Antibiotics for lower respiratory tract infection in children presenting in primary care in England (ARTIC PC): a double-blind, randomised, placebo-controlled trial

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Summary

Background Antibiotic resistance is a global public health threat. Antibiotics are very commonly prescribed for children presenting with uncomplicated lower respiratory tract infections (LRTIs), but there is little evidence from randomised controlled trials of the effectiveness of antibiotics, both overall or among key clinical subgroups. In ARTIC PC, we assessed whether amoxicillin reduces the duration of moderately bad symptoms in children presenting with uncomplicated (non-pneumonic) LRTI in primary care, overall and in key clinical subgroups.

Methods ARTIC PC was a double-blind, randomised, placebo-controlled trial done at 56 general practices in England. Eligible children were those aged 6 months to 12 years presenting in primary care with acute uncomplicated LRTI judged to be infective in origin, where pneumonia was not suspected clinically, with symptoms for less than 21 days. Patients were randomly assigned in a 1:1 ratio to receive amoxicillin 50 mg/kg per day or placebo oral suspension, in three divided doses orally for 7 days. Patients and investigators were masked to treatment assignment. The primary outcome was the duration of symptoms rated moderately bad or worse (measured using a validated diary) for up to 28 days or until symptoms resolved. The primary outcome and safety were assessed in the intention-to-treat population. The trial is registered with the ISRCTN Registry (ISRCTN79914298).

Findings Between Nov 9, 2016, and March 17, 2020, 432 children (not including six who withdrew permission for use of their data after randomisation) were randomly assigned to the antibiotics group (n=221) or the placebo group (n=211). Complete data for symptom duration were available for 317 (73%) patients; missing data were imputed for the primary analysis. Median durations of moderately bad or worse symptoms were similar between the groups (5 days [IQR 4–11] in the antibiotics group *vs* 6 days [4–15] in the placebo group; hazard ratio [HR] 1·13 [95% CI 0·90–1·42]). No differences were seen for the primary outcome between the treatment groups in the five prespecified clinical subgroups (patients with chest signs, fever, physician rating of unwell, sputum or chest rattle, and short of breath). Estimates from complete-case analysis and a per-protocol analysis were similar to the imputed data analysis.

Interpretation Amoxicillin for uncomplicated chest infections in children is unlikely to be clinically effective either overall or for key subgroups in whom antibiotics are commonly prescribed. Unless pneumonia is suspected, clinicians should provide safety-netting advice but not prescribe antibiotics for most children presenting with chest infections.

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Introduction

Acute respiratory tract infections (RTI) are among the commonest conditions managed in primary care.[1] WHO and the UK Department of Health[2] recognise that antibiotic resistance is an increasingly serious public health problem, with rising resistance rates for a range of antibiotics, and a clear relationship between primary care antibiotic prescribing (80% of all antibiotic prescribing) and antibiotic resistance at national[3] and individual[4–6] levels. The costs of resistance are also often not included in current estimates of cost-effectiveness and these can have an important impact on estimates.[7] Although consultation rates and antibiotic prescription rates for upper RTI (URTI) or chest infections declined sharply in the late 1990s until the early 2000s,[8] overall antibiotic use increased again, decreased 15% between 2015 and 2019,[9] and allowing for the reduced consultation rates, was 6·71% higher again during the COVID-19 pandemic than during previous years.[10] Children have higher consultation rates for RTI than adults, and even when antibiotic prescribing was at its lowest, most children labelled as having URTI or chest infection still were prescribed antibiotics in the UK,[11] with similar high rates of prescribing for RTIs among children internationally.[12,13]

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Research in context

Evidence before this study

We used the Cochrane systematic review as the basis for assessing the evidence. The authors of the Cochrane review searched for primary research of randomised controlled trials with no language restrictions in CENTRAL 2016, issue 11 (accessed Jan 13, 2017), MEDLINE (1966 to Jan week 1, 2017), Embase (1974 to Jan 13, 2017), and LILACS (1982 to Jan 13, 2017); and searched the WHO International Clinical Trials Registry Platform and ClinicalTrials.gov on April 5, 2017. Search terms are in the appendix (p 13). The review of antibiotics for acute bronchitis documented that antibiotics have a modest effect on cough duration (seven studies, 2776 participants, mean difference −0·46 days [95% CI −0·87 to −0·04]). However, the trials in the Cochrane review included very few children and the differences in immunity and anatomy between adults and children prohibit simply applying evidence derived in adults to the management of children.

Added value of this study

This study confirms that antibiotics (amoxicillin) do not provide a clinically important benefit for symptom duration among children presenting with uncomplicated lower respiratory tract infections (antibiotic median 5 days *vs* placebo 6 days, hazard ratio 1·13 [95% CI 0·90 to 1·42]), nor in the key clinical subgroups that clinicians commonly prescribe for (those with chest signs, fever, physician rating of unwell, sputum or chest rattle, and shortness of breath).

Implications of all the available evidence

The data from our study and previous studies suggest that unless pneumonia is suspected, clinicians should provide so-called safety-netting advice (ie, explain what illness course to expect and when it would be necessary to reattend) but not prescribe antibiotics for most children presenting with chest infections.

Data from our observational study in antibiotic prescribing confirmed that at least 40% of children are prescribed antibiotics for chest infections,[14] which translates to 2 million prescriptions for antibiotics for cough in this age group in the UK,[11,15] or about GBP £30 million annually in direct consultation and dispensing costs, not including the indirect costs incurred by so-called medicalising illness in the family and wider social networks, where perceived benefit of antibiotics because of symptom resolution, even if unrelated, leads to individuals being more likely to seek reconsultation in future, even if antibiotics are ineffective.[16,17]

Although trials among adults suggest only modest benefit, even among important clinical subgroups,[18] there is scarce randomised, placebo-controlled evidence to support or dispute the common use of antibiotics in children with chest infections: only one trial in a Cochrane review of antibiotic prescribing included young children aged 3 years and older.[17,19] It might be that antibiotics in children also have little benefit given the similarity of presentation of lower RTI (LRTI) to adults; however, the differences in immunity and anatomy between adults and children prohibit simply applying evidence derived in adults to the management of children.[20] Parents want help managing symptoms and improving the course of illness and are concerned about significant adverse outcomes.[21,22] Prescribing antibiotics could potentially reduce societal costs (eg, out-of-pocket expenses and time off work). Clinicians also face the difficulty of knowing whether patients presenting are an average patient, given the variation in pathophysiology and disease severity, and prescribing decisions are made by general practitioners (GPs) using traditional but non-evidence-based clinical signs like sputum production, fever, chest signs, and feeling unwell.[23–26]

Here, we report the ARTIC PC trial, which aimed to test the hypothesis that amoxicillin reduces the duration of moderately bad symptoms in children presenting with uncomplicated (non-pneumonic) LRTI in primary care, overall and in key clinical subgroups. We also did a parallel observational study where the same measures and outcomes were collected (to be fully reported separately).

Methods

Study design

ARTIC PC is a double-blind, randomised, placebo-controlled, parallel-group trial of amoxicillin versus placebo for children presenting with chest infections in primary care, done at 56 general practices in England.

The trial protocol was approved by the South West-Central Bristol Research Ethics Committee (reference 15/SW/0300).

Participants

Children aged between 6 months and 12 years presenting to primary care with an acute LRTI (as defined in several previous cohorts and trials as having an acute cough as the predominant symptom) judged by the GP to be infective in origin, lasting less than 21 days, and with other symptoms or signs localising to the lower respiratory tract (shortness of breath, sputum, or pain) were eligible for the trial.[27–30] These inclusion criteria reflect the clinical criteria used in daily practice to diagnose acute bronchitis,[31] were used in the previous Cochrane review,[19] and are the key drivers of prescribing.[23,24]

Exclusion criteria were non-infectious cause (eg, hay fever or a non-infective exacerbation of asthma) or almost certain viral cause (croup, where antibiotics are not commonly prescribed), as judged by the clinician; individuals who are immune compromised; and antibiotic use in the previous 30 days. Children for whom

the clinician did not have equipoise (the clinician judged that pneumonia was likely or children judged to be severely ill) were not enrolled, but they were eligible to enter the parallel observational study. Patients that were not enrolled as a result of patient or clinician beliefs of preference were invited to participate in the parallel observational study. The parent or guardian of the child provided written consent. Children able to understand the study read an age-appropriate patient information leaflet and signed an age-appropriate consent form.

Randomisation and masking

Parents and children who consented to the study and agreed to randomisation were randomly assigned in a 1:1 ratio to receive either amoxicillin or placebo. Treatment assignment was masked to investigators and participants. Investigational medicinal product packs were indistinguishable in appearance and packaging, and each was labelled with a unique identification number to maintain allocation concealment. A computer-generated random number list was provided by an independent statistician and kept only by the investigational medicinal product manufacturer. Random block sizes of 2 to 4 packs were used, with practice sites receiving whole blocks (multiple of six packs). Investigators randomised and dispensed by selecting the next sequentially numbered investigational medicinal product pack.

Procedures

Participants in the amoxicillin group received amoxicillin 50mg/kg per day orally in three divided doses for 7 days and those in the placebo group received three oral doses per day for 7 days.

Amoxicillin was chosen because it is the first choice antibiotic in LRTI, and with current levels of intermediate resistance should cover most susceptible organisms.[32] The dose was chosen in line with guidance from the British National Formulary for children and was supported by a Monte Carlo simulation to achieve a minimal inhibitory concentration of around 1·5, to cover *Haemophilus influenzae* as well as intermediate resistant pneumococci for 90% of the intended population.[32] We estimated that no fewer than 5 days of treatment at greater than minimal inhibitory concentration was needed to achieve bacterial eradication. A 7-day course was chosen to allow for poor adherence[33] and on pragmatic grounds to match current practice at the time the study commenced to achieve greater clinician and parent acceptability; similar consensus was required for the related trial in adults.[32] A 7-day course is also unlikely to result in more frequent side-effects (gastrointestinal; allergy) than a 5-day course.

The recruiting clinician completed a case report form of comorbidities, clinical signs, and the severity of baseline symptoms reported by the patient (rating each symptom as no problem, mild problem, moderate problem, or severe problem).[32] Co-morbidity and the number of RTIs in the previous year were also documented, and pulse oximetry was done.

We chose throat swabs for microbiological sampling because of high pick-up rates and acceptability for children of this method.[34] For parents and children willing to have a throat swab, a swab was taken and analysed in a central laboratory using multiplex PCR.

Parents kept a diary of symptoms and daily activities (including days away from work for parents) using a validated daily diary for at least 1 week and after that as long as symptoms persisted for up to 4 weeks after randomisation. The diary items recorded the severity of the following symptoms: cough, phlegm, shortness of breath, wheeze, blocked or runny nose, disturbed sleep, feeling generally unwell, fever, and interference with normal activities. Each symptom was scored from 0 to 6 (0=no problem, 1=very little problem, 2=slight problem, 3=moderately bad, 4=bad, 5=very bad, and 6=as bad as it could be).[32,35] If the diary was not returned, a short questionnaire was sent by post, and if that was not returned, a phone call was made. All patients were requested to return to their practice after 1 month with medication bottles for assessment of medication use and clinical review.

Information on resource use was collected by notes review, including resource use for major adverse events (eg, anaphylaxis and progression of illness requiring hospital assessment or admission) at baseline and 28 days after randomisation. This was used to assess NHS and social service use (primary care visits, community service, hospital inpatient and outpatient visits, and accident and emergency attendances). Additional analyses to include out-of-pocket spending and parent or carer's time off work in taking care of children were calculated. Unit costs of primary care consultation, community services, outpatient visits, and accident and emergency attendances were based on the Personal Social Services Research Unit. National reference costs were used to cost hospital stay on the basis of relevant diagnostic categories. Medications were priced on the basis of the NHS Drugs tariff. Cost per patient was calculated by the products of resource usage with corresponding unit costs. All costs were based on 2018–19 prices.

Outcomes

The primary outcome was the duration of symptoms rated moderately bad or worse, as used in previous studies on acute LRTI,[32,7] recorded in a validated daily diary for up to 28 days until the symptom resolved. The primary outcome matches parental concerns about more severe symptoms.[32,33] The diary has previously been validated and was shown to be sensitive to change in both adults and children, and internally reliable (Cronbach's α 0·75, ie, in optimal range).[17,35] The estimates based on the diary can also be compared directly with the major definitive trial of antibiotics for adults with LRTI.[32]

Secondary outcomes were severity of symptoms (cough, phlegm, shortness of breath, wheeze, blocked or runny nose, disturbed sleep, feeling generally unwell, fever, and interference with normal activities) each scored 0–6; total symptom duration, defined as the time from start of symptom to when severity reduced to 2 or less; reconsultation with new or worsening symptoms or complications; side-effects, including diarrhoea, rash, or nausea; health-care resource use; and adherence (number of doses taken). We chose to assess the severity of symptoms in the first 2–4 days after seeing the doctor (based on diary responses), because this is typically the period when symptoms are the most severe,[17] when antibiotics might make a difference. Reconsultation with new or worsening symptoms or complications was documented on the basis of a structured notes review, which we have shown to be feasible and reliable[36,37] and has demonstrated antibiotic effectiveness in the previous large trial in adults.[32]

We collected quality-adjusted life-years data in the diary but completion rates were very poor and they are not reported here.

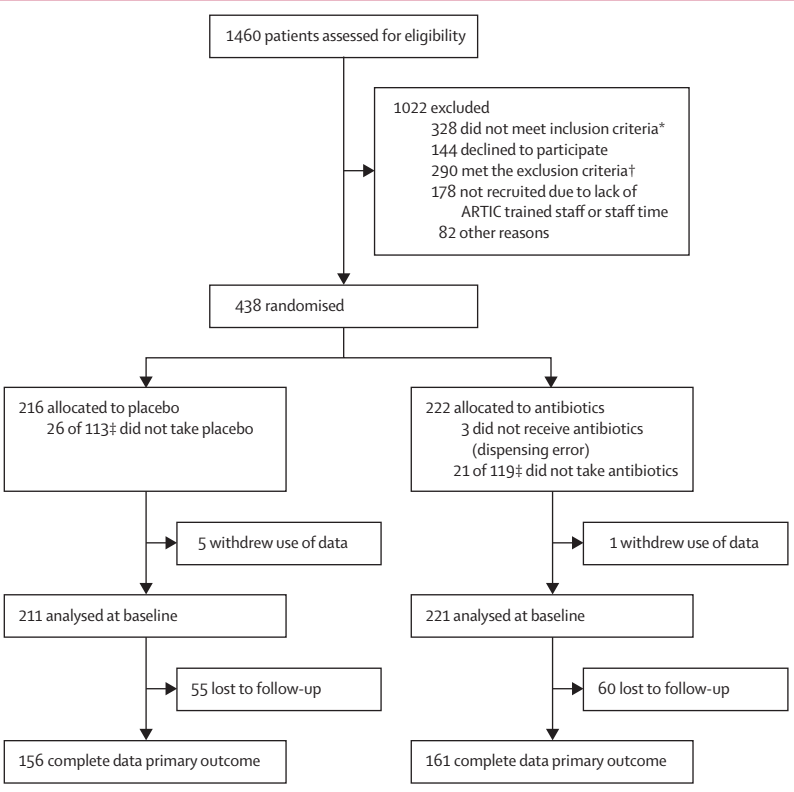

Figure 1: **Trial profile**
*61 younger than 6 months, 13 older than 12 years, 181 general practitioner judged as not having lower respiratory tract infection, 65 illness longer than 21 days, and eight other inclusion criteria not met. †25 had asthma or allergy-related cough, 83 general practitioner suspected viral infection, 26 had croup, 79 had previous antibiotics, three were allergic to penicillin, nine already enrolled or sibling already enrolled, 39 were admitted to hospital or too unwell, and 26 other exclusion criteria met (mostly other diagnoses, such as reflux, non-infective asthma exacerbation, or immunosuppression). ‡Denominators reflect number of participants for whom adherence data were available.

Statistical analysis

Balancing the threat posed by antibiotic resistance, a 3-day difference in symptom resolution (hazard ratio [HR] 1·7) for an illness lasting 14–21 days (ie, reducing the duration by 15–20%) was judged by the patient and public involvement team and agreed with the investigator team to be clinically important enough to warrant treatment. We originally estimated that 938 children were required (for α=0·01, 90% power, 80% follow-up) to detect an HR of 1·7 for the primary outcome among any one of five equally prioritised clinical subgroups (chest signs; fever; physician rating of unwell; sputum or chest rattle; and shortness of breath), assuming any subgroup was 30% or more of the sample. The sample size calculation was revised after agreement with the funder, trial steering committee, and data monitoring safety committee based on (1) evidence from systematic reviews that abnormal chest signs are the most important driver for antibiotic prescriptions[23] from six studies' odds ratios for prescribing antibiotics ranging from 3 to 20; and (2) using proportions of subgroups observed (masked to randomisation group) in the penultimate season of the trial. We used a traditional approach of powering for the subgroup sizes, adjusting the α for multiple subgroups (chest signs subgroups α 0·05, other subgroups α 0·01), and calculating the total sample size required based on the proportion in the smallest subgroup. For the primary analysis for the chest signs subgroup, we estimated we would need 119 cases (for α 0·05, 80% power) assuming 40% of the trial cohort had chest signs (based on study data at the time when calculations were revised), or a total trial sample of 298 for 80% power and 398 for 90% power. For other subgroups, we estimated we needed 225 cases for 90% power and an α of 0·01.

Cox regression was used for the primary outcome (duration of symptoms rated moderately bad or worse in days) and for total symptom duration, adjusting for age, baseline symptom severity, previous duration of illness, and comorbidity. Linear regression was used for symptom severity, and logistic regression for reconsultation, complications, and side-effects, adjusting for the same baseline covariates as in the primary analysis. Analysis was on an intention-to-treat basis, as randomised regardless of non-adherence or protocol deviations. Multiple imputation was chosen for the primary analysis and complete cases for a secondary analysis, because multiple imputation is generally more efficient than complete case analysis,[38] and particularly important to control for potential attrition bias. Multiple imputation included those in the analysis model (age, comorbidity, previous duration of illness, and baseline severity) and significant predictors of missingness (parental qualification) using 100 imputations.[39] A complete-cases analysis and a complier average causal effect (CACE) analysis were performed as sensitivity analyses. Prespecified subgroup analyses were done for chest signs (α=0·05), sputum or chest rattle, history of fever, physician rating of unwell, shortness of breath, oxygen saturation below 95%, and STARWAVe clinical

	Placebo group (n=211)	Antibiotics group (n=221)
Sex		
Female	99 (47%)	100 (45%)
Male	112 (53%)	121 (55%)
Age, years	3·1 (1·4–5·6)	3·2 (1·7–5·8)
Comorbidities	31 (15%)	24 (11%)
Asthma	27 (13%)	18 (8%)
Long-term illness	7/111 (6%)	13/120 (11%)
Hay fever or eczema	39/111 (35%)	44/121 (36%)
Family history of asthma	66/112 (59%)	81/117 (69%)
Breastfed at 3 months	49/110 (45%)	65/120 (54%)
Mother's age, mean (SD; n)	34·8 (6·4; n=105)	34·9 (7·2; n=114)
Number of times had cough in past 12 months, mean (SD; n)	2·5 (2·3; n=110)	2·8 (2·8; n=112)
Previous influenza vaccine in past 12 months	55/200 (28%)	59/201 (29%)
Previous pneumococcal vaccine (booster) in past 12 months	61/200 (31%)	64/201 (32%)
Smoker in household		
Yes	44 (21%)	50 (23%)
No	165 (78%)	166 (75%)
Don't know	2 (1%)	5 (2%)
Number of children in home		
1	87 (41%)	86 (39%)
2	73 (35%)	95 (43%)
3	35 (17%)	25 (11%)
4	13 (6%)	7 (3%)
5 or more	3 (1%)	8 (4%)
Parent highest qualification		
Degree	78 (37%)	81 (37%)
Diploma	27 (13%)	23 (10%)
A level	23 (11%)	16 (7%)
GCSE or O level	20 (9%)	27 (12%)
None	10 (5%)	7 (3%)
Not given	42 (20%)	53 (24%)
Other	11 (5%)	14 (6%)
Ethnic group*		
British, Irish, or other White	182 (86%)	189 (86%)
Mixed	8 (4%)	11 (5%)
South Asian	15 (7%)	14 (6%)
Other	4 (2%)	5 (2%)
Prefer not to say	1 (<1%)	2 (1%)

Data are n (%), median (IQR), or n/N (%), unless otherwise specified. *Data missing for one person in the placebo group.

Table 1: **Baseline characteristics of all participants**

	Placebo group (n=211)	Antibiotics group (n=221)
Baseline severity*	1·6 (0·3)	1·6 (0·3)
Cough severity	1·9 (1·1)	2·0 (1·1)
Duration of symptoms rated moderately bad or worse, days	6 (3–10)	5 (3–10)
Prespecified subgroups		
Abnormal chest signs†	72 (34%)	78 (35%)
Sputum or chest rattle	155/210 (74%)	170/219 (78%)
Fever during illness	161 (76%)	177 (80%)
Unwell according to physician‡	141 (67%)	143 (65%)
Shortness of breath	95 (45%)	104 (47%)
Oxygen saturation low (<95%)	9/166 (5%)	13/170 (8%)
STARWAVe[40]§		
Very low risk	110 (52%)	123 (56%)
Normal risk	95 (45%)	94 (43%)
High risk	6 (3%)	4 (2%)
Physician rating of unwell¶	5·5 (1·7)	5·5 (1·6)
Parent rating of unwell¶	3·8 (1·7)	3·7 (1·7)
Temperature, °C, mean (SD; n)	37·3 (0·8; n=208)	37·2 (0·8; n=220)
Oxygen saturation, %, mean (SD; n)	97·3 (1·6; n=166)	97·3 (1·6; n=170)
Heart rate, beats per min, mean (SD; n)	112·0 (20·3; n=207)	111·8 (17·9; n=213)
Respiratory rate, breaths per min, mean (SD; n)	24·8 (6·8; n=198)	25·4 (7·1; n=213)
Tachypnoea	25/198 (13%)	30/213 (14%)
Capillary refill >3 s	3 (1%)	2 (1%)
Consciousness‖		
Normal	203 (96%)	214 (97%)
Irritable	8 (4%)	5 (2%)
Drowsy	0	1 (<1%)
Ill appearance	48 (23%)	47 (21%)
Number of days unwell before seeing general practitioner, median (IQR; n)	5 (3–9; n=108)	5 (3–7; n=119)
Treated with over-the-counter medication	105/111 (95%)	107/121 (88%)

Data are mean (SD), median (IQR), n (%), or n/N (%), unless otherwise specified. *Scale of 1–4 as follows: 1=none, 2=mild, 3=moderate, and 4=severe. †Includes wheeze, stridor, grunting, nasal flaring, intercostal or subcostal recession, crackles or crepitations, and bronchial breathing. ‡Dichotomised at ≥5. §STARWAVe prediction rule for hospital admission (short illness, temperature, age, recession, wheeze, asthma, and vomiting). ¶Scale of 0–10. ‖Data missing for one person in the antibiotics group.

Table 2: **Illness presentation of randomised participants**

prediction rule for hospital admission[40] (all α=0·01). Analyses were done using Stata, version 16, and SPSS, version 26, and masked to group allocation.

Role of the funding source

The funder of this study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

1460 participants were assessed for eligibility between Nov 9, 2016, and March 17, 2020. 438 patients were enrolled and randomly assigned to the antibiotics group (n=222) or placebo group (n=216). Six patients withdrew the use of their data and so could not be used in the intention-to-treat analysis. Thus, 432 participants were included in analyses: 221 in the antibiotics group and 211 in the placebo group (figure 1). 312 children were recruited to the parallel observational study (appendix p 10).

See Online for appendix

233 (54%) of 432 participants were male and 199 (46%) were female, with a median age of 3·2 years (IQR 1·6–5·7), and 55 (13%) had a comorbidity (table 1). Regarding the prespecified key clinical subgroups,

	Placebo group	Antibiotics group
Duration of moderately bad or worse (score ≥3) symptoms in days, median (IQR; n)	6 (4–15; n=156)	5 (4–11; n=161)
Symptom severity, mean (SD; n)	2·1 (1·1; n=149)	1·8 (1·0; n=149)
Duration of symptoms until very little problem (score 1) in days, median (IQR; n)	8 (5–20; n=156)	7 (4–17; n=161)
Return with new or worsening symptoms	76/199 (38%)	60/202 (30%)
Assessment or admission needed in hospital*	4/204 (2%)	5/211 (2%)
Side-effects	52/153 (34%)	60/157 (38%)
Diarrhoea	26/88 (30%)	24/98 (24%)
Nausea	32/92 (35%)	35/102 (34%)
Rash	20/91 (22%)	25/99 (25%)

Data are n/N (%) unless otherwise stated. Symptom severity on a scale of 0–6 as follows: 0=no problem, 1=very little problem, 2=slight problem, 3=moderately bad, 4=bad, 5=very bad, and 6=as bad as it could be. *Within 1 month of index consultation.

Table 3: **Primary and secondary raw outcome measures (complete cases)**

	Placebo group (n=211)	Antibiotics group (n=221)	Adjusted* treatment estimate (95% CI)
Duration of moderately bad or worse (score ≥3) symptoms in days	6 (4 to 15)	5 (4 to 11)	Hazard ratio 1·13 (0·90 to 1·42)
Symptom severity	2·1 (1·1)	1·8 (1·1)	Difference −0·28 (−0·51 to −0·04)
Duration of symptoms until very little problem (score 1) in days	8 (5 to 19)	7 (4 to 17)	Hazard ratio 1·09 (0·86 to 1·38)
Return with new or worsening symptoms	38%	30%	Odds ratio 0·71 (0·46 to 1·09); risk ratio 0·80 (0·58 to 1·05)
Assessment or admission needed in hospital†	2%	2%	Odds ratio 1·24 (0·32 to 4·78); risk ratio 1·23 (0·32 to 4·44)
Side-effects	33%	39%	Odds ratio 1·33 (0·81 to 2·17); risk ratio 1·20 (0·87 to 1·55)

Data are median (IQR), mean (SD), or n (%). *Adjusted for previous duration of illness, baseline severity, age, and comorbidity. †Assessment or admission needed in hospital within 1 month of index consultation (appendix p 1).

Table 4: **Effectiveness of antibiotics on primary and secondary outcomes (imputed)**

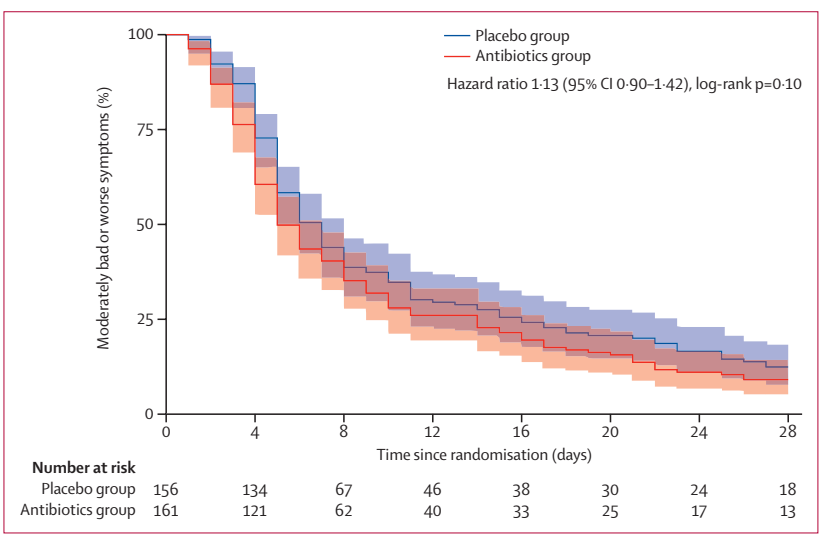

Figure 2: **Kaplan-Meier curve of duration of moderately bad or worse symptoms in days**

150 (35%) had abnormal chest signs, 325 (76%) of 429 had sputum or chest rattle (some data were missing from case report forms so these individuals are not included in the total), 338 (78%) had a fever during the illness, 284 (66%) were categorised as unwell according to the physician rating (rating of ≥5 on a scale of 1–10), and 199 (46%) had shortness of breath (table 2). 22 (7%) of 336 with available data had oxygen saturation less than 95%. According to the STARWAVe prediction rule,[40] 233 (54%) were at very low risk of hospital admission, 189 (44%) were at normal risk, and ten (2%) were at high risk of hospital admission. The key baseline characteristics were similar across the two randomised groups (tables 1, 2).

Of those who reported which medication they thought their child had received, 47 (47%) of 101 in the antibiotics group and 33 (39%) of 84 in the placebo group thought their child had received antibiotics.

Complete data were available on symptom duration for 317 (73%) participants, on symptom severity for 298 (69%), on reconsultation with new or worsening symptoms for 401 (93%), on complications for 415 (96%), and on side-effects for 310 (72%) participants (table 3). For the key subgroups, we had complete data for 109 children in the chest-signs subgroup, 247 for fever, 208 for physician rating of being unwell, and 146 for shortness of breath. The primary analysis for each subgroup used imputed data, and a secondary analysis was done using complete cases (appendix pp 3–4)

The median duration of moderately bad or worse symptoms was similar between groups (5 days [IQR 4–11] in antibiotics group *vs* 6 days [4–15] in the placebo group; HR 1·13 [95% CI 0·90–1·42]; table 4, figure 2). Although we did not achieve adequate power for the complete case analysis for the chest signs subgroup, none of the prespecified clinical subgroups nor additional post-hoc exploratory subgroups (low oxygen saturation, STARWAVe categories, or adjustment for asthma and vaccination status) modified the effect of treatment on duration of moderately bad or worse symptoms (table 5).

There was a small significant difference between the groups in symptom severity on days 2–4 after seeing the doctor (1·8 [SD 1·0] in the antibiotics group *vs* 2·1 [1·1] in the placebo group; mean difference –0·28 [95% CI –0·51 to –0·04]; table 4), which was equivalent to less than one child in three rating symptoms a slight problem (score 2) rather than very little problem (score 1).

The median duration of symptoms until rated absent or very little problem was also similar between the groups (7 days [IQR 4–17] in the antibiotics group *vs* 8 days [5–20] in the placebo group; HR 1·09 [95% CI 0·86–1·38]; table 4). The number of participants reconsulting with new or worsening symptoms was 60 (30%) of 202 in the antibiotics group compared with 76 (38%) of 199 in the placebo group (risk ratio 0·80 [95% CI 0·58–1·05]). Complications were uncommon (five [2%] of 211 *vs*

	Placebo group		Antibiotics group		Interaction term (99% CI)*	Adjusted† hazard ratio (99% CI)*
	n	Median (IQR)	n	Median (IQR)		
Abnormal chest signs						
Yes	54	6·0 (4·0–16·0)	52	6·0 (4·0–15·0)	0·84 (0·52–1·36)	0·97 (0·65–1·43)
No	102	7·0 (4·0–15·0)	109	5·0 (3·0–11·0)	..	1·21 (0·91–1·60)
Sputum						
Yes	115	7·0 (4·0–16·0)	124	5·0 (4·0–14·0)	1·11 (0·55–2·26)	1·16 (0·83–1·64)
No	41	5·0 (4·0–14·0)	36	5·0 (3·0–10·0)	..	0·99 (0·52–1·90)
Fever						
Yes	115	6·0 (4·0–16·0)	131	5·0 (3·0–10·0)	1·45 (0·71–2·98)	1·23 (0·88–1·73)
No	41	7·0 (4·0–13·0)	30	7·0 (4·0–26·0)	..	0·78 (0·40–1·53)
Physician rating of unwell‡						
Yes	104	6·0 (4·0–15·5)	101	5·0 (3·0–10·0)	1·32 (0·71–2·46)	1·25 (0·85–1·83)
No	52	8·0 (4·0–14·5)	60	6·0 (4·0–16·0)	..	0·96 (0·58–1·58)
Shortness of breath						
Yes	77	6·0 (4·0–11·0)	71	5·0 (3·0–14·0)	0·96 (0·54–1·73)	1·13 (0·72–1·77)
No	79	7·0 (4·0–18·5)	90	5·5 (4·0–11·0)	..	1·17 (0·78–1·75)
Oxygen saturation low						
Yes	7	11·0 (6·0–18·0)	8	8·0 (4·0–20·0)	0·95 (0·23–3·94)	1·20 (0·24–5·93)
No	119	6·0 (4·0–15·0)	116	5·0 (3·5–10·0)	..	1·11 (0·78–1·57)
STARWAVe[40]§						
Very low risk	78	7·0 (4·0–17·0)	93	5·0 (4·0–10·0)	0·77 (0·45–1·30)	1·27 (0·84–1·91)
Normal risk	72	6·0 (4·0–11·5)	65	6·0 (3·0–14·0)	..	1·06 (0·67–1·66)
High risk¶	6	..	3	..	..	..

*95% CI for the abnormal chest signs subgroup. †Adjusted for previous duration of illness, baseline severity, age, and comorbidity. ‡Scale of 1–10, dichotomised at ≥5. §STARWAVe prediction rule for hospital admission (short illness, temperature, age, recession, wheeze, asthma, and vomiting). ¶Too few data to obtain reliable estimates.

Table 5: **Duration of moderately bad or worse symptoms by subgroup (imputed)**

four [2%] of 204; risk ratio 1·23 [0·32–4·44]). The numbers of participants with side-effects were similar (60 [38%] of 157 *vs* 52 [34%] of 153; risk ratio 1·20 [0·87–1·55]). The number of complications and hospital admissions in both groups were low, and similar between groups (appendix p 1).

The main analyses (tables 4, 5) were calculated based on 100 multiply-imputed datasets. Complete-case analyses gave very similar results (appendix pp 3–4).

The treatment effects for all outcomes were similar for most subgroups (none of the interaction terms were significant), but the effect of antibiotics was slightly, but not significantly, greater among those with fever or those who were unwell (appendix pp 5–6). Reconsultations with antibiotics were slightly more frequent among the less unwell children (appendix p 7).

232 (54%) participants provided data on adherence to medication. Of those who reported medication adherence, 98 (82%) of 119 in the antibiotics group and 87 (77%) of 113 in the placebo group took at least 11 doses of medication over days 1–5. A per-protocol analysis including only those children who were recorded as having taken 11 doses of medication over 1–5 days documented no significant difference in the duration of moderately bad or worse (score ≥3) symptoms, with an HR of 1·06 (95% CI 0·77–1·46; appendix p 2). A CACE analysis gave an unadjusted HR for the duration of moderately bad or worse (≥3) symptoms of 1·31 (95% CI 0·90–1·89; which is similar to the unadjusted primary analysis HR of 1·21 [95% CI 0·95–1·53]).

A fuller economic evaluation using the limited quality of life data and cost data will be published elsewhere. The key finding was that only small and non-significant differences in costs were observed. Slightly higher total NHS costs per child were documented in the antibiotic group (£29·40 in the antibiotic group *vs* £25·80 in the placebo group). The cost of antibiotics was low at around 10%, the bulk of NHS costs being from reconsultations and referrals. The societal costs due to time off work or privately purchased remedies were also similar between groups (£32·90 *vs* £32·70; appendix p 8).

The microbiological analysis documented similar numbers of potential bacterial and viral pathogens (appendix p 9). A small number (two in the placebo group and five in the antibiotics group) of bacterial pathogens were identified that would not be expected to respond to amoxicillin or were not implicated in LRTI (*Chlamydia pneumoniae, Mycoplasma pneumoniae, Bordetella pertussis, Streptococcus pyogenes,* and *Fusobacterium necrophorum*). There was no evidence

of a differential effect of antibiotics where bacteria sensitive to amoxicillin (*H influenzae, Moraxella catarrhalis*, and *Streptococcus pneumoniae*) were present (appendix p 9).

The children in the observational study were similar to the trial, although the former included more children who had chest signs (appendix pp 10–12).

Discussion

Our results showed that for children presenting to primary care with uncomplicated acute LRTI, there is unlikely to be a clinically relevant effect of amoxicillin treatment on symptom burden, both overall and for key patient subgroups, in whom antibiotics are commonly prescribed. There was also no evidence of additional complications when antibiotics are not prescribed.

ARTIC PC is one of the very few studies to report on the effectiveness of prescribing antibiotics among younger children presenting with chest infections in primary care. It was designed to be able to detect a clinically important 3-day improvement in symptom duration (an HR of 1·7)—about a 15% difference considering a total illness duration of 20–25 days documented by a systematic review,[41] or roughly a 20% improvement for an illness lasting 14 days based on the placebo group of our trial. A 3-day improvement in a subgroup was judged to be important enough to be worth prescribing an antibiotic, given the public health danger from antibiotic resistance.[2,3] We used the most patient-relevant outcome (parent-reported symptoms), and documented complications (ie, the progression of illness requiring hospital assessment or admission). The study confirmed that complications are uncommon but it was not specifically powered to assess complications (a trial of several thousand children would be needed), nor reconsultations, nor microbiological subgroups. The sample size estimate was modified during the trial on the basis of a systematic review of the evidence, and informed by the proportions of subgroups observed during the penultimate season of the trial (masked to group assignment). In the final sample, imputed and complete cases analyses were adequately powered overall and for subgroups, except for the complete case analysis in the chest sign subgroup–in part due to slightly fewer children having chest signs than expected and the COVID-19 pandemic prematurely ending recruitment. However, the estimates for the primary outcome for complete and imputed cases in the chest signs subgroup were very similar (6 days in the antibiotic group and placebo group in both analyses), the HRs near unity (0·91 and 0·97), and the upper 95% CIs of the HRs (1·41 and 1·43) suggest the benefit for children with chest signs is unlikely to be more than 2 days—ie, not clinically important. The follow-up rate of 73% (317 of 432) raises concern about possible attrition bias, but the estimates when using imputed data are very similar to the complete case analysis, so attrition bias is unlikely. Although the study was placebo controlled, the study was at the pragmatic end of the spectrum in that there was no close monitoring of parents and children: parents behaved as they might in practice as to whether they gave their child medication, and per-protocol and CACE analyses provided similar estimates to the total trial population. The antibiotic (amoxicillin) was chosen because it is the first-choice antibiotic in UK national guidance for use in LRTIs among children (NICE guidance or antimicrobial prescribing guidelines). The trial population was similar to children recruited to the smaller parallel observational study, but compared with large representative observational cohorts, this trial population had slightly more severe clinical presentation.[40] Thus, if anything we are likely to have overestimated the effect of antibiotics in the UK setting, but results might not generalise to other settings—eg, countries with very different diagnostic approaches, prescription rates, complication rates (eg, low-income and middle-income countries [LMICs]), or distribution of pathogens.

Only one trial in the Cochrane review of antibiotics for acute bronchitis included children as young as 3 years of age presenting with uncomplicated acute chest infections.[17,19] In that trial, there were only 100 children aged 12 years or younger, and the estimate of immediate antibiotics compared with no offer of antibiotics on symptom duration (HR 1·00) and symptom severity (mean reduction –0·3 on a scale of 0–6) was similar to the non-significant result of the whole trial cohort.[17] These results are consistent with the results of the current study. A Cochrane review found inconclusive evidence for the effect of antibiotics in preventing RTIs,[42] but a more recent trial of azithromycin used in early infections was effective in preventing severe illness among preschool children with recurrent infection[43] (from 8% to 5%), although concern remains about the longer-term effects on antibiotic resistance from the use of long-acting macrolides.[6] A placebo-controlled trial of antibiotic versus placebo for pneumonia in young children in an LMIC setting found low failure rates in both placebo (5%) and antibiotic (3%) groups,[44] and a 5-day course is equivalent to 10 days for community-acquired pneumonia.[45]

Our results suggest that antibiotics do not provide a clinically important benefit on average for symptom reduction nor symptom severity. The question remains whether there are some children who receive a meaningful benefit, but the benefit is diluted by large numbers of children who receive no benefit. We explored this hypothesis by conducting subgroup analyses in five prespecified subgroups. Our subgroup analysis results suggest that none of the groups we specified were likely to achieve substantial benefits in terms of symptomatic improvement from antibiotics, although we did not have the power to exclude more moderate benefits. By contrast, the average benefit from antibiotics in the general population might be even weaker than our

findings suggest. We had significantly fewer children with a very low-risk STARWAVe score in this study compared with the STARWAVe observational study, which recruited a representative sample of children with RTIs from the population (67% had a very low risk compared with 54% in our trial).[40] This lower proportion of children with very low risk in our trial then in the STARWAVe observational study suggests that our trial successfully recruited more unwell children, in whom antibiotics might be expected to be more effective, and that the average effect of antibiotics in a more generalisable low-risk population is likely to be even weaker than reported here. Although the analysis was underpowered, there was no clear signal for selective benefit among children where pathogenic bacteria were isolated, which could possibly be due to high carriage rates among children rather than true infection. The estimates of resource use suggest that not only are consultation, referral, and hospital admission costs considerable,[46] but societal costs are high. Antibiotic prescribing was not associated with health or societal resource savings, and if anything resulted in slightly higher costs. If the costs of antibiotic resistance were included, the adverse effect on health and societal resource use would be even higher.[7]

Similar to adults, antibiotics are unlikely to make a clinically important difference to the symptom burden for uncomplicated lower respiratory tract infections in children—both overall, and for the key clinical subgroups where antibiotic prescribing is most common. Unless pneumonia is suspected, clinicians should provide so-called safety-netting advice (ie, explain what illness course to expect and when it would be necessary to reattend) but not prescribe antibiotics for most children presenting with chest infections.

Contributors

PL and TV developed the original idea. PL led the funding applications with input from TV, BS, ADH, KW, MS, AH, GY, JR, SZ, SC, CCB, SNF, GL, MW, KHo, JW, SR-H, RCR, PS, MT, and MM. The protocol was developed and modified by all coauthors. Study progress was supervised by PL, TV, GO'R, NT, JL, TB, ADH, CH, KR, JE, CCB, NAF, MW, KHa, RCR, MM, CW, and GL. BS, KHo, PS, TB, TV, and PL developed the statistical analysis plan and interpreted the analyses, with input from all the authors. TB did the statistical analysis supervised by BS and PS. JR, GY, SZ, and JL developed the economic analysis protocol, and the analysis was done by SZ supervised by JR and GY. PL led the writing of the paper and all authors contributed to interpretation of the analyses and to revisions of the paper. BS, NT, and TB accessed and verified the data, and PL and TV were responsible for the decision to submit the manuscript. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

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Data sharing

Deidentified participant data is available for further analyses. Requests for data, with justification, should be sent to PL or TV.

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