Predicting complications from acute cough in pre-school children in primary care: a prospective cohort study

Alastair D Hay, Tom Fahey, Tim J Peters and Andrew Wilson

SUMMARY

Background: There is uncertainty about which children with cough are most and least likely to experience complications.

Aim: To derive a clinical prediction rule for complications in pre-school children presenting to primary care with acute cough.

Design of study: Prospective cohort study.

Setting: Eight general practices in Leicestershire, United Kingdom.

Method: Pre-school children with cough for •28 days and without asthma were recruited. Sociodemographic, clinical history, and examination data were collected and univariable logistic regression used to explore the associations with complications. These were defined as any new symptom, sign or diagnosis identified by a primary care clinician at a parent initiated reconsultation, or hospital admission, before cough resolution. Those factors with stronger relationships ($P < 0.2$) were then modelled using multivariable logistic regression to identify the factors independently associated with complications.

Results: The pre-test probability of complications was 10%. On univariable analysis, fever (odds ratio [OR] = 4.86; 95% confidence interval [CI] = 1.74 to 13.6), chest signs (OR = 2.72; CI = 1.06 to 6.96), and tachypnoea (OR = 3.80; CI = 1.22 to 11.8) were associated with complications. On multivariable analysis, only fever (OR = 5.56; CI = 1.75 to 17.6) and chest signs (OR = 2.88; CI = 1.02 to 8.05) were independently associated with complications. These ORs translate into post-test probabilities of complications of 6% for children with neither fever nor chest signs, 18% for children with chest signs, 28% for children with fever, and 40% for children with fever and chest signs.

Conclusions: If validated, this clinical prediction rule could be used to individualise the management of acute cough in pre-school children.

Keywords: cough; prognosis; complications; clinical prediction rule.

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Introduction

COUGH is the most frequently managed problem in primary care and it becomes increasingly common at the extremes of age.[1,2] Twelve per cent of children experience complications[3] and up to 24% reconsult.[4] Although between 40% and 70% of children with cough receive antibiotics,[4-6] current evidence suggests that, on average, antibiotics do not reduce complications.[7] However, antibiotics may benefit a subgroup of children, currently unidentified, at high risk of poor outcome. Recent reductions in antibiotic prescribing for respiratory infections in primary care[8,9] may be related to rises in invasive bacterial infections,[10] suppurative complications,[11] and mortality due to pneumonia in adults.[12] Against this, clinicians have to weigh up concerns about antibiotic resistance,[13] side effects, and anaphylaxis. Therefore, clinicians need to be able to identify the children in whom antibiotics are most and least likely to be effective.[14]

From the parents' perspective, clear information is required to guide decision making[15] and provide reassurance that their child will not experience severe complications.[16] Such prognostic information has been shown to reduce both reconsultations[17] and antibiotic consumption[18] in adults with cough.

Unfortunately, there is a general paucity of information regarding the predictive value of symptoms and signs in primary care, and a search of MEDLINE from 1966 to date revealed no studies examining the predictive value of symptoms and signs for complications in children in primary care. Previous work has concentrated on the diagnosis of pneumonia at presentation in emergency care settings in the developing world[19] and hypoxaemia in paediatric outpatients.[20]

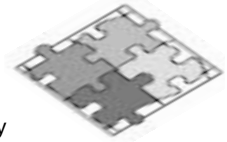
A primary care clinical prediction rule would individualise treatment and provide important prognostic information for parents. There are three stages in the development of a rule: derivation, validation, and assessment of impact on clinical behaviour.[21] The aim of this paper is to describe the first of these stages: the derivation of a clinical prediction rule for complications in pre-school children presenting with acute cough to primary care. This was secondary to the primary aim of the cohort study, which was to describe the duration of cough.[22]

Method

Practices and participants

The Leicestershire Research Ethics Committee approved the study and written parental consent was obtained for all children. To maximise the efficiency of child recruitment, practices with list sizes greater than 8000 were invited by letter

HOW THIS FITS IN



What do we know?

The amount of antibiotic prescribing for respiratory tract infections in primary care has decreased since 1993. Although not necessarily causally related, there has been a rise in invasive bacterial infections and suppurative complications of respiratory tract infections. Clinicians need to know which patients are most and least likely to experience complications.

What does this paper add?

This study shows that serious complications are rare, but that complications necessitating reconsultation occur in 10% of pre-school children with cough. If validated, this clinical prediction rule could be used to individualise the management of acute cough in pre-school children.

to participate. Recruitment took place from November to April over 2 years between 1999 and 2001, at morning and evening surgeries rotated between practices. A researcher was located in the surgery during recruitment sessions to ensure all eligible children were invited to participate. These were children aged 0–4 years with a cough of duration of •28 days presenting to a general practitioner (GP) or nurse practitioner, and without asthma (defined as recommended to be receiving preventive or regular reliever treatment) or any other chronic disease.

Data collection

To collect the explanatory variables for the clinical prediction rule, the parent recorded the child's sociodemographic and cough history details before seeing the clinician. The collected variables are listed in Supplementary table 1. The clinician was asked to perform a routine examination of the child and record the examination and diagnosis details. No additional instruction was given as to how to measure fever or examine the child. The parent was then asked to complete a validated symptom diary[23] modified for use with young children. This recorded the presence of cough on a daily basis until resolution (defined as 2 consecutive days without cough) allowing us to determine cough duration.

The outcome of interest was complications, but the clinicians were not aware of this. Once cough duration was known, the medical records of all children were reviewed for reconsultations (any primary care contact before cough resolution). Reconsultation diagnoses were then examined for complications (any new symptom, sign, or diagnosis suggesting a deterioration in condition, owing to treatment or the illness, or hospital admission). This was done blind to the child's sociodemographic and clinical data.

Data entry and analysis

The data were analysed using Stata statistical software version 7.0 (Stata Corporation, 2001). We summarised the complication rate, diagnosis, and whether the children were managed in primary or secondary care using descriptive statistics. The first stage of the analysis used logistic regression to investigate the univariable associations of the explanatory factors with the outcome of interest. These results are expressed as odds ratios (ORs) where a value greater than 1 indicates an increased odds of complications. Multivariable logistic regression was then used to identify the explanatory variables independently associated with complications. We assessed the effect of adjusting for a small set of pre-specified variables (age, sex, ethnicity, and deprivation) in all models. The explanatory variables were first considered in three separate groups (sociodemographic, clinical history, and examination findings) and then a final model was constructed across the groups. Owing to the exploratory nature of the analysis and to avoid missing potentially important variables, a relatively liberal threshold for *P*-values of 20% was employed to select explanatory variables for the multivariable modelling. Likewise, a 10% threshold was used for the within group modelling and the final model. The final model was checked for interactions between explanatory variables.

Table 1. Complications by primary or secondary care.

Complication	Frequency
Primary care	
Bronchiolitis	3
Possible asthma	2
Vomiting	2
Bronchitis	1
Viral illness	1
Cough and wheeze	1
Conjunctivitis	1
Lower respiratory tract infection	1
Baby asthma	1
Chest infection	1
Chicken pox	1
Viral induced wheeze	1
Pharyngitis	1
Otitis media	1
Hospital admissions	
Bronchiolitis	2
Pneumonia	1
Whooping cough	1
Viral induced wheeze	1
Total	23

Derivation of the clinical prediction rule

A receiver operator characteristic (ROC) curve was generated from the final regression model excluding the pre-specified variables unless these were influential in themselves. We then identified the cut points on the ROC curve and calculated the corresponding sensitivities, specificities, and likelihood ratios. We derived the post-test probability of complications using the equation $P = 1/(1+e^{-y})$ where P is the post-test probability and y is the sum of the constant coefficient and regression coefficients of the variables in the model. The 95% confidence intervals (CIs) were calculated using the exact binomial calculation.

Sample size

The target sample size of 220 was planned around the primary study outcome, which was cough duration.[22] Specifically, the aim was to achieve a margin of error of ±5%

for the 95% CI for the 90% recovery proportion from cough. With the attained sample of 222 children with complete complications data, we had at least 85% power to detect an absolute difference of 13–15% (equivalent to odds ratios [ORs] of 3.9–4.7) using a two-sided α of 5% and an average complication rate of 12%, and assuming equal numbers in the exposure groups. The larger difference of 15% is detectable with power above 80% even if the proportion of children with the symptom or sign is as low as 17%.

Results

Descriptive statistics

Recruitment and the cohort have been described elsewhere.[22] In brief, 29 practices were invited and nine agreed to participate. Recruitment from one practice was stopped owing to low recruitment rates related to its small pre-school population. The remaining practices were located in inner city, urban, and rural areas and served a total population of 105 689 of whom 6722 (6.4%) were pre-school children. Eligibility was assessed in 95% of 883 children presenting during the recruitment sessions. Of those eligible, 89% agreed to participate, making the total sample 256, of whom 71% were recruited at their first clinician contact for cough. Follow-up data for complications were available for 222 (87%) children. Most of the children were under 2 years of age and 51% were male. Of the whole cohort, 18% were prescribed an antibiotic, 13% a bronchodilator, 19% reconsulted, and 10% were recorded as having complications (Table 1). No child died.

Univariable and multivariable associations

Univariable analysis shows that children with chest signs, fever, and tachypnoea were more likely to experience complications (Supplementary table 1). On multivariable analysis, chest signs and fever attenuated the relationship between tachypnoea and complications, so tachypnoea was excluded. No evidence of an interaction was found between chest signs and fever (OR = 1.15 [95% CI = 0.09 to 14.6], *P* = 0.92). Table 2 shows the independent factors associated with complications after adjustment for the pre-specified variables age, sex, ethnicity, and deprivation. As not all children were recruited at first presentation, we looked to see if the variables in the final model had differential effects between children previously seen for the same cough and those recruited at their first consultation. No such interaction was found.

Likelihood ratios and post-test probabilities of complications

We did not include the pre-specified variables (age, sex, ethnicity, and deprivation) in the final model as they made it considerably more complex and added little to its predictive power (an increase in the area under the ROC curve from 0.68 to 0.70). Therefore, the ROC curve (shown in Figure 1) constructed from the final model for complications with fever and chest signs as risk factors had three cut points. Table 3 summarises the three likelihood ratios from each of these cut points. Table 4 summarises the post-test probabilities calculated from the constant and regression coefficients from the final model with fever and chest signs.

Discussion

Summary of main results

The absence of fever and chest signs (71% of children) appears to be most useful for ruling out future complications in children with cough in primary care, with a post-test probability of 6%. Post-test probabilities rise to 18% in the presence of chest signs (21% of children), to 28% in the presence of fever (11% of children), and to 40% in those with both fever and chest signs (3% of children).

Interpretation

Most secondary care clinical prediction rules are used to 'rule in' the target disorder. If validated, the primary care rule derived from this study would be very helpful in ruling out complications, offering reassurance that complications are unlikely in children without chest signs or fever. This information may enable parental self-care and could reduce the use of antibiotics. In addition, it offers the potential for more appropriate targeting of antibiotics for children with fever and/or chest signs, who are at higher risk of complications.

Where this fits in with other research

This is the first time the predictive value of symptoms and signs for complications has been evaluated in children with cough, and it is a response to calls for studies of prognosis

Table 2. Univariable and multivariable odds ratios (95% CI) for complications.

Variable	Univariable		Multivariable[b]		Multivariable[c]	
	n[a]	OR	*n*[a]	OR	*n*[a]	OR
Chest signs	212		209		209	
Absent		1		1		1
Present		2.72 (1.06 to 6.96)		2.78 (1.04 to 7.35)		2.88 (1.02 to 8.05)
P-value		0.046		0.048		0.051
Fever	217		209		209	
Absent		1		1		1
Present		4.86 (1.74 to 13.6)		4.65 (1.63 to 13.3)		5.56 (1.75 to 17.6)
P-value		0.005		0.007		0.005

[a]Numbers in the analyses differ owing to missing values. [b]Adjusted for the other clinical sign. [c]Adjusted for the other clinical sign and sociodemographic factors. OR = odds ratio.

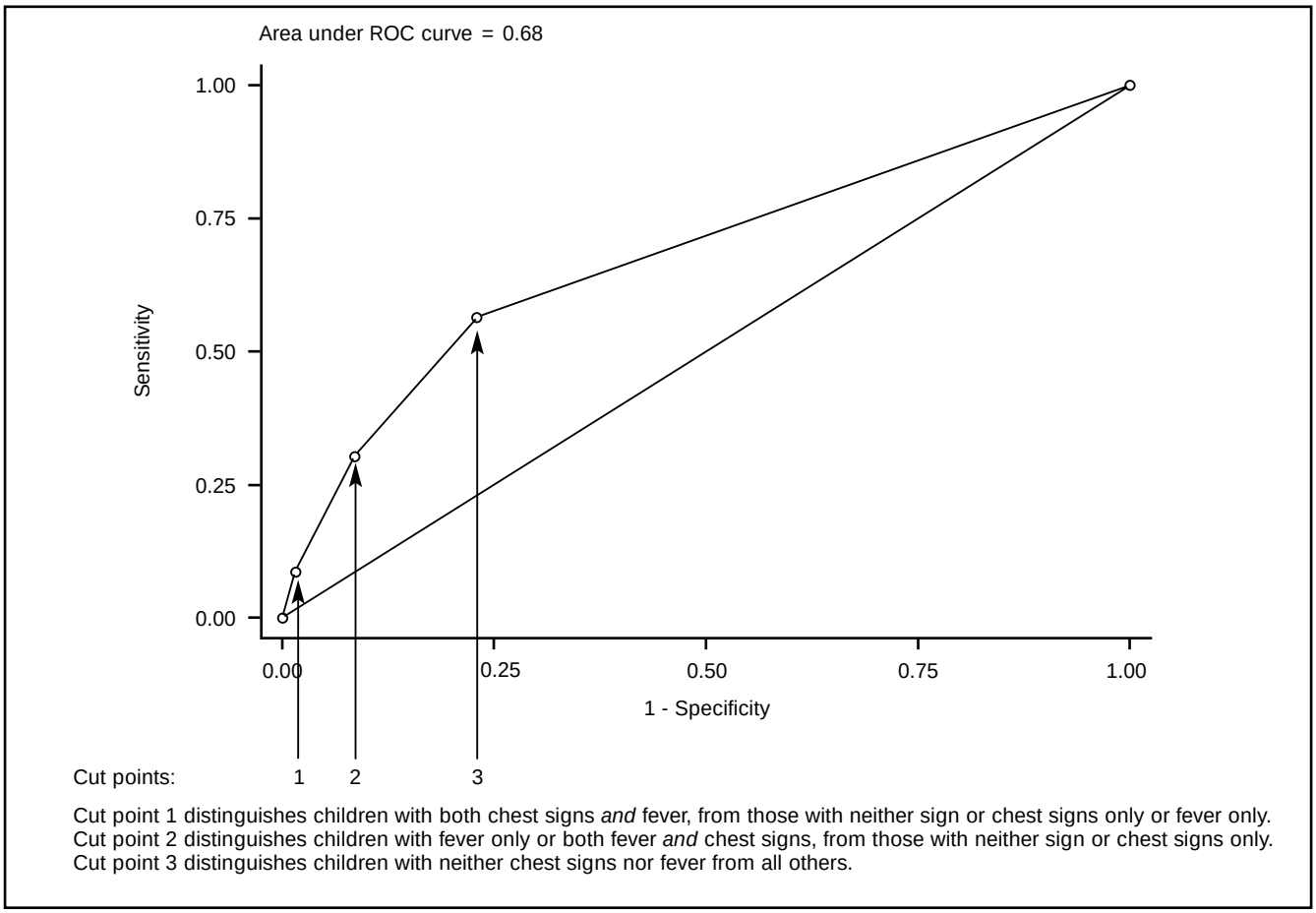


Figure 1. ROC curve for fever and chest signs predicting complications.

Table 3. Likelihood ratios.

Category of interest (%)	Reference category (%)	Likelihood ratio (95% CI)
Neither sign (71)	Either or both signs (29)	0.56 (0.35 to 0.91)
Fever only or both fever and chest signs (11)	Neither sign or chest signs only (89)	3.54 (1.62 to 7.68)
Both signs (2.4)	Either or neither sign (97.6)	5.39 (0.95 to 30.6)

Table 4. Post-test probabilities.

Category of interest (% with sign)	Post-test probability % (95% CI)
Neither sign (71)	6.5 (3.1 to 11.7)
Chest signs only (21)	18.2 (6.9 to 35)
Fever only (11)	27.8 (9.6 to 53)
Both signs (3)	40.0 (5.2 to 85)

in primary care.[24,25] Fever (along with vomiting, ear discharge, and cough) has also been shown to be associated with poor outcome in children presenting to primary care with otitis media; these children were also more likely to benefit from antibiotics.[26]

In common with other studies of acute cough,[6,27] we chose to include children with cough of duration of •28 days, although paediatricians acknowledge that this definition is arbitrary.[27] However, the longer a cough has lasted, the more likely it is owing to asthma. For this reason, some studies of adults exclude patients with cough of more than 21 days.[28] Had we used this definition, only 10 (4%) children would have been excluded. Our single symptom inclusion criterion allowed us to determine the prognostic value of fever and chest signs. This would not have been possible had we, like other authors,[28] chosen a symptom–sign complex, such as cough and one other lower respiratory tract symptom or sign.

For diagnosis at presentation, one systematic review, using unadjusted likelihood ratios, found that absence of tachypnoea was most useful for ruling out pneumonia, and that increased work of breathing (chest wall indrawing, nasal flaring, and grunting) increased the likelihood of pneumonia.[19] Another systematic review found that auscultatory findings contributed little to the accuracy of hypoxaemia diagnosis.[20] Our study differed in three ways. First, we used multivariable logistic regression to establish the factors independently associated with outcome, and found that fever and chest signs confounded tachypnoea. Second, our clinical predic-

tion rule identifies children at higher risk of complications as a future event, as opposed to the identification of children with pneumonia or hypoxaemia at presentation, and third, studies were based in secondary care.

Compared with the complications seen in secondary care, these primary care complications may seem relatively trivial. Although our definition of complications was chosen for comparability with that used by several other previous studies,[29-32] our study may have identified sicker children. The previous studies were placebo controlled trials of antibiotics in which children were reviewed at the discretion of the researcher. These investigators may have identified complications unlikely to lead to reconsultation. In our study, the parent had to initiate a reconsultation and the clinician had to report a new symptom, sign, or diagnosis, or arrange hospital admission. Unlike the previous studies, the reconsultation assessment in our study was not standardised, leading to a broad range of diagnostic labels. Despite these differences, overall complication rates are similar to the 12% reported in a previous meta-analysis.[3] The small number of complications leading to hospital admission (five) prevented meaningful statistical analysis of this outcome, but does emphasize that complications requiring hospital admission are uncommon, even in pre-school children.

Limitations

It is common in studies deriving clinical prediction rules in one population, for the strength of association between symptoms and signs and outcome to be stronger than in a second population.[21] For this reason, the clinical prediction rule presented here is not ready for application in clinical practice without validation.

There are two sources of error in our definition of complications. First, there was no standardised follow-up assessment for children reconsulting. Second, only one investigator examined the medical record for evidence of new symptoms, signs, or diagnoses. Ideally, either the same clinician should review each child, and compare the first and repeat assessment for evidence of complications or, to assess their reliability, two observers should examine the medical records.

Although we successfully minimised selection and attrition bias, deprivation and ethnicity measures were not regionally or nationally representative.[22] However, neither factor was associated with complications, so it seems unlikely that this would alter our conclusions. We wanted the clinicians' examinations to reflect real life clinical practice, but the lack of standardisation means that we do not know how they arrived at their judgments about fever, chest signs or tachypnoea. For example, clinicians may have accepted a recent history of fever from the parent as sufficient evidence. If this were so, it is possible that anxious parents reported fever and reconsulted more often. These limitations should be subjected to further research.

We may not have measured some other important explanatory variables. For example, we could have asked about recent paracetamol usage before the recruitment consultation, which may have concealed the presence of fever in some children. We could also have asked the clinicians to record the presence of unilateral chest signs, which though uncommon, have been shown to be highly predictive for pneumonia in adults.[33]

Conclusions

This study shows that serious complications are rare, but that complications necessitating reconsultation occur in 10% of pre-school children. We have derived a clinical prediction rule for young children with cough in primary care and have shown that it appears to be most useful in ruling out complications. Once validated, an assessment should be made of the impact of the prediction rule on antibiotic prescribing and parental satisfaction.

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Supplementary information

Additional information accompanies this paper at
http://www.rcgp.org.uk/journal/index.asp

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