low-dose antibiotics for 4–6 wks.	Isle of Wight-Department of Community Paediatrics (St. Mary's NHS Trust). Swindon - St. Margaret's Hospital. The researchers were qualified and experienced homeopathic practitioners, registered members of the SoH with some experience of treating URIs and otitis media;	No	-Audiometric measurements (3, 6 & 12 mths) -Tympanogram measures (3, 6 & 12 mths) -Course of antibiotics (number of courses in 12 mths) -Referral to specialists	Not assessed	**Funding:** Research Council for Complementary Medicine as part of a "First Rung Award' **CoI:** Andrew Vickers undertook the statistical analysis but was not involved in the day-to-day running of the trial. Local Research Ethics Committee for

(*continued on next page*)

TABLE 11 (*continued*)

ID	1st Author, year and country, study design	Aim: Total (n) Intervention (n) Control (n) No. analysed (An) if reported Total number of withdrawals	Patient population inclusion/exclusion criteria	Demographics (mean(SD) or n (%) unless otherwise stated)	Intervention	Comparator	Setting; Training levels of individuals who delivered the intervention	Delayed antibiotics strategy	Only outcome measures of interest reported (with measurement tools)	Adherence	Funding; conflicts of interest, ethics and registration
		using LOCF principle									Swindon and the Local Research Ethics Committee for the Isle of Wight.
3	Jacobs et al., 2001 USA RCT, double-blind, placebo control Pilot study **AOM**	Aim: to evaluate the safety and efficacy of homeopathy in the treatment of AOM using a double-blind randomized placebo-controlled trial and to determine which outcome measures seemed most appropriate and which homeopathic medicines would be most commonly prescribed in the study population. 75 children I = 36 (36) C = 39 (39) I = 2 Lost to FU C = 1 Lost to FU But ITT analysis used	**Inclusion** Children aged 18 mths to 6 yrs with a diagnosis of AOM, which was diagnosed when there was middle ear effusion, along with one or both of the ear pain characterized as moderate or severe and fever of >38.0 [degrees]C orally. Middle ear effusion was determined by pneumatic otoscopy, according to a clinical research form based on clinical signs from >10 000 cases found to have a predictive value of 0.80 or greater. **Exclusion** History of ear pain for >36 h or if received antibiotics within the past week or homeopathic medications within previous 72 h. Previous tonsillectomy, adenoidectomy or tympanostomy tubes or with a perforated tympanic membrane and/or a discharge from the ear. Children on concurrent medication for another acute or chronic	**Age mths, mean (sd)** I = 42.1 (15.9) C = 36.6 (13.6) **Sex M (%)** I = 53: C = 67 **1st episode of AOM (%)** I = 22.2:C = 15.4 **>2 episodes AOM in past yr (%)** I = 59.2:C = 48.4 **Most recent episode <1 mth (%)** I = 25:C = 18	Individualised homeopathy, 3 to 5 pellets of medication 3x daily for 5 days, or until improvement. Use of other medications, except analgesics, was discouraged.	Placebo medications had no detectable difference in taste, odour or colour with the treatment medication, packaged in identical tubes that were sealed at the laboratory and remained unopened until delivery. Patients took them orally 3x times daily for 5 days, or until symptoms subsided.	Private paediatric practice in Seattle; Diagnosis was made by either paediatrician or nurse practitioner in the group, none of whom was a validated otoscopist.	The occurrence of treatment failure during the first 5 days was determined by objective criteria and ascertained by a daily phone call by a study assistant for the first 5 days. Any child meeting these criteria were referred back to the clinic immediately for standard treatment.	-Daily diary symptom scores (3 times) during first 3 days (pain, temperature, irritability, appetite, energy, sleep, other UTI symptoms). -Total treatment failures (after 5 days, 2 wks, 6 wks) -Presence of MEE assessed by pneumatic otoscopy and tympanometry (at 2 & 6 wks)	Compliance was comparable in both groups (>90 %) as recorded in the symptom diary and during the follow-up daily phone calls.	**Funding**: a grant from the Standard Homeopathic Company **CoI**: NR Informed consent form was approved by ther Human Subjects Committee of the University of Washington.

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TABLE 11 (*continued*)

ID	1st Author, year and country, study design	Aim: Total (n) Intervention (n) Control (n) No. analysed (An) if reported Total number of withdrawals	Patient population inclusion/exclusion criteria	Demographics (mean(SD) or n (%) unless otherwise stated)	Intervention	Comparator	Setting; Training levels of individuals who delivered the intervention	Delayed antibiotics strategy	Only outcome measures of interest reported (with measurement tools)	Adherence	Funding; conflicts of interest, ethics and registration
			illness, or those with a cleft palate or Down's syndrome								
4	Sinha et al., 2012 India RCT,parallel group Pilot study **AOM**	Aim: To compare the effectiveness of Homeopathy and Conventional therapy in Acute Otitis Media (AOM). To evaluate number of patients requiring antibiotic treatment in both the groups. 81 children I = 40 (40) C = 41 (40) I = 2 did not report in last 2 FUs but missing results included using LOCF principle C = 1 did not complete the 21 days FU (referred to hospital because of convulsions and excluded from the study).	**Inclusion** Children of both sexes, between 2 and 6 yrs. Earache of not more than 36h duration. Tympanic membrane bulging with loss of landmarks. **Exclusion** Patients having any discharge or history of discharge from ear; history of convulsions; subperiosteal abscess of mastoid; grossly deviated nasal septum; suspected enlarged adenoids; OME; on antibiotics/steroids in the past 7 days; any systemic disease.	**Age group** 2 < 3 yrs I = 17(42.5):C = 15 (37.5) 3 < 4 yrs I = 6(15):C = 12(30) 4 < 5 yrs I = 7(17.5):C = 9 (22.5) 5 < 6 yrs I = 10(25):C = 4 (10) **Sex M (%)** I = 42.5:C = 57.5	Individualised homeopathy prescription selected using CARA Software. The medicines were in 50 millesimal (LM) potencies starting with 0/1 (LM potency) and ascended as required, repeated 2–6 hrly depending upon the severity of symptoms.	'Observation option' was adopted for first 3 days: patients were given symptomatic treatment without antibiotics. Conventional treatment including analgesics, antipyretics and anti-inflammatory drugs	General Paediatric clinic at the Regional Research Institute of Homeopathy, Jaipur, (Rajasthan), India of CCRH; An ENT specialist examined tympanic membrane using the Tympanic Membrane Examination scale; Administered by	No Yes: If less than 50 % improvement was observed in first 3 days, antibiotics were given in both groups.	-Tympanic Membrane Examination Scale assessed by ENT specialist on days 3,7,10,21 -Symptoms of AOM scale (AOM-SOS scale) assessed by parents on days 3,7,10,21	Not assessed	**Funding:** NR **CoI:** NR Ethical Committee of Central Council for Research in Homoeopathy (CCRH)
	NON-INDIVIDUALISED HOMEOPATHY										
5	Arrigi et al. 2003 Italy (translation) Clinical trial (not randomised) **OME**	Aim: the effectiveness of a homotoxicological protocol in the treatment of OME versus a standard allopathic reference protocol is evaluated. 157 children I = 81 C = 76	**Inclusion** Children presenting at Free Choice Paediatrics between September 1, 1998 to 31/8/01 Aged 4–8 yrs, Diagnosis of bilateral OME with endotypmanic versation present for >3 months and instrumentally	**Aged** between 8 mths and 5 years **Sex M (%)** I = 39.5: C = 44.7 **Adenoid hypertrophies (med t0 high grade)** I = 53 C = 53	**Homotoxicology protocol**: *Muscosa Comp.* vials 1 fl/os for 5 days, then 2 vials weekly for 4 weeks *Echinacea Comp forte* vials 1 fl/os daily for 5 days, then 2 vials weekly for 4 weeks VIS-HEEL vials – 2	*Amoxicillin + Clavuacid Lanico* 50 mg kg/day/os, 2 administrations/day on an empty stomach, for 3 weeks *Prednisone* 1 mg/kg/day/os, 2 administrations/day for10 days	Free Choice Pediatrics;	No	-Number of OME episodes in 180 day FU) -Otoscopy evaluation of endotympanic effusions with otoscopy performed after 90 and 180 days -Hearing function by audiometry &	Not reported	**Funding:** NR **CoI:** NR The standard reference protocol was drafted in accordance with the European Union Good Clinical Practice Standards and

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TABLE 11 (*continued*)

ID	1st Author, year and country, study design	Aim: Total (n) Intervention (n) Control (n) No. analysed (An) if reported Total number of withdrawals	Patient population inclusion/exclusion criteria	Demographics (mean(SD) or n (%) unless otherwise stated)	Intervention	Comparator	Setting; Training levels of individuals who delivered the intervention	Delayed antibiotics strategy	Only outcome measures of interest reported (with measurement tools)	Adherence	Funding; conflicts of interest, ethics and registration
			documented hearing loss. **Exclusion** All children with chronic pathology (diabetes, heart disease, chronic renal failure) under long term antibiotic prophylactic treatment, on immunosuppressants and corticosteroids		vials/os per settime for 5 weeks *Arnica Comp* (heels*) vials 1 fl endo-nasally daily for 5 days, then 2 vials weekly for 4 weeks	*Mometasone Furoate Monoidrato* nasal spray 1 puff in each nostril 1x day for 4 weeks after 10 days from start of systemic steroid therapy. The antibiotic dosage must be the optimal therapeutic dosage			tympanometry after 90 & 180 days. This follow up period included treatment period outlined in the intervention/ comparator columns		the Helsinki Decalration.
6	Pedrero-Escalas et al., 2016 Spain RCT, double blind, placebo control, Phase III study **OME**	To test the hypothesis that a protocoled homeopathic management of OME in childhood would: (i) Recover or reduce the recurrence of OME diagnosed with PNO and tympanometry; considering negative PNO (ii) reduce the rate of otological complications of OME (iii) be a safe treatment for children, recording adverse events occurring during the 3 mths of treatment 96 children I = 46 (42) C = 50 (44)	**Inclusion** aged 2 mths to 12 yrs with OME diagnosed by PNO examination **Exclusion** Neonatal screening fail, receptive language disorder, neurosensorial hearing loss, autism, craniofacial abnormalities, Down Syndrome, middle or internal ear malformation, ciliary motility disorders, cholesteatoma, acute mastoiditis, acute otitis media, recent vaccination (less of 30 days), obstructive sleep apnea, tympanic perforation or timpanostomy tubes, adenoidectomy, lactose or glucose intolerance, treating asthma, corticoid,	**Age mths, mean (sd)** I = 44.7 (19.3); C = 41.1 (17.9) **Sex M (%)** I = 63: C = 64 **AOM n/year (mean (sd)** I = 2.2 (2.6); C = 3.9(3.9)	Aerosol therapy (Model Aapex Mini-Nebe 230V 50Hrz 0.6A) consisting of 1 session every 24 h for 20 days of 1 vial of Ambroxol hydrochloride (7.5 mg/ml), 1 vial of Budesonide (0.25 mg/ml suspension), and 2 cc of physiological saline. Plus either: **Homeopathic treatment A** (*Agraphis nutans*5CH and *Thuja Occidentalis* 5CH) dosage of 5 granules of each, 1x day, Or **Homeopathic treatment B** (*Kalium mur.* 9CH and *Arsenicum iod.*	Same therapeutic drugs scheme with aerosol therapy and placebo treatment.	Department of Otorhinolaryngology and Head-Neck Surgery at Toledo Hospital Complex; A Paediatric Specialist (30+ yrs of experience in homeopathy) performed the homeopathic regimen selected. He is a registered member of the Society of Homeopaths of Spain .	No	"Recovery" pneumatic after 3 mths shown by a change in PNO negative to positive by 3rd visit. -"Recurrence" as shown by change from positive PNO in 2nd visit to negative by 3rd visit. -Otological complications of OME (AOM, eardrum perforation or mastoiditis) during 3 mths of treatment -Adverse events (mild, moderate, severe) during 3 mths of treatment -Tympanometry examination to support diagnosis	Empty aerosol containers and homeopathic-placebo tubes were checked each visit. Adherence to the treatment considered when the patient consumed at least 70 % of the treatment	**Funding:** Laboratorios Boiron Spain Avda **CoI:** NR The medical Ethics Committee of Toledo Hospital Complex and the Spanish Food and Drug Administration (EFDA)

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TABLE 11 (*continued*)

ID	1st Author, year and country, study design	Aim: Total (n) Intervention (n) Control (n) No. analysed (An) if reported Total number of withdrawals	Patient population inclusion/exclusion criteria	Demographics (mean(SD) or n (%) unless otherwise stated)	Intervention	Comparator	Setting; Training levels of individuals who delivered the intervention	Delayed antibiotics strategy	Only outcome measures of interest reported (with measurement tools)	Adherence	Funding; conflicts of interest, ethics and registration
		I = 1 abandoned study after randomisation, 3 withdrew (1 voluntary, 1 AE, 1 surgical procedure) C = 6 withdrew (1 voluntary, 4 AEs, 1 surgical procedure)	antihistamine or mucolytics therapy		9CH) with a dosage of 5 granules, 2x day.				of PNO (Jerger classification Type B -considered pathological Type A or C considered normal) assessment schedule: Day 45, 90 + 120 safety FU telephone call		
7	Taylor & Jacobs 2011 USA RCT stratified by antibiotic treatment plan (immediate or delayed therapy) **AOM**	To determine whether a commercially available homeopathic ear drop solution would be a safe and effective adjunctive treatment for children with AOM 120 children, I = 59 (56) C = 60 (57) Abstract n = 119, 1 too old. 1 immediately after randomisation (over age limit), assumed from I group I = 59 (56) C = 60 (57)	**Inclusion** Children aged 6 mths to 11 yrs diagnosed with AOM by a provider. If tympanic membrane(s) was distinctly abnormal or had significant discomfort with an OS-8 score of ≥4. Symptom severity in the preceding 24 h was assessed by the parent using the faces scale (AOM-FS), only children with an indicated symptom severity of ≥4 were included. **Exclusion** Children with a chronic medical condition, if taken antibiotics within the previous 2 days, had a diagnosis of AOM during the preceding 30 days, or who had a perforated tympanic membrane or received any homeopathic	Based on I = 44: C = 50 **Age yrs, mean (sd)** I = 3.8 (2.6):C = 3.4 (2.5) **No. of AOM in previous 12 mths, (mean)** I = 0.89: C = 0.90 **Otoscopy scale-8 score (mean)** I = 4.8:C = 4.9 **Ear treatment group-5 score at enrollment** I = 18.5: C-20.1 **AOM Faces Scale score at enrollment (mean)** I = 4.9:C = 5.1 **Prescribed amoxicillin for AOM (%)** I = 68.2:C = 76.0	Non-individualised homeopathic ear drops (Hylands Earache Drops), containing a combination of 6 homeopathic remedies: *Pulsatilla, Chamomilla, Sulphur, Calc carb*, *Belladonna*, and *Lycopodium*, (all 30c potency). Administered 3 to 4 drops up to 3x/day as needed max. of 5 days, plus standard therapy.	Standard therapy alone: Treatment included immediate prescription for an oral antibiotic, or a delayed antibiotic prescription, as well as treatments for otalgia such as acetaminophen, ibuprofen, or topical benzocaine ear drops.	University of Washington Medical Center Pediatric Care Centre	Yes, treatment included immediate prescription for an oral antibiotic, or a delayed antibiotic prescription,	-AOM-FS scores (the faces scale) -ETG-5 scores (5-item, ear treatment group symptom questionnaire) -Occurrence of adverse events -Use of symptomatic medications, -symptom logs -Data on return visits -FSIIR scores (Functional status) All assessments: completed by parents contacted by phone 5–7 days, and 12–15 days after the initial visit	Not assessed	**Funding:** Standard Homeopathic Company, LA, California **CoI:** Jennifer Jacobs has been a paid consultant for the study sponsor. James Taylor has no conflicts of interest to disclose. Approved by the University of Washington Human Subjects Committee Registered on Clinical Trial.gov (NCT00622518)

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TABLE 11 (*continued*)

ID	1st Author, year and country, study design	Aim: Total (n) Intervention (n) Control (n) No. analysed (An) if reported Total number of withdrawals	Patient population inclusion/exclusion criteria	Demographics (mean(SD) or n (%) unless otherwise stated)	Intervention	Comparator	Setting; Training levels of individuals who delivered the intervention	Delayed antibiotics strategy	Only outcome measures of interest reported (with measurement tools)	Adherence	Funding; conflicts of interest, ethics and registration
			medicine during the previous 30 days.								
8	Taylor & Jacobs 2014 USA RCT, parallel group **AOM**	Aim: To determine if use of a homeopathic ear drop preparation reduces antibiotic use in children diagnosed with AOM 210 children, I = 105 (104) C = 105 (102) I = 1 C = 3	**Inclusion** children 6 mths to 11 yrs diagnosed with AOM by a pediatric practitioner who manage the patient with a delayed antibiotic approach. **Exclusion** Suspected bacterial illness or who appeared "toxic" to the clinician. Myringotomy tubes or perforated tympanic membrane. Systemic antibiotic treatment in previous 7 days or homeopathic treatment in past 30 days.	**Age yrs, mean, (sd)** I = 3.9 (2.7):C = 4.1 (2.5) **Sex M (%)** I = 54.8:C = 33.3 **Mean baseline ETG-5 (sd)** I = 15.2 (6.4):C = 15.5 (7.2)	Non-individualised homeopathic ear drops (*Hylands Earache Drops*), containing a combination of 6 homeopathic remedies: *Pulsatilla, Chamomilla, Sulphur, Calc carb*, *Belladonna*, and *Lycopodium*, (all 30c potency). 3 to 4 drops in the affected ear(s) up to 3 x/day as needed to relieve symptoms alongside standard therapy.	Standard therapy for both groups included all treatments recommended by the examining clinician including use of analgesics and directions on when to fill the antibiotic prescription.	University of Washington Medical Center Roosevelt Pediatric Care Center or practices that are members of the Puget Sound Pediatric Research Network; Diagnosing clinician.	Yes: the examining clinician confirmed a delayed antibiotic approach and if a filled antibiotic prescription was given. Only if the child did not improve over 2–3 days or got worse, or had advised the parent to call the office for an antibiotic prescription using the same criteria	-ETG-5 scores (5-item, ear treatment group symptom questionnaire) -Logbooks recording other symptoms (adverse events) -Use of other analgesics -Use of Antibiotics -Prescription fill rates for antibiotics All assessments: completed by parents contacted by phone 5–7 days, and 12–15 days after the initial visit	Not assessed	**Funding:** Standard Homeopathic Company, LA, California Approved by the University of Washington Institutional review Board. Registered on Clincaltrials.gov (NTC01003210) **CoI:** Dr Jennifer Jacobs has served as a paid consultant to Standard Homeopathic Company. Dr Taylor has no financial disclosures or conflicts of interests related to this study.
9	Wustrow et al., 2004 Germany open, non-ran -domized, controlled, parallel-group study **AOM**	Aim: to compare the outcome of a conventional and an alternative treatment strategy, the latter based on the application of *Otovowen*, in childhood AOM in a real-life setting. 390 children (385 analysed) I = 194 (192) C = 196 (193) 350 patients lacking major protocol	**Inclusion** Children aged 1–10 yrs with uncomplicated AOM (no tympanic perforation, no indication for myringotomy or adenotomy) **Exclusion** Concurrent homeopathic treatment, complicated OM or immune deficiency, immunosuppressants, other homeopathic	**Age yrs, mean (sd), [range]** I = 4.4 (2.3) [0–14] C = 4.3 (2.3) [1–10] **Sex M (%)** I = 50:C = 55 C = 105(55): 85 (45)	Non-individualised naturopathic treatment: *Otovowen** drops (Conventional medication was also allowed. 100 ml of *Otovowen* drops contain highly concentrated liquid plant extracts (i.e. tinctures) of *Echinacea purpurea* (7.5 ml), *Sambucus*	Usual care: free combinations of decongestant nose drops, mucolytics, analgesics and antibiotics without restrictions. *Otowen* not allowed.	16 alternative centres and 13 conventional centres. Physicians assigned themselves to a treatment preference.	No	-pain-ratings on a scale from 1 to 10, -clinical symptoms, -absence from school or pre-school nursery and medications taken. -daily diary for a global judgment of recovery (yes/no) -otoscopic findings and pain-rating on a	Not assessed	**Funding:** Weber and Weber sponsored the study **CoI:** NR

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TABLE 11 (*continued*)

ID	1st Author, year and country, study design	Aim: Total (n) Intervention (n) Control (n) No. analysed (An) if reported Total number of withdrawals	Patient population inclusion/exclusion criteria	Demographics (mean(SD) or n (%) unless otherwise stated)	Intervention	Comparator	Setting; Training levels of individuals who delivered the intervention	Delayed antibiotics strategy	Only outcome measures of interest reported (with measurement tools)	Adherence	Funding; conflicts of interest, ethics and registration
		violations formed the per-protocol sample 5 excluded – no information on duration of disease from doctors' notes or diary. Additional 3 in each group did not recover within 14 day observation period 378/390 diaries were evaluated.	drugs or antibiotics within last 7 days		*nigra* (2.25 ml), *Sanguinaria canadensis* (0.75 ml) and *Chamomilla recutita* (2.25 ml) as well as liquid homeopathic potencies (dilutions) of *Aconitum napellus* (D6), *Capsicum annuum* (D4), *hydrargyrum cyanatum* (D6), *Hydrasti canadensis* (D4), *iodine* (D4) and *Natrium tetra boracicum* (D4). Ethanol is added to 53 % (v/v).				scale from 1 to 10, -the presence or absence of typical clinical symptoms (fever, irritability, un usual crying or screaming, lack of drive, loss of appetite, unusual sleep behavior) and medications prescribed, in standardized case report forms. - global judgment of effiicacy and tolerability by means of a 6-point Likert scale (very good, good, moderate, slight, not much, not at all). -Medical exam at 2–5 days. Final exam 14 days (at latest) after inclusion. -Parental diaries recording when medication was taken, absence from school, ear pain and symptoms 3x day.		

KEY: AOM = acute otitis media; AOM-SOS=Acute Otitis Media Severity of Symptoms Scale; BL = baseline; dbHL = decibel hearing level; ETG-5 = Ear Treatment Guide–5; hrs = hours; MEE = middle ear effusion; mths = months; OME=Otitis Media with effusion; fl/os = fluid by mouth; RCT = randomised controlled trial; SoH=Society of Homeopaths; URIs = upper respiratory infections; yrs = years.
Scales.
AOM-SOS - 0 to 14 Higher score indicated more severe.
Tympanic Membrane Examination scale on 3-point scale 0, 1 & 2 (Score range from 0 to 8, higher score indicating greater intensity) which was developed by CCRH with help of ENT specialist.
PNO examination (Halogen HPX with insufflation n 25021 from Welch Allyn).
NB: Otitis media with effusion (OME) and acute otitis media (AOM) are two main types of otitis media (OM).

TABLE 12
Results

ID	1st Author	Primary outcome: 1)Symptom relief (severity and duration) [(n or mean (SD) unless otherwise reported)]	Primary outcome: 2)antibiotic use [(n or mean (SD) unless otherwise reported)]	Secondary outcome: 3)recurrence [(n or mean (SD) unless otherwise reported)]	Secondary outcome: 4)Hearing loss [(n or mean (SD) unless otherwise reported)]	Secondary outcome: 5) health service & medication use [(n or mean (SD) unless otherwise reported)]	Secondary outcome: 7) re-consultations [(n or mean (SD) unless otherwise reported)]	Secondary outcome: 8) Type, frequency and severity of adverse events and complications [(n or mean (SD) unless otherwise reported)]	Conclusion	NOTES
INDIVIDUALISED HOMEOPATHY										
1	Friese et al., 1997	**Duration of pain, days, median (IQR) based on I=99: C=28** I = 2 (1–3): C = 3 (1–4), P = 0.12 **Duration of therapy, days, median (IQR) based on I=98: C=27** I = 4 (3–7):C = 10 (7–10), P = 0.0001 **Change of sides in OM (%)** I = 11.7: C = 0 **Disease progression 3 h after initial therapy (% subjective noticeable improvement)** I = 30.2: C = 11.5 **Tympanogram after 2 weeks,** based on I = 73:C = 19 Normal I = 56/73 (77 %) C = 12/19 (63 %) Restricted I = 13/73 (18 %) C = 5/19 (26 %) Flat I = 4/73 (5 %) C = 2/19 (11 %)	I: 5/99 [switched to C group] C:23/28 children received antibiotics	**Total recurrence/ patient/yr (mean) based on I-99:C=27** I = 0.41:C = 0.70, P = 0.39 **Free of recurrence of OM (%) after 1 yr** I = 70.7: C = 56.5	**Audiogram after 2 weeks** Without findings I = 30/38 (79 %) C = 9/12 (75 %) Pathological I = 8/38 (21 %) C = 3/12 (25 %)	Analgesics I = 0/99:C=NR	Not assessed	SAE; I = 0: C = 0 AE I = 0 C = diarrhoea and stomachaches occurred (No. NR)	*The homeopathic treatment of young otitis media patients seems to be unprobablematic because the type of therapy applied here is relatively easy to learn.*	5 children were switched to antibiotics treatment, 1 child was switched to homeopathy Most common remedies are reported in Friese 1994a but we had no access to the full paper
2	Harrison et al., 1999	**Tympanogram measures (after 12 months)** The difference	**Course of antibiotics (in 12 months)** 1 or more: I = 5/	Not assessed	**Audiometric measures (after 12 months)**	Not assessed	**Referral to specialists:** *Myringotomy/ grommets*	Not assessed	*The current trial provides some evidence that a package of homoeopathic care is*	Most common remedy used was not reported

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TABLE 12 (*continued*)

ID	1st Author	Primary outcome: 1)Symptom relief (severity and duration) [(n or mean (SD) unless otherwise reported)]	Primary outcome: 2)antibiotic use [(n or mean (SD) unless otherwise reported)]	Secondary outcome: 3)recurrence [(n or mean (SD) unless otherwise reported)]	Secondary outcome: 4)Hearing loss [(n or mean (SD) unless otherwise reported)]	Secondary outcome: 5) health service & medication use [(n or mean (SD) unless otherwise reported)]	Secondary outcome: 7) re-consultations [(n or mean (SD) unless otherwise reported)]	Secondary outcome: 8) Type, frequency and severity of adverse events and complications [(n or mean (SD) unless otherwise reported)]	Conclusion	NOTES
		between groups is significant ($X^2 = 6.8$; P = 0.015) *Normal* I = 13/17 (76.4 %) C = 5/16 (31.3 %) *Fluid* I = 4/17(23.5 %) C = 2/16 (12.5 %) *Flat* I = 0/17 (0 %): C = 9/16 (56.2 %)	17 (39.4 %*) vs C = 9/16 (56.2 %) None: I = 12/17 (70.6 %) vs C = 7/16 (43.7 %) (difference between proportions is 26.8 % (95%CI, −5.7 to 59.4 %); P = 0.16		*<20DB*: I = 11/17 (64.7 %) vs C = 9/16 (56.2 %) (difference between means 8.5 %; (95%CI, −24.8 to 41.7 %)], P > 0.2 *>20DB:* I = 6/17 (35.3 %) Vs C = 7/16 (43.7 %)		I = 3/17 (17.6 %) Vs C = 5/16 (31.3 %) *Speech therapist* I = 0/17 (0 %) vs C = 1/16 (6 %) The difference between proportions is 19.9 % (95% CI: 50 to 10 %), P > 0.2		*more effective than standard care alone at treating glue ear in children. Further research comparing homoeopathy to standard care is warranted. Assuming recovery rates of 50 and 30 % in homoeopathy and standard care groups respectively, 270 patients would be needed for a definitive trial.*	
3	Jacobs et al., 2001	**Symptom scores from diaries** 69 were returned (I = 36, C = 33) I = showed a decreased symptom score at all time points, (P < 0.05 after 24 and 64 h of treatment). C= NR **Treatment failure (total)** day 5: I = 7 (19.4); C = 12(30.8), RR = 0.71, (95%CI 0.37 to 1.35), P = 0.39 2 wks: I = 11 (30.6); C = 19 (48.7), RR = 0.66, (95%CI 0.39 to 1.13), P = 0.17 6 wks: I = 15 (41.6); C = 24 (61.5), RR = 0.66, (95%CI	Not assessed	Not assessed	Not assessed	**Use of analgesics** (Parental report) I = 5: C = 10	Not assessed	There were no adverse effects reported in either group	*These results suggest that a positive treatment effect of homeopathy when compared with placebo in acute otitis media cannot be excluded and that a larger study is justified.*	Most common remedies of the 16 remedies used (88 % cases) were *Pulsatilla nigrans* (62.7 %), *Chamomilla* (10.7 %), *Sulphur* (9.3 %) and *Calc carb* (5.3 %).

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TABLE 12 (*continued*)

ID	1st Author	Primary outcome: 1)Symptom relief (severity and duration) [(n or mean (SD) unless otherwise reported)]	Primary outcome: 2)antibiotic use [(n or mean (SD) unless otherwise reported)]	Secondary outcome: 3)recurrence [(n or mean (SD) unless otherwise reported)]	Secondary outcome: 4)Hearing loss [(n or mean (SD) unless otherwise reported)]	Secondary outcome: 5) health service & medication use [(n or mean (SD) unless otherwise reported)]	Secondary outcome: 7) re-consultations [(n or mean (SD) unless otherwise reported)]	Secondary outcome: 8) Type, frequency and severity of adverse events and complications [(n or mean (SD) unless otherwise reported)]	Conclusion	NOTES
		0.41 to 1.07),P = 0.13 **Presence of middle ear effusion** 2 wks: I = 26 (72.2); C = 30 (76.9), RR = 0.88 (95%CI 0.53 to 1.47), P = 0.83 6 wks: I = 20 (55.5); C = 16 (41.0), RR = 1.35 (95%CI: 0.84 to 2.18),P = 0.30 **Tympanograms** 335/376 (89.1 %) tympanograms were considered interpretable. only 54 (72 %) children had interpretable tympanograms at study entry, with evidence of middle ear effusion in 39/54 (52 %), 19 were in the I group and 20 in the C group. A subgroup analysis of these children with objective evidence of effusion at the first visit found 1 treatment failure in the homeopathy group and 4 in the placebo group after five days, 4 failures in the homeopathy group and 10 in the placebo group at 2 wks and 5 failures in the homeopathy								

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TABLE 12 (*continued*)

ID	1st Author	Primary outcome: 1)Symptom relief (severity and duration) [(n or mean (SD) unless otherwise reported)]	Primary outcome: 2)antibiotic use [(n or mean (SD) unless otherwise reported)]	Secondary outcome: 3)recurrence [(n or mean (SD) unless otherwise reported)]	Secondary outcome: 4)Hearing loss [(n or mean (SD) unless otherwise reported)]	Secondary outcome: 5) health service & medication use [(n or mean (SD) unless otherwise reported)]	Secondary outcome: 7) re-consultations [(n or mean (SD) unless otherwise reported)]	Secondary outcome: 8) Type, frequency and severity of adverse events and complications [(n or mean (SD) unless otherwise reported)]	Conclusion	NOTES
		group with 12 in the placebo group after 6 wks. MEE at 2 wks was present in 17 children in both homeopathy and placebo groups; at 6 wks 9 children in the homeopathy group had MEE compared with 8 in the group receiving placebo.								
4	Sinha et al., 2012	**Improvement status during follow-ups (cured)** day 3: I = 4/40:C = 1/40, P = 0.00 day 7: I = 23/40:C = 21/40, P = 0.36 day 10: I = 37/40:C = 40/40, P = 0.134 day 21: I = 38/40:C = 40/40, P = 0.20 **Changes in each symptom, mean (sd) at end point, Number of patients with the specified symptom [at entry: at end] Control: no patients with symptoms 'At end)')** (*Ear pain* I = 0.07 (0.34), [40:2]; C=NA, [40:0], P = 0.16 *Tugging* I = 0.05 (0.31), [39:1]; C=NA, [39:0], P = 0.32 *Crying* I = 0.05 (0.31), [38:1]; C=NA,	**Antibiotics prescribed** I = 0/40 (0 %):C = 39/40 (97.5 %)	Not assessed	Not assessed	Not assessed	Not assessed	Not assessed	*Individualised homeopathy is an effective conventional treatment in AOM, there were no significant differences between groups in the main outcome. Symptomatic improvement was quicker in the Homeopathy group, and there was a large difference in antibiotic requirements, favouring homeopathy. The most useful medicines prescribed and found effective were Pulsatilla nigricans, Mercurius solubilis, Silicea, Chamomilla, Lycopodium clavatum & Sulphur*	Medicines used in 85 % of patients were *Pulsatilla, Mercurius sol, Silicea, Chamomilla, Lycopodium* and *Sulphur*. Useful medicines and improvement status **Remedy No. cured** Arsenicum album 1/1 Calc. Carb 1/1 Chamomilla 4/4 Cina 1/1 Hepar sulph 1/1 Lycopodium 3/3 Merc Sol. 7/7 Pulsatilla 13/14 Silicea 6/6 Sulphur 1/2 **Symptom change**

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TABLE 12 (*continued*)

ID	1st Author	Primary outcome: 1)Symptom relief (severity and duration) [(n or mean (SD) unless otherwise reported)]	Primary outcome: 2)antibiotic use [(n or mean (SD) unless otherwise reported)]	Secondary outcome: 3)recurrence [(n or mean (SD) unless otherwise reported)]	Secondary outcome: 4)Hearing loss [(n or mean (SD) unless otherwise reported)]	Secondary outcome: 5) health service & medication use [(n or mean (SD) unless otherwise reported)]	Secondary outcome: 7) re-consultations [(n or mean (SD) unless otherwise reported)]	Secondary outcome: 8) Type, frequency and severity of adverse events and complications [(n or mean (SD) unless otherwise reported)]	Conclusion	NOTES
		[40:0], P = 0.32 *Irritable* I = 0.07 (0.34), [39:2]; C=NA, [39:0], P = 0.16 *Difficult to sleep* I = 0.05 (0.31); [37:1]; C=NA, [39:0], P = 0.32 *Playful* I = 0.05 (0.22), [40:2]; C=NA, [38:0], P = 0.16 *Eating less* I = 0.02 (0.15), [39:1]; C=NA, [40:0], P = 0.32 *Fever* I = 0.07 (0.34), [32:2]; C=NA, [38:0], P = 0.16 **Signs on Tympanic Membrane Examination, mean (sd)** *Colour at end*: I = 0.35 (0.48); C = 0.33 (0.47), P = 0.16 *Transparency at end*: I = 0.22 (0.42); C = 0.22 (0.42), P = 0.32 *Mobility at end*: I = 0.15 (0.36); C = 0.16 (0.38), P = 0.32 *Bulging at end*: I = 0.3 (0.46); C = 0.31 (0.47), P = 0.16								Reported P values unclear and same as Tympanic membrane examination **Tympanic membrane examination** Reported P values unclear and same as Symptom change
NON-INDIVIDUALISED HOMEOPATHY										
5	Arrighi et al., 2003 (translation)	**No. of episode of OMA after 180 days** **0 episodes:** I = 24/81(29.6 %): C = 15/76(19.7 %), P < 0.05	Not assessed	Not assessed	**Audiometry after 180 days** *No. with no improvement* I = 6/81(7.4 %): C = 12/76	**Adenoidectomy surgery** (after 1 yr) I = 3/81(3.7 %):C = 11/76(14.5 %)	Not assessed	Not assessed	*This study demonstrates the effectiviness of the homotoxicological protocol in the treatment of OME. The conventional therapies*	

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TABLE 12 (*continued*)

ID	1st Author	Primary outcome: 1)Symptom relief (severity and duration) [(n or mean (SD) unless otherwise reported)]	Primary outcome: 2)antibiotic use [(n or mean (SD) unless otherwise reported)]	Secondary outcome: 3)recurrence [(n or mean (SD) unless otherwise reported)]	Secondary outcome: 4)Hearing loss [(n or mean (SD) unless otherwise reported)]	Secondary outcome: 5) health service & medication use [(n or mean (SD) unless otherwise reported)]	Secondary outcome: 7) re-consultations [(n or mean (SD) unless otherwise reported)]	Secondary outcome: 8) Type, frequency and severity of adverse events and complications [(n or mean (SD) unless otherwise reported)]	Conclusion	NOTES
		No. with 1 to 5 episodes I = 54/81(66.7 %): C = 52/76 (68.4 %), NS **No. with > 5 episodes** I = 3/81(3.7 %): C = 9/76(11.9 %), P < 0.05 **MEE (otoscopy) after 90 days** No. with no reduction in EE I = 8/81 (9.9 %): C = 8/76 (10.5 %), NS >30 % EE I = 53/81(65.4 %): C = 51/76 (67.1 %), NS No.with normalized findings I = 20/81 (24.7 %): C = 17/76 (22.4 %), NS **MEE (otoscopy) after 180 days** *No. with no reduction in EE* I = 6/81(7.4 %): C = 12/76 (15.8 %) *No. >30 % reduction of EE* I = 46/81(56.7 %): C = 62/76(81.6 %) *No. with no EE* I = 29/81(35.8 %): C = 2/76 (2.6 %) **Tympanometry after 90 days** *No. with no improvement in hearing impairment*			(15.8 %) *No. with >30 % hearing function* I = 45/81 (55.5 %): C = 61/76(80.3 %) *No. with normalized findings* I = 30/81 (37.1 %): C = 3/76 (3.9 %)				*used produce mixed results and, at best, do not last.*	

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TABLE 12 (*continued*)

ID	1st Author	Primary outcome: 1)Symptom relief (severity and duration) [(n or mean (SD) unless otherwise reported)]	Primary outcome: 2)antibiotic use [(n or mean (SD) unless otherwise reported)]	Secondary outcome: 3)recurrence [(n or mean (SD) unless otherwise reported)]	Secondary outcome: 4)Hearing loss [(n or mean (SD) unless otherwise reported)]	Secondary outcome: 5) health service & medication use [(n or mean (SD) unless otherwise reported)]	Secondary outcome: 7) re-consultations [(n or mean (SD) unless otherwise reported)]	Secondary outcome: 8) Type, frequency and severity of adverse events and complications [(n or mean (SD) unless otherwise reported)]	Conclusion	NOTES
		I = 7/81(9 %): C = 5/76(7 %) *No. with >30 % improvement* I = 49/81(60 %): C = 48/76 (63 %) *No. with normalized findings* I = 25/81(31 %): C = 23/76 (31 %) **Tympanometry after 180 days** *No. with no improvement* I = 5/81(6 %): C = 10/76 (13 %) *No. with improvement >30 % hearing function* I = 44/81(54 %): C = 62/76(82 %) *No. with normalized findings* I = 32/81(40 %): C = 4/76 (53 %)								
6	Pedrero-Escalas et al., 2016	**Recovery (% Effectiveness)** I = 61.9: C = 56.8 were cured (PNO went from negative in the 1st visit to positive in the 3rd visit). P > 0.05 **Evolution of tympanometry from 1st to 3rd visit** There was no association between the administered treatment and the	Not assessed	**Recurrence of OME (%)** I = 4.8:C = 11.4 suffered a recurrence (positive PNO in the 2nd visit changed to negative in the 3rd visit), P = 0.543	Not assessed	Not assessed	Not assessed	Withdrawal from study due to AEs (not linked to treatments) I = 1:C = 4 **Adverse events in 3 months of treatment** AEs were distributed except in the case of URIs. *GI* I = 5:C = 3, P = 0.475 *URTI* I = 3:C =	*The homeopathic scheme used as adjuvant treatment cannot be claimed to be an effective treatment in children with OME.*	

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TABLE 12 (*continued*)

ID	1st Author	Primary outcome: 1)Symptom relief (severity and duration) [(n or mean (SD) unless otherwise reported)]	Primary outcome: 2)antibiotic use [(n or mean (SD) unless otherwise reported)]	Secondary outcome: 3)recurrence [(n or mean (SD) unless otherwise reported)]	Secondary outcome: 4)Hearing loss [(n or mean (SD) unless otherwise reported)]	Secondary outcome: 5) health service & medication use [(n or mean (SD) unless otherwise reported)]	Secondary outcome: 7) re-consultations [(n or mean (SD) unless otherwise reported)]	Secondary outcome: 8) Type, frequency and severity of adverse events and complications [(n or mean (SD) unless otherwise reported)]	Conclusion	NOTES
		change seen in tympanometry after 3 months of therapy. **Ontological complications** **AOM (N of episodes)** I = 10:C = 14 Otorrhea with tympanic perforation I = 2:C = 1 Mastoiditis I = 0:C = 0						13, p = 0.009 *LRTI I* = 2:C = 1, P = 1.0 *UTI I* = 0:C = 1,P = 1.0 *Fever without focus* I = 1:C = 0, P = 0.483 *Agitation* I = 0:C = 1,P = 1.0 *Vomits* I = 0:C = 1, P = 1.0		
7	Taylor & Jacobs 2011	**Ear treatment Group-5 scores, mean** Assessment 1 (N = 90) I = 14.2; C = 16.5, P = 0.19 Assessment 2 (N = 75) I = 10.5; C = 14.1, P = 0.04 Assessment 3 (N = 86) I = 6.1; C = 10.8 P = 0.003 Assessment 4 (N = 76) I = 6.7; C = 8.7, P = 0.35 Assessment 5 (N = 79) I = 6.1: C = 7.0, P = 0.91 Assessment 6 (N = 76) I = 5.2: C = 7.3, P = 0.46 Assessment 7 (N =	Follow-up data were collected on 28 patients whose provider had recommended a delayed antibiotic approach, including 14 in each treatment group. Prescriptions were filled for I:1/14 (7.1 %) C: 5/14 (36.5 %) (P = 0.17)	Not assessed	Not assessed	Use of symptomatic medications (including acetaminophen, ibuprofen and topical benzocaine) decreased in both treatment groups during the 5 days after the index visit. Overall, 60.6 % of study children received one or more doses of these medications on day 1; this dropped to 9.6 % by day 5. The use of these medications was significantly lower in children receiving ear drops than in those randomised to standard therapy alone on day 3 (9.1 % and 28.0 %, respectively, P = 0.02); no other	Not assessed	**Adverse events linked to treatment n (%)** *Vomiting* I = 5 (11 %); C = 10 (20 %) *Rash* I = 3 (7 %); C = 5 (10 %) *Diarrhoea* I = 3 (7 %); C = 12 (24 %) *'Hyper' behavior* I = 3 (7 %); C = 11 (22 %) Headache I = 7 (16 %); C = 6 (12 %) Lethargy I = 13 (30 %); C = 15 (30 %) Other symptom I = 19 (43 %); C = 22 (44.%)	*This study suggests that homeopathic ear drops were moderately effective in treating otalgia in children with AOM and may be most effective in the early period after a diagnosis of AOM. Pediatricians and other primary health care providers should consider homeopathic ear drops a useful adjunct to standard therapy*	

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TABLE 12 (*continued*)

ID	1st Author	Primary outcome: 1)Symptom relief (severity and duration) [(n or mean (SD) unless otherwise reported)]	Primary outcome: 2)antibiotic use [(n or mean (SD) unless otherwise reported)]	Secondary outcome: 3)recurrence [(n or mean (SD) unless otherwise reported)]	Secondary outcome: 4)Hearing loss [(n or mean (SD) unless otherwise reported)]	Secondary outcome: 5) health service & medication use [(n or mean (SD) unless otherwise reported)]	Secondary outcome: 7) re-consultations [(n or mean (SD) unless otherwise reported)]	Secondary outcome: 8) Type, frequency and severity of adverse events and complications [(n or mean (SD) unless otherwise reported)]	Conclusion	NOTES
		78) I = 3.8; C = 5.8, P = 0.25 Assessment 8 (N = 74) I = 3.3; C = 3.7, P = 0.83 Assessment 9 (N = 77) I = 2.8; C = 3.7, P = 0.24 Assessment 10 (N = 73) I = 2.3; C = 3.4, P = 0.36 **Improvement in AOM symptoms** after 70–82 % of doses of ear drops, but only 48–55 % of the time when the drops were given for non-AOM symptoms. Parents of 113/119 eligible study patients were contacted at approximately 12–15 days after enrollment (95.0 %). **Functional status,** based on FSIIR scores, was similar between groups. (mean scores I = 81.4:C = 81.5,P = 0.97. One or more return visits to a health care provider was noted by 23.2 % of parents of a child receiving ear drops				statistically significant differences were noted				

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TABLE 12 (*continued*)

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		and 14.0 % of those whose child received standard therapy alone (P = 0.21)								
8	Taylor & Jacobs 2014	**ETG -5 BL scores** mean (sd) I = 15.2 (6.4) C = 15.5 (7.2) ETG-5 data were collected from (I = 84 C = 91) parents at day 5–7 FU, mean (sd) I = 4.6(5.9):C = 3.3 (4.4), P = 0.14 By the 12- to 15-day FU, ETG-5 scores were 0 in 146/200 children whose parents completed the questionnaire (73 %); there were no differences in ETG-5 scores mean (sd) after adjusting for baseline ETG-5. I = 2.0 (4.5) C = 2.0 (3.8), P = 0.87 **"Other Symptoms" reported by parents in logbooks -day 15 (total n=150/206 returned)** *Vomit* I = 4/72 (6 %): C = 5/78 (6 %), P = 0.83 *Rash* I = 3/72 (4 %):C = 11/78 (14 %), P = 0.03	**Use of antibiotics within 15 days of diagnosis** *Filled original antibiotic prescription* I = 28/104(27 %): C = 42/102 (41 %)OR = 0.53 (95%CI, 0.29, 0.95), P = 0.032 *Filled original prescription or received another antibiotic prescription* I = 31/104 (29.8 %): C = 45/102 (44.1 %), OR = 0.54, (95%CI, 0.30, 0.95), P = 0.034 *Filled antibiotic prescription by day 7 after diagnosis* I = 23/89 (25.8 %): C = 37/96 (38.5 %), OR = 0.55, (95%CI, 0.29, 1.03),P = 0.062	Not assessed	Not assessed	ibuprofen % I = 20.8 % C = 37.2 %, P = 0.027 antipyrine/ benzocaine ear drops I = 0 % C= (10.3 %, P = 0.007 acetaminophen I = 44.4 % C = 51.3 %, P = 0.40.	Not assessed	**Adverse events** At the 5- to 7-day and 12- to 15-day telephone follow-up, no serious adverse events were reported in either group.	*Homeopathic ear drops may be effective in reducing the use of antibiotics in children with AOM managed with a delayed antibiotic approach.*	

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TABLE 12 (*continued*)

ID	1st Author	Primary outcome: 1)Symptom relief (severity and duration) [(n or mean (SD) unless otherwise reported)]	Primary outcome: 2)antibiotic use [(n or mean (SD) unless otherwise reported)]	Secondary outcome: 3)recurrence [(n or mean (SD) unless otherwise reported)]	Secondary outcome: 4)Hearing loss [(n or mean (SD) unless otherwise reported)]	Secondary outcome: 5) health service & medication use [(n or mean (SD) unless otherwise reported)]	Secondary outcome: 7) re-consultations [(n or mean (SD) unless otherwise reported)]	Secondary outcome: 8) Type, frequency and severity of adverse events and complications [(n or mean (SD) unless otherwise reported)]	Conclusion	NOTES
		Diarrhoea I = 5/72 (7 %):C = 6/78 (8 %), P = 0.86 *"Hyper" behavior* I = 6/72 (8 %): C = 10/78 (13 %), P = 0.37 *Headache* I = 9/72 (13 %): C = 10/78 (13 %), P = 0.95 *Lethargy* I=15/72 (21 %): C = 23/78 (27 %), p = 0.22 *Any additional symptom* I = 16/72 (22 %): C = 23/78 (30 %), p = 0.31 AOM Faces Scale scores, mean Assessment 1 (N = 91) I = 4.0; C = 4.3 Assessment 2 (N = 92) I = 3.4; C = 3.6 Assessment 3 (N = 89) I = 2.7; C = 3.0 Assessment 4 (N = 90) I = 2.5; C = 2.8 Assessment 5 (N = 89) I = 2.4; C = 2.4 Assessment 6 (N = 87) I = 2.1; C-2.3 Assessment 7 (N = 87) I = 1.9; C = 2.1 Assessment 8 (N =								

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ID	1st Author	Primary outcome: 1)Symptom relief (severity and duration) [(n or mean (SD) unless otherwise reported)]	Primary outcome: 2)antibiotic use [(n or mean (SD) unless otherwise reported)]	Secondary outcome: 3)recurrence [(n or mean (SD) unless otherwise reported)]	Secondary outcome: 4)Hearing loss [(n or mean (SD) unless otherwise reported)]	Secondary outcome: 5) health service & medication use [(n or mean (SD) unless otherwise reported)]	Secondary outcome: 7) re-consultations [(n or mean (SD) unless otherwise reported)]	Secondary outcome: 8) Type, frequency and severity of adverse events and complications [(n or mean (SD) unless otherwise reported)]	Conclusion	NOTES
		82) I = 1.7; C = 1.9 Assessment 9 (N = 84) I = 1.7; C = 1.7 Assessment 10 (N = 79) I = 1.5; C = 1.6								
8	Wustrow et al., 2004	**Time to recovery (days) within 14 days of start** I = 5.31 (2.36): C = 5.07 (2.22), p = 0.34 **Earache (SPID) pain resolution (10 step score)** Slightly better with conventional treatment I = −5.2 (2.5): C = −5.8 (2.4) **(**significant after adjusted for baseline otitis symptoms and otoscopic findings) **BL Otoscopic score** I = 5.6 (2.2) C = 6.6 (2.1) **BL Pain score** I = 5.5 (2.3) C = 6.6(2.0) **BL Clinical symptoms score** I = 5.3 (2.4) C = 5.6 (2.0)	**Antibiotics usage (%)** C group took more antibiotics than I group (I = 14.4 %:C = 80.5 %) Antibiotics I = 27/188 (14 %):C = 153/190 (81 %), P < 0.001	Not assessed	Not assessed	**Analgesic prescriptions (%)** C group took more analgesics than I group (I = 53.2 %: C = 67 %) *Otovowen* I = 187/188 (99.5 %): C = 2/190 (1.1 %), P < 0.000 Analgesics I = 100/188 (53 %): C = 127/190 (67 %), P = 0.007 Mucolytics I = 81/188 (43 %): C = 70/190 (37 %), P = 0.215 Decongestant nose drops I = 129/188 (68.6 %): C = 130/190 (68.4 %), P = 0.967	Not assessed	**Adverse drug reaction** 1 child in C group -exanthema after amoxicillin (switched and resolved) **Global assessment of tolerability** Parents assessment (95% CI: 0.42 [0.36–0.48], p = 0.002) and doctors assessment (95% CI: 0.41 [0.35–0.47], P < 0.001) judged naturopathy as superior in tolerability.	*In primary care management of uncomplicated acute otitis media in child hood, an alternative treatment strategy based on the natural medicine, Otovowen may substantially reduce the use of antibiotics without disadvantage to the clinical outcome.*	Difference at BL – C group had more severe otoscopy findings and ear pain than I group 2 patients in C group took *Otovowen*, 1 patient in I group did not take *Otovowen*

KEY: C = control; I = intervention; ITT = intention-to-treat; LOCF = last observation carried forward; MEE = middle ear effusion; NA = not applicable; No = number; OR = odds ratio, OME = otitis media with effusion; PNO = pneumatic otoscopy, SD = standard deviation; SPID = sum of pain intensity differences.

* Reported as 39.4 %.

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