Niamh M Redmond, Sophie Turnbull, Beth Stuart, Hannah V Thornton, Hannah Christensen, Peter S Blair, Brendan C Delaney, Matthew Thompson, Tim J Peters, Alastair D Hay and Paul Little

Impact of antibiotics for children presenting to general practice with cough on adverse outcomes:

secondary analysis from a multicentre prospective cohort study

Abstract

Background

Clinicians commonly prescribe antibiotics to prevent major adverse outcomes in children presenting in primary care with cough and respiratory symptoms, despite limited meaningful evidence of impact on these outcomes.

Aim

To estimate the effect of children's antibiotic prescribing on adverse outcomes within 30 days of initial consultation.

Design and setting

Secondary analysis of 8320 children in a multicentre prospective cohort study, aged 3 months to <16 years, presenting in primary care across England with acute cough and other respiratory symptoms.

Method

Baseline clinical characteristics and antibiotic prescribing data were collected, and generalised linear models were used to estimate the effect of antibiotic prescribing on adverse outcomes within 30 days (subsequent hospitalisations and reconsultation for deterioration), controlling for clustering and clinicians' propensity to prescribe antibiotics.

Results

Sixty-five (0.8%) children were hospitalised and 350 (4%) reconsulted for deterioration. Clinicians prescribed immediate and delayed antibiotics to 2313 (28%) and 771 (9%), respectively. Compared with no antibiotics, there was no clear evidence that antibiotics reduced hospitalisations (immediate antibiotic risk ratio [RR] 0.83, 95% confidence interval [CI] = 0.47 to 1.45; delayed RR 0.70, 95% CI = 0.26 to 1.90, overall $P = 0.44$). There was evidence that delayed (rather than immediate) antibiotics reduced reconsultations for deterioration (immediate RR 0.82, 95% CI = 0.65 to 1.07; delayed RR 0.55, 95% CI = 0.34 to 0.88, overall $P = 0.024$).

Conclusion

Most children presenting with acute cough and respiratory symptoms in primary care are not at risk of hospitalisation, and antibiotics may not reduce the risk. If an antibiotic is considered, a delayed antibiotic prescription may be preferable as it is likely to reduce reconsultation for deterioration.

Keywords

adverse outcomes; antibiotics; children; cohort studies; primary care; respiratory tract infections.

INTRODUCTION

Children presenting with cough and other symptoms of respiratory tract infection (RTI) are the most frequent attenders to general practice internationally, are almost all managed in primary care, and the majority still receive antibiotics.[1–3] A very small percentage of children are hospitalised for serious bacterial illnesses or complications.[4,5] However, GPs are risk averse and report prescribing antibiotics at the point of presentation to this patient group 'just in case'[6,7] and in fear of a poor outcome.[6–9]

This uncertainty is fuelled by the very limited experimental or observational evidence available regarding the impact of different antibiotic prescribing strategies on major adverse outcomes among children. Available systematic reviews suggest that antibiotics have limited efficacy in treating a large proportion of upper RTIs[10–13] but the reviews are underpowered to assess complications and there is little evidence for bronchitis, in particular. Although there is some evidence for adults,[14–19] there is almost no meaningful evidence in children regarding complications if antibiotics are withheld for respiratory infections. The major problem with continuing to prescribe for respiratory infections in children is that primary care antibiotic use is a major driver of antibiotic resistance internationally.[20]

Two large prospective cohort studies of adults with RTI symptoms demonstrated that either immediate or delayed antibiotic prescriptions can modify health outcomes.[18,19] The authors were aware of no comparable data in children. This paper used data from a large cohort study to establish whether an immediate or delayed antibiotic prescription given to children with acute cough and RTI in primary care modifies risk of subsequent hospitalisation or reconsultation with deterioration.

METHOD

A large, four-centre (England, UK) prospective cohort study was conducted that recruited children aged 3 months to <16 years presenting to primary care with acute cough and RTI between July 2011

NM Redmond, PhD, research fellow and manager, National Institute for Health Research Collaborations for Leadership in Applied Health Research and Care West, Bristol, UK. **S Turnbull**, MSc, PhD student; **HV Thornton**, PhD, senior research associate; **AD Hay**, FRCGP, GP and professor of primary care, Centre for Academic Primary Care; **H Christensen**; PhD, lecturer in infectious disease mathematical modelling, Population Health Sciences, Bristol Medical School, University of Bristol, Bristol, UK. **B Stuart**; PhD, associate professor; **P Little**, FMedSci, GP and professor of primary care research, Primary Care and Population Sciences Unit, University of Southampton, Aldermoor Health Centre, Aldermoor Close, Southampton, UK. **PS Blair**, PhD, professor in medical statistics, Population Health Sciences, Bristol Medical School, University of Bristol, St Michael's Hospital, Bristol, UK. **BC Delaney**, MD, GP and professor of medical informatics and decision making, Department of Surgery and Cancer, Imperial College London, London, UK. **TJ Peters**, FMedSci, professor of primary care health services research, Bristol Medical School, University of Bristol, Southmead Hospital, Westbury-on-Trym, Bristol, UK. **M Thompson**, PhD, GP and professor of family medicine, Department of Family Medicine, University of Washington, Seattle, WA, US.

Address for correspondence

Niamh M Redmond, National Institute for Health Research Collaborations for Leadership in Applied Health Research and Care West (NIHR CLAHRC West), University Hospitals Bristol NHS Foundation Trust, 9th Floor, Whitefriars, Lewins Mead, Bristol BS1 2NT, UK.

Email: niamh.redmond@bristol.ac.uk

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How this fits in

Antibiotic prescribing to children in primary care is one of the key areas of inappropriate prescribing. This is mainly due to the lack of evidence for, and uncertainty regarding, which children are at risk of poor outcome. This study investigated whether antibiotic prescribing had an impact on two adverse health outcomes for children: hospitalisation for respiratory tract infections and reconsultation for deteriorating symptoms. The study shows that there is little evidence to justify the use of antibiotics for reducing hospitalisation, which occurred very rarely, and supports previous research in adults that a delayed antibiotic prescribing strategy is likely to reduce reconsultation for deterioration.

and May 2013. The results from the primary aim of the study have been published.[5] Here are presented findings from a secondary analysis.

The protocol has been described elsewhere.[21] In summary, eligible children presenting to primary care were recruited by prescribing 'clinicians' (GPs and prescribing practice nurses) across four centres if they presented with acute cough as the most prominent symptom, combined with other symptoms or signs suggestive of RTI. Clinicians who self-reported prescribing antibiotics in ≤30% to children with RTIs were invited to participate. Following informed consent, clinicians completed a structured case report form (Appendix 1) that included sociodemographics, parent-reported symptoms, clinician-assessed signs, diagnosis, and whether an immediate or delayed antibiotic was prescribed (including number of days delayed) at the time of the consultation.

The main outcomes, hospitalisation for any RTI in the 30 days following recruitment and reconsultation for deterioration (a proxy marker for reconsultation for the same episode of RTI illness with evidence of worsening illness, shown to be reliably assessed),[22] were collected via a detailed review of the child's medical record. History of chronic conditions was also recorded. Medical record reviews were generally conducted 3 months post-recruitment for each child, to allow for adequate feedback to occur. On some occasions this was slightly longer than 3 months, and in all cases the period of time was sufficient to allow both reconsultations and complications to occur. Double, independent medical record review was undertaken in a random set of 1% of participants to estimate inter-reviewer error.

Data preparation

Children referred for acute hospitalisation at the consultation were excluded from the analysis, as clinicians' prescribing behaviour was expected to differ for children whom they had decided to refer to hospital on the same day as the consultation, compared with those they did not.

Common clinical cut-offs were used for continuous data where possible (high temperature >37.8°C)[23] and were age-related if appropriate (age-specific heart and respiratory rates and blood pressure).[24] UK guidelines for low oxygen saturation level (≤95%) were used.[25] Given the large number of variables, continuous variables were dichotomised using 25th or 75th percentile cut-offs as appropriate. For carer-reported symptom severity (mild, moderate, or severe) in the 24 hours prior to consultation, dichotomy for each variable was split, depending on the overall prevalence, to either 'severe' if more than 5% of the whole cohort fell into this category or 'moderate and severe' if the proportion was smaller. This pragmatic cut-off was chosen prior to analysis to avoid variables with very low prevalence. Capillary refill time (CRT) was coded as normal (≤2 seconds) or long (≥3 seconds).[26,27] Multiple deprivation score was based on the family postcode using the UK Indices of Multiple Deprivation 2007.[28]

Covariates

Variables measured at the baseline consultation (symptoms, signs, demographics) were identified as possible confounders/covariates. These variables were considered during the analysis of secondary outcomes (Appendix 2).

Statistical analysis

All data were analysed using STATA (version 13.1). The κ statistic to assess inter-rater reliability of the two main outcomes was calculated. Generalised linear modelling with a log link to produce risk ratios (RR) was used, accounting for clustering by clinician and controlling for potential covariates associated with the prescription strategy and the two outcomes. Two models were generated: in the first, variables were selected using backward stepwise selection with variables retained if the *P*-value <0.05. In the second model, analyses were conducted post-hoc, where a stratified propensity score was created, which allowed for more rigorous control of potential confounding by indication.[29,30]

RESULTS

Ascertainment and baseline characteristics

Between July 2011 and May 2013, 518 clinicians recruited children from 247 primary care practices across England. A total of 8613 children were recruited, and, of these, 219 (3%) children were excluded: 181 did not meet eligibility, 32 children did not have baseline data, and six children were withdrawn. Seventy-four children referred for acute hospital admission on the day of recruitment were excluded from the analysis, leaving a total of 8320 children. Antibiotic prescription data from the baseline consultation were available for 100% of these children and all analyses used this final sample of 8320. Figure 1 details the flow of participants through the study. The outcome of hospitalisation was obtained for 8320 (100%) children, and reconsultation for deterioration was obtained for 98% (n = 8136/8320).

Inter-reviewer agreement analysis for medical record data collection was assessed. For hospitalisation this was 90% (κ 0.80) and 84% for reconsultation within r the same episode of illness (κ 0.67). Missing data for candidate predictors were infrequent (<2%) with the exception of oxygen saturation (50% missing values) due to lack of available paediatric monitors.

Clinicians prescribed antibiotics for 3084/8320 children (37%), with 2313 (28%) children prescribed immediate and 771 (9%) delayed antibiotics. The range of days the prescription was delayed for was between 0–10, median 2 (interquartile range [IQR] 2–3).

Of the 8320 children included in the analysis, 65 (0.8%) were hospitalised for an RTI in the 30 days following recruitment. Median time to hospitalisation was 4 days (IQR 1–15) with 5% hospitalised on the day of recruitment (day 0), 52% on days 1–7, 17% on days 8–14, and 26% on days 15–30. Of the 65 children hospitalised, 25 (38.5%) had been prescribed an antibiotic.

The most common RTI discharge diagnoses (Table 1) were bronchiolitis (20%), lower RTI (14%), and upper RTI (12%); other diagnoses included viral wheeze, exacerbation of asthma, tonsillitis, croup, unspecified viral illness, chest infection, bronchiolitis and bronchitis, viral pneumonitis, pyrexia, and febrile convulsions.

Just over one-fifth (22.5%; 1830/8136) of children reconsulted for any RTI symptoms in the 30 days after consultation, 14% (1163/8136) reconsulted for the same episode of RTI illness, and 4% (350/8136) reconsulted for the same RTI with evidence in their medical records of deteriorating symptoms.

Appendix 3 shows the clinical history, sociodemographics, parent/carer-reported symptoms, clinical signs observed by the clinician, and adverse health outcomes (in the 30 days post-baseline) for the children with different antibiotic strategies at the baseline consultation. There is wide variation in the number of children prescribed an immediate, delayed, or no antibiotic with regard to parent-reported symptoms and clinical signs.

Figure 1. Flow of participants through the study.

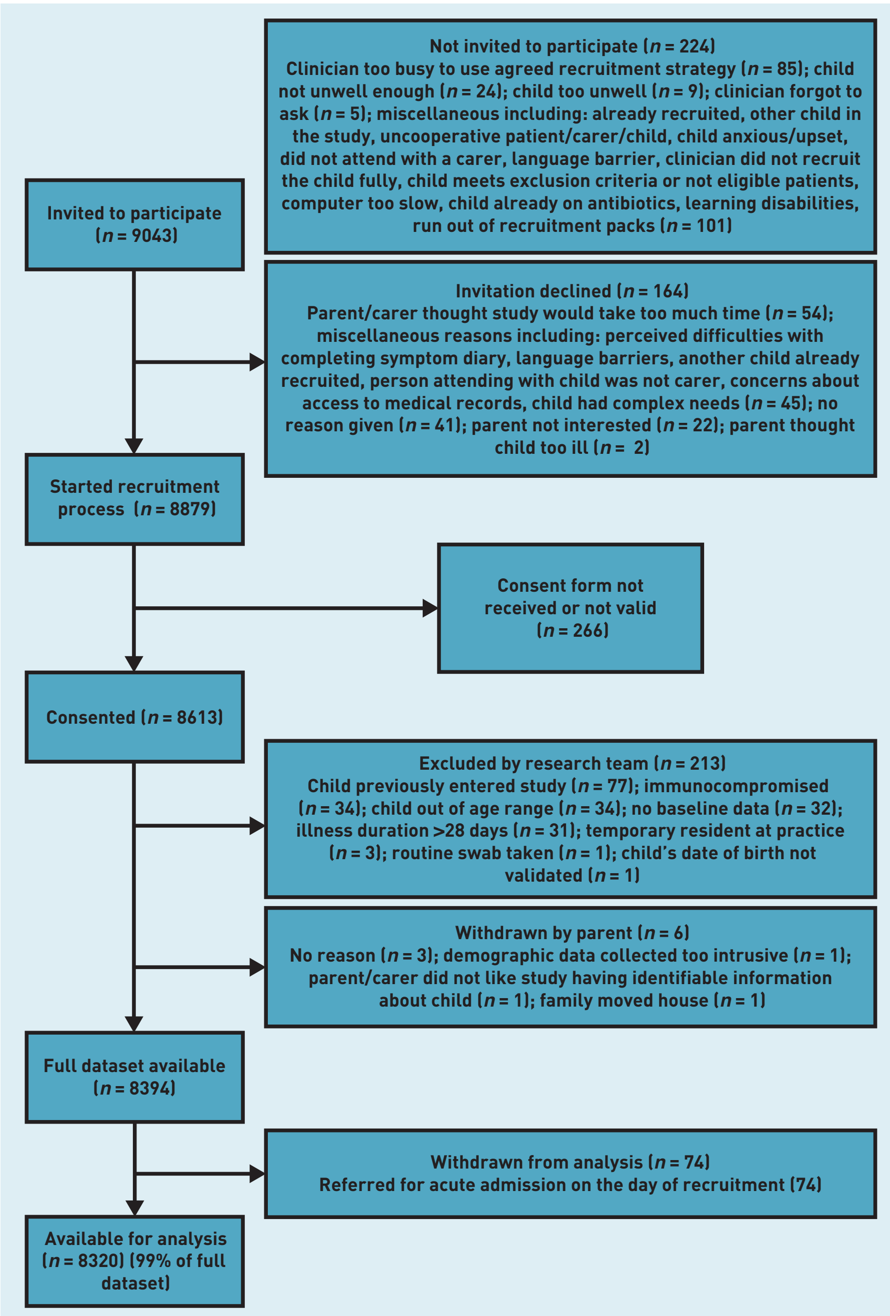

Table 1. Hospital discharge diagnoses in the 30 days post-recruitment for children who were and were not prescribed an antibiotic at the baseline general practice consultation

	Number of children			
Hospital diagnosis	**Immediate**	**Delayed**	**Not prescribed**	**Total**
Bronchiolitis	1	2	10	13
LRTI	6	0	3	9
URTI	0	3	5	8
Exacerbation of asthma	2	0	4	6
Tonsillitis	3	0	3	6
Viral wheeze	2	0	4	6
Croup	1	1	3	5
Unspecified viral illness	1	0	2	3
Chest infection	1	0	1	2
Bronchiolitis and bronchitis	0	0	1	1
LRTI/viral pneumonitis	1	0	0	1
Pyrexia	1	0	0	1
URTI and febrile convulsions	0	0	1	1
No record	0	0	3	3
Total	19	6	40	65

LRTI = lower respiratory tract infection. URTI = upper respiratory tract infection.

Relationships between baseline characteristics and health outcomes

Hospitalisation. Table 1 shows the discharge diagnoses for the hospitalised children and whether they received an antibiotic or not. There was no evidence of a difference between hospital diagnoses in children prescribed an antibiotic compared with those who were not (χ^2 test: $P = 0.46$).

Table 2 details the univariable and multivariable relationships between antibiotic prescribing at the baseline consultation and subsequent hospitalisation. There was no clear evidence at the univariable level or multivariable level that prescribing immediate or delayed antibiotics reduced the risk of a child being hospitalised in the 30 days post-baseline consultation (immediate RR 0.83, 95% confidence interval [CI] = 0.47 to 1.45; delayed RR 0.70, 95% CI = 0.26 to 1.90, overall $P = 0.44$).

Reconsultation within 30 days for deterioration. Table 3 describes the univariable and multivariable relationships between prescription at the baseline consultation and reconsultation for deterioration. Both univariable and multivariable analysis, accounting for clinician clustering, indicate there is evidence to suggest a difference in those reconsulting with deteriorating symptoms in the subsequent 30 days, for those prescribed an antibiotic compared with those who were not (immediate odds ratio [OR] 0.82, CI = 0.65 to 1.07; delayed OR 0.55, CI = 0.34 to 0.88, overall $P = 0.02$). Delayed antibiotics reduced reconsultation with deterioration by almost half and, although the point estimate for those prescribed immediate antibiotics suggests a reduction, the 95% CI means the absence of an effect cannot be ruled out.

DISCUSSION

Summary

This is the first cohort evidence available to date to indicate that prescribing immediate or delayed antibiotics in children does not prevent RTI-related hospitalisation in the 30 days post primary care consultation. Hospital admissions in the 30 days after the baseline consultation were rare and almost none of the reasons for admission were related to the withholding of antibiotics. This has demonstrated that delayed antibiotics reduced the risk of the child reconsulting for the same illness with deterioration. For those given immediate antibiotics, the trend was in the same direction, although no clear

Table 2. Association between children's antibiotic prescription strategies and hospitalisation in the 30 days following the baseline consultation

	Not hospitalised		Hospitalised		Univariable analysis clustering by clinician			Multivariable analysis accounting for covariates where $P<0.05$ and clustering by clinician			Analysis stratified by propensity score and accounting for clustering by clinician		
	n	**%**	***n***	**%**	**RR**	**95% CI**	***P*-value[a]**	**RR**	**95% CI**	***P*-value[a]**	**RR**	**95% CI**	***P*-value[a]**
No antibiotic	5196/8255	62.9	40/65	61.5	Ref	Ref	0.53 (2 df)	Ref	Ref	0.31 (2 df)[b]	Ref	Ref	0.44 (2 df)
Immediate	2292/8255	27.8	21/65	32.3	1.19	0. 70 to 1.88		0.81	0.40 to 1.32		0.83	0.47 to 1.45	
Delayed	767/8255	9.3	4/65	6.2	0.68	0.24 to 1.88		0.62	0.22 to 1.66		0.70	0.26 to 1.90	

[a]Overall P-value. [b]Covariates included (<0.05): age (<2 years), current asthma, short (<3 days) illness duration prior to baseline, moderate/severe vomiting in the 24 hours before baseline, clinician-reported wheeze, high temperature (age-related cut-offs). df = degrees of freedom. Ref = reference. RR = risk ratio.

Table 3. Association between children's antibiotic prescription strategies and reconsulting for the same RTI illness with evidence of deterioration in the 30 days following the baseline consultation

	No reconsultation		Reconsulted for deterioration		Univariable analysis clustering by clinician			Multivariable analysis accounting for where *P*<0.05 and clustering by clinician			Analysis stratified by propensity score and accounting for clustering by clinician		
	n	%	*n*	%	RR	95% CI	*P*-value[a]	RR	95% CI	*P*-value[a]	RR	95% CI	*P*-value[a]
No antibiotic	4864/7786	62.5	240/350	68.6	Ref	Ref	0.008 (2 df)	Ref	Ref	0.007 (2 df)[b]	Ref	Ref	0.024 (2 d.f)
Immediate	2175/7786	27.9	91/350	26.0	0.85	0.67 to 1.09		0.78	0.61 to 0.99		0.82	0.65 to 1.07	
Delayed	747/7786	9.6	19/350	5.4	0.52	0.32 to 0.87		0.56	0.34 to 0.91		0.55	0.34 to 0.88	

[a]*Overall* P*-value.* [b]*Covariates included (*P*<0.05): moderate/severe vomiting in the 24 hours before baseline, white ethnicity, age (<2 years), short (<3 days) illness duration prior to baseline, clinician-reported wheeze, parent-reported disturbed sleep in the previous 24 hours, moderate or severe vomiting and severe blocked nose in the previous 24 hours. df = degrees of freedom. Ref = reference. RR = risk ratio.*

evidence was found; it is not clear if this is due to a lack of power or a true finding. This supports previous research in adults that also suggests delayed prescribing should be considered if an antibiotic is being prescribed.

Strengths and limitations

The study's large observational dataset reflects a realistic primary care setting and the findings are likely to be generalisable to general practice in other high-income countries. Follow-up and case ascertainment were high. The study has several potential limitations. First, prescribing rates were relatively low in this cohort, particularly delayed prescribing, which may impact on the generalisability. The low prescribing rates are likely to be because clinicians who self-classified themselves as 'low prescribers' were eligible to recruit to the study. Second, establishing whether prescribed antibiotics were dispensed and consumed was not possible, although previous studies suggest that immediate prescriptions commonly are consumed.[31] Third, both health outcomes were rare and event rates low (as expected), particularly hospitalisation, which unavoidably limits analytic power. Fourth, as with any secondary analysis of observational data there may be residual confounding, although only a few variables predicted hospitalisation, which lessens any effect of confounding by indication. For reconsulting for deterioration, very little change in risk ratios were recorded when a wide range of potential covariates were included in the model, which suggests that confounding, for those variables that were recorded, was not a major issue.

Comparison with existing literature

The authors did not find evidence to support the use of an immediate antibiotic prescription as a means of clearly reducing hospitalisations for RTIs. Even if the lower confidence intervals for the estimate are taken, more than 200 children would need to be given an immediate antibiotic for one hospitalisation to be prevented. These findings are in agreement with evidence from systematic reviews[11–13,32] where little or no evidence was found to support their use in children or adults. The authors found similar estimates for reconsultations for deterioration with that of one large cohort study investigating new or non-resolving symptoms in adult sore throat.[18,19] Similarly, this evidence supports the idea that a delayed antibiotic script is not necessarily equivalent to a 'no prescription' strategy and can be a useful means to reduce reconsultations[18,19,33,34] as well as the use of antibiotics.[31,33–36] Evidence from this cohort demonstrated which symptoms and signs predict complications in children presenting to general practice with acute cough and RTI.[5] This may reduce uncertainty around distinguishing which children might benefit from antibiotics, from those who are at a much lower risk of poor health outcomes where the clinician can safely make a 'no prescription' decision.[21] However, a multifaceted approach and more complex behavioural interventions may be required to support clinicians to reduce their prescribing to children.[37–39]

Qualitative evidence suggests that the relationship between parents and clinicians, in relation to antibiotic prescribing for their child's RTI, is complex. Studies show that clinicians are prescribing 'just in case',[6] feel uncertain about prognostic outcomes,[7] and perceive pressure from parents to prescribe when parents want symptomatic relief and safety-netting advice.[40,41] The authors' evidence indicates a delayed

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prescription reduces the likelihood of a parent reconsulting with their child with deterioration. The reasons for this are not entirely clear, but may represent the timely access to antibiotics if illness is not settling, or prompt treatment of a secondary bacterial infection following an initial viral infection.

Implications for practice

These findings suggest that there is little evidence that antibiotics substantially reduce the risk of hospitalisation in children presenting to primary care; and that these risks are extremely low for the majority of children presenting with acute cough and RTI. The rates of prescribing in this cohort, even for self-classified 'low prescribers', indicate continued need for interventions and strategies to better target antibiotics. These results provide reassurance that, when faced with a child and uncertain prognosis, delayed prescribing can be a safe and effective method to reduce the child's probability of reconsulting with deterioration and can act as part of safety-netting strategies for parents.

The implications for clinical practice are that the majority of children presenting with acute cough and respiratory symptoms in primary care are not at risk of hospitalisation, and antibiotics may not reduce the risk. If clinicians are considering an antibiotic, a delayed prescription may be preferable as it is likely to reduce reconsultation for deterioration.

Ethical approval

The study was approved by the South West Central Bristol Research Ethics Committee, UK (reference number: 10/H0102/54) and research governance approvals obtained across all areas prior to the start of recruitment in those areas. The TARGET cohort study was sponsored by Research Enterprise and Development Department, University of Bristol, UK. The cohort study is registered on UK NIHR Clinical Research Network Portfolio as 'The TARGET study' (reference number: 9334).

Provenance

Freely submitted; externally peer reviewed.

Competing interests

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Appendix 1. Case report form used to record baseline data for the prospective TARGET cohort study (a similar online version was also used).

CASE REPORT FORM

TARGET

ID

Today's date D D / M M / 2 0 Y Y

Informed consent for study obtained ☐$_1$

Background information

DOB D D / M M / Y Y Y Y

Gender ☐ Female$_0$ ☐ Male$_1$

Ethnicity ☐☐ PTO for codes, if other ethnicity, please describe below

Mother's age ☐☐

children in home (inc. unwell child) ☐☐

Does the mother smoke? ☐ No$_0$ ☐ Yes$_1$ ☐ Don't know$_{88}$

Mother still breast feeding child at three months? ☐ No$_0$ ☐ Yes$_1$ ☐ Don't know$_{88}$

Carer reported Symptoms

How unwell does the parent consider the child to be? Well ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 Very unwell

Duration of illness ☐☐ days

Has illness got a lot worse recently? ☐ No$_0$ ☐ Yes$_1$

If Yes, how many days ago did it start to get worse? ☐☐ days

Symptoms present	During illness? No$_0$	Yes$_1$	If yes	Last 24 hours? No$_0$	Yes$_1$	If yes	Severity in last 24 hours (tick one) Mild$_1$	Moderate$_2$	Severe$_3$
Dry cough	☐	☐	>	☐	☐	>	☐	☐	☐
Productive/wet cough	☐	☐	>	☐	☐	>	☐	☐	☐
Banking/croupy cough	☐	☐	>	☐	☐	>	☐	☐	☐
Blocked or runny nose	☐	☐	>	☐	☐	>	☐	☐	☐
Change in cry	☐	☐	>	☐	☐	>	☐	☐	☐
Breathing faster than normal (shortness of breath)	☐	☐	>	☐	☐	>	☐	☐	☐
Wheeze or whistling in the chest	☐	☐	>	☐	☐	>	☐	☐	☐
Fever	☐	☐	>	☐	☐	>	☐	☐	☐
Chills/shivering	☐	☐	>	☐	☐	>	☐	☐	☐
Diarrhoea	☐	☐	>	☐	☐	>	☐	☐	☐
Vomiting (including after cough)	☐	☐	>	☐	☐	>	☐	☐	☐
Taking fewer fluids/ milk feeds	☐	☐	>	☐	☐	>	☐	☐	☐
Eating less	☐	☐	>	☐	☐	>	☐	☐	☐
Low energy/fatigue/lethargy	☐	☐	>	☐	☐	>	☐	☐	☐
Disturbed sleep	☐	☐	>	☐	☐	>	☐	☐	☐
Passing urine less often/dryer nappies	☐	☐	>	☐	☐	>	☐	☐	☐
Please tick NA if the child is too young/uncommunicative for the parent to know the following > NA ☐$_1$									
Chest/shoulder pain	☐	☐	>	☐	☐	>	☐	☐	☐
Headache	☐	☐	>	☐	☐	>	☐	☐	☐
Muscle aches all over	☐	☐	>	☐	☐	>	☐	☐	☐
Confusion/disorientation	☐	☐	>	☐	☐	>	☐	☐	☐

Clinician examination and management

	Absent$_0$	Present$_1$	
Pallor	☐	☐	
Grunting	☐	☐	
Nasal flaring	☐	☐	
Stridor	☐	☐	
Inter/subcostal recession	☐	☐	
Inflamed pharynx/tonsils	☐	☐	
	Absent$_0$	Unilateral$_1$	Bilateral$_2$
Wheeze	☐	☐	☐
Crackles/crepitations	☐	☐	☐
Bronchial breathing	☐	☐	☐

Temperature ☐☐☐☐ °C Pulse ☐☐☐ bpm

Respiratory rate ☐☐☐ bpm Pulse ☐☐☐ bpm

Consciousness level ☐ Normal$_0$ ☐ irritable$_1$ ☐ drowsy$_2$

Capillary refill time ☐ two seconds or less$_0$ ☐ three seconds or more$_1$

How unwell do you consider the child to be? Well ☐0 ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 Very unwell

Main working respiratory tract diagnosis ☐☐☐☐☐☐☐☐☐☐☐☐☐☐

My gut feeling is 'something is wrong' ☐ No$_0$ ☐ Yes$_1$

Antibiotics prescribed? ☐ No$_0$ ☐ Yes$_1$ immediate$_1$ ☐ Yes$_1$ delayed$_2$ by ☐☐ days

Referral for acute admission today? ☐ No$_0$ ☐ Yes$_1$

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Appendix 2. Potential covariates associated with hospitalisation and reconsultation in the 30 days following baseline

Characteristic		Data source
Sociodemographic variables		
Age	<2 years versus ≥2 years	Parent
Sex	Male versus female	Parent
Age of mother at child's birth	≤26 years versus >26 years	Parent
Breastfed for ≥3 months	Yes versus no	Parent
Mother smokes	Yes versus no	Parent
Children in the home	≥2 versus <2	Parent
IMD score	High, top quintile versus quintiles 1 to 4	Parent
Ethnicity	White versus mixed, Asian or Asian British, black or black British, Chinese, or other ethnic groups	Parent
Past medical history		
Consultations for RTI in the 12 months prior to baseline	≥2 versus <2	General practice medical notes
Asthma (current diagnosis)	Yes versus No	General practice medical notes
Chronic conditions (any)	Yes versus No	General practice medical notes
Asthma (previous diagnosis)	Yes versus No	General practice medical notes
Parent-reported symptoms (present during the illness)		
Illness duration prior to baseline (days)	<3 versus ≥3	Parent
Breathing faster than normal	Present versus absent	Parent
High parent illness severity score	≥7 versus <7	Parent
Low energy/fatigue/lethargy	Present versus absent	Parent
Fever	Present versus absent	Parent
Eating less	Present versus absent	Parent
Illness much worse recently	Yes versus no	Parent
Disturbed sleep	Present versus absent	Parent
Wheezing or whistling in the chest	Present versus absent	Parent
Chills/shivering	Present versus absent	Parent
Taken fewer fluids/milk feeds	Present versus absent	Parent
Productive wet cough	Present versus absent	Parent
Vomiting (including after a cough)	Present versus absent	Parent
Passing urine less often/drier nappies	Present versus absent	Parent
Change in cry	Present versus absent	Parent
Dry cough	Present versus absent	Parent
Diarrhoea	Present versus absent	Parent
Barking/croupy cough	Present versus absent	Parent
Blocked/runny nose	Present versus absent	Parent
Parent-reported symptoms (last 24 hours)		
Change in cry (moderate/severe)	Present versus absent	Parent
Vomiting (moderate/severe)	Present versus absent	Parent
Disturbed sleep (severe)	Present versus absent	Parent
Taking fewer fluids/milk feeds (moderate/severe)	Present versus absent	Parent
Passing urine less often/drier nappies (moderate/severe)	Present versus absent	Parent
Productive wet cough (severe)	Present versus absent	Parent
Chills/shivering (moderate/severe)	Present versus absent	Parent
Eating less (severe)	Present versus absent	Parent
Low energy/fatigue/lethargy (moderate/severe)	Present versus absent	Parent
Wheeze (moderate/severe)	Present versus absent	Parent

... continued

Appendix 2 continued. Potential covariates associated with hospitalisation and reconsultation in the 30 days following baseline

Fever (severe)	Present versus absent	Parent
Breathing faster than normal (moderate/severe)	Present versus absent	Parent
Blocked/runny nose (severe)	Present versus absent	Parent
Dry cough (severe)	Present versus absent	Parent
Barking/croupy cough (moderate/severe)	Present versus absent	Parent
Diarrhoea (moderate/severe)	Present versus absent	Parent
Clinical signs		
Inter/subcostal recession	Present versus absent	Clinician
Bronchial breathing (unilateral/bilateral)	Present versus absent	Clinician
Nasal flaring	Present versus absent	Clinician
Pallor	Present versus absent	Clinician
Wheeze (unilateral/bilateral)	Present versus absent	Clinician
Abnormal consciousness	Yes versus no	Clinician
High temperature	≥37.8°C versus <37.8°C	Clinician
High respiratory rate (age-related cut-offs)	Present versus absent	Clinician
High pulse (age-related cut-offs)	Present versus absent	Clinician
Inflamed pharynx	Present versus absent	Clinician
Grunting	Present versus absent	Clinician
Crackles/crepitations (unilateral/bilateral)	Present versus absent	Clinician
Slow capillary refill time	≥3 seconds versus ≤2 seconds	Clinician
Stridor	Present versus absent	Clinician
High clinician illness severity score	≥4 versus <4	Clinician
Clinician gut feeling that 'something is wrong'	Yes versus no	Clinician

IMD = Index of Multiple Deprivation. RTI = respiratory tract infection.

Appendix 3. Characteristics of the children and antibiotic prescribing strategies at the baseline general practice consultation

	No antibiotic		Immediate antibiotics		Delayed antibiotics	
	n/N	%	*n/N*	%	*n/N*	%
Clinical history						
RTI consultations in the 12 months prior to baseline (≥2 consultations)	1739/5106	34	839/2269	37	262/766	34
Any chronic condition[a]	916/5235	18	492/2311	21	157/771	20
Current asthma diagnosis[b]	415/5236	8	247/2313	11	77/771	10
Previous asthma diagnosis	184/5235	4	124/2313	5	41/771	5
Sociodemographics						
Sex (male)	2693/5236	51	1230/2313	53	365/771	47
Age (<2 years)	1875/5236	36	715/2313	31	212/771	28
Children in the home (>1)	3292/5213	63	1644/2303	71	526/765	69
Breastfeeding (at 3 months)	2132/4887	44	934/2117	44	350/718	49
Ethnicity (white)	4015/5212	77	1889/2298	82	585/766	76
Mother smokes	914/5178	18	447/2277	20	115/759	15
Young mother	1566/5222	30	652/2304	28	197/768	26
IMD quintile (most deprived)	1066/5236	20	436/2313	19	117/771	15
Parent-reported symptoms present at any time during the illness						
High severity score (parent: ≥7/10)	993/5218	19	914/2305	40	209/771	27
Short duration of illness (≤ 3 days)	1598/5233	31	533/2312	23	234/771	30
Illness worsened recently	3114/5230	60	1835/2310	79	527/770	68
Dry cough	3326/5234	64	1205/2309	52	447/771	58
Productive wet cough	2556/5230	49	1455/2310	63	440/770	57
Barking/croupy cough	1357/5232	26	605/2307	26	161/771	21
Blocked/runny nose	4202/5234	80	1833/2311	79	620/770	81
Change in cry	850/5221	16	385/2302	17	131/766	17
Breathing quickly[c]	1602/5235	31	1057/2311	46	279/771	36
Wheezing/whistling in chest	1885/5232	36	1058/2311	46	303/771	39
Chills	948/5233	18	679/2310	29	212/770	28
Fever	2865/5234	55	1733/2311	75	533/771	69
Diarrhoea	783/5233	15	340/2311	15	101/771	13
Vomiting[d]	1349/5234	26	765/2311	33	201/771	26
Eating less than normal	2855/5232	55	1627/2310	70	498/771	65
Fewer fluids	1529/5232	29	834/2309	36	253/771	33
Low energy	2512/5234	48	1475/2310	64	483/771	63
Disturbed sleep	3880/5234	74	1926/2311	83	592/770	77
Less urine than normal	652/5223	13	348/2307	15	131/770	17
Parent-reported symptoms present in the last 24 hours (severe)						
Dry cough	337/5215	6	174/2306	8	40/768	5
Productive wet cough	329/5215	6	270/2304	12	68/770	9
Blocked/runny nose	406/5202	8	201/2304	9	52/765	7
Fever	228/5217	4	236/2302	10	70/768	9
Eating less	208/5213	4	175/2299	8	38/769	5
Disturbed sleep	784/5208	15	430/2305	19	116/765	15
Parent-reported symptoms present in the last 24 hours (moderate or severe)						
Barking cough	957/5226	18	446/2303	19	111/771	14
Change in cry	480/5212	9	224/2301	10	73/765	10
Chills/shivering	382/5229	7	362/2305	16	84/769	11
Breathing quickly[c]	836/5224	16	619/2308	27	146/771	19

Appendix 3 continued. Characteristics of the children and antibiotic prescribing strategies at the baseline general practice consultation

Wheeze	878/5225	17	585/2305	25	128/771	17
Diarrhoea	216/5229	4	103/2309	5	22/771	3
Vomiting[d]	460/5227	9	290/2310	13	74/770	10
Taking fewer fluids/milk feeds	641/5224	12	388/2302	17	107/769	14
Low energy/fatigue/lethargy	1192/5213	23	824/2301	36	229/768	30
Passing urine less often	256/5213	5	158/2306	7	42/769	6
Physical examination signs						
Pallor	284/5227	5	439/2311	19	84/771	11
Nasal flaring	39/5228	1	51/2311	2	6/771	1
Grunting	25/5227	0	40/2310	2	6/771	1
Inter/subcostal recession	131/5227	3	226/2310	10	21/771	3
Wheeze	498/5228	10	624/2308	27	87/771	11
Crackles/crepitations	128/5227	2	1300/2310	56	130/770	17
Bronchial breathing	43/5225	1	210/2307	9	21/769	3
Inflamed pharynx	1250/5212	24	828/2308	36	299/771	39
Stridor	25/5226	0	11/2310	0	5/771	1
Abnormal consciousness	42/5229	1	73/2308	3	7/768	1
High respiratory rate	619/5212	12	492/2300	21	107/763	14
High temperature ≥37.8°C[e]	346/5223	7	567/2307	25	116/770	15
High pulse	170/5203	3	178/2297	8	33/766	4
Capillary refill rate (≥3 seconds)	41/5216	1	18/2304	1	6/763	1
High severity score (clinician: (≥4/10)	1038/5233	20	1502/2296	65	341/768	44
Gut feeling something is wrong	273/5230	5	1265/2307	55	110/766	14
Adverse health outcomes in the 30 days post-baseline						
Hospitalised	40/5236	1	21/2313	1	4/771	1
Reconsulted general practice for the same RTI illness with evidence of symptom deterioration	240/5104	5	91/2266	4	19/766	2

[a]Includes both current and previous asthma diagnosis. [b]Defined as present if asthma in medical notes problem list and asthma medication issued in the previous 12 months. [c]Faster than normal. [d]Including after a cough. [e]High temperature (age-related cut-offs). IMD = Index of Multiple Deprivation. RTI = respiratory tract infection.