Amoxicillin duration and dose for community-acquired pneumonia in children: the CAP-IT factorial non-inferiority RCT

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Declared competing interests of authors: David Dunn reports grants from the National Institute for Health Research during the conduct of the study (RP-PG-1212-20006). Saul N Faust reports personal fees or grants from AstraZeneca plc (Cambridge, UK)/Medimmune (Gaithersburg, MA, USA), Sanofi SA (Paris, France), Pfizer Inc. (New York, NY, USA), Seqirus UK Ltd (Maidenhead, UK), Sandoz (Holzkirchen, Germany), Merck KGAA (Darmstadt, Germany), GlaxoSmithKline plc (Brentford, UK) and Johnson & Johnson

(Brunswick, NJ, USA) outside the submitted work. In addition, Saul N Faust received grants for contract commercial clinical trials, which were paid to Saul N Faust's institution (with no personal payment of any kind). Last, Saul N Faust is a member of the Health Technology Assessment Commissioning Committee (2017–22). Adam Finn reports grants from GlaxoSmithKline plc, Pfizer Inc., Novavax (Gaithersburg, MA, USA), Sanofi Pasteur (Lyon, France), VBI Vaccines Inc. (Cambridge, MA, USA), Janssen Pharmaceuticals (Beerse, Belgium), Valneva SE (Saint-Herblain, France) and JITSUVAX outside the submitted work.

Published November 2021
DOI: 10.3310/hta25600

Scientific summary

The CAP-IT RCT

Health Technology Assessment 2021; Vol. 25: No. 60
DOI: 10.3310/hta25600

NIHR Journals Library www.journalslibrary.nihr.ac.uk

Scientific summary

Background

Antibiotics are among the most frequently prescribed medicines for children worldwide, and the most common indication is acute respiratory tract infection. Community-acquired pneumonia (CAP) accounts for a substantial proportion. Although the majority of pneumonia deaths occur in low- and middle-income countries, CAP is a major cause of morbidity in Europe and North America.

According to current guidance, including guidance from the *British National Formulary for Children* (BNFc) and the British Thoracic Society (BTS) in the UK, amoxicillin is the recommended treatment for childhood CAP. Twice-daily dosing is widely recommended internationally, but the BNFc currently recommends amoxicillin (250 mg) three times daily for children aged 1–5 years, with a total daily dose similar to countries using twice-daily dosing. Owing to this age-banded dose selection, there is considerable variability in the effective total daily dose for treated children in the UK. In terms of duration, the 2019 National Institute for Health and Care Excellence treatment guidelines for childhood pneumonia recommend a 5-day course be prescribed, European and World Health Organization guidance has suggested that a 3- to 5-day course be prescribed and the BTS recognises that there are no robust data to inform duration. Overall, there is insufficient evidence to inform optimal amoxicillin dose or duration for childhood CAP.

Streptococcus pneumoniae is the bacterial pathogen most commonly associated with childhood CAP. The pneumococcal conjugate vaccination (PCV13) covers 13 serotypes of *S. pneumoniae* and was introduced in the UK in 2010, with an uptake of nearly 95%. Despite this, there has not been a significant reduction in CAP-related hospital admissions in young children. *S. pneumoniae* resistance to penicillin in the UK is relatively rare and generally low level, reported to be identified in approximately 15% of respiratory isolates and 4–6% of blood culture isolates. To the best of our knowledge, there are virtually no data on the affect of duration and dose of antibiotic treatment on colonisation with resistant bacteria in children, but the relationship is likely to be dynamic and highly complex.

Although there is clear agreement that amoxicillin should be used as the first-line agent in children requiring antibiotic treatment, there are insufficient data on the impact of amoxicillin dose and duration on clinical cure, drug toxicity and resistance to key bacteria, including *S. pneumoniae*.

Objectives

The main objective CAP-IT (Community-Acquired Pneumonia: a protocol for a randomIsed controlled Trial) was to determine the following for young children with uncomplicated CAP treated after discharge from hospital if:

- a 3-day course of amoxicillin is non-inferior to a 7-day course, determined by receipt of a clinically indicated systemic antibiotic other than trial medication for respiratory tract infection (including CAP) in the 4 weeks after randomisation up to day 28
- lower-dose amoxicillin is non-inferior to higher-dose amoxicillin under the same conditions.

Secondary objectives were to evaluate the affect of lower-dose and shorter-duration amoxicillin on antimicrobial resistance, severity and duration of parent/guardian-reported CAP symptoms and specified clinical adverse events (AEs) (i.e. rash and diarrhoea).

Methods

Trial design

CAP-IT was a multicentre clinical trial with a target sample size of 800 participants conducted in hospitals in the UK and Ireland. It was a randomised, double-blind, placebo-controlled, 2 × 2 factorial, non-inferiority trial that evaluated amoxicillin dose and duration in young children with CAP.

Eligibility and recruitment

Patients presenting to 28 UK NHS hospitals and one children's hospital in Ireland were recruited in emergency departments (EDs), assessment/observation units and inpatient wards.

Participants

Children were eligible if they had a diagnosis of uncomplicated CAP, were aged > 6 months, weighed 6–24 kg and treatment with amoxicillin as the sole antibiotic was planned on discharge. CAP diagnosis was defined as cough within the previous 96 hours, fever (≥ 38 °C) in the previous 48 hours and respiratory distress and/or focal chest signs. Children could have received either no antibiotics or < 48 hours of beta-lactam antibiotics prior to randomisation.

Children were excluded for any severe underlying chronic disease with an increased risk of complicated CAP (including sickle cell anaemia, immunodeficiency, chronic lung disease and cystic fibrosis), documented penicillin allergy or other contraindication to amoxicillin, diagnosis of complicated pneumonia (i.e. shock, hypotension, altered mental state, ventilatory support, empyema, pneumothorax or pulmonary abscess) or bilateral wheezing without focal chest signs.

Interventions

Amoxicillin suspension was orally administered by parents/guardians twice daily. All children were weighed during eligibility screening to determine dose volume according to seven weight bands. Children were randomised to receive either a lower (35–50 mg/kg/day) or a higher (70–90 mg/kg/day) dose, and to receive either 3 or 7 days of amoxicillin at the point of discharge from hospital.

Randomisation and blinding

Patients underwent two simultaneous factorial 1 : 1 randomisations (dose and duration), resulting in their allocation to one of the four amoxicillin regimens (low dose, short duration; low dose, long duration; high dose, short duration; or high dose, long duration) using computer-generated random permuted blocks of size eight, stratified according to whether or not they had received non-trial antibiotics in hospital before being enrolled. Initially, stratification was by paediatric ED or ward group, reflecting whether participants were admitted to inpatient wards or observation units or discharged directly from the ED. Following an amendment for the joint analysis of these groups, stratification was effectively based on whether or not participants had received in-hospital antibiotics prior to randomisation. Blinded investigational medicinal product (IMP) labels were applied to each treatment pack and participants were randomised by dispensing the next sequentially numbered pack in the active block.

All treating clinicians, parents/guardians and outcome assessors were blinded to the allocated treatment. Dose blinding was achieved by using otherwise identical amoxicillin products of two different strengths (125 mg/5 ml and 250 mg/5 ml). A placebo manufactured to match oral amoxicillin suspension was used to blind the duration. One brand of amoxicillin was used for the first 3 days, followed by either a second brand of amoxicillin or placebo for days 4–7. Parents were informed to expect a taste change between bottles, but they did not know whether this was because of placebo or alternative amoxicillin.

Outcomes

The primary outcome for CAP-IT was defined as any clinically indicated systemic antibacterial treatment prescribed for respiratory tract infection (including CAP) other than trial medication within 4 weeks of randomisation (including if prescribed at the final follow-up visit at day 28). An expert clinician End-Point Review Committee (ERC) adjudicated the main clinical indication for all reported primary outcomes.

Secondary outcomes included phenotypic resistance to penicillin at day 28 measured in nasopharyngeal *S. pneumoniae* isolates, severity and duration of parent/guardian-reported CAP symptoms (including fever, cough, phlegm, fast breathing, wheeze, disturbed sleep, eating/drinking less, interference with normal activity and vomiting), adherence to trial medication, the occurrence of specified clinical AEs (including skin rash, thrush and diarrhoea) and serious adverse events (SAEs).

Data collection

Data on primary and secondary end points were collected on paper case report forms by site staff at trial entry, via telephone contact at days 3, 7, 14 and 21 and at a final face-to-face visit on day 28. In the case of children who did not attend the final face-to-face visit, consent was obtained for the trial team to contact their general practitioner (GP) to ascertain whether or not they had received a further course of antibiotics for any respiratory illness. In addition, parents/guardians completed a daily diary from day 1 to day 14.

Sample size

The sample size was calculated assuming a 15% event rate, an 8% non-inferiority margin (on a risk difference scale) assessed against a two-sided 90% confidence interval (CI), 90% power and 15% loss to follow-up, resulting in a sample size of 800 children.

Statistical methods

Statistical analyses were performed according to a modified intention-to-treat (ITT) principle, including all patients enrolled and analysed according to the group to which they were randomised. The one modification to the strict ITT principle was the exclusion of randomised patients who did not take any IMP from all statistical analyses.

The primary outcome was compared between the randomised groups using time-to-event methods, analysing time from enrolment to the first occurrence of the primary end point. Participants with incomplete primary outcome data were censored at the time of their last contact (including contact with their GP). Kaplan–Meier estimates were used to derive the risk difference between the randomised groups for the primary end point at day 28.

Four predefined sensitivity analyses for the primary outcome were performed: (1) including all systemic antibacterial treatments regardless of reason or indication; (2) limiting to end points where either CAP or chest infection (rather than respiratory tract infection generally) was adjudicated as the reason for treatment; (3) as the second analysis, but also including end points where the clinical indication was judged as 'unlikely' by the ERC; and (4) for the duration comparison only, disregarding prescriptions occurring within 3 days of randomisation because these cannot, by definition, be related to this randomisation.

Two predefined subgroup/stratified analyses were performed: (1) including participants at the higher end of the severity spectrum only, defined as two or more abnormalities at presentation [i.e. a raised respiratory rate (> 37 breaths/minute for children aged 1–2 years; > 28 breaths/minute for children aged 3–5 years), oxygen saturation < 92% in room air, presence of chest retractions]; and (2) a stratification by calendar time, based on Public Health England reports of circulating viruses/bacteria in the winter seasons spanned by CAP-IT.

Results

Primary end point

Of 814 participants in the analysis population, 100 (12.5%, 90% CI 10.7% to 14.6%) met the primary end point [51 (12.6%) participants in the lower-dose arm and 49 (12.4%) participants in the higher-dose arm (difference 0.2%, 90% CI −3.7% to 4.0%); 51 (12.5%) participants in the shorter-duration arm and 49 (12.5%) participants in the longer-duration arm (difference 0.1%, 90% CI −3.8% to 3.9%)].

For both comparisons, the upper 90% confidence limit was less than the non-inferiority margin of 8%, indicating non-inferiority of lower to higher dose and shorter to longer duration. There was no evidence of an interaction between the two randomisation arms or between the individual randomisation arms and pre-treatment with antibiotics.

All four of the sensitivity analyses supported the primary analysis, demonstrating non-inferiority for the dose and duration comparisons.

Community-acquired pneumonia symptoms

There was no evidence for a difference between the lower- and higher-dose groups in time to resolution of any of the nine parent/guardian-reported symptoms ($p > 0.05$).

There was evidence of a faster time to resolution of cough in the longer-duration group (median 10 days) than in the shorter-duration group (median 12 days) ($p = 0.040$). A similar difference was also observed for sleep disturbed by cough ($p = 0.026$). There was no significant difference between the duration groups in time to resolution of the other seven symptoms ($p > 0.05$).

Adverse events

A SAE was experienced by 43 of 814 (5.3%) participants. One participant (0.1%) experienced a serious adverse reaction and no participants experienced a suspected unexpected adverse reaction. The proportion of participants who experienced a SAE was similar in the different dose and duration groups.

There was no difference in the time to onset or severity of diarrhoea or thrush for either the dose or duration randomisation. The proportion of participants who reported skin rash after baseline was slightly higher in the longer-duration arm (106/387, 27.4%) than in the shorter-duration arm (87/404, 21.5%; $p = 0.055$).

Limitations

Limitations of the trial were that end-of-treatment swabs were not taken and 28-day swabs were collected in only 53% of children. In addition, we focused on phenotypic penicillin resistance testing in pneumococci in the nasopharynx, which does not describe the global affect on the microflora. Although 21% of children did not attend the final 28-day visit, we obtained data from general practitioners for the primary end point on all but 3% of children.

Conclusions

In summary, we found a 3-day treatment course of amoxicillin to be non-inferior to a 7-day course of amoxicillin, and a lower daily dose of amoxicillin to be non-inferior to a higher daily dose of amoxicillin, in terms of antibiotic retreatment for respiratory tract infection within 28 days. Time to resolution of parent/guardian-reported symptoms was similar in randomisation arms, except that mild cough lasted, on average, 2 days longer in participants in the shorter-duration arm than in participants in the longer-duration arm. AE rates and health-care services use within the 28-day follow-up period and penicillin non-susceptible pneumococcal colonisation rates at 28 days were similar in all dose and duration randomisation groups. No penicillin-resistant pneumococci were identified in samples from CAP-IT participants. Based on these findings, 3 days could be considered for the duration of amoxicillin treatment for children with uncomplicated pneumonia treated in the ambulatory setting. Current BNFc age-banded dosing in the UK results in a wide range of total daily doses, spanning both the lower and higher doses investigated in CAP-IT.

Future work

Antimicrobial resistance genotypic studies are ongoing, including whole-genome sequencing and shotgun metagenomics, to fully characterise the effect of amoxicillin dose and duration on antimicrobial resistance. The analysis of a randomised substudy comparing parental electronic and paper diary entry is also ongoing.

Trial registration

This trial is registered as ISRCTN76888927, EudraCT 2016-000809-36 and CTA 00316/0246/001-0006.

Funding

This project was funded by the National Institute for Health Research (NIHR) Health Technology Assessment programme and will be published in full in *Health Technology Assessment*; Vol. 25, No. 60. See the NIHR Journals Library website for further project information.

Health Technology Assessment

ISSN 1366-5278 (Print)

ISSN 2046-4924 (Online)

Impact factor: 4.014

Health Technology Assessment is indexed in MEDLINE, CINAHL, EMBASE, the Cochrane Library and Clarivate Analytics Science Citation Index.

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The research reported in this issue of the journal was funded by the HTA programme as project number 13/88/11. The contractual start date was in March 2016. The draft report began editorial review in October 2020 and was accepted for publication in June 2021. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the reviewers for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

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