# Febrile Children in Primary Care

Gijs Elshout

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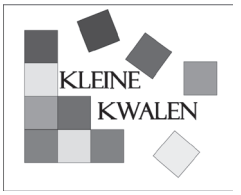



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# Febrile Children in Primary Care

## Kinderen met koorts in de eerste lijn

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ter verkrijging van de graad van doctor aan de
Erasmus Universiteit Rotterdam
op gezag van de
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ik tast in het donker
kloppen je slapen –

Ron Elshout, ‘Slaapliedje’,
uit: *Nomade nabij oase*, Breda, 2001

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# Chapter 1

# General introduction

## WHAT IS FEVER?

The definition of fever varies but, generally, a body temperature of 38.0°C or above is used in both clinical practice and research.[1-3] Fever is a physiological reaction to (in most cases) an infectious pathogen. Body temperature is regulated by the hypothalamus and keeps the core temperature normally within 1°C to 1.5°C in a range of 37°C to 38°C.[4] In case of an infection, macrophages and endothelial cells release endogenous pyrogenes that increase the set point of the thermoregulation. Consequently, neurons are activated in the vasomotor center, which leads to vasoconstriction. The blood flow is shunted to the internal organs to retain heat, leading to a decreased temperature of the skin; the patient feels cold. This can lead to shivering and behavioral instincts (e.g. putting on extra clothes), which help to increase body temperature.[5] At the end of a febrile episode, by a decrease in the concentration of pyrogenes, warmth is released by vasodilatation and sweating: the patient feels warm and starts sweating. Several mechanisms ensure that body temperature is – at maximum – 42°C. It is thought that fever may support the host defense by weakening the viability of some pathogens, and by supporting the immune mechanism and recovery of cellular components.[6] However, these potential benefits are not yet clearly established.[5]

The pattern of fever may vary depending on the age of the child.[4] Neonates may not develop fever or may become hypothermic despite a serious infection, while older infants (up to age 5 years) may have a high fever due to both serious or benign infections. An exaggerated febrile response is less common in older children and adolescents.

Overall, fever can be regarded as part of a normal physiological reaction against infectious pathogens, in adults as well as in children.

## SHOULD GPs CARE ABOUT FEBRILE CHILDREN?

Fever in children is a frequent reason to contact a general practitioner (GP).[7] The incidence of fever as a reason for consultation is 430 per 1000 children per year in the age 0 to 4 years.[2] During out-of-hours primary care, fever is present in more than half of the patient contacts concerning children (< 16 years of age) (unpublished data). Also, fever is the most presented symptom during out-of-hours primary care.[8] Fortunately, most febrile illnesses are caused by relatively harmless infections.[9, 10] The introduction of vaccinations against *Haemophilus influenza* type B, *Neisseria meningitides* type C, and *Streptococcus pneumoniae,* has lowered the incidence of serious infections that need medical treatment.[11-13] However, as a consequence, GPs' experience with severely ill children is diminishing, possibly making it more difficult to recognize rare but serious

infections.[14] Serious infections like meningitis, sepsis, pneumonia and urinary tract infections, have a potential risk of significant morbidity and mortality.[15] Therefore, it is important that GPs are able to adequately differentiate between children with fever who will recover spontaneously and without complications, and those who have an increased risk for a serious infection.

## HOW DO GPs ASSESS A FEBRILE CHILD?

When assessing a febrile child, GPs try to distinguish between children that will recover spontaneously and those that need medical intervention. As part of this assessment, GPs look for the presence of 'alarming signs and symptoms' (signs are objective characteristics as determined by the physician, symptoms are subjective experiences notified by the patient). These so-called alarming signs and symptoms are features found to be indicative for the presence of a serious infection, i.e. infections that need medical intervention to prevent possible future complications. The absence or presence of alarming signs and symptoms may lessen or increase the chance that a febrile child has a serious infection. Over the years, several clinical guidelines and numerous studies have been published on the assessment of febrile children and which signs/symptoms are considered predictive for serious infections in various clinical settings. [1, 2, 16-18] These guidelines help GPs to assess and treat febrile children using an evidence-based approach. However, the available evidence is mostly based on research performed in secondary care, while the alarming signs and symptoms may have a different predictive value for serious infections in a primary care setting.

## HOW DO GPs MANAGE A FEBRILE CHILD?

After assessment of a child with fever, GPs may decide to 'wait-and-see', or start (antibiotic) treatment, or refer the febrile child to secondary care. Febrile children may be presented to the GP early in their disease episode. When the child is not severely ill at time of presentation, a 'wait-and-see' management may be appropriate to deal with the uncertainty that the child may become more severely ill. An essential part of this watchful waiting should be 'safety netting'; although this concept is not well-defined in primary care[19-22] it should include information for the parents about: uncertainty about the diagnosis or the course of disease, when and how to seek re-consultation and what the expected course of the illness will be, as well as proper documentation in medical notes.[23]

GPs may also decide to prescribe antibiotics. The Dutch guidelines for specific febrile diseases are restrictive in terms of antibiotic prescription. Antibiotic treatment is only indicated if it is proven that antibiotics may significantly reduce the severity and duration of the febrile disease, or that further complications can be prevented by administering antibiotic treatment.[2, 24-29]

At the same time, the Dutch guideline for febrile children advises to refer a febrile child when ≥ 1 alarm sign is present; this is a relatively cautious approach, since it is reported that no single alarm sign is sufficiently discriminative for serious infections.[17]

## WHAT IS THE PROBLEM?

Several barriers are defined in diagnostic research among febrile children,[30] of which generalizability may be one of the most important problems. In primary care, the percentage of serious infections in children with an acute infection or fever is 1-10%,[9, 10] whereas the incidence of serious infections in secondary care is about 15-20%.[17, 31] This difference in the reported occurrence of serious infections can be partly explained by differences in the definitions of serious infection and/or the inclusion criteria used; in addition, the setting itself may also be of importance. The vast majority of the studies on signs/symptoms predictive for serious infections is based on research performed in secondary care; however, the suggested signs/symptoms may have a different predictive value in primary care than in the study populations from which they are originally derived.[17]

With regard to safety netting, an additional problem is that, in the Netherlands, the out-of-hours primary care is organized in large-scale cooperatives.[32, 33] In these general practitioner cooperatives (GPCs), GPs rotate shifts to cover the out-of-hours primary care. Because of this system, GPs are generally not familiar with the patients that they see. Also, follow-up of the patients will often be performed by a different GP; this makes safety netting more complicated, since re-consultation with the same GP may more easily reveal deterioration in the health of the child. All this may lead to a more defensive management strategy in terms of antibiotic prescription and referrals.

Research in the UK has shown that, despite the decline in incidence of serious infections, emergency admissions to hospital of children with common infections are increasing.[14] The Dutch guideline clearly describes when referral should be considered.[2] However, a GP may also consider to refer because of the characteristics of the parents (e.g. poor coping skills of the parents), because these may increase the risk for a complicated course.

Therefore, it is of interest to determine to what extent GPs use the guideline (with the defined alarming signs and symptoms) in their decision to refer the febrile child.

In conclusion, it is a major challenge for GPs to select the few children with a (potentially) serous infection from the vast majority of febrile children with a benign infection and, consequently, to deal adequately with both these groups.

## WHAT MAY BE HELPFUL?

Knowledge about the natural course of fever in children presenting in primary care, the frequency of occurrence of alarming signs and symptoms, and the predictive value of alarming signs and symptoms in primary care, may help to differentiate between uncomplicated illnesses and more serious infections. With this knowledge, GPs may be able to adequately identify the children at risk for a serious infection, parents can be better informed about the child's disease, and parents can be adequately instructed when to seek re-consultation. Furthermore, insight into GPs' current management of febrile children may reveal how well the recommendations in the guidelines are followed, and may indicate where improvements of the guidelines and GPs' management can be made. In addition, determining possible (new) 'predictors' for a serious infection, or the abnormal course of the febrile episode, may also support the GP's medical decision-making.

## AIM AND OUTLINE OF THIS THESIS

The overall objective of this thesis is to determine: i) the course of fever in children in primary care, ii) how febrile children are currently assessed and treated, and iii) which improvements can be made to achieve better health care for children with fever in primary care.

**Chapter 2** describes the duration of fever in febrile children with an uncomplicated illness and **Chapter 3** assesses the predictive value of the duration of fever for serious bacterial infections. The study in **Chapter 4** determines which signs and symptoms are related to a prolonged duration of fever. **Chapter 5** describes the relation between C-reactive protein and serious infections. In **Chapter 6** we assess which signs and symptoms are related to antibiotic prescription in febrile children in primary care. **Chapter 7** extends this knowledge by examining the relationship between alarming signs and symptoms and antibiotic prescription, and defining which proportion of antibiotic prescriptions

is explained by medical considerations. **Chapter 8** reports on how frequently alarming signs and symptoms occur in febrile children in primary care. **Chapter 9** explores to what extent alarming signals play a role in referral to the emergency department by general practitioners who are confronted with a febrile child during out-of-hours care. **Chapter 10** discusses the main results and recommendations for further research and practice. Finally, **Chapter 11** summarizes the main results of the studies in English and Dutch.

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# Chapter 2

# Duration of fever and course of symptoms in young febrile children presenting with uncomplicated illness

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## ABSTRACT

### Purpose

It is important to advice parents when to re-consult a (family) doctor when their child has fever. To provide evidence-based safety-netting advice for young febrile children, we studied the risk of complications, the occurrence of alarm symptoms, the duration of fever, and the daily variation in body temperature in febrile children with uncomplicated illnesses.

### Methods

In a 7-day prospective follow-up study, we included 463 consecutive children aged 3 months to 6 years who presented with fever at a general practitioner out-of-hours service. We excluded 43 children with complicated illnesses at presentation. In a structured assessment, the duration of fever before presentation was noted and a physical examination was performed. Parents reported alarm symptoms and rectal temperature in a diary for one week. The total duration of fever included its duration before presentation. Median duration of fever was estimated using the Kaplan-Meier test.

### Results

During follow-up, 3.2% of the children with uncomplicated illness at presentation developed a complicated illness. The presence of alarm symptoms dropped from 79.3% at day 2 of the fever episode to 36.7% at day 9. The estimated median duration of the total fever episode was 4.0 (95%CI 3.6-4.4) days. On most days of the fever episode, the evening body temperature was 0.1-0.3°C higher than the morning temperature.

### Conclusions

In children with uncomplicated illnesses, the daily occurrence of parent-reported alarm symptoms was high. The median duration of fever was 4 days. The predictive value of parent-reported alarm symptoms for complicated illness should be reconsidered.

## INTRODUCTION

Feverish illnesses in children are common in primary care, but the prevalence of serious infections is low.[1] Although most feverish illnesses (eg, respiratory infections) are self-limiting, fever is still a common reason to contact a general practitioner (GP) after office hours.[2–5]

Children with fever present in different stages of their illness, and alarming symptoms of serious disease may be absent at early presentation. Instructing parents of febrile children about what kind of alarming symptoms to expect during uncomplicated and complicated febrile illnesses, and when to contact the GP in the coming days of their child's illness, is important. This so-called safetynetting is a strategy to deal with situations of diagnostic uncertainty in otherwise uncomplicated illnesses.[6] Building a safety net should include information on the existence of uncertainty, what to look for (ie, alarming symptoms), how exactly to seek further help, and what to expect regarding the time course.[6] To give parents of young febrile children good safety-netting advice, it is essential to inform them about the risk of complications, the occurrence of alarming symptoms, the duration of fever, and the course of body temperature during follow-up.

To our knowledge, little is known about the course of uncomplicated feverish illnesses in primary care. Therefore, this study investigated the risk of complications, the presence of parent-reported alarming symptoms, the duration of fever, and the daily variation in body temperature among young febrile children with uncomplicated illnesses during a 1-week follow-up.

## METHODS

The study was performed at a GP out-of-hours service (OHS) in the southern part of Rotterdam, a large multiethnic city in the Netherlands. This GP OHS covers an area with approximately 300,000 inhabitants.

During midweek evenings and nights between December 13, 2004, and January 16, 2006, consecutive children aged 3 months to 6 years presenting with fever (as reported by the parents) were eligible for inclusion at the moment of presentation to the OHS. Fever had to be the main reason for encounter. Children were excluded if adequate communication in Dutch was impossible; if the child had already been enrolled in the study in the past 2 weeks; if there was no informed consent; or if they had a complicated illness at presentation (Figure 1).

A complicated illness was defined as a serious infection at presentation or admission to a hospital immediately after presentation. Serious infections included pneumonia, sepsis, meningitis, encephalitis, pyelonephritis, dehydration (caused by gastroenteritis

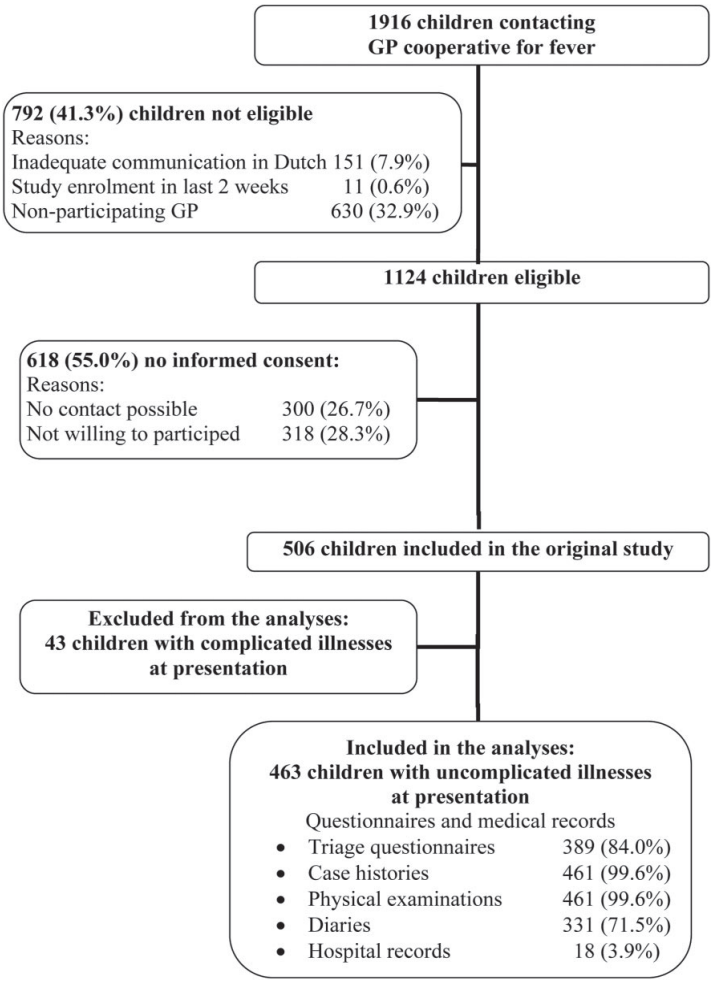


**Figure 1.** Flow chart of children eligible for study analysis. GP, general practitioner.

or unknown cause), osteomyelitis, cellulitis, erysipelas, abscess, febrile convulsion, asthma exacerbation with fever, and, in children ≤1 year old, bronchiolitis. Diagnosis of a serious infection was based on the diagnostic codes (registered according to the International Classification of Primary Care) noted by the GP in the OHS records. If a contact was not coded, a team of 3 GPs provided an International Classification of Primary Care code based on the (uncoded) diagnosis made by the GP at the OHS or, if the diagnosis was missing, based on noted symptoms and findings during the history or physical examination. The team was blinded for triage result and the management by the GP at the OHS. Final coding was based on consensus. Children who were immediately referred at initial presentation were defined as having a serious infection if the pediatrician diagnosed the child as such. During follow-up, a complicated illness

was defined as a serious infection diagnosed by a GP or a pediatrician or admission to hospital.

When parents phoned the OHS concerning their febrile child, the nurses performed their usual triage based on the triage guidelines of the Dutch College of General Practitioners[7] and filled out a structured triage questionnaire in which parental concern (among other topics) was noted. According to these guidelines, a child was invited for consultation if the child was younger than 3 months of age, was very ill, was rapidly deteriorating, drank less than half of their normal consumption, had a rash that occurred during fever, was crying inconsolably, had a change in skin color, had a change in breathing pattern, was moaning or had apnea, had relevant comorbidity, had fever for >3 days or that was increasing after a fever-free period. In addition, a child was seen when the parents showed agitation, aggression, or persistent anxiety. A child was triaged as "self-care advice" if none of the above were present.

Based on this triage, the triage nurse gave advice over the telephone and arranged a face-to-face contact at the OHS or a home visit by a GP. GPs were free to prescribe treatments of their choice or to refer the patient.

An additional home visit by a trained research nurse was arranged as soon as possible after the evening or night of inclusion—but within 24 hours of inclusion—for all children included in this study. Using a structured questionnaire, the research nurse recorded demographic data, symptoms and signs at time of presentation, and medication use reported by the parents. In addition, the research nurse performed a structured physical examination, including rectal temperature. Parents received a thermometer and instructions to measure rectal temperature. During 1 week of follow-up, parents recorded in a structured diary rectal temperature twice a day and symptoms and medication use daily, starting at the day of the home visit. Diaries were returned by mail. If the parents did not return the diary, they were contacted by telephone within 1 month after the end of their follow-up and asked whether the child had had fever 1 week after the initial contact. Fever was defined as a temperature of ≥38.0°C.

On the basis of national and international guidelines and before analyses, we defined 5 alarming symptoms.[2,7] Drowsiness was defined as dull or difficult to awaken, no eye contact, or no or little reaction toward the parent. Inconsolable was defined as crying inconsolably, crying when picked up, very or very much irritated, or groaning. Abnormal circulation was defined as pale, ashen, or mottled skin. Dehydration was defined as drinking less than half that of normal or much less or no urine voiding. Shortness of breath was defined as rapid breathing.

Before the analyses we established cut offs for multiple choice questions. "No or little reaction toward the parent" was contrasted with "normal or almost normal reaction toward the parent." "Very or very much irritated" was contrasted with "not or slightly irritated." "Drinking less than half that of normal" was contrasted with "drinking half to

twothirds that of normal" or "drinking two-thirds or more that of normal." "Much less or no urine voiding" was contrasted with "normal or slightly less than normal urine voiding." All other variables were dichotomous.

Antipyretic use before follow-up was defined as reported use of antipyretics at triage or reported use of antipyretics during this fever episode before presentation to the OHS. Daily antipyretic use during follow-up was defined as use of antipyretics reported in the diaries. Total antipyretic use was defined as antipyretic use before and during follow-up.

The Dutch Central Committee on Research Involving Human Subjects approved this study.

## Analyses

Age is presented as median years and range. Temperature, duration of fever, and duration of antipyretic use are presented as mean ± standard deviation, median and 5th (p5) and 95th (p95) percentiles. Data from children diagnosed with a serious infection or who were admitted to a hospital during follow-up were censored from all analyses from the day of diagnosis/admission onward.

Parents were asked about the first day of their child's fever as part of the structured assessment with the research nurse. This date was defined as the first day of the fever episode. In case of missing values (n = 2), the day of presentation was used as the first day of fever. The last day of fever was defined as the last known day of fever followed by ≥2 days without fever reported in the diaries. In case of missing values in the diaries, the last day with fever reported (either in the diary or during the telephone call) was used as the last day of fever. The total duration of fever was defined as the period starting on the first day of fever and ending on the last day of fever in the diary. Duration of fever was measured in days. If a child was free of fever for ≥2 days, a subsequent fever day was considered to be recurrent fever and not incorporated in the duration of the first fever episode. For the total duration of fever, the nonparametric Kaplan-Meier test was used; the survival function and the estimated median duration of fever with 95% confidence intervals (CIs) are presented. Using the Kaplan-Meier test, a child was censored from the last known day of fever if it was unclear whether the child had had fever during the following 2 days. We performed this analysis for all children and for subgroups of children by age (3–11 months, 12–23 months, and 24 months to 6 years).

To analyze differences between children presenting to the OHS on day 1 of their fever episode and children presenting after day 1 of their fever episode, comparisons between mean age, parental concern, reported temperature before presentation, and temperature during physical examination were performed using the Student *t* test for continuous variables (age and temperature) or with the $\chi^2$ test for dichotomous variables (parental concern). Comparisons between height of temperature in the morning and the evening of the same day were performed using a paired Student *t* test.

Statistical significance was set at $P < .05$. Analyses were performed with SPSS software version 17.0 for Windows (SPSS, Inc., Chicago, IL).



## RESULTS

Initially, 506 children were included in the study (Figure 1). Of these, 43 children (8.5%) with complicated illnesses were excluded from the analyses because of either a diagnosis of serious infection at presentation (n = 24, 4.7%) or admission to a hospital directly after presentation (n=19, 3.8%). A diagnosis at presentation was missing for 14 children included in the study. Finally, we analyzed data of 463 children (91.5%) with uncomplicated illness at presentation.

Diaries were returned for 331 children (71.5%). Characteristics of the children are presented in Table 1. The median highest reported temperature before presentation was 39.5°C (p5, p95: 38.1, 40.6°C). Duration of fever before presentation was reported in 461 children (99.6%). Median duration of fever before presentation was 2.0 days (p5, p 95: 1.0, 6.0 days). During followup, of the 463 children with uncomplicated illnesses at presentation, 15 (3.2%) developed a complicated illness; they were diagnosed with a serious infection (n = 4, 0.9%) or admitted to hospital (n = 11, 2.8%). The median day on which a child developed a complicated illness was day 5 (p5, p95: day 2, day 11).

Of all 463 children, 206 (44.5%) presented to the OHS on day 1 of their fever episode. These children did not differ from those who presented later during their fever episode with regard to age (mean age, 27 vs. 25 months; mean difference –2 months; 95% CI, –5 to 1 months) or degree of parental concern (worried or very worried vs. Not worried or

**Table 1.** Characteristics of febrile children with uncomplicated illness (N=463) presenting to a GP out-of-hours service.

| | ***Children with uncomplicated illness (N=463)*** |
|---|---|
| Age in months, median (range) | 21 (3-70) |
| Male sex | 260 (56.2) |
| Immigrant | 235 (50.8) |
| Triage result (face-to-face contact) | 332 (71.7) |
| Triage result (GP home visit) | 0 (0.0) |
| Duration of fever before presentation, median days (5th-95th percentile) | 2.0 (1.0-6.0) |
| Highest reported temperature before presentation, median °C (5th-95th percentile) | 39.5 (38.1-40.6) |
| Use of antipyretics before start of follow-up, *n/N (%)* | 398/459 (86.0) |

Values are n (%) unless otherwise indicated.

a little worried: 42.9% vs. 33.1%; $\chi^2$ =3.312; df = 1; $P$ = .07). However, these children did statistically significantly differ in highest reported temperature before presentation (39.4 vs. 39.6°C; mean difference, 0.2°C; 95% CI, 0.0–0.3) and in mean temperature at physical examination during the home visit (37.8 vs. 37.5°C; mean difference, –0.4°C; 95% CI, –0.5 to –0.2). Of 456 children, 189 (41.4%) received antibiotic treatment during this fever episode.

## Alarming symptoms

Table 2 (Figure 2) presents the percentages of parent- reported alarming symptoms during the Total fever episode. During follow-up, the presence of alarming symptoms decreased each day. The most frequent parent-reported alarming symptoms were inconsolable (decreasing from 53.4% at day 2 to 20.4% at day 9) and shortness of breath (decreasing from 47.7% at day 2 to 11.3% at day 9). At day 2, 79.3% of the parents reported at least one alarming symptom. At day 9 this percentage had decreased to 36.7% of the children with uncomplicated illness.

**Table 2.** Alarm symptoms reported by the parents of febrile children with uncomplicated illness.

| | Day 2 N=137 | Day3 N=220 | Day4 N=254 | Day 5 N=270 | Day 6 N=280 | Day 7 N=280 | Day 8 N=275 | Day 9 N=157 |
|---|---|---|---|---|---|---|---|---|
| **Drowsiness*** | 40/115 (34.8) | 43/189 (22.8) | 41/211 (19.4) | 44/204 (21.6) | 33/190 (17.4) | 32/187 (17.1) | 26/172 (15.1) | 20/98 (20.4) |
| **Inconsolable†** | 62/116 (53.4) | 79/190 (41.6) | 76/211 (36.0) | 51/203 (25.1) | 43/192 (22.4) | 40/186 (21.5) | 31/150 (20.7) | 20/98 (20.4) |
| **Abnormal circulation‡** | 34/112 (30.4) | 49/181 (27.1) | 41/202 (20.3) | 42/196 (21.4) | 33/183 (18.0) | 21/179 (11.7) | 18/164 (11.0) | 11/96 (11.5) |
| **Dehydration§** | 39/116 (33.6) | 56/189 (29.6) | 55/209 (26.3) | 38/201 (18.9) | 28/189 (14.8) | 22/185 (11.9) | 16/162 (9.9) | 12/96 (12.5) |
| **Shortness of breath‖** | 53/111 (47.7) | 58/181 (32.0) | 46/206 (22.3) | 36/195 (18.5) | 24/183 (13.1) | 23/179 (12.8) | 19/163 (11.7) | 11/96 (11.3) |
| **Minimal of 1 alarming symptom reported** | 92/116 (79.3) | 129/191 (67.5) | 138/212 (65.1) | 111/204 (54.4) | 85/192 (44.3) | 76/187 (40.6) | 66/173 (38.2) | 36/98 (36.7) |

Values are n/N (%).
*Defined as dull or difficult to awaken, little or no reaction toward parent, no eye contact with parent.
†Defined as crying inconsolably, crying when picked up, very irritated, groaning.
‡Defined as pale, ashen, or mottled skin.
§Defined as drinking less than half that of normal, much less or no urine voiding.
‖Defined as rapid breathing

## Total duration of fever and height of fever

The daily percentage of children with fever (temperature≥38.0°C) decreased from 65.0% at day 2 to 10.2% at day 8 of the total fever episode. The daily percentage of children with high fever (temperature≥40.0°C) decreased from 4.4% at day 2 to 0.0% at day 9 (Table 3).

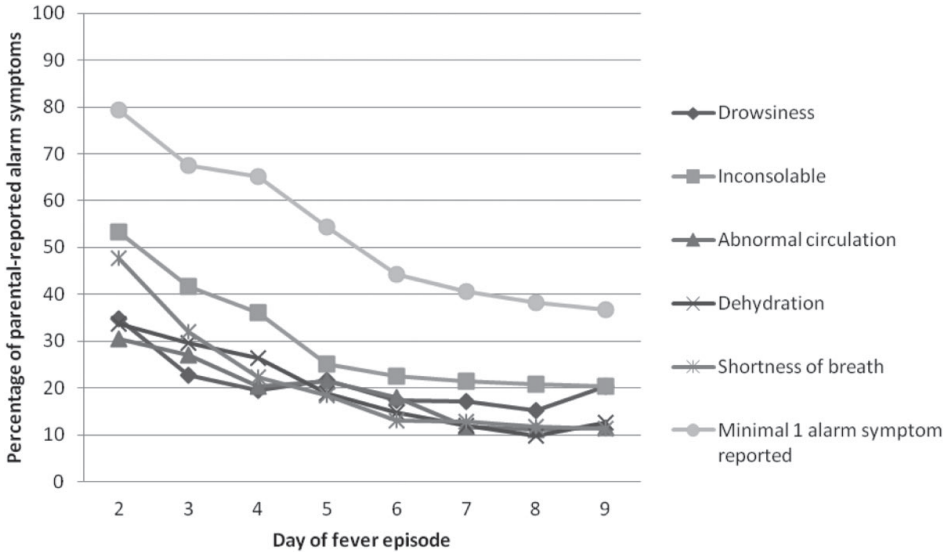


**Figure 2.** Rate of parental reported alarm-symptoms in febrile children with uncomplicated illnesses.

**Table 3.** Daily temperature reported by the parents of febrile children with uncomplicated illness.

| Temperature | Day 2 (n=137) | Day3 (n=220) | Day4 (n=254) | Day 5 (n=270) | Day 6 (n=280) | Day 7 (n=280) | Day 8 (n=275) | Day 9 (n=157) |
|---|---|---|---|---|---|---|---|---|
| Morning, median °C (5th-95th precentile) | 37.9 (36.5-39.7) | 37.5 (36.2-39.4) | 37.3 (36.1-39.4) | 37.1 (36.0-38.9) | 37.1 (36.1-38.3) | 37.1 (36.0-38.3) | 37.0 (35.9-38.0) | 37.0 (35.9-38.2) |
| Evening, median °C (5th-95th precentile) | 38.0 (36.0-39.8) | 37.8 (36.1-39.8) | 37.5 (36.0-39.2) | 37.3 (36.2-39.0) | 37.1 (36.1-38.8) | 37.1 (36.0-38.5) | 37.1 (36.1-38.2) | 37.1 (36.0-38.6) |
| ≥ 38.0°C, n/N (%) | 89/137 (65.0) | 107/212 (50.5) | 86/241 (35.7) | 68/255 (26.7) | 48/257 (18.7) | 36/249 (14.5) | 24/235 (10.2) | 16/136 (11.8) |
| ≥ 40.0°C, n/N (%) | 6/137 (4.4) | 7/212 (3.3) | 5/241 (2.1) | 4/255 (1.6) | 1/257 (0.4) | 1/249 (0.4) | 1/235 (0.4) | 0/136 (0.0) |

Figure 3 presents the course of fever in febrile children with uncomplicated illnesses. The estimated median total duration of fever was 4.0 days (95% CI, 3.6–4.4). The estimated median total duration of fever was 4.0 days (95% CI, 3.3 – 4.7) for children aged 3 to 11 months, 5.0 days (95% CI, 4.1 – 5.9) for children aged 12 to 23 months, and 4.0 days (95% CI, 3.4 – 4.6) for children aged 24 months to 6 years.

Of the 331 children for whom diaries were returned, fever recurred in 27 (8.2%). The median day of recurrent fever was day 6 (p5, p95: day 3, day 24) after the start of the first fever episode.

Median morning temperature per day dropped from 37.9°C (p5, p95: 36.5, 39.7°C) at day 2 to 37.0°C (p5, p95: 35.9, 38.2°C) at day 9 of the total fever episode. Median evening

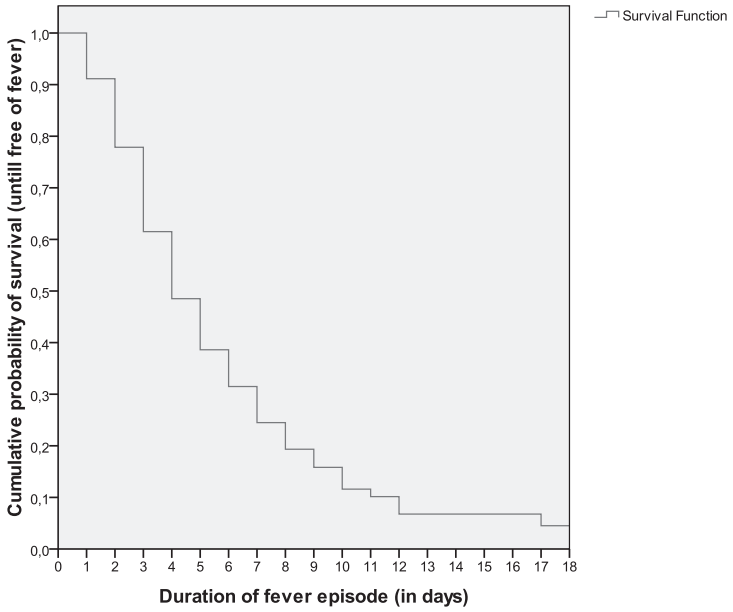


**Figure 3.** Fever curve in young febrile children with uncomplicated illnesses (n=463, number of events=292, number of censoring=171).

temperature per day dropped from 38.1°C (p5, p95: 36.0, 39.8°C) at day 2 to 37.2°C (p5, p95: 36.0, 38.6°C) at day 9 of the total fever episode (Table 3). Temperature in the evening was significantly higher (0.1– 0.3°C) compared with the morning temperature at days 3 to 6 and on days 8 and 9 of the total fever episode.

### Antipyretic use

Most children (398 of 459; 86.7%) used antipyretics before follow-up (Table 1). During follow-up, daily use of antipyretics decreased from 40.2% at day 2 to 4.6% at day 9. Of the 459 children, 411 (89.5%) children used antipyretics during this fever episode.

## DISCUSSION

This study describes the risk of complications, the course of fever, and alarming symptoms during 7 days of follow-up in young febrile children with uncomplicated illnesses at presentation to OHS. In children with uncomplicated illness at presentation, 3.2% developed a complicated illness. Parent-reported alarming symptoms were frequent and decreased daily during follow-up. Estimated median duration of fever was 4.0 days

(95% CI, 3.6–4.4). On most days, temperature in the evening was only marginally higher than in the morning.



### Strengths and Limitations

A strength of this study is that we prospectively collected daily alarming symptoms and daily body temperature in febrile children during 1 week after their presentation to OHS. This enabled us to describe the duration of fever and alarming symptoms in children with uncomplicated febrile illnesses at presentation. We present data for the total fever episode, not just starting from the presentation of the child to OHS. Children who presented at the first day of their fever episode did not differ from children who presented later.

A limitation of the study is that we had to collect data retrospectively for the days preceding the OHS contact. Although recall bias might have been present, the duration of fever before presentation had a median of only 2 days (p5, p95:1 day, 6 days); thus, based on this relatively short period of time, we assume that recall had no important effect on our analyses.

Alarming symptoms were frequently reported (≤79.3%) in comparison to the relatively small percentage of serious illness (3.2%). Many parents stopped filling out the diaries after their child recovered. Because the number of missing values in the diaries increased during follow-up, this might have resulted in an overestimation of the percentage of alarming symptoms at the end of follow-up. However, this cannot explain the discrepancy between the frequency of parent-reported alarming symptoms and the 3.2% of children who developed a complicated illness during the week of follow-up. This study indicates that parent-reported alarming symptoms as a trigger for reconsultation will give raise to a high percentage of false positive reconsultations. Parent-reported alarming symptoms may have been frequently reported because they also occur in children with uncomplicated illness or parents are not aware how to interpret the description of alarming symptoms given by their physician.

### Comparison with existing literature

We found no other studies that describe the total duration of fever episodes in children in general practice. Maguire et al[8] described a median duration of illness of 3 days, which was queried retrospectively in a study on how parents access acute services for febrile children; however, they did not prospectively follow the febrile children for the total duration of the fever episode. A systematic review found 7 studies of the predictive value of duration of fever for serious infections at the moment of presentation in 1644 febrile children; however, because of a lack of information on the duration of fever, no conclusions could be drawn about the predictive value for serious infection.[9]

### Implications for future research and clinical practice

This study describes the risks of complicated illness, parent-reported alarming symptoms, and duration of fever in young febrile children with uncomplicated illnesses. The median duration of fever was 4 days, and parents frequently reported alarming symptoms in children with an uncomplicated illness. To prepare safety-netting advice about alarming symptoms during the fever episode in children with uncomplicated illnesses, parent-reported alarming symptoms need to be reconsidered and validated. The cost effectiveness of advising reconsultation in the presence of alarming symptoms might be low and needs further evaluation.

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# Chapter 3

# Duration of fever and serious bacterial infections in children: a systematic review

Gijs Elshout, Miriam Monteny, Johannes C van der Wouden, Bart W Koes, Marjolein Y Berger.

BMC Family Practice 2011, 12:33.

## ABSTRACT

### Background

Parents of febrile children frequently contact primary care. Longer duration of fever has been related to increased risk for serious bacterial infections (SBI). However, the evidence for this association remains controversial. We assessed the predictive value of duration of fever for SBI.

### Methods

Studies from MEDLINE, Embase and Cochrane databases (from January 1991 to December 2009) were retrieved. We included studies describing children aged 2 months to 6 years in countries with high Haemophilus influenzae type b vaccination coverage. Duration of fever had to be studied as a predictor for serious bacterial infections.

### Results

Seven studies assessed the association between duration of fever and serious bacterial infections; three of these found a relationship.

### Conclusion

The predictive value of duration of fever for identifying serious bacterial infections in children remains inconclusive. None of these seven studies was performed in primary care. Studies evaluating the duration of fever and its predictive value in children in primary care are required.

## BACKGROUND

Fever is very common among young children and a frequent reason for parents to contact primary care.[1] Febrile children usually have self-limiting viral infections, and serious infections in need of medical intervention are rare. In primary care, clinical markers are the most appropriate evaluation tools in febrile children. In some studies, the duration of fever prior to presentation has been shown to be a predictor of serious bacterial infection (SBI).[2-6] However, the evidence for this association remains a subject of discussion.[7] For example, in the practice guideline for the management of febrile children in primary care, the Dutch College of General Practitioners (NHG) recommends that children with more than three days of fever at presentation should be seen by a general practitioner (GP).[7] In contrast, the NICE guideline for feverish illness in children in the UK states that duration of fever should not be used to predict the likelihood of serious illness, other than Kawasaki disease.[8] Both guidelines base these recommendations on studies performed in secondary and tertiary care, which may not be applicable for primary care settings.

Since the introduction of the *Haemophilus influenzae* type b (Hib) conjugate vaccine during the last two decades, the prevalence of Hib-induced infections has decreased.[9] This might have consequences for the association between duration of fever and SBI. Gaining more insight into the course of fever in the post-Hib era is essential for the evaluation and management of febrile children in primary and secondary care.

Therefore, we conducted a systematic review of studies on duration of fever in children aged two months to six years, in the post-Hib era. We aimed at answering the question: what is the association between duration of fever and an SBI in febrile children?

## METHODS

### Identification and selection of the literature

A systematic search of the literature was made from January 1991 to December 2009 in the MEDLINE, Embase and Cochrane databases. Since Hib vaccination was not widely distributed before 1991,[10] the search was restricted to the years after 1990. Sensitive search strategies ('clinical queries') were used for prognostic studies,[11] diagnostic studies[12] and randomized controlled trials (RCTs).[13] The following keywords and MeSH-headings were used: 'fever', 'preschool child', 'infant', 'childhood', 'course*', 'duration', 'disease', 'infection', 'bacterial infection', 'bacterial infections', 'serious bacterial infection*', 'mortality', 'child hospitalization', and 'hospitalization' (see supplement 1). Reference lists of selected publications were checked to identify additional relevant publications.

To identify eligible studies, titles and abstracts resulting from the search strategy were screened independently by two teams of reviewers (MM/GE and MYB/JCvdW). Studies had to meet the following criteria:

1) The design of the study was a prospective cohort study, cross-sectional study or RCT.
2) The majority of participants were children aged two months to six years (or an identifiable and separately analyzed subgroup of at least ten children aged two months to six years).
3) Enrolment occurred in a country with adequate Hib vaccination coverage, i.e. ≥ 80% according to WHO/UNICEF estimates,[10] during at least 50% of the enrolment period.
4) The outcome measure was duration of fever (prior to enrolment) as prognostic factor for SBI.
5) In case of SBI, eligible diagnoses included bacteremia, sepsis, bacterial meningitis, bacterial pneumonia, infectious arthritis, osteomyelitis, cellulitis, soft tissue infection, pyelonephritis, urinary tract infection, bacterial gastroenteritis, tonsillitis, or otitis media.

Studies focusing on immunocompromized children or fever syndromes were excluded. Studies in countries outside Europe, North America, Australia or New Zealand were excluded, because the etiology, prevalence and presentation of febrile illnesses differ significantly in these countries.

### Data extraction

Two teams of reviewers (MM/GE and MYB/JCvdW) independently extracted data from the selected studies using standardized forms. The extracted data concerned design, setting, study population, outcome measures and prognostic factors.

### Quality assessment

Two teams of reviewers (MM/GE and MYB/JCvdW) assessed the methodological quality of the studies independently, by means of a modified version of the criteria list for prognostic studies as developed by Hayden et al.[14] Since cross-sectional studies were also included, we added an item concerning the independent assessment of duration of fever and SBI diagnosis. The list consisted of 22 items (Table 1) that were scored positive (+), negative (–), unclear (?) or not applicable (NA). Disagreement between the reviewers was discussed in a consensus meeting.

Inter-assessor agreement of the methodological quality assessment was calculated using kappa scores.[15] The total quality score for each study was calculated by counting all positively scored criteria (maximum 22) and dividing this number by the number of applicable items. High quality was defined as a score of 50% or higher.

**Table 1.** Items included in the methodological quality assessment.

| | |
|---|---|
| *Study participation* | |
| 1 | Setting of recruitment is described |
| 2 | Moment of identification is described and equal for all included children (inception cohort) |
| 3 | Percentage participation of eligible children is described |
| 4 | Inclusion and exclusion criteria are described and age, fever and relevant co-morbidity are reported |
| 5 | Baseline study sample is described for key characteristics age and sex |
| *Study attrition* | |
| 6 | Number of loss to follow-up in cohort study/RCT is <20%, or the number missing for analysis (the difference between number included and number analyzed) in cross-sectional studies is <20% |
| 7 | Reasons for loss to follow-up/missing for analysis are provided |
| 8 | Key characteristics (at least age and sex) of participants lost to follow-up/missing for analysis do not differ significantly from the study sample |
| *Prognostic factor measurement* | |
| 9 | Prognostic factor duration of fever: method of measurement is described and valid (thermometer) |
| 10 | Prognostic factor duration of fever: duration prior to presentation is described |
| 11 | Prognostic factor SBI: definition of diagnosis is described and valid |
| 12 | If continuous variables are used, they are reported as continuous variables or appropriate cut-off points (not data dependent) are used |
| *Outcome measurement* | |
| 13 | A clear definition of the outcome (duration of fever, SBI or hospitalization) is provided |
| 14 | Method and setting of outcome measurement are the same for all study participants |
| 15 | SBI was assessed independently from the assessment of fever |
| *Confounding measurement and account* | |
| 16 | Antipyretics use before and/or during the study is assessed and reported |
| 17 | Antibiotics use before and/or during the study is assessed and reported |
| 18 | Level of illness is measured and measurement method is appropriate (e.g. Yale score) and the same for all children |
| 19 | The potential confounders antipyretics use, antibiotics use and illness level are accounted for in the study design or analysis |
| *Analysis* | |
| 20 | There is data presentation of the prognostic factors duration of fever and/or SBI |
| 21 | The association of prognostic factor and outcome is given in percentages or means/medians, or in OR/RRs with confidence interval/SD, or calculation of these measures is possible |

## Analysis

The studies included in this review were considered too heterogeneous (regarding setting, definition of fever and of SBI, and presentation of the results) to pool the data. Therefore, a best-evidence synthesis was used to summarize the value of prognostic factors. Four levels of evidence were defined, based on Sackett et al.[16] and Ariens et al.[17] (see supplement 2). Only significant associations were considered in this synthesis, defined by a threshold of $p \leq 0.05$ or odds ratios (OR) with a confidence interval (CI) not including 1.0.

Significance of differences between groups was assessed using chi-square analysis. When not reported but sufficient data were available, the association between prognostic factors and outcome was calculated as ORs with 95% CIs.

## RESULTS

The search strategy yielded 5458 citations, of which 96 could not be excluded based on title and abstract. Full-text versions of these 96 citations were retrieved. Figure 1 presents a flow chart of the process of identification and exclusion. Seven publications were included.[18-24]

All seven studies were cross-sectional studies and were performed in an emergency room setting. Three studies concerned children aged 1 to 36 months,[18, 21, 22] and two studies included children aged 3 to 36 months.[20, 24] The two remaining studies concerned children aged 2 to 6 months,[19] or 0 to 18 years.[23] The median or mean ages of the children in the studies were all within our two months to six years inclusion criterion.

Table 2 gives the results of the methodological quality assessment after consensus. The overall kappa before consensus was 0.73, indicating substantial agreement.[15] In all cases

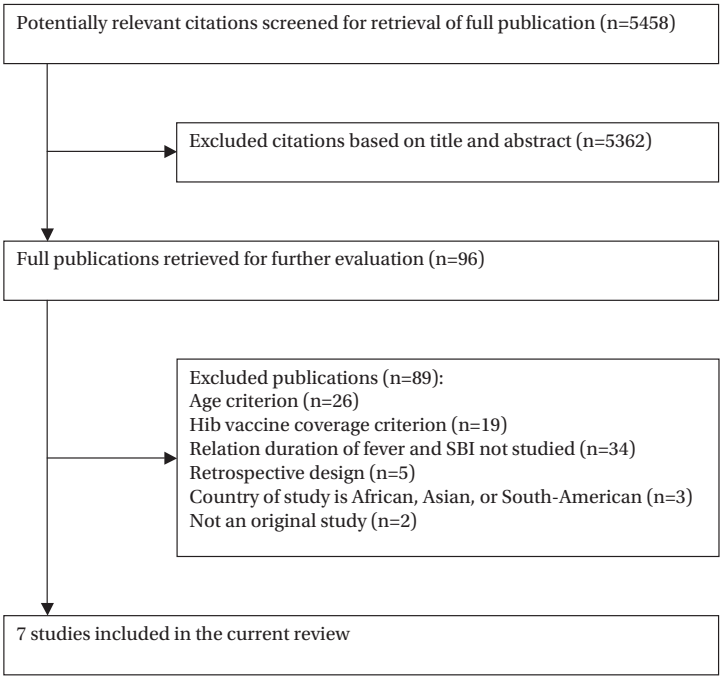


**Figure 1.** Identification and inclusion of studies in the present review.

of initial disagreement, consensus was achieved between the two teams of reviewers. Six studies were of high quality according to our predefined criterion; the median score was 63 (range 45-74%), one study had a score of 45%.[24] The details of the included studies are given in supplement 3. ORs were calculated using data from the studies by Pratt et al.[22]

**Table 2.** Results of quality assessment of the methodology of the included studies.

| *Item (see Table 1)* | *Pulliam et al.*[21] | *Isaacman et al.*[20] | *Fernandez Lopez et al.*[18] | *Hsiao et al.*[19] | *Trautner et al.*[23] | *Pratt et al.*[22] | *Guen et al.*[24] |
|---|---|---|---|---|---|---|---|
| 1 | + | + | + | + | + | + | + |
| 2 | + | + | + | + | + | + | + |
| 3 | – | – | – | + | + | – | – |
| 4 | + | – | + | – | + | + | + |
| 5 | + | – | – | – | + | + | – |
| 6 | + | + | ? | + | NA | + | ? |
| 7 | NA | NA | ? | + | NA | NA | NA |
| 8 | NA | NA | ? | ? | NA | NA | ? |
| 9 | – | – | + | + | + | – | – |
| 10 | + | + | + | + | + | + | + |
| 11 | NA | NA | NA | NA | NA | NA | NA |
| 12 | – | + | + | + | + | ? | + |
| 13 | + | + | + | – | + | + | – |
| 14 | + | + | + | ? | – | – | ? |
| 15 | + | + | ? | ? | + | + | + |
| 16 | – | – | – | – | – | – | ? |
| 17 | + | + | + | – | – | + | + |
| 18 | + | – | – | + | – | + | – |
| 19 | – | – | – | – | – | – | – |
| 20 | + | + | + | + | + | + | + |
| 21 | + | + | + | + | + | + | + |
| 22 | + | + | – | – | – | – | – |
| Total score (%) | 74 | 63 | 52 | 52 | 67 | 63 | 45 |

+; positive, –; negative, ?; unclear, NA; not applicable

## Predictive value of duration of fever for SBI

Seven studies, including a total of 1644 children, provided information on the predictive value of duration of fever at presentation for identifying SBI.[18-24] All seven studies were cross-sectional, five of which were performed in the USA,[19, 20, 21-23] one in France,[24] and one in Spain.[18] Fever was defined as a minimal temperature of 38°C[18-20] or 39°C.[21, 22, 24] One study investigated hyperpyrexia defined as ≥ 41.1°C.[23] Temperature was measured

rectally,[19-23] axillary,[18] or at an unspecified location.[20-22, 24] The definition of the outcome of SBI varied between occult bacterial infections only, and localized or invasive bacterial infections including occult bacteremia. Between and within the various studies, the diagnostic tests for SBIs (e.g. lumbar puncture) were performed in all patients or only in selected patients.

One study showed a significant univariate association of duration of fever at presentation with occult bacterial infection[19] and another study showed a significant association in a multivariate model.[20] One study of low quality provided an overall median prior duration of fever of 24 (range 0.25-192) hours versus 4.6 (± 3.13) hours in children with occult bacteremia.[24] However, no p-value or CI was provided. The remaining four studies showed no significant association, either in the univariate[18, 22, 23] or the multivariate analysis.[21] Therefore, according to our classification (Table 2), the level of evidence for the association between the duration of fever at presentation and a SBI is inconclusive.

## DISCUSSION

### Summary of main findings

The predictive value of duration of fever at presentation for SBI remains contradictory and hence inconclusive.

### Strengths and limitations of this study

The number of studies in this review is relatively small, with only a few studies available for our objective. Although we initially retrieved a high number of publications using a sensitive search strategy, many studies did not fulfill our inclusion criteria. This reflects the lack of information on the duration of fever in children in the post-Hib era, making it difficult to draw firm conclusions on the duration of fever and its predictive value for SBI.

Trautner et al. showed that duration of fever is not predictive for SBI.[23] However, their study included children with hyperpyrexia only, defined as a rectal temperature of ≥ 41.1°C, measured at the emergency room. Thereby, their study population is not representative for patients seen in general practice. By focusing on a subgroup with hyperpyrexia, other factors may better predict SBI in this latter study population than duration of fever.

None of the studies controlled for use of antipyretics or antibiotics, which may have confounded the results of these studies.

All studies were performed in secondary and tertiary care settings. Due to selected and different study populations, the results found may not be relevant for a primary care setting. For example, in the study of Trautner et al., seven of the twenty patients with a SBI had a pre-existing condition.

### Comparison with existing literature

A recent review described the diagnostic value of clinical features to identify serious infections in children;[25] however, they included fewer and different studies addressing duration of fever or illness. We excluded four out of five studies, because they did not meet our inclusion criteria for age,[26] Hib coverage,[2] study design,[3] and fever;[27] this makes the results of the reviews less comparable. Van den Bruel et al.[25] concluded that duration of fever or illness is not a strong predictor for serious infections, which is in line with our conclusion.



### Implications for future research or clinical practice

An explanation for the inconclusive findings for a predictive value of duration of fever might be the heterogeneity of the definition of SBI. One study reported a trend of shorter duration of fever and the possibility of bacteremia compared to the overall group.[24] Other studies, that did not meet the inclusion criterion for Hib vaccination coverage, found similar results.[28, 29] It is plausible that the predictive value of the duration of fever depends on the specific SBI under study. A comparable explanation was put forward in the NICE guideline.[8] For example, bacteremia, meningitis and sepsis are SBIs that can develop relatively quickly, whereas bacterial pneumonia or urinary tract infection may develop over a longer period of time. All the other studies in our review, looking at duration of fever as predictor for SBI, included bacteremia, but they may have diluted the prognostic value of duration of fever by analyzing bacteremia combined with other SBIs. However, in general practice a broad spectrum of both slow and quick-developing SBIs will be presented. Therefore, relations other than a linear association between duration of fever and SBI may be more appropriate. Multivariate analyses considering the interaction between duration of fever and other variables (e.g. level of illness, age), and stratification for different kinds of SBIs, may yield more data about the relationship between duration of fever and risk of SBI. Observational studies are needed to test this hypothesis and thereby elucidate the duration of fever and its significance in the management of febrile children in primary care. Until then, it seems appropriate not to use duration of fever to assess the risk of SBI in febrile children in primary care.

## CONCLUSION

The predictive value of duration of fever at presentation for SBI remains contradictory and hence inconclusive. None of these seven studies was performed in primary care. Studies evaluating the duration of fever and its predictive value in children in primary care are required.

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**Supplement 1.** Search strategy for Medline

1) Prognostic studies:
fever[mesh] and (child, preschool[mesh] or infant[mesh]) and (incidence[MeSH:noexp] OR mortality[MeSH Terms] OR follow up studies[MeSH:noexp] OR prognos*[Text Word] OR predict*[Text Word] OR course*[Text Word])

2) Diagnostic studies:
fever[mesh] and (child, preschool[mesh] or infant[mesh]) and (bacterial infections[mesh] or serious bacterial infection* or infection[mesh] or hospitalization) and (sensitiv*[Title/Abstract] OR sensitivity and specificity[MeSH Terms] OR diagnos*[Title/Abstract] OR diagnosis[MeSH:noexp] OR diagnostic *[MeSH:noexp] OR diagnosis,differential[MeSH:noexp] OR diagnosis[Subheading:noexp])

3) Randomized trials:
fever[mesh] and (child, preschool[mesh] or infant[mesh]) and (randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized controlled trials [mh] OR random allocation [mh] OR double-blind method [mh] OR single-blind method [mh] OR clinical trial [pt] OR clinical trials [mh] OR "clinical trial" [tw] OR ((singl* [tw] OR doubl* [tw] OR trebl* [tw] OR tripl* [tw]) AND (mask* [tw] OR blind* [tw])) OR "latin square" [tw] OR placebos [mh] OR placebo* [tw] OR random* [tw] OR research design [mh:noexp] OR comparative study [mh] OR evaluation studies [mh] OR follow-up studies [mh] OR prospective studies [mh] OR cross-over studies [mh] OR control* [tw] OR prospectiv* [tw] OR volunteer* [tw]) NOT (animal [mh] NOT human [mh])

**Supplement 2.** Levels of evidence for the prognostic factors.

| ***Level of evidence*** | ***Definition*** |
|---|---|
| Strong | Consistent findings (≥ 75%) in at least two high-quality studies |
| Moderate | Consistent findings (≥ 75%) in one high-quality study and at least one low-quality study |
| Limited | Findings of one high-quality study or consistent findings (≥ 75%) in at least three low-quality studies |
| Inconclusive | Inconsistent findings irrespective of study quality or less than three low-quality studies available |
| No evidence | No data presented |

**Supplement 3.** Details of the included studies on the predictive value of prior duration of fever and serious bacterial infection (SBI).

| *Author (year)* | *Design and setting* | *Inclusion criteria* | *Outcome* | *Prognostic factor* | *Results* |
|---|---|---|---|---|---|
| Pulliam et al.[21] (2001) | Cross-sectional study<br><br>Tertiary care emergency room,<br>USA<br><br>n=77 | - Age 1 to 36 months<br>- Fever ≥ 39°C<br>- Clinically undetectable source of fever | Serious bacterial infection (SBI): Occult bacteremia, urinary tract infection, pneumonia, meningitis, septic arthritis, osteomyelitis<br><br>Diagnosis based on laboratory or radiology | Duration of fever prior to presentation<br><br>Measurement method not given, duration probably obtained by history taking | Median duration of fever in<br>SBI: 24 (range 3-168) h<br>No SBI: 24 (range 1-168) h<br>p=0.24<br><br>Multivariate analysis:<br>Duration of fever prior to presentation reported as unrelated to SBI |
| Isaacman et al.[20] (2002) | Cross-sectional study<br><br>Secondary care emergency room, USA<br><br>n=256 | - Age 3 to 36 months<br>- Fever ≥ 39°C<br>- Requiring complete blood count and blood culture as part of evaluation | Occult bacterial infection (OBI): occult pneumonia, occult urinary tract infection, occult bacteremia, and no focal abnormalities on physical examination<br><br>Diagnosis based on blood or urine culture or radiology | Length of existing febrile illness in hours, not further specified, probably prior to presentation<br><br>Measurement method not given, duration recorded at emergency room, probably by history taking | Median period of febrile illness in<br>OBI: 24 (range 4-240) h<br>No OBI: 24 (range 0-288) h<br><br>Multivariate analysis:<br>Model 1:<br>Risk increase for each 1 h increase in period of febrile illness, adjusted for ANC and CRP:<br>OR 1.01 (95% CI 1.00-1.03, p=0.01)<br>Model 2:<br>Risk increase for each 1 h increase in period of febrile illness, adjusted for WBC and CRP:<br>OR 1.01 (95% CI 1.00-1.02, p=0.05) |

**Supplement 3.** Details of the included studies on the predictive value of prior duration of fever and serious bacterial infection (SBI). (continued)

| *Author (year)* | *Design and setting* | *Inclusion criteria* | *Outcome* | *Prognostic factor* | *Results* |
|---|---|---|---|---|---|
| Fernandez-Lopez et al.[18] (2003) | Cross-sectional study<br><br>Secondary/ tertiary care emergency room, Spain<br><br>n=445 | - Age 1 to 36 months<br>- Treated for fever ≥ 38°C<br>- Requiring blood analysis | Localized bacterial infection:<br>- Bacterial tonsillitis<br>- Peritonsillar abscess<br>- Acute otitis media<br>- Mastoiditis<br>- Gastroenteritis in children aged > 3 months<br>- Lower urinary tract infection<br>Invasive bacterial infection:<br>- Meningitis<br>- Sepsis<br>- Bone/joint infection<br>- Acute pyelonephritis<br>- Lobar pneumonia<br>- Bacterial enteritis, age < 3 months<br>- Occult bacteremia<br><br>Diagnosis based on culture or rapid test or radiology or otorhinolaryngologist | Evolution of fever time, in hours, not further specified, probably prior to presentation<br><br>Measurement method not given, duration probably obtained by history taking | Evolution of fever time in<br>Viral infection:<br>36.2 ± 42.5 h<br>Bacterial infection:<br>37.1 ± 43.7 h<br>Invasive bacterial infection:<br>41.2 ± 47.2 h<br>Noninvasive infection:<br>33.3 ± 39.6 h<br><br>Univariate analysis:<br>Mean evolution of fever time compared between the groups was not significantly different |
| Hsiao et al.[19] (2006) | Cross-sectional study<br><br>Tertiary care emergency room,<br>USA<br><br>n=429 | - Age 57 to 180 days<br>- Rectal temperature > 37.9°C | SBI:<br>Bacteruria<br>Bacteremia<br><br>Diagnosis based on urine or blood culture;<br>Final diagnosis from computerized hospital records | Duration of fever before evaluation<br><br>Measurement method not given, duration probably obtained by history taking | Duration of fever in<br>SBI: 26.5 ± 41.5 h<br>No SBI: 18.6 ± 21.7 h<br><br>Univariate analysis:<br>Duration of fever before evaluation was significantly longer in infants with SBI compared with those without ($p<0.001$) |

**Supplement 3.** Details of the included studies on the predictive value of prior duration of fever and serious bacterial infection (SBI). (continued)

| *Author (year)* | *Design and setting* | *Inclusion criteria* | *Outcome* | *Prognostic factor* | *Results* |
|---|---|---|---|---|---|
| Trautner et al.[23] (2006) | Cross-sectional study<br><br>Tertiary care emergency room, USA<br><br>n=103 | - Age <18 years<br>- Oral, axillary, or ear temperature >40°C, and a rectal temperature ≥ 41.1°C | SBI: growth of a clinical significant bacterial pathogen from blood, urine, stool, cerebrospinal fluid, or any normally sterile body site | Duration of fever before presentation categorized in <24 h, 24-48 h, and >48 h<br><br>Measurement method not given, duration probably obtained by history taking | Risk of SBI predicted by fever:<br>- <24 h: 40% OR: reference group<br>- 24-48 h: 15% OR 0.30 (95% CI 0.07-1.26)<br>- >48 h: 45% OR 1.04 (95% CI 0.35-3.12)<br><br>Univariate analysis: duration of fever is not predictive of SBI rather than viral infection. |
| Pratt et al.[22] (2007) | Cross-sectional study<br><br>Tertiary care emergency room, USA<br><br>n=119 | - Age 1-36 months<br>- Fever documented or reported ≥ 39°C | SBI: bacteremia, meningitis, urinary tract infection, pneumonia, septic arthritis, and osteomyelitis<br><br>Diagnosis based on:<br>- Bacteremia: recovery of a single bacterial pathogen using standard culture techniques<br>- Urinary tract infection: growth of a single urinary tract pathogen at $\geq 10^4$ c.f.u./mL on a catheterized specimen<br>- Pneumonia: presence of a local infiltrate on chest X-ray as interpreted by the pediatric radiologist | Duration of fever at presentation ≤12 h or >12 h<br><br>Measurement method not given, duration probably obtained by history taking | ≤ 12 h fever and SBI: 13%<br>>12 h fever and SBI: 15%<br>OR 0.881 (95% CI: 0.302-2.574)<br><br>Univariate analysis:<br>No significant difference between the SBI positive and negative group within the ≤12 h and >12 h groups when compared by duration of fever |

**Supplement 3.** Details of the included studies on the predictive value of prior duration of fever and serious bacterial infection (SBI). (continued)

| *Author (year)* | *Design and setting* | *Inclusion criteria* | *Outcome* | *Prognostic factor* | *Results* |
|---|---|---|---|---|---|
| Guen et al.[24] (2007) | Cross-sectional study<br><br>Tertiary care emergency room, France<br><br>n=215 | - Age 3-36 months<br>- Unexplained fever of >39°C documented in the emergency department or at home. | SBI: bacteremia<br><br>Diagnosis based on:<br>Positive blood culture.<br>(the following cultures were considered as contaminants: Corynebacteria, Staphylococcus epidermidis, Staphylococcus hominis, Staphylococcus capitis, Bacillus sp., Streptococcus mitis) | Duration of fever at presentation in hours<br><br>Measurement method not given, duration probably obtained by history taking | Duration of fever:<br>Overall median: 24 (range 0.25-192) h<br>SBI: 4.6 (± 3.13) h |

# Chapter 4

# Predictors of a prolonged duration of fever in febrile children: a prospective cohort study in primary care

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Submitted

## ABSTRACT

### Context

Although fever in children in primary care is often caused by benign infections, it often worries parents. Information about the duration of fever and its predictors may help to reassure parents, leading to diminished consultation of health care.

### Objective

To determine which signs and symptoms predict a prolonged duration of fever in febrile children in primary care and to evaluate whether C-reactive protein (CRP) measurement has an additive predictive value for these symptoms.

### Design

Prospective cohort study.

### Setting

General Practitioners Cooperative (GPC) out-of-hours service.

### Patients

Children (aged 3 months-6 years) presenting with fever as stated by the parents. Exclusion criteria were: no communication in Dutch possible, previous enrolment in this study in the past two weeks, referral to the hospital directly after visiting the GPC, or no informed consent.

### Main outcome measures

Prolonged duration of fever (>3 days) after initial contact.

### Results

Of the 480 children analysed, overall risk of prolonged duration was 13% (63/480). Multivariate analysis showed that 'throat ache' (OR:2.8; 95%CI:1.30-6.01) and 'lymph nodes palpable' (OR:1.87; 95%CI:1.01-3.49) are predictive for prolonged duration of fever. The discriminative value of the model was low (AUC:0.64). CRP had no additive value in the prediction of prolonged duration of fever (OR:1.00; 95%CI:0.99-1.01).

### Conclusions

The derived prediction model indicates that only a few signs and symptoms are related to prolonged duration of fever. CRP has no additional value in this model. Overall, because the discriminative value of the model was low, the duration of fever cannot be accurately predicted with our model.

## INTRODUCTION

Fever in children is a frequent reason for parents to contact a general practitioner (GP).[1] It is a common symptom in children, often caused by benign infections with no need for medical intervention. Little is known about the natural course of fever in children,[2, 3] and (prolonged) duration of fever before presentation to health care has no well-established predictive value for the presence of a serious bacterial infection.[4, 5] However, the health-related quality-of-life is reported to be significantly lower in febrile children who remained febrile after ≥7 days.[6] Therefore, prolonged duration of fever seems to play an important role in perceived health. A longer duration of fever in children is related to return visits to the emergency department (ED) and concerns about fever may contribute to a significant number of return visits to the ED.[7] Parents may have significant concerns about the potential adverse effects of fever; a phenomenon also known as 'fever phobia'.[8, 9] Knowledge of the expected duration and the signs/symptoms that are related to prolonged duration of fever may be helpful in informing and instructing patients or parents, resulting in more efficient healthcare use. Educating parents about the expected duration of fever may lead to a reduced rate of returning to medical care, without increased health risk. In addition to this, the value of measuring C-reactive protein (CRP) is not clearly established in primary care.[10]

Therefore, in this context, we assessed the predictive value of signs/symptoms for prolonged duration of fever in febrile children presenting at a GP cooperative (GPC) out-of-hours service, and determined the additive value of CRP to these signs/symptoms when predicting prolonged duration of fever.

## METHODS

This cohort study was performed at a GPC out-of-hours service in Rotterdam, a large multi-ethnic city in the Netherlands. This GPC covers an area encompassing about 300,000 inhabitants.

### Study procedures

Between December 2004 and January 2006 during Monday through Thursday, in the evenings and night, consecutive children were included if they were aged between 3 months and 6 years, and presented with fever as stated by the parents. Fever had to be the main reason for the contact. Children were excluded if communication in Dutch was impossible, if the child had already been enrolled in this study in the past two weeks, if the child was referred to the hospital directly after visiting the GPC, or if the parents declined to give informed consent.

When parents contacted the GPC by telephone concerning their febrile child, the receptionists performed the standard triage based on the triage guideline of the Dutch College of General Practitioners (NHG).[11] In addition, for the present study, the receptionists completed a questionnaire related to triage items. Based on this triage, parents received either telephone advice, or the advice to attend the GPC out-of-hours service (physical consultation), or a home visit by a GP was arranged. The GPs were free to prescribe treatments of their own choice, or to refer the child.

### Measurements

For the purpose of this study, for all children, an additional home visit by a trained research nurse was arranged within 24 h of inclusion. Using a structured questionnaire, the research nurse recorded demographic data, signs and symptoms, physician contacts, and prescribed medication, as reported by the parents. In addition, a standardised physical examination (including rectal temperature) was performed.

Dyspnoea was defined as an elevated respiratory rate, taking age into account,[12] and nasal flaring or chest wall retractions. The score on the Yale Observation Scale (YOS) was part of the structured physical examination; this has a six-item score used to predict the severity of illness in febrile children.[13] Duration of fever previous to the consultation with the GPC was determined in days and calculated using the date of contact, and the date of the first recognised fever. During the home visit, capillary blood was obtained to measure CRP values (Nycocard CRP test, Clindia Diagnostics, Leusden, the Netherlands).[14] Values of CRP measurements ranged from 8-250; for our analysis purposes values <8 and >250 were considered as 7 and 251, respectively.

### Follow-up

Parents received a thermometer and a demonstration on how to use the thermometer. Using a structured diary during 1 week, parents reported rectal temperature twice a day and, once a day, details of symptoms, medical care contacts and use of antibiotics. Diaries were returned to the researchers by post. Fever was defined as a rectal temperature of ≥ 38.0°C.

### Outcome measurement

The main outcome measure was prolonged duration of fever (>3 days), as reported by the parents in the diaries starting on the day of the home visit. We chose a duration of > 3 days as a definition for prolonged duration of fever, since the Dutch guideline for feverish children states that children with three days of fever need physical assessment by a physician.[15] Duration of fever was calculated per day. When a diary was not completed, but the child was not febrile on the last-notated day, we assumed that the child had recovered from the fever. When data were insufficient to calculate duration of fever, multiple imputation was performed using the data available from the diaries, and from

the patient history and physical examination (see Statistical analysis below). Within this period, febrile episodes with one 'fever-free' day were considered as one episode. When there were two fever-free days, the next day with fever was considered as a new episode; this new episode was not incorporated in the analyses (n=27). The study was approved by the Dutch Central Committee on Research Involving Human Subjects.

### Statistical analysis

Patient characteristics and frequency of prolonged duration of fever were analysed using descriptive statistics. Variables possibly related to prolonged duration of fever were analysed with bivariate and multivariate logistic regression. First, variables showing a bivariate statistical association of $p<0.157$ (Supplemental 1)[16] were entered in multivariate models concerning separate patient history, and physical examination. Second, variables with a multivariate statistical association of $p<0.157$ with prolonged fever were combined in one model. Manual backward logistic regression was performed on this model using a cut-off of $p<0.157$, adjusting for duration of fever prior to consultation. If multicollinearity was present between similar variables in patient history and physical examination (suspected when large changes occurred in the estimated regression coefficients when a variable was entered or deleted from the model) the variable concerning physical examination was dropped. Duration of fever prior to contact with the GPC was added to the multivariate model to adjust for confounding; additionally, antibiotic prescription at the GPC was tested for possible confounding by adding this to the final model and to search for significant changes in the odd ratios (ORs). Finally, CRP was added to this model to determine the additive value. The discriminative ability of both models was assessed using the area under the receiver operating characteristic (ROC) curve (AUC). Missing data were imputed using multiple imputation.[17] Multiple imputation was performed using MICE in R-2.11.1 for Windows. Data were analyzed using SPSS version 17.0.2 for Windows (SPSS, Inc, Chicago, Ill, USA).

## RESULTS

### Description of the population

A total of 506 children were included in the original cohort. Of these, 26 were directly referred to the hospital and excluded from this analysis, leaving 480 eligible children (Figure 1). Of 162 children, the duration of fever after consultation could not be directly calculated (due to incomplete diaries) but was estimated using multiple imputation. Median age of the included children was 21 (IQR 10-38) months. Median rectal temperature at the time of assessment was 37.6°C (IQR: 37.0-38.1°C). In total, 63 children had fever lasting > 3 days. Median duration of fever after initial contact with the GP was 1

day (IQR 0-2, follow-up was limited to 7 days). Median duration of fever prior to consultation was 2 (IQR 1-3) days. Additional patient characteristics are presented in Table 1.

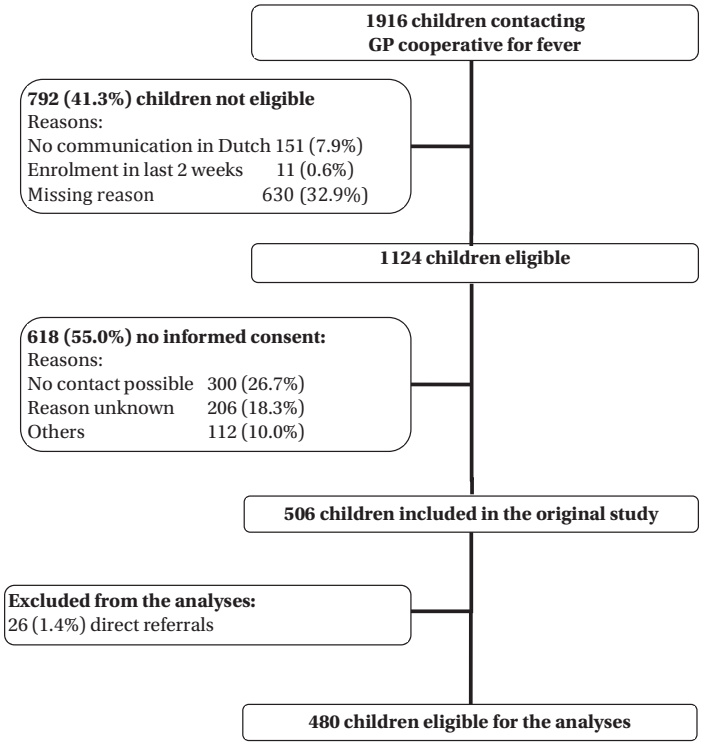


**Figure 1.** Flowchart of the eligible children.

**Table 1.** Characteristics of the study population (n=480).

| *Characteristics* | *No. of patients / Total no. of patients* | *Percentage* |
|---|---|---|
| Age: 3 - <6 months | 35/480 | 7.3 |
| 6 - <12 months | 95/480 | 19.8 |
| ≥12 months | 350/480 | 72.9 |
| Rectal temperature ≥ 38.0°C | 154/480 | 32.1 |
| Ill appearance | 43/480 | 9.0 |
| Duration of fever prior to consultation (days) | 2 (median) | 1-3 (IQR) |
| Duration of fever after consultation (days) | 1 (median) | 0-2 (IQR) |

IQR: Interquartile range.
The physical examination forms included categorical variables with possible answers: 'no, little, very, very much'. These variables were dichotomised using a cut-off point between 'little' and 'very'.

### Univariate logistic regression

Univariate logistic regression showed that most of the signs and symptoms were not related to prolonged duration of fever (Supplemental 1). CRP showed an univariate OR of 1.00 (95% CI 0.99-1.01).

### Multivariate logistic regression

Multivariate logistic regression for patient history showed that 'throat ache' (OR 2.26, 95% CI 1.17-5.37) was significantly (p<0.157) associated with prolonged duration of fever (Table 2). The multivariate logistics regression for physical examination indicated that 'signs of throat infection' (OR 2.21, 95% CI 1.10-4.41) and 'lymph nodes palpable' (OR 1.74, 95% CI 0.92-3.27) were related to prolonged duration of fever (Table 3).



**Table 2.** Multivariate analysis of variables concerning patient history.

| Variables | OR | 95%CI | p-value |
|---|---|---|---|
| Diarrhea | 1.60 | 0.82-3.09 | 0.17 |
| Moaning | 1.50 | 0.80-2.81 | 0.21 |
| Ear ache | 1.49 | 0.73-3.06 | 0.28 |
| **Throat ache** | **2.51** | **1.17-5.37** | **0.02** |

Bold: p<0.157
The patient history forms included categorical variables with possible answers: 'no, little, very, very much, and do not know'.
These variables were dichotomised using a cut-off point between 'little' (including 'do not know') and 'very'.

**Table 3.** Multivariate analysis of variables concerning physical examination.

| Variables | OR | 95%CI | p-value |
|---|---|---|---|
| **Palpable lymph nodes** | **1.74** | **0.92-3.27** | **0.09** |
| **Sign of throat infection** | **2.21** | **1.10-4.41** | **0.03** |
| Rectal temperature ≥38.0°C | 1.76 | 0.79-3.95 | 0.18 |

Bold: p<0.157
The physical examination forms included categorical variables with possible answers:
'no, little, very, very much'. These variables were dichotomised using a cut-off point between 'little' and 'very'.

The combined model of both patient history and physical examination showed that 'throat ache' (OR 2.80, 95% CI 1.30-6.01) and 'lymph nodes palpable' (OR 1.87, 95% CI 1.01-3.49) were predictive for prolonged duration of fever (Table 4). Of all the children, 34% with throat ache and palpable lymph nodes had a prolonged duration of fever compared with 11% of the children with none of these signs. The mean AUC was 0.64 (SD 0.02). CRP showed no additive value to this model for predicting prolonged duration of fever (OR 1.00, 95% CI 0.99-1.01), with the mean AUC remaining at 0.64 (SD 0.03). Table 5 shows the

**Table 4.** Prediction model for prolonged duration of fever, with and without CRP.

| Variables | OR | 95%CI | p-value | OR | 95%CI | p-value |
|---|---|---|---|---|---|---|
| **Throat ache (PH)** | **2.80** | **1.30-6.01** | **0.01** | **2.81** | **1.30-6.04** | **0.01** |
| Palpable lymph nodes (PE) | 1.87 | 1.01-3.49 | 0.05 | 1.87 | 1.00-3.49 | 0.05 |
| Duration of fever prior to consultation (PH) | 0.93 | 0.79-1.10 | 0.39 | 0.93 | 0.79-1.10 | 0.40 |
| CRP | | | | 1.00 | 0.99-1.01 | 0.89 |
| Area Under the Curve (Mean, SD) | | 0.64 (0.02) | | | 0.64 (0.03) | |

Bold: p<0.05
PH: patient history.
PE: physical examination.
Multicollinearity: There was multicollinearity between 'throat ache' and 'signs of throat infection.' Therefore, the variable concerning physical examination ('signs of throat infection') was dropped.
The patient history forms included categorical variables with possible answers: 'no, little, very, very much, and do not know'. These variables were dichotomised using a cut-off point between 'little' (including 'do not know') and 'very'.
The physical examination forms included categorical variables with possible answers: 'no, little, very, very much'. These variables were dichotomised using a cut-off point between 'little' and 'very'.

**Table 5.** Signs and symptoms of the final multivariate model and their relation with prolonged duration.

| | Percentage prolonged duration of fever: | |
|---|---|---|
| **Signs and symptoms included in analysis** | Sign present | Sign absent |
| Throat ache | 25% (18/72) | 11% (45/408) |
| Palpable lymph nodes | 17% (36/208) | 10% (27/272) |
| Duration of fever prior to consultation | NA | NA |
| CRP | NA | NA |

individual relation of the signs and symptoms of the final model with prolonged duration of fever.

## DISCUSSION

The present study shows that, for children not directly referred to secondary care, the median duration of fever after consultation with the GPC is 2 days. The multivariate analysis showed that throat ache and palpable lymph nodes were predictive for a duration of fever > 3 days. The predictive value of the model was considered low (AUC 0.64). CRP had no additive predictive value for prolonged duration of fever.

Throat ache had a predictive value for prolonged duration of fever. Other studies also reported that 60% of patients with a sore throat still have complaints after 3 days[18] and the duration of acute tonsillitis is approximately 5 days.[19] This is in line with our findings.

An acute infection (e.g. otitis media) has a relatively short symptomatic period (only 3% of children with otitis media has fever and/or pain after 3-4 days);[20] this is closer to our cut-off for prolonged duration and, therefore, had no predictive value in our model. A review on the duration of symptoms of respiratory tract infections reported similar trends; 28% of the children with sore throats had fever for ≥ 3 days.[21]

Besides duration of fever prior to contact with the GPC, antibiotic prescription at the GPC was added to the model to control for potential confounding (data not shown). However, because antibiotic prescription at the GPC did not influence the model, for reasons of clarity, this was removed from the model. Duration of fever prior to consultation with the GPC was not significantly related to prolonged duration of fever. We expected to find a relation between the duration of fever as reported on consultation and the duration of fever in the follow-up. However, due to a broad variation in the duration of fever in children in primary care,[2] a straightforward relation may not be applicable in this setting.



In this primary care cohort, CRP had no additional value for predicting prolonged duration of fever. Further research is needed to determine the additive role of CRP in managing febrile children in primary care, e.g. the predictive value for serious infections, support regarding whether or not to prescribe antibiotics, and/or the planning of scheduled revisits.

A limitation of the present study is that the research nurse noted the patient's history and made the physical examination the day after the patient had made contact with the out-of-hours service. This study design was chosen because we did not want to interfere with the regular care of the out-of-hours service (especially in the case of telephone advice without face-to-face contact).[2, 22] However, the research nurse specifically asked for the signs that were present at the time of consultation with the out-of-hours service. In addition, the median time that elapsed between time of consultation with the out-of-hours service and our home visit was only 14.5 h.

A further limitation is the substantial loss to follow-up, i.e. insufficient data to calculate the duration of fever. We performed a complete-case analysis with the final model, showing a stronger relation of the included variables to prolonged duration of fever (data not shown). We solved this problem by using multiple imputation; moreover, as multiple imputation is considered the most appropriate way of dealing with missing data[23] only the imputed results are presented here.

The derived model had a low predictive value for prolonged duration of fever. The median AUC was only 0.64 (SD 0.02), indicating that the performance of the model is suboptimal. Therefore, with this model it is not possible to make a valid prediction as to whether children will or will not have prolonged duration of fever.

In conclusion, although a few signs and symptoms are predictive for a prolonged duration of fever, the discriminative value of the model is low. It is of interest to know that fever in children has a median duration of 4 days[2] but, at present, we cannot predict prolonged duration of fever in any individual patient.

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**Supplement 1.** Univariate analyses of signs and symptoms and prolonged duration of fever.

| Variables | Percentage prolonged duration of fever: | |
|---|---|---|
| | Sign present | Sign absent |
| *Patient history (Signs present at moment of contacting out-of-hours service)* | | |
| Duration of fever prior to contact | NA | NA |
| Different illness than usual | 15% (39/261) | 11% (24/219) |
| Inconsolable crying | 13% (29/222) | 13% (34/258) |
| Crying during diaper change | 13% (18/143) | 13% (45/337) |
| Crying when picked up | 12% (16/139) | 14% (47/341) |
| Diarrhoea | 18% (21/117) | 12% (42/364) |
| Vomiting | 16% (26/160) | 11% (36/321) |
| Drowsy/difficult to wake | 11% (27/237) | 15% (36/243) |
| Pale/grey/spotted skin | 12% (29/239) | 14% (34/241) |
| Skin rash | 12% (12/98) | 13% (51/382) |
| Moaning | 16% (37/230) | 10% (26/250) |
| Febrile seizure | 26% (7/27) | 12% (55/453) |
| Comorbidity | 11% (11/96) | 14% (52/384) |
| Age (months) | NA | NA |
| Played as usual | 14% (40/283) | 12% (23/197) |
| Normal reaction to parents | 10% (4/42) | 13% (59/438) |
| Restless/confused | 14% (20/141) | 13% (43/339) |
| Irritable/irritated | 16% (28/172) | 11% (34/308) |
| Drinking less than half than usual | 14% (24/172) | 13% (39/308) |
| Ear ache | 18% (15/82) | 12% (47/398) |
| Runny nose | 15% (24/158) | 12% (39/322) |
| Coughing | 15% (25/163) | 12% (38/317) |
| Throat ache | 25% (18/72) | 11% (45/408) |
| Abdominal pain | 18% (14/78) | 12% (49/402) |
| Concerned parents during home visit | 18% (15/82) | 12% (47/398) |
| *Physical examination* | | |
| Yale Observation Scale | NA | NA |
| Ill appearance | 17% (7/42) | 13% (56/438) |
| Coughing | 16% (29/179) | 11% (34/301) |
| Rinorrhoea | 12% (31/257) | 14% (32/223) |
| Dyspnoea | 14% (19/140) | 13% (43/340) |
| Capillary refill (>2 sec) | 13% (4/31) | 13% (59/449) |
| Palpable lymph nodes | 17% (36/208) | 10% (27/272) |
| Chin on chest | 5% (1/21) | 13% (61/459) |
| Rectal temperature ≥ 38.0°C | 18% (28/154) | 11% (35/326) |
| Signs of throat infection | 20% (33/166) | 10% (30/314) |
| Earache resulting in altered reaction or sleeping pattern | 21% (8/38) | 12% (55/443) |
| CRP | NA | NA |

The history and physical examination forms included categorical variables with possible answers: 'no, little, very, very much'. These variables were dichotomised using a cut-off point between 'little' and 'very'.
Categorical variables with possible answers: 'no, little, almost normal, normal' were dichotomized using a cut-off point between 'no' and 'little'.
Diarrhoea was characterised as reported diarrhoea more than twice a day.
Comorbidity was considered positive when the child was under treatment of a paediatrician or ENT physician

# Chapter 5

# C-reactive protein level as prognostic marker in young febrile children presenting at a general practice out-of-hours service

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Submitted

## ABSTRACT

### Background

C-reactive protein (CRP) point-of-care tests are increasingly available in general practice. In young febrile children, it is unclear how well a CRP value predicts a serious infection (SI) in general practice.

### Objectives

To describe C-reactive protein (CRP) levels in young febrile children presenting to a general practitioners' cooperative (GPC) out-of-hours service and evaluate whether CRP-level has additive predictive value for diagnosing SI (defined as a general practitioners' (GP) diagnosis of a serious illness or referral to a pediatrician) either at presentation or during one week follow-up.

### Design

Prospective cohort study with one week follow-up.

### Setting

a GPC.

### Participants

children aged 3 months to 6 years presenting with fever.

### Methods

Capillary blood samples were obtained to measure CRP-level. GP and hospital records were examined for diagnoses and referrals during one week after initial presentation.

### Index test

CRP-level ≤20mg/L and CRP >80mg/L.

### Reference standard

SI at presentation or during follow-up.

### Main outcome measures

Post-test probability, positive and negative likelihood ratio (LR)

### Results

CRP-level was available for 440 children. To rule *out* SI, CRP ≤20mg/L did not change the probability to have *no* SI (87.5%); to rule *in* SI, CRP >80mg/L increased the probability to

have a SI from 12.5% (pre-test probability) to 21.2% (post-test probability). In children without a diagnosis of SI at presentation, CRP could not predict SI during follow-up (CRP > 80mg/L: LR+ 1.9, 95%CI 0.8-4.1, CRP ≤20mg/L: LR- 1.0, 95%CI 0.7-1.6). CRP-level did not change the probability of SI or of *no* SI in children with or without an alarming sign at physical examination.

### Conclusions

CRP has no clinically relevant additive predictive value for estimating the risk of SI in febrile children in general practice.

## INTRODUCTION

Most young febrile children presenting in primary care suffer from self-limiting infectious diseases. Very few children develop a serious infection (SI) that might require an antibiotic prescription or referral to a pediatrician.[1, 2]

C-reactive protein (CRP) is an acute-phase protein showing increased blood levels during infections.[3] A high CRP-level is a prognostic marker for pneumonia in adults presenting in primary care[4-6] and for serious bacterial infections in children visiting a pediatric emergency department.[7]

Although the CRP-level is often routinely measured at pediatric departments, testing for CRP-level has little influence on decision-making.[8] From that perspective, and based on a systematic review, it was suggested that different cut-off levels could be used to rule in or rule out SI in febrile children;[9] however, no study in the latter review was performed in a low prevalence general practice setting.

Furthermore, all studies performed until now evaluated whether CRP predicts SI at presentation (cross-sectional design). No study has evaluated whether CRP predicts the development of SI.

Using point-of-care tests, CRP-levels are available within minutes;[10] moreover, an increasing number of general practitioners (GP) has the possibility to test CRP-level at point-of-care. However, in Dutch primary care guidelines, CRP point-of-care tests are still not recommended for children due to lack of evidence regarding their diagnostic or prognostic value in this young population.[11, 12]

Therefore, the present study aims to evaluate whether the CRP level in young febrile children presenting to a GP cooperative (GPC) out-of-hours service has predictive value for diagnosing SI at presentation or during one week follow-up, and to determine whether this predictive value has additive value above history taking and physical examination.

## METHODS

### Design and setting

This prospective cohort study was performed at a GPC in the southern part of Rotterdam. This GPC serves an area of 300,000 inhabitants. The study was approved by the Dutch Central Committee on Research Involving Human Subjects.

### Population

Between December 2004 and January 2006 all consecutive children aged 3 months to 6 years for whom their parents called the GPC concerning their febrile child were eligible for inclusion. Fever (as reported by the parents) had to be a reason to contact the GPC. The

child was excluded if parents could not communicate in Dutch, if there was no informed consent, or if the child had been enrolled in the study in the previous two weeks.[2, 13]

### Index test

Capillary blood was obtained as soon as possible, but within 24 hours of inclusion. The measurement of CRP was performed with the Nycocard CRP test (Clindia Diagnostics, Leusden, the Netherlands) directly after physical examination. The Nycocard CRP test is a point-of-care test that can be carried out within 5 minutes and correlates well with a reference test performed in the laboratory.[10]

GPs, pediatricians and parents were not informed about the level of CRP. In some children CRP-level was not obtained for the purpose of the study due to referral to hospital at the moment of CRP measurement. These latter children were included if a CRP level measured by the pediatrician was available. If children showed resistance against the finger prick, this was interpreted as no informed consent from the child and the finger prick was not performed.



### Reference standard

'Serious infection (SI)' was our reference standard. We defined the presence of 'SI' when the child was referred to a pediatrician or was diagnosed with a serious illness by the GP at initial presentation or during follow-up. In addition, we defined 'SI at presentation' when the child was referred or was diagnosed with a serious illness at presentation, and we defined 'SI during follow-up' when the child was referred or was diagnosed with a serious illness during follow-up.

Serious illnesses included pneumonia, sepsis, meningitis, encephalitis, pyelonephritis, osteomyelitis, cellulitis, erysipelas, abscess, dehydration (caused by gastro-enteritis or unknown cause), febrile convulsion, asthma exacerbation with fever and, in children aged ≤ 1 year, bronchiolitis. The GPC records were examined for diagnostic codes registered according to the International Classification of Primary Care (ICPC) and noted by the GP. In children with a re-consultation of their own GP during follow-up, the GP records were examined for diagnostic codes. If a contact was not coded, a team of three GPs allocated an ICPC code based on the (uncoded) diagnosis made by the GP or, if this diagnosis was missing, based on noted symptoms and findings at physical or history examination. The team was blinded to the triage result, CRP level, and to the management of the GP. Final coding was based on consensus.[2, 13]

### Procedures

When parents contacted the GPC, the triage nurses performed their usual triage based on the practice guideline of the Dutch College of General Practitioners.[11] Based on this triage, parents received advice by telephone or a face-to-face contact was arranged. GPs

were free to prescribe the treatment of their choice or to refer the child to a pediatric emergency department.

A trained research nurse visited all children at home within 24 hours of inclusion (median 14 hours, range 5-21 hours). Using a structured questionnaire the research nurses recorded demographic data, physician contacts and prescribed antibiotics as reported by the parents. In addition, a standardized physical examination (including clinical features of alarming signs and rectal temperature) was performed. The records of the child's own GP were examined for diagnoses and referrals during 7 days after inclusion. In case of referral, pediatric records were examined for CRP-levels.

### Alarming signs

To test whether CRP-level has additive predictive value for diagnosing SI in the absence or presence of an alarming sign, we defined four serious alarming signs. The choice of alarming signs was based on national and international guidelines and defined before analyses.[11, 14] 'Alarming signs at physical examination' were defined as present if at least one of the four criteria listed was found during physical examination: i) 'drowsiness' was defined as 'a poor or moderate alertness'; ii) 'abnormal circulation' was defined as 'a capillary refill > two seconds', 'a poor or moderate peripheral circulation of the skin (skin color)' or a tachycardia'; iii) 'shortness of breath' was defined as 'chest indrawings', 'nasal flarings' or 'an increased respiratory rate'; and iv) 'dehydration' was defined as 'a capillary refill > two seconds' or 'sunken fontanel' if the child was aged ≤ 1 year.[15]

### Antibiotic prescription

Antibiotic prescription was reported by the parents and defined as 'antibiotic prescription at presentation' (either by the GP at the GPC or by the pediatrician after direct referral), or 'antibiotic prescription before contact with the GPC' or 'antibiotic prescriptions after one week'.

### Statistical analyses

Comparisons between children with and without measurement of CRP level were made with Students' t-test or Pearsons' Chi-square test, as appropriate.

We used two different cut-off levels for CRP based on those recommended by Van den Bruel et al, i.e. ≤ 20 mg/L to exclude SI and > 80 mg/L to include SI.[9] We constructed 2x2-contingency tables for the two cut-off levels of CRP and SI to calculate sensitivity, specificity, positive likelihood ratio (LR+) and negative likelihood ratio (LR-). Probabilities with a 95% confidence interval (CI ) were calculated using OpenEpi.[16] Children with 'SI at presentation' were excluded from the analyses of 'SI during follow-up'.

Subgroups of children with and without alarming signs were analyzed separately to test whether CRP has an additive predictive value for diagnosing SI.

We assumed that antibiotics given before the measurement of CRP could influence the relation between CRP and SI. We tested this assumption by evaluating the association between CRP and SI in children with antibiotic prescription before or at presentation and in children without antibiotic prescription before or at presentation.

### Missing values

Of the 440 included children, in 13 (3.0%) no alarming signs were noted. In 12 of these 13 children alarming signs were not noted due to admission to hospital. Given the recommendation in the Dutch guideline to refer a child with alarming symptoms[11] we assumed that, in those 12 admitted children, alarming signs were positive.

## RESULTS



In the original study 506 children were included. Of these, 66 children showed resistance to the finger prick, which was defined as no informed consent from the child for this analysis. Finally, a CRP-level was available for 440 children. Table 1 presents comparisons between the children with and without measurement of CRP-level.

**Table 1.** Characteristics of children with (n=440) and without measurement of CRP (n=66).

| | **Children with CRP measured (n=440) n (%)** | **Children without CRP measured (n=66) n (%)** |
|---|---|---|
| Age (in months),* mean (sd) | **25 (17)** | **30 (18)** |
| median (range) | 20 (3-70) | 28 (3-66) |
| Gender (male) | 254 (57.7) | 35 (53.0) |
| Immigrant (yes) | 228 (51.8) | 31 (47.0) |
| Face-to-face contact with general practitioner at presentation | 327 (74.3) | 44 (66.7) |
| Antibiotic prescriptions before presentation | 37 (8.4) | 7 (10.6) |
| Referral at initial presentation** | **18 (4.1)** | **8 (12.1)** |
| Serious illness at presentation | 30 (6.8) | 8 (12.1) |
| SI at presentation | 35 (8.0) | 10 (15.2) |
| Referral after one week | 34 (7.7) | 8 (12.1) |
| Serious illness after one week | 44 (10.0) | 8 (12.1) |
| SI after one week | 55 (12.5) | 10 (15.2) |
| Antibiotic prescriptions after one week | 181/432 (41.9) | 23/58 (39.7) |

*Significant difference (mean difference = 5.7, 95% CI 1.2-10.1)

** Significant difference ($\chi^2 = 7.593$, df = 1, p-value = 0.00)

Of all 440 children, 55 (12.5%) had a SI. Of this latter group, 35 (8.0%) had a SI at presentation and 20 (4.5%) developed a SI during follow-up. The CRP-level ranged from <7 mg/L to >251 mg/L. Of all 440 children, in 232 (52.7%) the CRP-level was ≤20 mg/L and 66 children (15.0%) had a CRP-level >80 mg/L.

## CRP levels to rule in or rule out SI

For the test characteristics of the CRP-test to detect a SI (either at presentation and during follow-up) or to detect a 'SI during follow-up' see tables 2 and 3, respectively.

A CRP >80mg/L significantly increased the probability of a SI from 12.5% (55/440 children, 95% CI: 9.7-15.9) to 21.2% (14/66 children, 95% CI:13.1-32.5; p-value 0.03). A CRP >80mg/L at presentation increased the probability of a 'SI during follow-up' from 4.9% (95% CI:3.2-7.5, 20/405 children) to 8.7% (95% CI:3.8-18.9, 5/57 children, difference not significant, p-value = 0.17). In both groups LR+ was 1.9 (LR+: 1.9, 95% CI: 1.1-3.2 and LR+:1.9, 95% CI: 0.8-4.1, respectively).

A CRP ≤20mg/L did not change the probability of having *no* SI (*no* SI: pre-test probability: 87.5%, 95% CI:84.1-90.3, 385/440 children, post-test probability: 87.5%, 95% CI:82.6-91.2, 203/232 children) ('*no* SI during follow-up': pre-test probability: 95.1%, 95% CI:92.5-96.8, 385/405 children, post-test probability: 96.2%, 95% CI:91.0-97.1, 203/214 children). In both these groups the LR- was 1.0.

**Table 2.** Sensitivities and specificities for detecting SI (n=55) or no SI (n=385) in all children with CRP (n=440).

| | SI (n=55) | No SI (n=385) | Sensitivity (95% CI) | Specificity (95%CI) | Positive predictive value (95% CI) | Negative predictive value (95% CI) | LR+ | LR- |
|---|---|---|---|---|---|---|---|---|
| CRP> 20 mg/L *(yes/no)* | 26/29 | 182/203 | 47.3 (34.1-60.5) | 52.7 (47.7-57.7) | 12.5 (8.0-17.0) | 87.5 (83.2-91.8) | 1.0 (0.7-1.3) | 1.0 (0.8-1.3) |
| CRP > 80 mg/L *(yes/no)* | 14/41 | 52/333 | 25.5 (13.9-37.0) | 86.5 (83.1-89.9) | 21.2 (11.3-31.1) | 89.0 (85.9-92.2) | 1.9 (1.1-3.2) | 0.9 (0.7-1.0) |

**Table 3.** Sensitivities and specificities for detecting 'SI during follow-up' (n=20) or 'no SI during follow-up' (n=385) in children who had no SI at presentation (n=405).

| | SI (n=20) | No SI (n=385) | Sensitivity (95% CI) | Specificity (95%CI) | Positive predictive value (95%CI) | Negative predictive value (95%CI) | LR+ | LR- |
|---|---|---|---|---|---|---|---|---|
| CRP > 20 mg/L *(yes/no)* | 9/11 | 182/203 | 45.0 (23.2-66.8) | 52.7 (47.7-57.7) | 4.7 (1.7-7.7) | 94.9 (91.9-97.8) | 1.0 (0.6-1.6) | 1.0 (0.7-1.6) |
| CRP > 80 mg/L *(yes/no)* | 5/15 | 52/333 | 25.0 (6.0-44.0) | 86.5 (83.1-89.9) | 8.8 (1.4-16.1) | 95.7 (93.6-97.8) | 1.9 (0.8-4.1) | 0.9 (0.7-1.1) |

### Alarming signs

Of all 440 children, in 439 (99.7%) alarming signs at physical examination were assessed (n=427) or were assumed to be present (n=12).

Of these 439 children, 205 (46.7%) had at least one alarming sign at physical examination; of these 205 children, 34 (16.6%, 95% CI:12.1-22.3) had a SI. Of the 439 children, 234 (53.3%) had *no* alarming signs at physical examination; of these 234 children, 20 (8.5%, 95% CI: 5.6-12.8) had a SI.

In children with an alarming sign CRP > 80mg/L increased the probability of SI from 16.6% to 23.3% (95% CI:11.8-40.9, 7/30 children, difference not significant). In children without an alarming sign the probability increased from 8.5% to 17.1% (95% CI:8.3-33.5, 6/35 children, difference not significant). The LR+ was almost the same in both groups (1.2, 95% CI: 0.8-1.9 and LR+:1.5, 95% CI: 0.7-3.3, respectively).

In children with or without alarming signs CRP ≤ 20 mg/L did not change the probability of having *no* SI (*with* alarming signs: pre-test probability 83.4%, 95% CI:77.7-87.9, 171/205 children, post-test probability 80.8%, 95% CI:72.2-87.2, 84/104 children) (*without* alarming signs: pre-test probability 91.5%, 95% CI:87.2-94.4, 214/234 children, post-test probability 93.0%, 95% CI:87.2-96.3, 119/128 children). In both these groups LR- was around 1.0 (LR- 1.2, 95% CI: 0.9-1.6 and LR- 0.8, 95% CI: 0.5-1.3, respectively).



### Antibiotic prescriptions

Of the 440 children, 415 (94.3%) registrations of antibiotic prescriptions were available. Of these 415 registrations, 146 children (33.2%) received an antibiotic prescription (37 children prescribed before presentation, 109 at presentation n=109). Of the 146 children with an antibiotic prescription, 25 (17.1%, 95% CI:11.9-24.1) had a SI (either at presentation or during follow-up). CRP > 80 mg/L had a LR+ of 1.5 (95% CI: 0.7-3.1) to predict SI. CRP < 20 mg/L had a LR- of 1.0 (95% CI: 0.6-1.7) to predict *no* SI.

In the 269 children *without* an antibiotic prescription, 29 had a SI (10.8%, 95% CI: 7.6-15.1). CRP > 80 mg/L had a LR+ of 1.8 (95% CI: 0.8-4.1) to predict SI. CRP < 20 mg/L had a LR- of 1.1 (95% CI: 0.8-1.5) to predict *no* SI.

## DISCUSSION

### Summary of main findings

In 440 children a CRP-level was measured. A CRP > 80 mg/L increased the probability of a SI (either at presentation or during follow-up) from 12.5% (95% CI: 9.7-15.9) to 21.2% (95% CI:13.1-32.5) (statistically significant), and of a SI during follow-up from 4.9% (95% CI:3.2-7.5) to 8.7% (95% CI:3.8-18.9, difference not significant). In both these groups LR+ was 1.9. A CRP ≤ 20 mg/L was not able to preclude SI; in both groups the LR- was 1.0.

In children with and without alarming signs, CRP > 80 mg/L showed positive likelihood ratios to detect 'SI at presentation' that were almost the same (LR+ 1.2, 95%CI: 0.8-1.9 and LR+ 1.5, 95%CI: 0.7-3.3, respectively). In both groups CRP < 20 mg/L showed a LR- of 1.0.

Antibiotic prescription did not influence the association between CRP and the probability of SI.

### Strengths and limitations

A strength of the present study was that the outcome 'SI' was independent of the CRP-level, since the CRP-test result was blinded for the GP and the research team. Therefore, the CRP results could not have influenced a diagnosis of SI.

A limitation is that, in 13 children referred directly after initial presentation and without CRP-levels obtained for the study, the CRP-levels obtained by the pediatrician were used. Even though the pediatricians were aware of the CRP-level in referred children, the outcome SI was not influenced by including these CRP-levels since referral was already part of the outcome. Referred children are more likely to have a high CRP-level and to have a serious illness; we excluded referred children in case of missing data and this may have led to underestimation of the sensitivity.

A total of 66 children from the original study gave no informed consent for the finger prick and were therefore excluded from the present analysis. These latter children had a probability for SI that was similar to that of the included children. However, children without a CRP-measurement were older (overall by 5.7 months) than the 440 included children. This difference might be because older children are more likely to offer resistance to a finger prick than younger children. In addition, we assumed that all referred children would have had an alarming symptom; if this was not the case, then this assumption would slightly overestimate the prevalence of SI in children with an alarming symptom.[17] A similar effect in children without an alarming symptom will be negligible, due to the small numbers involved.

### Comparisons with existing literature

A systematic review on the diagnostic value of laboratory tests to identify SI in febrile children, examined five studies performed in an ambulatory setting (mainly referred children with intermediate to high prevalences of SI) and included children aged 1 month to 18 years (9). Our study, that included children aged 3 months to 6 years presenting at a GPC, the specificity of the cut-off CRP level of 80 mg/L to detect SI (86.5%, 95% CI: 83.1-89.9) is similar to that reported by Van den Bruel et al. (specificity >90%,),[9] although we found a lower sensitivity (25.5%, 95% CI 13.9-37.0 vs 40-50%). However, in our study, the sensitivity and specificity for the cut-off CRP level of 20 mg/L (sensitivity: 47.3%, 95% CI: 34.1-60.5, specificity: 52.7 95% CI: 47.7-57.7) were much lower than those reported by Van den Bruel et al. (sensitivity > 80%, specificity 70%).[9] In our study, the prevalence

of SI of 12.5% is comparable to studies with an intermediate prevalence in the systematic review (intermediate was defined as 5-20%).[9] Therefore, a difference in prevalence is not likely to explain the differences seen in the diagnostic values of CRP. A possible explanation could be that the definition of serious illnesses we used is much broader than that used by Van der Bruel et al.[9] For example, we also considered an illness to be serious in case of asthma exacerbation, convulsion, or referral, because in general practice children with these conditions generally need (additional) medical care. However, by adding 'referral' to our definition of SI, we may have introduced some misclassification. We found that, in children directly referred after face-to-face contact at the GPC (n=25), the observed risk of serious illness was 72% and that 76% of the referred children was admitted to hospital (data not shown).[2] Therefore, misclassification of children without SI as having SI is estimated at around 30% to 25%; this might have influenced our results. However, after restricting our definition of SI to 'SI without referral' similar results were found (data not shown).



### Relevance for clinical practice

Using a CRP ≤ 20 mg/L to rule out SI, more than half of the children with a SI would have been missed (i.e. 29 of 55 children, 52.7%) and CRP > 80mg/L only identified 14 of the 55 children with a SI (25.5%) (Table 2). In addition, in children without SI at presentation, CRP had no clinically relevant predictive value for SI during follow-up (LR+:1.9, 95% CI: 0.8-4.1). In children with or without an alarming symptom, CRP had no additional discriminative value (LR+: 1.2, 95% CI: 0.8-1.9 and LR+:1.5, 95% CI: 0.7-3.3, respectively).

We assumed that antibiotics given before the measurement of CRP could influence the relation between CRP and SI. However, in children with and without antibiotics CRP ≤ 20mg/L the LR- was around 1. In children who received antibiotics before or at presentation (n=146), CRP > 80 mg/ had a LR+ of 1.5 (95%CI: 0.7-3.1). However, in children who received *no* antibiotic prescriptions at presentation (n=269), the LR+ of CRP > 80 mg/L was almost the same (LR+ 1.8, 95% CI 0.8-4.1). Therefore, we argue that an antibiotic prescription did not modify the association between CRP and SI.

Together, these findings lead us to conclude that CRP has no clinically relevant predictive diagnostic value for SI in this young population.

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# Chapter 6

# Antibiotic prescription in febrile children: a cohort study during out-of-hours primary care

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## ABSTRACT

### Background

Fever is common in children and often self-limiting, nevertheless antibiotics are frequently prescribed. We determined how often antibiotics were prescribed in children presenting with fever at a general practitioners' out-of-hours service and established the children's signs and symptoms related to antibiotic prescriptions.

### Patients

Children aged 3 months to 6 years with fever as the main reason for contact.

### Results

Of the 443 included children, 322 children had a face-to-face contact at the out-of-hours service. Of these, 117 (36.3%) were prescribed antibiotics, that is, 26.5% of the total study population. Concerned parents (OR, 2.02; 95% CI, 1.06 –3.58), ill appearance (3.26; 1.30–8.20), earache resulting in altered behavioral or sleeping patterns (2.59; 1.06–6.30), signs of throat infection (2.37; 1.35–4.15), and decreased urine production (2.00; 1.17–3.41) were positively associated with antibiotic prescription.

A negative association was found for age 3 to 6 months (0.17; 0.03– 0.74) and temperature (0.52; 0.37– 0.71).

### Conclusions

Antibiotics were prescribed in 1 out of 4 febrile children whose parents contacted the out-of-hours service. Items associated with antibiotic prescription provide insight into the general practitioners' decision-making process when assessing children with fever. These can be used as targets for strategies to diminish antibiotic prescription.

## INTRODUCTION

Fever in children is a frequent reason for parents to contact a primary care physician.[1] It is a common symptom in children, often caused by benign infections with no need for medical intervention. Nevertheless, because about 1% of the children with an acute infection have a serious infection,[2] there is a small risk for underlying serious infections that need medical treatment.

In the Netherlands, the management of children with fever in primary care is based on the guideline for the management of febrile children of the Dutch College of General Practitioners (NHG).[3] This guideline does not recommend routine use of antibiotics in children with fever without an apparent source. The American guideline for children with fever without source does have some recommendations about antibiotic treatment, – e.g. starting empirical antibiotics in children aged > 1 month when they are not meeting the predefined low-risk criteria for a serious bacterial infection.[4] However, these recommendations are subject to debate.[4-5]

In case of fever with a focus, Dutch treatment recommendations can be found in several disease-specific guidelines, most of which are relatively conservative concerning the use of antibiotics.[6-9] When compared to the American guidelines, the Dutch guidelines for sinusitis, and non-specific cough illness/bronchitis are comparable in their recommendations for antibiotic prescription.[10-11] The recommendations for antibiotic treatment for acute otitis media (AOM), and pharyngitis are in the Dutch guidelines more stringent than in the American.[12-13] For instance, in The Netherlands, AOM in children aged 6 months to 2 years is only treated with antibiotics under certain conditions (i.e. risk factors for complications, or sever illness), whereas in America for all these children antibiotic treatment is recommended. Another example is that in the Netherlands pharyngitis is not tested for a group A streptococcus infection, because it is thought not to make a difference in the general practitioners' (GP) decision making. In America however, it is common practice to test for a group A streptococcus infection, since it ís thought to influence the decision making process. All of these recommendations take into account patient characteristics (e.g. age, anatomic deformities); signs and symptoms (e.g. otorrhoea, no improvement after 3 days), and consider the possible risk of (progression to) a serious bacterial infection, but also that antibiotics may reduce the duration and severity of the disease.[14-15] Since serious infections are rare in primary care,[2] the latter reason may be applied more often. In addition, other (not medically-based) considerations may play a role in the GPs' decision to prescribe antibiotics (e.g. assuming that the patient or the parents expect antibiotics).[16-18]

In the last decades, the number of inappropriate prescriptions of broad-spectrum antibiotics has increased in the Netherlands.[19] Another Dutch study reported an overall antibiotic prescription rate of 35% for acute respiratory tract infections among preschool

children in primary care.[20] Overuse of antibiotics is an important factor in the development of bacterial resistance, and therefore prevention of unnecessary prescription is desirable.[21-22] Therefore, it is important to monitor the frequency of antibiotic prescriptions and to critically evaluate the signs and symptoms on which physicians base their decision to prescribe antibiotics. Appropriate consideration of these signs and symptoms may lead to better founded and, consequently, diminished antibiotic prescriptions.

The present study evaluates the frequency of antibiotic prescriptions in children presenting with fever at a GP cooperative (GPC) out-of-hours service, and assesses the patient characteristics associated with these prescriptions.

## METHODS

This cohort study was performed at a GPC in Rotterdam, a large multi-ethnic city in the Netherlands. This GPC covers an area encompassing about 300,000 inhabitants.

### Study procedures

Between December 2004 and January 2006 (during Monday through Thursday evenings) consecutive children were included if they were aged between 3 months and 6 years, presented with fever as stated by the parents. Fever had to be the main contact reason. Children were excluded: if communication in Dutch was impossible (n=151); if the child had already been enrolled in this study in the past two weeks (n=11); if the child was admitted to the hospital directly after visiting the out-of hours service (n=19); if they presented to the out-of hours service already having antibiotics for this condition (n=44); or if the parents declined to give informed consent (n=618).

When parents contacted the GPC by telephone concerning their febrile child, the receptionists performed the standard triage based on the triage guideline of the NHG.[23] In addition, for the present study, the receptionists completed a questionnaire related to triage items. Based on this triage parents received: either telephone advice; or the advice to attend the GPC (consultation); or a home visit by a GP was arranged. The GPs were free to prescribe treatments of their own choice, or to refer the patient. It should be noted that the GPC – in that time – had no access to the child's regular GP's medical record. Therefore, the GPC had no structured overview of the medical history of the patients. The records made at the GPC are digitally send to the childrens own GP the next day.

### Baseline and outcome measurements

For the purpose of this study, for all children an additional home visit by a trained research nurse was arranged within 24 h of inclusion. Using a structured questionnaire, the research nurse recorded demographic data, signs and symptoms that were present

at the time of contact with the GPC, physician contacts, and prescribed medication as reported by the parents; in addition, a standardized physical examination (including rectal temperature) was performed.

Tachypnea was defined as an elevated respiratory rate, taking age into account, as recommended by the guideline of the National Institute for Health and Clinical Excellence (NICE).[24] The Yale Observation Scale (YOS) score was part of the structured physical examination. The YOS has a six-item score to predict the severity of illness in febrile children.[25] Ill appearance was judged by the research nurse during the home visit. Duration of illness was determined in days and calculated using the date of contact, and the date of the first signs and symptoms of illness.

The Dutch Central Committee on Research Involving Human Subjects approved the study.

### Statistical analysis

The main outcome measure was antibiotic prescription (yes/no) by the GP at the GPC, as reported by the parents. Patient characteristics and frequency of antibiotic prescription were analysed using descriptive statistics. Variables possibly related to antibiotic prescription were analysed using bivariate and multivariate logistic regression. The choice of variables and the presumed associations were based on the recommendations of national and international guidelines.[3, 6-9, 24] All variables were bivariately tested, and the variables selected for multivariate analysis were based on their assumed relationship with antibiotic prescription. To allow for unexpected predictors, the multivariate analysis also included variables bivariately associated with antibiotic prescription (p-value <0.10). When there was an overlap between bivariately significant variables regarding patients' history and physical examination (e.g. runny nose), we selected the variables obtained during the patients' history taking, because these were considered to be the most valid for the signs and symptoms at the evening before, i.e. the moment of antibiotic prescription. Missing data were considered missing at random or missing completely at random (i.e. the missing data was not, or only slightly related to the outcome or other known variables), and were imputed using multiple imputation.[26] Multiple imputation was performed using MICE in R-2.11.1 for Windows.

Frequencies were calculated on the original data, and logistic regression was performed on the imputed data. In the multivariate logistic regression analysis, statistical significance was set at $p<0.05$. Calibration of the model was assessed using the Hosmer-Lemeshow test. The proportion of variability in the dataset that is accounted for by the statistical model was determined using Nagelkerke R-square. Data were analyzed using SPSS version 17.0.2 for Windows (SPSS, Inc, Chicago, Ill, USA).

## RESULTS

### Description of the population

We included 443 children in our analyses (figure 1). 247 (55.8%) were boys, and the median age of the total group was 20.0 (range 3-70) months. Mean rectal temperature at the time of assessment was 37.6°C (SD 0.90; median 36.7, range 34.8-40.0°C). In total, 117 children (26.5%) received a prescription for antibiotics at the GPC. The median duration between consultation of the GPC and home visit was 14.5 hours (range 5.42-25.4). Additional patient characteristics are presented in Table 1. Only children who had a face-to-face contact with a GP at the GPC(n=322) received a prescription for antibiotics; this occurred in 36.3% (117/322) of the children.

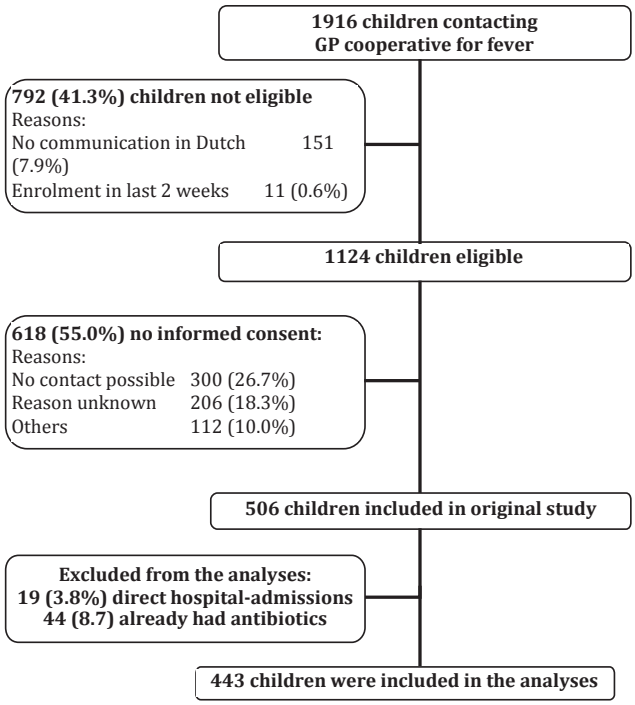


**Figure 1.** Flowchart of eligible children.

### Bivariate logistic regression

Bivariate logistic regression showed that (according to our predefined threshold of $p<0.10$), the following variables were significantly associated with antibiotic prescription: age 3 to 6 months, concerned parents at home visit, number of children in household, duration of illness, fever in past six months, vaccination in previous week, decreased urine production, increased rectal temperature, ill appearance, YOS score,

**Table 1.** Characteristics of the study population (n=443).

| Characteristics | No. of patients / Total no. of patients | Percentage |
|---|---|---|
| Age: 3 to 6 months | 35/443 | 7.9 |
| 6 to 12 months | 87/443 | 19.6 |
| ≥ 12 months | 321/443 | 72.5 |
| Male gender | 247/443 | 55.8 |
| Rectal temperature ≥ 38.0°C | 135/419 | 32.2 |
| Ill appearance | 42/436 | 9.6 |
| Duration of illness in days | 1.00 (median) | 0-43 (range) |

earache resulting in altered behavioural or sleeping pattern, signs of throat infection, and runny nose (based on patient history, and on physical examination). (Table 2, Table 3). Of these, 4 variables were based on the patients' history, 3 on physical examination, and 1 on demographic data.

### Multivariate logistic regression

Of the 15 variables included in the multivariate analysis, 8 were based on the expected association and 7 additional on the bivariate significance (Table 2). Signs and symptoms positively associated with antibiotic prescription were: concerned parents during home visit, ill appearance, earache resulting in altered behavioural or sleeping patterns, signs of throat infection, and decreased urine production. A negative association with antibiotic prescription was found for age 3 to 6 months, and increased rectal temperature. The model calibrated well: median p-value on the Hosmer-Lemeshow test was 0.55 (range 0.38-0.76). The median Nagelkerke R-square was 0.26 (range 0.24-0.28), indicating that only a small proportion of the antibiotic prescriptions is explained by the signs and symptoms.



## DISCUSSION

In the present study, about 1 in 4 children with fever, whose parents contacted the GPC, and who were not referred or already used antibiotics at initial presentation, received an antibiotic prescription. All antibiotics were prescribed during face-to-face contact with the GP: about 36% of the children with this type of contact were prescribed antibiotics. In the multivariate analysis, several signs and symptoms were significantly related to antibiotic prescription, providing insight into the GPs' decision-making process when assessing children with fever. Signs and symptoms, however, explained only a small proportion of the antibiotic prescriptions.

**Table 2.** Multivariate analysis of variables related to antibiotic prescription.

| Variables | Percentage antibiotic prescription | | Bivariate analysis | | | Multivariate analysis | | | |
|---|---|---|---|---|---|---|---|---|---|
| If characteristic is: | Present | Absent | OR | 95%CI | p-value | Selection | OR | 95%CI | p-value |
| *Patient characteristics* | | | | | | | | | |
| Age:3 to 6 months | **NA** | **NA** | **0.15** | **0.03-0.63** | **0.01** | **EA** | **0.17** | **0.03-0.74** | **0.03** |
| 6 to 12 months | | | 0.71 | 0.41-1.23 | 0.22 | | 1.03 | 0.55-1.94 | 0.93 |
| ≥12 months (reference group) | | | | | | | | | |
| Concerned parents at home visit | **36.1 (26/72)** | **25.1 (89/354)** | **1.70** | **0.99-2.91** | **0.05** | **EA** | **2.02** | **1.06-3.58** | **0.03** |
| Number of children in household | NA | NA | 1.25 | 1.00-1.56 | 0.05 | SS | 1.16 | 0.90-1.48 | 0.25 |
| *Patient history (Signs present at moment of contacting GPC)* | | | | | | | | | |
| Duration of illness at presentation (days) | NA | NA | 1.08 | 1.02-1.14 | 0.01 | EA | 1.05 | 0.99-1.12 | 0.11 |
| Fever in previous week | 35.5 (22/62) | 24.4 (73/299) | 1.58 | 0.82-3.04 | 0.17 | EA | 1.15 | 0.52-2.57 | 0.73 |
| Fever in past 6 months | 29.6 (85/287) | 20.3 (31/153) | 1.67 | 1.04-2.66 | 0.03 | SS | 1.33 | 0.78-2.26 | 0.30 |
| Vaccination in previous week | 10.7 (3/28) | 27.6(114/413) | 0.32 | 0.10-1.10 | 0.07 | SS | 0.34 | 0.08-1.38 | 0.13 |
| Decreased urine production | **35.7 (40/112)** | **22.6 (66/292)** | **1.84** | **1.16-2.91** | **<0.01** | **SS** | **2.00** | **1.17-3.41** | **0.01** |
| *Physical examination* | | | | | | | | | |
| Tachypnea | 19.1 (13/68) | 27.4 (75/274) | 0.71 | 0.36-1.40 | 0.33 | EA | 0.84 | 0.41-1.75 | 0.65 |
| Height of rectal temperature | **NA** | **NA** | **0.61** | **0.46-0.80** | **<0.01** | **EA** | **0.52** | **0.37-0.71** | **<0.01** |
| Ill appearance | **47.6 (20/42)** | **24.4 (96/394)** | **2.79** | **1.46-5.35** | **<0.01** | **EA** | **3.26** | **1.30-8.20** | **0.01** |
| YOS score | NA | NA | 1.08 | 0.99-1.18 | 0.07 | EA | 1.02 | 0.91-1.15 | 0.69 |
| Earache resulting in altered behavioural or sleeping pattern | **43.3 (13/30)** | **25.1 (95/378)** | **2.27** | **1.08-4.79** | **0.03** | **SS** | **2.59** | **1.06-6.30** | **0.04** |
| Signs of throat infection | **36.4 (40/110)** | **17.3 (38/220)** | **2.50** | **1.50-4.18** | **<0.01** | **SS** | **2.37** | **1.35-4.15** | **<0.01** |
| Runny nose (patient history) | 32.6 (46/141) | 23.2 (69/297) | 1.59 | 1.02-2.49 | 0.04 | SS | 1.57 | 0.94-2.60 | 0.08 |

Bold: multivariate p<0.05. NA= not applicable. EA = expected association. SS = bivariate statistical significance.

The physical examination forms included categorical variables with possible answers: 'no, little, very, very much'. These variables were dichotomised using a cut-off point between 'little' and 'very'.

Decreased urine production was considered if micturition was much decreased or if there was no micturition at all.

**Table 3.** Bivariate analysis of variables not included in the multivariate analysis of antibiotic prescription.

| Variables | OR | 95%CI |
|---|---|---|
| *Triage* | | |
| Concerned parents during triage | 1.17 | 0.70-1.93 |
| *Physical examination* | | |
| Coughing | 1.34 | 0.87-2.08 |
| Runny nose | **2.07** | **1.32-3.23** |
| Drooling | 1.33 | 0.79-2.23 |
| Nasal flaring during breathing | 1.11 | 0.12-10.64 |
| Capillary refill >2 sec | 1.45 | 0.63-3.33 |
| Abnormalities of the skin | 0.74 | 0.45-1.22 |
| Lymph nodes palpable in neck | 0.95 | 0.61-1.48 |
| Not able to get chin on chest | 1.55 | 0.42-5.77 |
| *Patient history (Signs present at moment of contacting out-of-hours service)* | | |
| Temperature measured at home before contacting the GPC | 0.63 | 0.32-1.22 |
| Child previously seen by own GP | 1.26 | 0.68-2.33 |
| GPC repeatedly contacted | 0.84 | 0.38-1.83 |
| Diarrhoea | 0.93 | 0.56-1.54 |
| Vomiting | 1.25 | 0.80-1.96 |
| Drowsy/difficult to wake | 1.41 | 0.92-2.16 |
| Pale/grey/spotted skin | 1.41 | 0.92-2.16 |
| Skin rash | 0.82 | 0.48-1.42 |
| Fast breathing | 1.44 | 0.93-2.23 |
| Moaning | 0.89 | 0.58-1.36 |
| Febrile seizure | 0.59 | 0.19-1.77 |
| Problems during previous febrile episode | 1.19 | 0.71-1.99 |
| Preterm labour | 0.81 | 0.45-1.46 |
| Under treatment of a paediatrician | 0.67 | 0.36-1.26 |
| Under treatment of an ENT physician | 1.33 | 0.56-3.16 |
| Received all recommended vaccinations | 1.49 | 0.41-5.37 |
| Language barrier | 1.44 | 0.67-3.07 |
| Played as usual | 0.80 | 0.51-1.23 |
| Drinking less than half than normal | 1.09 | 0.70-1.70 |
| Cough | 1.17 | 0.74-1.84 |
| Restless/confused | 0.99 | 0.62-1.58 |
| Irritable/irritated | 1.14 | 0.73-1.76 |
| Drooling | 0.95 | 0.55-1.65 |
| Different illness than usual | 1.21 | 0.78-1.88 |
| Eye contact | 1.10 | 0.60-2.03 |
| Inconsolable crying | 1.23 | 0.80-1.88 |
| Crying by picking up | 1.14 | 0.72-1.81 |

**Table 3.** Bivariate analysis of variables not included in the multivariate analysis of antibiotic prescription. (continued)

| Variables | OR | 95%CI |
|---|---|---|
| *Demographic data* | | |
| Gender (if male) | 1.27 | 0.83-1.95 |
| Country of birth of mother, not Dutch | 1.29 | 0.84-1.97 |
| Country of birth of father, not Dutch | 0.81 | 0.53-1.24 |
| Education of mother: high | 0.95 | 056-1.59 |
| Education of father: high | 1.10 | 0.69-1.76 |
| Ethnicity of child according to parents, not Dutch | 1.13 | 0.72-1.78 |
| Income | 1.08 | 0.92-1.26 |

Bold: p<0.10.
The history and physical examination forms included categorical variables with possible answers: 'no, little, very, very much'. These variables were dichotomised using a cut-off point between 'little' and 'very'.
Categorical variables with possible answers: 'no, little, almost normal, normal' were dichotomized using a cut-off point between 'no' and 'little'.
Diarrhoea was characterised as reported diarrhoea more than twice a day.
Decreased urine production was considered if micturition was much decreased or if there was no micturition at all.
Income was categorized before the analysis in net income per month: '<450 euro', '451-635', '636-860', '861-1135', '1136-1600', '1601-2270', '>2270 euro'.

In the present study, the amount of prescribed antibiotics was high. Especially when you consider that we excluded 44 children of our analysis who were already using antibiotics, so the total amount of antibiotic use is even higher (i.e. 161/506, 31.8%). In comparison with the US, and other European countries, Dutch GPs have one of the lowest overall rates of antibiotic prescriptions.[21, 27] In the Netherlands, Otters et al. investigated the antibiotic prescription in children per GP-contact and found that (in our age group of ≤ 6 years) about 12 percent was prescribed an antibiotic.[19] However, their percentage was based on all consultations, not solely on those concerning children with fever, and also included regular office hours. Other studies also described antibiotic prescription rates, but differences in the characteristics of the study population (e.g. only children with AOM, not solely febrile children)[27-30] complicate comparison.

An explanation for the considerable amount of antibiotic prescriptions in the present study could be that only children who contacted an out-of hours service were included. These children may be more seriously ill than those seen during regular office hours and therefore more eligible for antibiotic treatment. However, it seems unlikely that this selection of patients leads to more infections caused by bacteria, because the severity of illness is not solely determined by the causative agent. In addition, since only a small

proportion of the antibiotic prescription is explained by the reported signs and symptoms, other considerations may have contributed substantially.

Also, in the Netherlands, children and their families are all registered at one GP, who usually knows the child from previous visits. However, due to the organization of out-of-hours primary care, GPs in the Netherlands are generally not familiar with the patients they see at the GPC. Therefore, assessing the patient's expectations and providing adequate safety netting is more difficult. This could make managing the child's disease during out-of-hours service more difficult, leading to a more defensive treatment and, thus, to more antibiotic prescription.

The signs and symptoms that were multivariately related to antibiotic prescription can be clearly related to distinct disease profiles (i.e. rhinosinusitis, tonsillitis, acute otitis media). It was not our objective to judge whether or not the prescribed antibiotics were legitimate for individual cases, but rather to identify and discuss which factors may play a role in the GPs' decision-making process.

In the multivariate analysis, earache resulting in altered behavioural/sleeping patterns and signs of throat infection are significantly related to antibiotic prescription (OR 2.58; 95%CI 1.05-6.33 and OR 2.53; 95%CI 1.44-4.43, respectively). These can be related to the disease profiles for acute otitis media and tonsillitis, for which the Dutch guidelines for GPs have clear recommendations for antibiotic prescription under certain conditions.[6, 9] In these guidelines, the rationale for giving antibiotic treatment is mainly based on the possible reduction of duration and severity of illness.[14-15] Therefore, this seems to play an important role in the decision-making process of the GPs.

In the bivariate and multivariate analyses, both ill appearance, and parental concern as assessed by the research nurse were significantly associated with increased antibiotic prescription. Respectively, 47.6%, and 36.1% of the children had received antibiotics. Ill appearance is similar – although not identical – to the physician's opinion that 'something is wrong.' This, and parental concern has been shown to be important red flags in identifying children with serious infections in primary care.[31] Therefore, it seems rational to prescribe antibiotics for febrile children that appear to be ill, or have concerned parents. Because the home visit was performed *after* the GPs consultation, the research nurse might have assessed the child with antibiotics as more severely ill simply because the GP had prescribed antibiotics. Also, she might have judged the parents as more concerned. However, the research nurses were not aware of the research question thus it seems unlikely that this has led to important bias.

Decreased urine production was bivariately and multivariately associated with antibiotic prescription. Although this symptom indicates dehydration, none of the Dutch (or international) guidelines describes dehydration in children as an indication for antibiotic treatment.[24, 32] Therefore, it seems that, in at least a subgroup of our patients, antibiotics were not prescribed appropriately.

Children in the age of 3 to 6 months, and children with increased rectal temperature were associated with decreased antibiotic prescription. For logistical reasons, we did not include the children that were admitted to the hospital directly after their visit to the GPC (n=19). This seems to have introduced some selection bias, leading to these surprising findings. For instance, the children admitted to hospital were younger (median age 15 months, range 3-66, vs. 20 months in the children included in our analysis (range 3-70)), and it could be that they also had a higher rectal temperature (data not known), and may have received antibiotics but were not included in our analyses.

A further limitation is that the research nurse noted the patient's history and made the physical examination the day after the patient had contact with the GPC. We chose this study design, because we did not want to interfere with regular care of the GPC (especially in case of telephone advice without face-to-face contact). However, the research nurse specifically asked for the signs that were present at time of consultation of the GPC. In addition, the median time elapsed between time of consultation of the GPC and our home visit was only 14.5 hours. Given this short delay, it is unlikely that the antibiotic treatment started after the GP consultation influenced our findings by physical examination, as it generally takes longer to show effect than the interval we allowed between the GP consultation and our data collection.[33]

Only a small proportion of the antibiotic prescriptions is explained by the related signs and symptoms. Although our study does not allow further exploration of these unknown factors, it does indicate that other, non-medical factors may influence the GPs in their decision to prescribe antibiotics. This is in clear contrast with the national and international guidelines, that solely base their recommendations to prescribe antibiotics on medical considerations.[4-7,18] Previous studies have also shown that other (not medically-based) considerations may play a role in the GP's decision to prescribe antibiotics (e.g. assuming that the patient or the parents expect antibiotics).[10-12] In our study, we show that a substantial amount of the antibiotic prescriptions is prescribed on basis of these considerations.

## CONCLUSION

This study revealed a substantial amount of antibiotic prescriptions. Not all signs and symptoms associated with antibiotic prescription are in accordance with national and international guidelines for serious illness. It seems that the aim to decrease the duration and severity of the symptoms also plays a considerable role in the decision to prescribe antibiotic treatment. Moreover, since only a small proportion of the antibiotic prescriptions is explained by these signs and symptoms, other (non-medically-based) considerations may have played a role in the GP's decision to prescribe antibiotics. However, since serious infections are rare in primary care, and most febrile illnesses are self-limiting, GPs need to reflect on the legitimacy of their considerations regarding antibiotic treatment. Strategies that may diminish antibiotic prescriptions (e.g. safety netting) need to be further explored.

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# Chapter 7

# Alarming signs and antibiotic prescription in febrile children in primary care: an observational cohort study

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## 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.

## INTRODUCTION

General practitioners (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 (e.g. 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 alarming signs/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 that are clearly ill (e.g. 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 alarming sign or symptom, but do not appear to be seriously ill at 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/symptoms of these children.[4]

Therefore, the present study explores the prescription behavior of GPs in febrile children, with the aim to help diminish unnecessary antibiotic prescriptions in the future. For this, the study assesses whether well-defined alarming signs and symptoms[5-7] are related to antibiotic prescription in febrile children presenting at a general practitioners' cooperative (GPC) out-of-hours service.



## 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 GPC out-of-hours services of Rotterdam-Rijnmond between March 2008 and February 2009 (n=28,234). This district has five GPCs (totalling ≥ 250 GP practices) providing out-of-hours care for almost 1 million inhabitants living in this urban, multi-ethnic area. All five GPCs 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.[8-12] In the Netherlands, GPs rotate shifts at the GPCs to cover the out-of-hours primary care. Referral to the emergency department (ED) is required for about 5-10% of all primary care consultations[8, 13], which is similar to the referral rates in the UK, US and Canada.[14-15]

### 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 GPC 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 the ED, telephone consultations (in the Netherlands antibiotics are never prescribed by telephone), patients consulting the GPC 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[7], 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 (e.g. auscultatory sounds).[16] Selected, closely-related signs were grouped into a total of 18 alarming signs of serious febrile illness (Supplement 1). Using a data-entry computer program (Embarcadero Delphi XE, Version 15.0), all eligible contacts we recoded according to whether the grouped alarming signs were 'present', 'absent', or 'not mentioned' in the patient record. In addition, 'referral to ED,' or 'antibiotic prescription' by the GP was recoded as 'yes' or 'no.'

### Missing data

Since the alarming signs/symptoms were obtained from routinely collected, semi-structured data, missing values occurred for each variable (i.e. not mentioned in the record). Therefore, a consensus meeting was held with one GP, two paediatricians, one GP trainee, and one trainee-pediatrician 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; i.e. 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) we decided that the above statements were not applicable. For these variables, multiple imputation was performed if missing data were <70%.[17] 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 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.[18] 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-square. 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 GPCs 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, 8,676 patient contacts were available for the present analysis (Figure 1). In total, 3,167 of the contacts (36.5%) were prescribed antibiotics at the GPC. 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

Tables 2 presents the alarming signs/symptoms that were tested for their independent association with antibiotic prescription. Patient characteristics, and alarming signs/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-square of this final multivariate model was 0.19 (range 0.18 to 0.20).

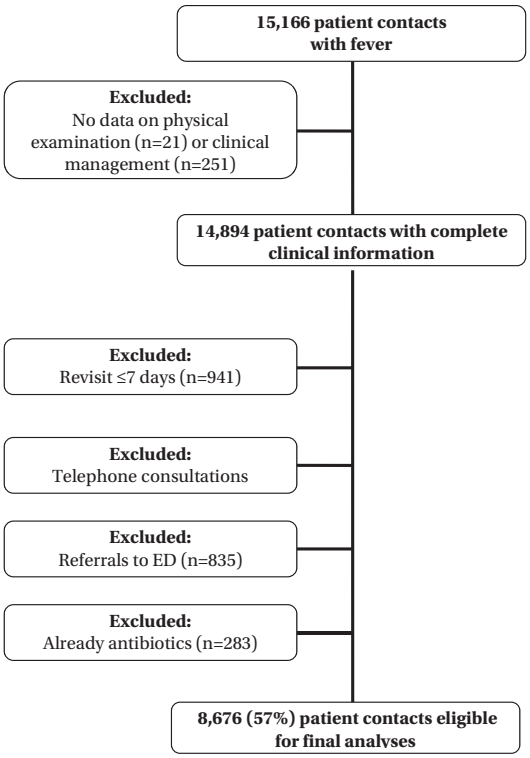


**Figure 1.** Selection of eligible contacts

**Table 1.** Characteristics of the study population (n=8,676).

| **Characteristics:** | |
|---|---|
| Age in years: median (IQR) | 2.4 (1.1-4.7) |
| Male gender: n (percentage) | 4,601 (53) |
| Rectal temperature in °C: median (IQR) | 38.4 (37.7-39.1) |
| Antibiotic prescription: n (percentage) | 3,167 (36.5) |
| Duration of fever in days (n= 6,933): median (IQR) | 2.0 (0-3) |

IQR: interquartile range

## DISCUSSION

### Summary

This large study, evaluating 8,676 face-to-face contacts of febrile children presenting at five GPC, shows that antibiotics were prescribed in 36.5% of the patient contacts. Multivariate analysis revealed that several alarming signs/symptoms were significantly related to antibiotic prescription, suggesting that treating a potentially serious bacterial

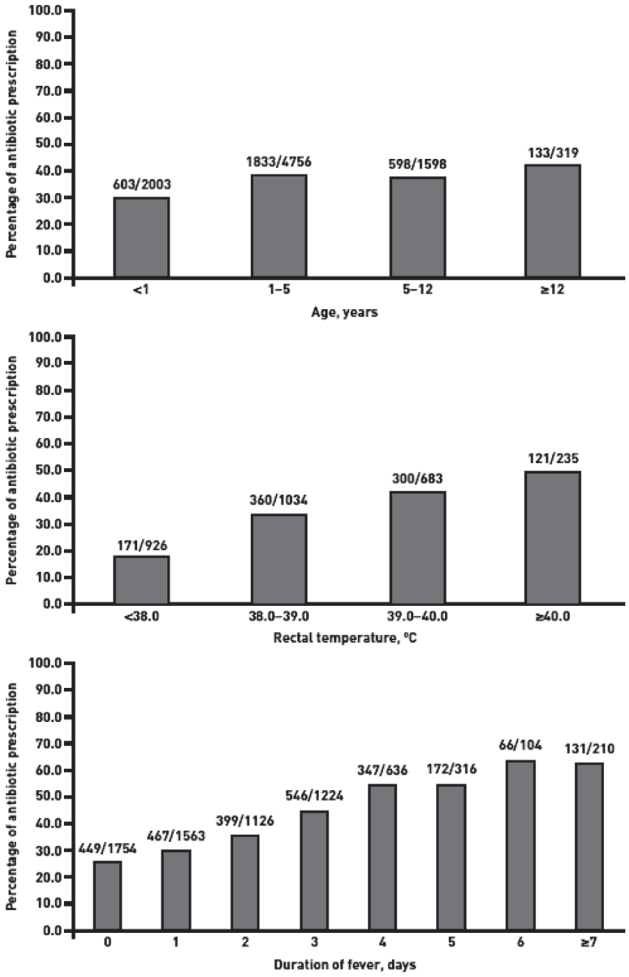


**Figure 2.** Distribution of percentage antibiotic prescription by age group, rectal temperature, and duration of fever.

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.

**Table 2.** Alarming signs and symptoms and prescribed antibiotics.

| Signs and symptoms included in the analysis | Percentage of antibiotic prescription: | | Missing (%) |
|---|---|---|---|
| | Sign present | Sign absent | |
| Temperature (at GP cooperative) | NA | NA | 66.8 |
| Abnormal circulation | 31.8 (27/85) | 31.0(657/2,121) | 25.4 |
| Signs of urinary tract infection | 24.6 (99/403) | 36.0 (1,112/3,093) | 40.3 |
| Parental concern[†] | 27.8 (416/1,497) | 25.0 (1/4) | 82.7 |
| Temperature ≥ 40°C[†] | 40.1 (878/2,190) | 35.2 (1,889/5,371) | 87.1 |
| Duration of fever[†] | NA | NA | 21.1 |
| Ill appearance | 76.3 (203/266) | 35.2 (2,964/8,410) | |
| Inconsolable | 54.1 (119/202) | 36.0 (3,048/8,474) | |
| Cyanosis | 66.7 (14/21) | 36.4 (3,153/8,655) | |
| Shortness of breath | 57.6 (144/250) | 35.9 (3,023/8,426) | |
| Meningeal irritation | 50.0 (3/6) | 36.5 (3,164/8,670) | |
| Neurological signs | 20.4 (21/103) | 36.7 (3,146/8,573) | |
| Vomiting and diarrhoea | 29.4 (517/1,760) | 38.3 (2,650/6,916) | |
| Dehydration | 29.4 (5/17) | 36.5 (3,162/8,659) | |
| Extremity problems | 37.5 (3/8) | 36.5 (3,164/8,668) | |
| Petechial rash | 36.8 (7/19) | 36.5 (3,160/8,657) | |
| Drowsy[‡] | 0.0 (0/3) | 36.5 (3,167/8,676) | |
| ABC-instability[‡] | NA | 36.5 (3,167/8,676) | |
| Unconsciousness[‡] | NA | 36.5 (3,167/8,676) | |

[†] Not included in the analyses due to missing values >70%.
[‡] Not included in the analyses due to no events (positive alarming signs/symptom and positive antibiotic prescription).
GP: general practitioner; NA: not applicable

**Table 3.** Final multivariate analysis of alarming signs and symptoms related to antibiotic prescription.

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

OR: odds ratio, CI: Confidence interval
[a] These variables showed a negative association with prescription of antibiotics.

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.[19] Therefore, these diagnoses are ultimately related to the signs/symptoms of the presenting febrile child. Therefore, investigating the relation between alarming signs/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 (e.g. 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 it. This is especially so since the Dutch guideline specifically advises to look for the various alarming signs/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 (i.e. more antibiotic prescriptions) could be expected. However, since febrile illnesses in young children can deteriorate quickly, the GP may take even more precautions than simply prescribing antibiotics. For example, in this study, children referred to the ED were significantly younger than those included in our analyses: median age 1.6 (years (interquartile range (IQR) 0.6 to 3.6 versus 2.4 (years, IQR 1.1 to 4.7) years (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/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/diarrhoea is that it is not reasonable to administer antibiotics in children with these alarming signs, since the risk of bacterial infection is considered to be low.[20]

Compared with other European countries, GPs in the Netherlands have one of the lowest overall rates of antibiotic prescription.[21-22] 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 (e.g. only children with acute otitis media, not solely febrile children)[22-25] 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 alarming 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 alarming signs/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 a 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 alarming signs and symptoms. This is not surprising, since other clinical features may also contribute to considering whether or not to prescribe antibiotics (e.g. otorrhea, bulging tympanic membrane, etc.).[26-29] 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 (e.g. ill appearance). This indicates that in ≥ 55% of the prescribed

antibiotics other (unknown) factors contribute to GP's decision to prescribe antibiotics. Earlier studies found that not medically-based considerations may also contribute to the GP's decision to prescribe antibiotics, e.g. assuming that the patient or the parents expect antibiotics.[30-32] However, these assumptions are not always valid[33-35] and GPs may need to reconsider their management of febrile children.

Bacterial resistance to antibiotics is a growing problem.[21] Since overuse of antibiotics contributes to this problem, prevention of unnecessary prescription is important.[21, 36] 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.[37] However, the role of CRP in febrile children in primary care needs further elucidation.[38] It may be useful to investigate whether a negative CRP can reassure both patient and GP 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/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),[28-29, 39-40] they are not useful in the initial treatment of rare serious bacterial infections like meningitis, 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.[40] 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/symptoms of a possible UTI. Recognition and treatment of UTIs in children is important since they can cause transient or permanent kidney damage.[41-42]

### 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 GPCs. Only a small proportion of antibiotic prescribing is explained by alarming signs/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.[38] This can be then used to provide more adequate management (e.g. more efficient safety-netting, and less prescribed antibiotics) of febrile children in primary care.

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**Supplement 1.** Grouping alarming signs into composed determinants of serious infection

| Composed alarming signs and symptoms | Total selection of alarming signs and symptoms |
|---|---|
| **Parental concern** | Parental concern |
| **Ill appearance** | Clinician's instinct something is wrong |
| | Clinically ill appearance |
| **ABCD-instability** | ABCD-instability |
| **Unconsciousness** | Unconsciousness |
| **Drowsy** | Child is drowsy |
| | Somnolence |
| | Reactivity/functional status (decreased) |
| | Hypotonia |
| **Inconsolable** | Child is inconsolable |
| | Irritability |
| | Changed crying pattern |
| | Child is moaning |
| **Abnormal circulation** | Abnormal skin color (pale, mottled, ashen) |
| | Capillary refill time > 2 sec |
| | 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 & diarrhoea** | Vomiting (>2x in disease period) |
| | Diarrhoea (>2x 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 |

**Supplement 1.** Grouping alarming signs into composed determinants of serious infection (continued)

| Composed alarming signs and symptoms | Total selection of alarming signs and symptoms |
|---|---|
| **Signs of urinary tract infection** | Pollakisuria |
| | Dysuria |
| | Tummy ache (without other focus for fever) |
| **Petechial rash** | Petechial rash |
| | Purpura |
| **Temperature ≥40°C** | Measured at home or at a General Practitioners' cooperative |
| **Duration of fever** | Duration of fever in days at time of consultation |

# Chapter 8

# Alarming signs and symptoms in febrile children in primary care: an observational cohort study in the Netherlands

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## ABSTRACT

### Context

Febrile children in primary care have a low risk for serious infection. Although several alarming signs and symptoms are proposed to have predictive value for serious infections, most are based on research in secondary care. The frequency of alarming signs/symptoms has not been established in primary care; however, in this setting differences in occurrence may influence their predictive value for serious infections.

### Objective

To determine the frequency of alarming signs/symptoms in febrile children in primary care.

### Design

Observational cohort study. Clinical information was registered in a semi-structured way and manually recoded.

### Setting

General practitioners' out-of-hours service.

### Subjects

Face-to-face patient contacts concerning children (aged ≤ 16 years) with fever were eligible for inclusion.

### Main outcome measures

Frequency of 18 alarming signs and symptoms as reported in the literature.

### Results

A total of 10,476 patient contacts were included. The frequency of alarming signs/symptoms ranged from n=1 (ABC instability; <0.1%) to n=2,207 (vomiting & diarrhea; 21.1%). Of all children, 59.7% had one or more alarming signs and/or symptoms. Several alarming signs/symptoms were poorly registered with the frequency of missing information ranging from 1,347 contacts (temperature >40°C as reported by the parents; 12.9%) to 8,647 contacts (parental concern; 82.5%).

### Conclusion

Although the prevalence of specific alarming signs/symptoms is low in primary care, ≥ 50% of children have one or more alarming signs/symptoms. There is a need to deter-

mine the predictive value of alarming signs/symptoms not only for serious infections in primary care, but as well for increased risk of a complicated course of the illness.

## INTRODUCTION

Even though most febrile illnesses in children are harmless, serious infections (e.g. pneumonia, urinary tract infection, meningitis and sepsis) do occur. Predicting the presence of a serious infection is a challenge for the primary care physician. Exploring the presence of so-called alarming signs or symptoms is their most important tool for triage. Alarming signs/symptoms are signs often observed in children with a serious infection and therewith associated with serious infections. Of the many studies investigating the value of alarming signs/symptoms in identifying a serious infection,[1, 2] the vast majority were performed in secondary care.[3] A recent study demonstrated that the associations between these alarming signs and serious infections were either weaker or were absent in primary care-datasets, as compared to associations found in secondary care populations.[4] Possible reasons for this lack of association includes differences in patient populations, the way a serious infection is diagnosed,[5] that alarming symptoms may also occur in children with viral self-limiting infections, or that primary care studies may include serious infections with a mild prognosis.

Nevertheless, until now the general practitioner's (GP) management is usually guided by the presence of alarming signs/symptoms. The alarming signs/symptoms published in the Dutch guideline and the NICE guideline for the assessment of a febrile child in primary care are based on research performed in secondary care only.[6, 7] However, it is important to determine how frequently these alarming signs/symptoms occur in febrile children presenting in primary care. Our hypothesis was that alarming signs/symptoms frequently occur in this setting. If this is correct, this finding contradicts a strong relation between alarming signs and serious infections because of the expected low prevalence of serious infections in primary care. Therefore, this study determines the frequency of alarming signs/symptoms in a large population of febrile children attending General Practitioner Cooperative (GPC) out-of-hours services in the Netherlands.

## METHOD

### Out-of-hours health care system

Out-of-hours primary care in the Netherlands is organized in large-scale cooperatives, which is comparable with the UK, Scandinavia and Australia.[8-12] The GPs rotate shifts at the GPCs, and are therefore generally not familiar with the patients they see. In only 5-10% of all primary care consultations, referral to the emergency department is needed.[8, 13] This is similar to the referral rates in the UK, USA and Canada.[14, 15] In the Netherlands, patients who contact the GPC are triaged by telephone by trained assistants to determine if a face-to-face contact is needed. When the GPC is contacted for a

febrile child, the assistant determines if alarming signs are present. If not, the assistant will give a telephone advice. When one or more alarming signs are present, a face-to-face contact is indicated.

### Study design

The study design of this study is previously described in detail.[16] In short, this cohort study used data of face-to-face patient contacts (physical consultations and home visits) of febrile children aged ≤ 16 years that took place at GPC in Rotterdam-Rijnmond between March 2008 and February 2009 (n=28,234). We excluded telephone consultations, and repeated contacts within 7 days of the initial presentation concerning the same febrile illness. By doing so, we made a selection of children with a new episode of feverish illness in which a GP has to make management decisions. The selection reflects daily practice. The GPs registered information from telephone triage, patient history, physical examination, diagnostic testing, (working) diagnosis, and treatment or referral is documented (by GPs and physician assistants) as written text lines in a semi-structured data sheet.

### Extraction of relevant clinical signs

Signs and symptoms indicative of a serious febrile illness were derived from one systematic review,[1] and two published guidelines on the management of febrile children.[6, 7] We included signs which: 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 inter-observer variability (e.g. auscultatory sounds).[17] Selected, closely-related signs were grouped into a total of 18 alarming signs of serious febrile illness (Supplement 1).

### Frequencies of alarming signs and symptoms over different age categories

In addition to the overall frequencies, we looked for the distribution of alarming signs and symptoms over different age categories, since it has been shown that serious infections occur more frequent in younger children.[18] The age categories were predefined, roughly based on ages when children may indicate more and more about their perceived signs and symptoms.

### Correlated alarming signs and symptoms

We grouped 18 alarming signs and symptoms, which is a substantial amount to look for in febrile children. It is of interest if some alarming signs/symptoms frequently occur together. Therefore, we determined the correlation between the different signs and symptoms.

### Missing data

Since the alarming signs/symptoms were obtained from routinely-collected, semi-structured data, missing values were present for each variable (i.e. not mentioned in the medical record). During a consensus meeting with 1 GP (MB), 2 pediatricians (HM, RO) and two residents [general practice (GE) and pediatrics (YvI)] it was decided to deal with missing values in two different ways: 1) the sign/symptom was believed to be so relevant that, if present, the physician would document it. Consequently, all missing values were interpreted as being absent. This was considered for the variables: ill appearance, ABC instability, unconsciousness, drowsy, inconsolable, cyanosis, shortness of breath, meningeal irritation, (febrile) convulsions, vomiting & diarrhea, dehydration, petechial rash, extremity problems; 2) for the remaining signs/symptoms (parental concern, abnormal circulation, signs of urinary tract infection, temperature ≤ 40°C, and duration of fever) it was decided that the above statements were not applicable, and the percentages of missing values were therefore reported. Contacts without any information from the GP were excluded.

### Details of 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).

### Statistical analyses

Patient characteristics and signs/symptoms were analysed using descriptive statistics. In addition, the frequency of the signs/symptoms were provided for different age categories, and tested for statistical significance using a Chi-square test, or a Fishers' exact test when the cell count was <5 events. Statistical significance was set at $p<0.05$. Correlations were calculated using Pearson's correlation coefficient in order to determine which signs and symptoms were correlated. A correlation – positive or negative – of $r = 0.10$ to 0.29 was considered low, $r = 0.30$ to 0.49 was medium, and $r = 0.50$ to 1.0 was considered high.[19] Data were analyzed using PASW version 17.0.2. for Windows (SPSS, Inc, Chicago, Ill, USA).

## RESULTS

### Description of the population

A total of 15,166 patient contacts concerned children with fever. After excluding the telephonic contacts (n=4,418), and patient contacts with missing data (n=272), 10,476 patient face-to-face contacts were included in the analysis (Fig. 1). Of these, 5,649 pa-

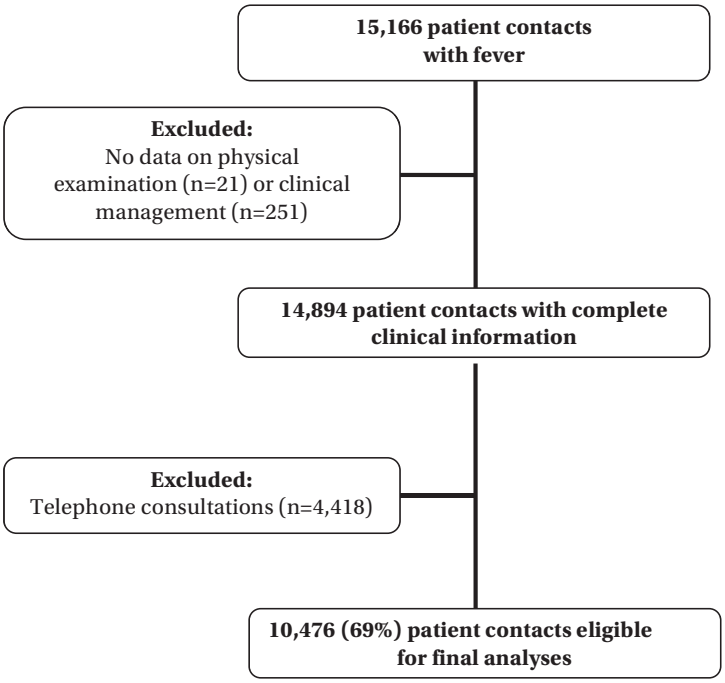


**Figure 1.** Selection of eligible contacts for the study.

tient contacts concerned boys (53.9%); overall median age was 2.2 (IQR 1.0-4.5) years. Median rectal temperature measured at the GPC was 38.5°C (IQR 37.7-39.1°C). Median duration of fever at time of presentation was 2 (IQR 0-3) days.

Table 1 presents the frequency of the alarming signs/symptoms per characteristic. The majority of the alarming signs/symptoms were present in ≤ 10%; vomiting & diarrhea (21%), parental concern (29.2%), temperature >40°C reported by parents (19.8%), and duration of fever >3 days (19.5%) were present in more contacts. Table 2 shows the distribution of the alarming signs/symptoms by age. The presence of one or more alarming signs/symptoms ranged from 49.1-61.6% in the various age categories. Most alarming signs and symptoms are more frequently observed in younger children. Symptoms of UTI were hardly reported under the age of 1 year (0.6%), inconsolable and dehydration are mainly reported under the age of 5 years, abnormal circulation is mostly reported above 12 years. Overall, in 59.7% of the contacts one or more alarming sign / symptom was present (Table 3). Figure 2 shows Pearson's correlation coefficients.; the highest correlations found were a medium correlation between a temperature >40.0°C reported by the parents and as measured by the GP (r = 0.301), and a medium correlation between ABC instability and unconsciousness (r = 0.353).

**Table 1.** Presence of alarming signs and symptoms.

| Alarming signs and symptoms | Present | | Absent | | Not registered | |
|---|---|---|---|---|---|---|
| (N=10.476) | N | Percentage | N | Percentage | N | Percentage of total (N=10476) |
| Ill appearance* | 428 | 4.1 | 10048 | 95.9 | NA | NA |
| ABC-instability* | 1 | <0.1 | 10475 | 100.0 | NA | NA |
| Unconsciousness* | 8 | 0.1 | 10468 | 99.9 | NA | NA |
| Drowsy* | 57 | 0.5 | 10419 | 99.5 | NA | NA |
| Inconsolable* | 426 | 4.1 | 10050 | 95.9 | NA | NA |
| Cyanosis* | 48 | 0.5 | 10428 | 99.5 | NA | NA |
| Shortness of breath* | 489 | 4.7 | 9987 | 95.3 | NA | NA |
| Meningeal irritation* | 59 | 0.6 | 10417 | 99.4 | NA | NA |
| Neurological signs* | 163 | 1.6 | 10313 | 98.4 | NA | NA |
| Vomiting and diarrhea* | 2207 | 21.1 | 8269 | 78.9 | NA | NA |
| Dehydration* | 115 | 1.1 | 10361 | 98.9 | NA | NA |
| Extremity problems* | 28 | 0.3 | 10448 | 99.7 | NA | NA |
| Petechial rash* | 35 | 0.3 | 10441 | 99.7 | NA | NA |
| Temperature >40°C (reported by GP) | 321 | 8.9† | 3268 | 91.1† | 6887 | 65.7 |
| Temperature >40°C (reported by parents) | 2681 | 19.8† | 6448 | 80.2† | 1347 | 12.9 |
| Parental concern | 1825 | 29.2† | 4 | 70.8† | 8647 | 82.5 |
| Abnormal circulation | 176 | 2.4† | 2614 | 97.6† | 7686 | 73.4 |
| Signs of UTI | 520 | 6.0† | 3744 | 94.0† | 6212 | 59.3 |
| Duration of fever >3 days | 1589 | 19.5† | 6580 | 80.5† | 2307 | 22.0 |

* Assumption: when not mentioned in the record, it is not present
† Percentage of N registered

## DISCUSSION

### Statement of principal findings

The frequency of single alarming signs and symptoms for serious infections in febrile children seen by a GP at an out-of-hours service is low; the majority was present in ≤ 10% of the contacts. However, ≥ 50% of all children had one or more alarming sign or symptom. These findings are consistent across all age categories. Several signs/symptoms which are expected to be related to serious infections are often poorly registered.

Most alarming signs/symptoms have different frequencies across the age groups. The majority of the alarming signs and symptoms are more frequently seen in younger age groups. However, it has been shown that younger children with fever more frequently suffer from serious infections.[18] Therefore, this finding is not surprising, and does not change our perspective on alarming signs and symptoms for serious infections.

**Table 2.** Alarming signs and symptoms by age category.

| | <1 year n=2609 | Percentage | ≥1 and <5 years n=5655 | Percentage | ≥5 and <12 years n=1833 | Percentage | ≥12and ≤16 years n=379 | Percentage |
|---|---|---|---|---|---|---|---|---|
| Temperature > 40 (stated by parents)* n=2681 | 590 | 22.6 | 1677 | 29.7 | 352 | 19.2 | 62 | 16.4 |
| Vomiting and diarrhoea* n=2207 | 642 | 24.6 | 1138 | 20.1 | 368 | 20.1 | 59 | 15.6 |
| Parental concern* n=1825 | 494 | 18.9 | 986 | 17.4 | 294 | 16.0 | 51 | 13.5 |
| Signs of urinary tract infection* n=520 | 15 | 0.6 | 281 | 5.0 | 193 | 10.5 | 31 | 8.2 |
| Shortness of breath* n=489 | 181 | 6.9 | 253 | 4.5 | 46 | 2.5 | 9 | 2.4 |
| Ill appearance* n=428 | 77 | 3.0 | 263 | 4.7 | 68 | 3.7 | 20 | 5.3 |
| Inconsolable* n=426 | 216 | 8.3 | 203 | 3.6 | 5 | 0.3 | 2 | 0.5 |
| Temperature > 40 (measured by GP)* n=321 | 70 | 2.7 | 203 | 3.6 | 42 | 2.3 | 6 | 1.6 |
| Abnormal circulation* n=176 | 42 | 1.6 | 75 | 1.3 | 41 | 2.2 | 18 | 4.7 |
| Neurological signs* n=163 | 15 | 0.6 | 133 | 2.4 | 12 | 0.7 | 3 | 0.8 |
| Dehydration* n=115 | 43 | 1.6 | 66 | 1.2 | 6 | 0.3 | 0 | 0.0 |
| Meningeal irritation* n=59 | 33 | 1.3 | 16 | 0.3 | 7 | 0.4 | 3 | 0.8 |
| Drowsy n=57 | 16 | 0.6 | 33 | 0.6 | 5 | 0.3 | 3 | 0.8 |
| Cyanosis* n=48 | 2 | 0.1 | 26 | 0.5 | 14 | 0.8 | 6 | 1.6 |
| Petechial rash* n=35 | 4 | 0.2 | 17 | 0.3 | 14 | 0.8 | 0 | 0.0 |
| Extremity problems* n=28 | 6 | 0.2 | 10 | 0.2 | 8 | 0.4 | 4 | 1.1 |
| Unconsciousness n=8 | 1 | 0.0 | 5 | 0.1 | 1 | 0.1 | 1 | 0.3 |
| ABC instability n=1 | 1 | 0.0 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 |
| ≥1 alarming sign or symptom* n=6252 | 1600 | 61.3 | 3484 | 61.6 | 982 | 53.6 | 186 | 49.1 |

*: p-value <0.05

**Table 3.** Frequency of combined presence of alarming signs and symptoms.

| Number of positive alarming signs and symptoms | N | Percentage |
|---|---|---|
| 0 | 4224 | 40.3 |
| 1 | 3837 | 36.6 |
| 2 | 1711 | 16.3 |
| 3 | 545 | 5.2 |
| 4 | 116 | 1.1 |
| 5 | 31 | 0.3 |
| 6 | 10 | 0.1 |
| 7 | 2 | 0 |
| Total | 10476 | 100 |

Some alarming signs and symptoms frequently occur together (e.g. unconsciousness and ABC instability); however, none has a relevant correlation with each other. This implies that it is important to look for the presence of every alarming sign and symptom separately, since all are suggested to be related to serious infections and it cannot be assumed that if one sign is absent, the others are also.

## Strengths and weaknesses of the study

A limitation of the study may be that the GPs did not record the clinical signs/symptoms for research purposes. We made the assumption that we can consider some signs (e.g. petechial rash) as being absent when the GP did not specifically report this; however, if this assumption is not correct, the frequency of alarming signs/symptoms will be higher, leading to an even larger discrepancy as compared to the low risk for serious infections in primary care.

Also, because we excluded telephone consultations, our results will overestimate the prevalence of alarming signs/symptoms in febrile children. Nevertheless, assuming that all children with a telephone consultation would have had no alarming signs/symptoms present, the prevalence of children with alarming symptoms is still 41.7%.

In the Netherlands, the out-of-hours service is the only primary care-facility that patients can contact outside regular working hours. This may have led to an overestimation of the alarming sign 'parental concern' in comparison to a population presenting during regular hours, since not-concerned parents will be more reluctant to contact the GPC. However, we feel that the described population is representative for a clinically relevant population of febrile children in primary care, since GPs are frequently consulted for febrile children during out-of-hours primary care.

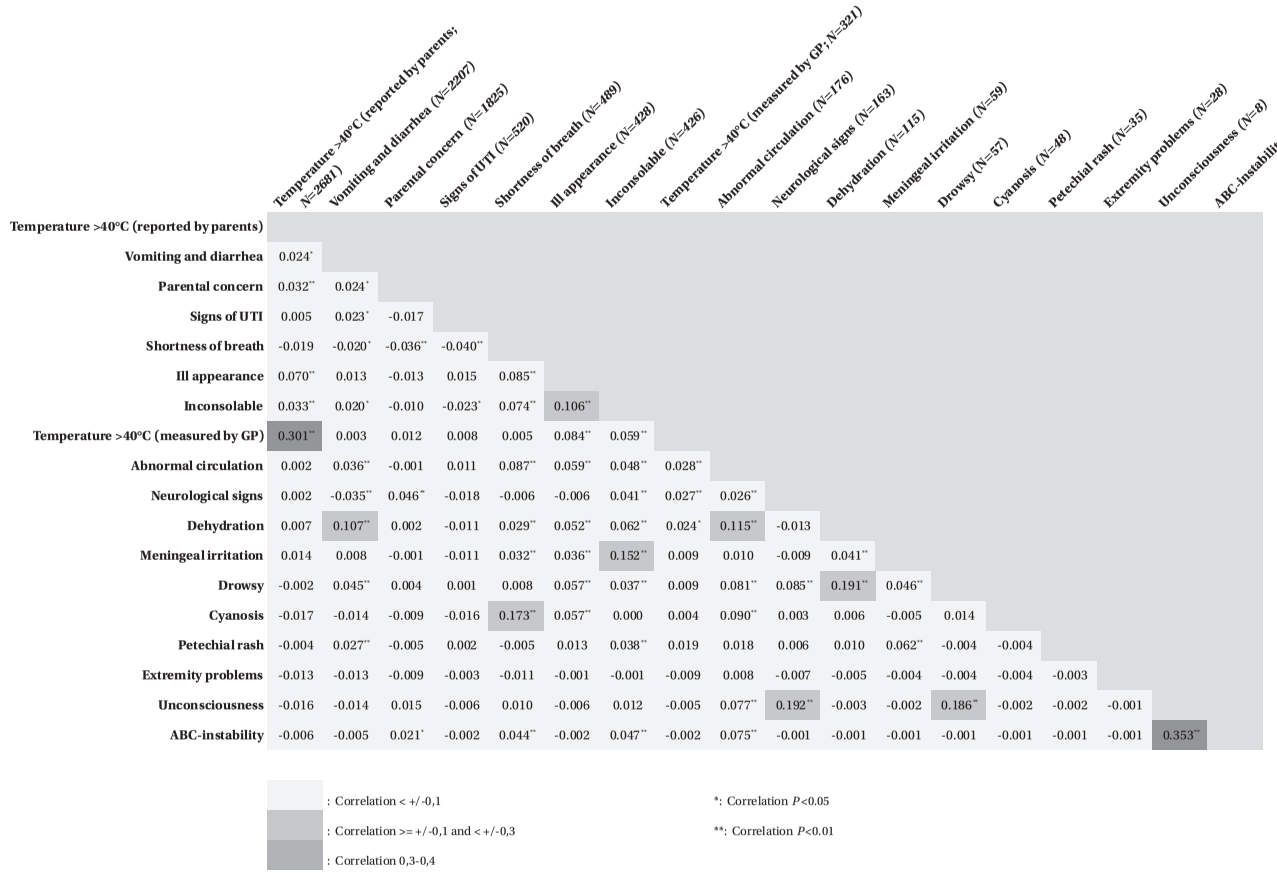


**Figure 2.** Correlation between alarming signs and symptoms (Pearson's correlation coefficient).

### Findings in relation to other studies

The prediction rules reported in the literature base their predicted risk for a serious infection on multiple alarming signs and symptoms.[1] In the present study, ≥ 50% of the children had one or more alarming signs/symptoms. This may have a negative effect on the specificity of the prediction rules in predicting serious infections. Since the incidence of serious infections is reported to be low in primary care,[18] the frequent occurrence of alarming signs/symptoms will lead to a high false-positive prediction of a serious infection.

### Meaning of the study

In conclusion, the frequency of specific alarming signs/symptoms in primary care is low. However, the proportion of children with more than one alarming signs or symptom is high. Given the high prevalence of alarming signs and symptoms, the low prevalence of serious infections, and the tendency in primary care to actively follow the course of disease in case of diagnostic uncertainty ('wait-and-see' management), we suggest that future research on alarming signs and symptoms in primary care should be related to the prognosis of the underlying disease (i.e. hospital admission or duration of complaints), rather than the presence of a serious infection.

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**Supplement 1.** Grouping of alarming signs into composed determinants of serious infection

| Composed alarming signs and symptoms | Total selection of alarming signs and symptoms |
|---|---|
| **Parental concern** | Parental concern |
| **Ill appearance** | Clinician's instinct something is wrong |
| | Clinically ill appearance |
| **ABCD instability** | ABCD instability |
| **Unconsciousness** | Unconsciousness |
| **Drowsy** | Child is drowsy |
| | Somnolence |
| | Reactivity/functional status (decreased) |
| | Hypotonia |
| **Inconsolable** | Child is inconsolable |
| | Irritability |
| | Changed crying pattern |
| | Child is moaning |
| **Abnormal circulation** | Abnormal skin color (pale, mottled, ashen) |
| | Capillary refill time > 2 sec |
| | 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 & diarrhea** | Vomiting (>2x in disease period) |
| | Diarrhea (>2x 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 |

**Supplement 1.** Grouping of alarming signs into composed determinants of serious infection (continued)

| Composed alarming signs and symptoms | Total selection of alarming signs and symptoms |
|---|---|
| **Signs of urinary tract infection** | Pollakisuria |
| | Dysuria |
| | Stomach ache (without other focus for fever) |
| **Petechial rash** | Petechial rash |
| | Purpura |
| **Temperature ≥40°C** | Measured at home or at GPC |
| **Duration of fever** | Duration of fever in days at time of consultation |

# Chapter 9

# Use of alarm features in referral of febrile children to the emergency department: an observational study

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## ABSTRACT

### Background

The diagnostic value of alarm features of serious infections in low prevalence settings is unclear.

### Aim

To explore to what extent alarm features play a role in referral to the emergency department (ED) by GPs who face a febrile child during out-of hours care.

### Design and setting

Observational study using semi-structured, routine clinical practice data of febrile children (<16 years) presenting to GP out-of-hours care.

### Method

Logistic regression analyses were performed to assess the association between alarm features of serious infections (selected from two guidelines and one systematic review) and referral to the ED. Adherence to the guideline was explored by a 2x2 contingency table.

### Results

In total 794 (8.1%) of 9794 eligible patients were referred to the ED. Alarm signs most strongly associated with referral were 'age <1 month', 'decreased consciousness', 'meningeal irritation', and 'signs of dehydration'. Nineteen percent of 3424 children with a positive referral indication according to the guideline were referred to the ED. The majority of those not referred had only one or two alarm features present. A negative referral indication was adhered to for the majority of children. Still, in 20% of referred children, alarm features were absent.

### Conclusion

In contrast to guidance, GPs working in primary out-of-hours care seem more conservative in referring febrile children to the ED, especially if only one or two alarm features of serious infection are present. In addition, in 20% of referred children, alarm features were absent, which suggests that other factors may be important in decisions about referral of febrile children to the hospital ED.

## INTRODUCTION

In primary care, general practitioners (GPs) frequently encounter febrile children, who are at risk of serious infections (e.g. meningitis, sepsis, and pyelonephritis),[1, 2] which can lead to morbidity and mortality.[3-5] The combined prevalence of serious infections in primary care; however, is less than 1%.[6] Therefore, GPs have the challenging task of distinguishing between the majority of children who have a low risk of serious infection and the minority at high risk who require further action.

Studies on identifying serious infections in low prevalence settings are scarce.[6-9] Current clinical guidelines supporting GPs in managing febrile children are predominantly based on consensus and evidence from hospital emergency care studies, which lack external validation in low-prevalence settings.[7, 9] The National Institute for Health and Care Excellence (NICE) guideline for children with feverish illness[10, 11] proposes a traffic light system, which advises referring a child for specialist consultation if either a 'red' or 'amber (in the absence of a diagnosis and sufficient safety net)' feature is present. Likewise, the Dutch GP guideline for febrile children[12] also bases its referral advice on the presence of single alarm features (all of which are also classified as 'red' or 'amber' features in the NICE guideline[10]). In 2010, a systematic review of mainly hospital emergency care studies, identified many of these alarm features as potentially useful in identifying children at high risk of serious infection.[13] However, there is still much debate about the diagnostic value of these alarm features in low-prevalence settings.[7, 8, 13]

This study aimed to explore to what extent alarm features play a role in referral management of GPs who encounter a febrile child in primary out-of-hours care and to what extent GPs adhere to the national guideline's advice on referral.

## METHOD

### Study design

An observational study was performed. Semi-structured, routine clinical practice data were collected of children with fever who had presented to GP out-of-hours care.

### Study setting and patient selection

In the Netherlands, patients should in principle first contact the General Practitioner Cooperative (GPC) for out-of-hours primary care. However, within the total amount of out-of-hours demand, 5% of patients present directly to the emergency department (ED; i.e. selfreferral).[2] Contacts eligible for this study were children (aged <16 years) who had a face-to-face consultation with a GP at the GPC and had fever, defined as: (1) fever reported by parents as the reason for contact; (2) fever within 24 hours prior to contact;

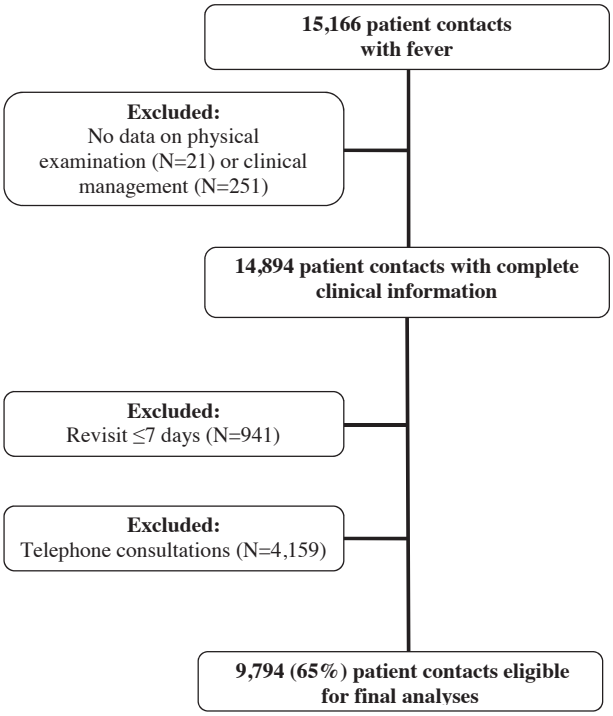


**Figure 1.** Selection of eligible contacts

or (3) a temperature >38°C measured at the GPC. Revisits for the same problem within 7 days of the initial presentation were excluded (figure 1).

## Data collection and data extraction process

Data collection of this study has been published previously.[14] In summary, data were collected from all GPC contacts in the Rotterdam-Rijnmond district during March 2008 to February 2009. For the data-extraction process clinical features indicative of a serious infection were derived from the Dutch national GP guideline for febrile children[12]; the NICE guideline for feverish illness in children;[10] and a systematic review.[13] Details on selection of the clinical features were reported previously.[11] Selected, closely-related features were grouped into 18 alarm signs and symptoms of serious infection (supplement 1). Whether alarm signs and symptoms were 'present', 'absent' or 'not mentioned' in the patient record, were manually recoded using a data-entry computer program Delphi XE (Version 15.0). Clinical management by the GP was recoded as 'referral to ED (yes/no)'.

## Statistical analysis

*Missing data*

Since clinical information was obtained from routine practice data, the study had to manage missing values (table 1).[11] For the purpose of this study, missing values were dealt with in two ways: 1) Alarm signs and symptoms were assumed to be so relevant that, if present, the GP would document them. Consequently, alarm signs and symptoms 'not mentioned' in the patient record were considered 'absent' (i.e. ill appearance, ABC instability, unconsciousness, drowsy, inconsolable, cyanosis, shortness of breath, meningeal irritation, neurological signs, vomiting and diarrhea, dehydration, joint or limb problems, and petechial rash). 2) For the remaining alarm signs and symptoms missing values were imputed 10 times using the MICE logarithm (R-Project)[15] (i.e. abnormal circulation, signs of urinary tract infection, temperature of ≥40°C, and duration of fever). The imputation model included sex, age, and all alarm signs and symptoms included in the analysis (describing casemix of the population) and the outcome variable 'referral to the ED'. Results of the imputation process are displayed in supplement 2. Vital signs, such as 'heart frequency', 'breathing frequency', and 'oxygen saturation' were reported in only 1% of the patient records and were therefore excluded from the analysis as individual alarming signs.

*Association between alarm features and referral management*

The study focused on the Dutch national guideline,[12] which advises to refer a febrile child to secondary care if at least one alarm feature is present. Guideline definitions for 'age ≤1 month', 'abnormal circulation', 'meningeal irritation', 'petechial rash', and 'signs of dehydration' matched with those of the dataset. For the other guideline features, alarm signs and symptoms were combined or best proxies were used in the dataset. The study selected 'age between 1-3 months' as a proxy for the guideline feature 'age between 1-3 months and fever of unknown origin', 'ill appearance and/or inconsolable and/or ABC-instability (i.e. respiratory or circulatory insufficiency)' as a proxy for 'ill appearance', 'unconsciousness and/or drowsy' as a proxy for 'decreased consciousness', 'vomiting and diarrhoea' as a proxy for 'persistent vomiting', and 'shortness of breath and/or cyanosis' as a proxy for 'severe shortness of breath'.

Logistic regression analyses was performed to assess the association between referral to the ED and the presence of alarm features selected from the national guideline. Additionally, the study included alarm features selected from the NICE guideline[10] and systematic review,[13] i.e. 'neurological signs', 'joint or limb problems', 'signs of urinary tract infection', 'temperature ≥40°C', and 'duration of fever'. For the multivariable analyses, we used multiple imputed data, as much relevant clinical information would be lost by performing a complete case analysis only.

**Table 1** Characteristics of study population (N= 9,794)

| **BASIC CHARACTERISTICS** | | **RANGE** |
|---|---|---|
| Female gender (N (%)) | 4,521 (46.2) | |
| Age in yrs (median, IQR) | 2.3 1.0 - 4.6 | 0.02 – 16 |
| Temperature at GPC in °C[1] (median, IQR) | 38.5 (37.7 - 39.1) | 35.5 - 41.3 |
| **ALARM FEATURES** | **PRESENT (N (%))** | **ABSENT (N (%))** |
| Parental concern[1] | 1,665 (17.0) | 4 (<0.1) |
| Ill appearance | 389 (4.0) | 9,405 (96.0) |
| ABC-instability | 1 (<0.1) | 9,793 (>99.9) |
| Unconsciousness | 8 (0.1) | 9,786 (99.9) |
| Drowsy | 53 (0.5) | 9,741 (99.5) |
| Inconsolable | 384 (3.9) | 9,410 (96.1) |
| Abnormal circulation[1] | 162 (1.7) | 2,424 (24.7) |
| Cyanosis | 46 (0.5) | 9,748 (99.5) |
| Shortness of breath | 465 (4.7) | 9,329 (95.3) |
| Meningeal irritation | 55 (0.6) | 9,739 (99.4) |
| Neurological signs | 152 (1.6) | 9,642 (98.4) |
| Vomiting and diarrhoea | 2,073 (21.2) | 7,721 (78.8) |
| Dehydration | 96 (1.0) | 9,698 (99.0) |
| Joint or limb problems | 27 (0.3) | 9,767 (99.7) |
| Signs of UTI[1] | 499 (5.1) | 3,467 (35.4) |
| Petechial rash | 34 (0.3) | 9,760 (99.7) |
| Temperature ≥40°C[1] | 2,462 (25.1) | 6,093 (62.2) |
| Duration of fever[1] | | |
| started today | 2,008 (24.9) | |
| 1 day | 1,729 (21.4) | |
| 2 days | 1,228 (15.2) | |
| 3 days | 1,325 (16.4) | |
| 4 days | 700 (8.7) | |
| 5 days | 731 (9.1) | |
| 6 days | 120 (1.5) | |
| ≥7 days | 230 (2.8) | |
| **OUTCOME MEASURE** | **YES (N (%))** | **NO (N (%))** |
| Referral to ED | 794 (8.1) | 9,000 (91.9) |

N: number of contacts; IQR: interquartile range; GPC: General Practitioner Cooperative; ABC-instability: respiratory or circulatory insufficiency; ED: emergency department.

[1] Missing values for: Temperature at GPC: 6,426 (65.6%); Parental concern: 8,125 (83.0%); Abnormal circulation: 7,208 (73.6%); Signs of UTI: 5,828 (59.5%); Temperature≥40°C: 1,239 (12.7%); Duration of fever: 2,073 (21.1%).

Finally, the study assessed GPs' adherence to the national guideline by constructing a two-by-two contingency table, i.e. referral indication according to guideline versus observed referral to the ED. Statistical analyses were performed with IBM SPSS Software version 20.0.

## RESULTS

Characteristics of the study population are displayed in table 1. In total, 794 (8.1%) of 9,794 contacts were followed by a referral to the ED. Frequencies of individual alarm signs and symptoms were generally higher among referred than non-referred children (table 2). Among the national guideline's alarm features, 'age ≤1 month', 'decreased consciousness', 'meningeal irritation', and 'signs of dehydration' were most strongly associated with referral. Together, the national guideline-specific alarm features explained 40% of the variability in referral by the GP. Taking into account the alarm features selected from the NICE guideline and the systematic review additionally, the explained variability increased up to maximally 45%.

### Adherence to the national guideline

Table 3 displays guideline adherence by GPs. Overall, 3,424 (35%) of 9,794 eligible contacts had a *positive* referral indication (i.e. at least one of the guideline-specific alarm features was present). Among these, 633 (19%) of 3,424 were referred to the ED. Among the children with a *negative* referral indication (i.e. none of the guideline-specific alarm features were present), the GP followed the guideline in 6,209 (97%) of 6,370 contacts. However, within the total group of referred contacts, still 161 (20%) of 794 children had no guideline-specific alarm feature present.

Table 4 shows the number of alarm features present in children with a *positive* referral indication. The majority of children for whom the GP overruled the guideline's advice (i.e. decided *not* to refer the child) had one or two alarm features present. When three or more alarm features were present, nearly all children were referred. Alarm features that GPs predominantly overruled were 'vomiting', 'ill appearance', 'abnormal circulation' and 'shortness of breath'.

**Table 2.** Associations between the presence of alarm features and referral by the GP

| Alarm features according to the national guideline | | NICE traffic light system[10] | Positive LR >5 in systematic review[12] | Referred (N=794; N (%)) | Non-referred (N=9,000; N (%)) | Univariate OR[1] OR (95% CI) | Adjusted OR[2,3] OR (95% CI) |
|---|---|---|---|---|---|---|---|
| Age < 1 month | yes | red | no | 25 (3.1) | 7 (0.1) | 42 (18 - 97) | 64 (26 - 161) |
| Age between 1-3 months | yes | red | no | 74 (9.3) | 98 (1.1) | 9.4 (6.8 - 13) | 11 (7.8 - 17) |
| Ill appearance | present | red | yes | 255 (32) | 463 (5.1) | 8.7 (7.3 - 10) | 6.8 (5.4 - 8.6) |
| Decreased consciousness | present | red | yes | 53 (6.7) | 4 (<0.1) | 161 (58 - 446) | 134 (45 - 399) |
| Abnormal circulation | present | red | yes | 71 (25) | 91 (4) | 8.1 (5.7 - 11) | 3.9 (2.4 - 6.4) |
| Persistent vomiting | present | red (if bile-stained) | no | 231 (29) | 1,842 (21) | 1.6 (1.4 - 1.9) | 1.3 (1.1 - 1.7) |
| Petechial rash | present | red | yes | 15 (1.9) | 19 (0.2) | 9.1 (4.6 - 18) | 12 (5.3 - 28) |
| Meningeal irritation | present | red | yes | 49 (6.2) | 6 (0.1) | 99 (42 - 231) | 90 (36 - 229) |
| Severe shortness of breath | present | amber/red | yes | 213 (27) | 270 (3.0) | 12 (9.7 - 15) | 12 (8.9 - 15) |
| Signs of dehydration (all ages) | present | amber/red | no | 78 (9.8) | 18 (0.2) | 54 (32 - 91) | 41 (22 - 77) |

[1] Univariate analyses was performed on complete case analyses for 'abnormal circulation' (Ntot=2,586); 'signs of UTI' (Ntot=3,966); 'temperature≥40°C' (Ntot=8,555) and 'duration of fever', truncated at the 97.5$^{th}$ percentile (= 7 days; Ntot=8,071).

[2] Multivariate analyses was performed on the multiple (10x) imputed dataset (Ntot=9,794).

[3] Nagelkerke's $R^2$ (median) = 0.40.

**Table 3.** GP's referral management and guideline adherence

| Referral indication according to the national guideline[1] | Observed in practice | | Total |
|---|---|---|---|
| | Referred[2] | Not-referred | |
| **Yes (% of total)** | 633 (19%) | 2,791 | **3,424 (35%)** |
| **No (% of total)** | 161 (3%) | 6,209 | **6,370 (65%)** |
| | **794 (8.1%)** | **9,000** | **9,794 (100%)** |

[1] Defined as the presence of at least one of the following alarm features: age below 1 month, age between 1-3 months with fever of unknown origin, ill appearance, decreased consciousness, abnormal circulation, persistent vomiting, petechial rash, meningeal irritation, severe shortness of breath, and signs of dehydration.

[2] 161 (20%) of 794 contacts were referred to the ED without an alarm sign present (i.e. no referral indication by the guideline).

**Table 4.** Alarm features among febrile children *with* a referral indication according to the national guideline

| Total number of alarm features present[1] | Referred (N=633) | Not-referred (N=2,791) |
|---|---|---|
| | **N (%)** | **N (%)** |
| 1 | 264 (42) | 2,456 (88) |
| 2 | 214 (34) | 304 (11) |
| 3 | 118 (19) | 29 (1.0) |
| 4 | 33 (5.2) | 2 (<0.1) |
| 5 | 4 (0.6) | 0 (0) |
| | **N (%)** | **N (%)** |
| Age < 1 month | 25 (4.0) | 7 (0.3) |
| Age between 1-3 months | 74 (12) | 98 (3.5) |
| Ill appearance | 255 (40) | 463 (17) |
| Decreased consciousness | 53 (8.4) | 4 (0.1) |
| Abnormal circulation | 205 (32) | 431 (15) |
| Vomiting | 231 (37) | 1,842 (66) |
| Petechial rash | 15 (2.4) | 19 (0.7) |
| Meningeal irritation | 49 (7.8) | 6 (0.2) |
| Severe shortness of breath | 213 (34) | 270 (9.7) |
| Signs of dehydration | 78 (12) | 18 (0.6) |

[1] Alarm features according to the national guideline: age below 1 month, age between 1-3 months with fever of unknown origin, ill appearance, decreased consciousness, abnormal circulation, persistent vomiting, petechial rash, meningeal irritation, severe shortness of breath, and signs of dehydration.

## DISCUSSION

### Summary

GPs adhered to a *positive* referral advice by the national guideline in only 19% of the out-of-hours consultations. If only one or two guideline-specific alarm features were present, GPs seemed to be more conservative in referring febrile children to the ED. Alarm features most strongly associated with referral were 'age ≤1 month', 'decreased consciousness', 'meningeal irritation', 'signs of dehydration', and 'joint or limb problems'. Even though a *negative* referral advice by the guideline, was adhered to in nearly all of the consultations, 20% of the children referred to the ED had no alarm feature present. This may indicate that for a considerable group of children, GPs base their referral decisions on other reasons than the presence of alarm features.

### Strengths and limitations

To the best of the study's knowledge, this is the first study provide an insight into the association between guideline and literature-based alarm features and GP's referral management in primary out-of-hours care practice.

Similar to the international NICE guideline for febrile children, the Dutch national guideline bases its referral advice on the presence of single alarm features, all of which are classified as 'red' or 'amber' features in the NICE guideline as well.

For this study a large, multicultural, urban cohort of nearly 10,000 febrile children was used, who presented to primary out-of-hours care. As GPCs function as acute primary care facilities and patients can present on their own initiative, the study believes that this population is likely to be generalisable to other large-scale out-of-hours primary care populations and may be extrapolated to children presenting to paediatric acute assessment units in settings with a low prevalence of serious infections.

As prospective data collection in low prevalence settings is difficult, the study made use of routine clinical practice data. Consequently, alarm features 'not mentioned' in the patient record could either mean 'not present' or 'not looked at by the physician'. It can be assumed that GPs have carefully documented alarm features to either justify their decision to refer a child or to ensure that their reasons for not referring a child were clear. In a consensus meeting, it was decided to use a multiple imputation strategy to limit the amount of clinical information missing and to best approximate true values. A sensitivity analysis on complete cases revealed no major differences in outcomes (data not shown). Therefore, the study assumes the verification bias to be limited.

### Comparison with existing literature

Several individual alarm features have been demonstrated to have potential value in identifying ('ruling-in') serious infections in children.[13] However, their applicability,

depends on the setting-specific prevalence of disease. Taking into account the low probability of serious infection in primary care (approximately 1%), the majority of individual alarm features will only raise the posterior probability to about 10% when present.[13] As these results were only based on a single primary care study, which lacks external validation, their generalisability to and diagnostic impact in other low prevalence populations may be questionable.[9, 16]

Both the Dutch national GP guideline[12] and the international NICE guideline[10] base their referral advice on the presence of single alarm features. In the study, it was observed that if one should follow the national guideline, 35% of all children consulted should be referred. Comparable results were reported by others, who validated the Dutch as well as the NICE guideline in low prevalence[17] and intermediate prevalence populations.[17, 18] They also found that 16% to 99% of the children consulted received a positive referral advice. Consequently, if one were to follow the guidelines' advice, most children with a serious infection would be referred, yielding high sensitivities (range 81-100%). However, as the prevalence of serious infections in primary care is only about 1%, an enormous group of children would be referred unnecessarily (i.e. false positives), resulting in (very) low specificities (range 1-85%). From a safety perspective, this may seem a valid approach, however the disadvantage may be a considerable overload of children who present at the ED without a serious infection. Besides, such unnecessary referrals may cause harm to children with minor illness through cross infection with more serious conditions as well as distress to children and their families.

Interestingly, in clinical practice, the study observed that GPs decided to refer only 19% of the patients with a positive referral indication, of whom the majority had three or more alarm features present. 'Meningeal irritation' and 'decreased consciousness' were nearly never neglected as alarm signs, whereas 'ill appearance' and 'abnormal circulation' were quite often overruled. This may suggest that some features have a broader clinical range in primary care than in high prevalence settings, where these signs and symptoms were identified as important indicators of serious infection.[13] From these results, it seems that GPs already apply a certain threshold above which they feel their referral is grounded (i.e. they balance the risk between false positive and false negative outcomes). They also seem to share the opinion that combinations of alarm features may do better in ruling-in serious infections than single features alone. In line with this finding, others have recently reported on the diagnostic value of three or more 'red features' of the NICE traffic light system (E. Kerkhof, personal communication, 2013). Unfortunately, the posterior probability of disease was still unsatisfactorily raised to a maximum of about 10% in low prevalence settings specifically.

Should we then better shift our focus towards ruling-out serious infections in low-prevalence settings? Previous reports have indicated that individual alarm features have insufficient rule-out value on their own.[6, 7, 13] However, combinations of absent alarm

features may significantly decrease the probability of disease.[13] For the majority of children without alarm features present, the GPs in the study seemed quite confident about the absence of a serious infection. However, the difficulty lies in determining the threshold of exactly how many alarm features must be absent to sufficiently rule-out serious febrile illness. Clinical prediction rules may, alongside to guidelines, help physicians to identify children at low risk of disease.[19-25] The only clinical prediction rule developed for primary care specifically showed a promising high sensitivity and low negative likelihood ratio at derivation,[6] however it lacked generalisability on external validation in other low-prevalence populations.[17] In addition, another study has shown that other clinical prediction rules developed for hospital emergency care were of limited use in the primary out-of-hours care setting as well.

Finally, our study demonstrated, that 20% of the referred children had no alarm feature present. This suggests that other reasons seem important in GPs' referral decisions.

### Implications for research and practice

Even though the exact harms and benefits of currently used clinical guidelines should be further elucidated, the question arises whether it is possible to develop a guideline with only clinical features that sufficiently rule in or rule out serious infections in children consulting in primary care. Future studies may answer this question by exploring the alternative reasons why GPs refer a febrile child; the potentially additive value of inflammatory marker point-of-care tests (e.g. CRP) to guidelines or clinical prediction rules, as these have shown promising results in adult primary care studies as well as studies performed at paediatric EDs;[26-28] and the disease course over time in longitudinal follow-up studies, to provide future guidelines with adequate safety-netting advice to fill the gap of insufficient rule-in or rule-out value reached by clinical alarm features alone.

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**Supplement 1.** Grouping of alarm features for serious infection

| Grouped alarm features (as coded in the GPC-database) | Total selection of alarm features |
|---|---|
| **Parental concern** | Parental concern |
| **Ill appearance** | Clinician's instinct something is wrong |
| | Clinically ill appearance |
| **ABC-instability** | Respiratory or circulatory insufficiency |
| **Unconsciousness** | Unconsciousness |
| **Drowsy** | Child is drowsy |
| | Somnolence |
| | Reactivity/functional status (decreased) |
| | Hypotonia |
| **Inconsolable** | Child is inconsolable |
| | Irritability |
| | Changed crying pattern |
| | Child is moaning |
| **Abnormal circulation** | Abnormal skin color (pale, mottled, ashen) |
| | Capillary refill time > 2 sec |
| | Tachycardia (APLS) |
| **Cyanosis** | Cyanosis |
| | Oxygen saturation <95% |
| **Shortness of breath** | Shortness of breath |
| | Nasal flaring |
| | Rapid breathing |
| | Changed breathing pattern |
| **Meningeal irritation** | Neck stiffness |
| | Bulging fontanelle |
| **Neurological signs** | Focal neurological signs |
| | Paresis/paralysis |
| | Seizures/fits |
| **Vomiting & diarrhoea** | Vomiting (>2x in disease period) |
| | Diarrhea (>2x in disease period) |
| **Dehydration** | Dry mucous membranes |
| | Sunken eyes |
| | Decreased skin elasticity |
| | Reduced urine output |
| | Hypotension (APLS) |
| | Poor feeding |
| **Joint or limb problems** | Swelling of limb or joint |
| | Non-weight bearing limb |
| | Not using an extremity |

**Supplement 1.** Grouping of alarm features for serious infection (continued)

| Grouped alarm features (as coded in the GPC-database) | Total selection of alarm features |
|---|---|
| **Signs of urinary tract infection** | Urinary frequency |
| | Dysuria |
| | Tummy ache (without other focus for fever) |
| **Petechial rash** | Petechial rash |
| | Purpura |
| **Temperature ≥40°C** | Measured at home or at GPC |
| **Duration of fever** | Duration of fever (>38.0°C) in days |

**Supplement 2.** Results of the multiple imputation process

| ALARM FEATURES | PRESENT N (%) | ABSENT N (%) |
|---|---|---|
| Temperature at GPC in °C (mean, SE) | 38.4 (0.02) | |
| Abnormal circulation | 636 (6.5) | 9,158 (93.5) |
| Signs of UTI | 1,213 (12.4) | 8,581 (87.6) |
| Temperature ≥40°C | 2,811 (28.7) | 6,983 (71.3) |
| Duration of fever | | |
| Started today | 2,560 (26.1) | |
| 1 day | 2,199 (22.5) | |
| 2 days | 1,543 (15.8) | |
| 3 days | 1,669 (17.0) | |
| 4 days | 885 (9.0) | |
| 5 days | 451 (4.6) | |
| 6 days | 154 (1.6) | |
| ≥7 days | 333 (3.4) | |

Missing values were imputed 10 times with MICE (R-project) for the alarm features 'Temperature at GPC', 'Abnormal circulation', 'Signs of UTI', 'Temperature ≥40°C', and 'Duration of fever'. All other alarming signs reported had no missing data and frequencies are displayed in table 1.

# Chapter 10

# General discussion

This thesis describes the course of fever in children in primary care in the Netherlands, how these febrile children are currently assessed and treated by the general practitioner (GP), and whether clinical features can help in identifying children with an abnormal course of the febrile episode.

## STRENGTHS AND LIMITATIONS OF THE STUDIES

The work in this thesis is based on two cohort studies, both performed in primary out-of-hours care. The 'KiKo' study (*Kinderen met Koorts*) was a prospective cohort study of 506 febrile children which was conducted at one GP cooperative out-of-hours service (GPC) (Chapters 2, 4, 5 and 6). Febrile children presenting at the GPC that were enrolled in the study, were visited at home the following day for a structured patient history and physical examination. Alarming symptoms were also assessed during the telephonic triage at initial presentation. Due to the prospective design with planned follow-up, we could present valuable and detailed data on the course of fever in children in primary care, including information on medical re-consultations, interventions, and disease progression. To our knowledge, ours is the only prospective cohort of febrile children in primary care with a follow-up of seven days. A limitation of the study was that the scheduled home visits for our research were not performed on the same day of consultation at the GPC. Although the median delay between consultation at the GPC and the home visit was only around 14 hours, the presence/characteristics of some of the symptoms may have changed during this short period. Therefore, the more acute signs and symptoms that may rapidly change over time (e.g. dyspnoea, meningeal irritation) and were determined at the time of the home visit, may not have been representative for these signs and symptoms at the time of consultation at the GPC. For example, some alarming signs and symptoms that may not have been present at the time of initial consultation at the GPC, may have developed and been present during our home visit.[1] This could have led to an overestimation of the relation between alarming signs and symptoms, and serious infections. Also, due to the short delay before the home visits, the structured patient history and physical examination could not be taken of those children admitted to hospital directly after consultation at the GPC. This topic of concern was addressed in Chapter 5; in that study we made the assumption that every child admitted to hospital had alarming signs, which may have led to an overestimation of alarming signs in this cohort.

The second prospective cohort study was performed using routinely collected data on febrile children using the electronic medical record system of five GPCs (Chapters 7-9). We were able to collect data on a large number of patient contacts (n=14,894), including the more severely-ill children that eventually needed referral. This implies that the results can probably be generalised to the whole primary care population of

febrile children. However, a limitation is that the data on signs and symptoms were not registered in a structured way. When an alarming sign or symptom was not recorded in the patient record, it may not have been present in the child, or the GP did not write it down, or the GP did not look for this particular sign or symptom and, therefore, its presence or absence is unknown. This problem was discussed in a consensus meeting: it was decided that it seems legitimate to consider some signs (e.g. unconsciousness) as being absent when the GP did not report this, since, if that sign had been present, the GP would have noticed and recorded it. For those signs and symptoms for which we considered that the assumption did not apply, we performed multiple imputation (e.g. parental concern). However, because the assumption we made may not have been valid for all alarming signs and symptoms included in that group, this may have led to an underestimation of the presence of alarming signs and symptoms.

## DISCUSSION OF FINDINGS

### How 'alarming' are alarming signs and symptoms?

When assessing a child with fever it is crucial for a GP to judge whether the child has a harmless illness that will recover without medical intervention, or (potentially) suffers from a more serious infection that needs further, more intensive assessment or treatment. At the moment, GPs mostly rely on specific characteristics in the patient's history and physical examination and try to find clues that may identify the more severely ill.[2] These specific characteristics are often referred to as 'alarming signs and symptoms': i.e. signs are objective characteristics as determined by the physician; symptoms are subjective experiences notified by the patient. The decision as to whether or not a sign or symptom is 'alarming' should be based on the predictive value of this characteristic for the presence of an underlying serious infection with a complicated course for which medical intervention is needed. However, due to the paucity of research on febrile children in primary care, alarming signs and symptoms are currently based on research performed in secondary care (mainly related to the presence of bacterial infections) and seldom include a prognosis.[3-5] In Chapter 8 we determined the frequency of these alarming signs and symptoms in febrile children in primary care and, although the prevalence of specific signs and symptoms is low, almost 60% of the children had at least one alarming feature. Without doubt, most of these children will have a 'false-positive' alarming sign or symptom, since the overall prevalence of serious infections in primary care is 1-10%.[6, 7] If GPs considered every alarming sign to be disturbing and responded to this, the referral rate in febrile children would increase considerable; if GPs referred febrile children strictly according to the Dutch clinical guideline, then about 35% of the febrile children would be referred (Chapter 9). We found that, in general,

GPs seem conservative in referring febrile children to secondary care; only 8% of the febrile children were referred to secondary care. At the same time, in 20% of the referred children there were no alarming signs or symptoms. Although this practice is in contrast to the Dutch clinical guideline for febrile children,[2] this may be more legitimate than referring all (and only) children with alarming signs and symptoms, especially since 72% of the febrile children in our studies referred by the GP to the emergency department had a serious infection and 76% was admitted to hospital.[6] Moreover, GPs might use different signs and symptoms to distinguish which child is at risk for a serious infection than those defined in our studies, or in the literature. Another explanation is that GPs may look for more disease-specific risk factors for a complicated (course of) infection, whereas the alarming signs and symptoms used in our studies are more general and may be less predictive. From this perspective, GPs may have legitimate considerations to refer children to hospital that are not solely based on the alarming signs and symptoms as described in the literature.

### Is duration of fever predictive for serious infections?

A specific clinical sign suggested to be indicative for a serious (bacterial) infection is prolonged duration of fever (i.e. ≥ 3 days).[2] However, the NICE guideline for the assessment of feverish children states that duration of fever should not be used as a predictor for serious illness, except for Kawasaki disease.[8] In Chapter 3, we found that the relation between duration of fever and serious infections is not clearly established; this finding supports the NICE guideline. However, some serious infections might be related to a longer duration of fever since they take time to develop (e.g. pneumonia, urinary tract infections),[9-12] whereas other serious infections may develop very rapidly and may be related to a shorter duration of fever.[1] Therefore, it is unlikely to find a meaningful relation when various serious infections are combined in one outcome.

However, it is reported that a prolonged duration of fever leads to re-consultations of the febrile child for medical care.[13] Parents may be concerned that their child is suffering from a more serious infection when their child does not recover within a few days.[14, 15] Therefore, it might be helpful to explain to parents how long a 'fever' generally persists. Furthermore, ideally, this may also help to identify those children who may remain febrile for a somewhat longer period of time. Chapter 2 shows that, for the whole febrile period in children without a serious illness, the median duration of fever is four days.

Also, in Chapter 4, we aimed to develop a model to predict prolonged duration of fever in non-referred children (defined as > 3 days after presentation at the GPC). The clinical signs and symptoms 'throat ache' and 'lymph nodes palpable' predict to some extent whether the child is 'at risk' to remain febrile over a longer period than normal (34% of the children with throat ache and palpable lymph nodes had a prolonged duration of fever, as compared to 11% of the children with none of these signs). However, the overall

model does not discriminate well and is not useful for the clinical management of febrile children in primary care.

In conclusion, it is useful for GPs to know that the median duration of fever in children is four days, but that they cannot predict the expected duration of fever in individual patients. This information on the duration of fever, in combination with knowledge on the duration of more disease-specific symptoms,[16] may help to inform parents about the course of the febrile episode in their sick child and may result in fewer (unnecessary) consultations for medical care.

### Which definition of serious infections should be used?

As mentioned earlier, heterogeneity in the definition of serious infections may result in a different predictive value of signs and symptoms for these serious infections.[17] Compared with the literature,[4, 7] we used a broader definition for serious infection, i.e. including febrile convulsions and asthma exacerbations. We believe that this is legitimate and justified, since both these latter conditions (as well as the infections already defined as 'serious' in secondary care, e.g. sepsis, pneumonia) need further medical assessment. However, we realise that this standpoint is debatable and tends to compromise direct comparison with other studies. For reasons of clarity, if we use the same definition for serious infection as used in secondary care, the prevalence of serious infections in primary care is 5%,[6] which is substantially lower than the observed prevalence of 15% of serious infections in secondary care. However, the prevalence of 5% is higher than the reported incidence of serious infections of only 1% in children with an acute infection in primary care.[7] This difference may be because we only included children with reported fever, and/or because our study was performed at a GPC out-of-hours service which may have led to the selection of more severely-ill children.

### Is CRP helpful in identifying serious infections in primary care?

In Chapter 5 we investigated whether the inflammatory marker C-reactive protein (CRP) is an indicator for a serious infection in febrile children in primary care. A review by Van den Bruel et al. suggests that CRP has predictive value for serious infections in secondary care.[18] Our study suggests that CRP is related to the presence of serious infections but, given the symptoms and signs, appears to have no additive value for either ruling-in or ruling-out serious illness. Nevertheless, CRP has shown to help in reducing antibiotic prescription,[19-21] probably by reassuring both the GP and the patient that there was no serious infection. In this context, the role of CRP in febrile children in primary care needs further elucidation.

### Why prescribe antibiotics for febrile children?

When assessing a febrile child, GPs may decide to treat the child with antibiotics. Although oral antibiotics have only limited value in the treatment of serious infections, other more mildly febrile diseases, such as otitis media and tonsillitis may (under certain conditions) benefit from antibiotic treatment in terms of duration and severity of discomfort.[22, 23] However, antibiotics frequently cause side-effects and antibiotic resistance is a major issue worldwide.[24, 25] Therefore, antibiotic treatment should not be prescribed too easily. From this perspective, it is important to establish to what extent antibiotics are prescribed to febrile children as well as the grounds for prescription. Chapters 6 and 7 show that antibiotics are prescribed in about 1 in 3 febrile children who had a face-to-face contact with a GP at the GPC. The signs and symptoms related to antibiotic prescription suggest that treating a potential serious infection, and decreasing the duration and severity of the symptoms, played a role in the decision to prescribe antibiotics. However, because these related signs and symptoms explained only a minority of the antibiotic prescriptions, other considerations seem to play a role. Due to the organisation of the primary care out-of-hours service in the Netherlands, patients at the GPC are generally not seen by their own GP. This makes it difficult for GPs to provide adequate safety-netting in diagnostic uncertainty, and to determine the parent's expectations. In turn, this may lead to a more defensive treatment and thereby to more antibiotic prescriptions.[19, 26] Furthermore, it is reported that the GP's assumption that the patient (or their parents) expects to receive antibiotics, also plays a role in antibiotic prescription.[27, 28] Interestingly, a recent study showed that parents of febrile children consulting a GP consider a thorough physical examination to be the most important element, and obtaining antibiotics was considered to be one of the least important components of a GP consultation.[29] Strategies to diminish the use of antibiotic treatment should focus on adequately dealing with the diagnostic uncertainty and parents' expectations when consulting the GP.

## FUTURE PERSPECTIVES

### Alarming signs and symptoms: severity of illness or disease specificity?

The alarming signs and symptoms reported in the literature are relatively broadly defined and refer to more general symptoms (e.g. shortness of breath, abnormal skin colour), whereas it remains debatable whether it is important to look for more disease-specific alarming signs or symptoms (e.g. trismus in tonsillitis). There is substantial variation in the relationship between specific predictors and the variety of serious infections predicted.[17] Because severe diseases like meningitis and sepsis tend to develop rapidly, they may have different alarming features compared with serious infections

that develop more slowly, such as pneumonia and urinary tract infections. Due to this diversity in diseases in primary care, it may be difficult to find discriminative signs and symptoms that are predictive for the broad variety of serious infections as a whole. This presents a serious challenge in primary care research, due to the low overall incidence of serious infections; also, dividing these serious infections into smaller subgroups would lead to problems in terms of statistical power. Therefore, in my opinion, future primary care research should focus on the more general alarming signs and symptoms and on how well they are discriminative in the presence of a serious infection.

## Ruling-in or ruling-out?

Regarding the prediction of serious infections, the different characteristics of alarming signs and symptoms are important in primary care, as compared to secondary care. In primary care, physicians want to safely rule-out serious infections (i.e. determine which children do not suffer from a serious infection). In secondary care, clinicians are more interested in adequately ruling-in serious infections (i.e. determining which children have a serious infection, making sure not to treat or admit false-positives). This is also related to the fact that, in primary care, the (overall) prevalence of serious infections is lower than in secondary care. For reasons of clarity, if we use the same definition for serious infection as used in secondary care, the prevalence of serious infections in primary care is then 5%.[6] Using this prevalence, and a sensitivity and specificity of 95% for a specific set of predictors for serious infections, the positive predictive value is only 50% whereas the negative predictive value is 99% (Table 1). Using a prevalence of 15% (secondary care), and the same 95% sensitivity and specificity, the positive predictive value is 77%, with a negative predictive value of 99% (Table 2). Since serious infections are rare in primary care, and a wide variety of different conditions are gathered under the nomenclature 'serious infections,' there may be no perfect prediction rule to adequately identify those who have a serious infection in primary care. The clinical guideline for GPs advises to refer children with one or more alarming signs and signals.[2] This margin is very 'safe' and leads to a substantial amount of false-positives. It is not

**Table 1.** Relation between positive predictive value and 5% prevalence of disease.

| | | Disease: | | |
|---|---|---|---|---|
| | | **Present** | **Absent** | **total** |
| Predictor: | Present | 475 | 475 | 950 |
| | Absent | 25 | 9025 | 9050 |
| | total | 500 | 9500 | 10000 |

Prevalence of disease: 5%
Sensitivity and specificity: 95%
Positive predictive value: (475/950) x 100 = 50%
Negative predictive value: (9025/9050 ) x 100 = 99%

**Table 2.** Relation between positive predictive value and 15% prevalence of disease.

| | | Disease: | | |
|---|---|---|---|---|
| | | **Present** | **Absent** | **total** |
| Predictor: | Present | 1425 | 425 | 1850 |
| | Absent | 75 | 8075 | 8150 |
| | total | 1500 | 8500 | 10000 |

Prevalence of disease: 15%
Sensitivity and specificity: 95%
Positive predictive value: (1425/1850) x 100 = 77%
Negative predictive value: (8075/8150) x 100 = 99%

desirable that all these children be referred to secondary care, since this will lead to unnecessary diagnostic interventions. Therefore, in primary care, adequately ruling-out of serious infections is more valid than ruling-in. In my opinion, research on children in primary care should focus on adequately identifying those who are at low risk for a serious infection. Therefore, research should focus on possible further assessment and/or on interventions in primary care to safely rule-out serious infections and to adequately deal with the majority of these non-severe illnesses. The current Dutch clinical guideline safely rules-out serious infections,[5] but with substantial 'false-positive serious infections.' Therefore, cut-offs should be determined for which level of risk for serious infections is allowed when assessing a febrile child: should every serious infection be identified as early as possible leading to substantial healthcare use and possible iatrogenic harm, or is a certain amount of physician delay permitted with (potentially) serious morbidity or even mortality? Qualitative studies among parents may be needed to establish which potential risks and harms are considered to be acceptable. After this, strategies to deal with febrile children with an 'intermediate' or 'high' risk of serious infections should be developed and evaluated.

### How to reduce antibiotic prescriptions?

Since antibiotic resistance is a growing problem, the development and evaluation of strategies to diminish antibiotic prescription are important. Antibiotic prescriptions might sometimes be used as a surrogate 'safety-net'; i.e. in prescribing antibiotics, a GP may hope to prevent a complicated course of an infection. In secondary care, many studies have investigated the predictive value of inflammatory markers, like CRP and procalcitonin, for serious infections.[18, 30] However, since no trials on CRP or procalcitonin have been performed in primary care, their predictive value for serious infections in a low-prevalence setting still needs to be established. Our study in Chapter 5 indicates that the predictive value of CRP for serious infections is low; however, in several studies, measurement of CRP has been shown to diminish antibiotic prescriptions in adult patients with respiratory tract infections.[19-21] Most probably, a low CRP decreases the

GP's diagnostic uncertainty about a potential serious infection and helps the GP to convince the patient that antibiotics are not indicated. However, it should be noted that similar results have been found in adults with acute cough after giving GPs a training in enhanced communication skills; i.e. compared with CRP measurement, this training is led to similar levels of patient recovery and outcome, and similar cost-effectiveness.[19, 31] Further research among febrile children needs to determine whether CRP supports the deliberations as to whether or not to prescribe antibiotics, again focusing on the group at low risk for a serious infections. A low CRP level may perhaps support the decision not to prescribe antibiotics. Furthermore, broadly implanted training for GPs in enhanced communication skills may also help to diminish antibiotic prescriptions in febrile children.

### Is safety-netting the answer?

Although safety-netting is not well defined in primary care,[32-35] it may be a legitimate way to deal with children who are at 'intermediate' risk for a serious infection. Safety-netting should include information about the uncertainty of the diagnosis, when and how to seek re-consultation, what the expected course of the illness will be, as well as documentation in the medical notes.[36] In this way, safety-netting may have the same function for the GPs as CRP, i.e. reassurance that febrile children with potential serious infections are diagnosed and treated before they deteriorate. Perhaps planned (telephonic) re-consultations should be scheduled. As described earlier, at first presentation, meningococcal disease was not recognised by a physician in about half of the children.[1] This situation might be prevented if GPs do not have to differentiate between children with and without a serious infection based on a single cross-sectional assessment. A more longitudinal approach with planned re-consultations might be an effective way to deal with diagnostic uncertainty. In adult patients presenting with acute abdominal pain at the emergency department, standard outpatient re-evaluation is a safe and effective means of improving diagnostic accuracy and helps to adapt medical management.[37] Furthermore, continuity of care reduces the use of specialist health care [38] and improves patient outcomes in other chronic diseases.[39] It is worthwhile to establish whether safety-netting in febrile children may provide such continuity of care with similar results. Studies need to focus on the efficacy and safety of safety-netting in febrile children in primary care as a legitimate well-delineated intervention. Besides prevention of a complicated course of an infection, this may also reduce inappropriate/improper antibiotic prescription. All this may hopefully lead to better management of febrile children in primary care, offering adequate and timely antibiotic prescriptions and referrals to secondary care, as well as a 'wait-and-see' management when appropriate.

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# Chapter 11

## Summary

Fever in children is a common symptom. Frequently, the underlying illness is self-limiting and medical intervention is seldom needed. However, general practitioners (GPs) need to be alert on those children who are at risk for serious infections. In this thesis, we studied the natural course of fever in children, how GPs manage febrile children, and which improvements can be incorporated to achieve better health care for febrile children in primary care.

**Chapter 2** describes the course of fever in children presenting with an uncomplicated illness. We investigated this in the KiKo (*Kinderen met Koorts*)-cohort, which consisted of 506 febrile children aged 3 months to 6 years whose parents contacted the general practitioners' cooperative (GPC) out-of-hours service. We excluded 43 children with complicated illnesses at presentation. In a structured assessment during a home visit by a research nurse, the duration of fever before presentation was noted and a physical examination was performed. Parents reported alarming symptoms and rectal temperature in a diary for 1 week. The total duration of fever included its duration before presentation. During follow-up, 3.2% of the children with uncomplicated illness at presentation developed a complicated illness. The presence of alarming symptoms dropped from 79.3% at day 2 of the fever episode to 36.7% at day 9. The estimated median duration of the total fever episode was 4.0 days (95% confidence interval, 3.6–4.4).

To determine whether duration of fever has predictive value for serious bacterial infections, we performed a systematic review in **Chapter 3**. Seven studies assessed the association between duration of fever and serious bacterial infections; three of these found a relationship. Therefore, the predictive value of duration of fever for identifying serious bacterial infections in children remains inconclusive. However, none of these seven studies was performed in primary care.

Although duration of fever has no predictive value for serious bacterial infection, it often worries parents. Information about the expected duration of fever and its predictors may help to reassure parents, leading to diminished consultation of health care. Therefore, in **Chapter 4**, we determined in the KiKo-cohort which signs and symptoms are predictive for a prolonged duration of fever (>3 days after initial contact) in children. In the 480 children analysed (children directly referred to the hospital were excluded), overall risk of prolonged duration was 13% (63/480). Multivariate analysis showed that 'throat ache' (OR:2.8; 95%CI:1.30-6.01) and 'lymph nodes palpable' (OR:1.87; 95%CI:1.01-3.49) are predictive for prolonged duration of fever. C-reactive protein (CRP) had no additive value in the prediction of prolonged duration of fever (OR:1.00; 95%CI:0.99-1.01). The discriminative value of the model was low (AUC:0.64). Therefore, the derived prediction model indicates that only a few signs and symptoms are related to prolonged duration of fever. Overall, because the discriminative value of the model was low, the duration of fever cannot be accurately predicted with our model.

CRP is an acute-phase protein showing increased blood levels during infections, and is a prognostic marker for serious bacterial infections in children visiting a pediatric emergency department. Therefore, this marker may be helpful in identifying febrile children with serious infections in primary care. **Chapter 5** describes the CRP-levels in the KiKo-cohort and evaluates whether CRP-level has additive predictive value above history taking and physical examination for diagnosing serious infections (SIs) (defined as a general practitioners' (GP) diagnosis of a serious illness or referral to a pediatrician) either at presentation or during one week follow-up. CRP-levels were available for 440 children. To rule *out* SI, CRP ≤20mg/L did not change the probability to have *no* SI (87.5%); to rule *in* SI, CRP >80mg/L increased the probability to have a SI from 12.5% (pre-test probability) to 21.2% (post-test probability). In children without a diagnosis of SI at presentation, CRP could not predict SI during follow-up (CRP > 80mg/L: LR+ 1.9, 95%CI 0.8-4.1, CRP ≤20mg/L: LR- 1.0, 95%CI 0.7-1.6). CRP-level did not change the probability of SI or of *no* SI in children with or without an alarming sign at physical examination. Therefore, we concluded that CRP has no clinically relevant additive predictive value (above history taking and physical examination) for estimating the risk of SI in febrile children in general practice.

After assessment of a child with fever, GPs may decide to 'wait-and-see', or start (antibiotic) treatment, or refer the febrile child to secondary care. In **Chapter 6**, we studied which signs and symptoms are related to antibiotic prescription in our KiKo-cohort. We excluded children that were admitted to the hospital directly after visiting the out-of hours service, presented to the out-of hours service already having antibiotics for this condition. Of the 443 included children, 322 children had a face-to-face contact at the out-of-hours service. Of these, 117 (36.3%) were prescribed antibiotics, that is, 26.5% of the total study population. Concerned parents (OR, 2.02; 95% CI, 1.06 – 3.58), ill appearance (OR, 3.26; 1.30 – 8.20), earache resulting in altered behavioral or sleeping patterns (OR, 2.59; 95% CI, 1.06 – 6.30), signs of throat infection (OR, 2.37; 95% CI, 1.35 – 4.15), and decreased urine production (OR, 2.00; 95% CI, 1.17 – 3.41) were positively associated with antibiotic prescription. A negative association was found for age 3 to 6 months (OR, 0.17; 95% CI, 0.03 – 0.74) and temperature (OR, 0.52; 95% CI, 0.37 – 0.71). The median explained variation of antibiotic prescriptions by these signs and symptoms was 26%. **Chapter 7** extends this knowledge by specifically looking at the relation between alarming signs and symptoms, and antibiotic prescription. We determined this in a large cohort study, based on patient-records concerning febrile children of five GPCs. 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. 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 (OR, 1.03;

95% CI, 1.02 – 1.05), temperature measured by GP (OR, 1.72; 95% CI, 1.59 – 1.86), ill appearance (OR, 3.93; 95% CI, 2.85 – 5.42), being inconsolable (OR, 2.27; 95% CI, 1.58 – 3.22), shortness of breath (OR, 2.58; 95% CI, 1.88 – 3.56), duration of fever (OR, 1.31; 95% CI, 1.26 – 1.35). Negative associations were found for neurological signs (OR, 0.45; 95% CI, 0.27 – 0.76), signs of urinary tract infection (OR, 0.63; 95% CI, 0.49 – 0.82), and vomiting and diarrhoea (OR, 0.65; 95% CI, 0.57 – 0.74). These variables explained 19% of the antibiotic prescriptions. Our overall conclusion was that the studies revealed a substantial amount of antibiotic prescriptions in febrile children who presented to the GPCs. Only a small proportion of antibiotic prescribing is explained by the investigated signs and/or symptoms, which implies that other, non-medically based considerations may also play a role in the GP's decision to prescribe antibiotics.

Predicting the presence of a SI is a challenge for the primary care physician. Exploring the presence of so-called alarming signs or symptoms for SIs is their most important tool for triage. The alarming signs/symptoms published in the primary care guidelines are based on research performed in secondary care only. However, it is important to determine how frequently these alarming signs/symptoms occur in febrile children presenting in primary care. Using the data of the same cohort as presented in chapter 7, we describe in **Chapter 8** the frequency alarming signs and symptoms in febrile children in primary care. Face-to-face patient contacts concerning children (aged ≤ 16 years) with fever were eligible for inclusion. A total of 10,476 patient contacts were included. The frequency of alarming signs/symptoms ranged from n=1 (ABC instability; <0.1%) to n=2,207 (vomiting & diarrhea; 21.1%). Of all children, 59.7% had one or more alarming signs and/or symptoms. Several alarming signs/symptoms were poorly registered with the frequency of missing information ranging from 1,347 contacts (temperature >40°C as reported by the parents; 12.9%) to 8,647 contacts (parental concern; 82.5%). We concluded that although the prevalence of specific alarming signs/symptoms is low in primary care, ≥ 50% of children have one or more alarming signs/symptoms. There is a need to determine the predictive value of alarming signs/symptoms not only for serious infections in primary care, but as well for increased risk of a complicated course of the illness.

Since these alarming signs/symptoms are potentially predictive for SIs who need further diagnostic or therapeutic interventions in secondary care, we explored in **Chapter 9** to what extent these alarming signs and symptoms play a role in referral to the emergency department (ED) by general practitioners (GPs). In the same cohort as described in chapter 7 and 8, 794 (8.1%) of 9,794 eligible patients were referred to the ED. Alarming signs most strongly associated with referral were 'age <1 month', 'decreased consciousness', 'meningeal irritation', and 'signs of dehydration'. Nineteen percent of 3,424 children with a *positive* referral indication according to the guideline were referred to the ED. The majority of those not referred had only one or two alarming signs present. A *negative*

referral indication was adhered to for the majority of children. Still, in 20% of referred children, alarming signs were absent. So, in the majority of consultations, GPs did not adhere to a positive referral advice by the guideline for febrile children, particularly not if only one or two alarming signs were present. Besides, in 20% of referred children alarming signs were absent. This suggests that other factors than alarming signs alone seem important in decisions on referral management. Finally, in **Chapter 10**, we reflect on the main findings in this thesis, and elaborate on their implications for clinical practice and research.

# Nederlandse samenvatting

Koorts bij kinderen is een veelvoorkomend symptoom. De onderliggende ziekte is vaak zelflimiterend en medische interventie is zelden noodzakelijk. Huisartsen moeten echter alert blijven op kinderen die een verhoogd risico op een ernstige infectie hebben. In dit proefschrift wordt beschreven wat het natuurlijk beloop is van koorts bij kinderen, hoe huisartsen kinderen met koorts behandelen en welke verbeteringen ingevoerd kunnen worden om betere huisartsenzorg te krijgen voor kinderen met koorts. **Hoofdstuk 2** beschrijft het beloop van koorts bij kinderen met een ongecompliceerde ziekte. We hebben dit onderzocht in het KiKo (*Kinderen met Koorts*)-cohort, dat bestaat uit 506 kinderen met koorts (leeftijd van 3 maanden tot 6 jaar) waarvoor de ouders contact zochten met de huisartsenpost. We excludeerden 43 kinderen die bij presentatie een gecompliceerde ziekte hadden. Tijdens een huisbezoek door een onderzoeksassistente werd middels een gestructureerde beoordeling de duur van de koorts voorafgaand aan presentatie genoteerd en werd er lichamelijk onderzoek uitgevoerd. Vervolgens rapporteerden de ouders gedurende één week alarmsymptomen en de rectale temperatuur middels een dagboek. Voor de totale duur van de koorts werd de duur voorafgaand aan presentatie meegenomen. Tijdens de *follow-up* ontwikkelde 3,2% van de kinderen alsnog een gecompliceerde ziekte. De aanwezigheid van alarmsymptomen verminderde van 79,3% op dag 2 van de koortsepisode naar 36,7% op dag 9. De geschatte mediane duur van de totale koortsepisode was 4.0 dagen (95% betrouwbaarheidsinterval (BI), 3.6-4.4).

Om te bepalen of de duur van koorts voorspellend is voor een ernstige bacteriële infectie hebben we in **hoofdstuk 3** een systematische review verricht. Zeven studies bepaalden de associatie tussen de duur van de koorts en een ernstige bacteriële infectie; drie vonden een relatie. Daardoor blijft de voorspellende waarde van duur van koorts voor het vaststellen van een ernstige bacteriële infectie in kinderen niet conclusief. Van deze studies was er echter geen in de eerste lijn uitgevoerd.

Hoewel de duur van de koorts niet voorspellend is voor een ernstige bacteriële infectie, maken ouders zich er vaak ongerust over. Informatie over de verwachte duur van de koorts en voorspellers van deze duur zou kunnen helpen in het geruststellen van ouders, met een verminderde medische consultatie als gevolg. Daarom hebben we in **hoofdstuk 4** in het KiKo-cohort onderzocht welke symptomen voorspellend zijn voor een verlengde duur van de koorts (>3 dagen na het initiële contact). Bij de 480 geanalyseerde kinderen (kinderen die direct naar het ziekenhuis werden verwezen zijn geëxcludeerd) was het risico op een verlengde duur van de koorts 13% (63/480). In een multivariaatanalyse waren 'keelpijn (OR:2.8; 95%BI:1.30-6.01) en 'palpabele lymfklieren' (OR:1.87; 95%BI:1.01-3.49) voorspellend voor een verlengde duur van de koorts. C-Reactive Protein (CRP) had geen aanvullende waarde bij de voorspelling van verlengde duur van de koorts. De discriminerende waarde van het model was laag (AUC:0.64). Daarom kan de duur van de koorts niet accuraat voorspeld worden met ons model.

CRP is een acutefase-eiwit dat bij infecties in verhoogde waarde in het bloed gevonden kan worden. Het is een prognostische marker voor ernstige bacteriële infectie bij kinderen die op een pediatrische spoedeisende hulp komen. Daarom is deze marker mogelijk nuttig bij het identificeren van ernstige infecties bij kinderen met koorts in de eerste lijn. **Hoofdstuk 5** beschrijft de CRP-waarden in het KiKo-cohort en bekijkt of de CRP-waarde een aanvullende voorspellende waarde (naast anamnese en lichamelijk onderzoek) heeft bij het diagnosticeren van een ernstige infectie (gedefinieerd als de diagnose gesteld door de huisarts of verwijzing naar de kinderarts) bij presentatie of tijdens één week *follow-up*. Wij hadden de CRP-waarde van 440 kinderen. Om een ernstige infectie uit te sluiten veranderde een CRP van ≤ 20mg/L niet de kans op *geen* ernstige infectie (87.5%). Om een ernstige infectie aan te tonen vergrootte een CRP van >80mg/L de waarschijnlijkheid op een ernstige infectie van 12.5% (pre-test waarschijnlijkheid) tot 21.2% (post-test waarschijnlijkheid). In de kinderen zonder een ernstige infectie bij presentatie kon CRP geen ernstige infectie tijdens de *follow-up* voorspellen (CRP > 80mg/L: positieve likelihood ratio (LR+) 1.9, 95%CI 0.8-4.1, CRP ≤20mg/L: negatieve likelihood ratio (LR-) 1.0, 95%CI 0.7-1.6). Bij kinderen met wel of geen alarmsymptoom bij lichamelijk onderzoek veranderde de CRP-waarde niet de kans op wel of geen ernstige infectie. Onze conclusie is daarom dat CRP geen klinisch-relevante, aanvullende voorspellende waarde (bovenop anamnese en lichamelijk onderzoek) heeft bij het inschatten van het risico op een ernstige infectie bij kinderen met koorts in de huisartsenpraktijk.

Na de beoordeling van een kind met koorts kan de huisarts een expectatief beleid voeren, een (antibiotische) behandeling starten, of het kind verwijzen naar de tweede lijn. In **hoofdstuk 6** bekeken we welke klachten en symptomen gerelateerd zijn aan antibioticumvoorschriften in ons KiKo-cohort. Wij excludeerden kinderen die meteen opgenomen werden in het ziekenhuis nadat ze de huisartsenpost hadden bezocht, en kinderen die reeds antibiotica gebruikten. Van de 443 geïncludeerde kinderen hadden er 322 een fysiek contact op de huisartsenpost. Van deze kinderen kregen 117 (36,3%) een antibioticum voorgeschreven, wat 26,5% van de totale studiepopulatie is. Ongeruste ouders (OR, 2.02; 95% CI, 1.06 – 3.58), een zieke indruk (OR, 3.26; 1.30 – 8.20), oorpijn die resulteerde in veranderd gedrag of slaappatroon (OR, 2.59; 95% CI, 1.06 – 6.30), tekenen van een keelontsteking (OR, 2.37; 95% CI, 1.35 – 4.15), en verminderde urineproductie (OR, 2.00; 95% CI, 1.17 – 3.41) waren positief geassocieerd met een antibioticumvoorschrift. Voor de leeftijd 3 tot 6 maanden (OR, 0.17; 95% CI, 0.03 – 0.74) en temperatuur (OR, 0.52; 95% CI, 0.37 – 0.71) werd een negatieve associatie gevonden. De mediaan verklaarde variatie van antibioticumvoorschriften was bij deze klachten en symptomen 26%. **Hoofdstuk 7** breidt deze kennis uit door specifiek naar de relatie tussen alarmsymptomen en antibioticumvoorschriften te kijken. Wij bekeken dit in een grote cohortstudie, die gebaseerd was op patiëntendossiers over kinderen met koorts van vijf huisartsenposten. Kinderen (<16 jaar) met koorts en een fysiek contact op de huisartsenpost werden geïncludeerd.

Kinderen die al antibiotica gebruikten, of werden verwezen naar de tweede lijn werden geëxcludeerd. Van de 8.676 patiëntencontacten (mediane leeftijd 2.4 jaar) werd er in 3.167 contacten (36,5%) een antibioticum voorgeschreven. Een hogere leeftijd (OR, 1.03; 95% CI, 1.02 – 1.05), temperatuur door de huisarts gemeten (OR, 1.72; 95% CI, 1.59 – 1.86), een zieke indruk (OR, 3.93; 95% CI, 2.85 – 5.42), ontroostbaarheid (OR, 2.27; 95% CI, 1.58 – 3.22), benauwdheid (OR, 2.58; 95% CI, 1.88 – 3.56), en duur van de koorts (OR, 1.31; 95% CI, 1.26 – 1.35) waren positief geassocieerd met een antibioticumvoorschrift. Voor neurologische symptomen (OR, 0.45; 95% CI, 0.27 – 0.76), kenmerken passend bij een urineweginfectie (OR, 0.63; 95% CI, 0.49 – 0.82), en braken en diarree (OR, 0.65; 95% CI, 0.57 – 0.74) werd een negatieve associatie gevonden. Al deze variabelen verklaarden 19% van de antibioticavoorschriften. Onze eindconclusie was dat onze studies lieten zien dat er op de huisartsenpost vaak antibioticum voorgeschreven wordt aan kinderen met koorts. Slechts een kleine proportie van de voorgeschreven antibiotica wordt verklaard door de onderzochte klachten en symptomen, wat impliceert dat andere, niet-medische overwegingen mogelijk ook een rol spelen in de beslissing van de huisarts om antibiotica voor te schrijven.

Het voorspellen van een ernstige infectie blijft een uitdaging voor de huisarts. Het belangrijkste triage-instrument is het beoordelen of er sprake is van zogenoemde 'alarmsymptomen' voor ernstige infectie. De alarmsymptomen die genoemd worden in de huisartsenrichtlijnen zijn alleen gebaseerd op tweedelijns-onderzoek. Het is echter belangrijk om te bepalen hoe vaak alarmsymptomen eigenlijk voorkomen in kinderen met koorts in de eerste lijn. Met data van hetzelfde cohort zoals beschreven in hoofdstuk 7 beschrijven wij in **hoofdstuk 8** de frequentie van alarmsymptomen in kinderen met koorts in de eerste lijn. Fysieke patiëntencontacten met kinderen met koorts (leeftijd ≤ 16 jaar) waren geschikt voor inclusie. In totaal werden 10.476 patiëntencontacten geïncludeerd. De frequentie van alarmsymptomen varieerde van n=1 (ABC-instabiliteit); <0,1%) tot n=2.207 (braken en diarree; 21,1%). Van alle kinderen had 59,7% één of meer alarmsymptomen. Verschillende alarmsymptomen waren slecht geregistreerd; de frequentie van missende informatie varieerde van 1.347 contacten (door de ouders gemeten temperatuur van >40°C; 12,9%) tot 8.647 contacten (ongerustheid van ouders; 82,5%). Wij concludeerden dat ondanks dat de individuele alarmsymptomen weinig voorkomen, ≥50% van de kinderen één of meer alarmsymptomen heeft. Het is nodig de voorspellende waarde van deze alarmsymptomen vast te stellen in de eerste lijn, niet alleen voor ernstige infecties, maar ook voor een verhoogd risico op een gecompliceerd beloop van de ziekte.

Omdat deze alarmsymptomen potentieel voorspellend zijn voor ernstige infecties die verdere diagnostiek of therapie in de tweede lijn vereisen, keken we in **hoofdstuk 9** in welke mate deze alarmsymptomen een rol speelden in de verwijzing door de huisarts naar de Spoed Eisende Hulp (SEH). In hetzelfde cohort zoals beschreven in hoofdstuk

7 en 8 werden 794 (8,1%) van de 9.794 geschikte kinderen verwezen naar de SEH. De alarmsymptomen die het sterkst gerelateerd waren aan verwijzing waren 'leeftijd <1 maand,' 'verminderd bewustzijn,' 'meningeale prikkeling' en 'kenmerken van dehydratie.' 19% van de 3.424 kinderen met volgens de richtlijn een *positieve* verwijsindicatie werd verwezen naar de SEH. De meerderheid van de niet-verwezen kinderen had slechts één tot twee alarmsymptomen. Een *negatieve* verwijsindicatie werd in een meerderheid van de kinderen opgevolgd. Toch was in 20% van de kinderen géén alarmsymptoom aanwezig. Dit suggereert dat andere factoren dan alarmsymptomen belangrijk lijken in de beslissing om te verwijzen. Afsluitend reflecteren we in **hoofdstuk 10** op de belangrijkste bevindingen van dit proefschrift en beschrijven we de hieruit volgende implicaties voor de klinische praktijk en onderzoek.

# List of publications

## LIST OF ARTICLES RELATED TO THIS THESIS

**Elshout G**, Van Ierland Y, Bohnen AM, De Wilde M, Moll, HA, Oostenbrink R, Berger MY. Alarming signs and symptoms in febrile children in primary care: an observational cohort study in the Netherlands. PLoS One. 2014;9(2):e88114.

Van Ierland Y, **Elshout G**, Moll HA, Nijman RG, Vergouwe Y, Van der Lei J, Berger MY, Oostenbrink R. Use of alarm features in referral of febrile children to the emergency department: an observational study. Br J Gen Pract. 2014;64(618):e1-9.

**Elshout G**, Van Ierland Y, Bohnen AM, De Wilde M, Oostenbrink R, Moll HA, Berger MY. Alarming signs and antibiotic prescription in febrile children: an observational cohort study. Br J Gen Pract. 2013;63(612):e437-44.

Kool M, **Elshout G**, Moll HA, Koes BW, Van der Wouden JC, Berger MY. Duration of fever and course of symptoms in young febrile children presenting with uncomplicated disease to a general practice out-of-hours service. J Am Board Fam Med. 2013 ;26(4):445-52.

**Elshout G**, Kool M, Van der Wouden JC, Moll HA, Koes BW, Berger MY. Antibiotica bij kinderen met koorts. Huisarts Wet. 2013;56(2):58-61.

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**Elshout G**, Monteny M, van der Wouden JC, Koes BW, Berger MY. Duration of fever and serious bacterial infections in children: a systematic review. BMC Fam Pract. 2011; 12:33.

**Elshout G**, Ernstige infecties bij kinderen met koorts. Huisarts Wet 2011;54:36.

Van Ierland Y, **Elshout G**, Berger MY, Vergouwe Y, De Wilde M, Van der Lei J, Moll HA, Oostenbrink R. Translation of clinical prediction rules for febrile children to primary care practice. Accepted in BJGP.

**Elshout G**, Kool M, Bohnen AM, Koes BW, Moll HA, Berger MY. Predicting prolonged duration of fever in children: a cohort study in primary care. Submitted.

Kool M, **Elshout G**, Koes BW, Bohnen AM, Berger MY. C-reactive protein level as prognostic marker in young febrile children presenting in a general practice out-of-hours service. Submitted.

Kool M, **Elshout G**, Bohnen AM, Monteny M, Moll HA, Koes BW, Berger MY. Serious infection and healthcare use in febrile children presenting at a general practice out-of-hours service. Submitted.

# Curriculum Vitae

## CURRICULUM VITAE

Gijs Elshout werd geboren op 13 juni 1984 te Schiedam. Hij volgde het voortgezet wetenschappelijk onderwijs op het Citycollege Sint Franciscus te Rotterdam, alwaar hij in 2002 zijn atheneumdiploma behaalde. In datzelfde jaar begon hij aan de studie geneeskunde aan de Erasmus Universiteit Rotterdam. Tijdens de studie geneeskunde behaalde hij in 2007 een Master of Science in Clinical Epidemiology aan het Netherlands Institute for Health Sciences (NIHES). In 2009 behaalde hij cum laude zijn artsexamen, waarna hij werd toegelaten tot de huisartsopleiding aan het Erasmus MC. Tijdens zijn opleiding begon hij aan zijn promotieonderzoek onder leiding van prof. dr. Berger, prof. dr. Koes en dr. Bohnen. De huisartsopleiding combineerde hij met verschillende bestuurlijke functies bij de Landelijke Organisatie Van Aspirant-Huisartsen (voorzitter LOVAH Rotterdam, Werkgroep Onderwijs). Daarnaast gaf hij onderwijs aan bachelor- en masterstudenten Geneeskunde van het Erasmus MC en doktersassistentes bij Leerpunt Kwaliteit en Ondersteuning EersteLijnszorg (KOEL). In 2013 rondde hij de huisartsopleiding af. Sindsdien is hij werkzaam als waarnemend huisarts in regio Rotterdam. Daarnaast heeft hij zijn onderwijstaken bij het Erasmus MC voortgezet als docent bij het studentenonderwijs en werd hij bestuurslid bij de WAGRO Rotterdam Rijnmond van de Landelijke Huisartsen Vereniging (LHV). Na afronding van zijn promotieonderzoek, dat resulteerde in het proefschrift dat nu voor u ligt, is hij als huisarts-onderzoeker werkzaam gebleven bij de afdeling Huisartsgeneeskunde van het Erasmus MC.

# Dankwoord

Zoals in ieder proefschrift te lezen is, blijkt het schrijven niet te lukken zonder de belangrijke hulp van anderen en de hulp van belangrijke anderen. Daarom wil ik hieronder verschillende mensen, soms met naam en toenaam, noemen en bedanken.

Allereerst gaat natuurlijk mijn waardering uit naar alle kinderen en ouders die hebben deelgenomen aan de KiKo-studie. Hoewel ik pas 'aan boord' kwam toen alle data verzameld was, heb ik met bewondering teruggelezen en –gekeken naar wat jullie allemaal hebben aangeleverd voor dit mooie onderzoek. Miriam Monteny was de onderzoekster die de KiKo-data vergaard heeft, en ik ben haar erg dankbaar voor al haar werk. Natuurlijk zijn ook de onderzoeksassistentes van onschatbare waarde geweest. Dankzij de huisartsenposten van de Centrale HuisartsenPosten Rijnmond is dit onderzoek mogelijk geweest en de doktersassistentes op de huisartsenpost Rotterdam-Zuid hebben hier een grote bijdrage geleverd.

Marjolein Berger, ik ben je dankbaar voor het vertrouwen dat ik reeds met het onderzoek mocht beginnen voordat er überhaupt geld voor een AIOTHO-traject was. De fysieke afstand tussen Groningen en Rotterdam is dan wel groot, maar volgens mij hebben we die meer dan adequaat kunnen slechten met de vele belafspraken. Dank je wel voor al je goede commentaar, aanvullingen en sturing.

Bart Koes, ik wil je bedanken voor je hulp bij en aanvullingen op mijn artikelen. Ik keek uit naar je feedback, die altijd begon met iets positiefs, waarbij 'het leest als een goed boek' mijn absoluut favoriete was. Dank je wel ook voor je vertrouwen in mij om mij na mijn promotie-onderzoek aan te stellen bij de kinderlijn.

Hans van der Wouden was mijn initiële co-promotor. Naast dat ik met veel plezier met je heb samengewerkt, heb ik diepe bewondering voor de enorme methodologische kennis. Nadat Hans wegging, heeft Arthur Bohnen met verve de rol van co-promotor overgenomen. Hoewel halverwege een onderzoek instappen natuurlijk wat verwarring op kan leveren ('Op welke data is dit artikel nu eigenlijk gebaseerd?'), verdient de voortvarendheid waarmee je mij begeleidde grote bewondering. Je scherpe inzichten en aanvullingen hebben mij erg geholpen. Met veel plezier heb ik tijdens mijn promotie met je samengewerkt en ik vind het een eer nu samen met je op de kinderlijn te blijven werken.

Henriëtte Moll en Rianne Oostenbrink wil ik bedanken voor de zeer waardevolle toevoegingen aan, opmerkingen bij en inzichten in mijn artikelen. De tweedelijnsvisie op dit huisartsenonderzoek was een meer dan waardevolle toevoeging.

Met Yvette van Ierland heb ik de Labelsoft-data kunnen temmen. Het is grappig om te merken hoe de gruwel van eindeloos woordjes coderen toch wegzakt in het geheugen. Ik heb altijd met plezier met je samengewerkt en ik heb grote bewondering en respect voor je oog voor detail, dat je in je verdere carrière als klinisch geneticus ongetwijfeld zeer van pas zal komen!

Marcel de Wilde heeft ons geholpen met het 'formatteren' van de Labelsoft-data; de technische goocheltruc die ervoor zorgde dat de volstrekt onleesbare excelbestanden omgetoverd werden tot begrijpelijke huisartsendossiers zal ik nooit volledig begrijpen, maar dat draagt alleen maar bij aan mijn dankbaarheid voor deze klus!

Samen met Marijke heb ik gewerkt aan het KiKo-project. Met veel plezier heb ik aan onze gezamenlijke artikelen gewerkt en ik dank je voor je inzichten en gedachtewisselingen. Zonder twijfel zal de verdediging van je proefschrift een mooi voorbeeld voor mij zijn!

De kleine commissie, prof. dr. Van der Lei en prof. dr. Verheij, wil ik bedanken voor het lezen van het manuscript. Prof. dr. Thompson: many thanks for taking the effort to oppose during the defense of my thesis. Dr. Hartwig, beste Nico, ik vind het geweldig hoe onze wegen zich weer kruisen en we hier de cirkel een beetje rond maken.

Naast alle aan mijn onderzoek gerelateerde collegae hebben ook de mensen van de afdeling Huisartsgeneeskunde en Verstandelijk Gehandicapten een aanzienlijke bijdrage geleverd aan mijn werkplezier! En natuurlijk verdient het studentenonderwijs hier ook een plekje, want hoewel jullie geen link hebben met mijn onderzoek, is jullie medeleven en gezelligheid altijd als een warm bad!

Lieve Emma en Lydi, als vrienden van het eerste 'geneeskunde'-uur hebben we al ontzettend veel mogen delen en voel ik mij vereerd dat jullie mij tijdens mijn promotie willen bijstaan. Lydi is mij al op succesvolle wijze voorgegaan op het promotiepad en met bewondering kijk ik naar hoe je je verdere carrière vorm geeft. Emma zal spoedig volgen in de promotie-estafette en ik twijfel er niet aan dat je daarna weer in de medische praktijk een fantastisch dokter zult zijn! Samen met Egbert en JW geniet ik altijd veel van onze gezamenlijke avonden en alle verhalen en perikelen die ons bezighouden. Dat er nog veel gezellige avonden mogen volgen!

Lieve Hans en Rosie, jullie leven altijd met mij mee. Hoewel geen vlees en bloed heb ik altijd het gevoel er volledig bij te horen en geniet van jullie interesse en meelevendheid. We hebben al een hoop mogen delen, op naar het vervolg!

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En met niemand anders zou ik dat kunnen dan met mijn lieve Janine. Natuurlijk was dit proefschrift er zonder jou niet geweest. Dat is niet zozeer door je geestelijke bijstand in de promotiebezigheden, maar juist door al het andere daarbuiten. Je bent een deskundige achterwacht die ik vol trots kan bewonderen, je bent een stoer wijf tijdens donkere duiken, je bent mijn mooie vrouw waar ik ademloos naar kan kijken, jij bent dat meisje voor wie ik stiekem iedere dag nog wel even hetzelfde voel als op de foto van onze trouwkaart, je bent een klankbord bij meer en minder belangrijke beslissingen, je bent de levensgenieter met wie ik van het leven wil genieten en jij bent mijn binnenste lepeltje. Ik kan niet wachten op wat er allemaal nog komen gaat!

# PhD portfolio

## PhD PORTFOLIO SUMMARY

ERASMUS UNIVERSITEIT ROTTERDAM

| | |
|---|---|
| Erasmus MC Department: | General Practice |
| PhD period: | March 2010 – August 2014 |
| Research school: | Netherlands Institute of Health Sciences (NIHES) |
| Promotor: | Prof. dr. B.W. Koes and prof. dr. M.Y. Berger |
| Co-promotor: | Dr. A.M. Bohnen |

| | Year | Workload (ECTS) |
|---|---|---|
| **PhD TRAINING** | | |
| **General academic skills** | | |
| English Biomedical Writing and Communication | 2011 | 4.0 |
| **Research skills** | | |
| Master of Science in Clinical Epidemiology, NIHES, Rotterdam | 2004-2007 | 60.0 |

**VOCATIONAL TRAINING**

GP training (PhD completed as 'Arts in opleiding tot huisarts-onderzoeker')
Department of General Practice, Erasmus MC, Rotterdam, 2009-2013.

| **CONFERENCES – PRESENTATIONS** | | |
|---|---|---|
| Global Congress for Consensus in Pediatrics & Child Health, Paris, France (poster presentation). | 2011 | 1.0 |
| NHG-Wetenschapsdag, Nijmegen (poster presentation). | 2011 | 1.0 |
| Annual Meeting of the European Society for Paediatric Infectious Diseases, Den Haag. | 2011 | 1.0 |
| North American Primary Care Research Group Annual Meeting, New Orleans, USA (oral and poster presentation). | 2012 | 2.0 |
| North American Primary Care Research Group Annual Meeting, Ottawa, Canada (poster presentation). | 2013 | 1.0 |

| | Year | Workload (ECTS) |
|---|---|---|
| **TEACHING ACTIVITITIES** | | |
| **Courses** | | |
| Didactics (Basisdidactiek, RISBO, Rotterdam) | 2013 | 1.0 |
| Designing education | | |
| Teaching | | |
| Accompanying education | | |
| **Workshops** | | |
| Making examination questions | 2013-2014 | 0.5 |
| E-learning | | |
| Dealing with groups | | |
| **Teaching** | | |
| Clinical reasoning for bachelor and masterstudents | 2013-2014 | 4.0 |
| 'Children with fever' for medical interns | 2013-2014 | 3.0 |
| Supervision of research project by medical student | 2014 | 1.5 |

# Febrile Children in Primary Care

Fever in children is a common symptom. Frequently, the underlying illness is self-limiting and medical intervention is seldom needed. However, general practitioners need to be alert on those children who are at risk for serious infections. In this thesis, we studied the natural course of fever in children, how general practitioners manage febrile children, and which improvements can be incorporated to achieve better health care for febrile children in primary care.

Cover painting: Gabriël Metsu, *The Sick Child*, Rijksmuseum, Amsterdam

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