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**Clinical predictors of antibiotic prescribing for acutely ill children in primary care: observational study**

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## **Abstract**

**Background:** Antibiotic overuse and inappropriate prescribing drive antibiotic resistance. Children account for a high proportion of antibiotics prescribed in primary care.

**Aim:** To determine the predictors of antibiotic prescription in young children presenting to UK general practices with undifferentiated acute illness.

**Design and Setting:** Prospective observational study in general practices in Wales (UK).

**Methods:** 999 children were recruited from thirteen practices between March 2008 and July 2010. Multilevel, multivariable logistic regression analysis was performed to determine predictors of antibiotic prescribing.

**Results:** 261 (26.1%) children were prescribed oral antibiotics. Respiratory infections were responsible for 77.4% of antibiotic prescriptions.

719 children were included in the multivariable model. Children were more likely to be prescribed antibiotics if they were older (Odds Ratio (OR) 1.33; 95% Confidence Interval (CI):1.06-1.68); presented with poor sleep (OR 2.74; 95% CI: 1.50-5.00); had abnormal ear (OR 6.53; 95% CI: 2.47-17.27), throat (OR 2.19; 95% CI: 1.07-4.50) or chest examination (OR 13.64; 95% CI: 5.78-32.17); were diagnosed with lower respiratory tract infection (LRTI) (OR 9.55; 95% CI: 3.71-25.54), tonsillitis/sore throat (OR 119.27; 95% CI: 28.22-504.12), ear infection (OR 26.56; 95% CI 7.36-95.85) or urinary tract infection (UTI) (OR 12.75; 95% CI 4.44-36.58); or if the responsible clinician perceived the child to be moderately to severely unwell (OR 4.01; 95% CI: 1.41-11.42). The area under the receiver operating characteristic curve (AUROC) was 0.9371.

**Conclusions:** Respiratory infections were responsible for more than 70% of antibiotic prescriptions. Diagnoses of tonsillitis, sore throat or ear infection were associated most with antibiotic prescribing, with antibiotics prescribed in 93.1% children with sore throat/tonsillitis and 82.4% children with ear infections. Clinician diagnosis seemed to be more important than abnormal examination findings in predicting antibiotic prescribing, although these were correlated.

## **Keywords**

**Primary health care, Child, Acute disease, Infection, Anti-bacterial agents**

## **How this fits in**

### **What is already known**

- Trials and systematic reviews have found evidence for limited or no benefit for antibiotics in most childhood common infections
- NICE guidelines recommend against routine use of antibiotics for common childhood respiratory tract infections
- There is limited evidence from prospective studies of antibiotic prescribing rates for children with unselected illness in primary care

### **What this study adds**

- Respiratory infections are still responsible for more than 70% of antibiotic prescriptions in children despite evidence-based guidelines that most such prescriptions are unwarranted.
- Diagnoses of tonsillitis or sore throat or ear infection were most associated with antibiotic prescribing with antibiotics.

## **Background**

Antibiotic resistance is an increasing public health problem worldwide, and has been highlighted as a national and international priority.<sup>1 2</sup> Antibiotic prescribing drives antibiotic resistance on both a population and individual level.<sup>1 3-7</sup> In addition, antibiotics may cause adverse effects and their overuse can result in “medicalisation” of self-limiting illness.<sup>8 9</sup>

In the UK, primary care is responsible for 80% of (human) antibiotic prescriptions, and the highest prescription rate is in children aged 1-4 years.<sup>10-12</sup> Both the decision to prescribe and choice of antibiotic are complex, and influenced by both clinical and non-clinical factors.<sup>13-20</sup> Most studies have focused on prescribing for respiratory tract infections (RTIs).<sup>17 18 21</sup> Some studies have considered antibiotic prescribing more generally in children but there are few UK general practice based studies.<sup>16 20</sup>

UK NICE guidelines recommend ‘no’ or ‘delayed’ antibiotic prescribing for most RTIs.<sup>22</sup> Antibiotics are not beneficial for most upper respiratory tract infections (URTIs; including tonsillitis, otitis, acute cough and colds), with little impact on illness course or complication incidence.<sup>22 23</sup> Antibiotic prescribing for specific RTI diagnoses in children decreased in the late 1990s but has been increasing again since the early 2000s, especially for non-specific URTI and

“abnormal symptoms and signs”.<sup>12 16 24</sup>

There is wide variation in antibiotic prescribing between countries, general practices and individual doctors.<sup>8 11 12 20 25</sup> Patient factors such as deprivation, co-morbidities; clinician factors such as previous experience, training and attitudes towards antibiotics; the doctor-patient relationship and perceived patient expectation; and other factors such as time and workload pressures have been identified as influencing prescribing.<sup>15 19 26</sup> Diagnostic uncertainty and concern about serious illness and possible complications may also be contributory factors.<sup>19 27</sup>

Presenting symptoms and signs are considered by clinicians as important in deciding whether to prescribe antibiotics or not.<sup>19</sup> However, we do not know which clinical or non-clinical features are most likely to result in antibiotic prescribing. Several studies, including one UK-based study, have examined antibiotic prescribing in primary care using routinely collected data.<sup>20 25 28 29</sup> Analyses of large routinely collected data are extremely important in understanding the scale of antibiotic prescribing and these studies can also provide information on the type of antibiotic and condition it is prescribed for. However, these studies are less able to examine in detail the clinical and non-clinical features which are most predictive of antibiotic prescribing at the individual level. For this, prospective observational studies are needed.

A study in the Netherlands described symptoms and signs associated with antibiotic prescribing in 443 febrile children.<sup>16</sup> They found that parental concern, ill appearance, altered sleep patterns due to earache, signs of throat infection and reduced urine production were all associated with antibiotic prescribing. A Danish study of 954 children with otitis media found fever and a red tympanic membrane were associated with antibiotic prescribing.<sup>18</sup> The study in the Netherlands only included children with fever presenting to an out-of-hours service and the Danish study only included children with otitis media.<sup>16 18</sup> The Netherlands and Denmark are also among the countries with the lowest antibiotic prescribing rates in Europe and USA.<sup>5</sup> We could find no prospective studies describing factors associated with antibiotic prescribing generally in ill children presenting routinely in UK primary care.

The aim of this study was to describe antibiotic prescribing in consecutive young children (<5 years) presenting to UK general practice with an acute illness (<28 days duration) and to identify which clinical features were most associated with antibiotic prescribing.

## Method

### *Inclusion criteria*

A cohort of consecutively presenting acutely ill children was recruited from general practices in Wales (UK) between March 2008 and July 2010. The cohort was originally recruited to determine childhood UTI prevalence among unselected acutely ill children.<sup>30</sup> Following a pilot study of feasibility, practices in South Wales (all practices in the Cardiff and Vale area) were sent a letter inviting them to take part in the study.<sup>31</sup> Subsequently, recruitment was extended, and thirteen practices across Wales agreed to participate in the study. Children were eligible for recruitment if they were less than five years old and presented with an acute illness of less than 28 days duration. Children were excluded if they were currently receiving immunosuppressive treatment (chemotherapy or oral/intra-muscular steroids  $\geq 2$  weeks), long-term antibiotic treatment ( $> 28$  days), or had already participated in the study.

### *Data collection*

Demographic data and clinical data were recorded by a practice or research nurse. Townsend scores for the general practices were calculated as an estimate for deprivation.<sup>32 33</sup> Clinical data included presenting symptoms and previous medical history; and basic observations included temperature, pulse and respiratory rates. Symptoms were recorded by ticking a list provided on the case record form. Examination findings, working diagnosis, management and whether oral antibiotics were prescribed were recorded by the treating clinician. Parents and clinicians were both asked to give an overall impression of the child's illness severity on a 5 point scale from 0 (not unwell) to 4 (severely unwell).

### *Analysis*

Data were analysed using SPSS (version 18.0) and R (version 3.0.2). For symptoms, if the item was not ticked as 'present', it was assumed that it was not present and analysed together with those ticked as 'absent'. For examination findings and working diagnosis, missing information was analysed as 'not examined' and 'no diagnosis given' respectively. For the analysis, the clinicians' working diagnoses were further grouped: 'pneumonia', 'chest infection', 'bronchitis' 'bronchiolitis' and 'croup' were grouped with LRTI<sup>34</sup>; 'throat infection' and 'sore throat' were grouped with 'tonsillitis'; 'coryza' and 'cough' and were grouped with URTI; exacerbation of asthma was included in the 'other' category unless URTI or LRTI was also mentioned. For the parent/carer and clinician illness severity measures, scores of 2,3 and 4 (moderately, very or severely unwell) were

grouped together due to low numbers in these groups compared to normal/not unwell (score of 0) and slightly unwell (score of 1).

Tachycardia and tachypnoea were calculated using the heart rates, respiratory rates and ages of the children according to the categories given in the NICE guideline for febrile illness.<sup>35</sup>

Multilevel modelling was used to account for clustering at the level of the general practices. Multilevel logistic regression was carried out using R (version3.0.2). All clinical factors with a *p*-value<0.1 on crude (unadjusted) analyses were entered into a multivariable (adjusted) analysis, where missing data were <30%. Variables with missing data of  $\geq 30\%$  and variables with a low overall prevalence, of <10%, were excluded from the multilevel model, due to insufficient data. To estimate the amount of influence the clusters (13 practices) had on the overall variation in antibiotic prescribing, the intra-class correlation coefficient (ICC) was calculated using the  $\frac{\pi^2}{3}$  estimator.<sup>36</sup>

A sensitivity analysis was conducted to investigate the impact of missing data. Multiple imputation with chained equations was implemented producing five imputed datasets.<sup>37</sup> Each fixed effect variable in the final model was imputed using all other fixed effect variables. The final model was fitted to these five and the results pooled.

## Results

Thirteen practices in Wales (UK) took part in the study. Practices were represented in affluent and less affluent areas covering Townsend scores from all quintiles. Practice list size ranged from 2121 to 25251. Numbers of children recruited into the cohort from each practice ranged from 14 to 251. Overall, 1003 children were recruited. Four children were later excluded as date of birth was incomplete or incorrectly recorded, and their age could not be confirmed (figure 1). Therefore, 999 children were included in this study. Nine practices completed recruitment logs and identified 63 children who were eligible but who were not recruited. Reasons for non-recruitment included consent not given; parent/carer did not have time or the parent felt that the child was too ill to participate.

Of the 999 children included in this study, 498 (49.8%) were female and the median age was 1.9 years (interquartile range [IQR] =0.9 to 3.3). The median age of non-recruited children was 1.6 years (IQR = 1.0 to 3.1), and 34 (53.9%) were male. Respiratory tract infections were responsible

for 496 (49.6%) consultations. The most frequent diagnosis was URTI in 297 (29.7%) children (table 1). Oral antibiotics were prescribed in 261 (26.1%) children (table 1). Antibiotics were frequently prescribed for children with a working diagnosis of tonsillitis or sore throat (54/58, 93.1%), ear infections (42/51, 82.4%) and LRTI (63/90, 70.0%). LRTI was responsible for 63/261 (24.1%) of all antibiotic prescriptions, and RTIs more widely were responsible for 202 (77.4%) of all antibiotic prescriptions (table 1).

The mean age of children prescribed antibiotics was 2.52 years (s.d. 1.30) and the mean age of children not prescribed antibiotics was 1.99 (s.d. 1.42). Amoxicillin was the most commonly prescribed antibiotic, in 150 (57.5%) antibiotic prescriptions. Penicillin was prescribed in 38 (14.6%); erythromycin in 20 (7.7%); trimethoprim in 19 (7.3%); cefalexin in 11 (4.2%); co-amoxiclav in 10 (3.8%); flucloxacillin in 10 (3.8%); clarithromycin in 2(0.8%) and metronidazole in 1 (0.4%).

Although requested for all participants, examination recordings were incomplete for temperature (recorded in 757; 75.8%), pulse (recorded in 502; 50.3%) and respiratory rate (recorded in 454; 45.4%). Pulse and respiratory rate were analysed as binary variables: tachycardia (high pulse for age) or normal pulse rate for age and tachypnoea (high respiratory rate for age) or normal respiratory rate for age. Only 2.4% of children were classified as tachycardic. There was no association between tachycardia and antibiotic prescribing with 4/140 (2.9%) of those prescribed antibiotics classified as tachycardic, and 8/362 (2.2%) of those not prescribed antibiotics classified as tachycardic ( $p=0.75$ ). Tachypnoea was present in 13.9% of children. Among those prescribed antibiotics, 12/129 (9.3%) were classified as tachypnoeic and 51/325 (15.7%) of those not prescribed antibiotics were classified as tachypnoeic ( $p=0.08$ )

Parent/carer-rated illness severity scores were provided for 931 children (93.2%). Children were most frequently scored as 1 (slightly unwell) in 374 (40.2%). Clinician impression was completed for 946 children (94.7%). The majority, 519 (54.9%), were considered to be 'slightly unwell'. Antibiotics were prescribed in 103/198 (52.0%) children scored as 2,3 or 4 (moderately, very or severely unwell) by clinicians, in 136/519 (26.2%) scored as 1 (slightly unwell) and in 18/229 (7.9%) scored as 0 (normal/not unwell).

### ***Multilevel multivariable analysis***

The ICC for clustering by practice was 9.1%. This suggests that approximately 9.1% of the overall variation in prescribing outcomes is attributable to practices rather than patients.



Variables which were significant in the crude (unadjusted) analysis but excluded from the multivariable (adjusted) model due to a low overall prevalence (of <10%) were: muscle aches/pains, colic, haematuria, poor urine flow, past history of UTI, past history of hypertension, and same day hospital referral (table 2) Respiratory rate (tachypnoea) was excluded from the multivariable (adjusted) model due to missing data in 55% (respiratory rate recorded in only 454/999).

### *Multiple imputation*

There were missing values for three of the variables included in the final model: whether the child was categorised as not unwell, mildly unwell or moderately, very or severely unwell by the parent/carer (68 missing observations); whether the child was categorised as not unwell, mildly unwell or moderately, very or severely unwell by the clinician (53 missing observations); and temperature measured at the time of presentation (242 missing observations). Multiple imputation did not appreciably alter the conclusions drawn from the complete case analysis (results presented in table 3). The ICCs for the imputed models were lower than observed in the complete case analysis (mean ICC: 7.0%, range: [6.9%, 7.2%]).

The results for the multivariable (adjusted) logistic regression analysis on complete cases is shown in table 3 alongside the multivariable (adjusted) logistic regression analysis with multiple imputation. The results of the complete case analysis will be described throughout the rest of the results.

Children were more likely to be prescribed antibiotics if they were older. For each one year increase in age, the odds of being prescribed an antibiotic increased by 33% (OR: 1.33, 95% CI: 1.06-1.68). The only *symptom* found to increase the likelihood of an antibiotic prescription in the logistic regression model was poorer sleep, with those children twice as likely to receive antibiotics (OR: 2.74; 95% CI: 1.50-5.00). Difficulty breathing was found to reduce the likelihood of antibiotics in the model (OR: 0.42; 95% CI: 0.21-0.85). Antibiotics were more likely to be prescribed if there were abnormal findings on ear (eardrum or ear canal red or inflamed; or discharge or blood seen; OR:6.53; 95% CI: 2.47-17.27), throat (red/inflamed or swollen tonsils or discharge/pus; OR: 2.19; 95% CI 1.07-4.50) or chest examination (wheeze or crackles or use of accessory muscles or recession; OR: 13.64; 95% CI: 5.78-32.17).

When GP working diagnosis was considered, URTI was the most prevalent diagnosis and was used as the reference category for comparison with other working diagnoses. Antibiotics were more likely to be prescribed when GPs gave a working diagnosis of LRTI (OR: 9.55; 95% CI: 3.71-25.54), tonsillitis/sore throat (OR: 119.27; 95% CI: 28.22-504.12), ear infection (OR: 26.56; 95% CI: 7.36-95.85) or UTI (OR: 12.75; 95% CI: 4.44-36.58). Children categorised as moderately, very or severely unwell by the clinician, were more likely to be prescribed antibiotics (OR: 4.01; 95% CI: 1.14-11.42) compared with children reported as normal/not unwell.

We calculated the area under the receiver operating characteristic curve (AUROC) to be 0.937 (figure 2). This suggests that the predictive strength of our model is excellent.

We performed further crude (unadjusted) analyses to explore the association between diagnosis and examination findings. Table 4 shows the association between GP diagnosis and examination findings for tonsillitis/sore throat, ear infection and LRTI. A diagnosis of tonsillitis/throat infection/sore throat was never given if the throat examination was normal or not examined. However, an abnormal throat examination did not necessarily lead to a diagnosis of tonsillitis/throat infection/sore throat, with 144 (71.3%) of those with abnormal throat examination not being given a diagnosis of tonsillitis/throat infection/sore throat. A similar picture was seen with ear infections, with only 2 (0.2%) children diagnosed with an ear infection in the context of a normal ear examination and 57 (53.8%) not diagnosed with ear infection despite abnormal examination findings. LRTI was diagnosed despite no abnormal chest findings in 17 (1.9%) and 50 (40.7%) of those with abnormal chest examination were not diagnosed with LRTI.

## **Discussion**

### *Summary*

This was a prospective cohort study of 999 consecutively recruited children less than five years old, presenting to general practices in Wales with an unselected acute illness. Half of all children were diagnosed with some form of RTI, and RTIs were responsible for 77.4% of antibiotic prescriptions. Oral antibiotics were prescribed for 261(26.1%) children. The strongest predictors of antibiotic prescribing were a clinician diagnosis of tonsillitis/sore throat, ear infection, LRTI or UTI and abnormal findings on chest, ear or throat examinations. Poor sleep, increasing age, and clinician impression that the child was moderately-severely unwell also increased the likelihood of children being prescribed antibiotics. Neither fever nor parental impression of illness severity was predictive of antibiotic prescribing in the multivariable model. For tonsillitis/sore throat and ear infections, the clinician's diagnosis was a more important predictor of antibiotic prescribing than abnormal

findings on examination. Diagnoses of tonsillitis/sore throat, ear infection or chest infection were rarely made if the examination findings were normal. However, abnormal examination findings did not necessarily result in the associated specific diagnoses.

### *Strengths and limitations*

This study reports recent consultation and antibiotic prescribing for different illnesses in young children in UK general practice. In contrast to routinely collected data, the prospective design of this study allowed us to explore the relative importance of symptoms, signs and clinician diagnosis in predicting antibiotic prescribing. Multi-level modelling corrected for the two-level sampling process (practices and patients). Multiple imputation was used to assess the impact of missing data. This sensitivity analysis was only very slightly different from the complete case analysis. The AUROC suggested that the multilevel logistic regression model was an excellent fit.

Not all eligible children who consulted were recruited into the study. Recruitment logs demonstrated that recruited children were older than those not recruited. A working diagnosis of UTI, and antibiotic prescribing for suspected UTI, may have been artificially high in this study as the cohort was originally recruited to determine the prevalence of UTI. Participating GPs were aware of this, which may have altered their level of UTI suspicion or prescribing for these children. Some data were incomplete (for example respiratory rate) which may have introduced bias if they were more or less often measured in children with more severe illness or in those who were prescribed antibiotics. Pulse and respiratory rate were only recorded in about half of all children despite this being specifically requested for the study. Recording of vital signs in routine clinical practice is likely to be even lower than this. The confidence intervals were wide for some of the variables in the model, for example tonsillitis under GP diagnosis. This is driven by the small numbers of children with this diagnosis who were not prescribed antibiotics (Table 1). Participants' postcodes were not collected, so Townsend (deprivation) scores were based on GP practice postcodes. Although we corrected for two-level sampling using a multilevel regression model, we did not have the data to explore variation by individual clinician/prescriber.

### *Comparison with other literature*

Respiratory tract infections were diagnosed in 49.6% of consultations for acute illness. Comparisons with other literature are difficult due to differences in definitions of RTI; use of routinely collected data and of different populations being studied. Many prospective studies have only included children with RTIs, therefore the frequency of these conditions cannot be calculated. A UK primary care study of children less than 14 years old found that 302/407 (74%) children with

a febrile illness were recorded as having RTI.<sup>38</sup> This is higher than in our study but excluded children without fever. Another reason for the difference may be because we did not include ‘viral illness’ in our definition of RTI. It is likely that most ‘viral illness’ episodes could also have been categorised as RTIs. If we included these, the proportion of consultations due to RTIs would be 641/999 (64.2%). A study of 284 children (< 14 years) in Italy found that RTIs were diagnosed in 69.6% of consultations if flu-like illnesses were included.<sup>39</sup>

Overall, 26.1% of children in our study received antibiotics. This is similar to an Italian study of 284 children where 25% were prescribed antibiotics.<sup>39</sup> A Dutch study of febrile children (<6 yrs) in out-of-hours primary care found that only 12% received antibiotics.<sup>16</sup> A US study found that antibiotic prescribing varied from 18% to 36% in paediatric acute visits.<sup>40</sup> Most of the studies discussed above present data collected prior to the data collection in our study (2010).<sup>16 38 40</sup> One study presents more recent data from 2011-2012, which found a similar level of antibiotic prescribing among children as we did in our study.<sup>39</sup>

Children with abnormal ear, throat and chest examination findings had an increased likelihood of receiving an antibiotic. However, a clinician diagnosis of sore throat/tonsillitis or ear infection predicted antibiotic prescribing to a greater extent than recorded examination findings. Antibiotics were prescribed for 93.1% of the children diagnosed with tonsillitis/sore throat, 82.4% with ear infection and 70.0% with LRTI. Not all children with abnormal throat or ear examinations were diagnosed with tonsillitis/sore throat or ear infection respectively. This suggests that clinicians are assessing features other than these specific examination findings when making their diagnosis. We found that if there were abnormal ear examination findings and the clinician made a diagnosis of ear infection, antibiotics were less likely to be prescribed if the child was complaining of earache. This may be due to the clinician assessing other features, perhaps more likely to prescribe antibiotics to a child with systemic signs of illness rather than local signs of ear infection. The high level of association between antibiotic prescribing and clinician diagnosis may indicate that clinicians only use certain diagnostic labels if they are planning to prescribe antibiotics. For example a child with a sore throat may be labelled as having tonsillitis if an antibiotic is felt to be necessary, but as an URTI if an antibiotic is not felt to be necessary. Other studies have found an association between diagnostic labels and antibiotic prescribing.<sup>5 41 42</sup>

#### *Implications for practice*

There are still high levels of antibiotic prescribing for RTIs in children. Antibiotic prescribing was most strongly predicted by the specific diagnostic labels of ear infection and tonsillitis/sore throat.

LRTI and UTI were also strong predictors of antibiotic prescribing. In some ill children, antibiotics are warranted. Further research and education is still needed to help clinicians identify those children who need antibiotics and those children in whom antibiotic prescribing can be safely reduced. Our study suggests that targeting tonsillitis/sore throat and ear infections may be a good approach. A change in emphasis away from a diagnosis-led approach (where specific diagnoses have traditionally been associated with needing antibiotics) may be helpful, perhaps towards clinical scoring systems or delayed prescribing approaches. Although prescribing for URTI was low (14.5%), antibiotics for this diagnosis represented 17% of all antibiotic prescriptions, suggesting that further improvements could also still be made in this common condition.

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### *Ethical approval*

Ethical approval for the study was obtained from the South East Wales Local Research Ethics committee (ref no. 08/WSE03/11). Informed, written consent was obtained from all participants.

### *Competing interests*

None.

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