Immediate oral versus immediate topical versus delayed oral antibiotics for children with acute otitis media with discharge: the REST three-arm non-inferiority electronic platform-supported RCT

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Foundation Trust and University College London Hearing Theme (London, UK) and is the National Specialty Lead of the NIHR Clinical Research Network Ear, Nose and Throat (ENT); in these roles, Anne Schilder advises companies in the hearing field on the design and delivery of clinical trials. Her evidENT research team at the University College London Ear Institute (London, UK) receives support from various funders, including NIHR, the European Union (EU) Horizon 2020 (Brussels, Belgium) and the Wellcome Trust (London, UK). Roderick Venekamp reports grants from the Netherlands Organisation for Health Research and Development (ZonMw; The Hague, the Netherlands) during the conduct of the study.

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Scientific summary

The REST three-arm non-inferiority RCT

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Scientific summary

Background

Clinical

Acute otitis media (AOM) is a painful infection of the middle ear that is commonly seen in children. Sometimes the eardrum spontaneously bursts, discharging visible pus into the outer ear [acute otitis media with discharge (AOMd)]. Current evidence suggests that most children with AOMd are treated with 'immediate' (i.e. to be started the same or next day) oral antibiotics.

However, there is uncertainty regarding whether or not oral antibiotics could be delayed ('wait and see with a standby prescription') and whether or not immediate topical (ear drop) antibiotics could be as effective as immediate oral antibiotics. Both options offer the advantages of reducing exposure to systemic antibiotics, reducing the risks of side effects and reducing the selective pressure that systemic antibiotics place on antimicrobial resistance.

Electronic trial platform supported recruitment

A review of AOM incidence suggested that the average general practice manages 76 children with AOM per annum, of whom around 15% have AOMd, equating to 11 AOMd presentations per annum. Our sample size requirement (399 children) necessitated working with 175 general practices, recruiting over two winters and one summer. We determined that an electronic trial platform to prompt and support recruitment would be necessary to maintain trial activity over this number of sites.

Objectives

The main objective was to investigate the clinical effectiveness and economic impact of immediate topical or delayed oral antibiotics, compared with immediate oral antibiotics, for symptom duration in children presenting to primary care with AOMd.

The secondary objectives were to:

- estimate the short-term cost implications of immediate topical or delayed oral antibiotics, compared with immediate oral antibiotics, from the perspective of the NHS
- compare the effects on the duration of 'moderately bad or worse' symptoms, parent satisfaction with treatment and adverse events
- compare hearing loss and AOM/AOMd recurrence rates at 3 months
- understand parent and clinician views of AOMd trial participation and adherence to and satisfaction with allocated treatment
- evaluate the relative antimicrobial resistance impact of immediate topical, delayed oral and immediate oral antibiotics.

Methods

Design

This was a pragmatic, three-arm, individually randomised (stratified by age < 2 vs. ≥ 2 years), non-inferiority, open-label trial, with economic and qualitative evaluations. Participant identification and data collection were supported by 'TRANSFoRm' (Translational Research and Patient Safety in Europe), an electronic trial platform integrated into the electronic health record (EHR) system.

Patient eligibility

Children whose parents or legal guardians (from here on 'parents') were seeking primary medical care for unilateral otorrhoea as the presenting symptom of acute (≤ 7 days) AOM.

Included

- Aged ≥ 12 months to < 16 years.
- Presenting with recent-onset (≤ 7 days) unilateral AOM with recent-onset (≤ 7 days) otorrhoea, currently visible or seen by parent within the last 24 hours.
- Attending with parent legally able to give consent.
- Parent willing and able to administer ear drops.
- Parent willing, able and available to complete the daily Symptom and Recovery Questionnaire (SRQ) and receive regular telephone calls from the study team.

Excluded

- Symptoms or signs suggestive of bilateral AOM or AOMd.
- Symptoms or signs suggestive of serious illness and/or complications (e.g. mastoiditis and/or requires immediate hospitalisation).
- Requiring immediate oral antibiotics.
- Child at high risk of serious complications because of significant immunosuppression; heart, lung, renal, liver or neuromuscular disease comorbidities; trisomy 21; cystic fibrosis; or craniofacial malformation, such as cleft palate.
- Grommet tube in situ in the otorrhoea ear.
- Currently on oral or topical antibiotics.
- Allergy to ciprofloxacin.
- Allergy to penicillin (or anaphylactic reaction to another beta-lactam agent) and allergy to the suggested alternative, clarithromycin.
- Child had taken part in any research involving medicines within the previous 90 days.
- Child already participated in the Runny Ear STudy (REST).

Randomisation and concealment

Following eligibility confirmation and consent, concealed randomisation, stratified by age (< 2 and ≥ 2 years), was conducted using the TRANSFoRm platform.

Interventions

Intervention 1

Four drops of immediate ciprofloxacin (0.3%) ear drop solution were given three times per day for 7 days, with an advice sheet on how to administer the ear drops, the importance of completing the course and symptom management.

Intervention 2

Delayed dose-by-age oral amoxicillin suspension was given three times per day (clarithromycin, or another suitable oral antibiotic chosen by the patient's general practitioner, was given if the child was allergic to penicillin) for 7 days, with an advice sheet that included information on standard, structured delaying advice; the importance of completing the course; and symptom management.

Comparator

Immediate dose-by-age oral amoxicillin (clarithromycin, or another suitable oral antibiotic chosen by the patient's general practitioner, was given if the child was allergic to penicillin) was given three times per day for 7 days, with an advice sheet that included information regarding the importance of completing the course and symptom management.

Outcomes

Primary outcome

The primary outcome was the time to resolution of all pain, fever, being unwell, sleep disturbance, otorrhoea and episodes of distress/crying (i.e. these symptoms were rated by parents as 'no problem' or a 'very slight problem', without the need for analgesia, using a validated self-report scale known to be sensitive to change). Parents were asked to complete the SRQ in the evening of each day as a record of the child's overall experience during the previous 24 hours.

Secondary outcomes

- Duration of 'moderately bad or worse' symptoms (i.e. pain, fever, being unwell, sleep disturbance, otorrhoea, episodes of distress/crying).
- Adverse events, defined as new or worsening symptoms, including diarrhoea, rash and vomiting.
- Serious adverse events, defined as death, hospitalisation or new/worsening disability.
- Parent satisfaction with treatment at day 14.
- Treatment adherence and analgesic use up to symptom resolution.
- NHS resource use and costs for 14 days.
- Antimicrobial resistance in stool samples.

Sample size

Our previous trial comparing immediate oral with delayed oral antibiotics showed that children with AOMd (combined immediate and delayed strategy) took a median of 3 days to achieve the REST primary outcome. Our patient and public involvement (PPI) group advised that the maximum difference that they regarded as unimportant was 1.25 days. With 20% loss to follow-up and 90% power to establish the above non-inferiority margin, 399 children (133 per arm) were necessary at the 1.25% (two comparison-adjusted) significance level.

Qualitative interviews

As recruitment was significantly slower than expected, qualitative interviews focused on understanding the views and experiences of staff of using the TRANSFoRm platform. Staff were purposively sampled in relation to site, role and whether or not the practice successfully recruited patients. In-depth interviews were conducted using a flexible topic guide, and were audio-recorded and transcribed. Data were analysed thematically.

Patient and public involvement

Extensive PPI was undertaken during the development of the protocol and study materials. Members provided input on the development of the primary outcome and identified the most significant symptoms that should be used to judge recovery as pain, fever, being unwell, sleep disturbance, otorrhoea and episodes of distress. The PPI group commented on the symptom recovery questionnaire and patient-facing materials. Our PPI contributor helped to determine the trial strategy following a European Medicines Agency report on the safety of fluoroquinolone antibiotics [European Medicines Agency. *Quinolone- and Flurioquinolone-Containing Medicinal Products*. URL: www.ema.europa.eu/en/medicines/human/referrals/quinolone-fluoroquinolone-containing-medicinal-products (accessed 17 September 2021)].

Results

Electronic trial platform

Delays in set-up and functionality of the TRANSFoRm platform led to critically low recruitment and early trial closure. Key challenges included:

- underestimating the technical challenge of integrating platform and EHR software
- underestimating the resources required to troubleshoot the resulting problems
- the need for repeated site platform reinstallations, which was time-consuming as it needed to be installed on individual workstations
- multiple and complex site information technology (IT) security arrangements, often involving third parties without contracts covering research
- failure to include a platform 'dashboard' function, resulting in the Trial Management Group being unaware when the platform was/was not functional
- progressively reduced site staff motivation to reinstall and use the software.

When the electronic trial platform was operational, clinicians reported strongly liking its features and also reported that it assisted recruitment as intended; however, the function of the platform was acknowledged as 'too little, too late'.

Trial

The first site opened on 5 April 2019 and the trial was closed on 31 March 2020, primarily because of critically low recruitment, but secondarily because of the onset of the 2019–20 SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) pandemic. At study closure, 122 general practices from 12 Clinical Research Networks had expressed an interest, of which 71 confirmed participation; 61 received sponsorship; 44 opened to recruitment, with the TRANSFoRm platform installed on 72 clinical computers; and seven sites randomised 22 children.

Overall, 62% of the recruited children were boys and the children had a median age of 5 years. Five, seven and 10 children were randomised to immediate oral, delayed oral and immediate topical antibiotics, respectively. All children received prescriptions as randomised. Seven (32%) parents fully adhered to treatment as allocated.

Symptom duration, parent satisfaction and resource use data were available for 17 (77%) children. The primary outcome of median symptom duration was 4 [interquartile range (IQR) 3–7] days for the whole group; the median (IQR) number of days to symptom resolution in the immediate oral, delayed oral and immediate topical antibiotic arms was 6 (4–9), 4 (3–7) and 4 (3–6), respectively. Formal comparative analysis was not conducted because of small numbers. There were six reports of new or worsening symptoms. There were no serious adverse events. A total of 88% of parents were either 'extremely satisfied' or 'satisfied' with treatment. NHS resource use and costs were low.

Qualitative

A total of 16 staff were interviewed, including general practitioners, practice managers, IT leads and research staff. Clinicians felt that the trial addressed an important question and they wanted a system that would automatically capture patient data. When the TRANSFoRm platform functioned as intended, it was liked. However, staff reported malfunctioning software for long periods, resulting in missed recruitment opportunities. The experience of getting the TRANSFoRm platform to work was frustrating and time-consuming, diverting staff from core activities. Staff felt that the TRANSFoRm platform was not sufficiently developed for use. Installation was reliant on practice-level IT expertise, which varied between practices. Although most had external IT support, this rarely included support for research IT. Arrangements for approving new software varied across practices and often, but not always, required authorisation from Clinical Commissioning Groups (CCGs).

Conclusions

An insufficient number of participants was recruited to answer the main research question. We were unable to establish the feasibility of running a platform-supported pragmatic trial for AOMd in primary care. The late development and intermittent functioning of the TRANSFoRm platform within the TPP SystmOne® [The Phoenix Partnership (Leeds) Ltd, Leeds, UK] EHR system resulted in low recruitment levels and failure to reach the required sample size. Our experience has highlighted the technical issues that need to be overcome before electronic trial platform technology should be adopted in the primary care setting.

We have carefully documented our experience and provided recommendations (see *Recommendations*) for those conducting the following activities: site identification, site training, platform development, platform installation and platform function monitoring. We consider that responding to these recommendations will help maintain the UK's position as a global leader in the delivery of pragmatic research that quickly and efficiently produces generalisable new knowledge to improve patient care.

Recommendations

The main research question remains unanswered. These recommendations focus on potential improvements to aid study management in the primary care setting and the implementation of an effective electronic trial platform. These recommendations are grouped by those responsible for the following activities: site identification, site set-up, site training, platform development, platform installation, troubleshooting, platform function monitoring and data management. Finally, there are two recommendations for national stakeholders, including the Department of Health and Social Care and the National Institute for Health Research (NIHR).

The National Institute for Health Research Clinical Research Network

1. Clinical research networks could keep logs of which sites have been invited, when and how many times. These could be shared with study teams to populate Consolidated Standards of Reporting Trials flow diagrams and allow a description of the generalisability of the recruiting sites.

Sponsors

2. Sponsors could consider accepting electronic versions of delegation logs with electronic signatures. These could be designed so that submission of incomplete logs/curricula vitae is not possible.
3. For large distributed trials with many sites, a robust electronic data management system to track documentation could be employed.

Trial management teams

4. When online site training is used, studies could provide training using a website that provides automated reminders and notifies the sponsor and study team when training is complete.

Electronic study platform

Developers

5. Electronic trial platforms could be used to harness the unprecedented opportunities to monitor, measure and test recruitment assumptions, identifying where in the recruitment process, from presentation to consent, the key 'drop-offs' occur.

6. All necessary platform preparatory activities and required resources could be clearly defined, taking care not to underestimate.
7. The skills needed to set up a trial platform and to set up a trial are distinct and complementary. Ideally, teams could be co-located to ensure that platform specifications meet individual trial requirements.
8. Platform software needs to be compatible with all practice software systems.
9. Closer integration with EHR providers could prevent incompatible updates (note that this could be obviated if national criteria were agreed or the trial platform was integral to the EHR).

Installers

10. Project teams need to work closely with EHR providers and CCGs from the study outset to agree on the software deployment process and the validation criteria required (note that this could be obviated if national criteria were agreed or the trial platform was integral to the EHR).
11. A pilot installation incapable of being used for recruitment (and, therefore, not a site agreement requirement) could be performed on one computer in each practice, tested and left to run for a week before installing software on other machines.
12. Where software reinstallation is required, it must be undertaken in a way that does not disrupt the work of the practice.

Troubleshooters

13. Electronic study platforms require teams dedicated to (1) development and (2) troubleshooting.
14. Careful consideration could be given to who is responsible for troubleshooting. Although it may seem obvious that this would be performed by the trial team (as it involves interacting with sites), it requires awareness of platform function and, therefore, may be better provided by the platform development team.

Function monitors

15. Electronic trial platforms could be best served by a dashboard function to monitor and log platform functionality in real time, providing real-time alerts and diagnostics for reduced function, and logging functionality across time and space.

Data managers

16. The format of the final data set to be extracted from the study database could be prespecified to ensure the appropriate data format and avoid the submission of linked clinical and personal data.

National stakeholders, including the Department of Health and Social Care and the National Institute for Health Research

17. Research funders need to formally recognise the potential of electronic study platforms if they wish to put the NHS on the leading edge of pragmatic research globally, allowing the delivery of new, near-real-time generalisable knowledge. This could also provide unprecedented opportunities to monitor, measure and test recruitment assumptions, identifying where in the recruitment process, from presentation to consent, the key 'drop-offs' that influence final study sample representativeness occur.
18. The NIHR and research funders could consider convening a meeting of national stakeholders to define a strategy for the development, implementation and ongoing management of electronic study platform software.

Trial registration

This trial is registered as ISRCTN12873692 and EudraCT 2017-003635-10.

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This report

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