Gijs Elshout, Yvette van Ierland, Arthur M Bohnen, Marcel de Wilde, Rianne Oostenbrink, Henriëtte A Moll and Marjolein Y Berger

Alarm signs and antibiotic prescription in febrile children in primary care:

an observational cohort study

Abstract

Background
Although fever in children is often self-limiting, antibiotics are frequently prescribed for febrile illnesses. GPs may consider treating serious infections by prescribing antibiotics.

Aim
To examine whether alarm signs and/or symptoms for serious infections are related to antibiotic prescription in febrile children in primary care.

Design and setting
Observational cohort study involving five GP out-of-hours services.

Method
Clinical information was registered and manually recoded. Children (<16 years) with fever having a face-to-face contact with a GP were included. Children who were already using antibiotics or referred to secondary care were excluded. The relation between alarm signs and/or symptoms for serious infections and antibiotic prescription was tested using multivariate logistic regression.

Results
Of the 8676 included patients (median age 2.4 years), antibiotics were prescribed in 3167 contacts (36.5%). Patient characteristics and alarm signs and/or symptoms positively related to antibiotic prescription were: increasing age (odds ratio [OR] = 1.03; 95% confidence interval [95% CI] = 1.02 to 1.05), temperature measured by GP (OR = 1.72; 95% CI = 1.59 to 1.86), ill appearance (OR = 3.93; 95% CI = 2.85 to 5.42), being inconsolable (OR = 2.27; 95% CI = 1.58 to 3.22), shortness of breath (OR = 2.58; 95% CI = 1.88 to 3.56), duration of fever (OR = 1.31; 95% CI = 1.26 to 1.35). Negative associations were found for neurological signs (OR = 0.45; 95% CI = 0.27 to 0.76), signs of urinary tract infection (OR = 0.63; 95% CI = 0.49 to 0.82), and vomiting and diarrhoea (OR = 0.65; 95% CI = 0.57 to 0.74). These variables explained 19% of the antibiotic prescriptions.

Conclusion
Antibiotics are often prescribed for febrile children. These data suggest that treatment of a supposed serious bacterial infection is a consideration of GPs. However, the relatively low explained variation indicates that other considerations are also involved.

Keywords
antibacterial agents; child; child, preschool; family practice; fever; infant; signs and symptoms; primary health care.

INTRODUCTION

GPs are frequently consulted for fever in children.[1] Fortunately, since most febrile illnesses are self-limiting, medical intervention is seldom necessary. However, identifying those children with a serious infection (for example, meningitis, sepsis, pneumonia, urinary tract infection [UTI]) is important, since early treatment of such diseases may prevent further complications. Several signs and symptoms are reported to have a predictive value for serious infections in febrile children.[2,3] However, because most studies on this topic were performed in secondary care, the predictive value of these alarm signs and/or symptoms in primary care still needs to be determined.[3] Therefore, management of febrile children in primary care remains a challenge. With respect to medical decision-making, children who are clearly ill (for example, with evident meningeal irritation and associated serious risk for infection) are generally immediately referred by the GP to secondary care. More challenging are children who have an alarm sign or symptom, but do not appear to be seriously ill at the time of consultation. In these patients, the GP is uncertain about the presence of a serious infection and management is less straightforward. It is of interest how GPs cope with these patients. A previous study showed that antibiotics are frequently prescribed in febrile children, but that these prescriptions are not sufficiently explained by the signs and/or symptoms of these children.[4]

Therefore, the present study explores GPs' prescription behaviour for febrile children, with the aim to help diminish unnecessary antibiotic prescriptions in the future. For this, the study assesses whether well-defined alarm signs and symptoms[2,5,6] are related to antibiotic prescription in febrile children presenting at GP cooperatives' out-of-hours services.

METHOD

Study design

This cohort study used data of face-to-face patient contacts (physical consultations and home visits) of children aged ≤16 years that took place at GP cooperative out-of-hours services of Rotterdam-Rijnmond between March 2008 and February 2009 (*n* = 28 234). This district has five GP cooperatives (totalling ≥250 GP practices) providing out-of-hours care for almost 1 million inhabitants living in this urban, multi-ethnic area. All five GP cooperatives

G Elshout, MD, MSc, GP trainee and PhD student; **AM Bohnen**, MD, PhD, GP and senior researcher, Department of General Practice, Erasmus MC, Rotterdam, the Netherlands; **Y van Ierland**, MD, MSc, PhD student; **R Oostenbrink**, MD, PhD, paediatrician and senior researcher; **HA Moll**, MD, PhD, paediatrician and professor in general paediatrics, Department of General Paediatrics, Erasmus MC — Sophia Children's Hospital, Rotterdam, the Netherlands. **M de Wilde**, BSc, scientific programmer, Department of Medical Informatics, Erasmus MC, Rotterdam, the Netherlands. **MY Berger**, MD, PhD, GP and professor of general practice, Department of General Practice, Erasmus MC, Rotterdam and Department of General Practice, University Groningen, University Medical Center Groningen, the Netherlands.

Address for correspondence
Marjolein Berger, University Groningen, University Medical Center Groningen, Department of General Practice, PO Box 196, 9700 AD Groningen, the Netherlands.
E-mail: m.y.berger@umcg.nl

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How this fits in

Although fever in children is often self-limiting, antibiotics are still frequently prescribed. Medical considerations for prescribing antibiotics are treatment of serious infections, or to reduce the duration of the illness. It is shown that alarm signs and symptoms explain only a small part of frequent antibiotic prescription. Therefore, considerations that are not medically based may play a considerable role in the GP's decision to prescribe antibiotics.

used the same information system ('Call Manager', Labelsoft, Zoetermeer, the Netherlands) to register patient data. In this system, information from telephone triage, patient history, physical examination, diagnostic intervention, (working) diagnosis, and treatment or referral is documented (by GPs and physician assistants) as written text lines in a semi-structured data sheet.

Out-of-hours healthcare system

In the Netherlands, and also in the UK, Scandinavia, and Australia, out-of-hours primary care (5 pm to 8 am daily and the entire weekend) is organised in large-scale cooperatives.[7–11] In the Netherlands, GPs rotate shifts at the GP cooperatives to cover the out-of-hours primary care. Referral to secondary care is required for about 5–10% of all primary care consultations,[7,12] which is similar to the referral rates in the UK, US, and Canada.[13,14]

Study population

Children aged ≤16 years with: (1) fever reported as the reason for contact; (2) fever within 24 hours prior to contact; or (3) a temperature ≥38°C measured at the GP cooperative were eligible for inclusion. Children could contribute more than one contact to the total of patient contacts if that contact was not related to the same illness episode, that is, it occurred more than 7 days after the initial contact. Exclusion criteria were: referral to secondary care, telephone consultations (in the Netherlands antibiotics are never prescribed by telephone), patients consulting the GP cooperative and already using antibiotics, and repeated contacts within 7 days of the initial presentation concerning the same febrile illness.

Extraction of relevant clinical signs

Signs and symptoms that are indicative of a potential serious infection ('red flags') were derived from one systematic review,[2] and two published guidelines on management of febrile children.[5,6] The study included signs that: (1) had a high predictive value (positive likelihood ratio >5.0 or negative likelihood ratio <0.2); (2) were mentioned in at least two of the three data sources; (3) did not represent a diagnosis; and (4) were not prone to high interobserver variability (for example, auscultatory sounds).[15] Selected, closely related signs were grouped into a total of 18 alarm signs of serious febrile illness (Appendix 1). Using a data-entry computer program (Embarcadero Delphi XE, Version 15.0), all eligible contacts were recoded according to whether the grouped alarm signs were 'present', 'absent', or 'not mentioned' in the patient record. In addition, 'referral to secondary care', or 'antibiotic prescription' by the GP was recoded as 'yes' or 'no'.

Missing data

Since the alarm signs and/or symptoms were obtained from routinely collected, semi-structured data, missing values occurred for each variable (that is, not mentioned in the record). Therefore, a consensus meeting was held, with one GP, two paediatricians, one GP trainee, and one trainee paediatrician, to discuss this. Based on the prevalence of serious illnesses in the primary care setting, clinical experience, and common knowledge, for the purpose of this study missing values were handled in two ways: (1) the sign or symptom was believed to be so relevant that, if present, the physician would document it. Consequently, all missing values were interpreted as being absent (ill appearance, ABC [airways, breathing, circulation] instability, unconsciousness, drowsiness, being inconsolable, cyanosis, shortness of breath, meningeal irritation, neurological signs; that is, typical and atypical febrile convulsions, focal neurological signs, vomiting and diarrhoea, dehydration, petechial rash, extremity problems); (2) for the remaining signs and symptoms (parental concern, abnormal circulation, signs of UTI, temperature ≥40°C, and duration of fever), it was decided that the above statements were not applicable. For these variables, multiple imputation was performed if missing data were <70%.[16] Signs and symptoms with ≥70% missing data were excluded from the analyses.

Statistical analyses

In the original dataset, patient characteristics and frequency of antibiotic prescription were analysed using descriptive

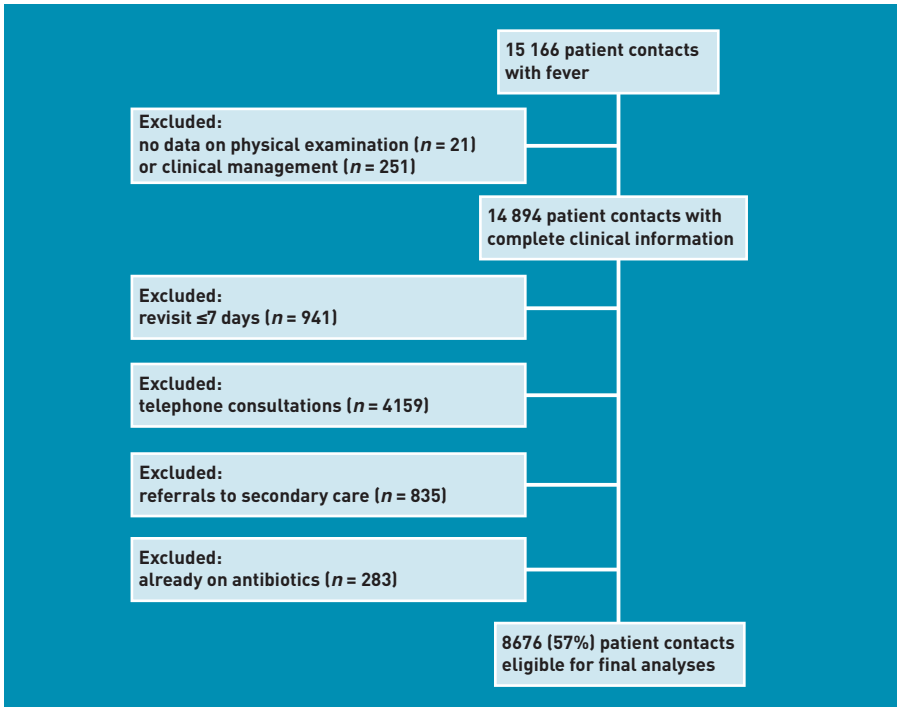


Figure 1 Selection of eligible patient contacts.

statistics. Missing data were imputed using MICE in R-2.11.1 for Windows. Backward stepwise logistic regression of variables was performed manually, using Akaike information criterion of $P>0.157$ for dropping variables.[17] If multicollinearity was present, the variable under investigation that least contributed to the model was dropped. The proportion of variability in the dataset that is accounted for by the final statistical model was determined using Nagelkerke R^2. Data were analysed using PASW (version 17.0.2 for Windows).

RESULTS

Description of the population

A total of 15 166 patient contacts at the five GP cooperatives concerned fever. Of 272 patient contacts, no data on physical examination or clinical management were available, and these were subsequently excluded. After applying the exclusion criteria, 8676 patient contacts were available for the present analysis (Figure 1). In total, 3167 of the contacts (36.5%) were prescribed antibiotics at the GP cooperative. Additional baseline characteristics of these patients are presented in Table 1. Figure 2 shows the distribution of antibiotic prescription by age, rectal temperature, and duration of fever.

Multivariate logistic regression

Table 2 presents the alarm signs and/or symptoms that were tested for their independent association with antibiotic prescription. Patient characteristics, and alarm signs and/or symptoms positively related to antibiotic prescription were: increasing age (years), temperature measured by the GP, ill appearance, being inconsolable, shortness of breath, and duration of fever (Table 3). A significant negative association was found for neurological signs, signs of UTI, and vomiting and diarrhoea. The median Nagelkerke R^2 of this final multivariate model was 0.19 (range = 0.18 to 0.20).

Table 1. Characteristics of the study population (*n* = 8676)

Characteristics	
Age in years, median (IQR)	2.4 (1.1 to 4.7)
Male sex, *n* (%)	4601 (53)
Rectal temperature in °C, median (IQR)	38.4 (37.7 to 39.1)
Antibiotic prescription, *n* (%)	3167 (36.5)
Duration of fever in days (*n* = 6933), median (IQR)	2.0 (0 to 3)

IQR = interquartile range.

DISCUSSION

Summary

This large study, evaluating 8676 face-to-face contacts of febrile children presenting at five GP cooperatives, shows that antibiotics were prescribed in 36.5% of the patient contacts. Multivariate analysis revealed that several alarm signs and/or symptoms were significantly related to antibiotic prescription, suggesting that treating a potentially serious bacterial infection is a consideration of the GP. However, the relatively low explained variation (R^2 = 0.19) shows that other considerations, not included in the analysis, also made a substantial contribution.

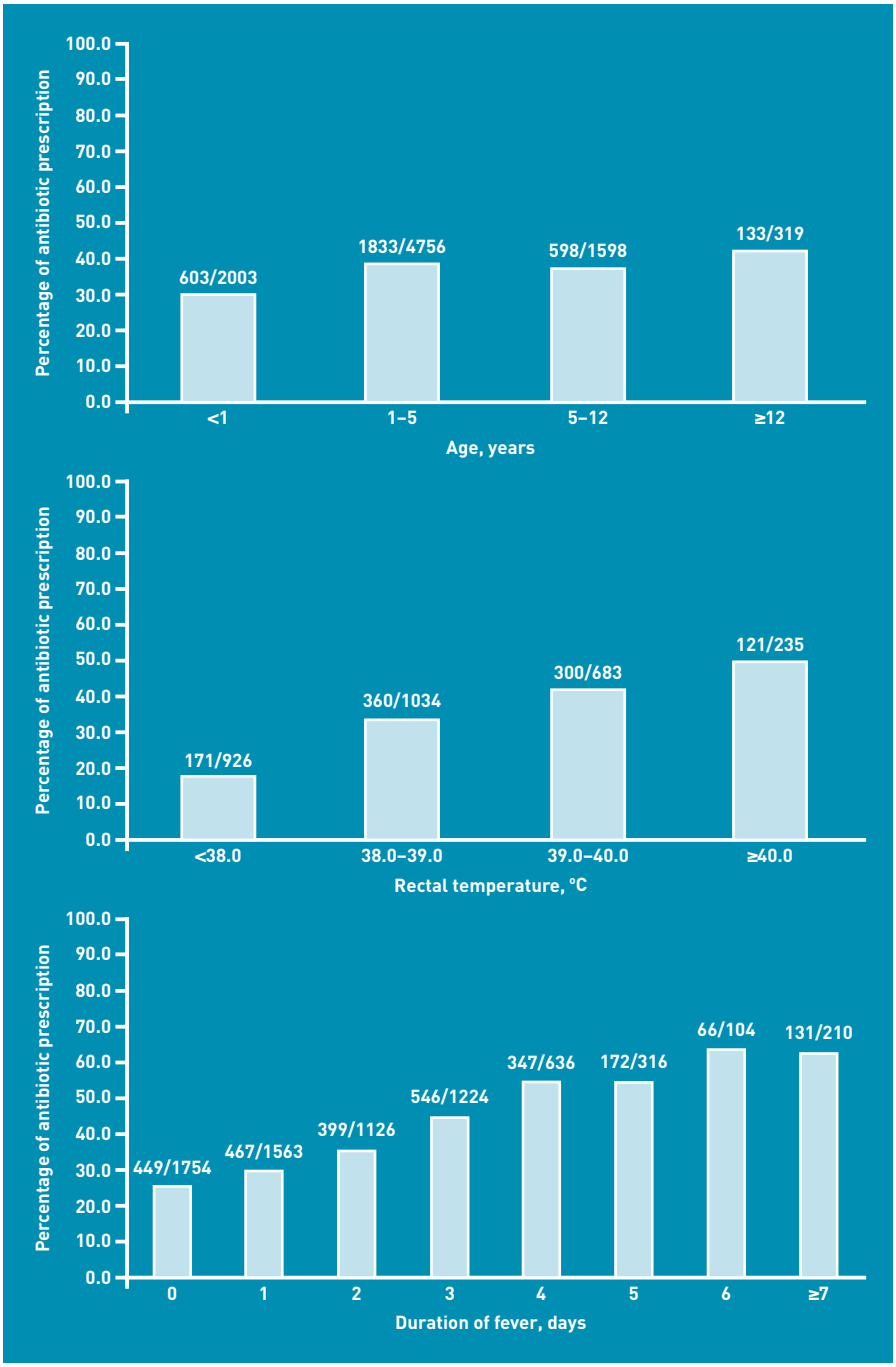
Strengths and limitations

A major strength of the study is the large number of patient records. This minimises the probability that the results are based on chance, and lack of power plays no role in the non-significant related variables.

The study did not look for any relation between (working) diagnosis and antibiotic prescription. This is based on the fact that GPs make diagnostic transfers to diagnoses that justify their antibiotic prescription.[18] Therefore, these diagnoses are ultimately related to the signs and/or symptoms of the presenting febrile child. Therefore, investigating the relation between alarm signs and/or symptoms and antibiotic prescription seems more appropriate.

The GPs did not record the signs and symptoms in a fully structured way. Therefore, when a characteristic was not recorded, it is possible that the variable was absent and that the GP did not write it down, or that the GP did not look for that particular sign or symptom. This problem was discussed in a consensus meeting including specialists in family medicine and paediatrics. It seems legitimate to consider some signs (for example, unconsciousness) as being absent when the GP did not report this, since if that sign had been present the GP would always notice and record

Figure 2. Distribution of percentage antibiotic prescription by age group, rectal temperature, and duration of fever.



it. This is especially so since the Dutch guideline specifically advises to look for the various alarm signs and/or symptoms when assessing a febrile child.[5]

Comparison with existing literature

In the present study, the amount of prescribed antibiotics (36.5%) is similar to the 36.3% prescribed in a previous study.[4] Although this latter study was performed in younger children, overall it is similar to the present one with regard to the setting, study population, and clinical guidelines used. When selecting the same age category in the present study, 35.0% of children aged 3 months to 6 years were prescribed antibiotics, that is, a rate very similar to the earlier report.

Surprisingly, increasing age was significantly related to antibiotic prescription. This was unexpected since younger children are more at risk of a serious infection, and therefore more cautious management (that is, more antibiotic prescriptions) could be expected. However, since febrile illnesses in young

Table 2. Alarm signs and symptoms and prescribed antibiotics

Signs and symptoms included in the analysis	Percentage of antibiotic prescription (*n*)[a]		
	Sign present	Sign absent	Missing, %
Temperature (at GPC)	NA	NA	66.8
Abnormal circulation	31.8 (27/85)	31.0(657/2121)	25.4
Signs of urinary tract infection	24.6 (99/403)	36.0 (1112/3093)	40.3
Parental concern[b]	27.8 (416/1497)	25.0 (1/4)	82.7
Temperature ≥40°C[b]	40.1 (878/2190)	35.2 (1889/5371)	87.1
Duration of fever	NA	NA	21.1
Ill appearance	76.3 (203/266)	35.2 (2964/8410)	
Being inconsolable	54.1 (119/202)	36.0 (3048/8474)	
Cyanosis	66.7 (14/21)	36.4 (3153/8655)	
Shortness of breath	57.6 (144/250)	35.9 (3023/8426)	
Meningeal irritation	50.0 (3/6)	36.5 (3164/8670)	
Neurological signs	20.4 (21/103)	36.7 (3146/8573)	
Vomiting and diarrhoea	29.4 (517/1760)	38.3 (2650/6916)	
Dehydration	29.4 (5/17)	36.5 (3162/8659)	
Extremity problems	37.5 (3/8)	36.5 (3164/8668)	
Petechial rash	36.8 (7/19)	36.5 (3160/8657)	
Drowsiness[c]	0.0 (0/3)	36.5 (3167/8676)	
ABC instability[c]	NA	36.5 (3167/8676)	
Unconsciousness[c]	NA	36.5 (3167/8676)	

[a]Number of patients with antibiotics/total number of patients per group. [b]Not included in the analyses, owing to missing values >70%. [c]Not included in the analyses, owing to no events (positive alarm signs/symptoms and positive antibiotic prescription). ABC = airways, breathing, circulation. GPC = GP cooperative. NA = not applicable.

Table 3. Final multivariate analysis of alarm signs and symptoms that were significantly related to antibiotic prescription

Variables	OR (95% CI)
Age, years	1.03 (1.02 to 1.05)
Temperature (measured by the GP in °C)	1.72 (1.59 to 1.86)
Ill appearance	3.93 (2.85 to 5.42)
Being inconsolable	2.27 (1.58 to 3.22)
Shortness of breath	2.58 (1.88 to 3.56)
Neurological signs[a]	0.45 (0.27 to 0.76)
Vomiting and diarrhoea[a]	0.65 (0.57 to 0.74)
Signs of urinary tract infection[a]	0.63 (0.49 to 0.82)
Duration of fever, days	1.31 (1.26 to 1.35

[a]These variables showed a negative association with prescription of antibiotics. OR = odds ratio.

children can deteriorate quickly, the GP may take even more precautions than simply prescribing antibiotics. For example, in this earlier study,[4] children referred to secondary care were significantly younger than those included in the analyses: median age 1.6 years (interquartile range [IQR] = 0.6 to 3.6 versus 2.4 years, IQR = 1.1 to 4.7) (Mann–Whitney U test <0.01). Perhaps the consideration of prescription of antibiotics is less important in younger children than the consideration of whether or not to immediately refer them to secondary care. A similar explanation may apply to the negative associations found between antibiotic prescription and neurological signs and vomiting and/or diarrhoea. Children with these signs are also more often referred to secondary care (data not shown). Another explanation for the findings related to children with vomiting and/or diarrhoea is that it is not reasonable to administer antibiotics in children with these alarm signs, since the risk of bacterial infection is considered to be low.[19]

Compared with other European countries, GPs in the Netherlands have one of the lowest overall rates of antibiotic prescription.[20,21] Nevertheless, in the present study more than one out of three children were prescribed antibiotics. Although other studies also reported antibiotic prescription rates, they were performed in different study populations (for example, only children with acute otitis media, not solely febrile children),[21–24] making comparison with the present results difficult.

The GP cooperative out-of-hours setting was chosen because a high number of consultations concerning fever was expected. One in five consultations at a GP cooperative out-of-hours service concerns children (aged 3 months to 5 years), and in almost half of these children, fever is the reason for encounter (unpublished data). Patient characteristics like sociodemographic status are expected to be similar to those of children seen during regular hours, since the region for the out-of-hours care, and the regular hours care is the same. However, at the GP cooperative, triage is performed to select the children that need immediate assessment, and those that can wait until regular hours. Therefore, the children in the present study might be more seriously ill compared with those seen during regular hours and, therefore, may have had more alarm signs and/or symptoms and have been more eligible for antibiotic treatment. However, if this was the case, the explained variation in antibiotic prescription should be even higher, since alarm signs and/or symptoms are thought to be indicative of the severity of disease.

Furthermore, in the Netherlands, GPs are not familiar with the patients assessed at the out-of-hours service, and follow-up of these patients is performed by another physician. This may make it more difficult to provide adequate safety netting. Ultimately, this may lead to more defensive management and to more antibiotic prescription.

The present study shows that only a small proportion of the antibiotic prescriptions is explained by the related alarm signs and symptoms. This is not surprising, since other clinical features may also contribute to considering whether to prescribe antibiotics (for example, otorrhoea, bulging tympanic membrane).[25–28] Unfortunately, information on these clinical features was not available in this study, and could therefore not be included in the analyses. The explained variation of antibiotic prescriptions might have been higher, if these variables could have been added. This assumption was confirmed by the

previous study in a similar setting, in which it was shown that variables like signs of throat infection or earache are also related to antibiotic prescription.[4] In that study, multivariate analysis explained 26% of the proportion of variation. Hypothetically, in the most positive perspective, 45% of the variation in antibiotic prescription is explained by the two studies; however, this is not actually the case, since there is some overlap in the signs and symptoms (for example, ill appearance). This indicates that in ≥55% of the prescribed antibiotics, other (unknown) factors contribute to the GP's decision to prescribe antibiotics. Earlier studies found that non-medically based considerations may also contribute to the GP's decision to prescribe antibiotics, for example, assuming that the patient or the parents expect antibiotics.[29–31] However, these assumptions are not always valid,[32–34] and GPs may need to reconsider their management of febrile children.

Bacterial resistance to antibiotics is a growing problem.[20] Since overuse of antibiotics contributes to this problem, prevention of unnecessary prescription is important.[20,35] Since ≥50% of the prescribed antibiotics do not appear to be based on medical considerations, strategies to diminish antibiotic prescription should focus on this aspect. Cals *et al* reported that point-of-care testing of C-reactive protein (CRP) and training in communication skills significantly reduced antibiotic prescribing for lower respiratory tract infection, without compromising patients' recovery and satisfaction with care.[36] However, the role of CRP in febrile children in primary care needs further elucidation.[37] It may be useful to investigate whether a negative CRP can reassure both patients and GPs in the decision-making process, and thereby diminish antibiotic prescription.

In the present study, ill appearance, being inconsolable, shortness of breath, increasing temperature, and longer duration of fever were significantly and positively related to antibiotic prescription. All of these signs and/or symptoms are suggested to be related to serious infections, mostly in secondary care settings.[2] Prescribing antibiotics in these children suggests that GPs may be concerned about the (future) course of the febrile disease, and therefore want to treat or prevent potential complications of a serious bacterial infection. However, although oral antibiotics are helpful in some serious bacterial infections like pneumonia, UTI, or acute tonsillitis (prevention of peritonsillar abscess),[27–28,38,39] they are not useful in the initial treatment of rare serious bacterial infections like meningitis or sepsis. In addition, antibiotics frequently cause side effects. Therefore, the disadvantages of antibiotics should be weighed against their limited benefits in treating and preventing serious bacterial infections.

Signs of UTI were significantly related to less antibiotic prescription; this is surprising because a UTI is a clear indication for antibiotics.[39] However, this result can be explained by the fact that this variable is composed of several signs, including pollakiuria, dysuria, and abdominal pain without diarrhoea or other focus of the fever (Appendix 1). This may explain the lack of a significant relation between signs of UTI and antibiotic prescription. Another, more disturbing, explanation may be that GPs do not endorse the signs and/or symptoms of a possible UTI. Recognition and treatment of UTIs in children is important since they can cause transient or permanent kidney damage.[40,41]

Implications for research and practice

In conclusion, the present study revealed a substantial amount of antibiotic prescriptions in febrile children who presented to the five GP cooperative out-of-hours services. Only a small proportion of antibiotic prescribing is explained by alarm signs and/or symptoms; this implies that other, non-medically based considerations may also play a role in the GP's decision to prescribe antibiotics. Future research should focus on the unexplained antibiotic prescriptions, and the value of CRP when assessing febrile children in primary care.[37] This can then be used to provide more adequate management (for example, more efficient safety netting, and fewer prescribed antibiotics) of febrile children in primary care.

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Ethical approval

This study was reviewed by the institution's medical ethics committee (Medisch Ethische Toetsings Commissie Erasmus MC) and the requirement for informed consent was waived (MEC-2012-378).

Provenance

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Competing interests

The authors have declared no competing interests.

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Appendix 1. Grouping alarm signs into composed determinants of serious infection

Composed alarm signs and symptoms	Total selection of alarm signs and symptoms
Parental concern	Parental concern
Ill appearance	Clinician's instinct something is wrong Clinically ill appearance
ABC-instability	ABCD-instability
Unconsciousness	Unconsciousness
Drowsiness	Child is drowsy Somnolence Reactivity/functional status (decreased) Hypotonia
Inconsolable	Child is inconsolable Irritability Changed crying pattern Child is moaning
Abnormal circulation	Abnormal skin colour (pale, mottled, ashen) Capillary refill time >2 seconds Tachycardia
Cyanosis	Cyanosis Oxygen saturation <95%
Shortness of breath	Shortness of breath Nasal flaring Rapid breathing Changed breathing pattern
Meningeal irritation	Meningeal irritation Neck stiffness Bulging fontanelle
Neurological signs	Focal neurological signs Paresis/paralysis Seizures/fits
Vomiting and diarrhoea	Vomiting (>2× in disease period) Diarrhoea (>2× in disease period)
Dehydration	Dry mucous membranes Sunken eyes Decreased skin elasticity Reduced urine output Hypotension (APLs) Poor feeding
Extremity problems	Swelling of limb or joint Non-weight-bearing limb Not using an extremity
Signs of urinary tract infection	Pollakiuri Dysuria Abdominal pain (without other focus for fever)
Petechial rash	Petechial rash Purpura
Temperature ≥40°C	Measured at home or at a GPs' cooperative out-of-hours service
Duration of fever	Duration of fever in days at time of consultation