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The effectiveness, safety and duration of step-down oral antibiotics for children hospitalised with severe pneumonia

Submission date 12/03/2020	**Recruitment status** No longer recruiting	[X] Prospectively registered [X] Protocol [X] Statistical analysis plan [X] Results [_] Individual participant data
Registration date 15/05/2020	**Overall study status** Completed	
Last Edited 10/04/2025	**Condition category** Respiratory	

Plain English summary of protocol

Background and study aims

Children with severe chest infections often receive long courses of antibiotics that are given by injection. Children have to stay in hospital for these injections, which is costly for parents/carers and the health system, and means the children may pick up other infections, including new infections which cannot be treated by standard antibiotics (antibiotic-resistant infections). Some doctors change children onto antibiotics that can be taken by mouth (oral antibiotics) as soon as they are well enough. Once children are doing better, oral antibiotics are likely to be as good as continuing with antibiotic injections. It also means that children can go home sooner as they don' t need injections for as long. However, to date no studies have looked at this specifically in this group of children in hospital with severe chest infections in low- and middle-income settings, so changing to oral antibiotics cannot be recommended by governments. It is also not known how long children with serious chest infections actually need to take antibiotics for. The longer antibiotics are taken, the more likely it is that other bacteria living in the body become more resistant to antibiotics, meaning that antibiotics won't work as well for infections in the future. So, children need to be given just enough antibiotics to make them well, but not so much that bacteria develop more resistance and perhaps won't work next time. Surprisingly almost no studies have looked at exactly how long children need to take antibiotics to get better. The aim of this study is to answer the following questions:

1. Is the rate of clinical cure better if children move from injectable antibiotics to oral co-amoxiclav or oral amoxicillin antibiotics once they are well enough to take drugs by mouth, and how does this compare to staying on injectable antibiotics?
2. What is the best duration of antibiotic treatment for children that gives good rates of clinical cure while reducing how long they have to stay in hospital, the side effects they experience and the presence of other antibiotic-resistant bacteria?
3. Does this best duration depend on other factors, such as age, having been exposed to HIV, having malnutrition or how serious the chest infection is, suggesting that how long children get antibiotics for should vary based on these risk factors?
4. What ratio of amoxicillin to clavulanate should be used in co-amoxiclav for children?

Who can participate?
Children aged 2 months to 6 years of age, who weigh between 3 kg and 30 kg, and who have pneumonia (chest infection) that has developed while they are at home and is so serious that they need to be treated in hospital.

What does the study involve?
All children will start on the World Health Organisation (WHO)-recommended injectable antibiotics. When they are well enough to take drugs by mouth, they will be randomly allocated to move to one oral antibiotic called co-amoxiclav, or another oral antibiotic called amoxicillin, or they will stay on injectable antibiotics. Both of these oral drugs should be highly effective, but the researchers want to find out if co-amoxiclav is actually any better. Co-amoxiclav is mostly given to children as a liquid, and needs to be kept cool. In the study tablets are used that become liquid when mixed with small amounts of other liquids (e.g. water). If co-amoxiclav really is better, these tablet formulations need to become more widely available. It is not known how long the antibiotic treatment needs to last. Children will be randomly allocated to get their antibiotics for 4, 5, 6, 7 or 8 days in total. These durations are used in different parts of the world and there is no evidence that any one is better than the other. The researchers will follow the children for 28 days over the telephone and through face-to-face visits to find out whether they have had any problems. They will focus on whether they have to be admitted to hospital again or whether they have died. They will also look at how long they have to stay in hospital (since parents/carers typically have to pay for this), how many antibiotics children take during the month after being admitted to hospital, how much they need other treatments like extra oxygen, and how much all their care costs. In an extra part of the study, the researchers will look at the amount of the two drugs that make co-amoxiclav. Across the world, different ratios are used and there are no data to tell us which might be the best for children. In the main part of the study, the researchers will use a tablet with 7 parts amoxicillin to 1 part clavulanate, because this is most commonly used in Europe. In a subset of these children, they will measure how much of the drug gets into their blood. In the extra part of the study, the researchers will measure drug levels in children getting either 4 parts amoxicillin to 1 part clavulanate or 14 parts amoxicillin to 1 part clavulanate. These ratios are each used elsewhere in the world. The researchers will also look to see whether these ratios lead to different rates of side-effects like tummy upsets which are important for parents.

What are the possible benefits and risks of participating?
Entering this study may not directly benefit the participants, but the information learnt from the PediCAP study will help to work out the best way to treat other children who have severe chest infections in the future. The child may also receive closer hospital care than in the general hospital. The main possible side effects associated with the antibiotics used are as follows. Diarrhoea and tummy upsets: these are common, but are usually mild and stop when the antibiotic is finished. Rashes: these are less common, but usually happen very soon after starting the drugs, which would be whilst children are still in hospital. Thrush: again this is less common, it is usually mild and stops when the antibiotic is finished. Very rarely, children can have an allergic reaction immediately after starting an antibiotic. This would happen in hospital and will be managed by hospital doctors in the same way whether or not the child joins the study. In the future, it may become apparent that a child may or may not have received what proved to be the best treatment. However, at the moment it is not known what the best treatment is, which is the reason the researchers are doing the study.

Where is the study run from?
1. Wits Health Consortium (South Africa)
2. Africa Health Research Institute (AHRI) (South Africa)
3. Makerere University (Uganda)

4. University of Zambia (Zambia)
5. University of Zimbabwe Clinical Research Centre (UZCRC) (Zimbabwe)
6. Universidade Eduardo Mondlane (UEM) (Mozambique)

When is the study starting and how long is it expected to run for?
April 2019 to March 2025

Who is funding the study?
European Developing Countries Clinical Trials Partnership (EDCTP)

Who is the main contact?
Prof. Michael Sharland
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Contact information

Type(s)
Scientific

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Additional identifiers

Study information

Scientific Title
Impact of oral step-down to amoxicillin or co-amoxiclav and of duration of antibiotic therapy on effectiveness, safety and selection of antibiotic resistance in severe childhood community-acquired pneumonia (CAP): a randomised controlled trial

Acronym
PediCAP

Study objectives
PediCAP-A:
1. Oral co-amoxiclav step-down is superior to oral amoxicillin step-down for preventing readmission or death within 28 days of commencing treatment.
2. Randomising children between 5 different total durations of antibiotics including intravenous

plus oral step-down will identify the minimum duration providing outcome rates within specific thresholds of the WHO-recommended 5 days' intravenous regimen.

PediCAP-A plus PediCAP-B:
1. Clavulanate PK exposures will be linear across the three formulation strengths used worldwide (4:1, 7:1, 14:1).

Ethics approval required
Old ethics approval format

Ethics approval(s)
1. Approved 13/08/2020, University College London Research Ethics Committee (Office of the Vice Provost Research, 2 Taviton Street, London, WC1H 0BT, United Kingdom; 020 7679 8713; ethics@ucl.ac.uk), ref: 16423 001
2. Approved 26/02/2020, University of Witwatersrand Human Research Ethics Committee: (Medical) (31 Princess of Wales Terrace, Parktown, Johannesburg,, Johannesburg, 2193, South Africa; 011 717 1788; HREC-Medical.ResearchOffice@wits.ac.za), ref: 190913B
3. Approved 12/12/2019, Makerere University School of Medicine Research Ethics Committee (SOMREC , Kampala, P. O Box 7072, Uganda; 256 0414533541; rresearch9@gmail.com), ref: 2019-162
4. Approved 23/03/2020, University of Zambia Biomedical Research Ethics Committee (Ridgeway Campus, Lusaka, P.O. Box 50110, Zambia; 260 1 256067; unzarec@unza.zm), ref: 328-2019
5. Approved 06/01/2020, Joint Research Ethics Committee for the University of Zimbabwe, College of Health Sciences and Parirenyatwa Group of Hospitals (Number 4 5th Floor, UZ New Health Sciences Building Parirenyatwa Group of Hospitals Grounds Mazoe Street, HARARE, Box A178, Zimbabwe; 263 4 708140; mrcz@mrcz.org.zw), ref: 221/19
6. Approved 26/05/2022, CNBS Committee for Bioethics in Health for Mozambique (Ministerio da Saude, 2 ando dto, Av Eduardo Mondlane/Salvador Allende, Maputo, 264, Mozambique; 258824066350; cnamocambique@gmail.com), ref: 323/CNBS/22

Study design
Open-label parallel-group 2 x 5 factorial randomized trial plus a parallel Phase II pharmacokinetic trial

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Paediatric community-acquired pneumonia

Interventions
Open-label parallel-group 2 x 5 factorial randomised trial assessing 2 different oral step-down antibiotics (amoxicillin and co-amoxiclav (amoxicillin:clavulanate 7:1)) given after intravenous antibiotics for a total of 5 different durations (factorial design) with an additional continued intravenous control group, using a novel design to optimise duration of treatment (main trial, PediCAP-A)

Plus a parallel Phase II pharmacokinetic (PK) trial comparing two additional different ratios for one of the oral step-down options, co-amoxiclav (14:1 and 4:1) (PediCAP-B), to enable the PK of all three ratios to be compared across the main trial (PediCAP-A) and the PK trial (PediCAP-B)

All children will initiate or have already initiated treatment with WHO-recommended intravenous antibiotics.

In the main trial (PediCAP-A), children who have received at most 24 hours of intravenous antibiotics will be randomised to step-down from intravenous antibiotics when they are clinically stable and able to take oral medication to either oral amoxicillin or oral co-amoxiclav (7:1 amoxicillin:clavulanate) (1:1), both as dispersible tablets for a total duration of 4, 5, 6, 7 or 8 days antibiotics (1:1:1:1:1) (from start of intravenous antibiotics) (total 10 groups), or to remain on intravenous antibiotics for a total of 5 days following current WHO recommendation (additional eleventh group of the same size as each duration/drug group).

In the parallel Phase II PK trial (PediCAP-B), children who have received at most 24 hours of intravenous antibiotics will be randomised to step-down from intravenous antibiotics when they are clinically stable and able to take oral medication to either oral co-amoxiclav 4:1 or 14:1 (1:1) for a total duration of 6 days antibiotics (from start of intravenous antibiotics) (two groups). All children will receive at least 24 hours of intravenous antibiotics before stepping down to oral medication.

Intervention Type
Drug

Phase
Phase II

Drug/device/biological/vaccine name(s)
Amoxicillin, clavulanate

Primary outcome(s)
For the main trial (PediCAP-A):
Hospital readmission occurring from the date of initial discharge to day 28 or death (all-cause) occurring from the date of randomisation to day 28

For the Phase II PK trial (PediCAP-B):
Plasma exposure to amoxicillin and clavulanate measured using LC-MS/MS methods in samples taken when children start oral antibiotics

Key secondary outcome(s))
For the main trial (PediCAP-A), within 28 days of randomisation:
1. CAP-related readmission occurring at any time from the date of initial discharge to day 28 or CAP-related mortality occurring at any time from the date of randomisation to day 28
2. Length of stay required during the index hospitalisation calculated from the date of randomisation to the initial date of discharge, and overall through 28 days calculated from the date of randomisation to the initial date of discharge plus any additional days of hospitalisation from the date of discharge to day 28
3. Mortality (all-cause) occurring at any time during the 28 days of trial follow-up
4. Duration of supplemental oxygen during the index hospitalisation calculated from the date of randomisation to the date of discharge

5. Total days of antibiotic exposure through 28 days calculated from the date of randomisation to day 28
6. Modification of randomised antibiotics for any reason except early stopping or receipt of subsequent course of antibiotics for any reason occurring at any time during the 28 days of trial follow-up
7. Modification of randomised antibiotics for inadequate response or additional courses for CAP relapse occurring at any time during the 28 days of trial follow-up
8. Serious adverse events occurring at any time during the 28 days of trial follow-up
9. Grade 3 or 4 adverse events occurring at any time during the 28 days of trial follow-up
10. Adverse events of any grade related to antibiotics occurring at any time during the 28 days of trial follow-up
11. Key solicited events, specifically diarrhoea, vomiting and gastrointestinal disorders, skin rash, thrush/candida occurring at any time during the 28 days of trial follow-up
12. Modification of antibiotics for adverse reactions occurring at any time during the 28 days of trial follow-up
13. Specific clinical complications, including sepsis, lung abscess, empyema occurring at any time during the 28 days of trial follow-up
14. Line complications occurring at any time during hospitalisation
15. Antimicrobial resistance measured using antimicrobial susceptibility testing or whole-genome sequencing of isolates cultured from nasal and faecal swabs taken at baseline, the earlier of discharge and day 3, and day 28
16. Cost and cost-effectiveness measured using a questionnaire at day 28

Completion date
31/03/2025

Eligibility

Key inclusion criteria
1. Aged 2 months to 6 years inclusive
2. Weighing >= 3 kg and <30 kg
3. Admitted to hospital with severe pneumonia judged to require at least 24h of intravenous antibiotics by the treating physician
4. Difficulty breathing (with or without cough reported by parent/carer) PLUS one or more of
4.1. Central cyanosis or hypoxaemia (room air pulse oximetry <90%)
4.2. Any sign of severe respiratory distress (e.g. severe chest indrawing, grunting, nasal flaring, head nodding)
4.3. Signs of pneumonia (fast breathing (defined as respiratory rate ≥50 breaths per minute at age 2-11 months and ≥40 breaths per minute at age 1 years or older) or chest indrawing) PLUS a general danger sign (inability to breastfeed or drink, lethargy or reduced level of consciousness, convulsions) occurring at any time from admission up to randomisation.
5. About to initiate or already initiated intravenous benzylpenicillin plus gentamicin, ampicillin plus gentamicin, benzylpenicillin or ampicillin alone, ceftriaxone alone or cefotaxime alone
6. Received at most 24h of these intravenous antibiotics at the point of randomisation (that is, first dose of any intravenous antibiotics must have been administered no more than 24h previously at randomisation)
7. Parent/carer willing to accept and adhere to all possible randomised allocations for their child, including 5 days of intravenous antibiotics, and signed written informed consent available from parent/carer

8. Available for follow-up for the entire study period; specifically, parent/carer willing to return with their child to clinic at 4 weeks, and be contacted at minimum by telephone at weeks 1, 2 and 3

For children enrolled in PK (Section 10.1) or microbiology (Section 10.2) substudies, additional inclusion criteria are:
9. If undergoing additional PK sampling: willing to provide samples and potentially to stay in hospital for up to an additional 12h (separate consent will be obtained for PK sampling which may be refused and the child still join the main trial (PediCAP-A): consent for PK sampling is required for inclusion in the Phase II PK trial (PediCAP-B))

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Child

Lower age limit
2 months

Upper age limit
6 years

Sex
All

Total final enrolment
1231

Key exclusion criteria
1. Point-of-care semi-quantitative C-reactive protein (CRP) test < 10 mg/l at screening (very unlikely to represent severe pneumonia requiring antibiotics)
2. Likely nosocomial pneumonia (onset >48h post-admission)
3. Admitted to hospital overnight in the last 28 days (possibility of nosocomially-acquired pneumonia)
4. Known or anticipated need for invasive ventilation or admission to intensive care
5. Clinician considers this episode to be predominantly due to reactive airways disease (e.g. asthma) (wheeze responsive to bronchodilators, see Manual of Operations (MOP) for more details)
6. Clinician considers this episode to be due to viral bronchiolitis alone in a child under 1 year
7. Documented penicillin allergy or contra-indications to penicillin/amoxicillin/co-amoxiclav
8. Anticipated need for systemic treatment with an antibiotic other than trial regimens during hospital admission or in the following 28 days (e.g. for Pneumocystis jiroveci)
9. On long-term antibiotics for prophylaxis or treatment (e.g. for tuberculosis treatment or cotrimoxazole prophylaxis for HIV infection)
10. Previously enrolled in PediCAP

Date of first enrolment

01/10/2020

Date of final enrolment
05/07/2024

Locations

Countries of recruitment
Mozambique

South Africa

Uganda

Zambia

Zimbabwe

Study participating centre
Wits Health Consortium
Chris Hani Baragwanath Academic Hospital, Soweto, Gautang Province
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Sponsor information

Organisation
PENTA Foundation

ROR
https://ror.org/00d7mpc92

Funder(s)

Funder type
Research organisation

Funder Name

European and Developing Countries Clinical Trials Partnership

Alternative Name(s)
Le partenariat Europe-Pays en développement pour les essais cliniques, A Parceria entre a Europa e os Países em Desenvolvimento para a Realização de Ensaios Clínicos, The European & Developing Countries Clinical Trials Partnership (EDCTP), The European & Developing Countries Clinical Trials Partnership, European and Developing Countries Clinical Trials, EDCTP

Funding Body Type
Private sector organisation

Funding Body Subtype
International organizations

Location
Netherlands

Results and Publications

Individual participant data (IPD) sharing plan
All data requests should be sent to mrcctu.pedicap@ucl.ac.uk. Data will be available for sharing after the publication of the primary trial results. All data will be anonymised. The possibility of data sharing is outlined in the Patient Information Sheet.
Data will be shared based on the following principles:
1. No data should be released that would compromise an ongoing trial or study.
2. There must be a strong scientific or other legitimate rationale for the data to be used for the requested purpose.
3. Investigators who have invested time and effort into developing a trial or study should have a period of exclusivity in which to pursue their aims with the data, before key trial data are made available to other researchers.
4. The resources required to process requests should not be under-estimated, particularly successful requests which lead to preparing data for release. Therefore adequate resources must be available in order to comply in a timely manner or at all, and the scientific aims of the study must justify the use of such resources.
5. Data exchange complies with Information Governance and Data Security Policies in all of the relevant countries.

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Abstract results		06/03/2024	08/04/2025	No	No
Protocol file	version 3.0	05/11/2020	28/04/2023	No	No
Statistical Analysis Plan	version 2.0	28/11/2023	22/04/2024	No	No
Study website	Study website	11/11/2025	11/11/2025	No	Yes