Febrile children at a general practice out-of-hours service

Kinderen met koorts op de huisartsenpost

Marijke Kool

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CHAPTER ***ONE***

General introduction

Marijke Kool

General introduction

Childhood fever occurs frequently in young children and is a common reason for parents to contact a general practitioner (GP).[1-3] On average children have suffered from 8 infective episodes at the age of 18 months.[4] In an English birth cohort of 13,617 young children, parents have reported at least one episode with high temperature in up to 74% of the children during a follow-up period of 14 months.[2] Most illnesses causing fever are self-limiting, however some children are at risk of developing serious infections that need medical treatment. After the introduction of vaccination programmes against Haemophilus influenzae and Streptococcus pneumoniae the incidence of serious infections is declining.[5,7] The annual incidence of serious infections is now estimated to be around 1% in primary care.[8] Although serious infections are rare in primary care, they may have serious consequences such as morbidity and mortality.[3,8-10] In the English birth cohort parents consulted a physician in case of fever in up to 39% of all children within a period of one year.[2] In addition, emergency admissions, mainly short-term admissions (less than one day), have increased in children aged under 15 in England in the past decade.[11] In another English study 34% of the febrile children with symptoms of a respiratory tract infection were prescribed antibiotics.[12] Fever was found to be the main reason for contact in 21% of the children for whom a Swiss pediatric telephone triage and advice center was contacted during after-hours.[13] So, childhood fever is a reason for parental concern, increasing healthcare use and substantial antibiotic prescription rates in young febrile children.[1-3,8,11,12]

In Europe, GP care during after-hours is increasingly provided by GP cooperative out-of-hours services (OHS). At these OHS triage is commonly performed by telephone to select the child at risk of a serious infection that needs medical care. In the Netherlands, trained triage nurses perform this triage based on the Telephone and Triage guideline of the Dutch College of General Practitioners.[14] The triage nurses at the OHS are supervised by GPs. Based on this triage, children and their parents receive self-care advice by telephone, are invited for face-to-face-contact with a GP at the OHS, or a home visit by a GP is arranged.[15] Telephone triage at an OHS differs from triage in face-to-face contacts during clinical practice. Telephone triage at the OHS intends to distinguish the child that needs immediate medical care from the child that can safely wait, whereas triage in face-to-face contacts is used to identify seriously ill children, ie those with a serious (bacterial) infection. Telephone triage at an OHS is based on parent-reported alarming symptoms. Substantial research on evaluating alarming symptoms that might be able to identify seriously ill children has been performed at emergency departments and hospital settings.[16] In contrast, the reliability of parent-reported alarming symptoms in young febrile children in general practice has hardly been studied.

With the change to OHS, GP care has changed from monitored care by the child's own GP, to a moment of care by the GP's colleague.[17] Nowadays, GPs at an OHS are challenged to select children at risk of a serious infection with limited knowledge

of the child's background and medical history.[18] In addition, GPs at an OHS have less possibilities to monitor the child during after-hours compared to daily general practice. Furthermore, examples of malpractice lawsuits in children with missed or delayed diagnoses of serious infections can be found.[19,20] Since missing a child with a serious infection might have serious consequences for the child (morbidity and mortality) and for the GP (guilt and disciplinary jurisdiction), GPs at an OHS probably use a more defensive strategy of management of febrile children than in daily general practice, which might result in more antibiotic prescriptions or referrals to a paediatrician. On top of that, GPs often think that patients expect antibiotic treatment.[21] However, in a Norwegian study on parents' attitude to physician's role in the prescription of antibiotics to their children, parents expected advice and guidance and not necessarily an antibiotic prescription.[22] In addition, a Dutch survey among parent showed that parents expect a thorough physical examination and information, rather than a prescription of antibiotics or antipyretics.[23] Overuse of antibiotics is an important factor in the development of bacterial resistance and a reason to decrease unnecessary prescription of antibiotics.[24,25]
So, with the change to OHS, triage of febrile children at an OHS might have negatively influenced healthcare use and antibiotic use of these children. At this moment, it is unknown what healthcare use and antibiotic use in young febrile children are after triage decisions at OHS and based on which signs and symptoms GPs decide to prescribe antibiotics.

Several national and international guidelines for the management of febrile children are available to support GPs in the diagnostic challenge on identifying a serious infection in these children.[3,14,26] However, recommendations in these guidelines are mostly based on research performed in secondary care. To provide parents of febrile children the expected advice and guidance, more knowledge is needed on characteristics of disease, such as duration of fever in children with uncomplicated illness, course of alarming symptoms, and signs and symptoms that are predictive for a prolonged duration of fever in febrile children in general practice. In addition, more knowledge is needed on diagnostic tests, such as rapid viral testing and C-reactive protein point-of-care tests, which are nowadays more easily available in general practice. Although recent reviews have provided evidence of the additive diagnostic value of these tests,[27,28] in febrile children presenting at an OHS this value is still unknown.

So, childhood fever is a common symptom in general practice. Although childhood fever is often self-limiting, uncertainty about rare serious infections with possible serious consequences generates a diagnostic dilemma. Research in children with fever presenting at a general practice out-of-hours service is scarce. The aims of this thesis were to study parent-reported alarming symptoms, characteristics of childhood fever, healthcare use and diagnostic strategies in young febrile children presenting at a GP OHS.

KiKo

To study triage and healthcare use in febrile children we performed an observational prospective cohort study named Kiko (acronym for the Dutch translation of children with fever, **Ki**nderen met **Ko**orts). This cohort study is established by the Department of General Practice of Erasmus MC, University Medical Center Rotterdam, in the Netherlands. The study was performed at a GP OHS in the southern part of Rotterdam (Huisartsenpost Rotterdam Zuid). Children aged three months to six years were eligible when they presented with fever, as stated by the parents, during midweek evenings or nights during the period of December 2004 till January 2006. Exclusion criteria were no informed consent, no communication in Dutch possible with the parents, and previous enrolment in the Kiko-study in the last two weeks. In total, 506 children were included in the study. After triage, 135 children received self-care advice by telephone, and 371 children were seen in a face-to-face contact with the GP at the OHS. There were no home visits by the GP.[15]

Contents of this thesis

Chapter 2 investigates the reproducibility of parent-reported alarming symptoms at triage and explores the association of parent-reported alarming symptoms with findings at physical examination in young febrile children.

Chapter 3 describes the risk of serious infection and the healthcare use (including antibiotic prescriptions) in young febrile children according to triage decisions.

Chapter 4 describes antibiotic prescription rate in young febrile children and examines which variables predict antibiotic prescription.

Chapter 5 presents the prevalence of serious infections and the course of fever and alarming symptoms in children with uncomplicated febrile illnesses.

Chapter 6 explores the predictive value of symptoms on prolonged duration of fever.

Chapter 7 describes the viruses found in young febrile children and the association with antibiotic prescription rate in children presenting with fever.

Chapter 8 investigates the predictive value of C-reactive protein for serious illness in young febrile children.

Chapter 9 discusses the main findings of the previous chapters, reflects on the strengths and limitations of the studies and examines the implications for daily practice and future research.

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CHAPTER ***TWO***

Reliability of parent-reported alarming symptoms in febrile children in general practice

submitted

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Abstract

Background: Telephone triage for febrile children at a general practitioner's (GP) out-of-hours service (OHS) is based on parent-reported alarming symptoms.

Aim: This study evaluates the reliability of parent-reported alarming symptoms in febrile children.

Design and Setting: a prospective cohort study in children with fever (aged 3 months to 6 years) contacting an OHS.

Methods:. Triage nurses noted parent-reported 'alarming symptoms *at triage*'. All children were visited by a research nurse within 24 hours after presentation. At this visit the research nurse asked for 'alarming symptoms *at triage*' as recalled by the parents and for 'alarming symptoms *at the home visit'*. At physical examination alarming symptoms were assessed by the research nurse. We analysed reproducibility of parent-reported alarming symptoms by comparing 'alarming symptoms *at triage*' with 'recalled alarming symptoms *at triage*' (kappa). We calculated sensitivity and specificity of 'alarming signs *at the home visit*' compared to findings at physical examination.

Results: In total, 422 children were included. Reproducibility of parent-reported alarming symptoms ranged from 0.30-0.50. 'Abnormal circulation' showed the highest sensitivity (52.8%, 95% CI: 39.4-66.3). Specificity was highest for 'drowsiness' (81.5, 77.5-85.4).

Conclusions: Reproducibility of parent-reported alarming symptoms was low to moderate, and associations between parent-reported symptoms and findings at physical examination were poor. Up to 68% of alarming symptoms found at physical examination were not reported by the parents. Future research should establish whether triage could be improved by educating parents and triage nurses to interpret alarming symptoms, or by having GPs deal with telephone triage instead of triage nurses.

Introduction

Fever in young children is a common reason for parents to contact a general practitioner (GP), mainly during after-hours.[1-3] Although most febrile illnesses are self-limiting, some children are at risk of developing serious infections.[3] Nowadays in Europe, GP care during after-hours is increasingly provided by GP out-of-hours services (OHS). At these services, telephone triage is used to identify the child at risk of a serious infection. Triage nurses select the child who requires face-to-face contact with a GP based on parent-reported alarming symptoms.

In a Dutch cohort study of young children presenting with fever at an OHS more than 70% of the children were invited for a face-to-face contact based on parent-reported symptoms at telephone triage.[4] This is in contrast with the low rates of serious infections in febrile children found in primary care.[5,6] In addition, there is an ongoing increase in very-short-term hospital admissions (less than one day) in children with common infections; also, most of the emergency admissions of children occur during out-of-hours, suggesting (among others) a systematic effect of out-of-hours care resulting in hospitalization.[7,8]

Since telephone triage at an OHS is based on parent-reported alarming symptoms, it is important that parents and triage nurses understand each other well.[4] However, investigation at a paediatric assessment unit revealed that parent-reported symptoms correlated poorly with nurse assessments in children with suspected acute respiratory infections.[9] A systematic review showed that reduced drowsiness (consciousness), abnormal circulation (cyanosis), and shortness of breath (rapid breathing) were important diagnostic features in identifying children with serious infections.[10] Although, nowadays, these symptoms are commonly used for triage in febrile children, little is known about how parent-reported symptoms correspond to findings in physical examinations in primary care.

Therefore, to evaluate the reliability of parent-reported alarming symptoms in young febrile children presenting at an OHS, this study examines the reproducibility of alarming symptoms reported at telephonic triage and the association between alarming symptoms and findings at physical examination as a measure of validity.

Methods

The study was conducted as part of a larger prospective cohort study evaluating the course of fever in children presenting at a GP cooperative OHS in Rotterdam. This OHS encompasses about 300,000 inhabitants. The study was approved by the Dutch Central Committee on Research Involving Human Subjects.

Between December 2004 and January 2006, consecutive febrile children (aged three months to six years) for whom parents contacted the OHS were eligible for inclusion. Fever, as reported by the parents, had to be the reason for contact. A child was excluded from the original study when parents could not communicate in Dutch, when the child was already included in the study in the previous two weeks, or when no informed consent was obtained.[4,6] Children without a triage questionnaire were excluded from this analysis.

When parents phoned the OHS about their febrile child, the triage nurses performed their usual triage based on the guideline for management of febrile children issued by the Dutch College of General Practice.[11,12] According to these guidelines, a child was invited for a face-to-face contact with the GP if the child was aged less than three months, 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 colour, had a change in breathing pattern, was moaning or had apnoea, had relevant comorbidity, and had fever for more than three 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' by telephone if none of the above symptoms was present.[4]

GPs were free to prescribe treatments of their choice or to refer the patient. For the purpose of this study, triage nurses completed a structured triage questionnaire directly after the triage decision. This triage questionnaire contained questions as used in their usual triage (alarming symptoms *at triage*). For all included children (irrespective of their triage results), an additional home visit by a trained research nurse was scheduled as soon as possible after inclusion, but within 24 hours of inclusion. The research nurse recorded demographic data, and questioned the parents about symptoms at the moment of triage (recalled alarming symptoms *at triage*) and at the moment of the home visit (alarming symptoms *at home visit*). In addition, using a structured questionnaire, the research nurse performed a physical examination and noted symptoms and findings (physical examination *at the home visit*).
Alarming symptoms indicative for a serious infection were derived from the national and international guidelines on febrile illness in children.[3,12] We excluded alarming symptoms that had an expected low prevalence (e.g. meningeal irritation) and those that could not be derived from history.
Alarming signs and symptoms were assessed in four separate measurements (Table 1).

In 'alarming symptoms *at triage*' we assessed five alarming symptoms as follows: i) 'drowsiness' as a positive answer to the question: 'Is your child dull or difficult to wake?', ii) 'inconsolable' as a negative answer to 'If your child is crying, can you comfort your child?', or a positive answer to at least one of the questions 'Does your child start crying when lifting the child?', 'Is your child restless?' or 'Is your child moaning?', iii) 'abnormal circulation' as a positive answer to the question: 'Does your child have a pale or ashen colour of the skin?', iv) 'shortness of breath' as a positive answer to the question: 'Is your child breathing more rapidly than normally?', and v) 'dehydration' was defined as a negative answer to the question: 'Does your child still have wet nappies?' or as a positive answer to 'Is your child drinking less than half of the normal amount?' or as a positive answer to the two questions 'Is your child vomiting?' and 'Does your child have diarrhoea?'.

'Recalled alarming symptoms *at triage*' and 'alarming symptoms *at the home visit*' were asked at the home visit and defined as described above, except for 'inconsolable' which was defined as a positive answer to the question 'Was your child crying inconsolably?' and 'dehydration' which was defined as above but with a positive answer to the question 'Did your child void much less or no urine?' instead of 'Does your child still have wet nappies?'

In 'physical examination *at the home visit*' alarming signs 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 colour)' 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 fontanelle' if the child was aged less than one year. 'Inconsolable' was not assessed at physical examination.

Capillary refill was measured by pushing firmly on the calcaneus or thenar for five seconds and counting the seconds after releasing.

Tachycardia was defined as a pulse rate ≥ 160 beats per minute (bpm) at age ≥ 1 year, ≥ 150 bpm at age 1-2 years, and ≥ 140 bpm at age ≥ 2 years.3 An increased respiratory rate was defined as ≥ 60 breaths per minute at age 3-5 months, ≥ 50 breaths per minute at age 6-12 months, and ≥ 40 breaths per minute at age ≥ 12 months.[3]

Triage nurses and research nurses were unaware of the research question and of the composition of the alarming symptoms.

Table 1.
Measurement of alarming symptoms

Alarming symptoms	Measurement	Presence of symptoms	Moment of measurement	Interviewer/ researcher
Alarming symptoms *at triage*	Parent-reported alarming symptoms	At triage	At triage	Triage nurse
Recalled alarming symptoms *at triage*	Parent-reported alarming symptoms	At triage	Home visit	Research nurse
Alarming symptoms *at the home visit*	Parent-reported alarming symptoms	Home visit	Home visit	Research nurse
Physical examination *at the home visit*	Alarming symptoms at physical examination	Home visit	Home visit	Research nurse

Statistical analysis

To calculate the reproducibility of parent-reported alarming symptoms at triage, we constructed 2x2 tables with 'alarming symptoms *at triage*' and 'recalled alarming symptoms *at triage*'. Cohen's kappa was also calculated. Kappa values were classified as follows: ≤ zero = poor, zero to 0.20 = slight, 0.21 to 0.40 = fair, 0.41 to 0.60 = moderate, 0.61 to 0.80 = substantial and 0.81 to 1.00 = almost perfect.13 To evaluate the association between 'alarming symptoms *at the home visit*' and 'physical examination *at the home visit*' 2x2 tables were constructed. 'Physical examination *at the home visit*' was used as reference standard. We calculated sensitivity, specificity, and positive and negative likelihood ratios (LR+ and LR-) with 95% confidence intervals (CI). If symptoms were answered with 'Not applicable' or 'Don't know', these values were counted as absent. All analyses were performed with SPSS 17.0 for Windows (SPSS, Inc, Chicago, Ill, USA).

Results

In total, 506 children were included in the original study. Because the triage questionnaire was lacking for 84 children (16.6%), a total of 422 children (83.4%) were included in the present analysis. Table 2 presents the characteristics of the children with and without a triage questionnaire.

Table 2.
Characteristics of children with and without a triage questionnaire.

	Children with triage questionnaire (n=422)	**Children without triage questionnaire (n=84)**
Age, in months, median (range)	21 (3 -71)	19 (3-71)
Male sex, n (%)	242 (57.3)	47 (56.0)
Immigrant, n (%)	214 (50.7)	45 (53.6)
Face-to-face contact, n (%)	309 (73.2)	62 (73.8)
Self-care advice by telephone, n (%)	113 (26.8)	22 (26.2)
Referral at presentation, n (%)	20 (4.7)	6 (7.1)
Admission to hospital, directly after presentation, n (%)	15 (3.6)	4 (4.8)

Of all 422 children, for 405 (96.0%) a structured physical examination was performed at the home visit. Table 3 presents the frequencies of 'alarming symptoms *at triage*', 'recalled alarming symptoms *at triage*,' 'alarming symptoms *at the home visit*' and 'physical examination *at the home visit*'. In ≤ 5% of the questionnaires some items were missing. The mean time between triage and home visit was 14 hours and 36 minutes (standard deviation, SD: 2 hours and 21 minutes).

Reproducibility of alarming symptoms at triage

Reproducibility of 'alarming symptoms *at triage*' with 'recalled alarming symptoms *at triage*' ranged from moderate to fair: moderate for 'dehydration' (kappa=0.46),

'shortness of breath' (kappa=0.50), and fair for 'abnormal circulation' (kappa=0.40), 'drowsiness' (kappa=0.39), and 'inconsolable' (kappa=0.30) (Table 4).

Association between alarming symptoms at the home visit and physical examination
The sensitivity of 'alarming symptoms *at the home visit*' compared with the 'physical examination *at the home visit*' was highest for 'abnormal circulation' (sensitivity 52.8%, 95% CI: 39.4-66.3, specificity 66.6%, 95% CI: 61.6-71.6, LR+ 1.6, 95% CI: 1.2-2.1, LR-0.7, 95% CI: 0.5-1.0), and lowest for 'drowsiness' (sensitivity 32.0%, 95% CI: 13.7-50.3, specificity 81.5%, 95% CI: 77.5-85.4, LR+ 1.7, 95% CI: 0.9-3.2, LR- 0.8 95% CI: 0.6-1.1).
Specificity was highest for 'drowsiness' (specificity 81.5%, 95% CI: 77.5-85.4, sensitivity 32.0%, 95% CI: 13.7-50.3, LR+ 1.7, 95% CI: 0.9-3.2, LR- 0.8 95% CI: 0.6-1.1), and lowest for 'dehydration' (specificity 66.4, 95% CI: 61.5-71.3, sensitivity 40.0, 95% CI: 22.5-57.5, LR+ 1.2, 95% CI: 0.7-1.9, LR- 0.9, 95% CI: 0.7-1.2).
Table 5 presents data on sensitivity, specificity, and LR+ and LR- for 'alarming symptoms *at the home visit*' validated with the 'physical examination *at the home visit*'.

Table 4.
Level of consistency between parent-reported alarming symptoms.

Alarming symptoms	**Alarming symptoms *at triage*** versus **Recalled alarming symptoms *at triage*** Kappa (number of valid cases)
Drowsiness	**0.39 (401)**
Inconsolable	**0.30 (405)**
Inconsolable while crying	0.17 (398)
Crying when lifting the child	0.44 (397)
Restless	0.37 (399)
Moaning	0.41 (397)
Abnormal circulation	**0.40 (395)**
Shortness of breath	**0.50 (395)**
Dehydration	**0.46 (406)**
Drinking ≤ half of normal	0.34 (356)
No wet nappy/Less voiding of urine	0.37 (184)
Vomiting and diarrhoea	0.53 (400)

Table 3.
Measurements of frequencies of alarming symptoms.

Alarming symptoms	**Alarming symptoms *at triage*** n/N (%) (n=not applicable)	**Recalled alarming symptoms *at triage*** n/N (%)	**Alarming symptoms *at home visit*** n/N (%)	**Physical examination *at home visit*** n/N (%)
Drowsiness Dull or difficult to awake	**188/421 (44.7)** (10)	**202/402 (50.2)**	**79/401 (19.7)**	**27/402 (6.7)**
Inconsolable	**300/421 (71.3)**	**336/406 (82.8)**	**198/405 (48.9)**	**Not applicable**
Inconsolable while crying	76/420 (18.1) (12)	181/400 (45.3)	68/404 (16.8)	
Crying when lifting the child	111/420 (26.4) (18)	116/399 (29.1)	40/395 (10.1)	
Restless	205/419 (48.9) (8)	232/402 (57.7)	114/402 (28.4)	
Moaning	172/419 (41.1) (17)	190/400 (47.5)	84/401 (20.9)	
Abnormal circulation Pale or ashen skin colour	**159/418 (38.0)** (20)	**200/399 (50.1)**	**144/399 (36.1)**	**53/404 (13.1)**
Shortness of breath Rapidly breathing	**200/414 (48.3)** (25)	**231/402 (57.5)**	**122/401 (30.4)**	**63/399 (15.8)**
Dehydration	**187/422 (44.3)**	**204/406 (50.2)**	**140/405 (34.6)**	**30/385 (7.8)**
Drinking < half of normal	152/411 (37.0) (6)	149/392 (38.0)	93/389 (23.9)	
No wet nappy/Less voiding of urine	36/233 (15.5) (53)	109/364 (29.9)	82/364 (22.5)	
Vomiting and diarrhoea	43/419 (10.3)	43/403 (10.7)	12/402 (3.0)	

Table 5.
Sensitivity and specificity of 'parent-reported alarming signs *at the home visit*' to determine abnormal findings at physical examination.

Alarming symptoms ***at the home visit***	**Physical examination** ***at the home visit*** (alarming symptom present)	**Physical examination** ***at the home visit*** (alarming symptom absent)	**Sensitivity** % (95% CI)	**Specificity** % (95% CI)	**Positive likelihood ratio** n (95% CI)	**Negative likelihood ratio** n (95% CI)
Drowsiness (yes/no)	8/17	69/303	32.0 (13.7-50.3)	81.5 (77.5-85.4)	1.7 (0.9-3.2)	0.8 (0.6-1.1)
Abnormal circulation (yes/no)	28/25	115/229	52.8 (39.4-66.3)	66.6 (61.6-71.6)	1.6 (1.2-2.1)	0.7 (0.5-1.0)
Shortness of breath (yes/no)	26/37	93/238	41.3 (29.1-53.4)	71.9 (67.1-76.7)	1.5 (1.0-2.1)	0.8 (0.7-1.0)
Dehydration (yes/no)	12/18	119/235	40.0 (22.5-57.5)	66.4 (61.5-71.3)	1.2 (0.7-1.9)	0.9 (0.7-1.2)

Discussion

Summary

The aim of this study was to evaluate the reliability of parent-reported alarming symptoms in febrile children presenting to an OHS. The reproducibility of alarming symptoms *at triage* ranged from moderate to fair.

The sensitivity of parent-reported alarming symptoms was generally low (highest 52.8, 95% CI: 39.4-66.3 for 'abnormal circulation' and lowest 32.0, 95% CI: 13.7-50.3 for 'drowsiness'). This finding shows that false-negative parent-reports were common (range 47-68%). Specificity of all alarming symptoms was moderate (highest 81.5%, 95% CI: 77.5-85.4 for 'drowsiness' and lowest 66.4, 95% CI: 61.5-71.3 for 'dehydration') indicating that percentages of false-positive parent-reports were moderate (range 18-34%). A positive parent-report for 'abnormal circulation' or 'shortness of breath' significantly increased the likelihood of finding these alarming symptoms at physical examination. However, the likelihood ratios were not of clinical relevance (LR+ 1.6, 95% CI: 1.2-2.1 for 'abnormal circulation' and 1.5, 95% CI: 1.0-2.1 for 'shortness of breath').

Strengths and limitations

The strength of this study is that we performed repeated structured questionnaires and structured physical examinations in children with self-care advice by telephone and in children with face-to-face contact. This allowed calculating the reproducibility of alarming signs, and the sensitivity and specificity, in all febrile children contacting an OHS. However, in children who were admitted to hospital directly after presentations (n=15) we were unable to make a home visit because these children were admitted to hospital at the time of the home visit; these children may have been more severely ill than the non-admitted children. Moreover, missing these children may have resulted in an underestimation of our associations, since alarming symptoms in admitted children are probably more distinct and better associated with findings at physical examination than in the non-admitted children.

We hypothesized that valid parent-reported alarming symptoms can be found at physical examination. However, the association between alarming symptoms *at the home visit* and physical examination was relatively low. The highest LR+ was 1.6 (95% CI: 1.2-2.1) and the lowest LR- was 0.7 (95% CI: 0.5-1.0), both for 'abnormal circulation'. One might expect that, after contact with the triage nurse or the GP, parents might have adjusted the parent-reported alarming symptoms more closely to the findings at physical examination than before these contacts. Therefore, in the present study, our estimates of LR+ and LR- might be slightly overestimated if generalized to the association at the time of telephonic triage.

Comparisons with existing literature

In the present study the reproducibility of parent-reported alarming symptoms at triage (kappa 0.30-0.50) was comparable to that of Blacklock et al. in their study

on children with respiratory tract infections presented to a paediatric emergency unit (kappa 0.22-0.56).[9] In our study, during the home visit parents may have been influenced in their report of alarming symptoms after reassurance by the triage nurse or the GP at presentation the previous day, indicating that our results might be overestimated.

Implications for future research and clinical practice

Since triage based on parent-reported symptoms is commonly used to select the child at risk of a serious illness, a better association is required than that found in the present study between parent-reported symptoms and findings at physical examination. Nevertheless, the association between reported symptoms and serious illness remains the most important issue at triage. A proxy for serious illness is referral. Based on these same data we used in our study, Monteny et al showed that children with two or more parent-reported alarming symptoms at triage were more likely to be referred than children without parent-reported alarming symptoms (0% versus 14% in children aged <18 months, and 2% versus 12% in children aged ≥18 months). This indicates that the parent-reported alarming signs do reflect serious illness to some extent.[4] Although triage is based on poorly performing parent-reported symptoms, the Dutch triage system at an OHS was able to discriminate between children at high and at low risk for serious infections.[14]

In the present study, the lack of an association between parent-reported alarming symptoms and alarming symptoms seen at physical examination might be due to communication problems; eg. using terminology/words that are interpreted differently by parents and caregivers. An improvement might be achieved by educating parents about alarming symptoms, training triage nurses in interpreting parent-reported alarming symptoms, or by requiring the GPs to perform telephonic triage. Evaluating the effects of education, training or telephonic triage by GPs should be the focus of future research.

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CHAPTER ***THREE***

Serious infections and healthcare use in febrile children presenting at a general practice out-of-hours service

Submitted

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Abstract

Background:
The introduction of a general practitioner (GP) out-of-hours service (OHS) changed triage.

Aim: to describe risk of serious infections (SI) and healthcare use in febrile children following triage decisions.

Design and Setting: a prospective cohort study performed at OHS

Methods: We included febrile children aged 3 months to 6 years. We describe risk of SI and healthcare use following 2 triage decisions. At presentation by telephone, parents received self-care advice or a face-to-face contact with a GP (first triage decision). After the latter, children were directly referred or sent home (second triage decision). We observed healthcare use and diagnoses of SI during one week after presentation.

Results: In total, 134 (26.5%) received self-care advice by telephone; 372 (73.5%) of 506 included children were invited for a face-to-face contact, and 26 (5.1%) were directly referred. Overall risk of SI was 9.9% (95% CI:7.6-12.8). In children with self-care advice the risk of SI was 3.7% (1.6-8.4%). At face-to-face contact the risk was 12.1% (95% CI:9.2-15.8); after direct referral this risk increased to 72.0% (95% CI:52.4-85.7).
In children who received self-care advice, 20% had a re-consultation, 2.2% were referred, 1.5% were admitted to hospital, and 19.3% were prescribed antibiotics. In total, 18.3% of the children with a face-to-face contact had a re-consultation, 10.5% were referred, 8.1% were admitted to hospital, and 48.0% were prescribed antibiotics.

Conclusion: Triage at OHS differentiates between children at high and low risk of SI, but at substantial costs in terms of antibiotic prescriptions for children without SI.

Introduction

Young children often suffer from febrile illnesses leading to parental concern and healthcare consultations, mainly during after-hours.[1-3] Because primary care is cost-effective when compared to specialist care, and febrile illnesses in general have a benign course, febrile children should preferably be managed in primary care. In this setting, healthcare use is generally based on triage.[4]

In Europe, out-of-hours primary care is increasingly provided by large-scale organizations.[5-7] In the Netherlands, telephone triage by trained nurses is common at general practitioner (GP) out-of-hours services (OHS). This triage aims to distinguish between children that urgently need to see a GP and those who can safely wait. Triage systems aiming to identify patients who need urgent care differ from triage systems in face-to-face contacts, where triage aims to predict risk of serious infections (SI) and to initiate adequate medical treatment.

In the last decade, incidence of SI is declining, however an increasing number of parents contact the OHS with low-urgent questions.[8] This increase further reduces the risk of a SI in contacting children. Despite this low risk of SI, parents are worried about the presence of fever and its possible complications.[9] In addition, increasing numbers of children are admitted to hospital for illnesses that could be treated in primary care.[10]

With the change to OHS, the continuity of GP care shifted from monitored care by the child's own GP, to a moment of care by the physician's colleagues.[11] Triage at an OHS implies that decisions regarding advice and medical treatment are made with limited knowledge of the child's background and medical history.[12] The decline in incidence of SI, the increasing number of contacts with the OHS and the change to OHS all have implications on the risk prediction of SI and subsequent healthcare use.[10,13] Healthcare use, for example re-consultation rates and hospital admissions, are seen as a measure of quality of care.[14] Therefore, it is important that healthcare use after triage is appropriately assessed.

This study aims to describe the observed risk of SI and healthcare use, - defined as re-consultations, referral, and hospital admissions and antibiotic prescriptions -, in young febrile children at a Dutch OHS according to the triage decisions.

Methods

This study was a prospective cohort study with one week of follow-up, performed at a GP OHS in Rotterdam. This OHS encompasses ± 300,000 inhabitants.

Between December 13 2004 and January 16 2006, consecutive children aged 3 months to 6 years who presented with fever (as stated by the parents) were eligible for inclusion. Children were excluded if communication in Dutch was impossible, if the child had been enrolled in the study in the past two weeks, or if no informed consent was obtained.[15,16]

When parents contacted the OHS by telephone (initial presentation), the triage nurses performed their usual triage based on the triage guideline of the Dutch College of General Practitioners.[17] Telephone triage decisions were noted in a

structured questionnaire by the triage nurses. GPs noted their diagnoses in the electronic medical OHS records.
A home visit by a trained research nurse was arranged for all children as soon as possible, but within 24 hours of inclusion. At this home visit, the research nurse recorded demographic data, antibiotic prescription and referrals in structured questionnaires.
Parents reported daily healthcare use in a structured diary for one week after initial presentation; diaries were returned by post. For all children, their GP's electronic medical records were checked for diagnoses and healthcare use for a period of one week after initial presentation. Pediatric hospital records were collected at the pediatric departments for all referred children.

Triage decisions
After telephonic triage the OHS nurse could decide to give self-care advice or offer a face-to-face contact with the GP (either at the OHS or at the child's home). After a face-to-face contact the GP could decide to refer the child directly to a pediatric emergency department or treat the child in primary care.

Serious infections
We defined SI as pneumonia, sepsis, meningitis, encephalitis, pyelonephritis, osteomyelitis, cellulitis, erysipelas, and abscess, and in addition dehydration (caused by gastro-enteritis or unknown cause), febrile convulsion, asthma exacerbation with fever, and in children under the age of one year, bronchiolitis. We examined OHS records for diagnostic codes registered according to the International Classification of Primary Care (ICPC) in order to define SI diagnoses at presentation. If a contact was not coded, a team of three GPs gave an ICPC code based on the (uncoded) diagnosis made by the GP at the OHS or, if this diagnosis was missing, based on noted symptoms and findings at physical or historical examination described in the contact notes. The team was blinded for triage decisions and for the management of the GP at the OHS. Final coding was based on consensus.[13] In case a consensus-based diagnosis could not be added due to missing data in the OHS records in non-referred children (n=14) we counted these children as having no SI at presentation.
During follow-up, a diagnosis of SI was based on the diagnoses (ICPC-coded) the GP had noted in his or her own electronic patient dossier (EPD) or in case of referral on the diagnosis made by the pediatrician. In case of disagreement in presence or type of SI between the GP and the pediatrician we presented the diagnosis of the pediatrician.

Healthcare use
Healthcare use was defined as all GP re-consultations, referrals to a pediatrician, admissions to hospital during this fever episode and antibiotic prescriptions. Antibiotic prescription at initial presentation was defined as antibiotic prescription noted by the research nurse. Antibiotic prescription during follow-up was based

on antibiotic prescription reported in the diaries, or as noted in the GP's or the pediatrician's medical records.

Statistical analysis
All analyses are descriptive. Frequencies are presented. Percentages of SI and healthcare use were calculated per outcome of triage decision. To calculate CIs of the presented frequencies we used OpenEpi.[18]
When parents stopped filling out the diaries (mostly because the child no longer had fever) and we did not find additional healthcare use in the record of the child's own GP, we assumed that there was no additional healthcare use for that child.

Approval for this study was obtained from the Central Committee on Research Involving Human Subjects.

Results
In a period of 1.1 years, 1916 children contacted the OHS with fever; of these 506 children were finally included. Figure 1 presents number of eligible children, reasons for non-participants and the number of available records. Table 1 presents the characteristics of the included and non-included children.

Table 1.
Characteristics of the included and non-included children.

	Included children (n=506)	**Non-included children** (non-eligible and no informed consent) (n=1410)
Age in months, median (range)	21 (3-70)	21 (3-71)
Male gender, n (%)	289 (57.1)	778 (55.2)
Immigrant, n (%)	287 (56.7)	910 (64.5)
Comorbidity, n (%)	113/487 (23.2)	unknown
GP contact before initial presentation, n (%)	53/496 (10.7)	unknown
Triage result (face-to-face contact), n (%)	371 (73.3)	1012 (71.8)
Triage result (GP home visit), n (%)	0 (0.0)	10 (0.7)
Referral at initial presentation, n (%)	26 (5.1)	76(5.4)
Hospital admission at initial presentation, n (%)	19 (3.8)	unknown
Triage result (GP home visit), n (%)	0 (0.0)	10 (0.7)
Referral at initial presentation, n (%)	26 (5.1)	76(5.4)
Hospital admission at initial presentation, n (%)	19 (3.8)	unknown

Figure 1.
Flowchart of all eligible children.

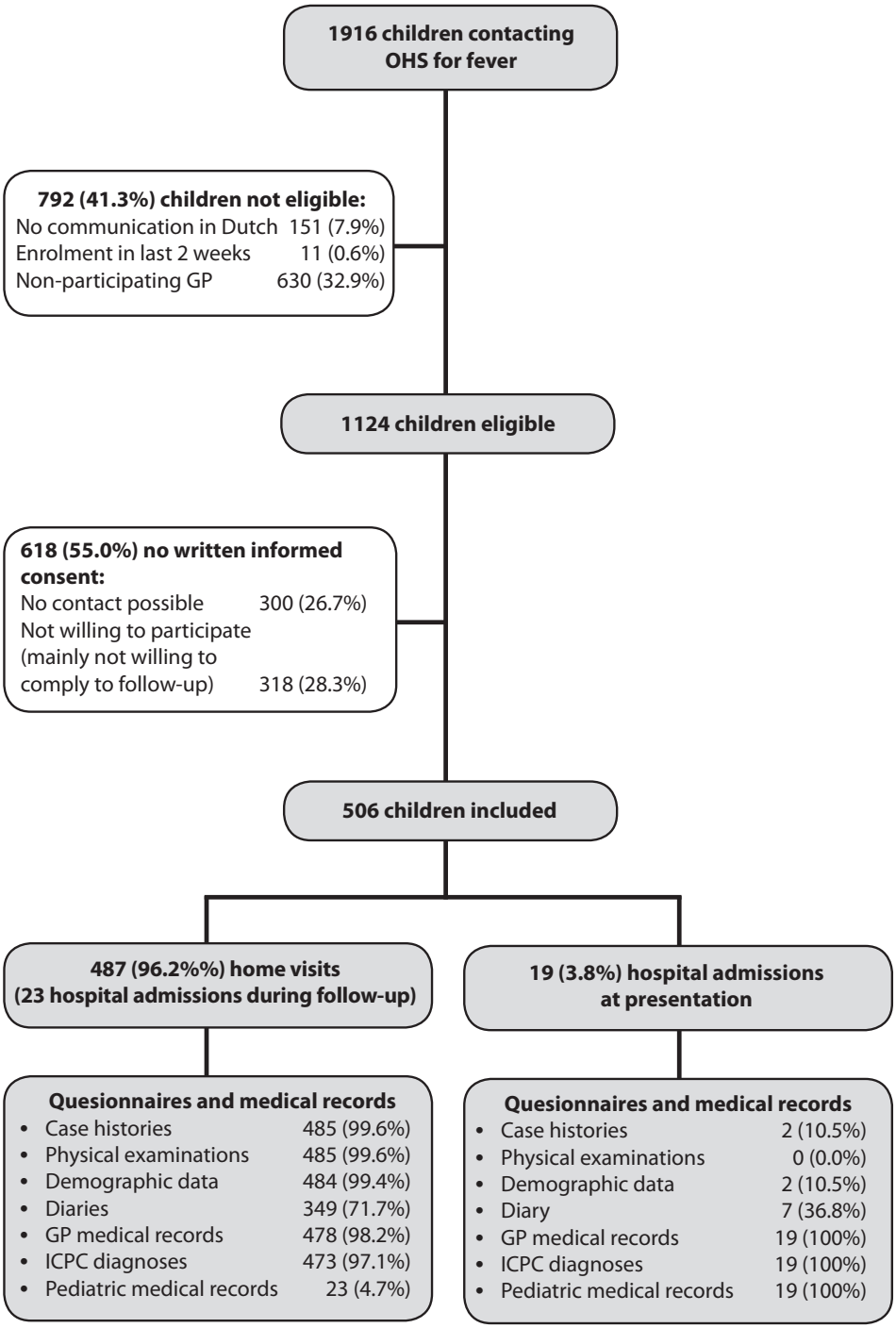

Figure 2.
Flowchart of triage result and subsequent healthcare use (n=506 children).

	Re-consultations *n (%)*	Referral (at presentation or during follow-up) *n (%)*	Hospital admissions *n (%)*	Antibiotic prescription *n (%)*
18 serious infections	1 (5.6)	18 (100.0)	17 (94.4)	9 (50.0)
7 no serious infections	1 (14.3)	7 (100.0)	4 (57.1)	3 (42.9)
27 serious infections	13 (48.1)	9 (33.3)	7 (25.9)	19 (70.4)
329 no serious infections	53 (16.6)	5 (1.6)	2 (0.6)	147 (46.1)
0 serious infections	0	0	0	0
1 no serious infection	1	1	0	1
5 serious infections	2 (40.0)	1 (20.0)	1 (20.0)	3 (60.0)
129 no serious infections	24 (18.6)	1 (0.8)	1 (0.8)	22 (17.1)
	95 (18.7)	**42 (8.3)**	**32 (6.3)**	**204 (40.3)**

Results of triage decisions
In total, 372 of all 506 included children (73.5%, 95%CI: 69.5-77.2) were invited for a face-to-face contact with the GP (371 children were actually seen by a GP and following on from this point they are called 'children with a face-to-face contact', one child was directly referred after telephonic consultation by a GP) and 134 children (26.5%, 95%CI: 22.8-30.5) received self-care advice by telephone.
In total, 26 children (5.1%, 95%CI: 3.5-7.4) were referred at presentation; that are 26 (7.0%, 95%CI: 4.8-10.0) of 372 children with an invitation for face-to-face contact (Figure 2).

Serious infections
Of the 506 children, ICPC codes were noted for 358 (70.8%) of them. A consensus-based ICPC code was added for 134 children (26.5%); for 70 of 135 children with a telephonic consultation (51.9%), and for 64 of 371 children with a face-to-face contact (17.3%).
Table 2 presents all SI diagnosed at initial presentation or during follow-up. In two referred children, the pediatrician did not confirm the presence of a SI diagnosed by the GP. Both children were offered a face-to-face contact, one child was directly referred, one child was referred during follow-up.

Table 2.
Serious infections at initial presentation and during one-week follow-up in all children (n=506).

Serious infection	Moment of diagnosis	
	At presentation	During follow-up
Pneumonia	12	5
Meningitis/encephalitis	1	-
Pyelonephritis	1	2
Dehydration	4	2
Abscess	-	1
Convulsion	7	1
Asthma exacerbation	6	-
Bronchiolitis (under the age of 1 year)	6	2
Total	**37**	**13**

Table 3 presents the observed risk of SI according to triage decisions. Overall risk of SI was 9.9% (95% CI: 7.6-12.8). In children with a self-care advice the risk of SI was 3.7% (95% CI: 1.6-8.4%). In children with a face-to-face contact the risk was 12.1% (95% CI: 9.2-15.8); after referral at presentation the risk of SI increased to 72.0% (95% CI: 52.4-85.7).

Table 3.
Risk of serious infection given triage decisions

Subgroup	Direct or no direct referral	Risk of serious infection % (95%CI)
Face-to-face contacts	All children	12.1 (9.2-12.8)
	Direct referrals	72.0 (52.4-85.7)
	No direct referrals	7.8 (5.4-11.1)
Self-care advices	All children	3.7 (1.6-8.4)
	Direct referrals	0
	No direct referrals	3.7 (1.6-8.4)
Total	**All children**	**9.9 (7.6-12.8)**

Healthcare use
Figure 2 presents a flowchart of triage decisions and subsequent total healthcare use (at initial presentation and during follow-up). In 135 children with initially only a telephonic consultation, 27 children (20.0%, 95%CI: 14.1-27.5) had a re-consultation of their GP, 3 children (2.2%, 95%CI: 0.8-6.3) were referred, 2 of them (1.5%, 95%CI: 0.4-5.2) were admitted to hospital, and 26 children (19.3%, 95%CI: 13.5-26.7) were prescribed antibiotics. Referral rate in the 371 children with a face-to-face contact at initial consultation was 10.5% (n=39, 95%CI: 7.8-14.1), 30 of them (8.1%, 95%CI: 5.7-11.3) were admitted to hospital. In total 68 children (18.3%, 95%CI: 14.7-22.6) had a re-consultation of their GP during follow-up, and 178 children (48.0%, 95%CI: 42.9-53.1) were prescribed antibiotics (Figure 2).

In all children, 42 children (8.3%, 95%CI: 6.2-11.0) were referred, 32 of them (76.2%, 95%CI: 61.5-86.5) were admitted to hospital (Table 1). Hospital admission rate was highest in children directly referred after a face-to-face contact (84.0%, 95%CI: 65.4-93.6). Of all children, 40.3% (95%CI: 36.1-44.6) were prescribed antibiotics. Antibiotic prescription rate was highest after a face-to-face contact in children who were not directly referred and who had an SI (70.4%, 95%CI: 51.5-84.2). In 464 non-referred children, 180 children (38.8%, 95%CI: 34.5-43.3) were prescribed antibiotics (Figure 2).

In children with a SI, 56.0% was referred (28 out of 50 children, 95%CI: 42.3-68.8) and 31 children (62.0%, 95%CI: 48.2-74.1) were prescribed antibiotics. Hospital admission rate was 50.0% (25/50, 95%CI: 36.7-63.4) and 89.3% (25/28; 95% CI: 73.6-97.2) in referred children. In 456 children *without* a diagnosis of SI, 14 children (3.1%, 95%CI: 1.8-5.1) were referred, and 173 children (37.9%, 95%CI: 33.6-42.5) were prescribed antibiotics. Hospital admission rate was 1.5% (7/456, 95%CI: 0.7-3.1) and 50.0% (7/14, 95%CI: 25.1-89.3) in referred children.

Discussion

This study describes the observed risk of SI and healthcare use in young febrile children at a Dutch OHS according to the triage decisions.

Strengths and limitations

This is the first study to describe observed risk of SI according to triage decisions in a prospective study of febrile children attending a primary care OHS. The use of diaries, as well as GP and hospital records, enabled us to obtain almost complete data for healthcare use and antibiotic prescriptions for all included children. Because we assumed that missing values on re-consultations and antibiotic prescription indicated a negative answer, our results may underestimate actual healthcare use. Since there were few missing data, we think this did not seriously affect our results.

Comparisons with existing literature

In the present study, the observed risk of SI was 9.9% (95% CI:7.6-12.8). An earlier systematic review found a prevalence of serious bacterial infections of 15.4%.[19] Most studies included in this review were not performed in a primary care setting. In contrast, we used a broader definition of SI, including acute medical conditions associated with infections (not necessarily bacterial infections, e.g. dehydration and asthma exacerbations) that were thought to benefit from intervention. And we added SI that occurred during a one-week follow-up. In an observational study with 9794 febrile children (aged < 16 years) with face-to-face contacts at a Dutch OHS 8.1% was directly referred to an emergency department.[20] The referral percentage is comparable to the direct referrals observed in children with face-to-face contacts in our study (6.7%).

GP's ability to predict SI needing intervention was good. In the 42 referred children we found that both SI percentages and hospital admission rates were high (referral rate: 66.7% and hospital admission rates of 89% in children with SI and 50% in children without a formal diagnosis of SI).

Most clinical prediction rules and evidence-based guidelines include several so called alarming symptoms or red flags. The definition of SI varies from only proven bacterial infections to specific diagnoses such as pneumonia or meningitis. The diagnostic accuracy of most clinical prediction rules for SI in children is found to be low. The probability of SI after a positive test did not surpass 60%.[21] In our study the posttest probability of SI in children directly referred after GP's consultation was 72.0%. In addition, we found that also without a formal diagnosis of SI a child could be seriously ill, recognized as such by the GP (3.1% was referred, and 50.0% of these referred children were admitted). Therefore, GPs seem to incorporate more then only alarming symptoms in their estimation of the risk of infections needing intervention (SIs), in febrile young children.

Implications for research and practice

More than 70% of the children consulting OHS by phone were invited for face-

to-face contact with a GP at the OHS, and 10.5% of them were referred. This is a relatively high workload if contrasted with the observed risk of SI of 12.1% in these children, leaving room for efficiency improvement of telephone triage. In a previous study performed in the same population we found that parents often misinterpret questions about the presence of alarming symptoms at telephonic triage.[15] Training of triage nurses in addressing questions on alarming symptoms and educating parents might improve telephonic triage.

A review on the reliability and validity of triage systems found that most common triage systems were not able to predict or preclude SI or were not studied in low urgent patients.[22] In our study, GPs were very able to predict SI in children seen in a face -to-face contact. The discrepancy between these findings urges for further research into the diagnostic reasoning of clinicians.

Although children of parents who received self-care advice were not examined by a GP, parents did not re-consult their GP more often (20.0% re-consultations in self-care advices versus 18.3% in face-to-face contacts). In addition, children with self-care advice were less often referred (2.2%), admitted to hospital (1.5%) or prescribed antibiotics (19.3%). In the perspective of the debate on the importance of a safety net[23], advising a scheduled revisit in safety netting protocols should be done with precaution in order not to increase healthcare use unnecessarily.

One third of the children *without* SI received an antibiotic prescription (37.9%). This high percentage might be explained by the prescription of antibiotics for infections that we did not label as "serious", i.e. acute otitis media (OMA), but for which antibiotics are recommended - under certain conditions - in guidelines of Dutch College of General Practitioners.[24] In our study, we found 67 children with OMA (13.2%), so even taking OMA into account antibiotic prescriptions in children *without* SI remained high. Reasons for this high percentage of antibiotic prescriptions might therefore be found in more pragmatic reasons such as the diagnostic uncertainty of the GP at the OHS who faces parents and children who's history he doesn't know, and the unfounded assumption of the GP that parents expect antibiotics.[25] In addition, the GP lacks the possibility of following the child over time, which might lead to a more defensive management, and therefore more antibiotic prescriptions. In a previous study based on the same data, we have shown that a substantial amount of antibiotic prescriptions is based on other not medically based considerations.[26]

To improve triage and avoid unnecessary healthcare contacts, improving patient education, communications skills of triage nurses and GPs in addition to safety-netting is required in order to allow children to stay safely at home, to reassure parents, to reduce antibiotic prescriptions, and to control the workload and costs in the care for febrile children.

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CHAPTER ***FOUR***

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

J Am Board Fam Med 2012;25:810–818.

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Abstract

Background: Fever is common in children and often self-limiting, but antibiotics are frequently prescribed for febrile illnesses. Determining children's signs and symptoms related to antibiotic prescription will give knowledge of physicians' considerations when assessing children with fever. 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.

Methods: Children aged 3 months – 6 years whose parents contacted a family physicians' out-of-hours service with fever as main reason for contact were eligible for inclusion. Signs, symptoms, and antibiotic prescription were in standardised format recorded. Statistical associations were assessed using bivariate and multivariate logistic regression analyses.

Results: Of the 443 included children, for 121 their parents received telephonic advice, and for 322 children the parents had face-to-face contact at the out-of-hours service. Of this latter group, 117 (36.3%) children were prescribed antibiotics, i.e. 26.5% (117/443) of the total study population. In the multivariate analysis, signs and symptoms positively associated with antibiotic prescription were concerned parents during home visit (OR:2.02;95%CI:1.06-3.58), (ill appearance (OR:3.26;95%CI:1.30-8.20), earache resulting in altered behavioural 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%CI:1.17-3.41). A negative association was found for age of 3 to 6 months (OR:0.17;95%CI:0.03-0.74), and height of rectal temperature (OR:0.52;95%CI:0.37-0.71).

Conclusions: Antibiotics were prescribed in about 25% of the febrile children whose parents contacted the out-of-hours service. Several signs and symptoms 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 US guideline for children with fever without source does have some recommendations about antibiotic treatment, - for example 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 with the US guidelines, the Dutch guidelines for sinusitis, and nonspecific 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 (ie. risk factors for complications, or sever illness), whereas in the United States 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 family physician's decision-making. In the United States however, it is common practice to test for a group A streptococcus infection, because it is 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 family physicians' decision to prescribe antibiotics (eg. 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 family physicians' out-of-hours service, and assesses the patient characteristics associated with these prescriptions.

Methods
This cohort study was performed at a family physicians' out-of-hours service in Rotterdam, a large multi-ethnic city in the Netherlands. This out-of-hours service 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 out-of-hours service 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 out-of-hours service (consultation); or a home visit by a family physician was arranged. The family physicians were free to prescribe treatments of their own choice or to refer the patient. It should be noted that the out-of-hours service – in that time – had no access to the child's regular family physician's medical record. Therefore, the out-of-hours service had no structured overview of the medical history of the patients. The records made at the out-of-hours service are digitally send to the childrens own family physician 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 hours 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 out-of-hours service, physician contacts, and prescribed medication as reported by the parents; in addition, a standardized physical examination (including rectal temperature) was performed.

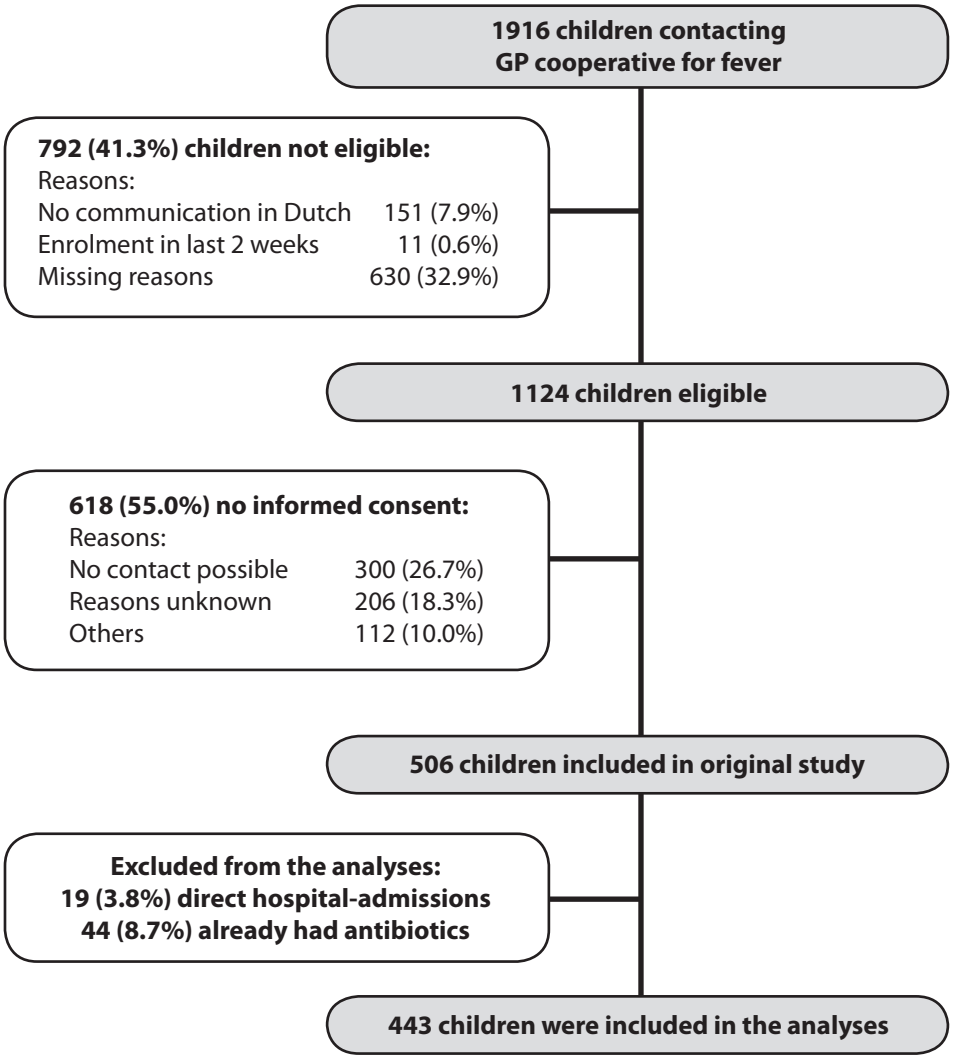
Tachypnea was defined as an elevated respiratory rate, taking age into account, as recommended by the guideline of the National Institute for Health and Clinical Excellence (NICE).[24] The Yale Observation Scale (YOS) score was part of the structured physical examination. The YOS has a six-item score 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 family physician at the out-of-hours service, 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 ($P < .10$). When there was an overlap between bivariately significant variables regarding patients' history and physical examination (eg. 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, that is the moment of antibiotic prescription. Missing data were considered missing at random or missing completely at random (ie. 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 $P<.05$. 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^2. 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).

Figure 1.
Flowchart of eligible children.



In total, 117 children (26.5%) received a prescription for antibiotics at the out-of-hours service. The median duration between consultation of the out-of-hours service 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 family physician at the out-of-hours service (n=322) received a prescription for antibiotics; this occurred in 36.3% (117/322) of the children.

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

Characteristics	No. of patients / Total no. of patients	Percentage
Age: 3 - 6 months	35/443	7.9
6 -12 months	87/443	19.6
> 12 months	321/443	72.5
Male sex	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)

Bivariate logistic regression
Bivariate logistic regression showed that (according to our predefined threshold of P<.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, 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, Supplement 1). 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^2 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 out-of-hours service, 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 family physician: approximately 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 family physicians' decision-making process

when assessing children with fever. Signs and symptoms, however, explained only a small proportion of the antibiotic prescriptions.

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 (ie. 161/506, 31.8%). In comparison with the United States, and other European countries, Dutch family physicians 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 family physician-contact and found that (in our age group of ≤ 6 years) approximately 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 (eg. 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, because 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 family physician, who usually knows the child from previous visits. However, as a result of the organization of out-of-hours primary care, family physicians in the Netherlands are generally not familiar with the patients they see at the out-of-hours service. 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, AOM). 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 family physicians' 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).

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

Variables			Bivariate analysis			Multivariate analysis			
	Percentage antibiotic prescription		OR	95%CI	p-value	Selection	OR	95%CI	p-value
If characteristic is:	Present	Absent							
Patient characteristics									
Age: **3 - 6 months**	**NA**	**NA**	**0.15**	**0.03-0.63**	**0.01**	**EA**	**0.17**	**0.03-0.74**	**0.03**
6 - 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 out-of-hours service)									
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

These can be related to the disease profiles for AOM and tonsillitis, for which the Dutch guidelines for family physicians 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 family physicians.

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 family physicians consultation, the research nurse might have assessed the child with antibiotics as more severely ill simply because the family physician 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 out-of-hours service (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 out-of-hours service. We chose this study design, because we did not want to interfere with regular care of the out-of-hours service (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 out-of-hours service. In addition, the median time elapsed between time of consultation of

the out-of-hours service and our home visit was only 14.5 hours. Given this short delay, it is unlikely that the antibiotic treatment started after the family physician consultation influenced our findings by physical examination, as it generally takes longer to show effect than the interval we allowed between the family physician 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 family physicians 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 family physician's decision to prescribe antibiotics (eg. 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, because 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 family physician's decision to prescribe antibiotics. However, since serious infections are rare in primary care, and most febrile illnesses are self-limiting, family physicians need to reflect on the legitimacy of their considerations regarding antibiotic treatment. Strategies that may diminish antibiotic prescriptions (eg. safety netting) need to be further explored.

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Supplement 1. 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 out-of-hours service	0.63	0.32-1.22
Child previously seen by own family physician	1.26	0.68-2.33
Out-of-hours service 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
Demographic data		
Sex (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<.10*
OR odds ratio
CI confidence interval

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'.

CHAPTER ***FIVE***

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 advise parents when to consult a doctor when their child has fever. To provide evidence-based, safety-net advice for young febrile children, we studied the risk of complications, the occurrence of alarm symptoms, the duration of fever.

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 alarming symptoms and rectal temperature in a diary for 1 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 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).

Conclusions: In children with uncomplicated illnesses, the daily occurrence of alarming symptoms reported by parents was high. The median duration of fever was 4 days. The predictive value of alarming symptoms reported by parents 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 safety-netting 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.

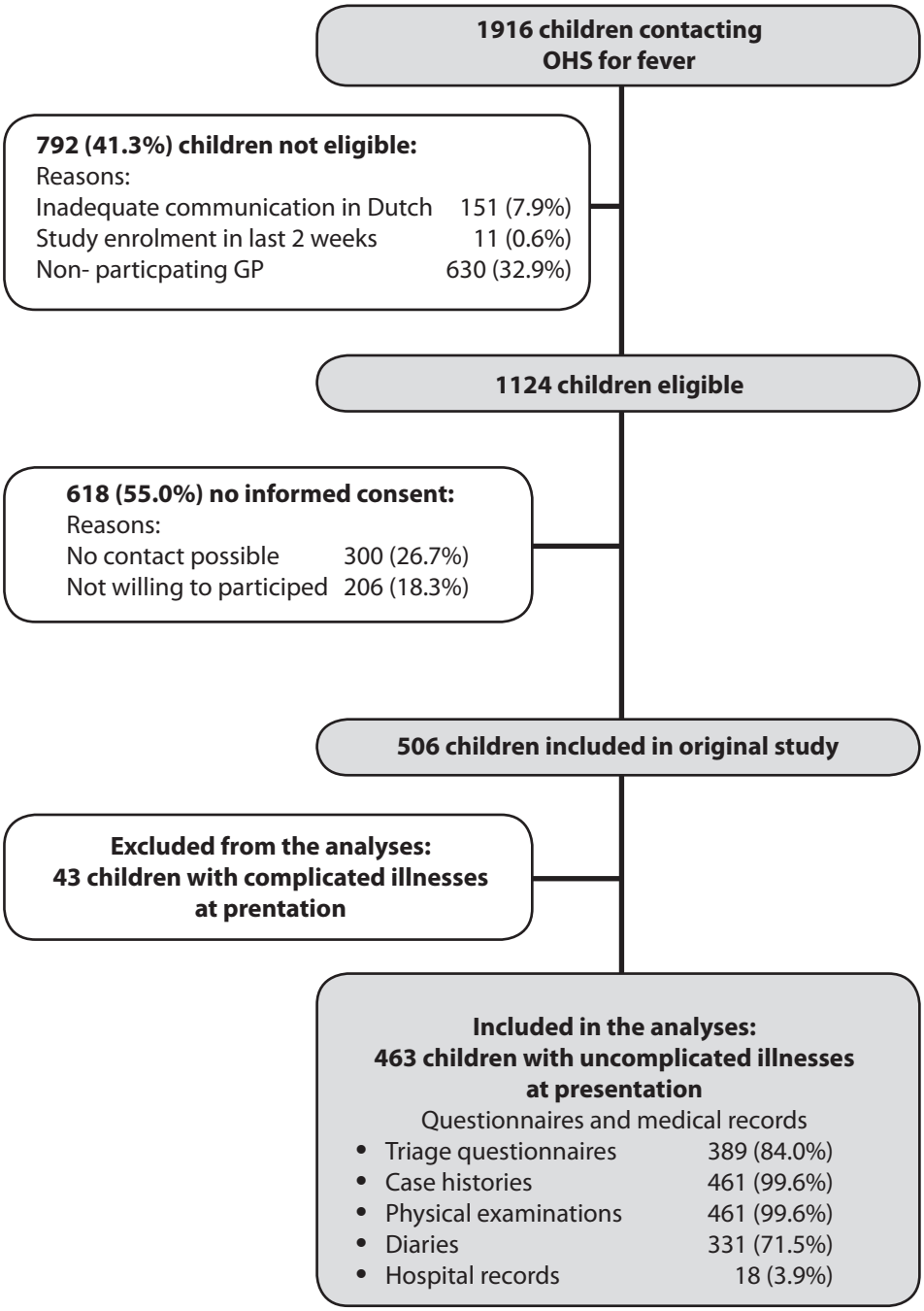
Methods

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 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)

Figure 1.
Flowchart of children eligible for study analysis.



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.

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 (86.0)

Values are n (%) unless otherwise indicated.

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 follow-up, 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 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.

Figure 2.
Rate of parental reported alarming symptoms in febrile children with uncomplicated illnesses.

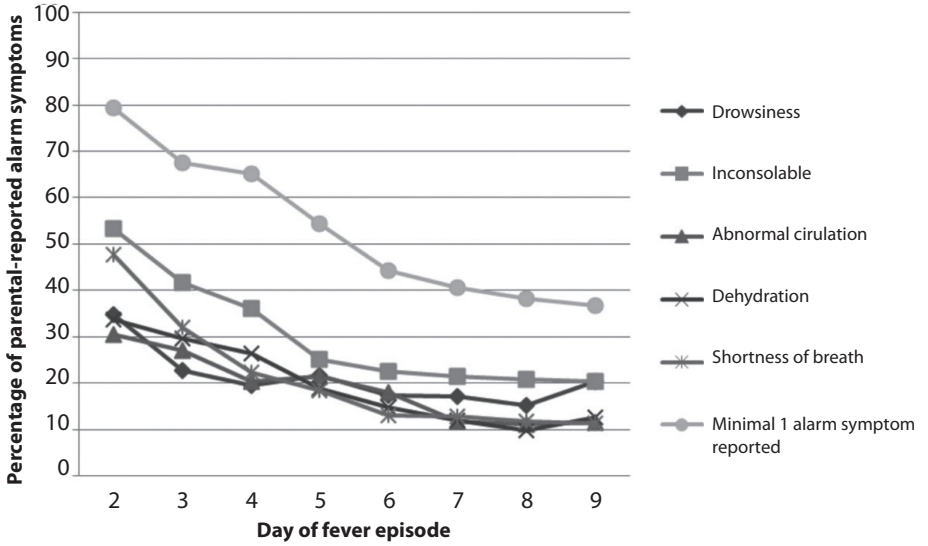


Table 2.

Alarming 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

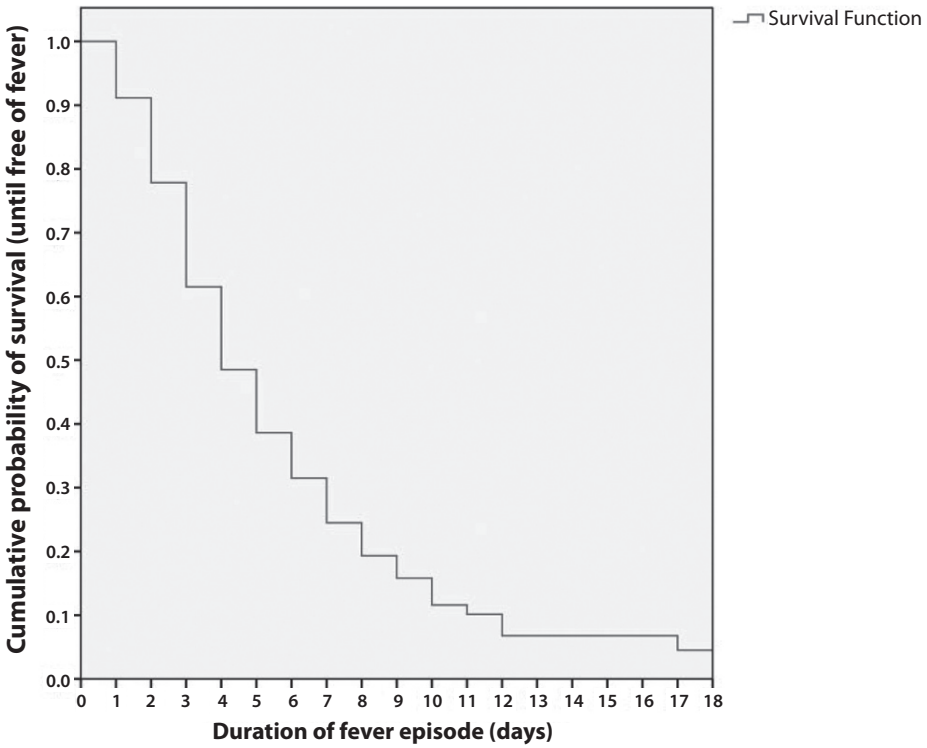
Table 3.
Daily temperature reported by the parents of febrile children with uncomplicated illness.

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)

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 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.

Figure 3.
Fever curve in young febrile children with uncomplicated illnesses (n = 463; 292 events, 171 censored).



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 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 ***SIX***

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

Submitted

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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 out-of-hours service (OHS).

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 OHS, 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:2.80; 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 $\geq$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 out-of-hours service (OHS), 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 GP OHS in Rotterdam, a large multi-ethnic city in the Netherlands. This OHS 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 OHS, or if the parents declined to give informed consent.

When parents contacted the OHS 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 OHS (face-to-face contact), 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 hours 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 ≥ 38.0ºC.

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 this duration 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 file 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 OHS was added to the multivariate model to adjust for confounding; additionally, antibiotic prescription at the OHS 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 37.6ºC (IQR: 37.0-38.1ºC). 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.

Univariate logistic regression

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

Figure 1. Flowchart of the eligible children.

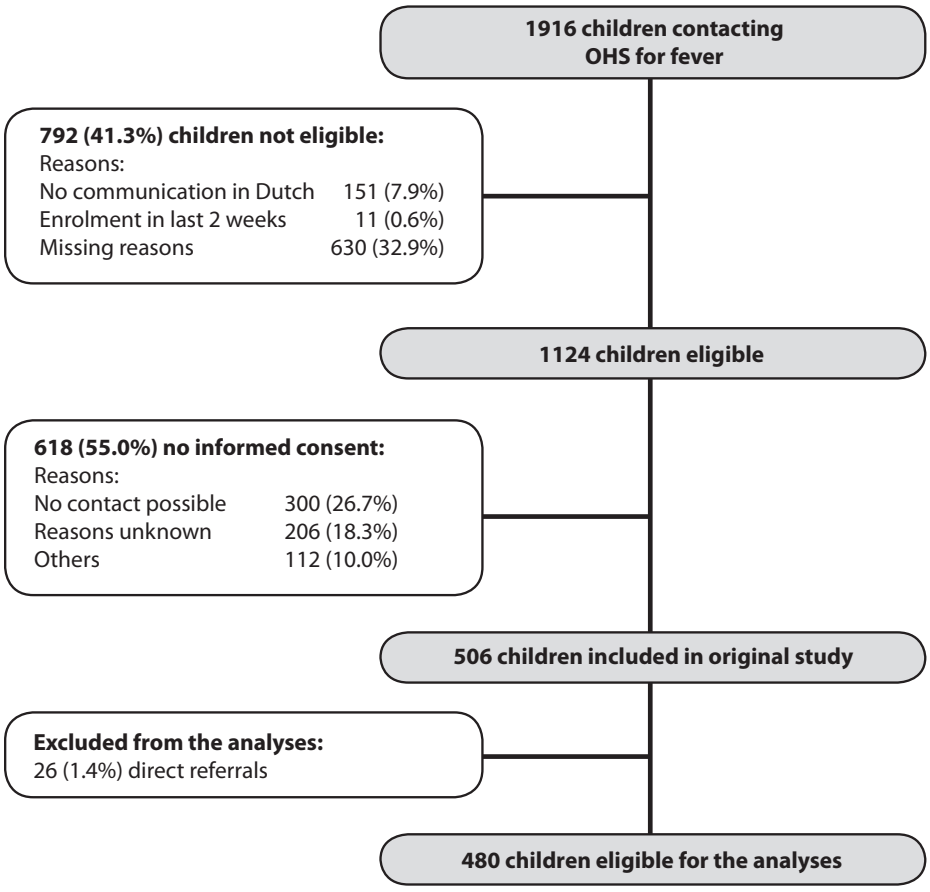

Table 1.
Characteristics of the study population (n=480).

Characteristics	No. of patients / Total no. of patients	Percentage
Age: 3 to 6 months	35/480	7.3
6 to 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'.

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

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.

Signs and symptoms included in analysis	Percentage prolonged duration of fever:	
	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

NA: not applicable

Discussion

The present study shows that, for children not directly referred to secondary care, the median duration of fever after consultation with the OHS 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 (eg. 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 OHS, antibiotic prescription at the OHS was added to the model to control for potential confounding (data not shown). However, because antibiotic prescription at the OHS did not influence the model, for reasons of clarity, this was removed from the model. Duration of fever prior to consultation with the OHS 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, eg. 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 OHS. This study design was chosen because we did not want to interfere with the regular care of the OHS (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 OHS. 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.ours.

A further limitation is the substantial loss to follow-up, ie. 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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Supplemental file 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

Bold: *P<0.157.*

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 ***SEVEN***

Respiratory virus infections in febrile children presenting to a general practice out-of-hours service

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Abstract

Background: Fever is common in young children and is assumed to be frequently caused by viral infections.

Objectives: To document respiratory viruses in children with fever presenting at a general practice out-of-hours service (OHS), evaluate presenting symptoms in febrile children with a virus infection, and examine the association between antibiotic prescription and the presence of a viral infection.

Methods: Nasopharyngeal swabs were obtained to detect respiratory viruses in non-hospitalized children aged three months to six years presenting with fever at an OHS. Symptoms were assessed using physical examinations and questionnaires. Logistic regression analysis was used to reveal associations between symptoms or diagnoses, and the presence of at least one virus.

Results: In total 257 nasopharyngeal swabs were obtained in 306 eligible children; 53% of these children were infected by at least one virus. The most frequently detected viruses were adenovirus (10.9%), RSV type A (10.5%) and PIV type 1 (8.6%). Cough (OR 2.6; 95% CI: 1.4 – 4.6) and temperature ≥ 38.0 ° C (OR 2.1; 95% CI: 1.3 – 3.5) were independent predictors of the presence of a virus, but the discriminative ability was low (AUC 0.64; 95% CI: 0.58 – 0.71). Antibiotic prescription rate was 37.3%. In 57.4% of children with an antibiotic prescription, a virus was found.

Conclusion: In over 50% of all febrile children presenting at an OHS, a virus was found. Antibiotic prescription rate was high and not associated to the outcome of viral testing.

Introduction

Young febrile children are frequently presenting to a general practitioner (GP) during after hours.[1,2] In the Netherlands, after-hours-care is increasingly provided by GP out-of-hours services (OHS). At the OHS triage is generally performed by triage nurses who decide, whether a child should consult a GP because it might need direct medical care.[3]

Most feverish illnesses are found to be viral and self-limiting.[4,5] The challenge for the GP is to select the child at risk of serious infections. It is assumed that most serious infections in febrile children are caused by bacterial infections that are less often self-limiting compared to virus infections. Some suggest that rapid virus testing can be used to distinguish between viral and bacterial infections. In addition, only a few young children with recognizable viral syndromes have bacteraemia.[6-10]

In daily practice clinical features are used to distinguish between seriously and non-seriously ill children. Despite this distinction, in the Netherlands antibiotic prescription rates of 35% are common.[11] This is in contrast to the low levels of serious bacterial infections reported in febrile children.[12]

The present study describes the presence of virus infections in a population of young children presenting with fever to the GP OHS. We evaluated whether symptoms, C-reactive protein level and diagnoses were related to the presence of a respiratory virus infection, and whether antibiotic prescription was related to the presence of a virus infection.

Methods

Study design

This cross-sectional study was conducted using baseline measurements of a 7-day prospective cohort study evaluating the course of feverish illness in young children.[3,13,14]

The study was approved by the Dutch Central Committee on Research Involving Human Subjects.[15]

Setting

The study was performed at a GP OHS in the southern part of Rotterdam ('Centrale Huisartsenpost Zuid'), covering an area of 300,000 inhabitants, which is a normal size for an average OHS in the Netherlands.

Patients

Consecutive children aged ≥ 3 months to 6 years presenting with fever (as stated by the parents) at a GP OHS between 1 June 2005 and 16 January 2006 were eligible for the original study. Excluded from the study were: children without informed consent, children of parents with a language barrier, a previous study enrolment in the last two weeks.

For this study we additionally excluded children in whom no nasopharyngeal swab was obtained, and children admitted to hospital directly after first presentation.

Procedures

OHS nurses give advice over the telephone, or arrange a face-to-face contact at the OHS or a home visit by a GP. OHS nurses are supervised by GPs.

When parents contacted the OHS by telephone concerning their febrile child, a nurse triaged into telephonic self-care advice or a face-to-face contact with the GP, based on commonly used triage guidelines.[3,16] According to these guidelines, a child was invited for a 'face-to-face' consultation if the child was younger than three 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 colour, had a change in breathing pattern, was moaning or had apnoea, had relevant co-morbidity, had fever for more than three days or fever increasing after a fever-free period. In addition, a child was seen when the parents showed agitation, aggression, or persistent anxiety. GPs were free to prescribe their treatment of choice, or to refer the child to a paediatrician. A child was triaged as 'self-care advice' if none of the above were present. Within 24 hours (mean 14, standard deviation 8) of the first contact with the OHS all children (regardless of their triage results) were visited at home by a trained research nurse who recorded demographic data, symptoms and signs, and antibiotic use (as reported by the parents) in a structured questionnaire. The research nurse performed a standardized physical examination and took a nasopharyngeal swab and a capillary blood sample.

Presence of respiratory virus infections in nasopharyngeal swabs

Nasopharyngeal swabs were examined using a MagnaPure isolation station to isolate nucleic acids, and real-time polymerase chain reaction assays to determine the following 10 groups of viral pathogens: adenovirus, human bocavirus, enterovirus, human coronaviruses types OC-43, 229E, NL63 and HKU, human metapneumovirus, influenza viruses types A and B, para-influenza viruses (PIV) types 1-4, parechovirus, respiratory syncytial viruses (RSV) types A and B, and rhinovirus.

C-reactive protein level

Capillary blood was obtained to measure C-reactive protein (CRP) levels (point-of-care test: Nycocard CRP test, Clindia Diagnostics, Leusden, the Netherlands).[17] Measurements were performed by the research nurse after symptoms were noted in the questionnaire and after physical examination was performed. The research nurse was unaware of the research question. A CRP level was classified as high when the level was >80 mg/l.[18]

Symptoms

Rectal temperature was measured during physical examination by the research nurse, and was also measured by the parents later that same day and noted in the diary (day 1).

Dyspnoea was defined as retractions and/or nasal flaring and/or tachypnoea.

Tachypnoea was classified as an increased respiratory rate (RR) depending on age, as stated in the NICE guideline (age 0-5 months RR >60 breaths/min; age 6-12 months RR >50 breaths/min; age >12 months RR >40 breaths/min).[4] Diarrhoea was defined as reported diarrhoea more than twice a day on day 1. The research nurse was unaware of the definitions of the symptoms (dyspnoea, tachypnoea and diarrhoea) that were used in the analyses.

Diagnoses

At the OHS, GPs and triage nurses recorded the diagnosis based on the International Classification of Primary Care (ICPC) in the medical record of the child. If the ICPC code was missing a team of three GPs allocated a code based on the (uncoded) diagnosis made by the GP at the OHS or, in case this diagnosis was missing, based on noted symptoms and findings at physical examination as recorded in the medical records of the OHS. This team was blinded for the management of the GP at the OHS. Final coding was based on consensus.

'Acute respiratory tract infection' was defined as ICPC chapter R (respiratory) or H (ear). 'Gastro-enteritis' was based on ICPC codes for vomiting, diarrhoea or gastro-intestinal infections; 'presumed viral syndrome' was based on ICPC codes for fever, erythema infectiosum (fifth disease), exanthema subitum (roseola infantum, sixth disease), mumps, rubella (German measles), varicella (chickenpox), virus infections with exanthema, and other virus infections.

Antibiotic prescription

Antibiotic prescription was defined as antibiotics prescribed at presentation or prior to presentation at the OHS, and reported by the parents during the structured assessment or noted in the diaries at day 1.

Statistical analysis

Prevalences of virus infections and 95% confidence intervals (CI) were calculated. Children without nasopharyngeal swabs were not included in the analyses (available case analysis). On the group level, if missing data were ≤5% regarding a variable we assumed that the variable was not present in the child with missing data for this variable, and imputed the missing data as absent. On the group level, if missing data were >5% regarding a variable, that child's record was excluded from the analysis in which the variable was analysed.

Univariable logistic regression analysis was used to relate patient characteristics, symptoms, diagnoses and triage result to the presence of at least one virus. Associations were expressed as odds ratios (ORs) with 95% CIs. Only significant univariable associations related to the presence of a virus ($p<0.05$) were included in a multivariable logistic regression model (backward LR method, entry 0.05, removal 0.10).[19]

Goodness-of-fit was assessed by calculating and comparing observed and expected probabilities of a virus infection. The expected probability was calculated using the regression coefficients of the independent variables found to be present

in each child. The area under the receiver operating characteristic curve (AUC) was used to assess the discriminative ability of the model.
An AUC of 0.5, 0.75 or 1.0 means no, moderate or perfect discriminative ability, respectively.
In case a virus was present in >10% of all children, we analysed the relation between patient characteristics, symptoms and the presence of this specific group, using logistic regression analyses as described above. For statistical analyses *SPSS* 15.0 *for Windows* (SPSS, Inc, Chicago, IL, USA) was used. To calculateCIs of the prevalences of the viruses we used OpenEpi.[20]

Results

Table 1. Patient characteristics, symptoms and CRP level in children aged ≥ 3 months to 6 years presenting with fever (as stated by the parents) at a general practice out-of-hours service in the Netherlands

Characteristics and symptoms	Included children, with swab (N=257) n (%)	Children excluded due to absence of swab* (N=49) n/N (%)	Children excluded due to admission* (N=13) n/N (%)
Characteristic			
Age (months; mean ± standard deviation)	23.8 ± 17.0	29.6 ± 14.3	23.1 ± 21.8
Female sex	106 (41.2)	23/49 (46.9)	3/13 (23.1)
Face-to-face contact	197 (76.2)	38/49 (77.6)	13/13 (100)
Referral to paediatrician	4 (1.6)	1/49 (2.0)	13/13 (100)
Symptoms			
Temperature ≥38.0 ºC	120 (47.2)	26/46± (56.5)	n.a.
Cough	76 (29.6)	13/47 (27.7)	n.a.
Rhinitis	135 (52.5)	24/47 (51.1)	n.a.
Dyspnoea	51/228± (22.4)	5/38± (13.2)	n.a
Rash	85 (33.6)	14/43± (32.6)	n.a.
Diarrhoea	60 (23.3)	3/49 (6.1)	n.a.
Diagnoses			
Acute respiratory tract infection	160/250 (62.3)	29/49 (59.2)	10/13 (76.9)
Gastro-enteritis	15/250 (6.0)	2/49 (4.1)	1/13 (7.7)
Presumed viral syndrome	54/250 (21.6)	12/49 (24.5)	1/13 (7.7)
CRP level: High CRP (>80 mg/l)	23/234± (9.8)	4/9± (44.4)	4/9± (44.4)
Antibiotic prescription	94/252 (37.3)	19/48 (39.6)	4/13 (30.8)

** All calculated with available cases ±calculated with available cases and missings > 5%*
n.a. not available

Patient characteristics

Characteristics of the patients are presented in Table 1. In total 257 children were included. Thirteen children were excluded due to admission to the hospital directly after presentation, and 49 children were excluded because nasopharyngeal swabs were not obtained due to resistance of the child. On average, children without nasopharyngeal swabs were 5.8 months older than children with nasopharyngeal swabs, and more often had a temperature ≥38°C or a CRP >80 mg/l.

Five children were included twice, each with two new episodes of fever. On physical examination at day 1, 120/257 children (47.2%) had a rectal temperature of ≥38.0 °C. Median rectal temperature was 37.5 (range 35.2-40.4) °C. CRP level was measured in 234/257 children (91.1%). Median CRP level was 16 (range <8 - >250) mg/l. Only 23 (8.9%) children had a high (>80 mg/l) CRP level. In 250/257 children (97.3%) a diagnosis could be made: in 182 (70.8%) an ICPC-code was available and in 68 children (26.5%) a consensus-based diagnosis was made. Of these 250 children, 160 (62.3%) were diagnosed with an 'acute respiratory tract infection', 54 (21.6%) were diagnosed as 'presumed viral syndrome', 15 (6.0%) had 'gastroenteritis' and seven (2.8%) children remained without a diagnosis.

Presence of a virus

At least one virus was detected in 136 (52.9%, 95% CI 46.8-58.9%) children, and in 26 (10.1%, 95% CI 7.0-14.4%) children two or more viruses were detected.

Table 2.
Detected viruses in children presenting with fever (as stated by the parents) at a general practice out-of-hours service in the Netherlands (N=257, age 3 months - 6 years).

Specific virus	Number of detected viruses* n	Prevalence in % (95%CI)
PIV types 1-4	39	15.2 (11.3-20.1)
- PIV Type 1	22	8.6 (5.7-12.6)
RSV types A-B	36	14.0 (10.3-18.9)
- RSV Type A	27	10.5 (7.3-14.9)
Adenovirus	28	10.9 (7.6-15.3)
Rhinovirus	21	8.2 (5.4-12.2)
Enterovirus	18	7.0 (4.5-10.8)
Human metapneumovirus	7	2.7 (1.3-5.5)
Parechovirus	6	2.3 (1.1-5.0)
Human bocavirus	4	1.6 (0.6-3.9)
Influenza viruses types A-B	4	1.6 (0.6-3.9)
Human coronaviruses±	3	1.2 (0.4-3.4)

** 22 children had 2 detected viruses and 4 children had 3 detected viruses*

± types OC-43, 229E, NL-63, HKU

Table 2 presents the frequency of the specific respiratory viruses. PIV types 1-4, RSV types A-B and adenovirus had a prevalence of ≥ 10% (Table 2).

Associations between symptoms, diagnoses, CRP level and presence of a virus
At least one virus was detected in 75/120 (62.5% 95% CI 53.6-70.7%) children with a temperature ≥ 38.0 °C.
At least one virus was detected in 93/160 (58.1%) children who were diagnosed with an 'acute respiratory tract infection', in 27/54 (50.0%) children with a 'presumed viral syndrome', in 4/15 (26.7%) children with 'gastroenteritis', and in 6/7 (85.7%) children without a diagnosis, respectively.

Table 3.
Association of clinical features with presence of a respiratory virus infection (univariable logistic regression) in children presenting with fever (as stated by the parents) at a general practice out-of-hours service in the Netherlands (N=257, age 3 months - 6 years).

Characteristics and symptoms	**Odds Ratio (95%CI) Absence of a virus versus at least one virus present**
Characteristics	
Age (per month increasing)	1.00 (0.99-1.02)
Female sex	1.3 (0.8-2.1)
Attending day-care	1.3 (0.8-2.1)
Siblings	0.9 (0.6-1.5)
Face-to-face contact versus telephone advice	1.0 (0.5-1.7)
Symptoms	
Temperature ≥38.0˚C	**2.1 (1.3-3.5)**
Cough	**2.5 (1.4-4.4)**
Rhinitis	1.6 (0.9-2.6)
Dyspnoea	1.4 (0.8-2.7)
Rash	0.7 (0.4-1.1)
Diarrhoea	0.8 (0.4-1.4)
Diagnoses	
Acute respiratory tract infection versus other diagnoses	**2.0 (1.2-3.4)**
Gastro-enteritis versus other diagnoses	0.3 (0.1-1.0)
Presumed viral syndrome versus other diagnoses	0.9 (0.5-1.7)
CRP level	
High (>80 mg/l) versus moderate/low (≤80 mg/l)	0.6 (0.3-1.5)

Bold *values are significant (p<0.05)*

Table 3 presents the univariable associations between characteristics, symptoms,

diagnoses and CRP levels and the presence of at least one virus. The symptoms 'cough' (OR 2.5; 95% CI 1.4-4.4) and 'temperature ≥38.0 °C' (OR 2.1; 95% CI 1.3-3.5) were positively associated with the presence of at least one virus, as was the diagnosis of 'acute respiratory tract infection' (OR 2.0; 95% CI 1.2-3.4). CRP > 80 mg/l was not associated with the presence of at least one virus.
The results of the multivariable analysis, including the AUC, are presented in Table 4. The presence of 'cough' with a 'temperature ≥38.0 °C' increased the probability of a respiratory virus infection from 52.9% to 76.8%; if both symptoms were absent, the probability of a respiratory virus infection decreased to 37.8%. Goodness of fit was good, observed and expected probabilities were comparable (data not shown).

Table 4.
Multivariable logistic regression and discriminative ability of clinical features with presence of any respiratory virus, adenovirus and RSV types A-B respectively, in children presenting with fever (as stated by the parents) at a general practice out-of-hours service in the Netherlands (N=257 age 3 months - 6 years).

Outcome (yes versus no) Independent variables (yes versus no)	Odds Ratio (95%CI)	Discriminative ability AUC (95%CI)
Children with any respiratory virus infection		0.64(0.58-0.71)
Temperature ≥38.0˚C	**2.3 (1.4-3.9)**	
Cough	**2.4 (1.3-4.3)**	
Children with adenovirus infection		0.71(0.62-0.80)
Temperature ≥38.0˚C	**3.8 (1.6-9.4)**	
Rhinitis	**2.4 (1.0-5.7)**	
Children with RSV infection types A-B		0.73(0.63-0.83)
Attending day-care	2.1 (0.9-4.7)	
Temperature ≥38.0˚C	**2.6 (1.1-5.9)**	
Cough	2.2 (1.0-4.9)	
Rhinitis	**2.6 (1.1-6.3)**	

Bold *values are significant (p<0.05)*

Associations between symptoms, diagnoses, CRP level and presence of a specific respiratory virus
The univariable logistic regression analyses showed that attending day-care, cough, rhinitis and a temperature of ≥ 38.0°C were positively associated with the presence of RSV types A-B; rhinitis and a temperature of ≥ 38.0°C were associated with the presence of adenovirus. No associations between symptoms and diagnoses were significantly related to the presence of PIV types 1-4. CRP >80 mg/l was not associated with the presence of a specific virus. Table 4 presents the results of multivariable logistic regression for these specific viruses.

Antibiotic prescription
Of the 252 children (missing n=5), antibiotics were prescribed in 94 (37.3%) (Table 1); of these children, 54 (57.4%) had at least one virus. There was no association between antibiotic prescription and the presence of a virus infection (OR 1.3, 95% CI 0.8 – 2.2).

Discussion

Main findings
Of all 257 children, 52.9% had at least one respiratory virus. The most frequently detected viruses were adenovirus (10.9%), RSV type A (10.5%) and PIV type 1 (8.6%). Cough and temperature ≥38.0°C were independently associated with the presence of a respiratory virus infection. Having a clinical diagnosis of an acute respiratory tract infection was associated with having at least one virus. CRP >80 mg/l was neither associated with the presence of at least one virus nor with the presence of a specific virus. In total, 37.3% of the children with fever were prescribed antibiotics; antibiotic prescription was not related to the presence of a virus infection (OR 1.3, 95% CI 0.8-2.2).

Strengths and limitations
The strength of this study is that we could test consecutive children with fever unrelated to further diagnosis or management of the child, which yielded a representative estimation of the prevalence of virus infections in the population of febrile children in general practice. In addition, the prevalences of the three main viral pathogens had similar patterns to those described in the weekly virology reports published by the National Institute for Public Health and the Environment in the Netherlands for that period.[21] Although viruses are evolutionarily malleable we did not find reasons to assume that diversity or pathogenicity changed in the nine years between data collection and presentation of results. Although the included children are representative for a population of young febrile Dutch children presenting to a GP OHS, generalization of the results to other geographical areas should be made with precaution.
A limitation of this study is that we were unable to obtain nasopharyngeal swabs from all children. Children without nasopharyngeal swabs (n=49) were overall 5.8 months older than children with nasopharyngeal swabs. Older children offer more resistance to collecting a nasopharyngeal swab than younger children; this was considered as non-informed consent from the child and a reason not to take a swab. Although older children probably are less vulnerable to virus infection due to a more mature immune system, the difference in age (less than 6 months) is likely to be too small to affect the frequency of respiratory viruses. Therefore, we do not think that exclusion of children without a nasopharyngeal swap will have affected the frequency of respiratory viruses.
Although (reported) fever was an entry criterion, only 47.2% of all febrile children had a rectal temperature of ≥38.0 °C at day 1. Because for inclusion it was not

necessary to measure the exact rectal temperature, some children may have been enrolled without a rectal temperature ≥ 38.0°C at the time of inclusion. It is reported that when parents feel their child's temperature by hand they rarely miss a fever, but do have a tendency to overestimate the child's body temperature.[22] Nevertheless, the included children do represent the population of 'febrile' children presenting in a routine GP OHS.

Although we found that temperature ≥ 38.0°C and rhinitis were associated with the presence of adenovirus and of RSV, the confidence intervals were rather wide due to the low number of children with that specific virus.

In the analyses we used a consensus-based diagnosis in 68 children (26.5%). Although a team of three GPs tried to resemble the diagnosis the GP at the OHS could have made based on his findings at the OHS, small differences between the consensus-based diagnosis and the actual diagnosis could have appeared. However, in the analyses we only evaluated broad definitions of diagnoses such as 'acute respiratory tract infection' (which was based on all diagnoses in ICPC Chapter R and H). Therefore, we assume that these differences did not have a big influence on the associations between the diagnoses and the presence of a virus.

Comparison with existing literature

In this study, the frequency of respiratory viruses was 52.9%. After selecting only those children with an observed rectal temperature of ≥ 38.0 °C at day 1, the frequency of respiratory viruses increased to 62.5%. Selecting only those children with a diagnosis of an acute respiratory tract infection hardly changed the prevalence of virus infections (58.1%). In the present study the prevalence of virus infections is low compared to that of Harnden et al. (77%) in their study of febrile children with respiratory tract infections, and also compared to Jansen et al. (72%) in their study of admitted children with respiratory tract infections.[5,23] In our study children with a temperature ≥ 38.0 °C and cough had a prevalence of 76.8%.

Implications for future research and clinical practice

Antibiotic prescription was high, and not related to the presence of viral infection. It is well recognized that in the presence of a viral infection causing symptoms, antibiotics should not be prescribed. In addition, also many bacterial infections are self-limiting. We found an association between symptoms and viral infection, which may point towards a causal relation. Therefore, we presume that antibiotic prescription in febrile children by Dutch GPs is not evidence based.

Whether viral testing will be helpful in deciding whether or not to prescribe antibiotics, however, cannot be concluded from our results. Even in the presence of a virus bacterial infection may be present. In the recently updated NICE guideline[4] it is recommended to assess bacterial urinary tract infections in febrile children with proven RSV or Influenza. Furthermore, the absence of a virus does not imply that a bacterial infection is present. Nevertheless, there is evidence that in children with RSV or Influenza bacterial infections are less prevalent than in children without viral infection.[24-26] Wishaupt et al. showed that testing for the presence of a virus

infection reduced the initiation of antibiotic treatment in hospitalised children.[27] Future research needs to evaluate whether testing for respiratory virus infections might effectively reduce antibiotic prescriptions by GPs in febrile non-hospitalised children.

Although one might expect an inverse association between CRP and viral infections, we did not find an association between CRP and the presence of a virus. The diagnostic value of CRP for serious (bacterial) infections in febrile children needs further evaluation.

Conclusions

Children with cough, a temperature ≥38.0°C or a clinical diagnosis of respiratory tract infection are likely to have a virus infection. More than half of all children with fever who were prescribed antibiotics, had at least one virus, suggesting an overtreatment of these children.

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CHAPTER ***EIGHT***

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

submitted

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

Methods: Prospective cohort study including consecutive children aged 3 months-6 years presenting with fever at an OHS. 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.

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 out-of-hours service (OHS) 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 an OHS in the southern part of Rotterdam. This OHS 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 OHS concerning their febrile child were eligible for inclusion. Fever (as reported by the parents) had to be a reason to contact the OHS. 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 OHS 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 OHS, 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 OHS or by the pediatrician after direct referral), or 'antibiotic prescription before contact with the OHS' 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. 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.

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) median (range)	**25 (17)** 20 (3-70)	**30 (18)** 28 (3-66)
Age (in months),* mean (sd)	2.3 (1.4-3.9)	
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 = 0.006)*

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.

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)

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.

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 > 80 mg/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, and 109 children at presentation). 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.[16] 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 GP OHS, 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 OHS (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 > 80 mg/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 ≤ 20 mg/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 ***NINE***

General discussion

Marijke Kool

General discussion

Childhood fever is a common symptom in general practice. Although childhood fever is generally self-limiting, the possibility of rare serious infections with serious consequences poses a diagnostic dilemma. The aims of this thesis were to study: i) parent-reported alarming symptoms, ii) characteristics of childhood fever, iii) healthcare use, and iv) diagnostic strategies in young febrile children presenting at a general practitioner's (GP) out-of-hours service (OHS). This chapter summarises the main findings and addresses some methodological challenges. Finally, implications of the results for daily clinical practice are discussed and some recommendations are made for future research.

Main findings of this thesis

Triage in young febrile children is based on alarming signs and symptoms. However, the validity of these alarming symptoms, as reported by the parents, has not previously been investigated. In Chapter 2 we showed that, when parents are asked a second time about the presence of an alarming symptom at a specific moment, they often do not give the same answer. Also, when parents report alarming symptoms, these symptoms are often not found on physical examination. In addition, alarming signs found at physical examination are often not reported by the parents (Chapter 2). These findings indicate that the communication about alarming symptoms between the parents and the OHS is often hampered by different interpretations of the presence of alarming signs and symptoms. Nevertheless, telephonic triage at a Dutch OHS based on alarming signs and symptoms was able to differentiate between high and low risk of serious infection (SI) (3.7%, 95% CI: 1.6-8.4% in children with a telephonic self-care advice, 12.1%, 95% CI:9.2-15.8 in face-to-face contacts). In addition, children with a telephonic consultation did not re-consult their GP more frequently (20.0%, 95% CI: 14.1-27.5 vs 18.3%, 95% CI: 14.7-22.6, respectively), and they were less often referred during follow-up (1.5%, 95% CI: 0.4-5.3 vs 4.0%, 95% CI: 2.4-6.7, respectively) than children with a face-to-face contact (based on Figure 2, Chapter 3). Thus, telephonic triage did not increase the amount of healthcare contacts during follow-up.

In children with a telephonic consultation 19.3% (95% CI: 13.5-26.7) were prescribed antibiotics at some point during their fever episode, whereas in children with a face-to-face contact 48.0% (95% CI: 42.9-53.1) were prescribed antibiotics at some point during the fever episode; this is in contrast with the risk of SI that we found in these groups (3.7% , 95% CI: 1.6-8.4 and 12.1%, 95% CI: 9.2-15.8, respectively). In all children, up to 40.3% (95% CI: 36.1-44.7) were prescribed antibiotics (Chapter 3). We found that concerned parents (OR: 2.0, 95% CI: 1.1-3.6), ill appearance (OR:3.3, 95% CI: 1.3-8.2), earache resulting in altered behavioural or sleeping patterns (OR:2.6, 95% CI: 1.1-6.3), signs of throat infection (OR:2.4, 95% CI: 1.4-4.2), and decreased urine production (OR:2.0, 95% CI: 1.2-3.4) were positively associated with antibiotic prescription. Only a small proportion of the antibiotic prescriptions could be explained by the child's signs and symptoms (Chapter 4).

In addition, we found that parents frequently reported alarming symptoms in febrile

children with an uncomplicated illness (ie. no SI and no referral at presentation); up to 79.3% of the parents reported alarming symptoms at day 2 of the fever episode (Chapter 5). Despite this high amount of parent-reported alarming symptoms in children with uncomplicated illness at initial presentation, only 3.2% developed a complicated illness during the one week follow-up period. Therefore, because of the frequent reporting of alarming symptoms by parents in children with uncomplicated illness, these alarming symptoms need to be reconsidered before they can be used to instruct parents to re-consult in the presence of alarming symptoms (i.e. so-called 'safety-netting').

In children with uncomplicated illness at presentation, the estimated median duration of the total fever episode was 4.0 days (95% CI: 3.6-4.4) (Chapter 5). In addition to the normal duration of fever in children with uncomplicated illness at presentation, we also studied prolonged duration of fever. Prolonged duration of fever was defined as a duration of more than 3 days after initial presentation. We found that throat ache (OR: 2.8; 95% CI: 1.3-6.0) and palpable cervical lymph nodes (OR: 1.9; 95% CI: 1.0-3.5) were predictive for a prolonged duration of fever. However, because the discriminative value of the model was low (median AUC was only 0.64, SD 0.03), for most individual patients the duration of fever cannot be predicted (Chapter 6).
To reduce diagnostic uncertainty different diagnostic strategies are proposed. In our study, we examined rapid viral testing and C-reactive protein (CRP). In 257 children a nasopharyngeal swab was obtained to analyse the presence of viruses. In total, 52.9% of these children had at least one virus. The most frequently detected viruses were adenovirus (10.9%), respiratory syncytial virus type A (10.5%) and para-influenza virus type 1 (8.6%). Cough (OR 2.6; 95% CI: 1.4-4.6) and temperature ≥ 38.0° C (OR 2.1: 95% CI: 1.3-3.5) were independent predictors of the presence of a virus, but the predictive value of clinical symptoms for a virus infection detected by testing was low (AUC 0.64; 95% CI: 0.58-0.71). More than half of all children in whom a virus was detected received an antibiotic prescription (Chapter 7).
In 440 children the level of CRP was available. In more than half of all children a CRP level ≤ 20 mg/L was found. To rule in SI, CRP > 80 mg/L changed the probability to have a SI from 12.5% (95% CI: 9.7-15.9, pre-test probability) to 21.2% (95% CI:13.1-32.5, post-test probability). In children without SI at presentation, CRP could not predict SI at follow-up (CRP > 80mg/L: LR+:1.9, 95% CI: 0.8-4.1, CRP ≤ 20 mg/L: LR-: 1.0, 95% CI: 0.7-1.6). CRP did not change the probability of SI nor did it preclude SI in febrile children given the presence (or absence) of alarming signs at physical examination. We found no evidence for a predictive value of CRP for SI that could change clinical practice in febrile children presenting at the OHS (Chapter 8).

Methodological considerations

Strengths and limitations of the KiKo study

A strength of the KiKo study is that, as far as we know, it is the first study that prospectively followed young febrile children who presented to an OHS and that

followed *all* children, irrespective of the result of triage. Children who had face-to-face contact with a GP at the OHS, as well as children who were not seen by a GP at the OHS but who received self-care advice by telephone, were visited at home and followed for one week after presentation. We performed the additional home visit as soon as possible after initial contact, but always within 24 hours. The median time between initial presentation and the home visit was 14 hours. However, by performing the physical examination with a median delay of 14 hours, the findings at physical examination might have changed during this delay, particularly in children with a fulminant course of disease. In these latter children, more alarming signs could be present, resulting in an overestimation of the presence of alarming signs. However, none of the children were referred during this delay, indicating that this bias did not occur. In children with a mild course of disease, alarming symptoms could have recovered during this delay resulting in an underestimation of the presence of alarming signs. The frequencies of single alarming symptoms at the home visit (range 19.7-48.9%) were lower than those of single alarming symptoms reported by the parents at telephonic triage (range 38.0-71.3%). However, the frequencies of alarming signs found at physical examinations (range 6.7-15.8%) were very low compared to the alarming symptoms reported by the parents at that moment (Table 3, Chapter 2). If physical examination was performed directly after presentation, the frequency of alarming signs at physical examination was probably only slightly higher.

Our study was performed at one OHS in the southern part of Rotterdam, a multi-ethnic city; this particular OHS was comparable to other OHSs in the Rotterdam area. The children included in our study have comparable characteristics as found in a larger cohort of 8,676 children aged ≤ 16 years with face-to-face contact that took place at all five OHSs in the Rotterdam area.[1] However, as in all studies performed in a single setting, the generalisability of the results to, for example, more rural areas should be done with care. However, conducting our study at only one OHS probably had very little effect on our results on healthcare use and antibiotic prescription. In the Netherlands, the GPs who work in shifts at an OHS are familiar with the multiple guidelines developed by the Dutch College of General Practitioners on specific diseases, such as diseases that can cause fever in children (i.e. otitis media acuta, pharyngitis).[2-4] Moreover, the adherence rate of GPs to these guidelines is high.[5]

Interpretation of main findings

Parent-reported alarming symptoms

Although the definitions of alarming signs and symptoms were based on national and international guidelines[2,6,] parent-reported alarming symptoms had a low reproducibility and a low association with findings at physical examination (Chapter 2). In our study, parents reported at least one alarming symptom in children with uncomplicated illness in almost 40% of the children at day 9 of this fever episode; the median duration of fever in these children was 4.0 days. At day 9, less than 20% of the children still had fever (Figure 2, Chapter 5). Thus, the frequency of reported

alarming symptoms is not in accordance with the frequency of children with fever on day 9. However, because the re-consultation rate during follow-up was 18.7% (Chapter 3) we can conclude that the alarming symptoms reported by the parents during follow-up did not concern them to such an extent that they re-consulted the GP.

In our study, alarming signs at physical examination were noted by trained research nurses; these nurses only noted the presence of each sign. Neither parents nor nurses were aware of the definition of alarming signs as used in the present analyses. Therefore, it is likely that the research nurses reported signs very close to what the parents had observed when they were asked about this during the telephonic triage. However, the parents, nurses and GPs differ in their interpretation of a sign as 'alarming'. This interpretation may well be dependent on education and/or expertise. The expertise required to judge a sign as 'alarming' can only be acquired when GPs (and medical trainees) frequently examine children with fever.

It is expected that triage based on relatively unreliable alarming symptoms will not result in different risks for SI according to triage decisions. However, we found that telephone triage did result in a risk of SI of only 3.7% (95% CI: 1.6-8.4) in self-care advice and a risk of 12.1% (95% CI: 9.2-15.8) in face-to-face contacts (these risks include SI at presentation and during follow-up). When the triage decision regarding referral is also taken into account, the Dutch triage system was able to find a high risk of SI (72.0%, 95% CI: 52.4-85.7) in directly referred children after face-to-face contact (Chapter 3). This is a better prediction of SI than was found in several prediction rules for SI in febrile children (most of which were studied in secondary care).[7] This suggests that, in the Dutch GP triage system, additional features for triage decisions were used. Based on the same data, Monteny et al. showed that parental concern increased the probability to be invited for face-to-face contact in children without alarming symptoms. However, parental concern hardly increased the probability of a consultation when alarming symptoms were present,[8] suggesting that the additional features that might be used in triage decisions were not solely due to parental concern. An additional feature might be that GPs use their expertise to judge whether a sign or symptom is alarming. According to national and international guidelines[2,6] alarming signs and symptoms are a reason for referral, although evidence for this advice is limited.[7,9,10] Earlier research found that, in case of at least one positive alarming sign, GPs adhered to a positive referral advice by the national guideline in only 19% of the consultations; most of the referred children in that same study had at least three positive alarming symptoms.[11] In our study, although parents reported alarming symptoms in children with uncomplicated illness in up to 80% of the children (Chapter 5), GPs only referred 8.3% of the children and, of these referred children, 72.0% had a SI (Chapter 3). This suggests that GPs have their own way of dealing with the high frequency of alarming signs and symptoms. For example, it is known that physicians look at the context when making their triage decisions.[12] They might judge a sign or symptom as alarming under certain conditions. For example, since

febrile children often present at an early stage in their febrile episode (median number of days of fever before initial presentation was 1-2 days) (Chapter 5), a SI may not yet be present but might develop during the subsequent days. GPs might include recovering or worsening of symptoms in their triage decision; however, research on the course of symptoms as predictor for serious or non-serious infections is scarce in general practice. In this thesis, we provide some evidence regarding the duration of fever and the frequency of alarming symptoms in febrile children with uncomplicated illness.

Healthcare use and antibiotic prescription

As mentioned above, triage as performed by GPs at an OHS can differentiate between high and low risk of SI. However, does this triage system perform as well when taking into account antibiotic prescriptions? After telephone triage 73.5% (95% CI: 69.5-77.2) of the children were invited for a face-to-face contact; this is a relatively high percentage when considering that, in these children, the risk of SI is 12.1% (95% CI: 9.2-15.8) (Chapter 3). In all 506 included children, 40.3% (95% CI: 36.1-44.7) had received an antibiotic prescription at the end of the one week follow-up, whereas the risk of SI in these children was only 9.9% (95% CI:7.6-12.8 (Chapter 3). Thus, even though a SI was not diagnosed in almost 90% of all children, an antibiotic was prescribed in more than 40% of the children. In non-referred children seen at face-to-face contact, the percentage of antibiotic prescriptions increased to 48.0% (95% CI: 42.8-53.2); in these 346 children, only 7.8% (95% CI: 5.4-11.1; 27 children) had a SI (Figure 2, Chapter 3).

These results indicate that there is an overuse of antibiotic prescriptions in young febrile children, leaving room for improvement in this area. An explanation for the high amount of antibiotic prescriptions in contrast to the low prevalence of SI, could be that signs and symptoms related to antibiotic prescription are associated with specific diseases (i.e. tonsillitis, and acute otitis media) for which the guidelines of the College of Dutch General Practitioners provide recommendations for antibiotic prescription under certain conditions.[3,4] In these guidelines, the rationale for prescribing antibiotics is mainly based on possible reduction of the duration and severity of illness. In our study, we showed that signs for otitis media acuta (earache resulting in altered behavioural or sleeping patterns: OR:2.59, 95% CI: 1.06-6.30), and signs of throat infection (OR:2.37, 95% CI:1.35-4.15) are positively associated with antibiotic prescription (Chapter 4). In that KiKo study, acute tonsillitis and acute otitis media were not considered as SI. In addition, it has been shown that physicians often think that parents expect/want an antibiotic prescription, whereas many parents may not in fact want an antibiotic prescription.[13] Generally, parents expect a physical examination and adequate information, rather than an antibiotic prescription.[14] GPs need to be aware of the expectations of parents when deciding to prescribe antibiotics.

Characteristics of childhood fever

In children with uncomplicated illness the median duration of a fever episode

was 4 days and, of these children, 32% developed a complicated disease (median day of diagnosis was on day 5) (Chapter 5). In those children with uncomplicated illness at presentation who developed a complicated disease, the median duration of the fever episode was 3 days (range 1-7 days; data not previously shown). In the estimate of the duration of fever, 'fever before presentation' was included. The duration of fever before initial presentation has no well-established predictive value for the development of a serious bacterial infection.[15,16] However, in children, a longer duration of fever before initial presentation is related to return a visit to the emergency department.[17] We found that at an OHS children with fever often present at the beginning of their episode of fever (Chapter 5). In these latter children, it is important to inform parents about the (expected) duration of fever in febrile children and to specify which children are at risk for a prolonged duration of fever after initial presentation. Although we found that throat ache and palpable cervical lymph nodes were predictive for a prolonged duration of fever, the discriminative ability of the model was low (Chapter 6).

Diagnostic strategies

To improve risk prediction of SI in young febrile children and to reduce the use of antibiotic prescriptions, various diagnostic strategies are available: eg. rapid detection of viral illnesses and CRP point-of-care tests.

Using rapid detection of a viral illness we found that in ≥ 50% of the febrile children contacting an OHS a virus could be detected. The most frequently detected viruses were adenovirus, respiratory syncytial viruses type A, and para-influenza viruses type 1 (Chapter 7). In the Kiko study we found that the human bocavirus was present in 4 children; our group was one of the first to report a relation between this virus and a mild course of disease with respiratory/gastrointestinal symptoms and skin rash.[18] In our study, we found that of the 136 children with a virus, 54 (39.7%) were prescribed antibiotics by the GP (Chapter 7).

The NICE guideline on feverish illness in children states that febrile children with a proven respiratory syncytial virus, or a proven influenza, have a lower incidence of bacterial infection. Seen in this light, the antibiotic prescription rate in our study is relatively high. In addition, the NICE guideline states that a serious bacterial infection cannot be excluded in these children. Therefore, the NICE guideline recommends to assess children with a proven virus for features of bacterial infections, especially urinary tract infection.[6]

To our knowledge, the efficiency of using rapid viral testing to reduce antibiotic prescription in febrile children has not yet been examined. In addition, it is not known whether viral testing can detect a complicated course of a viral infection.

Another diagnostic strategy is the CRP point-of-care test. Van den Bruel et al showed that measuring CRP level can be of value for diagnosing SI in children at an emergency department.[10] Furthermore, in adults CRP has a proven value in reassuring both the physician and the patient, resulting in less antibiotic treatments.[19] We did not test whether CRP testing can be used to reassure GP and parents and, thereby, reduces antibiotic prescriptions or healthcare contacts in

young febrile children. However, we did find that the CRP level had no additive predictive value for SI in febrile children in general practice (Chapter 8), and no additive value in the prediction of prolonged duration of fever (Chapter 6). It is debatable whether a test should be used to reassure both the physician and the parents in order to reduce antibiotic prescription, especially while the test itself has no proven additive predictive value in diagnosing SI.

Recommendations for future research

So far, we have discussed several important findings of this thesis as well as some methodological considerations of the KiKo study. Based on the above, several recommendations can be made for future research in febrile children in primary care.

Research on alarming signs and symptoms of SI has mainly focused on the presence of these alarming signs and symptoms, whereas future research could examine whether these alarming symptoms tend to resolve or worsen, as this might be an indication for the development of a SI. In addition, it is worthwhile to establish at what point physicians consider a sign or symptom to be alarming, ie. what is the cut-off value of the course and seriousness of signs and symptoms for them to become alarming. Furthermore, exploring the decision-making process of GPs might reveal other features that differentiate between high and low risk of SI. This decision-making process might also reveal symptoms that predict an uncomplicated illness in febrile children in primary care. Since most children in primary care will have an uncomplicated febrile illness, the identification of children not at risk of a SI might help in allowing these children to return home safely.

In children with uncomplicated illness at presentation we provided some evidence regarding the characteristics of fever in these children (Chapter 5). However, to provide safety-netting advice, more knowledge is needed on the characteristics of fever in children with complicated illness in primary care (eg. the duration of fever). Since SI in primary care are rare we need to study a large cohort of children and, to recruit sufficient febrile children, national and international collaboration is needed.

We have shown that in almost 40% of the children in our study, antibiotics were prescribed. Strategies to lower antibiotic prescriptions are urgently needed. Although CRP level had no additive predictive value for diagnosing SI in febrile children, CRP combined with training in communication skills was able to reduce antibiotic prescriptions in adults with respiratory tract infections.[19] Future research should test whether training in communications skills will also reduce antibiotic prescriptions and healthcare contacts in febrile children.

Recommendations for management of febrile children in general practice

For the management of febrile children in general practice some general recommendations can be made.

GPs in the Netherlands can be satisfied with the triage system they use in young

febrile children at an OHS, since this system differentiates between high and low risk of serious infections in febrile children relatively well. However, research on the triage of febrile children is still developing and revisions of the triage system based on evidence is desirable.

Alarming symptoms are reported frequently in children with fever. However, interpretation of the signs/symptoms as being alarming is probably dependent on the education and experience of the parents and the GPs. It is important for GPs (and GP trainees) to gain and/or maintain sufficient expertise to judge a sign as alarming in children with fever, by regularly examining these children and informing the parents properly.

As mentioned, there is an overuse of antibiotic prescriptions in young febrile children. Overuse of antibiotics is an important factor in the development of bacterial resistance and, therefore, prevention of unnecessary antibiotic prescriptions is needed.[20,21] GPs should discuss whether the recommendation in guidelines to prescribe antibiotics for possible reduction of the severity/duration of symptoms in non-serious infections is in fact desirable.[3,4] GPs are accustomed to work in a patient-centred way and should discuss with parents whether prescribing antibiotics for possible reduction of symptoms is desirable for their child. However, GPs should also reflect on the legitimacy of prescribing antibiotics for this reason, since prescribing antibiotics to reduce symptoms might lead to the development of bacterial resistance.

Although CRP point-of-care tests are commonly available in general practices, GPs should not use this test in febrile children in primary care, as CRP appears to have no additive value in diagnosing serious infections in these children.

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Conflict of interests

None of the authors reported a confict of interest.

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CHAPTER ***TEN***

English summary

English Summary

Fever occurs frequently in young children and is a common reason for parents to contact a general practitioner (GP), mainly during after-practice hours. Although fever leads to many healthcare consultations, fever itself is not an illness but mostly a symptom of self-limiting infections. However, some children are at risk of a serious infection and need medical care. In Europe, GP care during after-hours is nowadays increasingly provided by GP out-of-hours services (OHS). At these OHS triage is performed (often by telephone) to select the child that needs medical care. Triage is based on parent-reported alarming symptoms. Lots of research evaluating alarming symptoms that might be able to identify seriously ill children has been performed at emergency departments and hospital settings, however research on this topic is scarce in general practice.

To support these GPs in selecting young febrile children at risk of serious infections and to improve triage and the management of young febrile children more knowledge is needed on parent-reported alarming symptoms, characteristics of childhood fever, healthcare use, and diagnostic strategies in these children.

We performed a prospective cohort study in young febrile children presenting at a GP OHS. In our study children aged three months to six years were eligible when they presented with fever, as stated by the parents, during midweek evenings or nights during the period of December 2004 till January 2006. Exclusion criteria were no informed consent, no communication in Dutch possible with the parents, and previous enrolment in the study in the last two weeks. In total, 506 children were included in the study. After triage, 135 children received advice by telephone, and 371 children were seen in a face-to-face contact with the GP at the OHS. There were no home visits by the GP.

After triage, the triage nurse noted symptoms in the triage questionnaire. All included children, independently of their triage result, were visited at home by a trained research nurse as soon as possible, but within 24 hours after inclusion. The trained research nurse noted parent-reported symptoms at the time of triage and parent-reported symptoms at time of the home visit. In addition, the research nurse performed a physical examination (including rectal temperature). After physical examination, the research nurse obtained a nasopharyngeal swab and obtained capillary blood for the measurement of C-reactive protein. Parents were instructed to note symptoms, healthcare use and medication in a diary for one week starting at the home visit.

The aims of this thesis were to study parent-reported alarming symptoms, characteristics of childhood fever, healthcare use and diagnostic strategies in young febrile children presenting at a GP OHS.

Chapter 2 explores the reproducibility of parent-reported alarming symptoms measured at different time points and investigates the association between parent-reported alarming symptoms and findings during physical examination. Reproducibility varied from low to moderate (kappa 0.30-0.50). The association

between parent-reported alarming symptoms in febrile children and findings at physical examinations was poor. Up to 68% of alarming symptoms found at physical examination were not reported by the parents. And up to 34% of the parent-reported alarming symptoms were not found at physical examination. Therefore, we concluded that the reliability of parent-reported alarming symptoms was low. Future research should focus on whether triage can be improved by educating triage nurses in exploring and interpreting alarming symptoms, educating parents about alarming symptoms or by using GPs to perform triage.

Chapter 3 describes risk of serious infections and healthcare use, including antibiotic prescriptions in young febrile children according to triage decisions. Of all 506 included children, 73.3% were invited for face-to-face contact, 40.3% received an antibiotic prescription, and 5.1% were directly referred. The risk of a serious infection (at presentation or during follow-up) in all children was 9.9%. In children with self-care advice this risk was 3.7%, in face-to-face contacts the risk of a serious infection was 12.7%; after direct referral this risk increased to 72.0%.
After face-to-face contact 18.3% had a re-consultation of the GP, 10.5% were referred, 8.1% were admitted to hospital, and 48.0% were prescribed antibiotics. After self-care advice 20.0% had a re-consultation of the GP, 2.2% were referred, 1.5% were admitted to hospital, and 19.3% were prescribed antibiotics. We found that triage differentiated between children at high and low risk of serious infections, but that face-to-face contacts with the GP at the OHS resulted in substantial costs in terms of antibiotic prescriptions.

Chapter 4 describes antibiotic prescription rate in young febrile children and examines which variables predict antibiotic prescription. In 443 children who did not receive antibiotics before presentation and who were not directly admitted to the hospital at presentation, 322 children had a face-to-face contact at the OHS. Of these, 117 (36.3%) were prescribed antibiotics by the GP at the OHS, 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; 95%CI: 1.30–8.20), earache resulting in altered behavioural or sleeping patterns (OR: 2.59; 95%CI: 1.06–6.30), signs of throat infection (OR: 2.37; (%%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 rectal temperature ≥ 38.0°C (OR: 0.52; 95%CI: 0.37– 0.71). We concluded that antibiotics were prescribed in 1 out of 4 febrile children whose parents contacted the OHS. Items associated with antibiotic prescription provide insight into the GPs' decision-making process when assessing children with fever. These items can be used as targets for strategies to diminish antibiotic prescription in future research.

Chapter 5 presents the duration of fever, frequencies of alarming symptoms and prevalence of serious infections in children with uncomplicated illness at presentation (n=463). During follow-up, 3.2% of the children with uncomplicated

illness at presentation developed a complicated illness (i.e. serious infection at presentation of admission to the hospital directly after initial presentation). The total fever episode included days of fever before presentation and days of fever as noted in the diaries during the one week of follow-up. The estimated median duration of the total fever episode was 4.0 days (95% confidence interval, 3.6–4.4). The presence of alarming symptoms dropped from 79.3% at day 2 of the total fever episode to 36.7% at day 9 of the total fever episode. We concluded that in children with uncomplicated illnesses, the daily occurrence of alarming symptoms reported by parents was high. The median duration of fever was 4 days. Our findings suggest that the predictive value of the presence of an alarming symptom for a complicated course of infection will be low. 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 in future research.

Chapter 6 explores the predictive value of signs and symptoms on prolonged duration of fever. Prolonged duration of fever after initial contact was defined as duration of fever of more than three days. In total 480 children were included (children who were referred directly after initial presentation were excluded). Multivariate analysis showed that throat ache (OR:2.8; 95%CI: 1.3-6.0), and palpable cervical lymph nodes (OR:1.9;95%CI: 1.0-3.5) were predictive for a prolonged duration of fever. C-Reactive protein level (CRP) had no additive predictive value for prolonged duration of fever (OR:1.00; 95%CI: 0.99-1.01).
The conclusion of this chapter was that some signs and symptoms were related to a prolonged duration of fever. CRP had no additional value in the prediction of duration of fever. Overall, the discriminative value of the model was low (median AUC 0.64), therefore the duration of fever cannot be predicted for individual patients. Future research should determine the additive role of CRP in managing febrile children in primary care.

Chapter 7 describes the viruses found in young febrile children and the antibiotic prescription rate in children with or without detected virus. In 257 children a nasopharyngeal swap was obtained. In 53% of these children at least one virus was detected. The most frequently detected viruses were adenovirus (10.9%), respiratory syncytial virus type A (10.5%) and para-influenzavirus type 1 (8.6%). Cough (OR 2.6; 95% CI 1.4-4.6) and temperature ≥38.0°C (OR 2.1; 95% CI 1.3-3.5) were independent predictors of the presence of a virus, however the discriminative ability of the model was low (AUC 0.64; 95% CI 0.58-0.71). Antibiotic prescription rate was high (37.3%). In 57.4% of the children with an antibiotic prescription a virus was detected. We concluded that in more than 50% of all febrile children a virus was detected. Antibiotics were as often prescribed in children with as in children without viral infections. Future research could evaluate whether testing for virus infections effectively reduces the antibiotic prescription rates in febrile non-hospitalised children.

Chapter 8 addresses the diagnostic value of C-reactive protein (CRP) in young febrile children. A CRP≤20mg/L did not increase the probability of *not* having a serious infection (87.5%). A CRP>80mg/L increased the probability of having a serious infection from 12.5% (pre-test probability) to 21.2% (post-test probability). After adjustments for presence of an alarming symptom, we found that CRP had no additive value in predicting serious infection in febrile children at an OHS.

Chapter 9 discusses the main findings of the previous chapters, reflects on the strengths and limitations of the studies and examines the implications for daily practice and future research.

CHAPTER ***ELEVEN***

Samenvatting

Samenvatting

Koorts is een veelvoorkomend symptoom bij jonge kinderen. Koorts is voor veel ouders een gebruikelijke reden om de huisarts te consulteren met name tijdens de avond- en nachturen. Hoewel koorts tot veel zorgconsumptie leidt, is koorts op zichzelf geen ziekte maar een symptoom van veelal onschuldige infecties. Sommige kinderen hebben echter een verhoogd risico op een ernstige infectie en hebben medische zorg nodig. De huisartsenzorg in Europa wordt buiten kantooruren tegenwoordig steeds vaker verzorgd door huisartsenposten (HAPs). Op deze HAPs wordt met triage (vaak telefonisch) het kind dat medische zorg nodig heeft geselecteerd. Deze triage is gebaseerd op door ouders gerapporteerde alarmsymptomen die mogelijk geassocieerd zijn met een ernstige infecties. Het merendeel van de studies, die de voorspellende waarde voor een ernstige infectie van deze alarmsymptomen onderzochten, zijn uitgevoerd op spoedeisende hulpposten of in het ziekenhuis. Onderzoek naar kinderen met koorts in de eerstelijn is schaars.
Om de huisartsen te ondersteunen bij het selecteren van het kind met een verhoogd risico op een ernstige infectie, en om de triage van kinderen met koorts en het beleid bij kinderen met koorts te verbeteren, is meer kennis nodig over de door ouders gerapporteerde symptomen, over de karakteristieken van koorts bij kinderen, over de zorgconsumptie, en over diagnostische strategieën bij kinderen met koorts.

Wij hebben in een prospectieve cohortstudie onderzoek gedaan naar jonge kinderen met koorts die zich op een HAP presenteerden. In onze studie konden kinderen geïncludeerd worden wanneer zij tussen de 3 maanden en 6 jaar oud waren én zij zich met koorts (door ouders gerapporteerd) presenteerden op de HAP tijdens doordeweekse avonden of nachten in de periode van december 2004 tot en met januari 2006. Kinderen werden geëxcludeerd wanneer de ouders geen informed consent gaven, er geen communicatie in Nederlands mogelijk was met de ouders, of wanneer het kind reeds in de twee voorafgaande weken was geïncludeerd. In totaal werden er 506 kinderen geïncludeerd in de studie. Na de telefonische triage kregen 135 kinderen een telefonisch advies en 371 kinderen werden uitgenodigd voor een consult op de HAP. Er zijn geen huisvisites afgelegd door de behandelend arts.
Na de telefonische triage noteerden de triageverpleegkundigen de symptomen in een triagevragenlijst. Alle geïncludeerde kinderen werden, onafhankelijk van het resultaat van de triage, zo snel mogelijk maar binnen 24 uur na inclusie thuis bezocht door een daartoe opgeleidde researchverpleegkundige. Deze researchverpleegkundige noteerde de door ouders gerapporteerde symptomen ten tijde van de triage en ten tijde van het huisbezoek. Vervolgens verrichten de researchverpleegkundige een lichamelijk onderzoek (inclusief een rectale temperatuurmeting).
Na het lichamelijk onderzoek nam de researchverpleegkundige een neuskeelwat

af en wat capillair bloed voor de meting van de waarde van het C-reactieve proteïne (CRP).
Ouders werden vervolgens geïnstrueerd om de symptomen, de zorgconsumptie en het medicatiegebruik te noteren in een dagboek gedurende een week beginnend vanaf de dag van het huisbezoek.

De doelstellingen van dit proefschrift zijn om meer inzicht te krijgen in de door ouders gerapporteerde symptomen, de karakteristieken van koorts bij de kinderen, de zorgconsumptie en de diagnostische strategieën bij jonge kinderen met koorts die zich presenteren aan de HAP.

Hoofdstuk 2 verkent de reproduceerbaarheid van de door ouders gerapporteerde alarmsymptomen gemeten op verschillende momenten, en onderzoekt de associatie tussen de door ouders gerapporteerde alarmsymptomen en de bevindingen bij het lichamelijk onderzoek.
De reproduceerbaarheid varieerde van laag tot gemiddeld (kappa 0.30-0.50). De associatie tussen de door ouders gerapporteerde alarmsymptomen en de bevindingen bij het lichamelijk onderzoek was laag. Tot wel 68% van de alarmsymptomen die gevonden waren bij lichamelijk onderzoek werden niet door ouders gerapporteerd. En tot wel 34% van de door ouders gerapporteerde alarmsymptomen werden niet bij lichamelijk onderzoek gevonden. Daarom concludeerden wij dat de betrouwbaarheid van door ouders gerapporteerde alarmsymptomen laag was. De focus van toekomstig onderzoek zal erop gericht moeten zijn of triage verbeterd kan worden door ofwel de triageverpleegkundigen verder op te leiden in het uitvragen van alarmsymptomen en de interpretatie van deze alarmsymptomen ofwel door huisartsen de triage te laten verrichten.

Hoofdstuk 3 beschrijft het risico op ernstige infecties en het zorggebruik, inclusief antibioticumvoorschriften, bij jonge kinderen met koorts. Van alle 506 geïncludeerde kinderen werd 73,3% uitgenodigd voor een consult op de HAP, kreeg 40,3% een antibioticumvoorschrift, en werd 5,1% direct verwezen. Het risico op een ernstige infectie (bij presentatie en gedurende de follow-up) was 9.9% in alle kinderen. In de groep kinderen met een telefonisch advies was dit risico 3.7%. Bij kinderen met een consult op de HAP was het risico op een ernstige infectie 12,7%. Bij directe verwijzing steeg dit risico naar 72.0%.
In de groep kinderen die na triage uitgenodigd werd voor een consult op de HAP, consulteerde 18.3% van de kinderen de eigen huisarts opnieuw tijdens follow-up, werd 10.5% verwezen, werd 8.1% opgenomen in het ziekenhuis, en ontving 48.0% een antibioticumvoorschrift.
In de groep kinderen die na triage een telefonisch advies kregen, had 20,0% een herconsultatie van de eigen huisarts tijdens de follow-up, werd 2,2% verwezen, werd 1,5% opgenomen in het ziekenhuis, en ontving 19.3% een antibioticumvoorschrift.
We concludeerden dat triage onderscheid maakt tussen kinderen met een hoog

en een laag risico op een ernstige infectie, maar dat kosten van triage in termen van antibioticumvoorschriften na consultatie op de HAP aanzienlijk waren.

Hoofdstuk 4 beschrijft het percentage antibioticumvoorschriften bij jonge kinderen met koorts en onderzoekt welke variabelen een antibioticumvoorschrift voorspellen. Van de 443 kinderen die geen antibioticumvoorschrift kregen én die niet direct in het ziekenhuis werden opgenomen bij presentatie, hadden 322 kinderen een consult op de HAP. De huisarts op de HAP schreef aan 117 van deze kinderen (36,3%) een antibioticum voor. Dat is gelijk aan 26,5% van de totale studiepopulatie.
Bezorgde ouders (OR: 2,02; 95% Betrouwbaarheidsinterval (BI): 1,06-3,58), zieke indruk (OR: 3,26; 95%BI: 1,30–8,20), oorpijn die leidt tot veranderd gedrag of veranderd slaappatroon (OR: 2,59; 95%BI: 1,06–6,30), tekenen van een keelontsteking (OR: 2,37; (%%BI: 1,35–4,15), en verminderde urineproductie (OR: 2,00; 95%BI: 1,17–3,41) waren positief geassocieerd met een antibioticumvoorschrift. Een negatieve associatie werd gevonden voor een leeftijd tussen de 3 en 6 maanden oud (OR: 0,17; 95%BI: 0,03-0,74) en een rectale temperatuur van ≥ 38,0°C (OR: 0,52; 95%BI: 0,37– 0,71).
We concludeerden dat 1 op de 4 kinderen met koorts, van wie de ouders contact opnamen met de HAP, een antibioticum voorschrift kreeg. De variabelen die geassocieerd zijn met een antibioticumvoorschrift geven inzicht in het beslisproces van de huisarts die een kind met koorts onderzoekt. In toekomstig onderzoek kunnen deze items gebruikt worden in strategieën om antibioticumvoorschriften te reduceren.

Hoofdstuk 5 presenteren we de duur van de koorts, de frequentie van alarmsymptomen en de prevalentie van ernstige infectie in kinderen met een ongecompliceerde ziekte bij presentatie (n=463). Tijdens follow-up ontwikkelden 3,2% van deze kinderen een gecompliceerde ziekte (dat wil zeggen een ernstige infectie dan wel een ziekenhuisopname). Bij de berekening van de totale koortsperiode werden zowel de dagen koorts voorafgaande aan het contact met de HAP als de koortsdagen zoals genoteerd in het dagboek tijdens de week follow-up meegenomen. De geschatte mediane duur van de totale koortsepisode was 4 dagen (95%BI: 3,6-4,4). Op dag 2 van de totale koortsepisode was de frequentie van alarmsymptomen 79,3% , dit daalde naar 36,7% op dag 9 van de totale koortsepisode.
We concludeerden dat bij kinderen met koorts met een ongecompliceerd ziektebeeld ouders dagelijks veel alarmsymptomen rapporteerden. De mediane duur van de koorts was 4 dagen. Onze bevindingen suggereren dat de aanwezigheid van alarmsymptomen een lage voorspellende waarde zal hebben voor een ernstige beloop van de ziekte. Vooraleer alarmsymptomen te gebruiken in safety-net adviezen tijdens de koortsepisode bij kinderen met een ongecompliceerd ziektebeeld, moeten deze door ouders gerapporteerde alarmsymptomen heroverwogen en gevalideerd worden.

Hoofdstuk 6 verkent de voorspellende waarde van symptomen voor een verlengde duur van de koorts. Een verlengde duur van de koorts na initieel contact was gedefinieerd als een duur van de koorts van meer dan drie dagen. In totaal werden er 480 kinderen geïncludeerd (kinderen die direct verwezen waren bij initiële presentatie werden geëxcludeerd). Een multivariate analyse toonde dat keelpijn (OR:2,8; 95%BI: 1,3-6,0), en palpabele cervicale lymfeklieren (OR:1,9; 95%BI: 1,0-3,5) voorspellend waren voor een verlengde duur van de koorts. CRP had geen toegevoegde voorspellende waarde voor verlengde duur van de koorts (OR:1,00; 95%BI: 0,99-1,01).
De conclusie van dit hoofdstuk is dat enkele symptomen gerelateerd waren aan een verlengde duur van de koorts. CRP had geen toegevoegde voorspellende waarde voor verlengde duur van de koorts. Over het geheel bleek het onderscheidend vermogen van het model laag (mediane AUC 0,64), waardoor deze niet gebruikt kan worden voor het voorspellen van de duur van de koorts van de individuele patiënt. Toekomstig onderzoek zou de toegevoegde waarde van CRP bij het beleid bij kinderen met koorts moeten onderzoeken.

Hoofdstuk 7 beschrijft de gevonden virussen in jonge kinderen met koorts en het percentage antibioticumvoorschriften bij kinderen met en zonder een gedetecteerde virusinfectie. Bij 257 kinderen is er een neuskeelwat afgenomen. Bij 53% van deze kinderen werd tenminste 1 virus gedetecteerd. De meest voorkomende virussen waren het adenovirus (10,9%), het respiratoir-syncytieel virus type A (10,5%) en het para-influenza virus type 1 (8,6%).
Hoesten (OR 2,6; 95% BI 1,4-4,6) en een rectale temperatuur van ≥38.0°C (OR 2,1; 95% BI 1,3-3,5) waren onafhankelijke voorspellers van de aanwezigheid van een virus, hoewel het onderscheidend vermogen van het model laag was (AUC 0,64; 95%BI 0,58-0,71).
Het percentage antibioticumvoorschriften was hoog (37,3%). Bij 57,4% van de kinderen met een antibioticumvoorschrift werd een virus gevonden.
We concludeerden dat bij meer dan 50% van de kinderen met koorts een virus werd gevonden. Antibiotica werden regelmatig voorgeschreven bij kinderen met een virusinfectie. Toekomstig onderzoek zal moeten evalueren of het testen van virusinfecties bij kan dragen aan het effectief reduceren van antibioticumvoorschriften bij kinderen met koorts die niet opgenomen zijn in het ziekenhuis.

Hoofdstuk 8 gaat in op de diagnostische waarde van het CRP bij jonge kinderen met koorts. Een CRP van ≤20mg/L gaf geen verandering van de kans op het niet hebben van een ernstige infectie (87,5%). Een CRP van > 80 mg/L verhoogde de kans op het hebben van een ernstige infectie van 12,5% (voorafkans) naar 21,2% (achterafkans). Na een correctie vanwege de aanwezigheid van alarmsymptomen, bleek het CRP geen toegevoegde waarde te hebben in het voorspellen van de kans op een ernstige infectie bij kinderen met koorts op een HAP.

Hoofdstuk 9 bediscussieert de belangrijkste bevindingen van de voorgaande hoofdstukken, gaat in op de sterke en zwakke punten van deze studie, en beschrijft de implicaties voor de dagelijkse praktijk en toekomstig onderzoek.

CHAPTER ***TWELVE***

Dankwoord

Marijke Kool

Dankwoord

Zonder dankwoord geen proefschrift

Mijn proefschrift is af. Of eigenlijk, bijna af. Het laatste puntje op de i ontbreekt nog. En daar draait het juist om in de wetenschap. Zorgen dat analyses en manuscripten tot in de puntjes verzorgd zijn. Dat is een van de vele lessen die ik de afgelopen jaren geleerd heb.

Het begon in de zomer van 2008. Er viel een brief op de mat. 'Gefeliciteerd, u bent aangenomen voor de huisartsenopleiding'. Vervolgens een brief met vacatures voor de functie van aiotho (arts in opleiding tot huisarts en onderzoeker). Een unieke mogelijkheid om de opleiding tot huisarts te combineren met promotie-onderzoek. Promoveren was nooit zo mijn ding. Maar de vacature over kinderen met koorts veranderde dat. Dit onderzoek bood mij de gelegenheid om de opleiding te combineren met mijn passie voor kinderen binnen de huisartsgeneeskunde. Zwanger van onze tweeling Lies en Floor, besloot ik te solliciteren. En met mijn dikke buik verstopt onder een trui verscheen ik op het sollicitatiegesprek. Die zwangerschap bleek geen enkele belemmering voor de afdeling. 'Ach, vroeg of laat zijn nagenoeg alle vrouwelijke aiossen wel een keer zwanger, dat zijn we gewend.'
En zo begon ik aan de eerste voorbereidingen van mijn proefschrift. En nu is dat proefschrift af. Of, zoals ik al schreef, bijna af. Het laatste puntje op de i ontbreekt nog. Zonder hulp van de mensen om mij heen was dit proefschrift er niet gekomen. Dat laatste puntje op de i, is het dankwoord waarin ik al diegenen die mij, bewust of onbewust, hebben geholpen om dit proefschrift af te krijgen wil bedanken.

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Allereerst wil ik de ouders en kinderen die participeerden in het onderzoek bedanken. Hoewel ik zelf niet betrokken was bij het includeren en vervolgen van de kinderen, is mijn onderzoek uiteraard niet mogelijk als ouders en kinderen niet hadden meegedaan aan dit onderzoek. Mijn dank gaat ook uit naar de triagisten op de huisartsenpost Rotterdam Zuid. Ik waardeer jullie werk enorm. Destemeer nu ik in mijn derde jaar diensten heb gedaan op de post waar dit onderzoek is gedaan en ik zie hoe hectisch het er kan zijn.

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Bij het schrijven van de artikelen komt heel wat kijken. De juiste doelstellingen moeten geformuleerd worden. Geschikte statistische analyses moeten gekozen en aangepast worden. De manuscripten moeten gelezen, beoordeeld en herschreven worden totdat ze rijp zijn voor de lezer. Graag wil ik, naast eerder genoemde begeleiders, ook de andere co-auteurs van mijn artikelen bedanken: Professor Henriëtte Moll, Professor Gerard van Doornum, Miriam Monteny en Gijs Elshout. Ieder had zijn eigen inbreng vanuit het eigen perspectief: kinderarts, viroloog of huisarts. Bedankt voor jullie feedback.

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En nu is mijn proefschrift dan echt af. Hier staat het: het laatste puntje op de laatste i.

CHAPTER ***THIRTEEN***

Curriculum Vitae

Curriculum Vitae

Marijke Kool is geboren in 1981 in Dordrecht. Zij is de dochter van Hans Kool en Ria Kool-van Mourik. Zij groeide op samen met haar oudere broer Johan en jongere zusje Yvonne in Hendrik-Ido-Ambacht. Na het behalen van haar vwo-diploma aan het Marnix Gymnasium, begon zij in 2000 aan de Katholieke Universiteit Leuven in België aan de studie geneeskunde. In 2001 verruilde zij deze universiteit voor de Vrije Universiteit in Amsterdam waar zij haar studie geneeskunde voortzette. Tijdens haar studie was zij drie jaar bestuurslid van de Studentenraad en de Onderwijscommissie. In 2007 vertrok zij voor drie maanden naar Tanzania voor een tropencoschap. In januari 2008 rondde zij haar studie geneeskunde af met een oudste coschap kindergeneeskunde in het Ikazia in Rotterdam, waar zij vervolgens zeven maanden ervaring opdeed als arts-assistent kindergeneeskunde.
In september 2008 startte Marijke als AIOTHO (arts in opleiding huisarts en onderzoeker) op de afdeling huisartsgeneeskunde van het Erasmus MC in Rotterdam. Zij werkte samen met Gijs Elshout als promovendi op het project KiKo (Kinderen met Koorts) onder begeleiding van hoogleraar Marjolein Berger, hoogleraar Bart Koes, universitair hoofddocent Hans van der Wouden en co-promotor Arthur Bohnen. Haar eerste opleidingsjaar (2010-2011) voldeed zij in huisartsenpraktijk Nieuw-Beierland bij opleider Marco Heijkoop. In het tweede opleidingsjaar (2012-2013) volgde zij stages in de ambulante psychiatrie, dermatologie en het verpleeghuis. In 2012 voltooide zij de masteropleiding Clinical Epidemiology bij de NIHES. Het laatste jaar van de opleiding werkte zij in huisartsenpraktijk Het Doktershuis in Ridderkerk bij opleider Jan Huisman, waar zij in november 2014 de opleiding tot huisarts heeft afgerond. Sindsdien is zij werkzaam als waarnemend huisarts.
Marijke is getrouwd met Niels Bax. Zij hebben 3 kinderen, twee dochters Lies en Floor (beiden geboren op 28 november 2008) en zoon Thijs (geboren op 28 juni 2012).

PhD Portfolio Summary

Summary of PhD training and teaching activities

Name PhD student: **Marijke Kool** Erasmus MC Department: General Practice Research School: NIHES	PhD period: 01-09-2008 – 25-03-2015 Promotoren: prof.dr. M.Y. Berger, prof.dr. B.W. Koes Copromotor: dr. A.M.Bohnen

1. PhD training

	Year	Workload	
		Hours	**ECTS**
Research skills			
- NIHES: master of Clinical Epidemiology	2009-2012		70
- Biomedical English writing and communication	2011	40	
Professional Education			
- Vocational training for general practitioner, Department of General Practice, Erasmus MC, University Medical Center Rotterdam	2008-2014		
Presentations			
- NHG Science Conference (oral presentation)	2010	16	
- EGPRN Plovdiv Bulgaria (oral presentation)	2010	32	
- LOVAH Noordwijkerhout (oral presentation)	2012	16	
- NAPCRG Ottowa, Canada (two oral presentations)	2013	40	
International conferences and meetings			
- ERNIE meetings	2009/2011	16	
- ESPID The Hague	2011	16	
Seminars and workshops			
- AIOTHO-seminars	2008-2011	20	
- PhD-days	2009, 2013	8	
- NHG Science Conferences	2009, 2013	16	
- NHG Conferences	2009-2014	40	
- LOVAH Conferences	2009, 2012, 2013	24	
2. Teaching activities			
Supervising medical students	2009-2010, 2013	80	
Education in science to students of the Vocational Training for General Practitioners, Erasmus MC Rotterdam	2009	8	
Education medical students	2014	8	
Subtotal 2		***96***	**-**
Subtotal 1		***284***	***70***
Total		***380***	***70***

Childhood fever is a common symptom in general practice. Although childhood fever is often self-limiting, uncertainty about rare serious infections with possible serious consequences generates a diagnostic dilemma. Research in children with fever presenting at a general practice out-of-hours service is scarce. This thesis describes the reliability of parent-reported alarming symptoms, the characteristics of childhood fever, the healthcare use and diagnostic strategies in young febrile children presenting at a general practice out-of-hours service.