***Antibiotics for lower Respiratory Tract Infection in Children presenting in Primary Care (ARTIC PC): a randomised placebo controlled trial***

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**Abstract.**

**Background.** Antibiotic resistance is a global public health threat. Antibiotics are very commonly prescribed for children presenting with uncomplicated lower respiratory tract infections (LRTI) but there is little randomised evidence of the effectiveness of antibiotics, both overall or among key clinical subgroups.

**Methods.** Children aged 6 months to 12 years presenting in primary care with acute uncomplicated LRTI, where pneumonia was not suspected clinically, were randomised to receiveAmoxicillin 50mg/kg/day in divided doses orally for 7 days, or placebo. Theprimary outcome was the duration in days of symptoms rated moderately bad or worse (measured using a validated diary).

**Results.** 432 children were randomised (221 antibiotic, 211 placebo). The primary analysis imputed missing data. Duration of moderately bad symptoms was similar in antibiotic and placebo groups (median 5 vs 6 days, respectively; hazard ratio (HR) 1.13 (0.90 to 1.42)). Potential harms were similar in both groups: return with new or worsening symptoms (60/202(29.7%), 76/199 (38.2%), risk ratio 0.80 (0.58 to 1.05)), where hospital assessment was required (5/211(2.4%) vs 4/204(2.0%)) and side effects (60/157(38%) vs 52/153(34%)). No differences were seen for the primary outcome in the five pre-specified clinical subgroups where antibiotic prescribing is common (chest signs; fever; physician rating of unwell; sputum/rattly chest; short of breath). Estimates from complete cases (n=317) and a per protocol analysis were similar. NHS costs per child were slightly higher with antibiotics (antibiotic £29; placebo £26) and societal costs were similar (antibiotic £33, placebo £33).

**Interpretation.** Amoxicillin for uncomplicated chest infections in children is unlikely to be clinically effective both overall and for key subgroups where antibiotics are commonly prescribed, and unlikely to reduce health or societal costs.

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**Introduction.**

Acute respiratory tract infections (RTI) are among the commonest conditions managed in primary care. The WHO (<https://apps.who.int/iris/bitstream/handle/10665/112642/9789241564748_eng.pdf>) and the UK Department of Health (1) 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 (responsible for 80% of prescribing) and antibiotic resistance at national(2) and individual (3-5) levels. The costs of resistance are also often not included in current estimates of cost-effectiveness and these can make an important impact on estimates(6) Although consultation rates and antibiotic prescription rates for upper RTI (URTI) or chest infections declined sharply in the late 1990s until the early 2000s (7)), overall antibiotic use rose again, fell 15% between 2015 and 2019 (8), and allowing for the reduced consultation rates, was 6·71% higher again during the COVID-19 pandemic than previous years.(9) 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 (10), with similar high rates of prescribing for RTIs among children internationally(11, 12). Data from our observational study in lower prescribing practices confirmed that at least 40% of children are prescribed antibiotics for chest infections(13), which translates to 2 million prescriptions for antibiotics for cough in this age group in the UK(10, 14) or approximately 30 million pounds annually in direct consultation and dispensing costs, let alone the indirect costs incurred by ‘medicalising’ illness in the family and wider social networks(15, 16).

Although trials among adults suggest only modest benefit, even among important clinical subgroups(17), there is little 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 and over(16, 18). It may be that antibiotics in children also have limited benefit given the similarity of presentation of 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(19). Parents want help managing symptoms and improving the course of illness, and are concerned about significant adverse outcomes(20, 21). Prescribing antibiotics could potentially reduce societal costs. 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 being unwell (22-25).

We report a trial that aimed to test the hypothesis that amoxicillin reduces the duration of moderately bad symptoms overall and in key clinical subgroups of children presenting with uncomplicated (non-pneumonic) lower RTI (LRTI) in primary care.

**Methods**

**Design**: A randomised placebo controlled parallel group trial of amoxicillin or placebo with a 1:1 allocation ratio for children presenting with chest infections in primary care. Patients that were not randomised as a result of patient or clinician beliefs of preference were invited to participate in an observational study where the same measures and outcomes were collected (to be fully reported separately).

**Intervention**: Amoxicillin 50mg/kg/day orally in three divided doses for 7 days or placebo.

Amoxicillin was chosen as the first choice antibiotic in LRTI, and with current levels of intermediate resistance should cover most susceptible organisms(26). The rationale for the dose is in line with guidance from the British National Formulary (BNF) for children, and was supported by a Monte Carlo simulation to achieve a Minimal Inhibitory Concentration (MIC) of around 1.5 - to cover *H. influenzae* as well as intermediate resistant *Pneumococci* for 90% of the intended population(26). We estimated that no fewer than 5 days above the MIC was needed to achieve bacterial eradication. A 7 day course was chosen to allow for poor adherence(27), 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(26). A 7 day course is also unlikely to result in more frequent side effects (gastrointestinal; allergy) than a 5 day course.

**Inclusion criteria:** Children between 6 months and twelve years old presenting to primary care with an acute LRTI, defined in several previous cohorts and trials as an acute cough as the predominant symptom, judged by the GP to be infective in origin, lasting <21 days, and with other symptoms or signs localising to the lower respiratory tract (shortness of breath, sputum, pain)(28-31). These inclusion criteria reflect the clinical criteria used in daily practice to diagnose acute bronchitis(32) and were used in the Cochrane review(18), and are also the key drivers of prescribing(22, 23)).

**Exclusion criteria**: the cough was judged by the clinician to have a non-infectious aetiology (e.g. hay fever or a non-infective exacerbation of asthma) or almost certain viral aetiology (croup, where antibiotics are not commonly prescribed); immune-compromised; and antibiotic use in previous 30 days. Children where the clinician did not have equipoise (where the clinician judged that pneumonia was likely, or that the child was judged to be severely ill) were not randomised, but they were eligible to enter a parallel observational study.

**Consent:** The parent/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 assent form.

**Randomisation:** Parents and children who consented to the study and agreed to randomization received either amoxicillin or placebo oral suspension, randomised in a 1:1 ratio. Investigational medicinal product (IMP) 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 IMP 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 IMP pack.

**Data Collection**

**Measurements and follow-up**: The recruiting clinician completed a Case Report Form (CRF) of comorbidities, clinical signs and the severity of baseline symptoms reported by the patient (rating each symptom ‘no problem’, ‘mild problem’, a ‘moderate problem’, or ‘severe problem’)(26). Co-morbidity and the number of RTIs in the previous year were also documented, and pulse oximetry performed.

We chose throat swabs for microbiological sampling due to the experience of both high pick up rates and acceptability for children(33). For parents and children willing to have a throat swab a swab was taken and analysed in a central laboratory using multiplex PCR.

**Symptom diary**: The parents kept a diary of symptoms and daily activities (including days away from work of parents) using validated daily diary for at least one week and after that as long as symptoms persisted up to four weeks after inclusion. The diary items recorded the severity of the following symptoms: cough, phlegm, shortness of breath, wheeze, blocked/runny nose, disturbed sleep, feeling general 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)(26, 34). All patients were requested to return at one month with medication bottles.

**Outcomes Primary outcome:** The primary outcome was the duration of symptoms rated moderately bad or worse as used in previous studies on acute LRTI(26)(6), recorded for up to 28 days until symptom settled in a validated daily diary. When the diary was not returned, a short mailed questionnaire was sent, and if that was not returned, a phone call was made. The primary outcome matches parental concerns about more severe symptoms(26,27). The diary has previously been validated and was shown to be sensitive to change in both adults and children, and internally reliable (Cronbach’s alpha 0.75, i.e. in optimal range)(16, 34). The estimates based on the diary can also be compared directly with the major/definitive trial of antibiotics for adults with LRTI(26).

**Secondary outcomes**

**Severity of symptoms:** We chose the severity in the first 2-4 days after seeing the doctor (based on the diary responses), since this is typically the period when symptoms are the most severe(16), when antibiotics might make a difference.

**Total symptom duration.** The duration of symptoms until very little or no problem.

**Potential harms**

**Re-consultation with new or worsening symptoms or complications:** These outcomes were documented based on a structured notes review which we have shown to be feasible and reliable(35, 36), and demonstrated antibiotic effectiveness in the previous large trial in adults(26).

 **Side effects**: Diarrhoea, rash, or nausea are common side effects, and recorded in the daily diary.

**Health care resource use:** Information on resource usagewas collected by notes review including resource use for major adverse events (e.g. anaphylaxis, complications, hospital admissions) at baseline, and 28 days. This was used to assess NHS and social service use (primary care visits, community service, hospital inpatient and outpatient visits, and accident and emergency (A&E) attendances). Additional analyses to include out-pocket spending and parent/carer’s time of off work in taking care of children were calculated. We collected QALY data in the diary but completion rates were very poor, hence not reported here.

**Adherence**. The number of doses of medication taken were documented in the daily diary.

**Sample size calculation**: Balancing the threat posed by antibiotic resistance, a three day difference in symptom resolution (hazard ratio (HR) 1.7) for an illness lasting 14-21 days (i.e. reducing the duration by 15-20%) was judged to be clinically important enough to warrant treatment. We originally estimated that 938 children were required (for alpha=0.01, 90% power, 80% follow-up) to detect an HR of 1.7 for the primary outcome among any one of 5 equally prioritised clinical subgroups (chest signs; fever; physician rating of unwell; sputum/rattly chest; short of breath), assuming any subgroup was 30% or more of the sample. The sample size calculation was revised following agreement with the funder, TSC and DMSC based on a) evidence from systematic reviews that abnormal chest signs are the most important driver for antibiotic prescriptions(22) from 6 studies odds ratios for prescribing antibiotics ranging from 3 to 20, and b) using proportions of subgroups observed (blind to randomisation group) in the penultimate season of the trial. We used a traditional approach of powering for the subgroup sizes, adjusting the alpha for multiple subgroups (chest signs subgroups alpha 0.05, other subgroups alpha 0.01), and working out 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 alpha 0.05, 80% power) assuming 40% of the trial cohort had chest signs (based on the study data at the time 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 alpha 0.01.

**Statistical analysis**

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, prior 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 by intention-to-treat, as randomised regardless of non-adherence or protocol deviations. Multiple imputation was chosen for the primary analysis, and complete cases for a secondary analysis, since multiple imputation is generally more efficient than complete case analysis(37), and particularly important to control for potential attrition bias. Multiple imputation included those in the analysis model (age, comorbidity, prior duration of illness, baseline severity) and significant predictors of missingness (parental qualification) using 100 imputations(38). A complete cases analysis and a Complier Average Causal Effect (CACE) analysis were performed as sensitivity analyses. Prespecified subgroup analyses were carried out on chest signs (alpha=0.05), sputum/rattly chest, history of fever, physician rating of unwell, shortness of breath, oxygen saturation below 95%, and STARWAVe clinical prediction rule for hospitalisation(39) (all alpha=0.01). Analyses were carried out in Stata 16 and SPSS 26 and blind to group allocation. Where medians are reported with the ‘interquartile range’ (IQR) we report the lower to upper quartile (Q1-Q3).

**Resource use**: Unit costs of primary care consultation, community services, outpatient visits and A&E attendances were based on the Personal Social Services Research Unit (PSSRU). National reference costs were used to cost hospital stay based on relevant diagnostic categories. Medications were priced based on 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.

**Role of funder.** The funder had no role in data collection, analysis, interpretation, writing of the manuscript nor the decision to submit.

**Results**

Participants were recruited from 56 general practices between 9 November 2016 and 17 March 2020. 438 patients were randomised and 6 withdrew the use of their data and so could not be used in the ITT analysis; a total of 432 participants were then analysed in the randomised trial: 221 randomised to antibiotics and 211 randomised to placebo (see CONSORT diagram – Figure 1). 312 children were recruited to the observational study.

A total of 233 participants (53.9%) were male, with a median age of 3.2 years (interquartile range (IQR) 1.6 to 5.7 years), and 55 (12.7%) had a comorbidity (Table 1). Regarding the prespecified key clinical subgroups, 150 (34.7%) had abnormal chest signs, 325 (75.8%) had sputum/rattly chest, 338 (78.2%) had a fever during the illness, 284 (65.7%) were categorised as unwell according to the physician rating (rating of 5 or more on a scale of 1 to 10), and 199 (46.1 %) had shortness of breath (Table 2). 6.6% had oxygen saturation below 95%. According to the STARWAVe prediction rule(39) 53.9% were at very low risk of hospital admission, 43.8% were at normal risk and 2.3% were at high risk of hospital admission. The key baseline characteristics were similar across randomised arms (Tables 1 & 2)

Of those who reported which medication they thought their child had received, 47 (46.5%) in the antibiotics arm and 33 (39.3%) in the placebo arm thought their child had received antibiotics.

**Follow-up**

Complete data were available on symptom duration for 317 participants (73.3%), on symptom severity for 298 (69.0%), on re-consultation with new or worsening symptoms for 401 (92.8%), on complications for 415 (96.1%), and on side effects for 310 participants (71.8%) (Table 3). For the key subgroups we had complete cases for 109 children in the chest-signs subgroup, 247 for fever, 208 for physician rating of being unwell, and 146 for short of breath.

**Primary outcome**

The duration of moderately bad or worse symptoms was similar between groups (antibiotic group median 5 days (IQR 4 to 11); placebo 6 days (4 to 15); hazard ratio 1.13 (95% confidence interval (CI) 0.90 to 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 pre-specified clinical subgroups nor additional post-hoc exploratory subgroups (low oxygen saturation; STARWAVe categories; including adjustment for asthma and vaccination status) modified the effect of treatment on duration of moderately bad or worse symptoms (Table 5).

**Secondary outcomes**

There was a statistically significant small difference between the groups in symptom severity for days 2-4 after seeing the doctor (antibiotics 1.8, placebo 2.1; mean difference of -0.28 (95% CI -0.51 to -0.04)) (Table 4)); equivalent to less than one child in three rating symptoms a slight problem rather than very little problem.

The duration of symptoms until rated absent or very little problem was also similar comparing groups (antibiotics median 7 days (IQR 4-17); placebo 8 days (5-20)) with no significant difference between groups (HR 1.09 (95%CI 0.86 to 1.38)) (Table 4).

The number of participants re-consulting with new or worsening symptoms was 60 (29.7%) in the antibiotics group compared to 76 (38.2%) in the placebo group (risk ratio 0.80 (95% CI 0.58 to 1.05)) (Table 4). Complications were uncommon (5 (2.4%) antibiotics; 4 (2.0%) placebo; risk ratio 1.23 (0.32 to 4.44)) (Table 4). The number of participants experiencing side effects was similar (antibiotics 60 (38.2%), placebo 52 (34.0%); risk ratio 1.20 (0.87-1.55)) (Table 4).

**Serious adverse events**

The number of complications and hospitalisations in both groups were low, and similar between groups (Appendix table 6).

**Sensitivity analyses.**

The main analyses (Tables 4 and 5) were calculated based on 100 multiply imputed datasets. Complete case analyses gave very similar results (appendix tables 8 and 9).

**Exploratory post-hoc analyses for clinical subgroups**

The treatment effects for all outcomes were similar for most subgroups (none of the interaction terms were significant), but the impact of antibiotics was slightly greater (but not significantly) among those with fever or those being unwell (Tables 10, 11 Appendix). Re-consultations with antibiotics were slightly greater among the less unwell children (Table 12 Appendix).

**Adherence**

A total of 232 (53.7%) participants provided data on adherence to medication. Of those who reported medication adherence, 98/119 (82.4%) participants in the antibiotics group and 87/113 (77.0%) participants in the placebo group took at least 11 doses of medication over days 1 to 5. A per protocol analysis among these participants documented no statistically significant difference in the duration of moderately bad or worse symptoms, hazard ratio 1.06 (95% CI 0.77 to 1.46) (see Appendix for further adherence analysis). A CACE analysis gave an unadjusted hazard ratio for the duration of moderately bad or worse symptoms of 1.31, 95% CI 0.90 to 1.89 (cf. unadjusted HR for primary analysis 1.21, 95% CI 0.95 to 1.53).

**Resource use**

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 statistically significant differences in costs were observed. Slightly higher total NHS costs per child were documented in the antibiotic group (antibiotic £29.4; placebo £25.8). The cost of antibiotics was low at around 10%,the bulk of NHS costs being due to reconsultations and referrals. The societal costs due to time off work or privately purchased remedies were also similar between groups (antibiotic £32.9, placebo group £32.7) (see Table 13).

 **Microbiology**

The microbiological analysis documented similar numbers of potential bacterial and viral pathogens (Table 14 Appendix). A small number (2 placebo, 5 antibiotic) of bacterial pathogens were found that would not be expected to respond to amoxicillin or not implicated in LRTI(*Chalmydia pneumoniae, Mycoplasma pneumoniae, Bortetella pertussis, S Pyogenes, F Necrophorum).* There was no evidence of a differential effect of antibiotics where bacteria are sensitive to amoxicillin (*H Influenzae, M Catarrhalis, S Pneumoniae*) were present (Table 15 – Appendix).

**Observational study.**

The children in the observational study were similar to the trial, although the former included more children who had chest signs (See Appendix Table 16).

Table 1. Baseline characteristics of randomised participants

|  |  |  |  |
| --- | --- | --- | --- |
|  | Placebo(N = 211) | Antibiotics (N = 221) | Overall(N=432) |
| Male (n, %) | 112 (53.1) | 121 (54.8) | 233 (53.9) |
| Age in years (median, IQR) | 3.1 (1.4, 5.6) | 3.2 (1.7, 5.8) | 3.2 (1.6, 5.7) |
| Comorbidity (n, %) | 31 (14.7) | 24 (10.9) | 55 (12.7) |
| Asthma (n, %) | 27 (12.8) | 18 (8.1) | 45 (10.4) |
| Long term illness (n/N, %) | 7/111 (6.3) | 13/120 (10.7) | 20/231 (8.6) |
| Hay fever/eczema (n/N, %) | 39/111 (35.1) | 44/121 (36.4) | 83/232 (35.8) |
| Family history of asthma (n/N, %) | 66/112 (58.9) | 81/117 (69.2) | 147/229 (64.2) |
| Breast fed at 3 months (n/N, %) | 49/110 (44.6) | 65/120 (54.2) | 114/230 (49.6) |
| Mother age (mean, SD, N) | 34.8 (6.4) (N=105) | 34.9 (7.2) (N=114) | 34.9 (6.8) (N=219) |
| Number of times had cough in last 12 months (mean, SD, N) | 2.5 (2.3) (N=110) | 2.8 (2.8) (N=112) | 2.6 (2.6) (N=222) |
| Prior influenza vaccine in last 12 months (n/N, %) | 55/200 (27.5) | 59/201 (29.4) | 114/401 (21.4) |
| Prior pneumococcal vaccine (booster) in last 12 months (n/N, %) | 61/200 (30.5) | 64/201 (31.8) | 125/401 (31.2) |
| Smoker in household (n, %) |  |  |  |
| Yes | 44 (20.9) | 50 (22.6) | 94 (21.8) |
| No | 165 (78.2) | 166 (75.1) | 331 (76.6) |
| Don’t know | 2 (1.0) | 5 (2.2) | 7 (1.6) |
| Number of children in home (n, %) |  |  |  |
| 1 | 87 (41.2) | 86 (38.9) | 173 (40.1) |
| 2 | 73 (34.6) | 95 (43.0) | 168 (38.9) |
| 3 | 35 (16.6) | 25 (11.3) | 60 (13.9) |
| 4 | 13 (6.2) | 7 (3.2) | 20 (4.6) |
| 5 or more | 3 (1.4) | 8 (3.6) | 11 (2.5) |
| Parent highest qualification (n, %) |  |  |  |
| Degree | 78 (37.0) | 81 (36.7) | 159 (36.8) |
| Diploma | 27 (12.8) | 23 (10.4) | 50 (11.6) |
| A-level | 23 (10.9) | 16 (7.2) | 39 (9.0) |
| GCSE/O-level | 20 (9.5) | 27 (12.2) | 47 (10.9) |
| None | 10 (4.7) | 7 (3.2) | 17 (3.9) |
| Not given | 42 (19.9) | 53 (24.0) | 95 (22.0) |
| Other | 11 (5.2) | 14 (6.3) | 25 (5.8) |
| Ethnic group (n, %) |  |  |  |
| British/Irish/Other white | 182 (86.3) | 189 (85.5) | 371 (85.9) |
| Mixed | 8 (3.8) | 11 (5.0) | 19 (4.4) |
| South Asian | 15 (7.1) | 14 (6.3) | 29 (6.7) |
| Other | 4 (1.9) | 5 (2.3) | 9 (2.1) |
| Prefer not to say | 1 (0.5) | 2 (0.9) | 3 (0.7) |

Table 2. Illness presentation of randomised participants

|  |  |  |  |
| --- | --- | --- | --- |
|  | Placebo (N = 211) | Antibiotics(N = 221) | Overall(N=432) |
| Baseline severity\* (mean, SD) | 1.6 (0.3) | 1.6 (0.3) | 1.6 (0.3) |
| Cough severity (mean, SD) | 1.9 (1.1) | 2.0 (1.1) | 1.9 (1.1) |
| Duration of illness in days (median, IQR1)  | 6 (3, 10) | 5 (3, 10) | 5 (3, 10) |
| Abnormal chest signs\* (n, %) | 72 (34.1) | 78 (35.3) | 150 (34.7) |
| Sputum/rattly chest (n/N, %) | 155/210 (73.8) | 170/219 (77.6) | 325/429 (75.8) |
| Fever during illness (n, %) | 161 (76.3) | 177 (80.1) | 338 (78.2) |
| Unwell according to physician\*\* (n, %) | 141 (66.8) | 143 (64.7) | 284 (65.7) |
| Shortness of breath (Yes/No) (n, %) | 95 (45.0) | 104 (47.1) | 199 (46.1) |
| Oxygen saturation low (n/N, %) | 9/166 (5.4) | 13/170 (7.7) | 22/336 (6.6) |
| STARWAVe\* (n, %) |  |  |  |
| Very low risk | 110 (52.1) | 123 (55.7) | 233 (53.9) |
| Normal risk | 95 (45.0) | 94 (42.5) | 189 (43.8) |
| High risk | 6 (2.8) | 4 (1.8) | 10 (2.3) |
| Physician rating unwell\* (mean, SD) | 5.5 (1.7) | 5.5 (1.6) | 5.5 (1.6) |
| Parent rating of unwell\* (mean, SD) | 3.8 (1.7) | 3.7 (1.7) | 3.7 (1.7) |
| Temperature (mean, SD, N) | 37.3 (0.8) (N=208) | 37.2 (0.8) (N=220) | 37.3 (0.8) (N=428) |
| Oxygen saturation (mean, SD, N) | 97.3 (1.6) (N=166) | 97.3 (1.6) (N=170) | 97.3 (1.6) (N=336) |
| Heart rate (beats per min) (mean, SD, N) | 112.0 (20.3) (N=207) | 111.8 (17.9) (N=213) | 111.9 (19.1) (N=420) |
| Respiratory rate (breaths per min) (mean, SD, N) | 24.8 (6.8) (N=198) | 25.4 (7.1) (N=213) | 25.1 (7.0) (N=411) |
| Tachypnoea (n/N, %) | 25/198 (12.6) | 30/213 (14.1) | 55/411 (13.4) |
| Capillary refill >3 seconds (n, %) | 3 (1.5) | 2 (0.9) | 5 (1.2) |
| Consciousness (n, %) |  |  |  |
| Normal  | 203 (96.2) | 214 (97.3) | 417 (96.8) |
| Irritable | 8 (3.8) | 5 (2.3) | 13 (3.0) |
| Drowsy | 0 (0.0) | 1 (0.5) | 1 (0.2) |
| Ill appearance (n, %) | 48 (22.9) | 47 (21.3) | 95 (22.0) |
| Number of days unwell before seeing general practitioner (median,IQR, N) | 5 (3, 9) (N=108) | 5 (3, 7) (N=119) | 5 (3, 9) (N=227) |
| Treated with OTC medication (n/N, %) | 105/111 (94.6) | 107/121 (88.4) | 212/232 (91.4) |

\*Baseline severity on a scale 1 to 4: 1=none, 2=mild, 3=moderate, 4=severe; Abnormal chest signs include wheeze, stridor, grunting, nasal flaring, inter/subcostal recession, crackles/crepitations, bronchial breathing; STARWAVe prediction rule(39) for hospital admission (short illness, temperature, age, recession, wheeze, asthma, vomiting); Physician and parent rating of unwell on a scale 0 to 10;\*\*physician rating dichotomised at >=5

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

|  |  |  |
| --- | --- | --- |
|  | Placebo | Antibiotics |
|  | N |  | N |  |
| Duration of moderately bad or worse symptoms in days (median, IQR) | 156 | 6 (4, 15)  | 161 | 5 (4, 11) |
| Symptom severity (mean, SD) | 149 | 2.1 (1.1) | 149 | 1.8 (1.0) |
| Duration of symptoms until very little problem in days (median, IQR) | 156 | 8 (5, 20) | 161 | 7 (4, 17) |
| Return with new or worsening symptoms (n, %) | 199 | 76 (38.2) | 202 | 60 (29.7) |
| 1Complications (n, %) | 204 | 4 (2.0) | 211 | 5 (2.4) |
| Side effects (n, %) | 153 | 52 (34.0) | 157 | 60 (38.2) |
| Diarrhoea | 88 | 26 (29.6) | 98 | 24 (24.5) |
| Nausea | 92 | 32 (34.8) | 102 | 35 (34.3) |
| Rash | 91 | 20 (22.0) | 99 | 25 (25.3) |
|  |  |  |  |  |

Symptom severity on a scale 0 to 6 where 0=no problem, 1=very little problem, 2=slight problem, 3=moderately bad, 4=bad, 5=very bad, 6=as bad as it could be

1 assessment or admission needed in hospital within one month of index consultation.

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

|  |  |  |  |
| --- | --- | --- | --- |
|  | Placebo | Antibiotics | Adjusted\* treatment estimate (95% CI) |
| Duration of moderately bad or worse symptoms in days (median, IQR) | 6 (4, 15) | 5 (4, 11) | HR 1.13 (0.90, 1.42) |
| Symptom severity (mean, SD) | 2.1 (1.1) | 1.8 (1.0) | Diff -0.28 (-0.51, -0.04) |
| Duration of symptoms until very little problem in days (median, IQR) | 8 (5, 20) | 7 (4, 17) | HR 1.09 (0.86, 1.38) |
| Return with new or worsening symptoms (n, %) | 76 (38.2) | 60 (29.7) | OR 0.71 (0.46, 1.09)RR 0.80 (0.58, 1.05) |
|  |  |  |  |
| Assessment or admission needed in hospital1 (n, %) | 4 (2.0) | 5 (2.4) | OR 1.24 (0.32, 4.78)RR 1.23 (0.32, 4.44) |
|  |  |  |  |
| Side effects (n, %) | 52 (34.0) | 60 (38.2) | OR 1.33 (0.81, 2.17) |
|  |  |  | RR 1.20 (0.87, 1.55) |

1assessment or admission needed in hospital within one month of index consultation. See table 6 (appendix) for description of individual cases.

Analysis based on 100 multiply imputed data sets; \*Adjusted for prior duration of illness, baseline severity, age, and comorbidity

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

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Subgroup | Placebo | Antibiotics | Interaction term (99% CI)\*\* | Adjusted\* hazard ratio (99% CI)\*\* |
|  | N | Median (IQR) |  N | Median (IQR) |  |  |
| Abnormal chest signs |  |  |  |  |  |  |
| Yes | 54 | 6 (4, 16) | 52 | 6 (4, 15) | 0.84 (0.52, 1.36) | 0.97 (0.65, 1.43) |
| No | 102 | 7 (4, 15) | 109 | 5 (3, 11) | 1.21 (0.91, 1.60) |
|  |  |  |  |  |  |  |
| Sputum |  |  |  |  |  |  |
| Yes | 115 | 7 (4, 16) | 124 | 5 (4,14) | 1.11 (0.55, 2.26) | 1.16 (0.83, 1.64) |
| No | 41 | 5 (4, 14) | 36 | 5 (3, 10) | 0.99 (0.52, 1.90) |
| Fever |  |  |  |  |  |  |
| Yes | 115 | 6 (4, 16) | 131 | 5 (3,10) | 1.45 (0.71, 2.98) | 1.23 (0.88, 1.73) |
| No | 41 | 7 (4, 13) | 30 | 7 (4, 26) | 0.78 (0.40, 1.53) |
| Physician rating of unwell\*\* |  |  |  |  |  |  |
| Yes | 104 | 6 (4, 15.5) | 101 | 5 (3, 10) | 1.32 (0.71, 2.46) | 1.25 (0.85, 1.83) |
| No | 52 | 8 (4, 14.5) | 60 | 6 (4, 16) | 0.96 (0.58, 1.58) |
| Shortness of breath |  |  |  |  |  |  |
| Yes | 77 | 6 (4,11) | 71 | 5 (3, 14) | 0.96 (0.54, 1.73) | 1.13 (0.72, 1.77) |
| No | 79 | 7 (4, 18.5) | 90 | 5.5 (4, 11) | 1.17 (0.78, 1.75) |
| Oxygen saturation low |  |  |  |  |  |  |
| Yes | 7 | 11 (6, 18) | 8 | 8 (4, 20) | 0.95 (0.23, 3.94) | 1.20 (0.24, 5.93) |
| No | 119 | 6 (4, 15) | 116 | 5 (3.5, 10) | 1.11 (0.78, 1.57) |
| STARWAVe(39) |  |  |  |  |  |  |
| Very low risk | 78 | 7 (4, 17) | 93 | 5 (4, 10) |  | 1.27 (0.84, 1.91) |
| Normal risk | 72 | 6 (4, 11.5) | 65 | 6 (3,14) | 0.77 (0.45, 1.30) | 1.06 (0.67, 1.66) |
| High risk | 6\*\*\* | - | 3\*\*\* | - | - | - |

Analysis based on 100 multiply imputed datasets \*Adjusted for prior duration of illness, baseline severity, age, and comorbidity; \*\*95% CI for the abnormal chest signs subgroup \*\*\*too few data to obtain reliable estimates.

Physicians rating of unwell on a scale of 1 to 10, dichotomised at >=5

 Figure1 CONSORT DIAGRAM

1,460 assessed for eligibility

1,022 patients excluded

314 Did not meet inclusion criteria

144 Declined to participant

564 Other reasons

852 assessed for eligibility\*

1,022 patients excluded\*

328 Did not meet inclusion criteria

144 Declined to participate

290 met the exclusion criteria

178 not recruited due to lack of ARTIC trained staff or staff time

 82 other reasons

221 patients analysed at baseline

161 patients complete data primary outcome

216 patients allocated to placebo

 26/113 did not take placebo

222 allocated to antibiotics

 3 did not receive antibiotics (dispensing error)

 21/119 did not take antibiotics

438 patients randomized (n=438)

1 withdrew use of data

60 lost to follow-up

5 withdrew use of data

55 lost to follow-up

211 patients analysed at baseline

156 patients complete data primary outcome

\***Not meeting inclusion:** 61 too young; 13 too old; 181 GP judged not LRTI; 65 >21 days; 8 other. **Exclusion:** 25 asthma/allergy-related cough;83 GP suspected viral infection;26 croup;79 prior antibiotics;3 penicillin-allergic;9 already enrolled or sibling already enrolled ;39 admitted to hospital/ too unwell;26 other

Figure 2. Kaplan Meier curve of duration of moderately bad or worse symptoms in days



**Discussion.**

This trial documents that for children presenting to primary care with uncomplicated acute LRTI there is unlikely to be a clinically important impact of amoxicillin treatment on symptom burden both overall and for the key subgroups where antibiotics are commonly prescribed. There was also no evidence of additional complications when antibiotics are not prescribed.

**Strengths and Limitations.**

The study is one of the very few 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 (a hazard ratio (HR) of 1.7) - around a 15% difference considering a total illness duration of 20-25 days documented by a systematic review (40), or roughly a 20% improvement for an illness lasting 14 days in total based on the placebo group of the current sample. 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(1, 2). We used the most patient relevant outcome (parent reported symptoms), and documented complications. The study confirmed that complications are uncommon, but was not specifically powered to assess complications (a trial of several thousand children would be needed), nor re-consultations, nor microbiological subgroups. The sample size estimate was modified during the trial based on a systematic review of the evidence, and informed by the percentages of subgroups observed during the penultimate season of the trial (blind to group). 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 antibiotic and placebo groups in both analyses), the HRs near unity (0.91, 0.97 respectively), and the upper 95% confidence intervals of the HRs (1.41, 1.43) suggest the benefit for children with chest signs is unlikely to be more than 2 days i.e. not clinically important. The follow-up rate of 73.4% (317/422) 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 as it is the first choice antibiotic in UK national guidance for use in LRTIs among children (nice-guidance/antimicrobial-prescribing-guidelines). The trial population was similar to children recruited to the current smaller observational study, but compared with large representative observational cohorts this trial population had slightly more severe clinical presentation (39) (see below). Thus if anything we are likely to have overestimated the impact of antibiotics in the UK setting, but results may not generalise to other settings e.g. countries with very different diagnostic approaches, prescription rates, complication rates (e.g.Low and Middle Income countries), or in distribution of pathogens.

**Interpretation and comparison with previous literature**

Only one trial in the Cochrane review of antibiotics for acute bronchitis included young children as young as 3 presenting with uncomplicated acute chest infections (16, 18). In that trial there were only 100 children aged 12 and under, 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 to 6) was similar to the non-significant result of the whole trial cohort(16). 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(41), but a more recent trial of azithromycin used in early infections was effective in preventing severe illness among preschool children with recurrent infection(42) (from 8% to 5%) although concern remains about the longer term effects on antibiotic resistance from the use of long-acting macrolides(5). A placebo controlled trial of antibiotic versus placebo for pneumonia in young children in a LMIC setting found low failure rates in both placebo (4.9%) and antibiotic (2.6%) arms(43), and a 5 day course is equivalent to 10 days for community acquired pneumonia(44).

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 children that receive a meaningful benefit which is watered down by large numbers of children who receive no benefit. We explored this hypothesis by conducting subgroup analyses in five pre-specified subgroups. Our subgroup analysis results suggest that none of the groups we specified is likely to achieve substantial benefits in terms of symptomatic improvement from antibiotics, although we did not have the power to exclude more moderate benefits. On the other hand, the average benefit from antibiotics in the general population may be even less than our findings suggest. We had significantly fewer children with a very low risk STARWAVe score in this study when compared with the STARWAVe observational study which recruited a representative sample of children with RTIs from the population (children with a very low risk score 67%; current trial 54% - see Table 1)(39). This suggests that the present trial successfully recruited more unwell children, in whom antibiotics might be expected to be more effective, and that the average impact of antibiotics in a more generalisable low risk population is likely to be even lower 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 consultations, referral and hospitalisation costs considerable (45) 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 impact on health and societal resource use would be higher.(6).

**Conclusion.**  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 ‘safety-netting’ advice (i.e. 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.

**Research in context**

**Evidence before the study.**

The Cochrane review of antibiotics for acute bronchitis documented that antibiotics have a modest effect on cough duration (7 studies, 2776 participants, mean difference (MD) ‐0.46 days, 95% CI ‐0.87 to ‐0.04). However the trials in 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 (HR) 1.13 (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/’rattly’ chest; short of breath).

**Implications of all the available evidence**

Unless pneumonia is suspected, clinicians should probably provide ‘safety-netting’ advice (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.

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

**Competing Interests.** All authors have completed the Unified Competing Interest form at <http://www.icmje.org/coi_disclosure.pdf> (available on request from the corresponding author).

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**Contributorship**. PL and TV developed the original idea. PL led the funding applications with input from TV,BS,AH,KW,MS,AH,GY,JR,SZ,SC,CB,SF,GL,MW,KH,JW,SR,PS,MT,MM., and the protocol was developed and modified by all coauthors. The study progress was supervised by PL,TV,GOR,NT,JL,TB,AH,CH,KR,JE,CB,NF,MW,KH,MM. BS,KH, PS,TB,TV and PL developed the statistical analysis plan and interpreted the analyses, with input from all the authors; TB performed the statistical analysis supervised by BS and PS. JR, GY, SH and JL developed the economic analysis protocol, and the analysis was performed by SH 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. BLS, NT and TB accessed and verified the data, and PL and TV were responsible for the decision to submit the manuscript.

**Data sharing**. De-identified participant data is available for further analyses. Request for data, with justification, should be made to PL or TV.

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**Appendix.**

Table 6. Description of attendances or admissions to hospital

|  |  |
| --- | --- |
| Placebo | Antibiotics |
| Hospital admission - Worsening of symptoms/’Viral-Induced’ wheeze  | Hospital admission - stridor, floppy episode and febrile convulsion, croup, Short of breath |
| Hospital admission - Shortness of breath. Bronchiolitis, increased work of breathing requiring optiflow and NG feeding | Persistent symptoms of fever, increasing breathlessness, oxygen sats 91%, respiratory rate 32/min, expiratory wheeze; admission to hospital (not overnight) |
| Exacerbation of cough and phlegm/ cough getting worse, vomiting overnight, decreased feeding – not admitted overnight | Hospital admission - Bronchiolitis |
| Hospital admission - no further information available | Gastro-intestinal symptoms: hospital admission - not overnight |
|  | Temp 38.5, ‘rattle in throat/chest’, stomach pain |

Table 7. Hospital admissions (overnight) by STARWAVe prediction rule

|  |  |  |
| --- | --- | --- |
|  | Placebo | Antibiotics |
| STARWAVe |  |  |
| Very low risk | 1/104 (1.0%) | 0/118 (0.0%) |
| Normal risk | 2/94 (2.1%) | 2/89 (2.2%) |
| High risk | 0/6 (0.0%) | 0/4 (0.0%) |

**Adherence.**

Among those who reported adherence, most (95%) started taking their medication on day 1, adherence was maintained in the antibiotics arm over days 1 to 5, but decreased gradually to 84% by day 5 in the placebo arm. Reported adherence was higher for longer prior duration of illness (OR 1.08, 95% CI 1.01 to 1.16) adjusting for group and other prespecified covariates. Among those who thought their child was receiving antibiotics, 68 (85%) adhered to their medication, and among those who thought their child was receiving placebo 82 (82%) adhered to their medication. There was little evidence for clustering by GP practice, intra-cluster correlation ICC 0.01 (95% CI 0.00 to 0.99).

*Adherence sensitivity analyses*

In order to provide a lower bound to the adherence, we assume that all those who completed the diary but did not fill in medication dosage did not adhere to their medication. Under this assumption, 98/161 (60.9%) in the Antibiotics group and 87/156 (55.8%) in the Placebo group adhered to their medication. In order to provide an upper bound to the adherence, we assume all those who completed the diary but did not fill in medication dosage did adhere. Under this assumption, adherence was 140/161 (87.0%) in the antibiotics arm and 130/156 (83.3%) in the placebo arm. If adherence is low, the ITT effect of antibiotics on duration will be diluted. Therefore, as a sensitivity analysis, assuming all those who completed the diary but did not fill in medication dosage did not adhere in the antibiotics arm.

|  |  |
| --- | --- |
|  | Medication taken (n, %) |
| Day | Placebo | Antibiotics |
| 1 | 108 (95.6%) | 112 (94.1%) |
| 2 | 103 (92.0%) | 117 (98.3%) |
| 3 | 99 (88.4%) | 116 (97.5%) |
| 4 | 94 (84.7%) | 110 (93.2%) |
| 5 | 93 (83.8%) | 108 (91.5%) |

**

Figure 2. Number of doses of medication over days 1 to 5

Table 8. Effectiveness of antibiotics in primary and secondary outcomes (complete cases analysis)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Number analysed | Placebo | Antibiotics | Adjusted\* treatment estimate (95% CI) |
| Duration of moderately bad or worse symptoms in days (median, IQR) | 317 | 6 (4, 15) | 5 (4, 11) | HR 1.15 (0.91, 1.46) |
| Symptom severity (mean, SD) | 298 | 2.1 (1.1) | 1.8 (1.0) | Diff -0.29 (-0.53, -0.04) |
| Duration of symptoms until very little problem in days (median, IQR) | 317 | 8 (5, 20) | 7 (4, 17) | HR 1.10 (0.85, 1.40) |
| Return with new or worsening symptoms (n, %) | 401 | 76 (38.2) | 60 (29.7) | OR 0.71 (0.46, 1.08)RR 0.78 (0.61, 1.04) |
| Complications (n, %) | 415 | 4 (2.0) | 5 (2.4) | OR 1.21 (0.31, 4.67)RR 1.18 (0.33, 4.26) |
|  |  |  |  |  |
| Side effects (n, %) | 310 | 52 (34.0) | 60 (38.2) | OR 1.32 (0.81, 2.15) |
|  |  |  |  | RR 1.19 (0.64, 1.56) |

\*Adjusted for prior duration of illness, baseline severity, age, and comorbidity

Table 9. Duration of moderately bad or worse symptoms by subgroup (complete cases analysis)

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Subgroup | N | Placebo | Antibiotics | Interaction term (99% CI)\*\* | Adjusted \*hazard ratio (99% CI)\*\* |
| Abnormal chest signs |  |  |  |  |  |
| Yes | 106 | 6 (4, 16) | 6 (4, 15) | 0.82 (0.49, 1.36) | 0.91 (0.59, 1.41) |
| No | 211 | 7 (4, 15) | 5 (3, 11) | 1.25 (0.93, 1.68) |
|  |  |  |  |  |  |
| Sputum |  |  |  |  |  |
| Yes | 239 | 7 (4, 16) | 5 (4,14) | 1.20 (0.58, 2.49) | 1.22 (0.85, 1.75) |
| No | 77 | 5 (4, 14) | 5 (3, 10) | 0.95 (0.47, 1.90) |
| Fever |  |  |  |  |  |
| Yes | 246 | 6 (4, 16) | 5 (3,10) | 1.63 (0.74, 3.58) | 1.28 (0.90, 1.83) |
| No | 71 | 7 (4, 13) | 7 (4, 26) | 0.65 (0.30, 1.42) |
| Physician rating of unwell |  |  |  |  |  |
| Yes | 205 | 6 (4, 15.5) | 5 (3, 10) | 1.43 (0.74, 2.76) | 1.33 (0.89, 1.98) |
| No | 112 | 8 (4, 14.5) | 6 (4, 16) | 0.92 (0.54, 1.57) |
| Shortness of breath |  |  |  |  |  |
| Yes | 148 | 6 (4,11) | 5 (3, 14) | 1.07 (0.56, 2.02) | 1.24 (0.78, 1.99) |
| No | 169 | 7 (4, 18.5) | 5.5 (4, 11) | 1.16 (0.75, 1.81) |
| Oxygen saturation low |  |  |  |  |  |
| Yes | 15 | 11 (6, 18) | 8 (4, 20) | 0.80 (0.18, 3.55) | 1.45 (0.25, 8.46) |
| No | 235 | 6 (4, 15) | 5 (3.5, 10) | 1.12 (0.78, 1.61) |
|  |  |  |  |  |  |
| STARWAVe |  |  |  |  |  |
| Very low risk | 171 | 7 (4, 17) | 5 (4, 10 |  | 1.24 (0.89, 1.99) |
| Normal risk | 137 | 6 (4, 11.5) | 6 (3,14) | 0.88 (0.46, 1.66) | 1.09 (0.67, 1.78) |
| High risk | 9 | -\*\*\* | - | - | - |

\*Adjusted for prior duration of illness, baseline severity, age, and comorbidity; \*\*95% CI for the abnormal chest signs subgroup. \*\*\*too few data to obtain reliable estimates

Table 10. Duration of moderately bad or worse symptoms by subgroup (adjusted for other subgroups)

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Subgroup | N | Placebo | Antibiotics | Interaction term (99% CI)\*\* | Adjusted\* Hazard ratio (99% CI)\*\* |
| Abnormal chest signs |  |  |  |  |  |
| Yes | 106 | 6 (4, 16) | 6 (4, 15) | 0.83 (0.50, 1.40) | 0.92 (0.59, 1.42) |
| No | 211 | 7 (4, 15) | 5 (3, 11) | 1.27 (0.94, 1.71) |
|  |  |  |  |  |  |
| Sputum |  |  |  |  |  |
| Yes | 239 | 7 (4, 16) | 5 (4,14) | 1.24 (0.60, 2.58) | 1.23 (0.86, 1.78) |
| No | 77 | 5 (4, 14) | 5 (3, 10) | 0.93 (0.45, 1.89) |
| Fever |  |  |  |  |  |
| Yes | 246 | 6 (4, 16) | 5 (3,10) | 1.62 (0.74, 3.57) | 1.30 (0.91, 1.87) |
| No | 71 | 7 (4, 13) | 7 (4, 26) | 0.66 (0.30, 1.44) |
| Physician rating of unwell |  |  |  |  |  |
| Yes | 205 | 6 (4, 15.5) | 5 (3, 10) | 1.49 (0.76, 2.89) | 1.35 (0.91, 2.02) |
| No | 112 | 8 (4, 14.5) | 6 (4, 16) | 0.87 (0.50, 1.50) |
| Shortness of breath |  |  |  |  |  |
| Yes | 148 | 6 (4,11) | 5 (3, 14) | 1.07 (0.56, 2.03) | 1.27 (0.79, 2.04) |
| No | 169 | 7 (4, 18.5) | 5.5 (4, 11) | 1.20 (0.76, 1.88) |
| Oxygen saturation low |  |  |  |  |  |
| Yes | 15 | 11 (6, 18) | 8 (4, 20) | 0.80 (0.18, 3.53) | 1.20 (0.24, 5.93) |
| No | 235 | 6 (4, 15) | 5 (3.5, 10) | 1.15 (0.79, 1.66) |
| STARWAVe |  |  |  |  |  |
| Very low risk | 171 | 7 (4, 17) | 5 (4, 10) |  | 1.32 (0.86, 2.04) |
| Normal risk | 137 | 6 (4, 11.5) | 6 (3,14) | 0.88 (0.65, 1.19) | 1.12 (0.67, 1.88) |
| High risk | 9 | \*\*\*- | - | - | - |

\*Adjusted for prior duration of illness, baseline severity, age, comorbidity, and all other subgroups; \*\*95% CI for the abnormal chest signs subgroup. \*\*\*too few data to obtain reliable estimates

Table 11. Symptom severity by subgroup

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | PlaceboMean (sd) | AntibioticsMean (sd) | Interaction term (99% CI) | Adjusted\* Mean difference (99% CI) |
| \*\*Abnormal chest signs - yes | 2.2 (1.2) | 2.0 (0.9) | -0.01 (-0.70, 0.69) | -0.21 (-0.80, 0.38) |
| no | 2.0 (1.1) | 1.7 (1.1) |  | -0.27 (-0.67, 0.13) |
| Sputum - yes | 2.1 (1.1) | 1.8 (1.0) | -0.04 (-0.79, 0.73) | -0.30 (-0.65, 0.05) |
| no | 2.0 (1.2) | 1.8 (1.3) |  | -0.29 (-1.16, 0.59) |
| Fever - yes | 2.2 (1.1) | 1.8 (1.0) | -0.31 (-1.10, 0.48) | -0.36 (-0.71, -0.01) |
| no | 1.6 (1.2) | 1.6 (1.2) |  | -0.07 (-0.92, 0.79) |
| Unwell - yes | 2.2 (1.1) | 1.8 (1.1) | -0.22 (-0.90, 0.46) | -0.35 (-0.76, 0.07) |
| no | 1.8 (1.2) | 1.7 (0.9) |  | -0.12 (-0.67, 0.42) |
| Shortness of breath - yes | 2.2 (1.1) | 2.0 (1.1) | 0.10 (-0.56, 0.76) | -0.14 (-0.64, 0.34) |
| no | 1.9 (1.2) | 1.6 (1.0) |  | -0.31 (-0.76, 0.14) |
| STARWAVe |  |  |  |  |
| Very low risk | 2.0 (1.2) | 1.7 (1.1) |  | -0.25 (-0.71, 0.21) |
| Normal risk | 2.2 (1.1) | 1.8 (1.0) | -0.11 (-0.78, 0.55) | -0.37 (-0.85, 0.11) |
| High risk | 2.2 (1.2) | 2.4 (1.4) | 0.65 (-1.38, 2.68) | 1.73 (-4.71, 8.16) |

\*Adjusted for prior duration of illness, baseline severity, age, and comorbidity; \*\*95% CI for the abnormal chest signs subgroup

*Exploratory subgroup analyses*

Table 12. Re-consultation by subgroup

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | Placebon (%) | Antibioticsn (%) | Interaction term (99% CI) | Adjusted\* Odds ratio (99% CI) | Adjusted\* Risk ratio (99% CI) | NNT (99% CI) |
| Abnormal: yes chest signs\*\*  | 31 (44.9) | 26 (38.2) | 1.37 (0.42, 4.48) | 0.81 (0.31, 2.10) | 0.89 (0.45, 1.40) | -15 (7, -4) |
| no | 45 (34.6) | 34 (25.4) |  | 0.62 (0.30, 1.28) | 0.72 (0.40, 1.17) | -9 (16, -4) |
| Sputum - yes | 57 (39.3) | 50 (32.7) | 1.60 (0.56, 4.62) | 0.77 (0.40, 1.46) | 0.85 (0.52, 1.24) | -15 (13, -5) |
| no | 18 (34.0) | 9 (18.8) |  | 0.45 (0.13, 1.58) | 0.55 (0.18, 1.32) | -6 (17, -3) |
| Fever - yes | 52 (34.2) | 48 (29.8) | 1.97 (0.70, 5.53) | 0.82 (0.43, 1.56) | 0.87 (0.53, 1.30) | -23 (11, -6) |
| no | 24 (51.2) | 12 (29.3) |  | 0.41 (0.12, 1.41) | 0.59 (0.22, 1.17) | -5 (20, -2) |
| Unwell - yes | 52 (38.8) | 40 (30.8) | 1.25 (0.38, 4.12) | 0.75 (0.37, 1.51) | 0.83 (0.49, 1.26) | -12 (14, -4) |
| no | 24 (36.9) | 20 (27.8) |  | 0.64 (0.24, 1.71) | 0.74 (0.33, 1.35) | -11 (9, -3) |
| Shortness of breath - yes | 33 (36.7) | 37 (38.9) | 2.81 (0.89, 8.92) | 1.15 (0.51, 2.61) | 1.09 (0.62, 1.64) | 44 (5, -6) |
| no | 43 (39.4) | 23 (21.5) |  | 0.42 (0.18, 0.95) | 0.54 (0.26, 0.97) | -6 (-56, -3) |
| STARWAVe |  |  |  |  |  |  |
| Very low risk | 28 (27.2) | 30 (26.6) |  | 1.04 (0.47, 2.36) | 1.03 (0.55, 1.72) | -157 (7, -6) |
| Normal risk | 46 (51.1) | 28 (32.9) | 0.44 (0.14, 1.40) | 0.43 (0.19, 1.01) | 0.61 (0.32, 1.00) | -6 (99, -3) |
| High risk  | 2 (33.3) | 2 (50.0) | - | - | - | - |

\*Adjusted for prior duration of illness, baseline severity, age, and comorbidity; \*\*95% CI for the abnormal chest signs subgroup; - too few data to obtain reliable estimates

Table 13 Intervention and health service use costing between groups

|  |  |  |
| --- | --- | --- |
| **Group** | **Service**  | **Mean cost (£, SD)** |
| Placebo N=211 | Re-consultation | 13.2 (25) |
| medication | 0.6 (1.6) |
| Referral  | 5.7 (28.1) |
| Hospitalisation  | 7 (58.5) |
| Total NHS  | 25.8 (78.8) |
| Societal  | 32.7 (105.8) |
| NHS and societal  | 58.6 (128.9) |
| Antibiotics N=221 | Re-consultation | 9.4 (20.4) |
| medication | 0.3 (1.2) |
| Referral  | 7.7 (33.2) |
| Hospitalisation  | 9.1 (67.9) |
| Intervention | 3 (0) |
| Total NHS  | 29.4 (86.2) |
| Societal  | 32.9 (93) |
| NHS and societal  | 62.3 (130.2) |

Table 14. Potential pathogens

|  |  |  |
| --- | --- | --- |
|  | Placebo (n=150) | Antibiotics (n=156) |
|  |  |  |
| 1Bacterial pathogens potentially responsive to amoxicillin(n, %) | 76 (50.7) | 76 (48.7) |
| Bacterial pathogens not implicated in causing LRTI or not responsive to amoxicillin(n, %) | 2 (1.3) | 5 (3.2) |
| Viruses (n, %) | 80 (53.3) | 78 (50.0) |
| Carriage organisms (n, %) | 63 (42.0) | 61 (39.1) |
|  |  |  |
| Dual bacterial & viral infection (n, %) | 49 (32.7) | 47 (30.1) |
|  |  |  |

Viruses – Adenovirus, Bocavirus, Coronavirus, Enterovirus, HMPV, Influenzae, Parainfluenza, Parechovirus, Rhinovirus, RSV

1Potential bacterial pathogens that could respond to amoxicillin: H Influenzae, M Catarrhalis, S pneumoniae

Bacterial pathogens either not implicated in LRTI or would not respond to amoxicillin (B pertussis, C Pneumoniae, F Necrophorum, , S Pyogenes, M Pneumoniae,) were found among 7 children (2 placebo group, 5 antibiotic group):

Carriage organisms – CN Staph, Staph NUC, Staph PVL, MecA resistance, N Meningiditis

Table 15. Duration of moderately bad or worse symptoms by pathogen subgroups

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Subgroup | N | Placebo | N | Antibiotics | Unadjusted interaction term (99% CI) | Unadjusted median difference (99% CI) | Adjusted\* interaction term (99% CI) | Adjusted\* median difference (99% CI) |
| Bacteria1 |  |  |  |  |  |  |  |  |
| Yes | 57 | 6 (4, 5) | 57 | 4 (3, 10) | -1 (-6.8, 4.8) | -2 (-6.6, 2.6) | -1.2 (-7.6, 5.1) | -1.8 (-7.5, 3.8) |
| No | 54 | 7 (4, 17) | 61 | 6 (4,10) |  | -1 (-5.5, 3.5) | -0.6 (-5.3, 4.0) |

\*Adjusted for age, baseline severity, comorbidity and prior duration of illness

1Potentially amoxicillin sensitive bacteria - H Influenzae, M Catarrhalis, S Pneumoniae

Table 16. Characteristics of observational and randomised participants

|  |  |  |
| --- | --- | --- |
|  | Observational Overall (N=312) | RCTOverall(N=432) |
| Male (n, %) | 168 (53.9) | 233 (53.9) |
| Age in years (median, IQR) | 3.1 (1.6, 5.0) | 3.2 (1.6, 5.7) |
| Comorbidity (n, %) | 35 (11.2) | 55 (12.7) |
| Asthma (n, %) | 19 (6.1) | 45 (10.4) |
| Long term illness (n/N, %) | 19/196 (9.7) | 20/231 (8.6) |
| Hay fever/eczema (n/N, %) | 69/195 (35.4) | 83/232 (35.8) |
| Family history of asthma (n/N, %) | 114/196 (58.2) | 147/229 (64.2) |
| Breast fed at 3 months (n/N, %) | 98/192 (51.4) | 114/230 (49.6) |
| Mother age (mean, SD, N) | 35.6 (6.1) (N=182) | 34.9 (6.8) (N=219) |
| Number of times had cough in last 12 months (mean, SD, N) | 2.3 (1.9) (N=184) | 2.6 (2.6) (N=222) |
| Prior influenza vaccine in last 12 months (n/N, %) | 195/268 (72.8) | 114/401 (21.4) |
| Prior pneumococcal vaccine (booster) in last 12 months (n/N, %) | 182/266 (68.2) | 125/401 (31.2) |
| Smoker in household (n, %) |  |  |
| Yes | 60 (19.3) | 94 (21.8) |
| No | 242 (77.8) | 331 (76.6) |
| Don’t know | 9 (2.9) | 7 (1.6) |
| Number of children in home (n, %) |  |  |
| 1 | 118 (37.8) | 173 (40.1) |
| 2 | 131 (42.0) | 168 (38.9) |
| 3 | 47 (15.1) | 60 (13.9) |
| 4 | 13 (4.2) | 20 (4.6) |
| 5 or more | 3 (0.9) | 11 (2.5) |
| Parent highest qualification (n, %) |  |  |
| Degree | 131 (42.0) | 159 (36.8) |
| Diploma | 46 (14.7) | 50 (11.6) |
| A-level | 26 (8.3) | 39 (9.0) |
| GCSE/O-level | 30 (9.6) | 47 (10.9) |
| None | 5 (1.6) | 17 (3.9) |
| Not given | 63 (20.2) | 95 (22.0) |
| Other | 11 (3.5) | 25 (5.8) |
| Ethnic group (n, %) |  |  |
| British/Irish/Other white | 275 (88.2) | 371 (85.9) |
| Mixed | 12 (3.8) | 19 (4.4) |
| South Asian | 16 (5.1) | 29 (6.7) |
| Other | 2 (0.6) | 9 (2.1) |
| Prefer not to say | 6 (1.9) | 3 (0.7) |

Table 17. Illness presentation of observational and randomised participants

|  |  |  |
| --- | --- | --- |
|  | Observational Overall (N=312) | RCT Overall(N=432) |
| Baseline severity\* (mean, SD) | 1.6 (0.4) | 1.6 (0.3) |
| Cough severity (mean, SD) | 1.8 (1.0) | 1.9 (1.1) |
| Duration of illness in days (median, IQR) | 5 (3, 8) | 5 (3, 10) |
| Abnormal chest signs\* (n, %) | 164 (52.6) | 150 (34.7) |
| Sputum/rattly chest (n/N, %) | 243 (78.4) | 325/429 (75.8) |
| Fever during illness (n, %) | 241 (77.2) | 338 (78.2) |
| Unwell (according to physician) (n, %) | 204 (65.8) | 284 (65.7) |
| Shortness of breath (Yes/No) (n, %) | 166 (53.2) | 199 (46.1) |
| Oxygen saturation low (n/N, %) | 35/237 (14.8) | 22/336 (6.6) |
| STARWAVe\* (n, %) |  |  |
| Very low risk | 154 (49.4) | 233 (53.9) |
| Normal risk | 137 (43.9) | 189 (43.8) |
| High risk | 21 (6.7) | 10 (2.3) |
| Physician rating unwell\* (mean, SD) | 5.6 (1.9) | 5.5 (1.6) |
| Parent rating of unwell\* (mean, SD) | 4.3 (1.9) | 3.7 (1.7) |
| Temperature (mean, SD, N) | 37.3 (0.8) (N=309) | 37.3 (0.8) (N=428) |
| Oxygen saturation (mean, SD, N) | 96.8 (2.1) (N=237) | 97.3 (1.6) (N=336) |
| Heart rate (beats per min) (mean, SD, N) | 117.6 (21.3) (N=305) | 111.9 (19.1) (N=420) |
| Respiratory rate (breaths per min) (mean, SD, N) | 27.4 (9.6) (N=295) | 25.1 (7.0) (N=411) |
| Tachypnoea (n/N, %) | 59/293 (20.1) | 55/411 (13.4) |
| Capillary refill >3 seconds (n, %) | 4/301 (1.3) | 5 (1.2) |
| Consciousness (n, %) |  |  |
| Normal  | 292 (94.5) | 417 (96.8) |
| Irritable | 12 (3.9) | 13 (3.0) |
| Drowsy | 5 (1.6) | 1 (0.2) |
| Ill appearance (n, %) | 88 (28.2) | 95 (22.0) |
| Number of days unwell before seeing general practitioner (median, IQR, N) | 5 (3, 7) (N=193) | 5 (3, 9) (N=227) |
| Treated with OTC medication (n/N, %) | 173/195 (88.7) | 212/232 (91.4) |

\*Baseline severity on a scale 1 to 4: 1=none, 2=mild, 3=moderate, 4=severe; Abnormal chest signs include wheeze, stridor, grunting, nasal flaring, inter/subcostal recession, crackles/crepitations, bronchial breathing; STARWAVe prediction rule(39) for hospital admission (short illness, temperature, age, recession, wheeze, asthma, vomiting); Physician and parent rating of unwell on a scale 0 to 10