

Title:

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

Short title:

The early use of Antibiotics for at Risk Children with Influenza-like illness (ARCHIE)

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Take home message:

This trial did not find evidence that early co-amoxiclav use reduces re-consultation due to clinical deterioration in 'at risk' children who present with influenza-like illness during influenza season.

Abstract

Introduction

The UK government stockpiles co-amoxiclav to treat bacterial complications during influenza pandemics. This pragmatic trial examines whether early co-amoxiclav use reduces re-consultation due to clinical deterioration in 'at risk' children presenting with influenza-like illness (ILI) in primary or ambulatory care.

Methods

'At risk' children aged 6 months to 12 years presenting within five days of ILI onset were randomly assigned to oral co-amoxiclav 400/57 or placebo twice daily for five days (dosing based on age +/- weight). 'At risk' groups included children with respiratory, cardiac, and neurological conditions. Randomisation was stratified by region and used a non-deterministic minimisation algorithm to balance age and current seasonal influenza vaccination status. Our target sample size was 650 children, which would have allowed us to detect a reduction in the proportion of children re-consulting due to clinical deterioration from 40% to 26% with 90% power and 5% two-tailed alpha error, including allowance for 25% loss to follow-up and an inflation factor of 1.041. Participants, caregivers and investigators were blinded to treatment allocation. Intention-to-treat analysis included all randomised participants with primary outcome data on re-consultation due to clinical deterioration within 28 days. Safety analysis included all randomised participants. Trial registration: ISRCTN 70714783. EudraCT 2013-002822-21.

Results

We recruited 271 children between 11 February 2015 and 20 April 2018. Primary outcome data were available for 265 children. Only 61/265 children (23.0%) re-consulted due to clinical deterioration. No evidence of a treatment effect was observed for re-consultation due to clinical deterioration (co-amoxiclav 33/133 (24.8%), placebo 28/132 (21.2%), adjusted risk ratio [RR] 1.16, 95% confidence interval [CI] 0.75 to 1.80). There was also no evidence of a difference between groups in the proportion of children for whom one or more adverse events were reported (co-amoxiclav 32/136 (23.5%), placebo 22/135 (16.3%), adjusted RR 1.45, 95% CI 0.90 to 2.34). Sixty-six adverse events were reported in total (co-amoxiclav n=37, placebo n=29). Nine serious adverse events were reported per group; none were considered related to study medication.

Conclusion

Our trial did not find evidence that treatment with co-amoxiclav reduces risk of re-consultation due to clinical deterioration in 'at risk' children who present early with ILI during influenza season. Our findings therefore do not support early co-amoxiclav use in children with seasonal ILI.

Introduction

Influenza is mostly a mild, self-limiting illness. However, children with respiratory, cardiac, liver, and neurological conditions, as well as diabetes mellitus, immunosuppression[1] and children who were born prematurely[2] are considered at higher risk of complications such as pneumonia. A nearly six-fold increase in hospitalisation is reported in children aged 5 to 14 years in clinical risk groups.[3]

The UK government stockpiles co-amoxiclav for treating bacterial complications during influenza pandemics. Consistently high susceptibility to co-amoxiclav has been demonstrated in lower respiratory tract bacterial isolates associated with influenza.[4] Immediate antibiotic treatment is recommended for respiratory tract infections (RTIs) in individuals with significant underlying disease.[5] However, primary care clinicians report uncertainty about prescribing antibiotics to children with mild or moderate risk factors.[6] Routinely collected general practice data show that antibiotics are prescribed to 28% of patients with comorbidities versus 18% of otherwise healthy individuals with influenza-like illness (ILI).[7]

Although routine antibiotic use is not recommended for viral RTIs,[5] preliminary data suggest that early antibiotic treatment may reduce clinical deterioration in patients with influenza or ILI. One randomised placebo-controlled trial found that treatment with sultamicillin significantly reduced incidence of pneumonia in children with ILI.[8] An open-label trial in adults with confirmed influenza found that treatment with oseltamivir and azithromycin was associated with more frequent improvement in sore throat on day 2 than oseltamivir alone.[9] Additionally, observational data from children with laboratory-confirmed influenza demonstrated that by day 7, fever had settled in all children treated early with antibiotics but persisted beyond 7 days in around one-fifth of those who did not receive antibiotics.[10]

Since point-of care testing for influenza is not currently available in most primary and ambulatory care settings, we conducted a pragmatic trial to determine whether early co-amoxiclav use reduces risk of re-consultation due to clinical deterioration in 'at risk' children with ILI.

Methods

Study design and participants

In this double-blind randomised placebo-controlled phase IV trial, participants were recruited from general practices and other ambulatory care settings in England and Wales. Recruitment began on February 11, 2015. Subsequent recruitment seasons commenced in October and continued until the end of March the following year or later if data from the Royal College of General Practitioners Research and Surveillance Centre indicated that the weekly influenza-like illness (ILI) GP consultation rate was still above the baseline seasonal threshold calculated each season using the Moving Epidemic Method.[11] In total, we opened 151 general practices, 42 hospitals and two walk-in centres for recruitment.

We recruited 'at risk' children with known risk factors for influenza-related complications who were aged 6 months to 12 years and presented within the first five days of an influenza-like illness (ILI).[12] Appendix 1 lists our full eligibility criteria. Appendix 2 summarises our 'at risk' groups. ILI was defined as presence of cough and fever; fever could be child-reported, parent/guardian-reported or axillary or tympanic temperature $>37.8^{\circ}\text{C}$. We excluded children with known contraindications to co-amoxiclav and children who required immediate antibiotics or hospital admission based on their clinician's judgement. We also excluded children with known cystic fibrosis because immediate antibiotic treatment of acute respiratory tract infections is recommended in these children.[13]

To increase our pool of potential recruits, we made minor changes to our eligibility criteria before the 2017/18 recruitment season. Firstly, we included children permanently registered at general practices anywhere in the UK, not just England. Secondly, we only excluded children given antibiotics within the last 72 hours for an acute infection rather than long-term prophylaxis. Thirdly, we clarified that children requiring immediate hospitalisation would only be excluded if this was for treatment of an influenza-related complication or observation period lasting longer than 24 hours. The trial received ethical approval from the National Research Ethic Service Committee North West Coast – Liverpool East. Additional approvals were received from the Health Research Authority, Medicines and Healthcare products Regulation Agency and where applicable local governance organisations. Written informed consent was obtained from a parent or guardian for all participants.

The trial is registered at the ISRCTN registry (identifier ISRCTN70714783) and the EudraCT database (identifier 2013-002822-21).

Randomisation and blinding

Following assessment of eligibility and baseline characterisation, participants were randomly assigned (1:1) to receive co-amoxiclav 400/57 (amoxicillin 400 mg as trihydrate and clavulanic acid 57 mg as potassium salt/5 mL when reconstituted with water) or placebo suspension using Sortition®, a web-based randomisation system developed and fully validated by the Primary Care Clinical Trials Unit at the University of Oxford.

Randomisation was stratified by region (five regions) and minimised, using a non-deterministic algorithm, for age (6 to 23 months or 2 to 12 years) and current seasonal influenza vaccination status (yes or otherwise). The chance of being allocated to the minimising group was set to 80%. Each site was sent study medication in blocks of eight. Allocations were computer generated using block randomisation (block sizes of two and four) by the trial statistician using Stata version 13.1. This ensured that each site maintained equal supplies of co-amoxiclav and placebo.

Health care professionals dispensed study medication. Health care professionals, the study team, participants, and parents/guardians were blinded to treatment allocation. Co-amoxiclav and placebo had identical packaging and appearance when reconstituted but were not taste matched. Blinding was therefore maintained by only allowing each child to be recruited once.

Procedures

Our protocol[12] describes our study procedures. In summary, we collected baseline data on age, sex, comorbidities, household smoking status, influenza vaccination status, medications given during the current illness episode, duration of fever, duration of symptoms, heart rate, and respiratory rate. Nasal swabs were obtained and placed in viral transport medium. Throat swabs were also obtained where possible and placed in a bacterial transport medium. Appendix 3 details laboratory analysis of swab samples.

Participants were asked to take study medication orally twice daily for five days. Appendix 4 summarises our dosing regimen, which was based on British National Formulary guidance for prescribing co-amoxiclav 400/57.

Parents/guardians were given four one-week diaries to record doses of study medication taken (week 1 diary only), axillary temperature (daily at bedtime or before giving antipyretics, whichever occurred sooner), symptoms and adverse events. Symptom data were collected daily until the child had recovered; data collection resumed if symptoms relapsed. Parents/guardians were asked to record temperature daily for 28 days or until it had been below 37.5°C for two consecutive days.

Health care professionals contacted parents/guardians by telephone one and two weeks after randomisation to collect data on adverse events, duration of fever and study medication doses taken in case diary data were not provided.

Data were extracted from participants' medical records on medical conditions, regular medications, vaccinations, acute consultations during the 12-month period before randomisation, antibiotic prescriptions during the 3-month period before randomisation and re-consultations. Data on re-consultations, medication prescriptions, investigations, hospitalisations and deaths within 28 days of randomisation were also extracted.

Outcomes

Our primary outcome was re-consultation due to clinical deterioration within 28 days of randomisation. We defined clinical deterioration as worsening symptoms, development of new symptoms or development of complications requiring medication or hospitalisation. This definition was successfully used in a large trial involving adults with lower respiratory tract infection[14] and a cohort study involving children with acute cough.[15] 'Worsening symptoms' were identified through documented evidence of deterioration in symptoms reported at the index consultation. Given the pragmatic nature of our trial, we did not require health care professionals to use validated scales to score symptom severity at the index consultation or during re-consultation episodes. 'New symptoms' included any symptoms not reported at the index consultation. Hospitalisations included hospital admissions following primary care referrals and direct admissions from hospital ambulatory care settings. To ensure accurate recording of clinical outcome data, a clinician independent from the study team reviewed a random selection of medical records.

Secondary outcomes were medication prescriptions and/or further investigations, adverse events, hospitalisations or deaths (all within 28 days of randomisation), duration of fever and duration of symptoms. Our protocol did not require recruiting sites to report oral mucocutaneous candidosis (thrush), diarrhoea, nausea, vomiting or rash as adverse events if they were assessed as being of mild or moderate clinical severity and did not result in a serious adverse event, as these are already known common side-effects of co-amoxiclav.

Data on other outcomes relating to health-related quality of life measures, health care resource utilisation, bacterial carriage and antibiotic resistance were also collected but will be reported in separate papers.

Statistical analysis

Primary care data report that complications occur in 17.6% of children with chronic underlying conditions who present with ILI[16] and account for 44% of unplanned re-consultations due to complications, new symptoms or delayed resolution in children presenting in primary care with acute RTIs (61/138 children).[17] We therefore estimated that 40% of participants in the placebo group would re-consult due to clinical deterioration.

Our target sample size was 650 participants, including allowance for 25% loss to follow-up and an inflation factor of 1.041 to allow for potential clustering within recruiting sites due to differences in physician care and prescribing rates.[12] Our estimate was based on a conservative intracluster correlation estimate of 0.03,[18] a coefficient of variation value of 0.6,[19] and an average cluster size of two participants.[20] This would allow detection of a reduction in proportion of participants re-consulting due to clinical deterioration from 40% to 26% (35% relative risk reduction [RRR]) with 90% power and 5% two-tailed alpha error.

Due to slow recruitment, we had interim discussions with our funder, who agreed to support continuation of the trial after discussing strategies for enhancing recruitment[12] and recognising that an effective sample size of 266 participants would still allow detection of a reduction in clinical deterioration from 40% to 23% (RRR 42.5%) with 80% power and 5% two-tailed alpha error. This effect size was still considered conservative since a previous trial[8] reported a RRR of 85% in incidence of pneumonia in children with ILI who were treated with sultamicillin (1/42 children) versus placebo (7/43 children). Although this trial was relatively small and did not collect outcome data on re-consultations due to clinical deterioration, it had similarities to the present trial in that it also recruited children with ILI (rather than laboratory-confirmed influenza) and involved a medication which, like co-amoxiclav, contains a penicillin antibiotic (ampicillin) and a beta-lactamase inhibitor (sulbactam).

Data were double-entered and verified in OpenClinica open source software (V.3.13; Waltham MA, USA). Statistical analyses were performed using Stata version 15.1 (SE).

We performed an intention-to-treat analysis and participants were analysed in the groups to which they were allocated. The proportions of children re-consulting due to clinical deterioration in the two groups was compared using a χ^2 test and log-binomial regression model with adjustment for region, age and current seasonal influenza vaccination status. The treatment effect is reported as a relative risk with 95% confidence interval (CI); the P value is also presented. An unadjusted risk difference is also presented with 95% CI.

Durations of fever and symptoms were compared between groups using the Wilcoxon rank sum test and quantile regression. Analyses performed using quantile regression were adjusted for region, age, and current seasonal influenza vaccination status. Binary outcomes (proportions of children prescribed medication and/or requiring further investigations, children in whom adverse events are reported and children who were hospitalised or died within 28 days of randomisation) were compared using χ^2 /Fisher's exact test for the unadjusted analysis and log-binomial regression, adjusting for region, age, and current seasonal influenza vaccination status.

Exploratory subgroup analyses of the primary outcome were pre-specified in the statistical analysis plan to explore whether laboratory-confirmed influenza and treatment with antiviral medications during the index ILI episode moderated the treatment effect. The log-binomial regression model was fitted on the outcome of re-consultation due to clinical deterioration and adjusted for region, age and current seasonal influenza vaccination status with an additional main effect for the subgroup variable and an interaction term for randomised group and subgroup variable.

Results

Recruitment

Between February 11, 2015 and April 20, 2018, we screened 756 children. However, 370 did not meet study eligibility criteria. A further 115 children were eligible but their parents/guardians did not give consent for study participation. Our decision during the 2017/18 season to only exclude children given antibiotics within the last 72 hours if these were for an acute infection did not increase the proportion of children screened who were excluded for this reason (2015/16: 9/197 [4.6%], 2016/17: 23/229 [10.0%], 2017/18: 25/330 [7.6%]). Prophylactic antibiotic prescriptions were only recorded in five participants (azithromycin n=2, amoxicillin n=1, co-trimoxazole n=1, trimethoprim n=1).

We randomly assigned 271 participants to receive co-amoxiclav (n=136) or placebo (n=135). Parents/guardians reported that all study medication doses were taken by 81/95 participants in the co-amoxiclav group (85%) and 74/89 participants in the placebo group (83%) for whom adherence

data were available (i.e. data on whether or not all ten doses of study medication had been taken). Appendix 5 summarises data on number of study medication doses taken by participants whose parents/guardians reported that they took less than ten doses. Appendix 5 also includes data on participants whose parents/guardians reported that less than ten doses had been taken but were unable to specify the exact number of doses.

Figure 1 summarises recruitment and follow-up of participants. Data on re-consultations due to clinical deterioration were available for 265 participants (co-amoxiclav n=133, placebo n=132). The parents/guardians of five participants withdrew consent for data extraction from medical notes (co-amoxiclav n=2, placebo n=3). The general practice of one child (co-amoxiclav) refused the research team access to the medical notes for internal reasons.

Participant characteristics

Table 1 summarises participants' baseline characteristics. Nearly three-quarters of risk factors were in the respiratory category (198/271 participants, 73.1%), most commonly asthma (n=99) and recurrent viral wheeze (n=70). Around one-third of participants received the influenza vaccination relating to the season during which they were recruited. Laboratory-confirmed influenza was detected in 37/271 children (13.7%). However, rhino/enteroviruses were more commonly isolated (119/271 children, 43.9%). Throat swabs were obtained from 225 participants (co-amoxiclav n=114, placebo n=111). The commonest bacterial isolate was *Haemophilus influenzae*, which was detected in 52/225 throat swabs (23.1%) and 13/37 participants with laboratory-confirmed influenza (35.1%).

Table 1: Baseline characteristics

Participant characteristics	Co-amoxiclav (n=136) Number (%), Median (IQR) or Mean (SD)	Placebo (n=135) Number (%), Median (IQR) or Mean (SD)
Age (months)	40.8 (19.4 to 85.6)	36.4 (20.9 to 70.8)
Gender: Male	83 (61.0)	80 (59.3)
Region		
A	45 (33.1)	44 (32.6)
B	32 (23.5)	30 (22.2)
C	25 (18.4)	25 (18.5)
D	23 (16.9)	24 (17.8)
E	11 (8.1)	12 (8.9)
'At risk' categories*		
Respiratory	99 (72.8)	99 (73.3)
Premature birth ^a	13 (9.6)	15 (11.1)
Genetic	9 (6.6)	9 (6.7)
Cardiac	12 (8.8)	4 (3.0)
Neurological	6 (4.4)	9 (6.7)
Previous recurrent or serious respiratory problems	6 (4.4)	8 (5.9)
Renal	3 (2.2)	0
Immunodeficiency	1 (0.7)	0
Metabolic	1 (0.7)	5
Other	3 (2.2)	3 (2.2)
One or more smokers in household	21 (15.4)	27 (20.0)
Received current season's influenza vaccination	45 (33.1)	45 (33.3)
Received previous season's influenza vaccination	48 (35.3)	41 (30.4)
Received Hib vaccination	124 (91.2)	124 (91.9)
Received PCV vaccination	122 (89.7)	122 (90.4)
Duration of illness (days)	2.7 (1.2)	2.7 (1.2)
Duration of fever (days) ^b	1.9 (1.2)	2.2 (1.2)
Antipyretics given since ILI episode started	115 (84.6)	118 (87.4)
Heart rate (beats per minute) ^c	115 (22.4)	117 (22.8)
Respiratory rate (breaths per minute) ^d	28 (9.1)	28 (9.9)
Temperature (°C) ^e	37.0 (0.8)	37.0 (0.9)
One or more acute consultations during 12-month period before study entry	123 (90.4)	119 (88.2)
Antibiotics prescribed during the 3-month period before study entry	33 (24.3)	25 (18.5)
One or more virus isolates ^f	121 (89.0)	112 (83.0)
Influenza (any strain)^{f,g}	21 (15.4)	16 (11.9)
• Influenza A	3 (2.2)	1 (0.7)
• Influenza A/H1-2009	1 (0.7)	3 (2.2)
• Influenza A/H3	7 (7.0)	6 (6.0)
• Influenza B	10 (7.4)	7 (5.2)
Other respiratory viruses^f	93 (68.4)	108 (80.0)
• Rhinovirus/Enterovirus	55 (40.4)	64 (47.4)
• Respiratory Syncytial Virus	24 (17.7)	24 (17.8)
• Coronavirus	15 (11.0)	11 (8.2)
• Parainfluenza (any strain)	10 (7.4)	16 (11.9)
• Adenovirus	8 (5.9)	15 (11.1)
• Human metapneumovirus	8 (5.9)	9 (6.7)

Table 1 continued

Participant characteristics	Co-amoxiclav (n=136) Number (%), Median (IQR) or Mean (SD)	Placebo (n=135) Number (%), Median (IQR) or Mean (SD)
One or more bacterial isolates ^{f,h}	28 (20.6)	40 (29.6)
Bacterial isolates in children with evidence of laboratory-confirmed influenza		
• <i>Haemophilus influenzae</i> ^h	6 (4.4)	7 (5.2)
• Group A Streptococcus ^h	1 (0.7)	0
• Group C Streptococcus ^h	1 (0.7)	0
• Group G Streptococcus ^h	0	1 (0.7)
• <i>Staphylococcus aureus</i> ^h	2 (1.5)	0
Bacterial isolates in children without evidence of laboratory-confirmed influenzaⁱ		
• <i>Haemophilus influenzae</i> ^h	14 (10.3)	25 (18.5)
• Group A Streptococcus ^h	2 (1.5)	3 (2.2)
• Group G Streptococcus ^h	0	2 (1.5)
• <i>Staphylococcus aureus</i> ^h	2 (1.5)	1 (0.7)
• <i>Streptococcus pneumoniae</i> ^h	1 (0.7)	0
• MRSA ^h	0	1 (0.7)
• <i>Mycoplasma pneumoniae</i> ^f	3 (2.2)	1 (0.7)
• <i>Chlamydia pneumoniae</i> ^f	0	2 (1.5)

IQR = interquartile range, SD = standard deviation, Hib = *Haemophilus influenzae* b; PCV = Pneumococcal conjugate vaccine, MRSA = Methicillin-resistant *Staphylococcus aureus*

Region A: Thames Valley and South Midlands Clinical Research Network (CRN), West Midlands CRN, North Thames CRN, North West London CRN, South London CRN; Region B: West of England CRN, South West Peninsula CRN, Cardiff and Vale University Health Board, Aneurin Bevan University Health Board, Abertawe Bro Morgannwg University Health Board; Region C: Greater Manchester CRN, North East and North Cumbria CRN, North West Coast CRN, Yorkshire and Humber CRN; Region D: Kent Surrey and Sussex CRN, Wessex CRN.; Region E: Eastern CRN, East Midlands CRN

*Not mutually exclusive.

^aFour children in whom premature birth was recorded as a risk factor were aged 2 years or over at baseline (co-amoxiclav n=3, placebo n=1). Although premature birth was only considered a risk factor in children aged 6 to 23 months in this trial, all four children had other risk factors.

^bData available for 134 children in the co-amoxiclav group and 132 children in the placebo group.

^cData available for 133 children in the co-amoxiclav group and 134 children in the placebo group.

^dData available for 134 children in each treatment group.

^eData available for 136 children in the co-amoxiclav group and 134 children in the placebo group.

^fBased on real-time Polymerase Chain Reaction analysis of nasal swabs.

^gOne participant in the placebo group had both influenza A/H3 and influenza B and was thus only counted once

^hBased on analysis of throat swabs (culture). Throat swabs were obtained from 114 participants in the co-amoxiclav group (laboratory-confirmed influenza, n=19) and 111 participants in the placebo group (laboratory-confirmed influenza, n=13).

ⁱIncludes six children for whom influenza results were missing (co-amoxiclav n=4, placebo n=2)

Outcomes

Figure 2 summarises re-consultations due to clinical deterioration within 28 days of randomisation. At least one re-consultation was recorded in 33/133 children randomised to co-amoxiclav (24.8%) and 28/132 children randomised to placebo (21.2%). There was no evidence of a difference in clinical deterioration between groups after adjustment for stratification and minimisation factors (adjusted risk ratio [RR] 1.16, 95% confidence interval [CI] 0.75 to 1.80; unadjusted RR 1.17, 95% CI 0.75 to 1.82, unadjusted risk difference 3.6%, 95% CI -6.5% to 13.7%). No adjustment for clustering was performed because the average cluster size was only 1.4 (271 participants from 195 sites).[21] No statistically significant differences were observed in proportions of children requiring medication or further investigations, or hospitalisation (Figure 2). No deaths were recorded.

Figure 3 summarises diary data on durations of fever and other symptoms. Median duration of disturbed sleep was significantly shorter in children who received co-amoxiclav versus placebo (co-amoxiclav: median 4 days, interquartile range [IQR] 2 to 6 days; placebo: median 7 days, IQR 3 to 11 days; $P = 0.021$). No evidence of differences between groups was found for other symptoms or fever.

Table 2 summarises adjusted median differences in durations of fever and other symptoms between the co-amoxiclav and placebo groups. After adjustment, a statistically significant difference in duration of disturbed sleep was no longer observed between the co-amoxiclav and placebo groups. However, duration of shortness of breath was found to be significantly shorter in the co-amoxiclav group (adjusted median difference [days] -2.00, 95% confidence interval -3.89 to -0.11, $P = 0.038$).

Table 2: Adjusted median differences in duration of fever and symptoms

Duration (days)	Adjusted median difference for co-amoxiclav vs. placebo (95% confidence interval)	P Value ¹
Fever	0.00 (-0.30 to 0.30)	1.000
Cough	-1.57 (-4.83 to 1.69)	0.343
Phlegm	-0.96 (-3.78 to 1.87)	0.504
Shortness of breath	-2.00 (-3.89 to -0.11)	0.038
Disturbed sleep	-2.44 (-5.24 to 0.36)	0.087
Feeling generally unwell	-1.00 (-2.72 to 0.72)	0.250
Interference with normal activities	-0.87 (-2.69 to 0.95)	0.346

¹ P-value for the difference in medians between co-amoxiclav and placebo from a quantile regression model on outcome, region, age and current seasonal influenza vaccination status.

Adverse events

Table 3 summarises adverse events which occurred within 28 days of randomisation. At least one adverse event was reported in 32/136 children in the co-amoxiclav group (24%) and 22/135 children in the placebo group (16%). Thirty-seven adverse events were reported in the co-amoxiclav group and 29 in the placebo group. One adverse event was reported in 44 children (co-amoxiclav $n=27$, placebo $n=17$). Two adverse events were reported in 22 children (co-amoxiclav $n=5$, placebo $n=6$). Only 12 adverse events were reported as being possibly related to study medication (co-amoxiclav $n=5$, placebo $n=7$) and only three as being probably related to study medication (co-amoxiclav $n=2$, placebo $n=1$). The most commonly reported adverse events were skin complaints and respiratory tract infections (RTIs). These RTIs were considered to be separate from the index ILI episode for

which the participant was entered into the trial. Nine serious adverse events (SAEs) were reported per group. All reported SAEs required participants to be hospitalised. However, none were considered related to study medication. Appendix 6 summarises further details of these SAEs.

Table 3: Adverse events

Adverse events	Co-amoxiclav (n=37) Number (%)	Placebo (n=29) Number (%)
Infections		
Respiratory tract infections	7 (18.9) ^a	4 (13.8) ^b
ENT infections	4 (10.8) ^c	3 (10.3)*
Viral rash	2 (5.4) ^d	0
Other viral infection	1 (2.7) ^e	4 (13.8)
Conjunctivitis	1(2.7)	1 (3.4)
Respiratory/ENT		
Asthma	2 (5.4)	1 (3.4)
Cough	1 (2.7) ^f	0
Dyspnoea	1 (2.7)	2 (6.9) ^g
Epistaxis	0	1 (3.4)
Hypoxia	1 (2.7)*	4 (13.8)*
Rhinorrhoea	2 (5.4) ^h	0
Wheezing	1 (2.7)*	1 (3.4)*
Gastrointestinal		
Diarrhoea	4 (10.8) ⁱ	1 (3.4)
Vomiting	3 (8.1) ^{j,*}	3 (10.3)
Other	1 (2.7)	1 (3.4)
Skin	7 (18.9) ^k	6 (20.7)
Neurological/psychiatric	2 (5.4)*	3 (10.3)*
Other		
Pain/discomfort	4 (10.8)*	0
Pyrexia	3 (8.1)*	0
Adverse drug reaction	3 (8.1)*	0
Adverse reaction to MMR vaccination	1 (2.7)*	0
Reduced fluid intake	0	1 (3.4)*
Oxygen supplementation	0	1 (3.4)*

n = total number of adverse events reported. One adverse event was reported in 44 children (co-amoxiclav n=27, placebo n=17). Two adverse events were reported in 11 children (co-amoxiclav n=5, placebo n=6).

ENT = Ear, nose and throat

MMR = Measles, mumps and rubella

^aIncludes events for which wheezing (n=1) and hypoxia (n=1) were also reported.

^bIncludes events for which hypoxia (n=1), hypoxia and oxygen supplementation (n=1) and an ENT infection (n=1) were also reported.

^cIncludes one event for which pain/discomfort was also reported.

^dBoth events were also reported as adverse drug reactions.

^eNeurological/psychiatric complaint also reported for this event.

^fPyrexia also reported for this event.

^gIncludes one event for which wheezing was also reported and one event for which hypoxia, reduced fluid intake and a neurological/psychiatric complaint were also reported.

^hIncludes one event for which pain/discomfort and a neurological/psychiatric complaint were also reported.

ⁱIncludes one event for which vomiting was also reported.

^jIncludes one event for which pyrexia was also reported.

^kIncludes one event which was also reported as an adverse drug reaction and one event which was also reported as an adverse reaction to the MMR vaccination. Pyrexia was also reported for the latter event.

*Includes one or more events for which other symptoms were also reported as detailed in footnotes a to k.

Subgroup and exploratory analyses

Table 4 presents our pre-specified subgroup analysis in children with laboratory-confirmed influenza. The proportion of children with clinical deterioration was lower in the co-amoxiclav group (5/21, 23.8%) than in the placebo group (6/16, 37.5%). However, no statistically significant difference was demonstrated. There was no evidence of an interaction between treatment arm and laboratory-confirmed influenza status ($P=0.241$). We did not perform our planned subgroup analysis in children who had been prescribed antiviral medication at or before their baseline visit, as no participants received antivirals.

Table 4: Subgroup analysis in participants with laboratory-confirmed influenza

	Co-amoxiclav (n=133)	Placebo (n=132)	Unadjusted Risk Ratio for Co- amoxiclav vs. Placebo (95% CI)	Adjusted Risk Ratio for Co- amoxiclav vs. Placebo (95% CI)	P-value for test of interaction^a
Evidence of laboratory- confirmed influenza (n=37), n (%) of re- consultations	5/21 (23.8%)	6/16 (37.5%)	0.63 (0.24 to 1.71)	0.55 (0.20 to 1.55) ^b	0.241
No evidence of laboratory- confirmed influenza ^c (n=228), n (%) of re- consultations	28/112 (25%)	22/116 (19%)	1.32 (0.80 to 2.16)	1.29 (0.79 to 2.11) ^b	

CI = confidence interval

^a P-value for the interaction between treatment and lab-confirmed influenza from a log binomial regression model on re-consultation, adjusting for region, age and current seasonal influenza vaccination status

^b Log binomial regression model on re-consultation, adjusting for age and current seasonal influenza vaccination status.

^cIncludes three children for whom primary outcome data were available but influenza results were missing (co-amoxiclav n=2, placebo n=1)

We performed two post hoc exploratory analyses. Firstly, we compared duration of fever between groups whereby data collected during telephone follow-ups were considered alongside diary data. Where data were available from both sources, the longest duration was analysed. This approach allowed analysis of 99 children in the co-amoxiclav group and 92 in the placebo group. Median duration of fever was one day (IQR 0 to 3 days) in both groups. Secondly, we summarised data on proportions of participants requiring medication or further investigations among those who re-

consulted due to clinical deterioration. These were similar in the co-amoxiclav (23/33, 70%) and placebo groups (21/28, 75%).

Discussion

We did not find evidence that early co-amoxiclav treatment reduces clinical deterioration in 'at risk' children who consult with ILI in primary or ambulatory care. This finding is highly generalisable to community-based health care settings during non-pandemic periods due to our wide geographical coverage, recruitment from primary and other ambulatory care settings, pragmatic ILI case definition, and high retention rate for our primary outcome.

The percentage of 'at risk' children who re-consulted due to clinical deterioration in our sample (61/265 participants, 23%) was lower than anticipated, but still nearly six times higher than the 4% observed in a primary care cohort of children with acute RTI who did not have known risk factors for complications from influenza or ILI.[22] Three-quarters of 'at risk' children with clinical deterioration in our placebo group required medication or further investigations (21/28 children). However, our sample size estimation assumed that complications only occur in 44% of clinical deterioration episodes.[17] These data were based on a general paediatric primary care population, as no equivalent data in 'at risk' children were available to inform our estimation.

The statistical power of our trial was limited as a result of only being able to recruit 271 participants versus our original target sample size of 650 participants. However, our original sample size estimation allowed for a 25% loss to follow-up rate for the primary outcome, which was much higher than the 2% loss to follow-up rate (6/271 children) which we actually observed. Additionally, our sample was still sufficient to detect a reduction in the primary outcome from 21% (percentage observed in the placebo group) to 6.5% (absolute risk reduction [ARR] 14.5%) with 90% power or 21% to 8% (ARR 13%) with 80% power and 5% two-tailed alpha error. These ARR are similar to the treatment effect we considered for our target sample size (40% to 26%, 14% ARR), albeit from a lower baseline. A larger sample would have allowed us to estimate our result with greater precision and detect a more conservative treatment effect. However, we would need to consider the clinical importance of a smaller effect size in the context of numbers needed to treat for benefit versus harm.

The relatively small number of participants with laboratory-confirmed influenza in our sample meant that we did not have sufficient statistical power to determine whether early co-amoxiclav treatment reduces risk of clinical deterioration in this subgroup. Our exploratory subgroup analysis found that a lower proportion of children in the co-amoxiclav group re-consulted due to clinical deterioration compared to the placebo group. However, the difference between groups was not statistically significant. Nevertheless, this finding is consistent with the results of two trials which demonstrated clinical benefit from antibiotics in participants who were influenza positive[9] or presented with ILI during an influenza epidemic.[8]

The low proportion of influenza cases in our sample most likely resulted from modest seasonal influenza activity[23-26] and a seasonal influenza vaccination programme initiated in 2013 for all children over 2 years of age that rolled out in successive years to include a school vaccination programme and increased awareness of 'at risk' children's eligibility for vaccination.[27] We did not collect data on whether children received the live attenuated or inactivated influenza vaccine. However, it is likely that the proportions of participants who received each type of vaccine would have been balanced between the co-amoxiclav and placebo groups because randomisation was minimised for age (6 to 23 months versus 2 to 12 years). In the absence of contraindications, children aged 2 years and over would have been offered the live attenuated vaccine and 'at risk'

children aged 6 to 23 months inclusive would have been offered the inactivated vaccine, as the live attenuated vaccine is not licensed for use in this age group.[1]

We acknowledge that our ILI case definition was broad and non-specific. However, including additional symptoms may not have increased our influenza positivity rate[28] and using point-of-care testing would have made our findings less generalisable. Furthermore, primary care clinicians feel that whether a child has influenza versus another virus is less important outside pandemic settings.[6] The higher numbers of children in our trial population in whom other respiratory viruses were found, particularly rhinovirus and respiratory syncytial virus, are consistent with the current absence of national childhood vaccination programmes relating to these infections, and national laboratory data indicating higher detection rates for these infections during the early part of each recruitment season.[29]

The relatively low bacterial carriage rate we observed in our trial may have limited our ability to evaluate the effectiveness of co-amoxiclav in our target population. One or more bacterial isolates were only found in around one-quarter of participants. Additionally, nearly one-third of children in the placebo group were found to have one or more bacterial isolates compared to only around one-fifth of children in the co-amoxiclav group. These percentages were higher than those reported by a study which performed real-time Polymerase Chain Reaction (PCR) analysis of nasopharyngeal swabs in children with fever or ILI and found evidence of bacterial infection in 16.7% of children aged 5 to 18 years and 6.5% of children younger than 5 years of age who did not have known risk factors for influenza or ILI-related complications.[30] Nevertheless, a placebo-controlled trial which recruited adults with common cold reported that co-amoxiclav treatment was only associated with improved clinical cure rates in the subgroup from whom bacteria were cultured from nasopharyngeal secretions.[31]

We did not have sufficient resources or infrastructure to opportunistically obtain throat swabs for bacterial culture from children when they re-consulted. However, the findings of a longitudinal study nested within the trial will report data on long-term bacterial carriage in the co-amoxiclav versus placebo arms in a separate paper. We were also unable to consistently obtain definitive diagnoses in children who re-consulted due to clinical deterioration, as immediate or on site access to further investigations, such as blood tests and chest X-rays, was not available in all health care settings, particularly general practices.

Our findings on duration of fever and other symptoms should be interpreted with caution. The statistically significant reductions we observed in duration of disturbed sleep (unadjusted analysis) and shortness of breath (adjusted analysis) may have been chance findings reflecting multiple observations from seven inter-related parent/guardian-reported outcomes. We could only analyse diary data on duration of fever or other symptoms in around half of children. However, these follow-up rates are comparable to that of a diary-based cohort study of children with acute RTIs.[32]

Although our co-amoxiclav and placebo preparations were matched for appearance, it was not possible to match them for taste despite extensive efforts to do so. Therefore, to minimise the chance of children or their caregivers detecting a difference, we only allowed each child to be recruited into the trial once. Additionally, use of a fully validated web-based randomisation system meant that health care professionals' allocation of study medication could not be influenced by any awareness of a difference. Our similar medication adherence and loss to follow-up rates between groups suggest these measures were sufficient.

We were only able to obtain data on medication adherence from 184/271 participants (68%) even though we used two different methods to collect these data (study diaries and telephone follow-

ups). The pragmatic nature of our trial meant that we did not make further efforts to follow up families who did not respond to either method, or employ more resource intensive measures, such as collecting and weighing study medication bottles. However, we do not feel that this unduly impacted our findings, since we obtained medication adherence data from similar proportions of participants in both groups (co-amoxiclav: 95/136, 70%; placebo: 89/135, 66%).

In summary, our findings do not support immediate antibiotic prescribing in 'at risk' children who present with ILI in primary or ambulatory care outside influenza pandemic periods. However, health care professionals may wish to consider factors other than pre-existing conditions in their risk assessment, including clinical symptoms and signs[33] and underlying disease control.[34] We cannot rule out the possibility that co-amoxiclav may be effective at reducing clinical deterioration in 'at risk' children with laboratory-confirmed influenza or presenting with ILI during influenza epidemics or pandemics. Antibiotic stockpiles should therefore still be maintained for use during such periods, when incidences of influenza infections and bacterial complications are likely to be high.[35] Future trials should determine whether early antibiotic treatment is beneficial in 'at risk' children with confirmed influenza infection by recruiting during periods of high influenza activity or using point-of-care tests for influenza.[36]

Conclusions

Our findings do not support early antibiotic treatment in 'at risk' children who present with seasonal ILI in primary or ambulatory care. Future research should determine whether antibiotics reduce clinical deterioration in individuals with confirmed influenza or ILI during influenza pandemics.

Contributors

KW, TC, ST, MGS, ADH, MM, PL, CCB, AF, RP, LMY and AH contributed to the study protocol. KW was Chief Investigator of the trial until going on maternity leave in September 2018, after which AH became Chief Investigator. KW, TC and ST contributed to day-to-day management of the trial and data collection. JG was responsible for data management. LMY and JM oversaw development of the statistical analysis plan. UG performed the statistical analysis. RP provided overall statistical supervision. KW, MGS, ADH, MM, JM, PL, CCB, AF and AH contributed to data interpretation. KW wrote the first draft of the manuscript. All authors contributed comments and edits to the manuscript.

Data sharing

The trial protocol, statistical analysis plan and de-identified participant level data collected for the trial are available on request. Research data requests should be submitted to the corresponding author for consideration by the research team.

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