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Original article

Antibiotics for lower respiratory tract infection in children presenting in primary care (ARTIC-PC): the predictive value of molecular testing

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ABSTRACT

Objectives: This study aimed to assess whether the presence of bacteria or viruses in the upper airway of children presenting with uncomplicated lower respiratory tract infection (LRTI) predicts the benefit of antibiotics.

Methods: Children between 6 months and 12 years presenting to UK general practices with an acute LRTI were randomized to receive amoxicillin 50 mg/kg/d for 7 days or placebo. Children not randomized (ineligible or clinician/parental choice) could participate in a parallel observational study. The primary outcome was the duration of symptoms rated moderately bad or worse. Throat swabs were taken and analyzed for the presence of bacteria and viruses by multiplex PCR.

Results: Swab results were available for most participants in the trial (306 of 432; 71%) and in the observational (182 of 326; 59%) studies. Bacterial pathogens potentially sensitive to amoxicillin (*Haemophilus influenzae, Moraxella catarrhalis, Streptococcus pneumoniae*) were detected among 51% of the trial placebo group and 49% of the trial antibiotic group. The median difference in the duration of symptoms rated moderately bad or worse between antibiotic and placebo was similar when potentially antibiotic-susceptible bacteria were present (median: −1 day; 99% CI, −12.3 to 10.3) or not present (median: −1 day; 99% CI, −4.5 to 2.5). Furthermore, bacterial genome copy number did not predict benefit. There were similar findings for all secondary outcomes and when including the data from the observational study.

Discussion: There was no clear evidence that antibiotics improved clinical outcomes conditional on the presence or concentration of bacteria or viruses in the upper airway. Before deploying microbiologic point-of-care tests for children with uncomplicated LRTI in primary care, rigorous validating trials are needed. **Paul Little, Clin Microbiol Infect 2022;28:1238**

Introduction

Lower respiratory tract infection (LRTI) among children presenting to general practitioners (GPs) is common, frequently resulting in antibiotic treatment [1–3] despite being mostly viral in aetiology [2,4–7]. Antibiotic treatment for adults with dual

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bacterial and viral infections is associated with reduced reconsultations for ongoing illness, but there is no such evidence for children [8,9].

Point-of-care (POC) tests could potentially target antibiotics for bacterial infections. In routine primary care, throat swabs could be used despite having a slightly lower yield than alternative methods [7,10]. Sputum collection from young children is impractical in this setting, and nasopharyngeal swabs are less acceptable [7]. Although the presence of bacteria may simply reflect asymptomatic carriage in the upper airway, their presence in throat swabs correlates to more severe presentations of pneumonia [11]. The pathogen load may also correlate with symptom severity [12], the odds of pneumonia in children [11], and the severity of pulmonary involvement for *Streptococcus pneumoniae* [13] and *Haemophilus influenzae* [14]. We are not aware of a randomized trial in children that has explored the impact of pathogen detection or pathogen load on antibiotic effectiveness.

We report the findings of PCR testing of throat swab samples in children from a placebo controlled trial of antibiotics and a parallel observational study. We explored whether the presence of pathogens or pathogen load was associated with a greater benefit from antibiotics.

Methods

The aim of this study was to assess the impact of antibiotics on symptom resolution among children presenting in primary care with acute LRTI according to microbiological findings, using data from the ARTIC-PC trial and a linked observational study.

Overview of methods

The main trial results and methods have been published elsewhere [15]. Where parents and clinicians were willing for children to be randomized, children aged 6 months to 12 years were randomized to receive amoxicillin 50 mg/kg/d in three divided doses for 7 days or placebo, using preprepared packs randomized with a computer-generated random number by an independent statistician. Children whom the parents or clinician did not allow to be randomized were invited to participate in an observational study where the same data were collected. Where parents and child were willing, a single-sweep, dual viral/bacterial throat swab was taken using a standard commercial swab set that included a viral transport medium suitable for PCR testing. A throat swab was chosen due to reasonable yields and acceptability of throat swab sampling in previous large primary care cohorts [7].

Inclusion criteria

Children between 6 months and 12 years old presenting to primary care with an acute LRTI, defined in several previous cohorts and trials as having acute cough as the predominant symptom, judged by the GP to be infective in origin, lasting <21 days, and with other symptoms or signs localizing to the lower respiratory tract (shortness of breath, sputum, pain) [8,16,17]. These inclusion criteria reflect the clinical criteria used in daily practice to diagnose acute bronchitis [19], as used in the Cochrane review [20], and are also the key drivers of prescribing [21,22].

Exclusion criteria

Exclusion criteria included cough that was judged by the clinician to have noninfectious aetiology (e.g. hay fever or noninfective exacerbation of asthma) or almost certain to be of viral aetiology (e.g. croup, for which antibiotics are not commonly prescribed), immune-compromised patients, and antibiotic use during the previous 30 days. Children for whom the clinician did not have equipoise (where the clinician judged that pneumonia was likely or that the child was severely ill) were not randomized, but they were eligible to enter a parallel observational study.

Sample processing for multiplex PCR

Throat swabs in a virus transport medium were stored at −80°C until required for testing. Batches of samples for extraction were allowed to thaw at room temperature. A 200 μL volume of virus transport medium was extracted using the QIAsymphonySP, along with an internal process control containing bacteriophages T4 and MS2. Extraction was done using the QIAsymphony DSP Virus Pathogen Mini Kit (QIAGEN) and the 60 μL elution protocol. Real-time PCR samples were amplified and analyzed using a Life Technologies Custom TaqMan Low Density Array (TLDA) system on the ViiA 7 Real-Time PCR System (Thermo Fisher Scientific, Horsham and Loughborough, UK), which has excellent validation properties [23].

Reaction mixes (104 μL) were prepared containing the 26 μL Fast Virus One Step Master Mix (Life Technologies, Carlsbad, CA), 58 μL molecular grade water, and 20 μL nucleic acid extract. Samples were vortex mixed and pulse centrifuged briefly before loading 100 μL of the reaction mix into the chamber of the TLDA card. The TLDA cards were centrifuged twice at 1200 rpm (336 × g) for 1 minute to load the wells with the reaction mix. The TLDA cards were sealed twice with the staking device before loading into the ViiA-7 and initiating amplification (50°C for 5 minutes, 95°C for 20 seconds, followed by 45 cycles of 95°C for 1 second and 60°C for 20s). Upon completion of the amplification reactions, fluorescent traces were inspected and analyzed for sigmoidal curves.

Baselines and thresholds were set automatically using software algorithms or, where necessary, by manual adjustment to avoid background fluorescence noise. The cycle threshold (Ct) of positive samples was recorded as the point at which the fluorescent trace rises above the background and passes through the threshold.

Sample size

The study was not specifically powered for microbiologic subgroups, but was powered for clinical subgroups. For a subgroup representing 40% of the sample, we estimated we would need 119 cases of that subgroup to detect a clinically important difference of 3 days in the duration of illness due to antibiotics ($\alpha = 0.05$; 80% power).

Statistical analyses

We assessed whether there was an effect of antibiotics among subgroups with (a) bacterial infections where a GP might consider that the PCR indicated infection with a potentially amoxil-sensitive organism (*H influenzae, Moraxella catarrhalis, S pneumoniae*), (b) viral infections, or (c) dual infections. When *Neisseria meningitidis, Staphylococcus aureus*, or coagulase-negative staphylococci were detected, they were classified as commensal carriage organisms [24].

For the trial data we compared antibiotics with placebo, and for the observational data we compared patients given antibiotics at the index consultation with those not given antibiotics. For the observational data, we planned to control for confounding by indication by using inverse probability of treatment weighting and propensity scores in each of the regression models. However, the inverse probability of treatment weighting approach did not achieve a good balance on the key covariates, whereas stratification by

propensity score did improve the balance. Therefore, propensity scores were used in analyzing both the observational data and the combined dataset, including both the observational and trial data. Given the levels of missing data, we imputed missing data using a chained equations model with 100 imputations.

The initial plan was to use Cox regression for the primary outcome (the duration of symptoms rated moderately bad or worse). However, for some subgroups (particularly the dual bacterial/viral subgroup), the proportional hazards assumption was not met, so quantile regression was used. Linear regression was used for symptom severity, and logistic regression for reconsultations with ongoing, new, or worsening symptoms. We report both adjusted analyses (adjusting for age, duration of illness, baseline severity, and comorbidity) and unadjusted analyses (since microbiologic status may be linked to prior duration and severity, so controlling for them could be controlling for microbiologic status).

Potential pathogens were categorized as the presence, according to the Ct value, of bacterial pathogens that could potentially respond to amoxicillin, or viruses. We assumed that indeterminate Ct values were negative, but we also performed a sensitivity analysis assuming that indeterminate CT values were positive. We also looked at the interaction between the mean Ct value (inversely related to bacterial/viral load) and antibiotic group. We performed a Cox regression of symptom duration on antibiotic group, bacterial Ct value, and their interaction, adjusting for baseline covariates. We repeated this analysis using the mean viral Ct value, and then repeated these analyses for symptom severity and reconsultation outcomes. These analyses were repeated including the observational data.

Results

Trial results

The flow diagram for samples in both the trial and observational data is shown in Fig. 1. A total of 306 throat swabs were analyzed in the randomized clinical trial. Potential pathogens that were categorized as bacterial pathogens, viruses, or carriage organisms were balanced across the randomized groups (Table 1; see Tables S11 and S12 for individual organisms and dual infections). Bacterial pathogens that were potentially susceptible to amoxicillin (*H influenzae, M catarrhalis, S pneumoniae*) were found among 51% of the placebo group (76 of 150) and 49% of the antibiotic group (76 of 156). Where prescription data were available in the observational cohort, amoxicillin was prescribed for most children (47 of 53; 89%).

Results assuming intermediate cycle threshold values were negative

There were no statistically significant interactions of bacterial, viral, or dual bacterial/viral subgroups with the antibiotic group for any outcome, and the adjusted effect of antibiotics on the primary outcome (duration of symptoms rated moderately bad or worse) for the 114 children with potential bacterial pathogens (adjusted median difference: −1.8 days; 99% CI, −7.5 to 3.8) was similar to those without (adjusted median difference: −0.6 days; 99% CI, −5.3 to 4.0). When broken down further into bacterial viral and dual subgroups (Table 2), the only subgroup with potentially important differences in duration of illness with antibiotics was the dual bacterial/viral subgroup, where the quantile regression suggested that the estimate of the effect of antibiotics in this group was a nonsignificant reduction in the median duration of illness of 3 days (99% CI, −9.9 to 3.9). A *post hoc* analysis splitting the trial participants by age (Table 3) suggested that there may be an impact of antibiotics among younger children aged <6 years.

The effect of antibiotics on symptom severity was also similar no matter whether there were bacteria, viruses, or dual infections, albeit nonsignificantly greater when no viruses were detected or with dual infections (Table 4). The effect of antibiotics on reducing reconsultation documented a nonsignificantly greater effect when no viruses were present (Table 5).

The regression of symptom duration in the antibiotic group, bacterial Ct value, and their interaction, adjusting for baseline covariates, is shown in Table 6. There was no evidence of antibiotics having a greater effect on symptom resolution with high bacterial loads—if anything, there was a nonsignificant trend for the impact of antibiotics to increase as the bacterial load decreased (i.e. as Ct value increases (hazard ratio: 1.05; range, 0.96–1.13)) and no evidence of an interaction with virus Ct value. There was also no clear

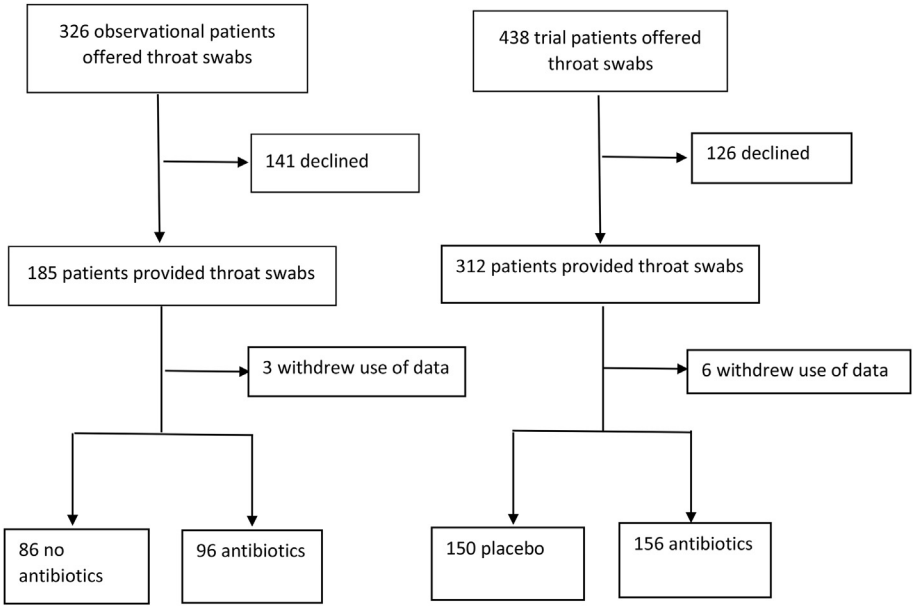

Fig. 1. Flow diagram for throat swabs.

Table 1
Potential pathogens in trial sample

Bacteria[a]	Viruses[b]	Carriage organisms[c]	Placebo ($n = 150$)	Antibiotics ($n = 156$)	Total ($N = 306$)
			n (%)	*n* (%)	*n* (%)
Yes	No	Yes	7 (4.7)	13 (8.3)	56 (18.3)
Yes	No	No	20 (13.3)	16 (10.3)	
No	Yes	Yes	12 (8.0)	12 (7.7)	64 (20.9)
No	Yes	No	19 (12.7)	19 (12.2)	
Yes	Yes	Yes	28 (18.7)	19 (12.2)	96 (31.4)
Yes	Yes	No	21 (14.0)	28 (18.0)	
No	No	Yes	16 (10.7)	17 (10.9)	90 (29.4)
No[d]	No	No	25 (16.7)	32 (20.5)	

[a] Potentially amoxicillin sensitive bacteria: *Haemophilus influenzae*, *Moraxella catarrhalis*, and *Streptococcus pneumoniae*.
[b] Adenovirus, bocavirus, coronavirus, enterovirus, human metapneumovirus, influenzae, parainfluenza, parechovirus, rhinovirus, and respiratory syncytial virus.
[c] Coagulase-negative staphylococci, staphylococcus NUC gene, staphylococcus Panton-Valentine leukocidin, mecA gene resistance, and *Neisseria meningiditis*.
[d] Other potential pathogens, but not sensitive to amoxicillin or linked with lower respiratory tract infection, are included in the bottom section of the table (seven cases: *Bordetella pertussis, Chlamydophila pneumoniae, Mycoplasma pneumoniae, Fusobacterium necrophorum, Streptococcus pyogenes).*

Table 2
Median duration of moderately bad or worse symptoms by pathogen subgroups[a]

Subgroup	*n*	Placebo, *n* (range)	Antibiotics, *n* (range)	Unadjusted interaction term (99% CI)	Unadjusted median difference (99% CI)	Adjusted interaction term (99% CI)	Adjusted median difference (99% CI)
Bacteria[b]							
Yes	40	5 (3.5–14)	4 (3.5–9.5)	0 (−6.1 to 6.1)	−1 (−12.3 to 10.3)	0.1 (−7.7 to 7.9)	−0.9 (−10.4 to 8.6)
No	189	7 (4–17)	5.5 (3–10)		−1 (−4.5 to 2.5)		−1.2 (−4.7 to 2.2)
Virus							
Yes	52	5 (4–17)	6 (4–11)	3 (−3.3 to 9.3)	1 (−8.1 to 10.0)	2.4 (−5.6 to 10.4)	0.7 (−10.1 to 11.4)
No	177	6.5 (4–16)	5 (3–10)		−2 (−5.3 to 1.3)		−1.7 (−5.4 to 2.1)
Dual							
Yes	74	8 (4–18)	5 (3–10)	−3 (−8.9 to 2.9)	−3 (−9.9 to 3.9)	−3.1 (−10.3 to 4.2)	−2.7 (−9.2 to 3.8)
No	155	6 (4–16)	6 (4–10)		0 (−3.6 to 3.6)		−0.2 (−4.2 to 3.9)

[a] Adjusted for age, baseline severity, comorbidity, and prior duration of illness.
[b] *Haemophilus influenzae*, *Moraxella catarrhalis,* and *Streptococcus pneumoniae*.

Table 3
Median duration of moderately bad or worse symptoms by pathogen subgroup and age group (trial participants)

Subgroup	Age 0–5 y			Age 6–12 y		
	n	Placebo, *n* (range)	Antibiotics, *n* (range)	*n*	Placebo, *n* (range)	Antibiotics, *n* (range)
Bacteria[a]						
Yes	27	5.5 (3–14)	4 (3–22)	13	5 (3.5–14.5)	4 (3–9)
No	138	6 (4–18)	6 (4–11)	51	7 (5–15.5)	5 (3–10)
Virus						
Yes	44	5 (4–17)	6 (5–11)	8	17.5 (7–28)[b]	5 (3–6)
No	121	6.5 (4–18)	5 (3–10)	56	6.5 (4–15)	5 (3–10)
Dual						
Yes	61	10 (4–25)	5 (3–10)	13	7 (4–9)	4 (2–10)
No	104	6 (4–15)	6 (4–12.5)	51	7 (5–17)	5 (4–9)

[a] *Haemophilus influenzae*, *Moraxella catarrhalis,* and *Streptococcus pneumoniae*.
[b] This outlier is due to only two children in this group.

Table 4
Mean symptom severity on days 2–4 by pathogen subgroup

Subgroup	*n*	Placebo, *n* (mean)	Antibiotics, *n* (mean)	Unadjusted interaction term (99% CI)	Unadjusted mean difference (99% CI)	Adjusted interaction term (99% CI)	Adjusted mean difference (99% CI)[a]
Bacteria[b]							
Yes	39	1.9 (1.1)	1.8 (1.3)	0.25 (−0.80 to 1.31)	−0.05 (−1.09 to 0.98)	0.18 (−0.84 to 1.23)	−0.19 (−1.23 to 0.85)
No	102	2.1 (1.2)	1.8 (1.1)		−0.31 (−0.76 to 0.14)		−0.29 (−0.74 to 0.16)
Virus							
Yes	48	2.2 (1.0)	2.4 (1.4)	0.59 (−0.37 to 1.56)	0.18 (−0.78 to 1.15)	0.53 (−0.42 to 1.48)	0.16 (−0.87 to 1.19)
No	167	2.1 (1.2)	1.8 (0.8)		−0.41 (−0.85 to 0.03)		−0.40 (−0.82 to 0.03)
Dual							
Yes	69	2.2 (1.3)	1.8 (0.8)	−0.29 (−1.16 to 0.59)	−0.45 (−1.15 to 0.25)	−0.30 (−1.16 to 0.56)	−0.40 (−1.10 to 0.31)
No	146	2.0 (1.1)	1.8 (1.2)		−0.17 (−0.67 to 0.34)		−0.19 (−0.69 to 0.30)

[a] Adjusted for age, baseline severity, comorbidity, and prior duration of illness.
[b] *Haemophilus influenzae*, *Moraxella catarrhalis,* and *Streptococcus pneumoniae*.

Table 5
Reconsultation by pathogen subgroup within 1 month

Subgroup	*n*	Placebo, *n* (mean)	Antibiotics, *n* (mean)	Unadjusted interaction term (99% CI)	Unadjusted RR (99% CI)	Interaction term (99% CI)	Adjusted RR (99% CI)[a]
Bacteria[b]							
Yes	51	6 (24.0)	8 (30.8)	1.89 (0.53–6.77)	1.28 (0.39–4.21)	1.64 (0.47–5.77)	1.01 (0.30–3.37)
No	238	51 (42.5)	34 (28.8)		0.68 (0.43–1.08)		0.74 (0.47–1.17)
Virus							
Yes	60	10 (31.3)	10 (35.7)	1.72 (0.60–4.95)	1.14 (0.45–2.92)	1.57 (0.47–4.07)	0.88 (0.43–1.53)
No	229	47 (41.6)	32 (27.6)		0.66 (0.41–1.07)		0.65 (0.27–1.24)
Dual							
Yes	90	25 (53.2)	17 (39.5)	0.98 (0.42–2.26)	0.74 (0.41–1.35)	0.99 (0.55–1.22)	0.83 (0.38–1.34)
No	199	32 (32.7)	25 (24.8)		0.76 (0.42–1.36)		0.79 (0.40–1.34)

[a] Adjusted for age, baseline severity, comorbidity, and prior duration of illness.
[b] *Haemophilus influenzae*, *Moraxella catarrhalis*, and *Streptococcus pneumoniae*.

evidence of treatment benefit from the interaction with Ct value for symptom severity nor reconsultations for either bacteria or viruses (Table 6; Figs. S2 and S3 graphically for symptom severity).

Results assuming intermediate cycle threshold values are positive

Potential bacterial, viral pathogens, and carriage organisms were balanced across the randomized arms (Table S7). There were no statistically significant interactions between any of the pathogen subgroups and the antibiotic group for any outcome, and there were no consistent trends. There was no evidence of an increased effect of antibiotics on any outcome for those with potential bacterial pathogens (Tables S8–10). When viruses were not present, there was a trend for increased impact on symptom severity, reconsultation, and duration of symptoms. For dual infections, there was a trend for impact on symptom severity and duration, but not reconsultation.

Analyses including observational data

A further 182 swabs were added from the observational cohort. In the observational cohort and overall, these potential pathogens were fairly balanced across the antibiotics and no-antibiotics groups (Table S12). There were no statistically significant interactions of any of the pathogen subgroups with antibiotics for any outcomes, and there was no evidence of important clinical benefits from antibiotics in the subgroups (Tables S14–16) or of any impact of Ct values (Table S17; Figs. S3 and S4).

Discussion

Principal findings

There was no clearly demonstrated effect of antibiotics on duration or severity of symptoms nor on reconsultations, according to microbiological subgroups.

Strengths and limitations

The current trial is one of the few among children with uncomplicated LRTIs and had an almost 80% power to assess whether antibiotics in the presence of bacteria shortened symptom duration, albeit with less power for dual infections or specific pathogens. The combined trial/observational data (using propensity scores [15]) provided greater power. Throat swabs were chosen given their common use in practice without special training; their yield reflecting routine practice, similar to nasopharyngeal samples (albeit a little less than the lower tract [10,25]); their use in previous large primary care child cohorts [7]; and the difficulties of getting sputum samples in routine primary care, where nasopharyngeal sampling is less acceptable [7]. We did not assess the antibiotic resistance of strains; resistant strains will dilute the apparent effectiveness of antibiotics, but most strains are susceptible to amoxicillin in community samples of children [26–28]. Current PCR tests also do not provide reliable genotypic resistance testing; therefore, the readout available to a GP would only be at the species level. *H influenzae, M catarrhalis, and S pneumoniae* are all organisms that a GP might consider to be susceptible to amoxicillin, in contrast to others (e.g. *Bordetella pertussis, Chlamydophila pneumoniae*) that are not, or that are unlikely to cause uncomplicated LRTI (e.g. *S. aureus*).

Relationship to previous studies

The trial data set documents similar prevalences of pathogens and the impact of antibiotics in microbiological subgroups compared with very large observational data sets of children [7,9] and adults [12,29] in primary care. For the dual-infection subgroup, there was no clear impact of dual infections on reconsultations, unlike in adults [8], but the current study had less power. We did find a nonsignificant, 3-day reduction in the median duration of symptoms with antibiotics for the dual-infection subgroup and in younger children, but the analyses were underpowered and chance is a likely explanation. Assuming the effect in this subgroup might be real, three children would have to be assessed to identify one child who might benefit, and the cost-effectiveness of such an approach would need to be demonstrated.

Meaning of the study and potential mechanisms

Detection in the throat swab by PCR of *C pneumoniae*, *B pertussis*, and *Mycoplasma pneumoniae* in a child with symptoms of respiratory tract infection would likely prompt a GP to implicate these pathogens in the disease process. Pathobionts such as *S pneumoniae, M catarrhalis,* and *H influenzae* are also detected by PCR; however, because these organisms are frequently detected in throat swabs of normal children [26–28], detection does not mean a role in disease, and asymptomatic carriage will dilute the apparent effectiveness of antibiotics for bacterial subgroups. Once the disease process is initiated, the inflammatory processes may predominate by the time of presentation, and the causative organisms become less important.

Implications for practice

The lack of clear evidence between microbiological findings in the upper tract, the only site that could be feasibly sampled in routine primary care, and the impact of antibiotics suggests there may be a limited role for microbiological POC tests for children with uncomplicated LRTIs in primary care.

Table 6
Treatment interaction between pathogen concentration (Ct value) and antibiotic group for duration of moderately bad or worse symptoms, mean severity in days 2–4 and reconsultation within 1 month

	Bacterial concentration (Ct value[a])			Viral concentration (Ct value[a])		
	n	Unadjusted interaction term	Adjusted interaction term[b]	*n*	Unadjusted interaction term	Adjusted interaction term[b]
Duration, hazard ratio (95% CI)	146	1.05 (0.96–1.13)	1.06 (0.97–1.15)	151	1.04 (0.97–1.13)	1.02 (0.94–1.10)
Severity, mean difference (95% CI)	141	−0.07 (−0.20 to 0.05)	−0.07 (−0.20 to 0.05)	141	0.01 (−0.11 to 0.13)	−0.01 (−0.13 to 0.11)
Reconsultation, OR (95% CI)	181	0.93 (0.75–1.16)	0.90 (0.72–1.13)	184	1.01 (0.84–1.22)	1.01 (0.84–1.22)

Ct, cycle threshold.
[a] Higher Ct values reflect lower pathogen concentration.
[b] Adjusted for age, baseline severity, comorbidity, and prior duration of illness.

Implications for future research

Prior to the introduction of microbiological POC tests for children presenting with acute uncomplicated LRTIs in primary care, POC tests should be subject to rigorous trials of effectiveness and cost effectiveness.

Research ethics statement

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

Transparency declaration

Theo Verheij reports grants from European Union and The Netherlands Organization of Health Research and Development during the conduct of the study, as well as grants from Abbott, Becton Dickinson, bioMérieux, and Janssen Pharmaceuticals outside of the submitted work. All other authors declare (other than the grant support from the National Institute for Health Research for the submitted work) no support from other organizations for the submitted work, no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years, and no other relationships or activities that could appear to have influenced the submitted work. All authors report no conflicts of interest.

Author contributions

PL and TV developed the original idea. PL led the funding applications with input from all authors, and the protocol was developed and modified by all coauthors. The study progress was supervised by all authors. TB, BS, TV, RR, and PL developed the statistical analysis plan and interpreted the analyses, with input from all authors. TB performed the statistical analysis supervised by BS. PL led the writing of the paper, and all authors contributed to interpretation of the analyses and 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.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmi.2022.02.033.

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