Clinical trial results:
Antibiotics for lower Respiratory Tract Infection in Children presenting in Primary Care

Summary

EudraCT number	2015-002455-97
Trial protocol	GB
Global end of trial date	17 April 2020

Results information

Result version number	v1 (current)
This version publication date	18 December 2021
First version publication date	18 December 2021
Summary attachment (see zip file)	Antibiotics for lower respiratory tract infection in children presenting in primary care in England (ARTIC PC): a double-blind, randomised, placebo-controlled trial (PIIS0140673621014318.pdf)

Trial information

Trial identification

Sponsor protocol code	13381

Additional study identifiers

ISRCTN number	ISRCTN79914298
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	Sponsor R&D reference: 13381

Notes:

Sponsors

Sponsor organisation name	University of Southampton
Sponsor organisation address	University Road, Southampton, United Kingdom, SO17 1BJ
Public contact	Paul Little, University of Southampton, 0044 02380241050, p.little@soton.ac.uk
Scientific contact	Paul Little, University of Southampton, 0044 02380241050, p.little@soton.ac.uk

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	29 June 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	17 April 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Our aim is to provide evidence to inform the use of antibiotics for the management of chest infections in children. The objectives are:

1) To estimate the effectiveness of amoxicillin overall and in key clinical subgroups of children presenting with uncomplicated (non-pneumonic) lower respiratory tract infection in primary care

2) To estimate the cost-effectiveness of antibiotics overall and in key clinical subgroups of children presenting with uncomplicated lower respiratory tract infection in primary care

3) To explore the estimates of effectiveness according to key pathophysiological subgroups (the presence of bacterial pathogens; raised C reactive protein measurement or white cell count; the presence of clinically undetected consolidation on X ray; oximetry; lung function)

Protection of trial subjects:

None

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 August 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 438
Worldwide total number of subjects	438
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	438

Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was a randomised control trial (placebo vs amoxicillin) carried out in a Primary Care setting, investigating the effectiveness of amoxicillin in treating lower respiratory tract infections in Children (6mth to 12 yrs).

Pre-assignment

Screening details:

Inclusion criteria: Acute uncomplicated LRTI (acute cough as the most prominent symptom and lower tract symptoms/signs (sputum/'rattly chest'/coarse rhonchi; breathless; pain).
Exclusion criteria: Non-infective (e.g. reflux, Pulmonary Embolism (PE)) or croup (where viral aetiology is very likely).

Period 1

Period 1 title	Overall (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Data analyst

Blinding implementation details:

Randomisation will per pts will be either antibiotic or placebo. The clinician will dispense sequentially numbered pre-prepared randomised packs. The randomisation codes for antibiotic or placebo will be kept by the manufacturer and with a dedicated unblinding service.

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Amoxicillin placebo. Oral suspension. Powder for reconstitution.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for oral suspension
Routes of administration	Oral use

Dosage and administration details:

250mg/5ml. Dosing as follows:

Weight (kg)	Dose (for oral administration)	Duration
4.5 to <6.5	100mg (2ml) TDS	7 days
6.5 to <9	150mg (3ml) TDS	7 days
9 to <12	200mg (4ml) TDS	7 days
12 to <15	250mg (5ml) TDS	7 days
15 to <18	300mg (6ml) TDS	7 days
18 to <24	400mg (8ml) TDS	7 days
24 to <30	500mg (10ml) TDS	7 days
30 to <36	600mg (12ml) TDS	7 days
36 +	700mg (14ml) TDS	7 days

Arm title	Amoxicillin

Arm description:

Oral suspension, 250mg/5ml of amoxicillin. Powder for reconstitution.

Arm type	Active comparator

Investigational medicinal product name	Amoxicillin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for oral suspension
Routes of administration	Oral use

Dosage and administration details:

250mg/5ml. Dosing as follows:

Weight (kg)	Dose (for oral administration)	Duration
4.5 to <6.5	100mg (2ml) TDS	7 days
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9 to <12	200mg (4ml) TDS	7 days
12 to <15	250mg (5ml) TDS	7 days
15 to <18	300mg (6ml) TDS	7 days
18 to <24	400mg (8ml) TDS	7 days
24 to <30	500mg (10ml) TDS	7 days
30 to <36	600mg (12ml) TDS	7 days
36 +	700mg (14ml) TDS	7 days

Number of subjects in period 1[1]	Placebo	Amoxicillin
Started	211	221
Completed	211	221

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: 6 pts withdrew the use of their data.

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Amoxicillin placebo. Oral suspension. Powder for reconstitution.	
Reporting group title	Amoxicillin
Reporting group description:	
Oral suspension, 250mg/5ml of amoxicillin. Powder for reconstitution.	

Reporting group values	Placebo	Amoxicillin	Total
Number of subjects	211	221	432
Age categorical			
All participant ages range from 6month to 12 years of age.			
Units: Subjects			
6 months - 12 years	211	221	432
Gender categorical Units: Subjects			
Female	99	100	199
Male	112	121	233

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Amoxicillin placebo. Oral suspension. Powder for reconstitution.	
Reporting group title	Amoxicillin
Reporting group description:	
Oral suspension, 250mg/5ml of amoxicillin. Powder for reconstitution.	

Primary: PRIMARY: Mean duration of symptoms rated less than moderately bad or worse

End point title	PRIMARY: Mean duration of symptoms rated less than moderately bad or worse
End point description:	
The length of time (mean) symptoms were rated less than moderately bad or worse on the follow up questionnaire.	
End point type	Primary
End point timeframe:	
Maximum 28 days.	

End point values	Placebo	Amoxicillin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	156	161		
Units: days	6	5		

Statistical analyses

Statistical analysis title	Primary Outcome
Statistical analysis description:	
Cox regression was used for the primary outcome (duration of symptoms rated moderately bad or worse in days) and for total symptom duration, adjusting for age, baseline symptom severity, previous duration of illness and comorbidity. Multiple imputation was chosen for the primary analysis because multiple imputation is generally more efficient than complete case analysis and particularly important to control for potential for potential attrition bias.	
Comparison groups	Placebo v Amoxicillin
Number of subjects included in analysis	317
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.05
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.13

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.92
upper limit	1.42
Variability estimate	Standard deviation

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

Serious Adverse Events are to be reported to Study Team with 24 hours of site staff becoming aware. The Chief Investigator (CI) or their designated representative will be responsible for assessing the expectedness of SAEs reported.

Adverse event reporting additional description:

Amoxicillin is a licensed medicine whose most common side-effects are mucocutaneous candidosis (thrush), diarrhoea, nausea, vomiting and rash (occurrence >=1/100 to <1/10). If these occur and are non-serious and of mild to moderate severity (based on clinician's assessment) an Adverse Event Report form will not be necessary. We will collect data on

Assessment type	Systematic

Dictionary used

Dictionary name	none
Dictionary version	0

Frequency threshold for reporting non-serious adverse events: 0 %

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: Amoxicillin is a licensed medicine whose most common side-effects are mucocutaneous candidosis (thrush), diarrhoea, nausea, vomiting and rash (occurrence >=1/100 to <1/10). If these occur and are non-serious and of mild to moderate severity (based on clinician's assessment) an Adverse Event Report form will not be necessary. We will collect data on severe reactions.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported