Clinical trial results:
The early use of Antibiotics for at Risk CHildren with InfluEnza in primary care
(ARCHIE): a double-blind randomised placebo-controlled trial

Summary

EudraCT number	2013-002822-21
Trial protocol	GB
Global end of trial date	15 August 2019

Results information

Result version number	v1 (current)
This version publication date	05 March 2020
First version publication date	05 March 2020

Trial information

Trial identification

Sponsor protocol code	ARCHIE001

Additional study identifiers

ISRCTN number	ISRCTN70714783
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University of Oxford
Sponsor organisation address	Joint Research Office, 1 st floor, Boundary Brook House, Churchill Drive, Headington, Oxford, United Kingdom, OX3 7GB
Public contact	Prof Anthony Harnden, University of Oxford, 44 01865 289314, anthony.harnden@phc.ox.ac.uk
Scientific contact	Prof Anthony Harnden, University of Oxford, 44 01865 289314, anthony.harnden@phc.ox.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	16 December 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 March 2019
Global end of trial reached?	Yes
Global end of trial date	15 August 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine whether early treatment with co-amoxiclav reduces the likelihood of re-consultation due to clinical deterioration in ‘at risk’ children with influenza/influenza-like illness (ILI) within 28 days of study entry.

Protection of trial subjects:

We consulted with groups representing both patients and parents when designing the trial and had representatives of on our steering committe. A full risk assessment was conducted before commencing the trial and this was reviewed througout. Informed consent from every participant's parent/guardian was obtained and the trial was reviewed and approved by a Research Ethics Commitee (NRES Committee North West - Liverpool East 13/NW/0621).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 November 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 271
Worldwide total number of subjects	271
EEA total number of subjects	271

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)	89
Children (2-11 years)	179
Adolescents (12-17 years)	3
Adults (18-64 years)	0
From 65 to 84 years	0

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment opened on 11th Feb 2015 and closed 20th April 2018 (seasonal recruitment only running from Oct – end of ILI season following spring). An additional winter season (2017-2018) was added after an extension from the funder. Follow up was completed by 31st July 2019. The trial was not stopped early.

Pre-assignment

Screening details:

756 patients were screened for eligibility. Of these, 485 were not eligible and 115 were eligible but declined to consent

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Co-amoxiclav

Arm description:

Co-amoxiclav 400mg/57mg/5ml Sugar Free Powder for Oral Suspension (70ml)

Arm type	Experimental
Investigational medicinal product name	Co-amoxiclav
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for oral suspension
Routes of administration	Oral use

Dosage and administration details:

Dosage was given following British National Formulary Guidelines

Arm title	Placebo

Arm description:

Placebo contains the same excipients as the test product. In order to match the test product for fill weight, bulk density, and viscosity, tests were carried out with different excipients ratios in order to identify the most comparable formulation.

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

Dosage and administration details:

Dosage was given following British National Formulary Guidelines

Number of subjects in period 1	Co-amoxiclav	Placebo
Started	136	135
Completed	134	135
Not completed	2	0
Consent withdrawn by subject	1	-
Physician decision	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Co-amoxiclav
Reporting group description:	
Co-amoxiclav 400mg/57mg/5ml Sugar Free Powder for Oral Suspension (70ml)	
Reporting group title	Placebo
Reporting group description:	
Placebo contains the same excipients as the test product. In order to match the test product for fill weight, bulk density, and viscosity, tests were carried out with different excipients ratios in order to identify the most comparable formulation.	

Reporting group values	Co-amoxiclav	Placebo	Total
Number of subjects	136	135	271
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	45	44	89
Children (2-11 years)	89	90	179
Adolescents (12-17 years)	2	1	3
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: months			
median	41	36	
inter-quartile range (Q1-Q3)	19 to 86	21 to 71	-
Gender categorical Units: Subjects			
Female	53	55	108
Male	83	80	163
Region			
Region A: Thames Valley & South Midlands, West Midlands, North Thames, North West London, South London; Region B: West of England, South West Peninsula, Cardiff & Vale University Health Board, Aneurin Bevan University Health Board, Abertawe Bro Morgannwg University Health Board; Region C: Greater Manchester, North East and North Cumbria, North West Coast, Yorkshire & Humber; Region D: Kent Surrey & Sussex, Wessex & Region E: Eastern, East Midlands			
Units: Subjects			
Region A	45	44	89
Region B	32	30	62
Region C	25	25	50
Region D	23	24	47
Region E	11	12	23
Current seasonal influenza vaccination			
Received this season’s seasonal influenza vaccination?			
Units: Subjects			
Yes	45	45	90

No	88	86	174
Don't know	3	4	7
Last year seasonal influenza vaccination			
Received last season’s seasonal influenza vaccination?			
Units: Subjects			
Yes	48	41	89
No	63	72	135
Don't know	25	21	46
Missing	0	1	1
Household smoking status Units: Subjects			
Non-Smoking	113	107	220
Smoking	21	27	48
Missing	2	1	3
Antibiotics prescribed in the 3 months preceding randomisation Units: Subjects			
Yes	33	25	58
No	95	105	200
Unknown	5	2	7
Missing	3	3	6
Antivirals taken during current episode Units: Subjects			
Yes	0	0	0
No	133	135	268
Unknown	2	0	2
Missing	1	0	1
Antipyretics taken during current episode Units: Subjects			
Yes	115	118	233
No	19	15	34
Unknown	2	2	4
Other medications taken during current episode Units: Subjects			
Yes	80	71	151
No	55	64	119
Unknown	1	0	1
Hib Vaccination Status Units: Subjects			
Yes	124	124	248
No	8	5	13
Unknown	1	3	4
Missing	3	3	6
PCV Vaccination Received Units: Subjects			
Yes	122	122	244
No	10	6	16
Unknown	1	4	5
Missing	3	3	6
Any acute consultations in the 12 month			

period before entering the study			
Units: Subjects			
Yes	123	119	242
No	8	12	20
Unknown	2	1	3
Missing	3	3	6
Any Influenza strain			
Units: Subjects			
Yes	21	16	37
No	115	119	234
Influenza strains			
Units: Subjects			
Influenza A	3	1	4
Influenza A/H1-2009	1	3	4
Influenza A/H3	7	6	13
Other	125	125	250
Influenza B			
Units: Subjects			
Yes	10	7	17
No	126	128	254
Any Parainfluenza strain			
Other respiratory infections (nasal swab)			
Units: Subjects			
Yes	10	16	26
No	126	119	245
Adenovirus			
Other respiratory infections (nasal swab)			
Units: Subjects			
Yes	8	15	23
No	128	120	248
Coronavirus			
Other respiratory infections (nasal swab)			
Units: Subjects			
Yes	15	11	26
No	121	124	245
Human Metapneumovirus			
Other respiratory infections (nasal swab)			
Units: Subjects			
Yes	8	9	17
No	128	126	254
Rhinovirus/Enterovirus			
Other respiratory infections (nasal swab)			
Units: Subjects			
Yes	55	64	119
No	81	71	152
Respiratory Syncytial Virus			
Other respiratory infections (nasal swab)			
Units: Subjects			
Yes	24	24	48
No	112	111	223
Bordetella pertussis			

Other respiratory infections (nasal swab)			
Units: Subjects			
Yes	0	0	0
No	136	135	271
Mycoplasma pneumoniae			
Other respiratory infections (nasal swab)			
Units: Subjects			
Yes	3	1	4
No	133	134	267
Chlamydophila pneumoniae			
Other respiratory infections (nasal swab)			
Units: Subjects			
Yes	0	2	2
No	136	133	269
Risk category - Respiratory			
At risk categories (not mutually exclusive)			
Units: Subjects			
Yes	99	99	198
No	37	36	73
Risk category - Neurological			
At risk categories (not mutually exclusive)			
Units: Subjects			
Yes	6	9	15
No	130	126	256
Risk category - Cardiac			
At risk categories (not mutually exclusive)			
Units: Subjects			
Yes	12	4	16
No	124	131	255
Risk category - Renal			
At risk categories (not mutually exclusive)			
Units: Subjects			
Yes	3	0	3
No	133	135	268
Risk category - Immunodeficiency			
At risk categories (not mutually exclusive)			
Units: Subjects			
Yes	1	0	1
No	135	135	270
Heart rate (beats/minute)			
(n=267)			
Units: beats/minute			
arithmetic mean	115	117	
standard deviation	± 22	± 23	-
Respiratory rate			
(n=268)			
Units: breaths/minute			
arithmetic mean	27.6	28.3	
standard deviation	± 9.1	± 9.9	-
Temperature			
(n=270)			

Units: Degrees Celsius			
arithmetic mean	37	37	
standard deviation	± 0.8	± 0.9	-
Total number of acute consultations in the 12 month period before entering the study			
(n=202)			
Units: units			
median	6.0	5	
inter-quartile range (Q1-Q3)	3 to 10	3 to 9	-
Duration of illness			
Medical history (n=271)			
Units: days			
arithmetic mean	2.7	2.7	
standard deviation	± 1.2	± 1.2	-
Duration of fever			
Medical history (n=266)			
Units: days			
arithmetic mean	1.9	2.2	
standard deviation	± 1.2	± 1.2	-

End points

End points reporting groups

Reporting group title	Co-amoxiclav
Reporting group description:	
Co-amoxiclav 400mg/57mg/5ml Sugar Free Powder for Oral Suspension (70ml)	
Reporting group title	Placebo
Reporting group description:	
Placebo contains the same excipients as the test product. In order to match the test product for fill weight, bulk density, and viscosity, tests were carried out with different excipients ratios in order to identify the most comparable formulation.	

Primary: Proportion of children re-consulting due to clinical deterioration

End point title	Proportion of children re-consulting due to clinical deterioration
End point description:	
Re-consultation was defined as any subsequent visit to a primary care or other equivalent ambulatory care setting within 28 days of entering the trial. Clinical deterioration was defined as any of: worsening symptoms, development of new symptoms or development of a complication requiring medication or hospitalisation after randomisation. This definition is based on that used by the GRACE (Genomics to combat Resistance against Antibiotics in Community-acquired lower respiratory tract infection in Europe) consortium in relation to lower respiratory tract infections (Little et al., 2013). Date of study entry was defined as the date of randomisation.	
End point type	Primary
End point timeframe:	
within 28 days of study entry	

End point values	Co-amoxiclav	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	133	132		
Units: re-consultations				
Yes	33	28		
No	100	104		

Statistical analyses

Statistical analysis title	Primary Outcome Analysis
Statistical analysis description:	
The primary analysis of the primary outcome (i.e. proportion of participants having a re-consultation) was conducted using a log binomial regression model. The model adjusted for region, age (as a continuous variable rather than categorised as per the minimisation criteria) and current seasonal influenza vaccination status (yes, no/unknown). The treatment effect is reported as a relative risk and 95% confidence interval with a corresponding P-value.	
Comparison groups	Placebo v Co-amoxiclav

Number of subjects included in analysis	265
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.513
Method	log binomial regression model
Parameter estimate	Risk ratio (RR)
Point estimate	1.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.75
upper limit	1.8

Secondary: Duration of fever (days)

End point title	Duration of fever (days)

End point description:

A fever was defined as a temperature equal to or above 37.5C. If the temperature was not recorded on any day, and there were not 2 consecutive days of temperature below 37.5C, this outcome was classed as missing. Duration of fever was defined as the number of days from randomisation until the last day the temperature was recorded as ≥37.5 C, followed by being recorded as less than 37.5C for two consecutive days.

End point type	Secondary

End point timeframe:

The child's temperature was recorded each day for 28 days or until it had been below 37.5C for 2 consecutive days.

End point values	Co-amoxiclav	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	71	65		
Units: days				
median (inter-quartile range (Q1-Q3))	0 (0 to 1)	0 (0 to 1)		

Statistical analyses

Statistical analysis title	Wilcoxon rank sum test

Statistical analysis description:

The data for this outcome followed a skewed distribution and could not be transformed to Normality. Therefore, medians and IQRs are presented and a Wilcoxon rank sum test applied to the data. As the Wilcoxon test is a non-parametric univariate test, no adjustment was possible for stratification/minimisation factors.

Comparison groups	Co-amoxiclav v Placebo

Number of subjects included in analysis	136
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.614
Method	Wilcoxon (Mann-Whitney)

Secondary: Duration of Cough

End point title	Duration of Cough

End point description:

Duration of cough was computed as the number of days from randomisation until the last day the symptom was recorded as >0, followed by being recorded as 0 (normal/not affected) for two consecutive days.

End point type	Secondary

End point timeframe:

Cough was scored each day for 28 days from 0-6 (0 being normal/not affected and 6 being as bad as it could be). Once all symptoms were scored 0 for 2 consecutive days recording was stopped

End point values	Co-amoxiclav	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	47		
Units: days				
median (inter-quartile range (Q1-Q3))	8 (5 to 13)	11 (7 to 14)		

Statistical analyses

Statistical analysis title	Wilcoxon rank sum test

Statistical analysis description:

The data for this outcome followed a skewed distribution and could not be transformed to Normality. Therefore, medians and IQRs are presented and a Wilcoxon rank sum test applied to the data. As the Wilcoxon test is a non-parametric univariate test, no adjustment was possible for stratification/minimisation factors.

Comparison groups	Co-amoxiclav v Placebo
Number of subjects included in analysis	97
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.199
Method	Wilcoxon (Mann-Whitney)

Secondary: Duration of Phlegm

End point title	Duration of Phlegm

End point description:

Duration of phlegm was computed as the number of days from randomisation until the last day the symptom was recorded as >0, followed by being recorded as 0 (normal/not affected) for two

consecutive days.

End point type	Secondary

End point timeframe:

Phlegm was scored each day for 28 days from 0-6 (0 being normal/not affected and 6 being as bad as it could be). Once all symptoms were scored 0 for 2 consecutive days recording was stopped

End point values	Co-amoxiclav	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	57	55		
Units: days				
median (inter-quartile range (Q1-Q3))	6 (3 to 9)	6 (3 to 10)		

Statistical analyses

Statistical analysis title	Wilcoxon rank sum test

Statistical analysis description:

The data for this outcome followed a skewed distribution and could not be transformed to Normality. Therefore, medians and IQRs are presented and a Wilcoxon rank sum test applied to the data. As the Wilcoxon test is a non-parametric univariate test, no adjustment was possible for stratification/minimisation factors.

Comparison groups	Co-amoxiclav v Placebo
Number of subjects included in analysis	112
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.513
Method	Wilcoxon (Mann-Whitney)

Secondary: Duration of Shortness of breath

End point title	Duration of Shortness of breath

End point description:

Duration of Shortness of breath was computed as the number of days from randomisation until the last day the symptom was recorded as >0, followed by being recorded as 0 (normal/not affected) for two consecutive days.

End point type	Secondary

End point timeframe:

Shortness of breath was scored each day for 28 days from 0-6 (0 being normal/not affected and 6 being as bad as it could be). Once all symptoms were scored 0 for 2 consecutive days recording was stopped

End point values	Co-amoxiclav	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	66	58		
Units: days				
median (inter-quartile range (Q1-Q3))	3 (1 to 6)	5 (2 to 7)		

Statistical analyses

Statistical analysis title	Wilcoxon rank sum test

Statistical analysis description:

The data for this outcome followed a skewed distribution and could not be transformed to Normality. Therefore, medians and IQRs are presented and a Wilcoxon rank sum test applied to the data. As the Wilcoxon test is a non-parametric univariate test, no adjustment was possible for stratification/minimisation factors.

Comparison groups	Co-amoxiclav v Placebo
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.119
Method	Wilcoxon (Mann-Whitney)

Secondary: Duration of Disturbed sleep

End point title	Duration of Disturbed sleep

End point description:

Duration of disturbed sleep was computed as the number of days from randomisation until the last day the symptom was recorded as >0, followed by being recorded as 0 (normal/not affected) for two consecutive days.

End point type	Secondary

End point timeframe:

Disturbed sleep was scored each day for 28 days from 0-6 (0 being normal/not affected and 6 being as bad as it could be). Once all symptoms were scored 0 for 2 consecutive days recording was stopped

End point values	Co-amoxiclav	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	59	55		
Units: days				
median (inter-quartile range (Q1-Q3))	4 (2 to 6)	7 (3 to 11)		

Statistical analyses

Statistical analysis title	Wilcoxon rank sum test

Statistical analysis description:

The data for this outcome followed a skewed distribution and could not be transformed to Normality. Therefore, medians and IQRs are presented and a Wilcoxon rank sum test applied to the data. As the Wilcoxon test is a non-parametric univariate test, no adjustment was possible for stratification/minimisation factors.

Comparison groups	Co-amoxiclav v Placebo
Number of subjects included in analysis	114
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.021
Method	Wilcoxon (Mann-Whitney)

Secondary: Duration of Feeling generally unwell

End point title	Duration of Feeling generally unwell

End point description:

Duration of Feeling generally unwell was computed as the number of days from randomisation until the last day the symptom was recorded as >0, followed by being recorded as 0 (normal/not affected) for two consecutive days.

End point type	Secondary

End point timeframe:

Feeling generally unwell was scored each day for 28 days from 0-6 (0 being normal/not affected and 6 being as bad as it could be). Once all symptoms were scored 0 for 2 consecutive days recording was stopped

End point values	Co-amoxiclav	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	65	55		
Units: days				
median (inter-quartile range (Q1-Q3))	5 (3 to 8)	7 (4 to 8)		

Statistical analyses

Statistical analysis title	Wilcoxon rank sum test

Statistical analysis description:

The data for this outcome followed a skewed distribution and could not be transformed to Normality. Therefore, medians and IQRs are presented and a Wilcoxon rank sum test applied to the data. As the Wilcoxon test is a non-parametric univariate test, no adjustment was possible for stratification/minimisation factors.

Comparison groups	Co-amoxiclav v Placebo

Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.231
Method	Wilcoxon (Mann-Whitney)

Secondary: Duration of Interference with normal activities ratings

End point title	Duration of Interference with normal activities ratings

End point description:

Duration of Interference with normal activities ratings was computed as the number of days from randomisation until the last day the symptom was recorded as >0, followed by being recorded as 0 (normal/not affected) for two consecutive days.

End point type	Secondary

End point timeframe:

Interference with normal activities ratings was scored each day for 28 days from 0-6 (0 being normal/not affected and 6 being as bad as it could be). Once all symptoms were scored 0 for 2 consecutive days recording was stopped

End point values	Co-amoxiclav	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	65	61		
Units: days				
median (inter-quartile range (Q1-Q3))	4 (2 to 6)	6 (3 to 8)		

Statistical analyses

Statistical analysis title	Wilcoxon rank sum test

Statistical analysis description:

The data for this outcome followed a skewed distribution and could not be transformed to Normality. Therefore, medians and IQRs are presented and a Wilcoxon rank sum test applied to the data. As the Wilcoxon test is a non-parametric univariate test, no adjustment was possible for stratification/minimisation factors.

Comparison groups	Co-amoxiclav v Placebo
Number of subjects included in analysis	126
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.096
Method	Wilcoxon (Mann-Whitney)

Secondary: Medication or further investigations required

End point title	Medication or further investigations required

End point description:

From case notes review, information on whether the child was prescribed antibiotics, other treatments

or investigations at re-consultation episode or hospital admission was used to generate a binary variable to indicate medication or further investigations (Yes/No)

End point type	Secondary

End point timeframe:

All medications and investigations had to be within 28 days from randomisation

End point values	Co-amoxiclav	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	133	132		
Units: number				
Yes	41	33		
No	92	99		

Statistical analyses

Statistical analysis title	Adjusted log-binomial regression

Statistical analysis description:

The analysis was carried out using a log-Binomial regression model adjusted for region, age and current vaccination status

Comparison groups	Placebo v Co-amoxiclav
Number of subjects included in analysis	265
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.274
Method	log binomial regression model
Parameter estimate	Risk ratio (RR)
Point estimate	1.24
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.84
upper limit	1.83

Secondary: Hospitalisation or death within 28 days

End point title	Hospitalisation or death within 28 days

End point description:

'Hospitalised' was defined as admitted to a hospital ward or intensive care unit for at least one overnight stay. The child has a positive response for this outcome if any of the following were recorded as 'yes':
o Admitted to intensive care unit with an overnight stay and this occurred within 28 days of study entry.
o The participant had an acute hospital admission episodes, when he or she has had to spend one or more nights in hospital and the admission occurred within 28 days of study entry.
o The participant died and the death occurred within 28 days of study entry.
If the date of the event was missing, the CRF was reviewed and followed up in order to attempt to fill in the missing data. If the start date could not be established, the event was not included in the analysis.

End point type	Secondary

End point timeframe:
Within 28 days of study entry

End point values	Co-amoxiclav	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	133	132		
Units: number				
Yes	7	7		
No	126	125		

Statistical analyses

Statistical analysis title	Adjusted log-binomial regression

Statistical analysis description:

The analysis was carried out using a log-Binomial regression model on treatment group, adjusted for age and current vaccination status only

Comparison groups	Co-amoxiclav v Placebo
Number of subjects included in analysis	265
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.997
Method	Log-binomial regression
Parameter estimate	Risk ratio (RR)
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.36
upper limit	2.77

Secondary: Adverse event occurred within 28 days

End point title	Adverse event occurred within 28 days

End point description:

End point type	Secondary

End point timeframe:
Within 28 days from study entry

End point values	Co-amoxiclav	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	136	135		
Units: Number of events				
Yes	32	22		
No	104	113		

Statistical analyses

Statistical analysis title	Adjusted log-binomial regression

Statistical analysis description:

The analysis was carried out using a log-Binomial regression model adjusted for region, age and current vaccination status

Comparison groups	Co-amoxiclav v Placebo
Number of subjects included in analysis	271
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.131
Method	Log-binomial regression
Parameter estimate	Risk ratio (RR)
Point estimate	1.45
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.9
upper limit	2.34

Secondary: Adverse event occurred within 28 days (Including AE information for the participant with no AE start date)

End point title	Adverse event occurred within 28 days (Including AE information for the participant with no AE start date)

End point description:

End point type	Secondary

End point timeframe:

Within 28 days of study entry

End point values	Co-amoxiclav	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	136	135		
Units: Number of events				
Yes	32	23		
No	104	112		

Statistical analyses

Statistical analysis title	Adjusted log-binomial regression

Statistical analysis description:

The SAP specified that if no adverse event start date was indicated, then the AE should not be counted as it is not known if it commenced within 28 days of randomisation. In this additional analysis, one participant with an AE but no AE start date is counted as having an AE. The analysis was carried out using a log-Binomial regression model adjusted for region, age and current vaccination status.

Comparison groups	Co-amoxiclav v Placebo
Number of subjects included in analysis	271
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.194
Method	Log-binomial regression
Parameter estimate	Risk ratio (RR)
Point estimate	1.37
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.85
upper limit	2.18

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All AEs occurring in participants within 28 days of study entry observed by the investigator or reported by the participant, whether or not attributed to study medication, will be recorded on the CRF

Adverse event reporting additional description:

Co-amoxiclav is a licensed medication whose most common side-effects are mucocutaneous candidosis (thrush), diarrhoea, nausea, vomiting and rash (occurrence >=1/100 to <1/10) (GlaxoSmithKline UK 2012). If these occur and are non-serious and of mild to moderate severity (based on clinician's assessment), they will not be recorded

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	Co-amoxiclav

Reporting group description:

Subjects randomised to receive co-amoxiclav

Reporting group title	Placebo

Reporting group description:

Subjects randomised to receive Placebo

Serious adverse events	Co-amoxiclav	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 134 (5.97%)	7 / 135 (5.19%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Nervous system disorders			
Lethargy			
subjects affected / exposed	0 / 134 (0.00%)	1 / 135 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	1 / 134 (0.75%)	1 / 135 (0.74%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Asthma			

subjects affected / exposed	0 / 134 (0.00%)	1 / 135 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	3 / 134 (2.24%)	4 / 135 (2.96%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	3 / 134 (2.24%)	5 / 135 (3.70%)	
occurrences causally related to treatment / all	0 / 3	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	1 / 134 (0.75%)	0 / 135 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachypnoea			
subjects affected / exposed	1 / 134 (0.75%)	0 / 135 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wheezing			
subjects affected / exposed	2 / 134 (1.49%)	3 / 135 (2.22%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Musculoskeletal chest pain			
subjects affected / exposed	1 / 134 (0.75%)	0 / 135 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bronchiolitis			
subjects affected / exposed	0 / 134 (0.00%)	1 / 135 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Lower respiratory tract infection			
subjects affected / exposed	3 / 134 (2.24%)	3 / 135 (2.22%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngitis			
subjects affected / exposed	1 / 134 (0.75%)	0 / 135 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 134 (0.00%)	1 / 135 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Fluid intake reduced			
subjects affected / exposed	0 / 134 (0.00%)	1 / 135 (0.74%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Co-amoxiclav	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	32 / 134 (23.88%)	23 / 135 (17.04%)	
Injury, poisoning and procedural complications			
Vaccination complication			
subjects affected / exposed	1 / 134 (0.75%)	0 / 135 (0.00%)	
occurrences (all)	1	0	
Surgical and medical procedures			
Oxygen supplementation			
subjects affected / exposed	0 / 134 (0.00%)	1 / 135 (0.74%)	
occurrences (all)	0	1	
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 134 (0.75%)	0 / 135 (0.00%)	
occurrences (all)	1	0	
Lethargy			

subjects affected / exposed	0 / 134 (0.00%)	1 / 135 (0.74%)	
occurrences (all)	0	1	
Psychomotor hyperactivity			
subjects affected / exposed	0 / 134 (0.00%)	1 / 135 (0.74%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Adverse drug reaction			
subjects affected / exposed	3 / 134 (2.24%)	0 / 135 (0.00%)	
occurrences (all)	3	0	
Discomfort			
subjects affected / exposed	1 / 134 (0.75%)	0 / 135 (0.00%)	
occurrences (all)	1	0	
Pyrexia			
subjects affected / exposed	3 / 134 (2.24%)	0 / 135 (0.00%)	
occurrences (all)	3	0	
Ear and labyrinth disorders			
Ear Pain			
subjects affected / exposed	1 / 134 (0.75%)	0 / 135 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Anal fissure			
subjects affected / exposed	0 / 134 (0.00%)	1 / 135 (0.74%)	
occurrences (all)	0	1	
Constipation			
subjects affected / exposed	1 / 134 (0.75%)	0 / 135 (0.00%)	
occurrences (all)	1	0	
Diarrhoea			
subjects affected / exposed	4 / 134 (2.99%)	1 / 135 (0.74%)	
occurrences (all)	4	1	
Vomitting			
subjects affected / exposed	3 / 134 (2.24%)	3 / 135 (2.22%)	
occurrences (all)	3	3	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	2 / 134 (1.49%)	1 / 135 (0.74%)	
occurrences (all)	2	1	

Cough			
subjects affected / exposed	1 / 134 (0.75%)	0 / 135 (0.00%)	
occurrences (all)	1	0	
Dyspnoea			
subjects affected / exposed	1 / 134 (0.75%)	2 / 135 (1.48%)	
occurrences (all)	1	2	
Epistaxis			
subjects affected / exposed	0 / 134 (0.00%)	1 / 135 (0.74%)	
occurrences (all)	0	1	
Hypoxia			
subjects affected / exposed	1 / 134 (0.75%)	4 / 135 (2.96%)	
occurrences (all)	1	4	
Rhinorrhoea			
subjects affected / exposed	2 / 134 (1.49%)	0 / 135 (0.00%)	
occurrences (all)	2	0	
Wheezing			
subjects affected / exposed	1 / 134 (0.75%)	1 / 135 (0.74%)	
occurrences (all)	1	1	
Skin and subcutaneous tissue disorders			
Dermatitis allergic			
subjects affected / exposed	1 / 134 (0.75%)	0 / 135 (0.00%)	
occurrences (all)	1	0	
Dermatitis diaper			
subjects affected / exposed	1 / 134 (0.75%)	0 / 135 (0.00%)	
occurrences (all)	1	0	
Rash			
subjects affected / exposed	4 / 134 (2.99%)	3 / 135 (2.22%)	
occurrences (all)	4	3	
Rash generalised			
subjects affected / exposed	0 / 134 (0.00%)	1 / 135 (0.74%)	
occurrences (all)	0	1	
Rash macular			
subjects affected / exposed	1 / 134 (0.75%)	0 / 135 (0.00%)	
occurrences (all)	1	0	
Rash papular			

subjects affected / exposed	0 / 134 (0.00%)	1 / 135 (0.74%)	
occurrences (all)	0	1	
Swelling face			
subjects affected / exposed	0 / 134 (0.00%)	1 / 135 (0.74%)	
occurrences (all)	0	1	
Psychiatric disorders			
Delirium			
subjects affected / exposed	1 / 134 (0.75%)	0 / 135 (0.00%)	
occurrences (all)	1	0	
Irritability			
subjects affected / exposed	0 / 134 (0.00%)	1 / 135 (0.74%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Myalgia intercostal			
subjects affected / exposed	1 / 134 (0.75%)	0 / 135 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Bronchiolitis			
subjects affected / exposed	0 / 134 (0.00%)	1 / 135 (0.74%)	
occurrences (all)	0	1	
Conjunctivitis			
subjects affected / exposed	1 / 134 (0.75%)	1 / 135 (0.74%)	
occurrences (all)	1	1	
Ear Infection			
subjects affected / exposed	1 / 134 (0.75%)	2 / 135 (1.48%)	
occurrences (all)	1	2	
hand-foot -and-mouth disease			
subjects affected / exposed	0 / 134 (0.00%)	1 / 135 (0.74%)	
occurrences (all)	0	1	
Infection			
subjects affected / exposed	0 / 134 (0.00%)	1 / 135 (0.74%)	
occurrences (all)	0	1	
Lower respiratory tract infection			
subjects affected / exposed	3 / 134 (2.24%)	1 / 135 (0.74%)	
occurrences (all)	3	1	
Otitis externa			

subjects affected / exposed	1 / 134 (0.75%)	0 / 135 (0.00%)	
occurrences (all)	1	0	
Pneumonia			
subjects affected / exposed	1 / 134 (0.75%)	1 / 135 (0.74%)	
occurrences (all)	1	1	
Pneumonia viral			
subjects affected / exposed	1 / 134 (0.75%)	0 / 135 (0.00%)	
occurrences (all)	1	0	
Rhinitis			
subjects affected / exposed	1 / 134 (0.75%)	0 / 135 (0.00%)	
occurrences (all)	1	0	
Scarlet fever			
subjects affected / exposed	0 / 134 (0.00%)	1 / 135 (0.74%)	
occurrences (all)	0	1	
Tonsillitis			
subjects affected / exposed	1 / 134 (0.75%)	0 / 135 (0.00%)	
occurrences (all)	1	0	
Viral infection			
subjects affected / exposed	0 / 134 (0.00%)	1 / 135 (0.74%)	
occurrences (all)	0	1	
Viral rash			
subjects affected / exposed	2 / 134 (1.49%)	0 / 135 (0.00%)	
occurrences (all)	2	0	
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 134 (0.75%)	0 / 135 (0.00%)	
occurrences (all)	1	0	
Influenza			
subjects affected / exposed	0 / 134 (0.00%)	1 / 135 (0.74%)	
occurrences (all)	0	1	
Respiratory tract infection			
subjects affected / exposed	0 / 134 (0.00%)	1 / 135 (0.74%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
Fluid intake reduced			
subjects affected / exposed	0 / 134 (0.00%)	1 / 135 (0.74%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 June 2017	1. Addition of investigator and updating of contact details 2. Clarified dosing regime based on BNF guidelines and addition of advice if child under 6kg 3. Clarified data collected during telephone follow up calls including compliance data 4. Addition of vaccination data collection in trial design summary as previously omitted in error 5. Modified eligibility criteria to: a. Remove requirement that children should be registered at a GP surgery in England and replaced with requirement that child should be registered at a GP surgery in UK. b. Clarify that exclusion criterion relating to antibiotic use within the last 72 hours refers specifically to use of antibiotics for treatment of acute infection. c. Clarify exclusion criteria relating to hospitalisation. 6. Addition of hospitalization with pneumonia as a potential risk category 7. Clarify recruitment and screening & eligibility processes to allow flexibility across different sites and site types. 8. Removal of term 'high' in reference to nasal swabs to better reflect actual procedure 9. Addition of availability of emergency randomization procedures 10. Changed reference to trial SOP's to working instructions to reflect PC CTU internal policy that the term SOP's should be used to refer to general and trial procedures while work instructions should be used to refer to trial specific procedures. 11. Clarified SAE reporting procedures 12. Clarified extension of planned trial period to May 2019.
12 September 2018	1. Change of Chief Investigator (CI) 2. Addition of investigators 3. Clarification that end of trial is considered to be the date of the last data capture of the last trial participant. 4. Gift vouchers to be offered to children participating in the follow up swab sub study 5. Change of Principal Investigators at CRN's with open sites where former CI has acted as regional PI.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported