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Outcome measures for use in trials of paediatric otorrhoea: A systematic review

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ABSTRACT

Introduction: Paediatric otorrhoea (PO) describes a middle ear infection that results in a perforation of the tympanic membrane and ear discharge, in children and young people (CYP). Prolonged infection may be associated with hearing loss and developmental delay. The current management of paediatric otorrhoea is variable, including non-invasive treatments (conservative, oral antibiotics, topical antibiotics) and surgery, reflecting the lack of a sufficiently strong evidence base. Outcome reporting is fundamental to producing reliable and meaningful evidence to inform best practice.

Objectives: Primary objective: to determine which outcome measures are currently used to evaluate treatment success in studies of non-surgical treatments for paediatric otorrhoea. Secondary objectives: to identify outcome measurement instruments used in the literature and assess their applicability for use in clinical trials of PO.

Methods: This systematic review was registered with PROSPERO (CRD42023407976). Database searches of EMBASE, MEDLINE and Cochrane was performed on June 6, 2023, covering from Jan 1995 to May 2023. Randomised controlled trials or study protocols involving CYP with PO were included following PRISMA guidelines. Risk of bias was assessed with Cochrane's tool.

Results: Of the 377 papers identified, six were included in the systematic review. The primary outcome of five of the studies related to otorrhoea cessation; both time to cessation and proportion recovered at various time points were used as measures. Two measurement instruments were identified: Otitis Media-6 Questionnaire and the Institute for Medical Technology Assessment Productivity Cost Questionnaire. Both were shown to be applicable measurement instruments when used in clinical trials of PO.

Conclusions: To promote homogeneity and facilitate meaningful comparison and combination of studies, we propose that time to cessation of otorrhoea from onset of otorrhoea should be used as the primary outcome in future studies. Further research is needed to establish if this is the most important outcome to children and their caregivers.

1. Introduction

Paediatric otorrhoea (PO) results from a middle ear infection with a perforation of the tympanic membrane in children and young people (CYP). This condition is called acute otitis media with discharge; prolonged infection is termed chronic suppurative otitis media or chronic otitis media mucosal type [1].

In clinical practice there is heterogenous use of the definitions and variable time frames are used to define acute or chronic otorrhoea. The authors therefore prefer to use PO to encompass both acute and chronic mucosal infections of the middle ear with a perforation of the tympanic membrane.

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It is estimated that PO affects 50 million CYP per year globally [2,3]. PO may result in hearing loss and in turn developmental delay [1]. The World Health Organization (WHO) estimates it is the most common cause of hearing loss worldwide [1]. Intracranial and extracranial spread of the infection can result in morbidity or mortality in CYP. It is therefore essential that patients receive appropriate and timely treatment. Currently, literature investigating optimal management for PO is limited. A Cochrane collection of systematic reviews demonstrated that current evidence is of poor quality [4]. High quality randomised controlled trials (RCT) which will inform patient management are required.

The aim of this study was to review and collate outcome measures and measurement instruments used in published randomised controlled trials of PO, to help standardise results in future studies to allow comparison.

2. Materials and methods

2.1. Search strategy and selection criteria

The study was conducted using the PRISMA guidelines [5]. The protocol was registered on PROSPERO (CRD42023407976). Database searches of EMBASE, MEDLINE and Cochrane were performed on June 6, 2023 for studies published in English between Jan 1995 to May 2023. Study inclusion criteria are outlined in Table 1. Manuscripts were exported onto the Eppi reviewer software where duplicates were removed. Studies were firstly reviewed by title and abstract by two independent reviewers (EH and JD). A full text review was performed for studies which met the inclusion criteria on title and abstract review. Studies were included if they pass the full text review stage. If disagreements could not be resolved between the two reviewers, then a third reviewer (IAB) was used to make a final decision. Data from included studies were extracted into an Excel spreadsheet. Data domains included: source of data, study setting, participants, intervention, outcome measure/s and measurement method.

2.2. Data synthesis

The outcome measure and measurement instruments were extracted and tabulated. Outcome measures were defined as "a method of measuring health intervention" (e.g. time to pain cessation or quality of life score). Measurement instruments were defined as "a tool required to calculate or determine the outcome measure" (e.g. quality of life questionnaire).

Acute otorrhoea is defined as <2 weeks and chronic otorrhoea is defined as ≥2 weeks according to WHO guidelines [1].

Measurement instruments were graded in eight different domains (reliability, reproducibility, validity, responsiveness, precision, interpretability, acceptability, feasibility) described by Fitzpatrick et al. to help assess the value of each outcome measurement tool [6]. Two reviewers (EH and JD) agreed an appropriate grade in each domain. If agreement couldn't be made, a third reviewer (IAB) was used and the majority opinion was taken. Each domain was graded as low, moderate or high, in relation to the measurement tool's applicability to PO studies.

2.3. Risk of bias assessment

Study quality for randomised control trials was assessed with the Cochrane Collaboration's tool for assessing risk of bias [7]. The risk of bias was classified as 'low', 'high' or 'unclear' for each of the six measured domains (random sequence generation, allocation concealment, blinding of participants and researchers, blinding of outcome assessment, incomplete outcome data, selective reporting, other bias). This was graded by two reviewers (EH and JD); disagreement was resolved by a third independent reviewer (IAB).

3. Results

The searches identified 377 publications, of which, six were included in the final review (Fig. 1) [8–13]. Two studies were RCT protocols which included patients with acute otorrhoea (<2 weeks) and four completed RCTs which included patients with chronic otorrhoea (≥2 weeks) (Table 2). Age range for inclusion varied in all studies. All studies included an antibiotic treatment arm.

3.1. Outcome measures

Of the primary outcome measures used, cessation of otorrhoea was used in five studies. Timing of assessment from treatment varied from 14 days to 6 weeks. Pain and fever outcomes were used as primary outcome measures for the two RCT protocols. Outcome measures included as secondary objectives included disease, treatment and productivity domains.

3.2. Outcome measurement instruments

The most frequently used outcome measure instrument was the Otitis Media-6 (OM-6) Questionnaire [14] which was used in two studies [8,9]. The OM-6 questionnaire is disease specific and has been translated and validated in multiple languages [15]. Both RCT protocols intended to use the OM-6 questionnaire at 2 weeks and 3 months post treatment [8,9]. The Institute for Medical Technology Assessment (iMTA) Productivity Cost Questionnaire (iPCQ) is a generic productivity questionnaire used by Hullegie et al. [8,16]. Assessed against the domains outlined by Fitzpatrick et al. both measurement instruments scored moderate to high in all areas (Table 3).

3.3. Risk of bias assessment

Risk of bias was variable amongst all 6 studies (Fig. 2). One study had a low risk of bias through all domains [11].

4. Discussion

Our results demonstrate there are few randomised controlled studies investigating non-surgical treatment of PO worldwide. Only four RCTs were identified all of which study the management of chronic otorrhoea. The two study protocols published investigate patients with acute otorrhoea. Overall, it appears that cessation of otorrhoea is the most frequently used primary outcome measure. Both time to cessation and proportion recovered at various time points (range: 2–6 weeks) were used. High quality data exists for treatment of children with tympanostomy tube (grommets, ventilation tubes) infections. Children treated with topical drops, on average, had otorrhoea cessation at day 4 and those patients with no treatment had otorrhoea cessation at day 12 [17]. Therefore, a fixed time point of otorrhoea cessation at 2 weeks may not identify a true difference between treatment arms. The authors would therefore suggest using time to cessation of otorrhoea.

There is variation in the secondary outcome measures and assessment time points used throughout all studies. Both RCT protocols include more numerous secondary outcome measures compared with the published RCTs which include patient signs and symptoms, clinical findings, patient-reported outcome measures (PROMs), and microbiological analysis of otorrhoea. The published RCTs investigating chronic otorrhoea have few secondary outcomes; the most frequent is assessment of hearing thresholds which is more clinically relevant to this patient population due to the higher risk of hearing impairment.

Patient-reported outcomes are becoming increasingly popular in RCTs, as they provide patient centred results which may inform clinical practice [18]. Within the papers identified in this study, symptoms such as pain and fever were used in two studies as primary outcome measures [8,9]. Pain was either graded on a 0–6 Likert scale at day 3 [8] or

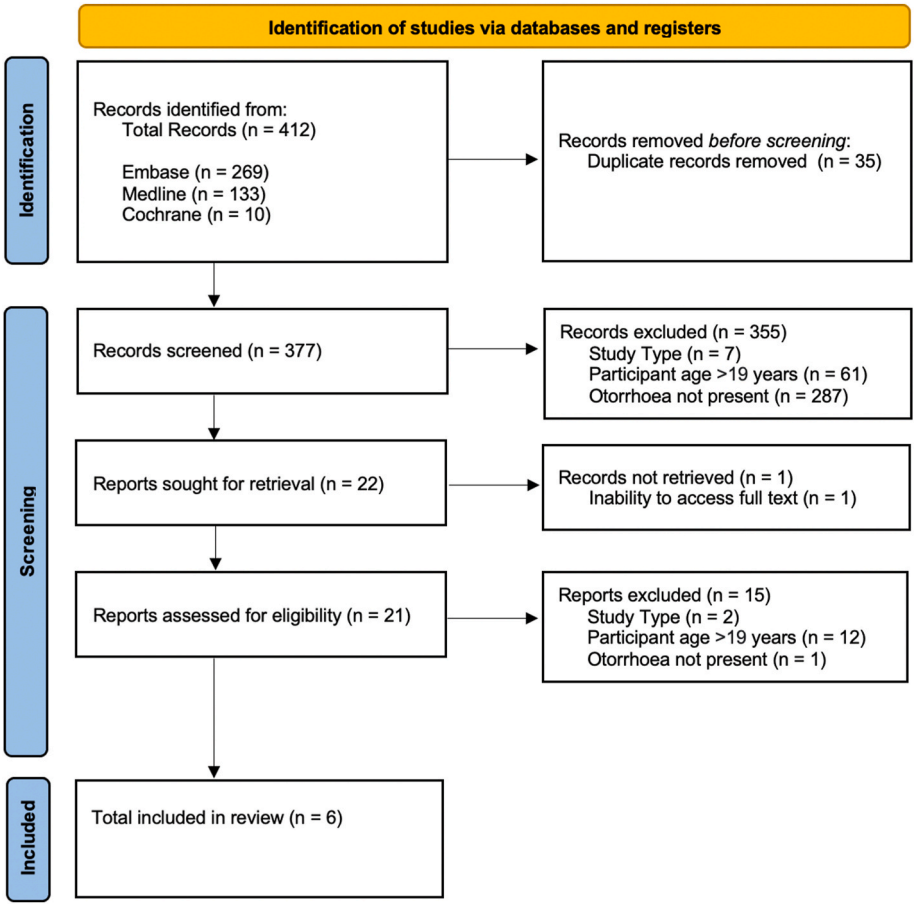

Fig. 1. PRISMA flow diagram of included studies.

Table 1
PICOS table of study inclusion characteristics.

Domain	Characteristics
Population	CYP aged 19 years and younger with otorrhoea. This age cut off was chosen because children in Kenya attend secondary school up to 19 years of age. Otorrhoea is discharge from the ear canal which can be classified into: acute otitis media with discharge (AOMd), chronic otitis media (COM), and chronic suppurative otitis media (CSOM).
Intervention	Patients treated with non-surgical management
Comparators	None
Outcomes	Primary and secondary outcome measures used
Study Designs	Randomised controlled trials (RCT) or trial protocols

reported as time to resolution [9]. Fever was also recorded when it resolved. Pain and fever are not commonly associated with non-complicated middle ear mucosal infections which are discharging [1]. It may be, therefore, preferable to use pain and fever as secondary outcome measures in future studies.

A variety of secondary outcome measures were assessed within the included studies and protocols. The outcome measures can be categorised as: patient-reported symptom scores, disease-specific patient signs, treatment-related, antimicrobial resistance and productivity domains. Future studies should look to include a range of secondary outcome measures from each domain described but ensure that the number of outcome measures collected is feasible so not to overburden the participant.

Within the paediatric otolaryngology population, there is a drive to use PROMs in research to better reflect the patient's experience [19]. The OM-6 questionnaire was used in two study protocols. It is a six-item measurement instrument which has been validated in children with otitis media (acute otitis media and otitis media with effusion) [20–22]. It appears to demonstrate global quality of life changes but cannot differentiate severity of disease [22]. Assessment of the OM-6 questionnaire in this study determined it was moderately-to highly-applicable for use in PO studies.

The iMTA Productivity Cost Questionnaire was used in a single study and is a generic productivity questionnaire [9,10]. It involves 12 questions which focus on impact on work as a direct result of illness, rather than absence from work due to parental caring responsibilities. It scored highly when assessed by the authors due to its general characteristics, but it's not able to assess parental absence from work due to child illness.

The use of the term PO to encompass both acute and chronic middle ear infections is used to reflect real world practice within a primary care setting where patients are more frequently managed. The pathway from acute to chronic middle ear disease is not fully understood. It is thought middle ear mucosal hyperplasia and polymicrobial biofilms contribute to the development of chronic otorrhoea through a tympanic membrane perforation [23]. There are limitations when combining both disease processes, acute and chronic middle ear infections, which have different causative organisms, disease courses, and management strategies. Once the research in this field grows it may be possible to analyse these disease processes separately.

A key limitation of this study include that only six studies were included and two of these were protocols. There is lacking high quality evidence in this field. The protocols were recently published; it is unknown if it was feasible to perform the trial. Variable risk of bias was identified in all but one of the studies included.

Table 2
Summary of trials and protocols.

Author	Study Type	Location	Pathology	Sample Size (Treatment arm)	Age	Primary Outcome Measures	Secondary Outcome Measures
Hullegie (2021)	Protocol	Netherlands	Otorrhoea ≤7 days	350 (175 Hydrocortisone bacitracin colistin drops: 175 oral amoxicillin)	6 months −12 years	• Proportion of children without ear pain (ear pain score 0 on the 0–6 Likert scale) at day 3 • Fever at day 3	• Proportion of children with at most mild ear pain (ear pain score less than 3 on the 0–6 Likert Scale) at day 3 • Mean ear pain score over days 0–3, number of days with ear pain (ear pain score 1 or higher on the 0–6 Likert scale) • Mean body temperature over days 0–3 • Number of days with fever (body temperature of 38.0 °C or higher) during the first 2 weeks • Proportion of children with parent-reported ear discharge at day 3 • Number of days with parent-reported ear discharge at day 3 and during the first 2 weeks • Proportion of children with otoscopically confirmed ear discharge at 2 weeks • Time to resolution of total symptoms (time to all of pain, fever, discharge, being unwell, sleep disturbance, and distress/crying being rated 0 or 1 on the Likert scale) • MEE and proportion of children with otoscopically confirmed eardrum perforation at 2 weeks • OM-specific Quality of Life at baseline, 2 weeks and 3 months; antibiotic consumption during the first 2 weeks and at 3 months • Number of AOM recurrences at 3 months • Number of adverse events during the first 2 weeks • Costs and cost-effectiveness at 2 weeks and 3 months • Prevalence of viruses and bacteria in otorrhoea and nasopharynx samples at baseline and 2 weeks • Antimicrobial susceptibility profiling of the bacteria and the impact of the treatment regimens on antimicrobial • Impact of the treatment regimens on antimicrobial resistance genes in the human gut • Microbiome profile of nasopharynx at baseline and 2 weeks • Parental productivity losses
Curtis (2020)	Protocol	UK	Otorrhoea ≤7 days	399 (133: ciprofloxacin drops: 133 delayed amoxicillin: 133 immediate amoxicillin)	1–16 years	• Time to resolution of the following symptoms: pain, fever, being unwell, sleep disturbance, otorrhoea and episodes of distress	• Duration of 'moderately bad or worse' symptoms (pain, fever, being unwell, sleep disturbance, otorrhoea; episodes of distress/crying • Appetite and interference with normal activities up to 14 days • Antibiotic and analgesic use • Adverse events – diarrhoea, rash, vomiting, serious complications • Treatment adherence • Parent/legal guardian satisfaction with treatment • NHS resource use at 14 days • Repeat AOM and AOMd episodes, serious complications and the OM6 hearing questionnaire at 3 months • Qualitative evaluation of recruitment, medication

(*continued on next page*)

Table 2 (*continued*)

Author	Study Type	Location	Pathology	Sample Size (Treatment arm)	Age	Primary Outcome Measures	Secondary Outcome Measures
							satisfaction, adherence and follow-up • Analysis of stool sample to assess burden of resistance
Boonacker (2008)	RCT	Netherlands	Otorrhoea ≥3 months	98 (47 Trimethoprim-sulfamethoxazole: 51 placebo)	1–12 years	• Prescence of otorrhoea at 6 weeks	• Cost-effectiveness analysis
Macfayden (2005)	RCT	Kenya	Otorrhoea ≥2 weeks	427 (216 ciprofloxacin: 211 boric acid)	4–19 years	• Resolution of otorrhoea at 2 weeks	• Healing of tympanic membrane • Change in hearing threshold
Somekh (2000)	RCT	Israel	Otorrhoea ≥6 weeks	30 (15 ceftazidime: 15 aztreonam)	6 months - 15 years	• Cessation of otorrhoea at 14 days	• Mean time to otorrhoea cessation • Recurrence within 3 months
Smith (1996)	RCT	Kenya	Otorrhoea ≥2 weeks	524 (201 dry mopping: 221 dry mopping, sofradex drops and oral amoxicillin: 102 no treatment)	5–17 years	• Cessation of otorrhoea at two successive 4 weekly visits • Proportion whose ears healed (complete repair of the tympanic membrane perforation at any visit) at 8, 12, and 16 weeks	• Hearing thresholds

*MEE = middle ear effusion, OM = otitis media, AOM = acute otitis media, AOMd = acute otitis media with discharge.

Table 3
Applicability of measurement instruments for paediatric otorrhoea by domain.

Measurement Instrument	Domain							
	Reliability	Reproducibility	Validity	Responsiveness	Precision	Interpretability	Acceptability	Feasibility
OM-6	High	High	High	High	High	Moderate	High	High
iPCQ	High	Moderate	High	n/a	Moderate	High	High	High

•OM-6 = Otitis Media-6 Questionnaire, iPCQ = iMTA Productivity Cost Questionnaire.

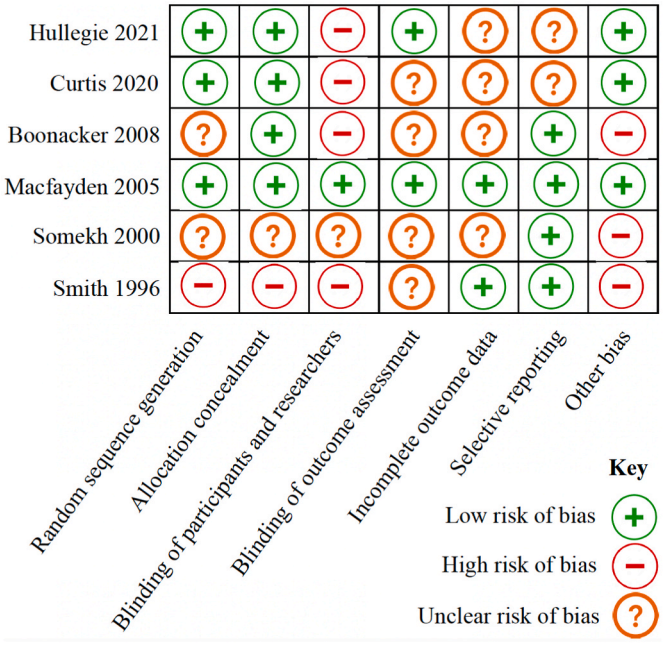

Fig. 2. Risk of bias assessment for included studies.

5. Conclusions

To promote homogeneity and facilitate meaningful comparison we propose that time to cessation of otorrhoea from onset of otorrhoea should be used as the primary outcome in future studies. Further research is needed to establish the most important outcome measures for children and caregivers. Of the two measurement instruments identified the OM-6 questionnaire is probably best place to be used to identify secondary outcomes.

CRediT authorship contribution statement

Elliot Heward: Conceptualization, Formal analysis, Methodology, Software, Writing – original draft, Writing – review & editing. **James Dempsey:** Formal analysis, Writing – original draft, Writing – review & editing. **John Molloy:** Conceptualization, Writing – review & editing. **Rachel Isba:** Conceptualization, Writing – review & editing. **Judith Lunn:** Conceptualization, Writing – review & editing. **Darren M. Ashcroft:** Conceptualization, Writing – review & editing. **Alastair D. Hay:** Conceptualization, Writing – review & editing. **Jaya R. Nichani:** Conceptualization, Writing – review & editing. **Iain A. Bruce:** Conceptualization, Supervision, Writing – original draft, Writing – review & editing.

Declaration of competing interest

No completing interests declared for all authors.

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