The early use of Antibiotics for at Risk CHildren with InfluEnza-like illness (ARCHIE): a double-blind randomised placebo-controlled trial

Online appendices

Appendix 1: Study eligibility criteria

Inclusion Criteria

- Aged 6 months to 12 years inclusive.
- In 'at risk' category.
- Presenting with influenza-like illness (i.e. cough and fever*) during influenza season.
- Presenting within 5 days of symptom onset.
- Permanently registered at a general practice in UK.
- Parent /guardian able to complete study diary and questionnaires.

Exclusion Criteria

The participant may not enter the trial if ANY of the following apply:

- Known contraindication to co-amoxiclav.
- Child given antibiotics for treatment of an acute infection within the last 72 hours.
- Child requires immediate antibiotics (clinician's judgement).
- Child requires immediate hospital admission for treatment of an influenza-related complication (clinician's judgement).
- Child has been observed on hospital ward or ambulatory care unit for longer than 24 hours.
- Presence of any reason to prevent healthcare professional from obtaining nasal swab.
- Child with known cystic fibrosis.
- Child previously entered into the ARCHIE study.
- Child has been involved in another medicinal trial within the last 90 days.

*Fever is defined as any of the following: child-reported fever, parent-reported fever or temperature >37.8°C (axillary or tympanic temperature measurement).

Appendix 2: 'At risk' groups

Respiratory

- Asthma requiring continuous or repeated use of controller therapy (e.g. inhaled steroids, leukotriene receptor antagonists, long-acting beta agonists, systemic steroids).
- Admitted to hospital with exacerbation of asthma within the last 12 months.
- Admitted to hospital with bronchiolitis or pneumonia within the last 12 months.
- Recurrent viral wheeze (3 or more episodes within the last 12 months).
- Bronchopulmonary dysplasia.

Cardiac

- Congenital heart disease being actively managed or monitored by cardiology team.
- Chronic heart failure being actively managed or monitored by cardiology team.

Neurological

- Chronic neurological or neuromuscular disorder which compromises respiratory function (e.g. cerebral palsy).

Renal

- Chronic kidney disease defined as either of the following:
    - Impaired eGFR[§] (estimated glomerular filtration rate) measurement within the last 12 months.
    - Known hereditary or structural kidney abnormality with or without impairment in eGFR.
- Nephrotic syndrome.
- Kidney transplantation.

Liver[§§]

- Cirrhosis
- Biliary atresia
- Chronic hepatitis

Immunodeficiency

- Asplenia or splenic dysfunction.
- HIV infection.
- Undergoing chemotherapy leading to immunosuppression.
- Taking systemic steroids at a dose equivalent to prednisolone 20mg or more per day (any age) or >=1mg per kg per day (children under 20kg).

Other

- Diabetes mellitus (type 1 or type 2) or other metabolic condition.
- Genetic abnormality (e.g. Down's syndrome)
- Sickle cell disease
- Malignancy
- Prematurity (born before 37 weeks gestation) in children aged 6 to 23 months.

[§]Impaired eGFR is defined as an eGFR measurement of 59 ml/min/1.73m^2 or less within the last 12 months before study entry. However, to enter the trial the following two conditions must also be satisfied:

1. eGFR >=30 ml/min/1.73m^2 based on most recent measurement within the last 12 months;
2. no reason to suspect further deterioration in eGFR at time of study entry.

[§§]Children with mild or moderate liver disease may enter the trial. However, to minimise the risk of serious hepatic complications related to study medication, children with severe liver disease may not enter the trial. Severe liver disease is defined as hepatic impairment associated with any of the following: jaundice, impaired coagulation/increased bleeding risk, bilirubin persistently greater than 50 micromol/litre (two measurements within last 12 months).

Appendix 3: Laboratory analysis of nasal and throat swab samples

Nasal and throat swabs were processed at Alder Hey Children's Hospital, Liverpool, UK. Nasal swabs were analysed by real-time Polymerase Chain Reaction analysis (FILMARRAY® Respiratory panel, Biomérieux UK Ltd.) to detect influenza A (A/H1, A/H1pdm2009 & A/H3) and B (among other viruses), *Bordetella pertussis, Chlamydia pneumoniae and Mycoplasma pneumoniae*. Aliquots (1µl & 10µl loops) of the bacterial transport medium were spread onto *Streptococcus* selective blood agar (with and without ampicillin) to culture *Streptococcus pneumoniae* and beta-haemolytic streptococci, and *Haemophilus* selective chocolate agar (with and without ampicillin) to culture *Haemophilus influenzae and Staphylococcus aureus*. Identification of these and other organisms was performed in line with Public Health England Standards for Microbiological Investigations.

Appendix 4: Study medication dosing regimen

Child's age	**Study medication dose**
6 months to 23 months Under 6 kg	Calculate dose according to British National Formulary (BNF) instructions for co-amoxiclav 400/57. Advise two doses daily for 5 days.
6.0 – 7.9 kg	1 ml twice daily for 5 days
8.0 – 10.9 kg	1.5 ml twice daily for 5 days
11.0 – 12.9 kg	2 ml twice daily for 5 days
2 to 6 years	2.5 ml twice daily for 5 days
7 to 12 years	5 ml twice daily for 5 days

Medically qualified individuals were advised to use clinical judgement in deciding doses for any children to whom they felt standard British National Formulary (BNF) dosing recommendations should not apply.

Appendix 5: Number of study medication doses taken by participants whose parents/guardians reported that they had not taken all ten doses of study medication

Number of study medication doses taken	Co-amoxiclav (n=14)	Placebo (n=15)
0	1	2
1	2	1
2	1	4
3	0	1
4	3	1
5	0	1
6	2	1
8	0	2
9	2	1
Not known	3	1

Appendix 6: Serious Adverse Events

Co-amoxiclav (n=9)		Placebo (n=9)	
Participant ID	**Details of SAE**	**Participant ID**	**Details of SAE**
100/0001	Breathing difficulties, admitted for observation.	210/0676	Likely viral-induced wheeze, admitted for observation, required oxygen supplementation.
167/0497	Wheezing, admitted for observation.	210/0677	Viral respiratory tract infection, required admission for observation and oxygen supplementation.
179/0782 (1)*	Viral pneumonitis requiring oxygen supplementation.	210/0785 (1)	Viral respiratory tract infection, required admission for oxygen and respiratory support.
179/0782 (2)*	Acute lower respiratory tract infection requiring oxygen supplementation.	210/0785 (2)	Likely bronchiolitis, required admission for oxygen, steroids and antibiotics.
191/0447	Chest wall pain, fever, tachypnoea.	222/0767 (1)	Wheezing and increased work in breathing.
210/0678	Chest infection requiring admission for oxygen and intravenous antibiotics.	222/0767 (2)	Lethargic, increased work of breathing, low oxygen saturations, reduced fluid intake.
215/0706	Worsening cough and fever, admitted for observation.	240/0998	High temperature, cough, tachycardia. Commenced on antibiotics.
222/0761	Tonsillitis, vomiting and distressed, taking short sharp inspiratory breaths.	246/0218	Pneumonia, admitted for intravenous antibiotics.
240/0993	Viral-induced wheeze, increased work of breathing.	318/0523	Exacerbation of asthma.

n=number of serious adverse events reported.
SAE = Serious Adverse Event
(1) indicates first serious adverse event in participant
(2) indicates second serious adverse event in participant
*Not re-consultations due to clinical deterioration because not considered to be due to same illness episode as the index illness episode for which the participant was recruited into the trial.