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Dose and duration of antibiotic treatment in young children with community-acquired pneumonia

Submission date
14/12/2015

Recruitment status
No longer recruiting

Registration date
15/12/2015

Overall study status
Completed

Last Edited
18/01/2024

Condition category
Respiratory

[X] Prospectively registered
[X] Protocol
[X] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
Pneumonia (an infection of the lungs) is one of most common infections in young children worldwide. Because there are no good tests to clearly identify whether pneumonia is caused by bacteria in children, the decision to prescribe antibiotics has to be made based on clinical assessment. Therefore antibiotics are very commonly prescribed to children for possible pneumonia. We know that treatment with antibiotics can lead to changes in the bacteria carried by the person taking them, making the bacteria become more resistant to the effect of the antibiotics. These resistant bacteria can subsequently cause an infection in the treated children or spread to other persons in close contact. Infections caused by resistant bacteria are more difficult to treat. The amount of antibiotic (dose) and the number of days of treatment (duration) is likely to have an effect on the development of resistant bacteria in individual patients. Currently, we do not know which antibiotic treatment duration and dose are best for treating childhood pneumonia. Also the relationship between dose, duration and the development of resistant bacteria in the nose and gut (two preferred places where bacteria live) is not understood. This study will look at whether lower doses and shorter duration of antibiotic treatment with amoxicillin, the antibiotic most commonly used for pneumonia in children, are as good at treating pneumonia as higher doses and longer duration of treatment. The aim of the study is to investigate whether 3 days of treatment is as good as 7 days of treatment, and whether a low dose is as good as a high dose for treating pneumonia, and whether these different doses and durations affect the appearance of resistant bacteria. The lower dose and shorter treatment could reduce side effects and cause less resistance. The results of the study could inform how children in the UK and also in other countries should best be treated for pneumonia.

Who can participate?
Parents or carers of children aged greater than 6 months and weighing 6-24 kg are asked to join the study if the child has pneumonia and will be treated at home, as long as there are no signs of very severe pneumonia or other complications. Children seen in the emergency department who

can go home can join the study immediately. Children in hospital often need a short period of intravenous treatment or observation; their carers would be invited to join the study after up to 48 hours of inpatient therapy.

What does the study involve?
Participating children are randomly allocated to be treated with either high or low dose amoxicillin for either 3 or 7 days. In order to treat the groups of children in the same way, neither the doctors nor the families know whether their child is receiving high or low dose amoxicillin. Similarly, while children receiving 7 days have amoxicillin every day, those receiving 3 days have 3 days of amoxicillin followed by 4 days of placebo (medicine with no active ingredients). We compare how frequently children have to be treated again with antibiotics in the different groups. To look at the development of resistant bacteria, nose swabs are collected before starting treatment and up to twice during and after treatment, to find out whether shorter treatments and/or those using a specific dose lead to less resistant bacteria in the nose at the end of treatment.

What are the possible benefits and risks of participating?
The potential benefits of participating are:
1. Dosing of medication is more accurate because it is based on the child's weight.
2. Participants are contacted by the study nurse weekly during the study i.e. participants have more follow-up than normal for a child with pneumonia. Participants are also given a phone number for the study team in case of questions or concerns.
3. The improved understanding of the impact of amoxicillin duration and dose on the development of antibiotic resistance, together with evidence of the effectiveness of different courses, will enable the most appropriate treatment to be identified.
The potential drawbacks of participating are:
1. Amoxicillin given for 3 days may not be as good at treating pneumonia as treatment for 7 days. We think this is unlikely and shorter treatment has been shown to be safe in adults.
2. Participants need to come to the hospital for two extra visits with the study nurse at the end of weeks 1 and 4.

Where is the study run from?
St George's Hospital (UK)

When is the study starting and how long is it expected to run for?
May 2015 to July 2019

Who is funding the study?
National Institute for Health Research Health Technology Assessment Programme (UK)

Who is the main contact?
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Contact information

Type(s)
Public

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Additional identifiers

Clinical Trials Information System (CTIS)
2016-000809-36

Protocol serial number
HTA 13/88/11

Study information

Scientific Title
Efficacy, safety and impact on antimicrobial resistance of duration and dose of amoxicillin treatment for young children with community-acquired pneumonia (CAP): a randomised controlled trial

Acronym
CAP-IT

Study objectives
Current hypothesis as of 21/02/2017:
1. Lower dose (35-50 mg/kg per day given in two divided doses) oral amoxicillin treatment is non-inferior to higher dose (70-90 mg/kg per day in two divided doses) amoxicillin treatment for uncomplicated childhood community-acquired pneumonia (CAP) in terms of resolution /prevention of relapse of lower respiratory illness requiring retreatment with antibiotics.
2. Shorter duration (3 days) amoxicillin treatment is non-inferior to longer duration (7 days) amoxicillin treatment for uncomplicated childhood CAP.

Previous hypothesis:
1. Lower dose (35-50 mg/kg per day given in two divided doses) oral amoxicillin treatment is non-inferior to higher dose (70-120 mg/kg per day in two divided doses) amoxicillin treatment for uncomplicated childhood community-acquired pneumonia (CAP) in terms of resolution /prevention of relapse of lower respiratory illness requiring retreatment with antibiotics.
2. Shorter duration (3 days) amoxicillin treatment is non-inferior to longer duration (7 days) amoxicillin treatment for uncomplicated childhood CAP.

More details can be found here: https://www.journalslibrary.nihr.ac.uk/programmes/hta/138811/#/

Ethics approval required
Old ethics approval format

Ethics approval(s)
London - West London & GTAC Research Ethics Committee, 30/06/2016

Primary study design
Interventional

Study design
Multi-centre UK-based randomised double-blind placebo-controlled 2x2 factorial non-inferiority trial

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Community-acquired pneumonia

Interventions
Current interventions as of 21/02/2017:
Children will be enrolled from Paediatric Emergency Departments (PEDs) at university centres (main sites) and from the wards of the main sites and their affiliated secondary care hospitals (satellite sites).

Participants will be randomised to:
Randomisation 1: Lower dose (35-50 mg/kg per day given in two divided doses) oral amoxicillin treatment versus higher dose (70-90 mg/kg per day in two divided doses) oral amoxicillin treatment. Dose volumes will be identical in the lower and higher dose groups.
Randomisation 2: Three days of oral amoxicillin followed either by placebo for 4 days (3 days active treatment) or by a further 4 days of amoxicillin (7 days active treatment).

This will result in four treatment groups:
1. Longer/lower dose: 7 days at 35-50 mg/kg/day
2. Shorter/lower dose: 3 days at 35-50 mg/kg/day
3. Longer/higher dose: 7 days at 70-90 mg/kg/day
4. Shorter/higher dose: 3 days at 70-90 mg/kg/day

Previous interventions:
Children will be enrolled from Paediatric Emergency Departments (PEDs) at university centres (main sites) and from the wards of the main sites and their affiliated secondary care hospitals (satellite sites).

Participants will be randomised to:
Randomisation 1: Lower dose (35-50 mg/kg per day given in two divided doses) oral amoxicillin treatment versus higher dose (70-120 mg/kg per day in two divided doses) oral amoxicillin treatment. Dose volumes will be identical in the lower and higher dose groups.
Randomisation 2: Three days of oral amoxicillin followed either by placebo for 4 days (3 days active treatment) or by a further 4 days of amoxicillin (7 days active treatment).

This will result in four treatment groups:
1. Longer/lower dose: 7 days at 35-50 mg/kg/day
2. Shorter/lower dose: 3 days at 35-50 mg/kg/day

3. Longer/higher dose: 7 days at 70-120 mg/kg/day
4. Shorter/higher dose: 3 days at 70-120 mg/kg/day

Intervention Type
Drug

Phase
Phase III

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

Primary outcome(s)
Current primary outcome measure as of 05/07/2018:
The primary outcome is defined as any systemic antibacterial treatment in addition to the allocated trial medication as an inpatient or outpatient up to and including week 4 final follow-up. This includes re-treatment, increase in amoxicillin dose, extension of treatment and treatment with additional agents.

Previous primary outcome measure:
Any antibiotic treatment prescribed in addition to the allocated trial medication as an in- or out-patient up to and at final follow-up. This includes retreatment, extension of treatment and treatment with additional agents. Measured at weeks 1, 2, 3 and 4.

Key secondary outcome(s)
Current secondary outcome measures as of 05/07/2018:
1. Morbidity assessed using:
1.1. Specified clinical adverse events, including thrush, skin rashes and diarrhoea assessed at weeks 1, 2, 3 and 4 (final visit)
1.2. Severity and duration of parent/guardian-reported CAP symptoms assessed using a validated symptom diary at days 1-7 and weeks 2, 3 and 4
1.3. Number of days off work for parents/guardians and number of days away from out-of-home child care (where relevant), assessed using the parent diary on day 7 and day 14
2. Phenotypic resistance to penicillin at week 4 measured through microbiological analysis of S. pneumoniae isolates colonising the nasopharynx from nasopharyngeal samples at the baseline, final visit and any unscheduled visits
3. Adherence to trial drug assessed on days 1-7 via the parent diary and at follow up visit at week 1 or 4
4. Antibiotic use, collected at weeks 1, 2, 3 and 4, assessed using:
4.1. Cumulative number of additional courses of antibiotics
4.2. Total number of days of re-treatment with antibiotics
5. Health-economic outcomes assessed at day 7 and day 14 through the parent diary and at days 7, 15, 22 and 29 on follow up calls/visits:
5.1. Quality of life (using EQ-5D adapted for use in the paediatric population) assessed at weeks 1, 2, 3 and 4 (final visit)
5.2. Cost-causing events and associated resource use, including costs based on patient admission and discharge dates, treatment costs and costs associated with treatment failure such as re-admissions and re-treatments. Assessed through completion of a table of the number of times contacted and number of times visited for A&E/walk-in centres, out of hours service, paediatrician, GP practice, pharmacist, NHS direct/NHS 111

Previous secondary outcome measures:
1. Adverse events, assessed at weeks 1, 2, 3 and 4 (final visit)
2. Severity and duration of parent-reported CAP symptoms, assessed using a validated symptom diary at days 1-7 and weeks 2, 3 and 4
3. Health economics measured using EQ-5D adapted for use in the paediatric population at weeks 1, 2, 3 and 4 (final visit)
4. Details of additional courses of antibiotics and total number of days of re-treatment with antibiotics, collected at weeks 1, 2, 3 and 4
5. Adherence, assessed on days 1-7 via the parent diary and at follow up visit at week 1 or 4
6. Penicillin resistance, assessed using samples taken at baseline, week 1 (during the pilot phase) and week 4

Completion date
31/07/2019

Eligibility

Key inclusion criteria
Current participant inclusion criteria as of 31/05/2019:
PED:
1. Age greater than 6 months and weighing 6 - 24kg
2. Clinical diagnosis of CAP at presentation to PED as defined by all of the following:
2.1 Presence of cough (reported by parents/guardians within 96 hours prior to presentation) AND
2.2 Temperature ≥38oC measured by any method OR likely fever within 48 hours prior to presentation AND
2.3 Signs of laboured/difficult breathing or focal chest signs at presentation in the PED (i.e. one or more of the following):
2.3.1 Nasal flaring
2.3.2 Chest retractions
2.3.3 Abdominal breathing
2.3.4 Focal dullness to percussion
2.3.5 Focal reduced breath sounds
2.3.6 Crackles with asymmetry
2.3.7 Lobar pneumonia on chest X-ray (if obtained)
3. Prior antibiotic treatment:
3.1 Not on systemic antibiotic treatment at presentation OR
3.2 Treated in the community as an outpatient with uninterrupted oral beta-lactam antibiotics for ≤48 hours
4. Decision to treat with oral amoxicillin for CAP on discharge from hospital
5. Parent/guardian willing to accept all possible randomised allocations
6. Available for follow up for the entire study period, parent/guardian willing to be contacted by telephone at day 4, weeks 1, 2 and 3, and attend a face-to-face follow up visit at 4 weeks after randomisation, unless discussed with MRC CTU
7. Informed consent form for trial participation signed by parent/guardian.

WARD:
1. Age greater than 6 months and weighing 6 - 24kg.
2. Clinical diagnosis of CAP at presentation to hospital as defined by all of the following:
2.1 Presence of cough (reported by parents/guardians within 96 hours prior to presentation) AND;

2.2 Temperature ≥38oC measured by any method OR likely fever within 48 hours prior to presentation AND;
2.3 Signs of laboured/difficult breathing or focal chest signs (i.e. one or more of the following):
2.3.1 Nasal flaring
2.3.2 Chest retractions
2.3.3 Abdominal breathing
2.3.4 Focal dullness to percussion
2.3.5 Focal reduced breath sounds
2.3.6 Crackles with asymmetry
2.3.7 Lobar pneumonia on chest X-ray (if obtained)
3. Prior antibiotic treatment including doses administered in hospital (see Figure 2):
3.1 Treated in-hospital only with any oral or intravenous beta-lactam for ≤48 hours after admission
3.2 Treated initially in the community and subsequently in hospital with any oral or intravenous beta-lactam, without interruption, for ≤48 hours in total
4. Decision to further treat with oral amoxicillin for CAP on discharge from hospital
5. Child is considered fit for discharge at time of randomisation
6. Available for follow up for the entire study period, parent/guardian willing to be contacted by telephone at weeks 1, 2 and 3 and attend face-to-face follow up visit at 4 weeks after randomisation, unless discussed with MRC CTU
7. Parent/guardian willing to accept all possible randomised allocations
8. Informed consent for trial participation signed by a parent/guardian

Previous participant inclusion criteria from 05/07/2018 to 31/05/2019:
PED group:
1. Age greater than 6 months and weighing 6-24 kg
2. Clinical diagnosis of CAP at presentation to PED as defined by all of the following:
2.1. Presence of cough (reported by parents/guardians in last 96 hours) AND
2.2. Temperature ≥38 °C measured by any method or likely fever in last 48 hours AND
2.3. Signs of laboured/difficult breathing or focal chest signs at presentation in the PED (i.e. one or more of the following):
2.3.1. Nasal flaring
2.3.2. Chest retractions
2.3.3. Abdominal breathing
2.3.4. Focal dullness to percussion
2.3.5. Focal reduced breath sounds
2.3.6. Focal crackles
3. Prior antibiotic treatment:
3.1. Not on systemic antibiotic treatment at presentation OR
3.2. Treated in the community as an outpatient with uninterrupted oral beta-lactam antibiotics for ≤48 hours
4. Decision to treat with oral amoxicillin for CAP on discharge from hospital
5. Parent/guardian willing to accept all possible randomised allocations
6. Available for follow up for the entire study period, parent/guardian willing to be contacted by telephone at day 4, weeks 1, 2 and 3, and attend a face-to-face follow up visit at 4 weeks after randomisation, unless discussed with MRC CTU
7. Informed consent form for trial participation signed by parent/guardian.

WARD group:
1. Age greater than 6 months and weighing 6-24 kg
2. Clinical diagnosis of CAP at presentation to PED as defined by all of the following:
2.1. Presence of cough (reported by parents/guardians in last 96 hours) AND

2.2. Temperature ≥38 °C measured by any method or likely fever in last 48 hours AND
2.3. Signs of laboured/difficult breathing or focal chest signs at presentation in the PED (i.e. one or more of the following):
2.3.1. Nasal flaring
2.3.2. Chest retractions
2.3.3. Abdominal breathing
2.3.4. Focal dullness to percussion
2.3.5. Focal reduced breath sounds
2.3.6. Focal crackles
3. Child admitted to a paediatric assessment unit or inpatient ward at a participating hospital
4. Decision to treat with oral or intravenous beta-lactam for ≤48 hours after admission
5. Decision to further treat with oral amoxicillin for CAP on discharge from hospital
6. Child is considered fit for discharge at time of randomisation
7. Available for follow up for the entire study period, parent/guardian willing to be contacted by telephone at day 4, weeks 1, 2 and 3, and attend a face-to-face follow up visit at 4 weeks after randomisation, unless discussed with MRC CTU
8. Parent/guardian willing to accept all possible randomised allocations
9. Informed consent for trial participation signed by a parent/guardian

Original participant inclusion criteria:
The inclusion criteria differ between the PED and WARD group patients and these are presented separately for clarity.
PED group:
1. Age from 1 to 5 years (up to their 6th birthday)
2. Clinical diagnosis of CAP as defined by the following (note: all four criteria must be met for the child to be eligible):
2.1. Presence of cough (reported by parents/guardians in last 96 hours)
2.2. Temperature ≥38oC measured by any method or history of fever in last 24 hours reported by parents/guardians
2.3. Increased age-specific respiratory rate (first or second triage or clinical examination by a member of clinical staff)
2.4. Signs of laboured/difficult breathing or focal chest signs at presentation in the PED (one or more of the following):
2.4.1. Nasal flaring
2.4.2. Chest retractions
2.4.3. Abdominal breathing
2.4.4. Focal dullness to percussion
2.4.5. Focal reduced breath sounds
2.4.6. Focal crackles
3. Decision to treat with oral amoxicillin for CAP
4. Decision to be discharged from the paediatric emergency department immediately
5. Parent/guardian willing to accept all possible randomised allocations
6. Available for follow up for the entire study period and parent/guardian willing to be contacted by telephone
7. Informed consent form for trial participation signed by parent/guardian.

WARD group:
1. Age from 1 to 5 years (up to their 6th birthday)
2.1. Presence of cough (reported by parents/guardians in last 96 hours)
2.2. Temperature ≥38oC measured by any method or history of fever in last 24 hours reported by parents/guardians
2.3. Increased age-specific respiratory rate (first or second triage or clinical examination by a

member of clinical staff)
2.4. Signs of laboured/difficult breathing or focal chest signs (one or more of the following):
2.4.1. Nasal flaring
2.4.2. Chest retractions
2.4.3. Abdominal breathing
2.4.4. Focal dullness to percussion
2.4.5. Focal reduced breath sounds
2.4.6. Focal crackles
3. Child admitted to a paediatric assessment unit or inpatient ward at a participating hospital (main site or satellite site).
4. Decision to treat with antibiotics during the ≤48 hours after admission with oral or intravenous amoxicillin or co-amoxicillin
5. Child planned for discharge on the same day as randomisation
6. Available for follow up for the entire study period and parent/guardian willing to be contacted by telephone
7. Parent/guardian willing to accept all possible randomised allocations
8. Informed consent for trial participation signed by a parent/guardian

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Child

Sex
All

Total final enrolment
824

Key exclusion criteria
Current participant exclusion criteria as of 31/05/2019:
PED:
1. Severe underlying chronic disease with an increased risk of developing complicated CAP including sickle cell anaemia, primary or secondary immunodeficiency, chronic lung disease and cystic fibrosis
2. Documented penicillin allergy
3. Any other known contra-indication to amoxicillin
4. Need for systemic treatment with an antibiotic other than amoxicillin on discharge from hospital
5. Bilateral wheezing without focal chest signs (most likely to represent respiratory tract infection of non-bacterial aetiology)
6. Complicated pneumonia
7. Receipt of initial antibiotic treatment in hospital in PAU or on the ward*
8. Parents/guardians unlikely to reliably complete the diary because of significant language barriers.

WARD:
1. Severe underlying chronic disease with an increased risk of complicated CAP including sickle cell anaemia, primary or secondary immunodeficiency, chronic lung disease and cystic fibrosis
2. Documented penicillin allergy
3. Any other known contra-indication to taking amoxicillin
4. Bilateral wheezing without focal chest signs (most likely to represent respiratory tract infection of non-bacterial aetiology)
5. Complicated pneumonia
6. Receipt of antibiotic other than a beta-lactam during admission
7. If treated in the community prior to admission, receipt of a non-beta-lactam antibiotic in the community at presentation
8. Clinically relevant positive blood culture (i.e. positive blood culture and clinical decision to prolong intravenous treatment for more than 48 hours or inappropriate to switch to amoxicillin therapy)
9. Receipt of >48 hours oral or intravenous antibiotic treatment in total
10. Decision to treat with oral antibiotic other than amoxicillin on discharge from hospital
11. Parents/guardians unlikely to reliably complete the diary because of significant language barriers.

Previous participant exclusion criteria from 05/07/2018 to 31/05/2019:
PED group:
1. Severe underlying chronic disease including sickle cell anaemia, primary or secondary immunodeficiency, chronic lung disease and cystic fibrosis
2. Documented penicillin allergy
3. Any other known contra-indication to taking amoxicillin
4. Need for system treatment with an antibiotic other than amoxicillin on discharge from hospital
5. Bilateral wheezing without focal chest signs (most likely to represent respiratory tract infection of non-bacterial aetiology)
6. Complicated pneumonia
7. Receipt of initial antibiotic treatment as inpatient in PAU or on the ward
8. Parent/ guardians unlikely to reliably complete the diary because of significant language barriers

WARD group:
1. Severe underlying chronic disease including sickle cell anaemia, primary or secondary immunodeficiency, chronic lung disease and cystic fibrosis
2. Documented penicillin allergy
3. Any other known contra-indication to taking amoxicillin
4. Already on antibiotic treatment at presentation
5. Bilateral wheezing without focal chest signs (most likely to represent respiratory tract infection of non-bacterial aetiology)
6. Complicated pneumonia
7. Receipt of antibiotic other than a beta-lactam during admission
8. Clinically relevant positive blood culture (i.e. positive blood culture and clinical decision to prolong intravenous treatment for more than 48 hours or inappropriate to switch to amoxicillin therapy)
9. Receipt of >48 hours oral or intravenous inpatient antibiotic treatment
10. Decision to treat with oral antibiotic other than amoxicillin on discharge from hospital
11. Parent/ guardians unlikely to reliably complete the diary because of significant language barriers

Original participant exclusion criteria:
The exclusion criteria differ between the PED and WARD group patients and these are presented separately for clarity.
PED group:
1. Severe underlying chronic disease including sickle cell anaemia, primary or secondary immunodeficiency, chronic lung disease and cystic fibrosis
2. Documented penicillin allergy
3. Any other known contra-indication to taking amoxicillin
4. Already on antibiotic treatment at presentation
5. Wheezing (most likely to represent respiratory tract infection of non-bacterial aetiology)
6. Complicated pneumonia
7. Antibiotic exposure within the last month
8. Weight is >24 kg

WARD group:
1. Severe underlying chronic disease including sickle cell anaemia, primary or secondary immunodeficiency, chronic lung disease and cystic fibrosis
2. Documented penicillin allergy
3. Any other known contra-indication to taking amoxicillin
4. Already on antibiotic treatment at presentation
5. Wheezing (most likely to represent respiratory tract infection of non-bacterial aetiology)
6. Complicated pneumonia
7. Antibiotic exposure within the last month
8. Clinically relevant positive blood culture (i.e., positive blood culture and clinical decision to prolong intravenous treatment for more than 48 hours or to switch to antibiotic therapy other than co-amoxicillin/amoxicillin)
9. Persistent or increasing oxygen requirement at ≤48 hours of admission compared with on admission
10. Persistent or deteriorating tachypnoea at ≤48 hours of admission compared with on admission
11. Receipt of non-amoxicillin-based therapy since admission (either as combination therapy with amoxicillin or as standalone antibiotic therapy)
12. Receipt of >48 hours oral or intravenous inpatient antibiotic treatment
13. Decision to treat with oral antibiotic other than amoxicillin on discharge from hospital
14. Weight is >24 kg

Date of first enrolment
01/02/2017

Date of final enrolment
30/04/2019

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
St George's Hospital
United Kingdom
SW17 0QT

Sponsor information

Organisation
University College London (UK)

ROR
https://ror.org/02jx3x895

Funder(s)

Funder type
Government

Funder Name
Health Technology Assessment Programme

Alternative Name(s)
NIHR Health Technology Assessment Programme, Health Technology Assessment (HTA), HTA

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are/will be available upon request from Prof. David Dunn (d.dunn@ucl.ac.uk).

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article		02/11/2021	03/11/2021	Yes	No
Results article		01/11/2021	08/11/2021	Yes	No
Results article	Pneumococcal diversity and persistence of vaccine types	27/04/2024	20/04/2026	Yes	No
Protocol article	protocol	22/05/2019	01/06/2020	Yes	No
Statistical Analysis Plan	version 2.0	02/12/2020	18/01/2024	No	No
Study website	Study website	11/11/2025	11/11/2025	No	Yes