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

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Shareable abstract (@ERSpublications)
This trial did not find evidence that early co-amoxiclav use reduces reconsultation due to clinical deterioration in "at risk" children who present with influenza-like illness during influenza season
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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 reconsultation due to clinical deterioration in "at risk" children presenting with influenza-like illness (ILI) in primary or ambulatory care.

Methods "At risk" children aged from 6 months to 12 years presenting within 5 days of ILI onset were randomly assigned to oral co-amoxiclav 400/57 or a placebo twice daily for 5 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 reconsulting 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 reconsultation 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 February 11, 2015 and April 20, 2018. Primary outcome data were available for 265 children. Only 61 out of 265 children (23.0%) reconsulted due to clinical deterioration. No evidence of a treatment effect was observed for reconsultation due to clinical deterioration (33 out of 133 for co-amoxiclav (24.8%) and 28 out of 132 (21.2%) for placebo; adjusted risk ratio (RR) 1.16, 95% confidence interval (CI) 0.75–1.80). There was also no evidence of a difference between groups in the proportion of children for whom one or more adverse events (AEs) were reported (32 out of 136 (23.5%) for co-amoxiclav and 22 out of 135 (16.3%) for placebo; adjusted RR 1.45, 95% CI 0.90–2.34). In total, 66 AEs were reported (co-amoxiclav, n=37; placebo, n=29). Nine serious AEs were reported per group, although none were considered related to study medication.

Conclusion Our trial did not find evidence that treatment with co-amoxiclav reduces risk of reconsultation 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 and 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 from 5 years 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]. Clinical practice guidelines recommend that immediate antibiotic treatment should be considered in individuals with acute respiratory tract infections (RTIs) who are identified as being at higher risk of complications [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 reconsultation 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 ILI general practitioner (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 from 6 months to 12 years and who presented within the first 5 days of an ILI [12]. Appendix 1 lists our full eligibility criteria. Appendix 2 summarises our "at risk" groups. ILI was defined as the presence of cough and fever; fever could be child-reported, parent/guardian-reported, or axillary or tympanic temperature >37.8 °C. We excluded children with known contra-indications 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 RTIs is recommended in these children [13].

To increase our pool of potential recruits, we made minor changes to our eligibility criteria before the 2017/2018 recruitment season. First, 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 h for an acute infection rather than long-term prophylaxis. Thirdly, we clarified that children who required immediate hospitalisation would only be excluded if this was for treatment of an influenza-related complication or an observation period lasting >24 h. The trial received ethical approval from the National Research Ethics Service Committee (North West Coast – Liverpool East). Additional approvals were received from the Health Research Authority, the Medicines and Healthcare Products Regulatory 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/clavulanic acid (57 mg) as potassium salt; 5 mL when reconstituted with water) or a placebo suspension. Assignment was performed 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 (6–23 months or 2–12 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 (Stata version 13.1, Stata Corp., College Station, TX, USA). This ensured that each site maintained equal supplies of co-amoxiclav and placebo.

Healthcare professionals dispensed the study medication. Healthcare 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 (HR) 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 5 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 1-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 (AEs). 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 <37.5 °C for two consecutive days. Healthcare professionals contacted parents/guardians by telephone 1 week and 2 weeks after randomisation to collect data on AEs, duration of fever and study medication doses taken in case diary data were not provided.

Data 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 reconsultations were extracted from participants' medical records. Data on reconsultations, medication prescriptions, investigations, hospitalisations and deaths within 28 days of randomisation were also extracted.

Outcomes

Our primary outcome was reconsultation 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 RTI [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 healthcare professionals to use validated scales to score symptom severity at the index consultation or during reconsultation 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, AEs, 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 AEs if they were assessed as being of mild or moderate clinical severity and did not result in a serious AE, as these are already known common side-effects of co-amoxiclav.

Data on other outcomes relating to health-related quality of life measures, healthcare 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 reconsultations due to complications, new symptoms or delayed resolution in children presenting in primary care with acute RTIs (61 out of 138 children) [17]. We therefore estimated that 40% of participants in the placebo group would reconsult due to clinical deterioration.

Our target sample size was 650 participants, including an 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 the proportion of participants reconsulting due to clinical deterioration from 40% to 26% (relative risk reduction 35%) 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], recognising that an effective sample size of 266 participants would still allow detection of a reduction in clinical deterioration from 40% to 23% (relative risk reduction 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 relative risk reduction of 85% in incidence of pneumonia in children with ILI who were treated with sultamicillin (one out of 42 children) *versus* placebo (seven out of 43 children). Although this trial was relatively small and did not collect outcome data on reconsultations 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, contained a penicillin antibiotic (ampicillin) and a β-lactamase inhibitor (sulbactam).

Data were double-entered and verified in open-source software (OpenClinica version 3.13, OpenClinica, Waltham, MA, USA). Statistical analyses were performed using Stata version 15.1 (Stata Corp.). We performed an intention-to-treat analysis and participants were analysed in the groups to which they were allocated. The proportions of children reconsulting due to clinical deterioration in the two groups was compared using a Chi-squared 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) and 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 AEs are reported and children who were hospitalised or died within 28 days of randomisation) were compared using the Chi-squared test (or Fisher's exact test in the case of small numbers) for the unadjusted analysis and the 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 reconsultation 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 the 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 and a further 115 children were eligible but their parents/guardians did not give consent for study participation. Our decision during the 2017/2018 season to only exclude children given

antibiotics within the last 72 h if these were for an acute infection did not increase the proportion of children screened who were excluded for this reason (2015/2016: nine out of 197 (4.6%); 2016/2017: 23 out of 229 (10.0%); 2017/2018: 25 out of 330 (7.6%)). Prophylactic antibiotic prescriptions were only recorded in five participants (azithromycin, n=2; amoxicillin, n=1; co-trimoxazole, n=1; and trimethoprim, n=1).

We randomly assigned 271 participants to receive co-amoxiclav (n=136) or a placebo (n=135). Parents/guardians reported that all study medication doses were taken by 81 out of 95 participants (85%) in the co-amoxiclav group and 74 out of 89 participants (83%) in the placebo group for whom adherence data were available (*i.e.* data on whether or not all 10 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 10 doses. Appendix 5 also includes data on participants whose parents/guardians reported that less than 10 doses had been taken but who were unable to specify the exact number of doses.

Figure 1 summarises recruitment and follow-up of participants. Data on reconsultations 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 out of 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 out of 271 children (13.7%); however, rhino/enteroviruses were more commonly isolated (119 out of 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 out of 225 throat swabs (23.1%) and 13 out of 37 participants with laboratory-confirmed influenza (35.1%).

Outcomes

Figure 2 summarises reconsultations due to clinical deterioration within 28 days of randomisation. At least one reconsultation was recorded in 33 out of 133 children (24.8%) randomised to co-amoxiclav and 28 out of 132 children (21.2%) randomised to a placebo. 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% CI 0.75–1.80; unadjusted RR 1.17, 95% CI 0.75–1.82; 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 the proportions of children requiring medication or further investigation, or requiring 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* a placebo (median (co-amoxiclav) 4 days, interquartile range (IQR) 2–6 days *versus* median (placebo) 7 days, IQR 3–11 days; p=0.021). No evidence of difference 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 −2.00 days, 95% CI −3.89 to −0.11; p=0.038).

Adverse events

Table 3 summarises AEs which occurred within 28 days of randomisation. At least one AE was reported in 32 out of 136 children (24%) in the co-amoxiclav group and 22 out of 135 children (16%) in the placebo group. Thirty-seven AEs 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) and 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

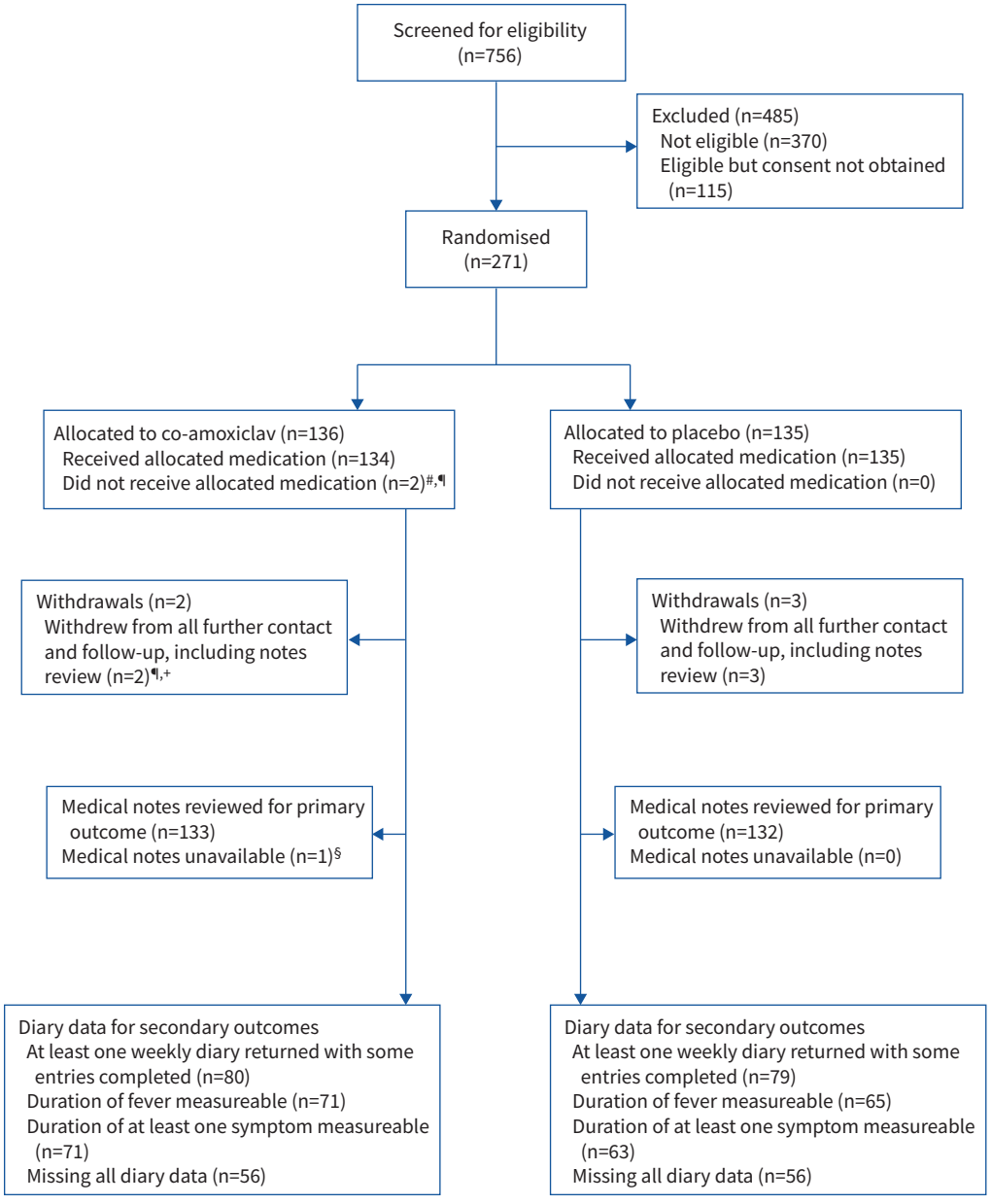

FIGURE 1 Participant recruitment and follow-up. #: protocol deviation (treating clinician withdrew study medication; medical notes were available for review); ¶: parent left without study medication (withdrew consent after discussion with the child's father); +: child received study medication (parent subsequently withdrew consent for further contact and notes review); §: medical notes for primary outcome withheld by GP surgery for internal reasons (participant not withdrawn; diary data available for secondary outcomes).

AEs were skin complaints and RTIs. These RTIs were considered as 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.

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 (five out of 21 (23.8%)) than in the placebo group (six out of 16 (37.5%)); however, no statistically significant difference was demonstrated. Furthermore, there was no evidence of an interaction between treatment arm and

TABLE 1 Baseline characteristics

Participant characteristics	Co-amoxiclav (n=136)	Placebo (n=135)
Age months	40.8 (19.4–85.6)	36.4 (20.9–70.8)
Male gender	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[¶]	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 (0)
Immunodeficiency	1 (0.7)	0 (0)
Metabolic	1 (0.7)	5 (3.7)
Other	3 (2.2)	3 (2.2)
One or more smokers in the 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	1.9±1.2	2.2±1.2
Antipyretics given since ILI episode started	115 (84.6)	118 (87.4)
HR[§] beats·min^{-1}	115±22.4	117±22.8
Respiratory rate[ƒ] breaths·min^{-1}	28±9.1	28±9.9
Temperature[##] °C	37.0±0.8	37.0±0.9
One or more acute consultations during the 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[¶¶]	121 (89.0)	112 (83.0)
Influenza (any strain)[¶¶,++]	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[¶¶]	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)
One or more bacterial isolates[¶¶,§§]	28 (20.6)	40 (29.6)
Bacterial isolates in children with evidence of laboratory-confirmed influenza		
Haemophilus influenzae[§§]	6 (4.4)	7 (5.2)
Group A Streptococcus[§§]	1 (0.7)	0 (0)
Group C Streptococcus[§§]	1 (0.7)	0 (0)
Group G Streptococcus[§§]	0 (0)	1 (0.7)
Staphylococcus aureus[§§]	2 (1.5)	0 (0)
Bacterial isolates in children without evidence of laboratory-confirmed influenza[ƒƒ]		
Haemophilus influenzae[§§]	14 (10.3)	25 (18.5)
Group A Streptococcus[§§]	2 (1.5)	3 (2.2)

Continued

TABLE 1 Continued

Participant characteristics	Co-amoxiclav (n=136)	Placebo (n=135)
Group G Streptococcus[§§]	0 (0)	2 (1.5)
Staphylococcus aureus[§§]	2 (1.5)	1 (0.7)
Streptococcus pneumoniae[§§]	1 (0.7)	0 (0)
MRSA[§§]	0 (0)	1 (0.7)
Mycoplasma pneumoniae[¶¶]	3 (2.2)	1 (0.7)
Chlamydia pneumoniae[¶¶]	0 (0)	2 (1.5)

Data are presented as n (%), median (interquartile range) or mean±SD. Region A: Thames Valley and South Midlands Clinical Research Network (CRN), West Midlands CRN, North Thames CRN, North West London CRN and South London CRN; Region B: West of England CRN, South West Peninsula CRN, Cardiff and Vale University Health Board, Aneurin Bevan University Health Board and Abertawe Bro Morgannwg University Health Board; Region C: Greater Manchester CRN, North East and North Cumbria CRN, North West Coast CRN, and Yorkshire and Humber CRN; Region D: Kent, Surrey and Sussex CRN, and Wessex CRN; Region E: Eastern CRN and East Midlands CRN. Hib: *Haemophilus influenzae* b; PCV: pneumococcal conjugate vaccine; ILI: influenza-like illness; HR: heart rate; MRSA: methicillin-resistant *Staphylococcus aureus*. [#]: not mutually exclusive. [¶]: four children in whom premature birth was recorded as a risk factor were aged 2 years or older at baseline (co-amoxiclav, n=3; placebo, n=1). Although premature birth was only considered a risk factor in children aged 6–23 months in this trial, all four children had other risk factors. [+]: data available for 134 children in the co-amoxiclav group and 132 children in the placebo group. [§]: data available for 133 children in the co-amoxiclav group and 134 children in the placebo group. [ƒ]: data available for 134 children in each treatment group. [##]: data available for 136 children in the co-amoxiclav group and 134 children in the placebo group. [¶¶]: based on real-time PCR analysis of nasal swabs. [++]: one participant in the placebo group had both influenza A/H3 and influenza B, and was thus counted only once. [§§]: based on analysis (culture) of throat swabs 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). [ƒƒ]: includes six children for whom influenza results were missing (co-amoxiclav, n=4; placebo, n=2).

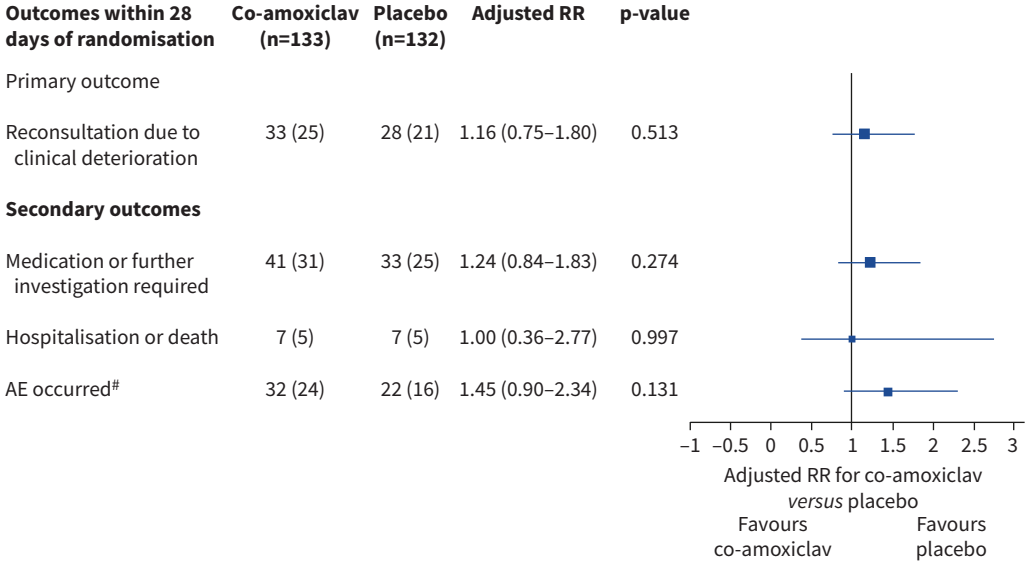

FIGURE 2 Adjusted risk ratios (RRs) with 95% confidence intervals (CIs) for primary and binary secondary outcomes. Data are presented as n (%) or adjusted RR (95% CI). Percentage values are based on the number of participants in whom at least one outcome event was reported (relative to the number of participants analysed for outcomes relating to reconsultation due to clinical deterioration, medication or further investigations being required, as well as hospitalisation or death). All models were adjusted for region, age and current seasonal influenza vaccination status, except for hospitalisations or deaths where the model was only adjusted for age and current seasonal vaccination status (as no hospitalisations or deaths were reported in some regions). n: number of participants for whom medical notes were reviewed. AE: adverse event. [#]: data were analysed for all randomised participants (co-amoxiclav, n=136; placebo, n=135).

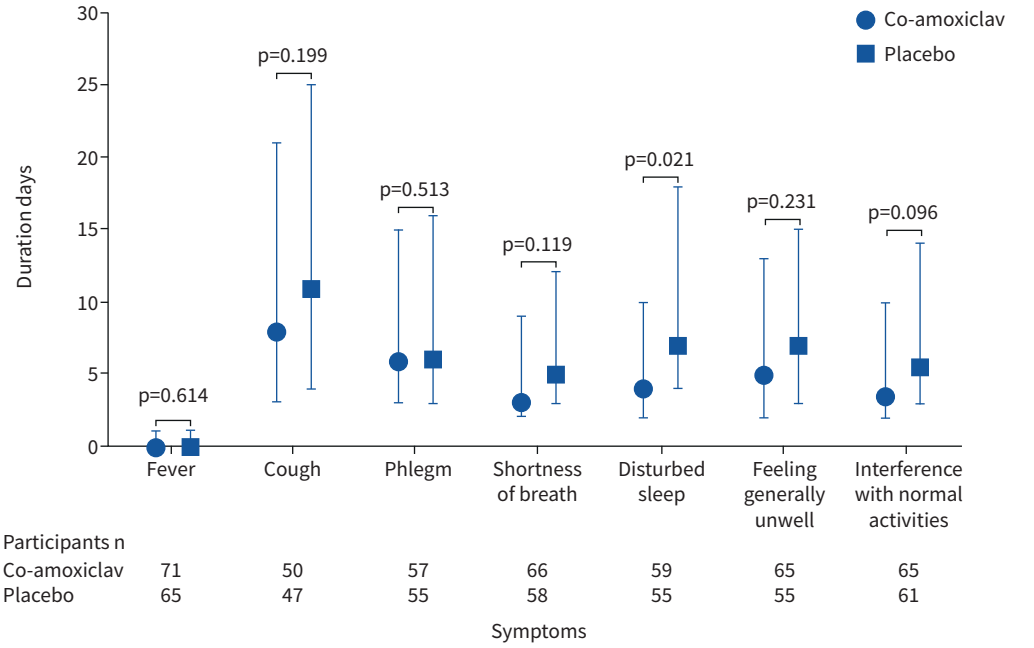

FIGURE 3 Duration of fever and symptoms. Duration data are presented as median (interquartile range). p-values are calculated using the Wilcoxon rank-sum test.

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.

We performed two *post hoc* exploratory analyses. First, we compared duration of fever between groups, wherein 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 1 day (IQR 0–3 days) in both groups. Secondly, we summarised data on the proportions of participants requiring medication or further investigation amongst those who reconsulted due to clinical deterioration. These were similar in the co-amoxiclav group (23 out of 33 (70%)) and the placebo group (21 out of 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 healthcare settings during non-pandemic periods due to our wide geographical coverage,

TABLE 2 Adjusted median differences in duration (in days) of fever and symptoms

Symptom	Adjusted difference for co-amoxiclav *versus* placebo	p-value[#]
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

Data are presented as median (95% confidence interval). [#]: p-values for the difference in medians between co-amoxiclav and placebo were obtained from a quantile regression model based on outcome, region, age and current seasonal influenza vaccination status.

TABLE 3 Adverse events (AEs)

AEs	Co-amoxiclav (n=37)	Placebo (n=29)
Infections		
Respiratory tract infections	7 (18.9)[#]	4 (13.8)[¶]
ENT infections	4 (10.8)[+]	3 (10.3)[§]
Viral rash	2 (5.4)[f]	0 (0)
Other viral infection	1 (2.7)[##]	4 (13.8)
Conjunctivitis	1(2.7)	1 (3.4)
Respiratory/ENT		
Asthma	2 (5.4)	1 (3.4)
Cough	1 (2.7)[¶¶]	0 (0)
Dyspnoea	1 (2.7)	2 (6.9)[++]
Epistaxis	0 (0)	1 (3.4)
Hypoxia	1 (2.7)[§]	4 (13.8)[§]
Rhinorrhoea	2 (5.4)[§§]	0 (0)
Wheezing	1 (2.7)[§]	1 (3.4)[§]
Gastrointestinal		
Diarrhoea	4 (10.8)[ff]	1 (3.4)
Vomiting	3 (8.1)[###,§]	3 (10.3)
Other	1 (2.7)	1 (3.4)
Skin	7 (18.9)[¶¶¶]	6 (20.7)
Neurological/psychiatric	2 (5.4)[§]	3 (10.3)[§]
Other		
Pain/discomfort	4 (10.8)[§]	0 (0)
Pyrexia	3 (8.1)[§]	0 (0)
Adverse drug reaction	3 (8.1)[§]	0 (0)
Adverse reaction to MMR vaccination	1 (2.7)[§]	0 (0)
Reduced fluid intake	0 (0)	1 (3.4)[§]
Oxygen supplementation	0 (0)	1 (3.4)[§]

Data are presented as n (%). The total number of AEs reported was as follows: co-amoxiclav, n=37; placebo, n=29. One AE was reported in 44 children (co-amoxiclav, n=27; placebo, n=17). Two AEs were reported in 11 children (co-amoxiclav, n=5; placebo, n=6). ENT: ear, nose and throat; MMR: measles, mumps and rubella. [#]: includes events for which wheezing (n=1) and hypoxia (n=1) were also reported; [¶]: includes events for which hypoxia (n=1), hypoxia and oxygen supplementation (n=1), and an ENT infection (n=1) were also reported; [+]: includes one event for which pain/discomfort was also reported; [§]: includes one or more events for which other symptoms were also reported, as detailed in these footnotes; [f]: both events were also reported as adverse drug reactions; [##]: a neurological/psychiatric complaint was also reported for this event; [¶¶]: pyrexia was also reported for this event; [++]: includes 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; [§§]: includes one event for which pain/discomfort and a neurological/psychiatric complaint were also reported; [ff]: includes one event for which vomiting was also reported; [###]: includes one event for which pyrexia was also reported; [¶¶¶]: includes 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.

TABLE 4 Subgroup analysis in participants with laboratory-confirmed influenza

Evidence	Co-amoxiclav (n=133)	Placebo (n=132)	Co-amoxiclav *versus* placebo		p-value[#]
			Unadjusted RR	Adjusted RR	
Evidence of laboratory-confirmed influenza (n=37), n (%) of reconsultations	5/21 (23.8)	6/16 (37.5)	0.63 (0.24–1.71)	0.55 (0.20–1.55)[¶]	0.241
No evidence of laboratory-confirmed influenza[+] (n=228), n (%) of reconsultations	28/112 (25)	22/116 (19)	1.32 (0.80–2.16)	1.29 (0.79–2.11)[¶]	

Data are presented as n/n (%) or risk ratio (95% confidence interval). [#]: p-value for the interaction between treatment and lab-confirmed influenza from a log binomial regression model on reconsultation (adjusting for region, age and current seasonal influenza vaccination status); [¶]: log binomial regression model on reconsultation (adjusting for age and current seasonal influenza vaccination status); [+]: includes three children for whom primary outcome data were available but influenza results were missing (co-amoxiclav, n=2; placebo, n=1).

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 reconsulted due to clinical deterioration in our sample (61 out of 265 participants (23%)) was lower than anticipated, but was 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 out of 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 (six out of 271 children) that was 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 14.5%) with 90% power or from 21% to 8% (absolute risk reduction 13%) with 80% power and 5% two-tailed alpha error. These absolute risk reductions are similar to the treatment effect we considered for our target sample size (40% to 26%, absolute risk reduction 14%), 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 reconsulted 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 who 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 (which 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 (6–23 months *versus* 2–12 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 6–23 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 nonspecific; 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 with 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 PCR analysis of nasopharyngeal swabs in children with fever or ILI and which found evidence of bacterial infection in 16.7% of children aged 5–18 years and 6.5% of children younger than 5 years who did not have known risk factors for influenza or ILI-related complications [30]. Nevertheless, a placebo-controlled trial which recruited adults with the 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 reconsulted. 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 reconsulted due to clinical deterioration, as immediate or on-site access to further investigations (such as blood tests and chest radiography) were not available in all healthcare settings, particularly in 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 healthcare 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 out of 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 of these methods, nor did we employ more resource intensive measures such as collecting and weighing study medication bottles. Despite this, 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 out of 136 (70%) *versus* placebo: 89 out of 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, healthcare 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 who present 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.

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The study is registered as ISRCTN 70714783/EudraCT 2013-002822-21. 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.

Author contributions: K. Wang, T. Carver, S. Tonner, M.G. Semple, A.D. Hay, M. Moore, P. Little, C.C. Butler, A. Farmer, R. Perera, L-M. Yu and A. Harnden contributed to the study protocol. K. Wang was Chief Investigator of the trial until going on maternity leave in September 2018, after which A. Harnden became Chief Investigator. K. Wang, T. Carver and S. Tonner contributed to day-to-day management of the trial and data collection. J. Grabey was responsible for data management. L-M. Yu and J. Mollison oversaw development of the statistical analysis plan. U. Galal performed the statistical analysis. R. Perera provided overall statistical supervision. K. Wang, M.G. Semple, A.D. Hay, M. Moore, J. Mollison, P. Little, C.C. Butler, A. Farmer and A. Harnden contributed to data interpretation. K. Wang wrote the first draft of the manuscript. All authors contributed comments and edits to the manuscript.

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