Alarming Signs of Serious Infections in Febrile Children:

Studies in Primary Care and Hospital Emergency Care

Yvette van Ierland

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COLOFON

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Studies binnen de spoedzorgketen

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General introduction, aims and outline

GENERAL INTRODUCTION

The febrile child

Children constitute a substantial part of the workload of physicians in primary care and hospital emergency care. In the Netherlands, about 70% of the 3.9 million inhabitants less than 20 years of age had one or more contacts with their general practitioner (GP) in 2011.[1] Primary out-of-hours care is annually visited by approximately 600,000 children younger than 14 years of age and hospital emergency departments (EDs) by nearly 400,000 children in this age group.[2,3]

Fever is one of the most common reasons for children to consult a physician. The incidence of fever as a reason for contacting primary care is approximately 430 per 1,000 patients/year under the age of 5 years.[4] The overall incidence rate of the diagnosis of fever (without apparent source) in primary care is 19.2 per 1,000 patients/year, with the highest rate for children less than one year (100 per 1,000 patients/year) and the lowest rate for children aged 10 to 17 years (2.7 per 1,000 patients/year).[5] At the ED, fever is also one of the main presenting problems and accounts for about 10% to 30% of all visits by children.[6-9]

Most acute febrile illnesses are caused by self-limiting viral infections, which do not require antibiotic treatment, diagnostic procedures, or hospitalization. However, a minority of febrile children develop a serious infection, such as meningitis, sepsis, pneumonia or urinary tract infection, for which timely diagnosis and targeted therapy are necessary to prevent harm. In primary care, the annual incidence of serious infections is about 1%, with a peak incidence rate among the youngest children (0 to 4 years: 21.1 per 1,000 patients/year).[10] At the hospital ED about 15% to 20% of febrile children are diagnosed with a serious infection.[11,12] Serious infections are an important cause of morbidity and mortality, especially in young children. Infections accounted for about 15% to 20% of all childhood deaths by natural cause in the Netherlands[13] and the United Kingdom.[14]

National and international health care systems

In the Netherlands, primary care is provided by GPs and specialist care is provided by physicians who work at general hospitals (secondary care) and university hospitals (tertiary care). Primary care is freely accessible and nearly all inhabitants are registered with a local GP, who is available during regular working hours. GPs have a formal 'gatekeeping-role', which means they refer patients to secondary or tertiary care in case specialist consultation, extensive diagnostic or therapeutic interventions, or hospitalization are necessary.

Primary out-of-hours care is provided by general practitioner cooperatives (GPCs), in which GPs located in a certain area work together and rotate shifts during the evenings, nights, and weekends. In case of an acute medical problem, patients should in principle first call the GPC. After telephone triage by a trained nurse, the patient receives a telephone advice, a consultation at the GPC or a home visit by the GP (<1% in children).

Hospital EDs are accessible 24/7 for ambulance services, patients referred by GPs or medical specialists, and patients who present on their own initiative (by-passing primary care), who currently constitute nearly half of the total ED population.[15]

In many other European countries (e.g. the United Kingdom, Italy, Norway, Denmark, Sweden), Australia and New Zealand, primary care is also mainly provided by GPs, who act as gatekeepers for referral to more specialized care.[16,17] In many of these countries, out-of-hours primary care has similarly shifted towards large-scale cooperatives. However, in Australia, less than half of all GPs provide out-of-hours care themselves, resulting in considerable numbers of patients who present to hospital EDs on their own initiative.[16]

On the contrary, in Canada and the United States, GPs have no formal gatekeeping role and registration with a GP is not required. Most primary care physicians do not provide out-of-hours care, which is therefore mainly hosted by walk-in clinics and hospital EDs[16-18], resulting in high numbers of self-referred patients, which may be one of the causes of ED overcrowding in these countries.[19,20]

Identification of serious infections in febrile children

The first step in patient assessment at both primary out-of-hours care and hospital EDs is triage. At the moment of presentation, triage systems categorize patients according to urgency on the basis of clinical signs and symptoms in order to distinguish patients who need immediate medical attention from those who can wait safely. At the GPC, the National Telephone Guide (NTG) developed by the Dutch college of general practitioners is available.[21] Recently, it has been demonstrated that appropriate triage decisions were made in over 90% of the patients who had contacted the GPC.[22] At many European EDs, the Manchester Triage System (MTS) is used[23], which has been shown to be valid for triage of both adult and paediatric patients.[7,24]

The second step in patient assessment is consultation by the physician, who has the availability of guidelines to support clinical management of febrile children. For example, the National guideline of the Dutch college of general practitioners[4] advices primary care physicians to refer children for further assessment in case one of the specified alarming signs is present. The international NICE guideline[6,25] proposes a traffic light classification of clinical features, which is designed to assess the risk of serious infection in children below the age of five years. The system gives specific advices on what to do at telephone triage, at consultation in primary care, or at the ED, when a low (green), intermediate (amber) or high (red) risk feature is present. The major drawback of both guidelines is, however, that management strategies proposed for primary care physicians are predominantly based on consensus and expert opinion, since primary care studies are lacking and evidence is primarily based on studies performed in high prevalence (i.e. ED) settings. Besides, validation of both guidelines in settings with a low and high prevalence of serious infections showed unsatisfactory results.[26,27]

In addition to guidelines, diagnostic algorithms and clinical prediction rules can be used to identify patients at risk of serious illness. Already in the 1980's, the Yale Observation Scale[28] and the Rochester Criteria[29] were successfully implemented to support physicians in identification and management of children at risk of serious infections. However, after the introduction of the conjugate vaccines against *Haemophilus influenza* type B, *Neisseria meningitides* type C, and *Streptococcus pneumonia*, the incidence rates of serious infections (i.e. mainly sepsis, meningitis and pneumonia) significantly dropped and clinical presentations changed.[30-32] Consequently, experience in recognizing serious infections declined, especially in young professionals with limited paediatric training, and urgent need for new diagnostic research arose in the post-vaccination era.

Recently, a systematic review summarized all published diagnostic accuracy studies and studies deriving a clinical prediction rule on the basis of clinical signs and symptoms only or in combination with laboratory tests.[11] Strikingly, most of the 30 studies included in this systematic review were undertaken at hospital EDs, and only one study was performed in primary care.[33] Authors concluded that all important clinical features ('alarming signs') identified had not enough value on their own to exclude (i.e. rule-out) serious infections in both low and high prevalence settings. Based on the single primary care study included, some signs were suggested to be useful at ruling-in disease in the low prevalence setting (i.e. parental concern that the illness was different from previous illnesses, the clinician's gut feeling something is wrong, changed child behaviour or temperature above 40ºC), however their diagnostic ability was limited in intermediate and high prevalence settings. Only the presence of meningeal irritation, petechial rash, decreased consciousness and seizures were consistently identified as potential 'red flags' for bacterial meningitis specifically in all settings. However, such features mainly occur late in the course of disease and may not be seen very frequently in primary care practice, possibly rendering them less useful in this setting.

Gaps in evidence-based guidance of febrile children and translation to clinical practice

Several gaps exist in evidence-based guidance of febrile children presenting to low and high prevalence settings, which request and justify ongoing diagnostic research in this specific patient group. Since in the Netherlands, primary (out-of-hours) care is firmly incorporated as a gatekeeper for hospital emergency care, our health care system forms a good base to facilitate diagnostic research at both of these settings simultaneously.

Differences in case-mix and prevalence of disease may considerably influence the diagnostic ability of clinical signs and symptoms in low and high prevalence settings. Before we can adequately interpret and translate currently performed research into practice, more insight is needed in the differences in clinical characteristics between (febrile) children presenting to primary out-of-hours care and hospital EDs (**aims 1 - 3**). Next, studies performed at hospital EDs already gave some insight in the occurrence of alarming signs in the high prevalence

setting. However, frequencies of alarming signs in low prevalence populations are still unclear (**aim 4**). Do alarming signs appear frequently enough to be sufficiently useful in discriminating children who need further treatment from the ones who can be sent home safely?

Up and till today, we still have difficulties in identifying the small group of febrile children with a serious infection from the vast majority with self-limiting viral infections. Examples of this can be found in malpractice lawsuits, which mainly account for children with missed or delayed diagnoses of serious infections.[34,35] For meningococcal disease in particular, it was observed that in half of all children admitted, the diagnosis was not recognized at first consultation by a physician.[36] A possible explanation may be the absence of alarming signs early in the disease course, which makes it difficult for a physician to recognize the disease. Another explanation may be that the physicians' awareness of important clinical signs during consultation may be limited. Structural assessment and documentation of alarming signs may therefore help in identifying those patients who are at risk of serious illnesses and may give insight in reasons why certain management decisions were made at a certain point in time (**aim 5**).

Lastly, a mismatch seems to exist between the setting where febrile children are most often encountered for consultation, i.e. primary care, and the setting where evidence is mainly collected, i.e. hospital EDs. The vast majority of clinical prediction rules published were developed in high prevalence populations. Studies which validate clinical prediction rules in external populations are lacking, in particular for the low prevalence setting, which hampers their implementation in clinical practice.[37,38] Exploration of the applicability of published clinical prediction rules in the primary out-of-hours care population may fill some of the gap in diagnostic research for febrile children presenting to this setting specifically (**aim 6**).

AIMS OF THIS THESIS

The general aim of this thesis is to improve early recognition of febrile children at risk of serious infections and to support clinical management decisions for febrile children presenting to primary out-of-hours care and hospital emergency care settings.

Specific aims of this thesis:

1. To get insight in the differences in clinical characteristics between (febrile) children presenting to primary out-of-hours care and hospital emergency care.
2. To validate a uniform triage system for telephone triage at the general practitioner cooperative and physical triage at the hospital emergency department.
3. To evaluate whether referral-status is associated with disease severity of febrile children who present to the hospital emergency department.
4. To describe the prevalence of alarming signs of serious infections in the primary out-of-hours care population.
5. To assess the role of alarming signs of serious infections in clinical management of febrile children who present to primary out-of-hours care and hospital emergency care.
6. To assess the diagnostic value of published clinical prediction rules for serious infections in primary out-of-hours care.

OUTLINE OF THIS THESIS

The first part of this thesis focuses on clinical characteristics of children with and without fever who present to the GPC and the hospital ED. In **Chapter 2** we validate the Netherlands Triage System, which is a triage system specifically developed for uniform triage at the GPC, the hospital ED, and recently the ambulance dispatch center. In this study, we describe clinical characteristics, such as urgency classifications, referral management at the GPC, and diagnostic tests, therapeutic interventions, and hospital admissions required at the ED for both adult and paediatric patients. **Chapter 3** evaluates the difference in severity of illness between febrile children referred to the ED by a GP and febrile children self-referred by their parents. As markers for severity of illness, we used the triage urgency classification, and the need for diagnostic tests, therapeutic interventions, and hospitalization.

The second part of this thesis focuses on the presence of alarming signs of serious infections among febrile children who present to primary out-of-hours care and the hospital ED. Besides, it describes their (potential) role in clinical decision making for febrile children consulting both of these settings. Firstly, in **Chapter 4** the prevalence of alarming signs of serious infections among febrile children who present to the GPC is displayed. Next, the current role of alarming signs in clinical management by GPs is explored. **Chapter 5** describes the association between

the presence of alarming signs and antibiotics prescription by GPs. This knowledge may give insight in (some of) the considerations of GPs to prescribe antibiotics and may provide clues to reduce antibiotic prescription management. **Chapter 6** explores to what extent evidence-based alarming signs of serious infections play a role in referral management of GPs. Our national guideline is used as an example to assess guideline adherence of GPs in primary out-of-hours care practice. **Chapter 7** evaluates whether the presence of alarming signs at triage of febrile children at the hospital ED can be of additional value in predicting the need for hospitalization. This knowledge may improve throughput and output times at the ED by acceleration of the application of medical interventions or admissions to the ward.

The last part of this thesis tries to fill some of the gap in evidence-based guidance of febrile children consulting primary care. **Chapter 8** assesses the diagnostic value of previously published clinical prediction rules for serious infections, mainly developed in high prevalence settings, in the primary out-of-hours care population.

Chapter 9 provides a general discussion of the main findings of this thesis and future research perspectives. In **Chapter 10** the main study results presented in this thesis are summarized in English and Dutch.

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PART I

Characteristics of paediatric emergency care populations

CHAPTER 2

Validity of telephone and physical triage in emergency care: the Netherlands Triage System

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ABSTRACT

Background Due to emergency care overcrowding, right care at the right place and time is necessary. Uniform triage of patients contacting different emergency care settings will improve quality of care and communication between health care providers.

Objective Validation of the computer-based Netherlands Triage System (NTS) developed for physical triage at emergency departments (EDs) and telephone triage at general practitioner cooperatives (GPCs).

Methods Prospective observational study with patients attending the ED of a university-affiliated hospital (September to November 2008) or contacting an urban GPC (December 2008 to February 2009). For validation of the NTS, we defined surrogate urgency markers as best proxies for true urgency. For physical triage (ED): resource use, hospitalization and follow-up. For telephone triage (GPC): referral to ED, self-care advice after telephone consultation or GP advice after physical consultation. Associations between NTS urgency levels and surrogate urgency markers were evaluated using chi-square tests for trend.

Results We included nearly 10,000 patients. For physical triage at ED, NTS urgency levels were associated with resource use, hospitalization and follow-up. For telephone triage at GPC, trends towards more ED referrals in high NTS urgency levels and more self-care advices after telephone consultation in lower NTS urgency levels were found. The association between NTS urgency classification and GP advice was less explicit. Similar results were found for children; however, we found no association between NTS urgency level and GP advice.

Conclusion Physically and telephone-assigned NTS urgency levels were associated with majority of surrogate urgency markers. The NTS as single triage system for physical and telephone triage seems feasible.

INTRODUCTION

In the Netherlands, out-of-hours emergency care is provided by general practitioner cooperatives (GPCs), emergency departments (EDs) and ambulance services. In emergency situations, patients can call the national emergency number, answered by the ambulance dispatch centre (ADC), phone the GPC or visit the GPC or ED on their own initiative.

Efforts to concentrate primary out-of-hours care (development of GPCs), increasing assertiveness of patients to refer themselves to the ED and longer throughput times at the ED have led to emergency care overcrowding[1-3]. To prevent harm, it is important to distinguish patients who need immediate medical attention from those who can wait safely. Currently, different triage systems are used to achieve this goal. EDs mainly use the Manchester Triage System (MTS)[4-7], GPCs the National Telephone Guide of the Dutch college of general practitioners (NTG)[8] and ADCs the National Standard for Dispatch Centre Ambulance Care (LSMA).

In order to improve the right care at the right place and time, as well as provide better communication between health care organizations, it is more favourable to triage each patient uniformly, regardless of the health care provider contacted.[10,11] For this purpose, a new standardized computer-based five-level triage system, the Netherlands Triage System (NTS), has been developed for both physical triage at the ED and telephone triage at the GPC and ADC.

The NTS showed substantial reliability. We recently conducted an inter-rater agreement study, consisting of 55 written case scenarios (adult and child), triaged by 20 ED and 30 GPC nurses with a stand-alone computer application of the NTS. The results showed a quadratically weighted kappa of 0.63 (95% confidence interval (CI) 0.53-0.73) for ED nurses and 0.67 (95% CI 0.57-0.77) for GPC nurses (M. van Veen, personal communication) comparable to other triage systems used worldwide.[6,12-17] Validation studies ideally evaluate whether triage systems accurately categorize patients in true urgency levels.[18] Unfortunately, no single measure captures this concept and one needs to select a best proxy for true urgency, e.g. by defining a reference standard[6,19] or surrogate marker(s) of urgency, such as resource use[12,19-22], ED length of stay[12,21-24], hospitalization[12,15,19-24] or costs.[21,24]

The aim of this study was to validate physical and telephone triage by the NTS, using surrogate urgency markers as a best proxy for true urgency. Results for children were analysed separately since children constitute 25% to 30% of the workload of out-of-hours emergency care in the Netherlands[25] and validity of other triage systems has been shown to differ substantially between adult and paediatric patients.[6,17]

METHODS

Netherlands Triage System

The NTS is a computer-based standardized five-level triage protocol, derived from the MTS, NTG and LSMA. It is, like most triage systems, primarily based on expert opinion and consensus. The NTS consists of 56 presenting problems with 238 different triage criteria (signs and symptoms). When vital signs (airway, breathing, circulation, and consciousness) are threatened, Urgency Level 1 is applicable. If not, after selection of the main complaint and discriminators (triage criteria), one of the remaining four urgency levels is advised (Figure 1).

Urgency level 1 - *Life threatening*
Immediate action required, the vital functions are threatened or delaying treatment will cause serious and irreparable damage to the patient's health
Urgency level 2 - *Emergent*
Vital functions are not (yet) in danger, but there is a fair chance that the patient's condition will soon deteriorate or delaying treatment will cause serious and irreparable damage to the patient's health. Take action as soon as possible
Urgency level 3 - *Urgent*
Do not postpone too long. Treat within a few hours because of medical- or humane reasons
Urgency level 4 - *Non-urgent*
There is no pressure resulting from medical- or other grounds. Time and place of treatment should be discussed with the patient
Urgency level 5 - *Advice*
A physical examination can wait until the next day

FIGURE 1 Definitions of the NTS urgency levels

Study setting

This observational study was conducted at an urban ED and GPC located in the centre of the Netherlands. The ED belongs to a regional university-affiliated hospital and is 24-hour covered. The GPC can be contacted by all patients living in a specified postal code area surrounding the GPC, outside regular service hours of the patient's own GP practice (weekdays from 5 p.m. till 8 a.m. and weekends from Friday 5 p.m. till Monday 8 a.m.). Annually, the ED is visited by ~20,000 patients, the GPC receives ~60,000 calls. All GPC and ED nurses had previous experience with triage and received a standardized training how to apply the NTS. Triage with the NTS started in October 2007 at the ED and May 2008 at the GPC.

Study population

Triage and corresponding electronic medical records of patients attending the ED from September till November 2008 or contacting the GPC from December 2008 till February 2009 were collected. Medical records were extracted from the hospital information system at the ED and Call Manager at the GPC, both computer databases containing medical patient information. Relevant data from GPC-records was recoded by two medical students, blinded for the assigned NTS urgency level of the patient, using SPSS Data builder and Data entry (SPSS Version 15.0; SPSS Inc., Chicago, IL). For all patients, information on gender, date of birth, date of contact with ED or GPC, mean patient load/hour at the moment of contact, self-referral and urgency level was collected. Nurses were asked to triage all patients with the NTS; still for logistical reasons, the previously used triage tools (MTS at the ED and NTG at GPC) were also kept available. Only NTS-triaged patients were selected for the validation analysis.

Validation analysis

We defined surrogate markers of urgency (outcome measures) as best proxy for the patient's true urgency. For the ED-setting: (1) resource use: laboratory blood test, simple radiological examination (X-ray or ultrasound) and advanced radiological examination (computed tomography (CT) scan or magnetic resonance imaging (MRI) scan); (2) hospital admission: medium and intensive care units (MCU and ICU); and (3) follow-up at outpatient clinic or GP. Patients transferred to another hospital (N=25) were assumed to be admitted to the MCU. Due to smaller sample size, for children, the ED markers were defined as: (1) resource use: laboratory blood test and radiological examination; (2) hospital admission (MCU + ICU); and (3) follow-up at outpatient clinic or GP.

After telephone triage at the GPC, the triage nurse could decide to give the patient either a telephone consultation (i.e. immediately send an ambulance, give a (medical) advice herself or let the GP call the patient) or physical consultation (i.e. advise the patient to visit the GPC or organize a GP home visit). For the telephone consultation group, we defined two surrogate urgency markers: (1) referral to ED (with or without ambulance); and (2) self-care advice (advice after telephone consultation by triagist/GP, with or without self-care medication (e.g. paracetamol, oral rehydration solution) and without prescription of other medication or referral to hospital). For the physical consultation group, we defined the following surrogate urgency markers: (1) referral to ED (with or without ambulance); and (2) GP advice (advice after physical consultation by GP, with or without self-care medication but without prescription of other medication, diagnostics, interventions or referral to hospital). Decisions on diagnostics, therapy and follow-up were made by the treating physicians, independently of the assigned NTS urgency.

Data analysis

We performed analysis for the total patient population and paediatric patients separately (age ≤16 years). For comparison of general patient characteristics between NTS- and no-NTS-triaged patients, Pearson's chi-square and Mann-Whitney U-tests were used where appropriate. For trends, Pearson's chi-square linear-by-linear association was used. *P* values <0.05 were considered significant. Statistical analysis was performed using SPSS Version 15.0.

RESULTS

Compliance

The ED was visited by 5,209 patients. Among them, 3,300 patients were triaged with the NTS (63%) of which 3,207 records were available for analysis (Figure 2). The GPC was contacted by 11,045 patients. Among the 6,952 (63%) patients triaged with the NTS, 6,668 GPC records were available for analysis (Figure 2). Due to logistic reasons, both the NTS and the previously used triage tools (MTS at ED and NTG at GPC) were available for triage. Reasons why nurses triaged the remaining part of the patients with the previous tools were not evaluated. Comparison of general patient characteristics between NTS- and MTS- or NTG-triaged patients at both locations showed no differences for gender and median patient load/hour at the moment of contact (data not shown). NTS-triaged patients were slightly younger than patients triaged with the previously used triage tools (median age: ED 39 versus 44 years, *P*<0.001; GPC 27 versus 36 years, *P*<0.001). At the ED, more self-referred patients were NTS triaged (42% versus no NTS 34%; *P*<0.001). Comparison of urgency distributions between NTS and MTS/NTG could not be made, due to different definitions of the urgency categories.

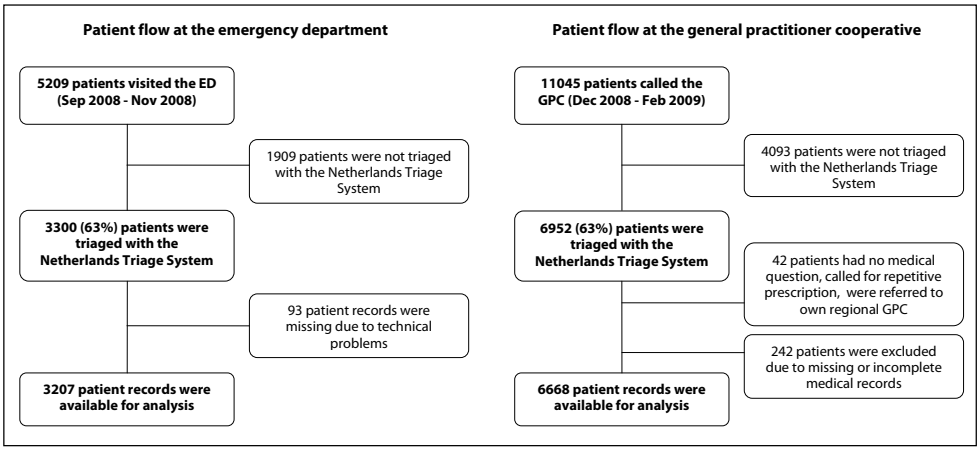

FIGURE 2 Patient flows at the ED and GPC

Validation analysis

Physical triage at the ED. Table 1 displays the NTS urgency classification of all patients visiting the ED and the presence of surrogate urgency markers. A trend of increase in resource use, hospital admission and follow-up at the outpatient clinic towards the higher urgency categories was observed (P_{trend}<0.001). Follow-up visits at the GP were more frequently seen in the lower NTS urgency levels, compared to the higher levels (P_{trend}<0.001). For paediatric patients similar trends were found, although numbers were smaller (Table 2).

Telephone triage at the GPC. After telephone triage by the GPC-nurse, 35% of all patients only received a telephone consultation and 65% had a physical consultation at the GPC or at home. Similar proportions were observed for children (data not shown). For patients with a telephone consultation, a trend towards more ED referrals in the high urgency levels and more self-care advices in the low urgency levels was found (P_{trend}<0.001). In the physical consultation group, 23% (148/652) of the high-urgent patients (U1 + U2) were referred to the ED compared to 9% (142/1,664) of the low-urgent patients (U4 + U5; P_{trend}<0.001). The association between NTS urgency classification and GP advice after physical consultation was, although significant (P_{trend}<0.001), less explicit (Table 3). Twenty-seven per cent (177/652) of high-urgent patients ended with a GP advice only compared to 34% (574/1,668) of low-urgent patients.
For paediatric patients, significant trends towards more ED referrals in the high urgency categories were observed in both consultation groups. A trend towards more self-care advices in low urgency levels was found for children with telephone consultation. No clear association could be demonstrated between NTS urgency level and GP advice after physical consultation (Table 4).

DISCUSSION

For the total patient population and children separately, NTS urgency levels assigned by physical triage at the ED were associated with resource use, hospital admission and follow-up visits. For telephone triage at the GPC, trends towards more ED referrals in the high NTS urgency levels and more self-care advices in the lower NTS urgency levels were found for the telephone consultation group. For the physical consultation group, an association between NTS urgency level and referral to ED was found; the association with GP advice was less explicit in the total patient population and absent for children.

TABLE 1 NTS urgency distribution of the total ED population and surrogate urgency markers

NTS URGENCY	N	RESOURCE USE (N; %)			ADMISSION (N; %)		FOLLOW-UP (N; %)	
		Laboratory	Radiology		Admission to hospital		Follow-up visit	
		Blood test	X-ray and/or ultrasound	CT scan and/or MRI scan	MCU	ICU	Outpatient clinic	GP
1	150	124 (82.7)	104 (69.3)	18 (12.0)	66 (44.0)	53 (35.3)	102 (68.0)	3 (2.0)
2	754	447 (59.3)	406 (53.8)	39 (5.2)	367 (48.7)	40 (5.3)	514 (68.2)	10 (1.3)
3	1394	352 (25.3)	648 (46.5)	21 (1.5)	282 (20.2)	19 (1.4)	823 (59.0)	168 (12.1)
4	462	99 (21.4)	153 (33.1)	8 (1.7)	86 (18.6)	4 (0.9)	238 (51.5)	124 (26.8)
5	447	79 (17.7)	107 (23.9)	4 (0.9)	57 (12.8)	2 (0.4)	168 (37.6)	170 (38.0)
Total	3207	1101 (34.3)	1418 (44.2)	90 (2.8)	858 (26.8)	118 (3.7)	1845 (37.5)	475 (14.8)
P_{trend}		<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

N: Number of patients; GP: general practitioner; P_{trend}: *P*-values for trend calculated with Pearson's chi-square linear-by-linear association.

TABLE 2 NTS urgency distribution of paediatric ED patients and surrogate urgency markers

NTS URGENCY	N	RESOURCE USE (N; %)		ADMISSION (N; %)	FOLLOW-UP (N; %)	
		Laboratory	Radiology	Admission to hospital	Outpatient clinic	GP
1	10	5 (50.0)	5 (50.0)	6 (60.0)	6 (60.0)	1 (10.0)
2	120	41 (34.2)	55 (45.8)	46 (38.3)	69 (57.5)	2 (1.7)
3	347	46 (13.3)	155 (44.7)	42 (12.1)	179 (51.6)	37 (10.7)
4	104	14 (13.5)	37 (35.6)	10 (9.6)	45 (43.3)	23 (22.1)
5	120	6 (5.0)	28 (23.3)	4 (3.3)	37 (30.6)	49 (40.8)
Total	701	112 (16.0)	280 (39.9)	107 (15.3)	336 (47.9)	112 (16.0)
P_{trend}		<0.001	<0.001	<0.001	<0.001	<0.001

N: Number of patients; GP: general practitioner. P_{trend}: *P*-values for trend calculated with Pearson's chi-square linear-by-linear association. Laboratory: any blood test performed; radiology: X-ray, ultrasound, CT scan or MRI scan; admission: MCU or paediatric intensive care unit.

TABLE 3 NTS urgency distribution of the total GPC population according to the type of consultation and surrogate urgency markers

NTS URGENCY	TELEPHONE CONSULTATION (N; %)					PHYSICAL CONSULTATION (N; %)				
	N	Referral to ED		Self-care advice		N	Referral to ED		GP advice	
1	56	52	(92.9)	3	(5.4)	57	18	(31.6)	15	(26.3)
2	92	27	(29.3)	39	(42.4)	595	130	(21.8)	162	(27.2)
3	521	33	(6.3)	338	(64.9)	1996	231	(11.6)	591	(29.6)
4	594	8	(1.3)	457	(76.9)	850	61	(7.2)	284	(33.4)
5	1093	16	(1.5)	859	(78.6)	814	81	(10.0)	290	(35.6)
Total	2356	136	(5.8)	1696	(72.0)	4312	521	(12.1)	1342	(31.1)
P_{trend}		<0.001		<0.001			<0.001		<0.001	

N: number of patients; GP: general practitioner. P_{trend}: *P*-values for trend are calculated with Pearson's chi-square linear-by-linear association.

TABLE 4 NTS urgency distribution of the paediatric GPC population according to the type of consultation and surrogate urgency markers

NTS URGENCY	TELEPHONE CONSULTATION (N;%)					PHYSICAL CONSULTATION (N;%)				
	N	Referral to ED		Self-care advice		N	Referral to ED		GP advice	
1	3	1	(33.3)	2	(66.7)	15	2	(13.3)	8	(53.3)
2	16	2	(12.5)	12	(75.0)	208	28	(13.5)	103	(49.5)
3	195	1	(0.5)	173	(88.7)	823	50	(6.1)	377	(45.8)
4	217	1	(0.5)	202	(93.1)	308	20	(6.5)	165	(53.6)
5	407	1	(0.2)	380	(93.4)	255	15	(5.9)	148	(58.0)
Total	838	6	(0.7)	769	(91.8)	1609	115	(7.1)	801	(49.8)
P_{trend}		<0.001		0.004			0.015		0.004	

N: number of patients; GP: general practitioner. P_{trend}: *P*-values for trend are calculated with Pearson's chi-square linear-by-linear association.

We demonstrated that the majority of adult and paediatric patients assigned to NTS Urgency Level 1 by physical triage at the ED were hospitalized comparable to validation analyses of other triage systems used in ED settings (Table 5).[12,15,19-23] The proportion of hospital admissions among low-urgent patients was somewhat higher, compared to these studies. For the association between urgency level and resource use, similar results are described for other triage systems as well, although definitions are not completely concordant (Table 5). Since, many triage systems required separate validation analyses for children in order to improve the system[27], we simultaneously performed these analyses in our study. Overall, our results suggest that the NTS might be a valid triage tool for physical triage at the ED.

Similar to the UK, all GPC-calls in the Netherlands are initially answered by a triage nurse, who decides what type of consultation the patient requires.[28] The distribution of telephone and physical consultations in our study is comparable to previous reports.[3,25,29] Telephone triage and telephone consultation by nurses instead of physicians appeared to be efficient and

safe.[30-32] Still, validation analyses of telephone triage tools are scarce. Previously, two Dutch studies evaluated whether triage nurses, using a paper version of the NTG, correctly estimated urgency levels for telephone incognito standardized patients compared to a predefined expert opinion-based urgency level. Giesen *et al*. reported that 118 triage nurses from four GPCs correctly estimated the level of urgency in 69% of 352 calls (20 different clinical cases).[33] Derkx *et al*. showed that triage nurses from 17 GPCs achieved the appropriate triage outcome in only 58% of 357 calls (7 different clinical cases). The number of obligatory questions asked, was consistently below the previously defined standard.[34] It has been suggested that the safety of telephone triage may be enhanced by using computer-based decision support systems.[34-36] Dale *et al.* demonstrated feasibility of a computerized decision support system for emergency ambulance calls.[37,38] Likewise, in out-of-hours primary care and Children's Hospitals in the UK and USA, nurse telephone triage and consultation, using computerized decision support, have been reported to be a safe and effective gatekeeper as well.[30,39]

Unfortunately, GPCs, EDs and ADCs from all over the world use different triage tools to categorize patients according to their urgency. Unequal definitions of urgency levels obviously hamper communication and collaboration between (emergency) health care providers, which is essential to guarantee quality and safety, especially in times of increasing emergency care overcrowding. Uniform triage may be one solution for this problem. Similar definitions and understanding of triage criteria used for urgency level assignment will improve collaboration. For example, this will potentiate referral of non-urgent patients from the ED to alternative care settings more appropriate for the patient's presenting problem and urgency, like the fast-track area within the ED, the GPC or the patient's own GP.[40] Besides, patients will only be triaged once and uniformly regardless of the health care provider contacted, which may result in improved patient satisfaction, health care efficiency and decreased health care costs.[10]

Strengths and limitations

Due to the lack of a golden standard for true urgency, one must choose a second best method to validate a triage system.[18] Like studies validating the MTS, (paediatric) Canadian Triage and Acuity Scale and Emergency Severity Index,[12,15,19-24] we used surrogate urgency markers as a best proxy for true urgency. These markers, however, do not indicate the exact number of patients (potentially) harmed. To evaluate the safety of the NTS, we previously conducted a retrospective pilot study (L. Huibers, personal communication).

TABLE 5 Studies on validity of triage systems in hospital emergency care making use of surrogate markers of urgency

	ADULTS (%)				CHILDREN (%)									
Triage system	**CTAS[21]**	**CTAS[22]**		**ESI[15]**	**pCTAS[20]**		**pCTAS[23]**	**CTAS[22]**			**ESI[12]**		**MTS[19]**	
No of patients	**29524**	**23099**		**403**	**1281**		**58529**	**9162**			**510**		**1065**	
Urgency markers[a]	**Hospital admission**	**Hospital admission**	**Resource use**	**Hospital admission**	**Hospital admission**	**Resource use**	**Hospital admission**	**Hospital admission**	**Lab test**	**Radiology**	**Hospital admission**	**Resource use**	**Hospital admission**	**Resource use**
Urgency level														
1	83	70	85	80	100	100	63	83	67	83	80	100	54	87
2	41	54	81	73	24	29	37	23	28	28	34	76	29	71
3	23	29	57	51	12	25	14	12	14	23	13	63	16	73
4	10	7	24	6	4	15	2	2	6	17	3	51	6	59
5	5	3	7	5	2	11	1	1	2	37	0	15	1	32

ESI = Emergency Severity Index; MTS = Manchester Triage System; (p)CTAS = (paediatric) Canadian Triage and Acuity Scale.
[a] Urgency markers were defined as follows:
(12): Hospital admission: MCU, ICU, transfer and deaths; Resource use: cardiac monitoring, specialty consultation, electrocardiography, laboratory test, radiology test, fluid or medication or blood product administration, mechanical ventilation.
(15): Hospital admission: MCU, ICU, telemetry and deaths.
(19): Hospital admission: not specified; Resource use: laboratory tests, radiology tests, medication or intervention at ED.
(20): Hospital admission: not specified; Resource use: complete blood count.
(21): Hospital admission: all admissions, transfers and deaths.
(22): Hospital admission: all hospitalizations and transfers; Laboratory test: not specified; Radiology: not specified.
(23): Hospital admission: MCU.

Two independent reviewers identified 18 (5.6%) out of 319 randomly selected GPC and 8 (2.1%) out of 375 randomly selected ED contacts to be potentially unsafe. A potentially unsafe incident was defined as an unintended event during the care process that resulted, could have resulted or still might result in harm to the patient (criteria for inclusion of incidents: (1) acts of omission, (2) acts of commission, (3) related to unnecessary harm or risk for the patient, (4) harm is mainly thought of as somatic or serious psychiatric diseases and (5) risk has to be scientifically proven or broadly accepted as valid; exclusion criteria: (1) minor psychological harm or (2) events completely caused by the patient him/herself).[41,42] An independent physician panel then assessed that triage with the NTS was a possible cause in three (1%) of these GPC and two (0.5%) of these ED contacts. These preliminary results raise no major doubts about the safety of the NTS. Still, more extensive critical event analyses must be performed to confirm these findings on a larger scale.

Since we know that the predictive value of a certain discriminator (e.g. triage criterion) for high urgency might be different in settings with different disease prevalence[43], we performed our validation analysis in both the ED and GPC setting. By our best knowledge, we are the first to validate a standardized computer-based telephone triage tool at the GPC for the whole spectrum of presenting problems, using surrogate urgency markers. Even though such markers have been widely used to validate triage systems in ED-settings,[12,15,19-24] they have never been described for telephone triage in primary care. Due to minor availability of diagnostic tests and interventions in primary care, it is difficult to define adequate surrogate markers for telephone triage at the GPC, which may somewhat limit the choice of proxy markers for urgency. Triage was performed by experienced nurses, as evidenced by a substantial inter-rater agreement [44] at both settings (ED: *kappa* 0.67 (95% CI 0.53 to 0.73) and GPC: *kappa* 0.63 (95% CI 0.57 to 0.77)) comparable to previous triage tools.[12-17,27] Compliance to triage with the NTS was good. Patient characteristics between NTS and no-NTS-triaged patients were mainly comparable at both the ED and GPC and selection bias seems unlikely, however, cannot be ruled out. The high number of patients included from the large regional inner-city GPC and ED constitute a good case mix and results seem generalizable to other general patient populations. Still, larger study populations are desirable to enable validation analyses of specific patient subgroups, as described before[6]. This will identify patients for which the NTS currently has a low performance and where modifications of the triage system are required.

Conclusion and implications for future research

Our study demonstrates that both physically and telephone-assigned NTS-urgency levels were associated with the majority of urgency markers for the total patient population and children separately. Still, some over and under triage may have occurred. To specify over and under triage by the NTS, either standardized incognito patients must be used [33,34] or an independent reference standard ('silver standard' for true urgency) must be defined.[6] Still, the NTS as a single

triage system for both physical and telephone triage seems feasible. Larger study populations will enable validation analysis of patient subgroups, which will guide specific modifications of the triage system to improve its performance.

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CHAPTER 3

Self-referral and serious illness in children with fever

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ABSTRACT

Objective The goal of this study was to evaluate parents' capability to assess their febrile child's severity of illness and decision to present to the emergency department. We compared children referred by a general practitioner (GP) with those self-referred on the basis of illness-severity markers.

Methods This was a cross-sectional observational study conducted at the emergency departments of a university and teaching hospital. GP-referred or self-referred children with fever (aged <16 years) who presented to the emergency department (2006-2008) were included. Markers for severity of illness were urgency according to the Manchester Triage System, diagnostic interventions, therapeutic interventions, and follow-up. Associations between markers and referral type were assessed by using logistic regression. Subgroup analyses were performed for patients with the most common presenting problems that accompanied the fever (i.e. dyspnea, gastrointestinal complaints, neurological symptoms, fever without specific symptoms).

Results Thirty-eight percent of 4,609 children were referred by their GP and 62% were self-referred. GP-referred children were classified as high urgency (immediate/very urgent categories) in 46% of the cases and self-referrals in 45%. Forty-three percent of GP referrals versus 27% of self-referrals needed extensive diagnostic intervention, intravenous medication/aerosol treatment, hospitalization, or a combination of these (odds ratio: 2.0 (95% confidence interval: 1.75 to 2.27)). In all subgroups, high urgency was not associated with referral type. GP-referred and self-referred children with dyspnea had similar frequencies of illness-severity markers.

Conclusions Although febrile self-referred children were less severely ill than GP-referred children, many parents properly judged and acted on the severity of their child's illness. To avoid delayed or missed diagnoses, recommendations about interventions that would discourage self-referral to the emergency department should be reconsidered.

INTRODUCTION

Worldwide, emergency departments (EDs) are challenged by increasing numbers of patients who bypass primary care and present to the ED on their own initiative (self-referral).[1-9] For adult patients, self-referral has been associated with nonurgent symptoms that can easily be handled in primary care.[8,10] Consequently, interventions to redirect self-referrals to fast-track areas, placement of primary care facilities next to EDs, or governmental policies for self-payment of ED visit costs by self-referrals have been introduced.[2,11] Such interventions will reduce the number of adult self-referrals; however, they may also discourage parents from self-referring their child to the ED, even though knowledge on the severity of illness of self-referred children is scarce.

Fever is one of the main presenting problems at pediatric EDs.[12-14] Among febrile children, ~15% are diagnosed with bacterial infections (e.g. meningitis, bacteremia, urinary tract infection), severe dehydration (caused by gastroenteritis) or dyspnea. For these illnesses, diagnostic or therapeutic interventions, or hospitalization are often required.[3,15-17] Delay in diagnosing these conditions by discouraging parents from self-referring their child to the ED may result in significant morbidity and mortality.[18-20]

This study aimed to assess severity of illness of febrile children who where self-referred to the ED by their parents compared with those referred by the general practitioner (GP). We hypothesized that parents are capable of assessing their child's severity of illness and adequately decide to present their child to the ED. Urgency according to the Manchester Triage System (MTS), diagnostic interventions, therapeutic interventions, and follow-up were used as markers for severity of illness and were compared between GP-referred and self-referred children.

METHODS

Study design

In this cross-sectional observational study, we compared severity of illness of children with fever referred by a GP with those who presented to the ED on their parent's initiative on the basis of markers for severity of illness. This study is part of an ongoing prospective study on triage of pediatric patients.[1] Institutional medical ethics committees reviewed the study, and the requirement for informed consent was waived.

Health care system in the Netherlands

In the Netherlands, both primary care (provided by GPs) and secondary care (provided by medical specialists (e.g. pediatricians)) function as emergency care facilities. All inhabitants are registered with a local GP, who is available during office hours. Out-of-hours primary care

(5 p.m. to 8 a.m. daily and entire weekend) is organized in general practitioner cooperatives, in which GPs rotate shifts.[21,22] Similar large-scale cooperatives have been observed in the United Kingdom, Scandinavia and Australia.[23-25]

In principle, patients should first consult their local GP or phone the general practitioner cooperative. After (telephone) triage by a trained nurse,[26] the patient receives telephone advice or consultation. The availability of acute diagnostic and therapeutic interventions in primary care is predominantly limited to analysis of urine dipstick test results and administration of rescue medication (e.g. adrenaline, antihistaminic agents). In the event a specialist consultation, laboratory examinations, radiologic examinations, or extensive therapeutic interventions (e.g. aerosol treatment, intravenous (IV) medication) are necessary, the patient is referred to the ED, accompanied with a referral note (i.e. gate-keeping). Referral is required for ~5% to 10% of all primary care consultations,[22,27] similar as in the United Kingdom, United States, and Canada[28,29]

In addition, patients can directly present to the ED on their own initiative (self-referral). Only in life-threatening situations should patients call the national emergency number for ambulance services. Ambulance personnel judge the patient's acuity of illness on arrival and bring the patient directly to the ED when necessary. At the ED, all children with medical problems are consulted by a pediatrician or resident in pediatrics supervised by a pediatrician.

Study setting and participants

Our study population comprised all GP-referred or self-referred children with fever (aged <16 years), who presented to the ED of 2 large inner-city hospitals located in the southwest of the Netherlands. The Erasmus MC/Sophia Children's Hospital (Rotterdam) is a university hospital with a pediatric ED that provides 90% general pediatric care to ~9,000 patients annually.[13] The inclusion period at this hospital ran from January 2006 to January 2007 and May 2007 to April 2008. The Haga Hospital/Juliana Children's Hospital (The Hague) is a large teaching hospital with a mixed pediatric-adult ED that delivers care to nearly 15,000 children annually. In this hospital, the inclusion period ran from January to August 2006 and August to December 2007. To avoid inclusion of patients who did not receive 'usual care', we excluded children 'referred by others'. This group mainly comprised children with co-morbidity and children referred by pediatric specialists (e.g. cardiologist, oncologist).

Manchester Triage System

The MTS is a triage algorithm that consists of 49 flowchart diagrams suitable for children. Each flowchart is specific to a patient's presenting problem and contains 6 key discriminators (life threat, pain, hemorrhage, acuteness of onset, consciousness level and temperature) and specific discriminators (signs and symptoms) relevant to the presenting problem. Selection of a discriminator leads to 1 of the 5 urgency categories and maximum waiting time. Both participating hospitals used the first edition of the MTS (official Dutch translation).[30] Compliance with triage with the MTS was 99% (14,078 of 14,276), as in our MTS validation study.[1]

Data collection

We obtained information on demographic and contact characteristics, referral type, flowchart, discriminators and urgency category from the computerized MTS. Parents were informed about the assigned urgency level. Only 0.5% of the parents left before being seen by the physician. These patients were not followed up because this number was very small. Over a 2-month period, the reason for self-referral was recorded by the triage nurses at Sophia Children's Hospital. Clinical data on diagnostic and therapeutic interventions, and follow-up were recorded on structured electronic or paper ED forms by nurses or physicians. We obtained data on laboratory tests from the hospital information systems. Trained medical students entered these data in a separate database (SPSS data entry version 4.0 (SPSS Inc., Chicago, IL)), independent of triage outcome or referral type. The database was checked for outliers and consistency.

Referral type was documented for 13,922 of 14,078 (99%) triaged children. Demographic and clinical characteristics were comparable between patients with missing data (N=354) and complete data (N=13,922). Selection of all febrile self-referred and GP-referred children resulted in a study population of 4,609 children (Fig 1). Eight percent (354 of 4,609) of all eligible children presented to the ED more than once during the study period. Among these, 14 (0.3%) children presented frequently (≥4 presentations). Children who presented more than once were younger (median age: 1.4 vs. 1.8 years) and slightly more frequently self-referred (68% vs. 61%) than those who presented once. Because the MTS urgency distribution and frequency of hospitalization (as measures of severity of illness) were similar for both groups and the number of children with >1 visit was small, we decided not to exclude these patients.

Definitions

Fever was defined as 'fever as reason for attendance,'[31,32] 'fever selected as triage discriminator,' or a body temperature rectally measured at the ED ≥38.5°C. Referral type was recoded into the following: (1) self-referred: children who presented to the ED on their parent's initiative and children brought in by ambulance after their parents had telephoned the national emergency number; (2) referred by GP: children referred to the ED after consultation by a GP; and (3) referred by others: children referred to the ED by other health care workers (e.g. pediatric specialists (e.g. cardiologist/oncologist), police physician or midwife). MTS flowcharts were categorized into 9 presenting problems (Table 1). We defined high MTS urgency as 'immediate' or 'very urgent' classification. As reported in our MTS validation study,[1] diagnostic interventions were categorized into simple laboratory (complete blood count, electrolytes, liver enzymes, renal function, urine/stool cultures, and nasal swabs), simple radiology (radiograph or ultrasound imaging), extensive laboratory (blood culture, cerebral spinal fluid puncture, or a combination of ≥2 simple laboratory tests), and extensive radiology (computed tomography or MRI). Therapeutic interventions were categorized into self-care advice (no medication), medication on prescription (e.g. antibiotics), oral medication at ED (e.g. prednisone), and extensive

therapeutic interventions (e.g. IV medication, aerosol treatment). Follow-up was categorized into no follow-up, hospital admission, outpatient clinic appointment and other (e.g. telephone appointment, appointment by GP). Both EDs used similar criteria for hospitalization: (1) abnormal or threatened vital signs; (2) requirement of IV medication or IV fluids; and (3) inability to ingest prescribed medication (e.g. need for nasogastric tube). Hospitalization was further subdivided into admission to the medium care unit or intensive care unit. MTS urgency, diagnostic interventions, therapeutic interventions, and follow-up were considered as markers for severity of illness.

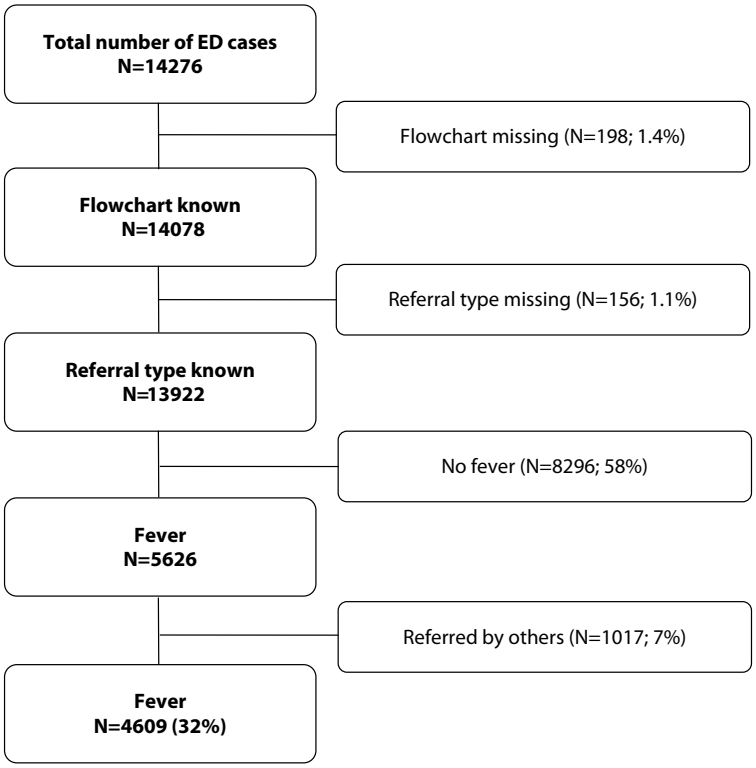

FIGURE 1 Selection of the study population

Sample size

We assumed that the percentage of GP-referred patients who needed extensive medical interventions or hospitalization was 50%.[3,5,17] To find at least a 5% difference in outcome measure between GP-referred and self-referred children, we calculated the sample size for each referral group to be at least 1,561 patients ($\alpha = 0.05$; $\beta = 0.20$).

TABLE 1 MTS flowcharts categorized into presenting problems

PRESENTING PROBLEM	FLOWCHART
Dyspnea	Asthma, shortness of breath, shortness of breath in children
Gastrointestinal	Vomiting, abdominal pain, abdominal pain in children, diarrhea, gastrointestinal bleeding
Neurological	Headache, fits, neck pain, unwell child, irritable child, behaving strangely
Ear, nose, and throat	Sore throat, nasal problems, ear problems
Rash	Rashes
Urinary tract	Urinary problems
Local infection/abscess/wound	Local infection/abscess, wounds, burns
Fever without specific symptoms	General, worried parent or crying baby with a positive 'fever' discriminator
Other	Other remaining flowcharts

Statistical analysis

Where appropriate, demographic characteristics, contact characteristics and illness-severity markers of GP-referred and self-referred patients were compared using χ^2 tests (categorical variables) and Mann-Whitney *U* tests (continuous variables). To evaluate the association between referral type and illness-severity markers, multivariate logistic regression analyses were performed. Self-referred children were chosen as the reference category. We considered age (continuous), gender, presenting problem, time of contact (day, evening, or night) and day of contact (weekday or weekend) as potential confounders, as they may be related to both the decision to refer the child to the ED (by GP or parent) and physicians' decisions on diagnostic or therapeutic interventions or hospitalization. The associations between illness-severity markers and referral type did not significantly change when children brought in by ambulances (n = 378) were excluded from the analysis (data not shown). We included these children in our main analyses. Statistical analyses were performed using SPSS PASW software version 17.0.2. *P* values <0.05 were considered significant.

RESULTS

Thirty-eight percent of the 4,609 eligible children with fever were referred by a GP and 62% were self-referred. Gender was comparable between both groups (Table 2). Median age was 1.5 years (interquartile range: 0.7-3.8) for GP-referred children and 1.9 years (interquartile range: 1.0 to 3.8) for self-referred children (*P*=0.16). Self-referred children were presented significantly more often during out-of-hours periods and more of them were brought in by ambulance services than GP-referred children (*P*<0.01). In both referral groups, the most common presenting problems that accompanied the fever were dyspnea, gastrointestinal complaints, neurological symptoms, and fever without specific symptoms. Table 2 displays differences in illness-severity markers between GP-referred and self-referred children.

TABLE 2 Distribution of illness-severity markers in GP-referred and self-referred children with fever

CHARACTERISTICS	GP-REFERRED (N=1774)		SELF-REFERRED (N=2835)		*P*
Gender[a]					
Male	997	(56)	1630	(58)	.40
Age, y[b]					
≤ 1	655	(37)	759	(27)	<.01
1-3	707	(40)	1399	(49)	<.01
4-7	265	(15)	489	(17)	.04
8-16	147	(8)	188	(7)	.04
Time of consultation					
Out-of-hours	917	(52)	2203	(78)	<.01
Transport to ED					
Aambulance services	64	(4)	314	(11)	<.01
Presenting problem[b]					
Dyspnea	387	(22)	396	(14)	<.01
Gastro-intestinal	240	(14)	323	(11)	.03
Neurological	131	(7)	317	(11)	<.01
Ear, nose, and throat	53	(3)	178	(6)	<.01
Rash	59	(3)	79	(3)	.30
Urinary tract problems	60	(3)	45	(2)	<.01
Local infection/abscess/wound	11	(1)	13	(1)	.46
Fever without specific symptoms	611	(34)	1101	(39)	<.01
Other problem	222	(13)	383	(14)	.33
MTS urgency[b,c]					
Immediate	28	(2)	69	(2)	.05
Very urgent	783	(44)	1216	(43)	.41
Urgent	610	(34)	861	(30)	<.01
Standard	341	(19)	658	(23)	<.01
Nonurgent	12	(1)	31	(1)	.15
Diagnostic interventions[b]					
No diagnostic intervention	555	(31)	1435	(51)	<.01
Simple laboratory[d]	461	(26)	661	(23)	.04
Simple radiology[e]	310	(18)	318	(11)	<.01
Extensive laboratory or extensive radiology[f]	284	(16)	292	(10)	<.01
Extensive laboratory and any radiology	164	(9)	129	(5)	<.01
Therapeutic interventions[b]					
No therapy	159	(9)	259	(9)	.84
Self-care advice	256	(14)	425	(15)	.60
Medication on prescription	756	(43)	1470	(52)	<.01
Oral medication at ED[g]	171	(10)	262	(9)	.65
IV medication/aerosol treatment[h]	432	(24)	419	(15)	<.01
Follow-up[b]					
No follow-up	696	(39)	1723	(61)	<.01
Outpatient clinic	375	(21)	396	(14)	<.01
Hospital admission[b]					
MCU[i]	444	(25)	396	(14)	<.01
ICU	13	(1)	15	(1)	.39
Other follow-up	246	(14)	305	(11)	<.01

Data are presented as *n* (%). MCU: medium care unit; ICU: intensive care unit.

[a] One missing value.

[b] Overall χ^2 P <.01.

[c] MTS urgency classification (and maximum waiting time): immediate: 0 min, very urgent: 10 min, urgent: 60 min, standard: 120 min, and non-urgent: 240 min.

[d] Complete blood cell count, electrolytes, liver enzymes, renal function, urine/stool cultures, nasal swabs.

[e] Radiography and/or ultrasound.

[f] Extensive laboratory: blood culture, cerebrospinal fluid puncture, or combination of ≥ 2 simple laboratory tests. Extensive radiology: computed tomography and/or MRI.

[g] Examples include oral rehydration salts, prednisone, or antibiotics.

[h] Examples of IV medication include fluids and antibiotics.

[i] All admissions to the hospital other than ICU admissions.

Parents of a subsample of 88 self-referred children (response: 68%) were asked to give their main reason for ED attendance. Eighty-five percent of them reported that they considered the ED to be the most appropriate place to present their child (i.e. they thought their child would need a pediatrician's expertise or diagnostic and therapeutic interventions only available at the ED), 8% had been unable to contact their own GP or general practitioner cooperative, and 4% had other reasons.

Associations between referral type and illness-severity markers

Forty-three percent of GP-referred children needed extensive diagnostic interventions, IV medication/aerosol treatment, hospitalization, or a combination of these, compared with 27% of self-referred children (odds ratio (OR): 2.0 (95% confidence interval (CI): 1.75 to 2.27)). Table 3 displays the associations between referral type and illness-severity markers separately. GP-referred children were classified as high-urgency in 46% of the cases and self-referred children in 45% (OR: 1.2 (95% CI: 1.02 to 1.35)). Compared with self-referrals, GP-referred children required significantly more extensive diagnostic interventions (OR: 2.0 (95% CI: 1.74 to 2.38)) and IV therapy or aerosol treatments (OR: 1.6 (95% CI: 1.39 to 1.93)) and were more frequently hospitalized (OR: 2.0 (95% CI: 1.74 to 2.39)). Due to small numbers, we could not analyze medium care unit and intensive care unit admissions separately in our regression analysis (Table 2).

TABLE 3 Associations between referral type and illness-severity markers for children who presented to the ED with fever

ILLNESS-SEVERITY MARKERS	GP-REFERRED (N=1774)	SELF-REFERRED[a] (N=2835)	UNADJUSTED OR	ADJUSTED OR[b]
	N (%)	N (%)	OR (95% CI)	OR 95% CI
High MTS urgency[c]	811 (46)	1285 (45)	1.0 (0.90-1.14)	1.2 (1.02-1.35)
Extensive diagnostic interventions[d]	448 (25)	421 (15)	1.9 (1.67-2.25)	2.0 (1.74-2.38)
IV therapy/aerosol treatment	432 (24)	419 (15)	1.9 (1.60-2.16)	1.6 (1.39-1.93)
Hospital admission	457 (26)	411 (15)	2.1 (1.76-2.38)	2.0 (1.74-2.39)

[a] Reference category: self-referred children.
[b] Adjusted for gender, age, presenting problem, time of contact (day, evening, or night), and day of contact (weekday or weekend).
[c] High MTS urgency (maximum waiting time): immediate (0 min) or very urgent (10 min).
[d] Extensive laboratory or radiology examinations.

Presenting problems

Table 4 presents a subgroup analysis of children with the 4 most common presenting problems that accompanied the fever. The proportion of children classified according to the MTS as high urgency was comparable between GP-referred and self-referred children in all presenting problem groups. The odds of requiring extensive diagnostic interventions or IV medication were higher for GP-referred children than for self-referred children with gastrointestinal complaints, neurological symptoms, or those without specific symptoms that accompanied the fever. In these subgroups, hospitalization ranged from 20% to 37% among GP-referred children and from 11% to 22% among self-referred children. The frequencies of all illness-severity markers for feverish children with dyspnea were comparable between GP-referrals and self-referrals.

DISCUSSION

Our study revealed that even though self-referred children with fever were less severely ill than GP-referred children, at least 1 in 4 self-referrals needed extensive diagnostic interventions, IV medication/aerosol treatment, or hospitalization. The most common presenting problems that accompanied the fever as well as classification according to the MTS as high urgency were similar for GP-referred and self-referred children. Our subgroup-analyses further revealed that for children with fever and dyspnea, severity of illness was similar in both referral groups. Obviously, many parents properly judged and acted on their child's severity of illness by presenting their child to the ED on their own initiative.

The majority of parents self-referred their child because they thought their child needed pediatrician's expertise or diagnostic or therapeutic interventions, for which they had to visit the ED anyway, which is comparable to previous reports.[4,33] We further observed that 11% of the self-referred children were brought in by ambulance services. In all of these cases, the ambulance dispatch centre assessed and agreed upon the urgent need for medical care, indicating the child was seriously ill and parents adequately decided to ring the national emergency number.

TABLE 4 Association between referral type and illness-severity markers categorized according to the most common presenting problems among children who presented at the ED with fever

ILLNESS-SEVERITY MARKERS	DYSPNEA			GASTROINTESTINAL			NEUROLOGICAL			FEVER WITHOUT SPECIFIC SYMPTOMS		
	GP (N=387)	SR (N=396)	OR[a] (95% CI)	GP (N=240)	SR (N=323)	OR[a] (95% CI)	GP (N=131)	SR (N=317)	OR[a] (95% CI)	GP (N=611)	SR (N=1101)	OR[a] (95% CI)
High MTS urgency[b]	199 (51)	200 (51)	1.1 (0.82-1.48)	13 (5)	12 (4)	1.4 (0.59-3.25)	99 (76)	252 (80)	0.8 (0.49-1.34)	382 (63)	648 (59)	1.2 (0.97-1.48)
Extensive diagnostic interventions[c]	52 (13)	46 (12)	1.2 (0.77-1.92)	65 (27)	47 (15)	2.0 (1.27-3.04)	56 (43)	99 (31)	1.6 (1.06-2.52)	180 (30)	151 (14)	2.4 (1.90-3.13)
IV medication/ aerosol treatment	168 (43)	160 (40)	1.1 (0.79-1.44)	36 (15)	31 (10)	1.7 (1.02-2.98)	38 (29)	58 (18)	1.9 (1.17-3.10)	127 (21)	110 (10)	2.1 (1.61-2.85)
Hospital admission	111 (29)	102 (26)	1.3 (0.92-1.79)	49 (20)	45 (14)	1.5 (0.97-2.45)	49 (37)	68 (22)	2.5 (1.55-3.89)	174 (29)	125 (11)	2.9 (2.22-3.80)

GP: GP-referred patients; SR: self-referred patients.
[a] Adjusted for age, gender, time of contact (day, evening, or night) and day of contact (weekday or weekend). Reference category: self-referred children.
[b] High MTS urgency (maximum waiting time): immediate (0 min) or very urgent (10 min).
[c] Extensive laboratory or radiology examinations.

Comparison with literature

Our results support, to some extent, the findings of Rinderknecht *et al.*[5] that GP-referred children with fever are more severely ill than self-referred children; however, the magnitude of the difference in our population was much smaller. Their study revealed that febrile children referred by a GP to their quaternary, international referral center had higher triage acuities and higher frequencies of abnormal vital signs and hospitalizations than self-referred children. On the basis of these results, they suggested incorporating referral type in triage algorithms used at the ED. It is likely that our much smaller difference in severity of illness between GP-referred and self-referred children can be explained by the difference in study settings. Children referred to their quaternary care center are likely to be more seriously ill and to need more specialized care than children referred to our study EDs, which mainly provide basic pediatric care.[13] According to our finding that the frequency of high-urgent classification was comparable between GP-referred and self-referred children, we disagree with the recommendation to use referral type alone to influence triage algorithms at community EDs.

Although the health care system is organized differently in the Netherlands as compared with other countries, we think our results are generalizable to community EDs of countries in which primary care and ED care are both available as emergency care facilities. In other European countries,[3,4,25,34] Australia,[6,7] the United States,[8,9] and Canada,[5,35] ED populations constitute a case-mix of referred and nonreferred children, with numbers of self-referrals ranging from about 30% to 80%,[3,8,34-38] comparable with the frequency of self-referrals in the Netherlands.[1,33,39] Our finding that 1 in 4 self-referred children required some form of extensive intervention or hospitalization is much higher than one would expect if parents were unable to judge their child's medical need. In addition, it is only slightly lower than the frequency found among GP-referred children. Primary care, which is only provided by GPs in the Netherlands, has been shown to be adequate,[22,27] safe,[40] and satisfactory.[22,25,41] Because in our health care system GPs only refer patients who need specialist care, we have used GP-referred children as a reference group of true severely ill patients. This study revealed that many parents, who could choose between primary or secondary care facilities for emergency care, presented to the ED adequately and were capable of judging their child's severity of illness. Therefore, we think that our results and the medical implications are important for community EDs in other countries as well.

Because increasing numbers of self-referrals at the ED cause a high workload for ED nurses and physicians, future research should focus on demographic and clinical characteristics of self-referred febrile children that point towards severe illness. By knowing these characteristics, one can distinguish severely ill from nonseverely ill children on arrival at the ED. For example, our subgroup analyses already revealed that GP-referred and self-referred children with fever and dyspnea were equally ill. Such determinants, rather than referral type alone, should be used to guide decisions on accepting or diverting self-referrals at the ED.

Study weaknesses and strengths

The first limitation of this study is our use of MTS urgency, diagnostic interventions, therapeutic interventions, and follow-up as proxies for severity of illness. However, because such proxies have been extensively used to validate triage systems worldwide[42-45], we think this method is valid to approximate true severity of illness.

Second, we had no information on whether self-referred children were seen by a GP (but not referred) before their presentation to the ED. Possibly, parents were instructed by the GP about specific symptoms to be aware of or to go to the ED when symptoms worsened. Potentially, this information could have influenced our results towards more severely ill patients in the self-referred group.

Third, our interpretation that 1 in 4 self-referred children who required at least some extensive medical intervention or hospitalization is a significant number is primarily based on our own clinical experience and intuition. We concluded that discouragement of all parents to self-refer their feverish child to the ED is unacceptable. Unfortunately, this statement is not evidence based, because cutoff values for what we generally think is an acceptable number of patients to delay or miss diagnosis in (e.g. by discouragement of self-referral) are unavailable.

We are, however, to the best of our knowledge, the first to report differences in severity of illness between GP-referred and self-referred children with fever who presented to a large community ED. Our study sample constitutes a good case-mix selected from a multicultural, inner-city ED-population of >14,000 children.

In addition, our subgroup analysis is the first to demonstrate that self-referral is justifiable for a considerable number of febrile children with specific accompanying symptoms, especially for those with dyspnea.

Data collection was complete for 98% of all children who presented to the ED during our study period. General patient and clinical characteristics of children with and without missing data were comparable, indicating that selection bias was unlikely.

Differences in the level of expertise between residents and pediatricians may have led to differences in diagnostic management[46]. At our study EDs, all residents were supervised by a paediatrician, and we found no differences in the number of diagnostic interventions performed by residents or pediatricians (χ^2-test: P=0.28 (data not shown)).

The magnitude of the difference in diagnostic and therapeutic interventions performed between self-referred and GP-referred children is similar to that of the number of hospitalizations required. Because hospitalization depends on the patient's clinical condition rather than referral type, information bias (i.e. pediatricians will perform more diagnostic and therapeutic interventions when they know a child is referred by a GP) is unlikely.

CONCLUSION

Our study emphasized that many parents properly judged and acted on their febrile child's severity of illness by presenting to the ED on their own initiative. Self-referred children with fever must not be generalized and approached as a uniform group of nonseverely ill patients. General measures to discourage self-referrals to present to the (community) ED are undesirable for children with fever; this action may result in delayed or missed diagnoses and potentially increase morbidity and mortality.

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PART II

Alarming signs of serious infections in febrile children

CHAPTER 4

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

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ABSTRACT

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

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

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

Setting General practitioners' out-of-hours service.

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

Main outcome measures Frequency of 18 alarming signs as reported in the literature.

Results A total of 10,476 patient contacts were included. The frequency of alarming signs ranged from N=1 (ABC instability; 0.0%) to N=2,207 (vomiting & diarrhea; 21.1%). Of all children, 59.7% had one or more alarming signs present. Several alarming signs were poorly registered with the frequency of missing information ranging from 1,347 contacts (temperature >40°C as reported by the parents; 12.9%) to 8,647 contacts (parental concern; 82.5%).

Conclusion Although the prevalence of specific alarming signs is relatively low in primary care, ≥50% of children have one or more alarming signs present. There is a need to determine the predictive value of alarming signs not only for serious infections in primary care, but as well for increased risk of a complicated course of the illness.

INTRODUCTION

Even though most febrile illnesses in children are harmless, serious infections (e.g. pneumonia, urinary tract infection, meningitis and sepsis) do occur. Of the many studies investigating alarming signs to help physicians identify children with a serious infection,[1,2] the vast majority were performed in secondary care.[3] In the few studies performed in primary care, the associations between these alarming signs and serious infections were either weaker or were absent. Possible reasons for this lack of association include: (1) differences in patient populations; (2) the way a serious infection is diagnosed;[4] (3) that alarming symptoms may also occur in children with viral self-limiting infections; or (4) that primary care studies may include serious infections with a mild prognosis (*submitted*).

Nevertheless, until now the general practitioner's (GP) management is usually guided by the presence of alarming signs. The alarming signs published in the Dutch guideline and the NICE guideline for the assessment of a febrile child in primary care are based on research performed in secondary care only.[5,6] However, it is important to determine how frequently these alarming signs occur in febrile children presenting in primary care. Our hypothesis was that alarming signs frequently occur in this setting. If this is correct, this will contradict the reported low prevalence of serious infections in primary care and may influence the assumed diagnostic value of alarming signs for serious infections mainly based on research in secondary care. Therefore, this study determines the frequency of alarming signs in febrile children in a large primary care population.

METHOD

Study design

In this observational study, we prospectively collected semi-structured, routine clinical practice data of children who had presented to out-of-hours primary care with fever. The institution's medical ethics committee reviewed the study and the requirement for informed consent was waived (MEC-2012-378).

Out-of-hours health care system

In the Netherlands (as also in the United Kingdom, Scandinavia and Australia) out-of-hours primary care (5 p.m. to 8 a.m. daily and the entire weekend) is organized in large-scale cooperatives.[7-11] In the Netherlands, GPs rotate shifts at the GPCs to cover the out-of-hours primary care. Referral to the emergency department is required for about 5 to 10% of all primary care consultations,[7,12] which is similar to the referral rates in the United Kingdom, United States, and Canada.[13,14]

Study population

We selected all contacts of children <16 years of age that took place at the general practitioner cooperative (GPC) out-of-hours services in Rotterdam-Rijnmond between March 2008 and February 2009. This district has 5 GPCs (encompassing >250 GP services) providing out-of-hours care for almost 1 million inhabitants in this urban multi-ethnic area. All 5 GPCs used the same information system (Call Manager, Labelsoft, Zoetermeer, the Netherlands) to register patient data. In this information system, data on telephone triage, patient history, physical examination, diagnostic intervention, (working) diagnosis, and treatment or referral to the ED were documented as written text lines in a semi-structured data sheet. Eligible for inclusion were children with: (1) fever reported as the reason for contact; (2) fever within 24 hours prior to contact; or (3) a temperature >38°C measured at the GPC. All telephone consultations were excluded.

Extraction of relevant clinical signs

Signs and symptoms indicative of a serious febrile illness (i.e. alarming signs) were derived from one systematic review,[2] and two published guidelines on the management of febrile children.[5,6] We included signs which: (1) had a high predictive value (positive likelihood ratio >5.0 or negative likelihood ratio <0.2); (2) were mentioned in at least two of the three data sources; (3) did not represent a diagnosis; and (4) were not prone to high inter-observer variability (e.g. auscultatory sounds).[15] Selected, closely-related signs were grouped into a total of 18 alarming signs of serious febrile illness (Appendix 1, see page 68). Using a data-entry computer program (Embarcadero Delphi XE, Version 15.0, Embarcadero Technologies Inc. 2010), all eligible contacts were recoded to whether the grouped alarming signs were 'present', 'absent', or 'not mentioned' in the patient record.

Missing data

Since the alarming signs were obtained from routinely-collected, semi-structured data, missing values were present for each variable (i.e. not mentioned in the medical record). During a consensus meeting with 1 GP (MB), 2 paediatricians (HM, RO) and two residents (general practice (GE) and paediatrics (YvI)) it was decided to deal with missing values in two different ways for the purpose of this study: (1) the sign or symptom was believed to be so relevant that, if present, the physician would document it. Consequently, all missing values were interpreted as being absent. This was considered for the variables: ill appearance, ABC instability, unconsciousness, drowsy, inconsolable, cyanosis, shortness of breath, meningeal irritation, (febrile) convulsions, vomiting and diarrhea, dehydration, petechial rash, extremity problems; (2) for the remaining alarming signs (parental concern, abnormal circulation, signs of urinary tract infection, temperature ≤40°C, and duration of fever) it was decided that the above statements were not applicable, and the percentages of missing values were therefore reported.

Statistical analyses

Patient characteristics and alarming signs were analysed using descriptive statistics. In addition, the frequency of the alarming signs were provided for different age categories. Correlations were calculated using Pearson's correlation coefficient in order to determine which signs and symptoms were correlated. Data were analyzed using PASW version 17.0.2. for Windows (SPSS, Inc., Chicago, IL).

RESULTS

Description of the population

A total of 15,166 patient contacts concerned children with fever. After excluding the telephone consultations (N=4,418), 10,476 patient contacts were included in the analyses (Figure 1). Of these, 5,649 (53.9%) patient contacts concerned boys, overall median age was 2.2 (interquartile range (IQR): 1.0 to 4.5) years. Median rectal temperature measured at the GPC was 38.5°C (IQR: 37.7 to 39.1°C). Median duration of fever at the time of presentation was 2 days (IQR: 0 to 3).

Table 1 presents the frequency of the alarming signs per characteristic. The majority of the alarming signs were present in <5%; only vomiting and diarrhoea was present in more contacts (21%). Table 2 shows the percentage of missing values and registrations for the alarming signs, for which the assumption that 'not registered in the patient record' is not equivalent to 'not present'. When registered, the frequency of the alarming signs ranged from 6.3% (abnormal circulation) to 99.8% (parental concern). Table 3 shows the distribution of the alarming signs by age category. The presence of one or more alarming signs ranged from 49.1% to 61.6% in the various age categories. Overall, in 59.7% of the contacts one or more alarming signs were present (Table 4). Figure 2 shows which alarming signs are correlated with each other; the highest correlation coefficient was 0.353, which we consider to be relatively low.

TABLE 1 Presence of alarming signs during GPC contacts

ALARMING SIGNS	PRESENT		ABSENT	
	N	(%)	N	(%)
Ill appearance	428	(4.1)	10048	(95.9)
ABC-instability	1	(<0.1)	10475	(>99.9)
Unconsciousness	8	(0.1)	10468	(99.9)
Drowsy	57	(0.5)	10419	(99.5)
Inconsolable	426	(4.1)	10050	(95.9)
Cyanosis	48	(0.5)	10428	(99.5)
Shortness of breath	489	(4.7)	9987	(95.3)
Meningeal irritation	59	(0.6)	10417	(99.4)
Neurological signs	163	(1.6)	10313	(98.4)
Vomiting and diarrhoea	2207	(21.1)	8269	(78.9)
Dehydration	115	(1.1)	10361	(98.9)
Extremity problems	28	(0.3)	10448	(99.7)
Petechial rash	35	(0.3)	10441	(99.7)

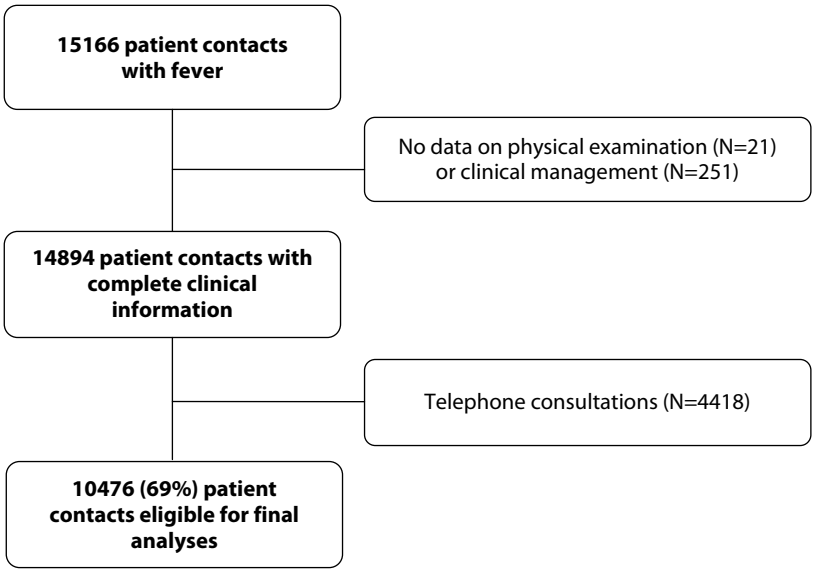

FIGURE 1 Selection of eligible contacts for the study

DISCUSSION

Statement of principal findings

The frequency of single alarming signs for serious infections in febrile children is relatively low and the majority of alarming signs were present in less than 5% of the contacts. However, in more than 50% of contacts one or more alarming signs were present. These findings are consistent across all age categories. Several signs and symptoms which are expected to be related to serious infections are often poorly registered.

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

TABLE 2 Presence and registration of alarming signs

ALARMING SIGNS	REGISTERED - PRESENT		REGISTERED - ABSENT		NOT REGISTERED	
	N	(% of N_{tot} registered)	N	(% of N_{tot} registered)	N	(% of N_{tot} = 10476)
Temperature >40°C (measured by GP)	321	(8.9)	3268	(91.1)	6887	(65.7)
Temperature >40°C (reported by parents)	2681	(29.4)	6448	(70.6)	1347	(12.9)
Parental concern	1825	(99.8)	4	(0.2)	8647	(82.5)
Abnormal circulation	176	(6.3)	2614	(93.7)	7686	(73.4)
Signs of UTI	520	(12.2)	3744	(8.8)	6212	(59.3)
Duration of fever >3 days	1589	(19.5)	6580	(80.5)	2307	(22.0)

GP: general practitioner; UTI: urinary tract infection.

TABLE 3 Alarming signs by age category

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

GP: general practitioner, UTI: urinary tract infection.

TABLE 4 Frequency of combined presence of alarming signs

NUMBER OF ALARMING SIGNS PRESENT	N	(%)
0	4224	(40.3)
1	3837	(36.6)
2	1711	(16.3)
3	545	(5.2)
4	116	(1.1)
5	31	(0.3)
6	10	(0.1)
7	2	(<0.1)

Strengths and weaknesses of the study

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

Also, because we excluded telephone consultations, our results may overestimate the prevalence of alarming signs in febrile children. Nevertheless, even if all children with a telephone consultation had no alarming signs, the prevalence of children with alarming symptoms is still 41.7%.

Findings in relation to other studies

The prediction rules reported in the literature base their predicted risk for a serious infection on multiple alarming signs.[2] In the present study, >50% of the children had one or more alarming signs present. This may have a negative effect on the specificity of the prediction rules in predicting serious infections. Since the incidence of serious infections is reported to be low in primary care,[16] the frequent occurrence of alarming signs will lead to a high false-positive prediction of a serious infection. Given the high prevalence of alarming signs, the low prevalence of serious infections, and the tendency in primary care to actively follow the course of disease in case of diagnostic uncertainty ('wait-and-see' management), we suggest that future research on alarming signs in primary care should be related to the prognosis of the underlying disease (i.e. hospital admission or duration of complaints), rather than the presence of a serious infection.

	Temperature >40°C (reported by parents; N=2681)	Vomiting and diarrhea (N=2207)	Parental concern (N=1825)	Signs of UTI (N=520)	Shortness of breath (N=489)	Ill appearance (N=428)	Inconsolable (N=426)	Temperature >40°C (measured by GP; N=321)	Abnormal circulation (N=176)	Neurological signs (N=163)	Dehydration (N=115)	Meningeal irritation (N=59)	Drowsy (N=57)	Cyanosis (N=48)	Petechial rash (N=35)	Extremity problems (N=28)	Unconsciousness (N=8)	ABC-instability (N=1)
Temperature >40°C (reported by parents)																		
Vomiting and diarrhea	0.024*																	
Parental concern	0.032**	0.024*																
Signs of UTI	0.005	0.023*	-0.017															
Shortness of breath	-0.019	-0.020*	-0.036**	-0.040**														
Ill appearance	0.070**	0.013	-0.013	0.015	0.085**													
Inconsolable	0.033**	0.020*	-0.010	-0.023*	0.074**	0.106**												
Temperature >40°C (measured by GP)	0.301**	0.003	0.012	0.008	0.005	0.084**	0.059**											
Abnormal circulation	0.002	0.036**	-0.001	0.011	0.087**	0.059**	0.048**	0.028**										
Neurological signs	0.002	-0.035**	0.046**	-0.018	-0.006	-0.006	0.041**	0.027**	0.026**									
Dehydration	0.007	0.107**	0.002	-0.011	0.029**	0.052**	0.062**	0.024*	0.115**	-0.013								
Meningeal irritation	0.014	0.008	-0.001	-0.011	0.032**	0.036**	0.152**	0.009	0.010	-0.009	0.041**							
Drowsy	-0.002	0.045**	0.004	0.001	0.008	0.057**	0.037**	0.009	0.081**	0.085**	0.191**	0.046**						
Cyanosis	-0.017	-0.014	-0.009	-0.016	0.173**	0.057**	0.000	0.004	0.090**	0.003	0.006	-0.005	0.014					
Petechial rash	-0.004	0.027**	-0.005	0.002	-0.005	0.013	0.038**	0.019	0.018	0.006	0.010	0.062**	-0.004	-0.004				
Extremity problems	-0.013	-0.013	-0.009	-0.003	-0.011	-0.001	-0.001	-0.009	0.008	-0.007	-0.005	-0.004	-0.004	-0.004	-0.003			
Unconsciousness	-0.016	-0.014	0.015	-0.006	0.010	-0.006	0.012	-0.005	0.077**	0.192**	-0.003	-0.002	0.186**	-0.002	-0.002	-0.001		
ABC-instability	-0.006	-0.005	0.021*	-0.002	0.044**	-0.002	0.047**	-0.002	0.075**	-0.001	-0.001	-0.001	-0.001	-0.001	-0.001	-0.001	0.353**	

: Correlation < +/-0,1

: Correlation >= +/-0,1 and < +/-0,3

: Correlation 0,3-0,4

*: Correlation $P < 0.05$

**: Correlation $P < 0.01$

FIGURE 5 Correlation between alarming signs
GP: general practitioner, UTI: urinary tract infection.

Meaning of the study

In conclusion, the frequency of specific alarming signs in primary care is relatively low. However, the proportion of children with more than one alarming sign is high. Further research in febrile children in primary care should not only determine the predictive value of alarming signs for serious infections, but also for an increased risk of a complicated course of the illness.

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APPENDIX 1 Grouping alarming signs into composed determinants of serious infection

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

CHAPTER 5

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

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ABSTRACT

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

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

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

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

Results Of the 8,676 included patients (median age 2.4 years), antibiotics were prescribed in 3,167 contacts (36.5%). Patient characteristics and alarming signs and/or symptoms positively related to antibiotic prescription were: increasing age (odds ratio (OR): 1.03; 95% confidence interval (95% CI): 1.02 to 1.05), temperature measured by GP (OR: 1.72; 95% CI: 1.59 to 1.86), ill appearance (OR: 3.93; 95% CI: 2.85 to 5.42), being inconsolable (OR: 2.27; 95% CI: 1.58 to 3.22), shortness of breath (OR: 2.58; 95% CI: 1.88 to 3.56), duration of fever (OR: 1.31; 95% CI: 1.26 to 1.35). Negative associations were found for neurological signs (OR: 0.45; 95% CI: 0.27 to 0.76), signs of urinary tract infection (OR: 0.63; 95% CI: 0.49 to 0.82), and vomiting and diarrhoea (OR: 0.65; 95% CI: 0.57 to 0.74). These variables explained 19% of the antibiotic prescriptions.

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

INTRODUCTION

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

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

METHOD

Study design

This cohort study used data of face-to-face patient contacts (physical consultations and home visits) of children aged <16 years that took place at GP cooperative out-of-hours services of Rotterdam-Rijnmond between March 2008 and February 2009 (N=28,234). This district has five GPCs (totalling >250 GP practices) providing out-of-hours care for almost 1 million inhabitants living in this urban, multi-ethnic area. All five GP cooperatives used the same information system ('Call Manager', Labelsoft, Zoetermeer, the Netherlands) to register patient data. In this system, information from telephone triage, patient history, physical examination, diagnostic intervention, (working) diagnosis, and treatment or referral is documented (by GPs and physician assistants) as written text lines in a semi-structured data sheet.

Out-of-hours health care system

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

Study population

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

Extraction of relevant clinical signs

Signs and symptoms that are indicative of a potential serious infection ('red flags') were derived from one systematic review,[2] and two published guidelines on management of febrile children.[5,6] The study included signs that: (1) had a high predictive value (positive likelihood ratio >5.0 or negative likelihood ratio <0.2); (2) were mentioned in at least two of the three data sources; (3) did not represent a diagnosis; and (4) were not prone to high interobserver variability (e.g. auscultatory sounds).[15] Selected, closely related signs were grouped into a total of 18 alarming signs of serious febrile illness (Appendix 1, see page 83). Using a data-entry computer program (Embarcadero Delphi XE, Version 15.0, Embarcadero Technologies Inc. 2010), all eligible contacts were recoded to whether the grouped alarming signs were 'present', 'absent', or 'not mentioned' in the patient record. In addition, 'referral to secondary care', or 'antibiotic prescription' by the GP was recoded as 'yes' or 'no.'

Missing data

Since the alarming signs and/or symptoms were obtained from routinely collected, semi-structured data, missing values occurred for each variable (that is, not mentioned in the record). Therefore, a consensus meeting was held, with one GP, two paediatricians, one GP trainee and one trainee paediatrician, to discuss this. Based on the prevalence of serious illnesses in the primary care setting, clinical experience and common knowledge, for the purpose of this study missing values were handled in two ways: (1) the sign or symptom was believed to be so relevant that, if present, the physician would document it. Consequently, all missing

values were interpreted as being absent (ill appearance, ABC (airways, breathing, circulation) instability, unconsciousness, drowsiness, being inconsolable, cyanosis, shortness of breath, meningeal irritation, neurological signs; that is, typical and atypical febrile convulsions, focal neurological signs - that is, typical and atypical febrile convulsions, focal neurological signs, vomiting and diarrhoea, dehydration, petechial rash, extremity problems); (2) for the remaining signs and symptoms (parental concern, abnormal circulation, signs of UTI, temperature ≥40°C, and duration of fever), it was decided that the above statements were not applicable. For these variables, multiple imputation was performed if missing data were <70%.[16] Signs and symptoms with ≥70% missing data were excluded from the analyses.

Statistical analyses

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

RESULTS

Description of the population

A total of 15,166 patient contacts at the five GP cooperatives concerned fever. Of 272 patient contacts, no data on physical examination or clinical management were available, and these were subsequently excluded. After applying the exclusion criteria, 8,676 patient contacts were available for the present analysis (Figure 1). In total, 3,167 of the contacts (36.5%) were prescribed antibiotics at the GP cooperative. Additional baseline characteristics of these patient are presented in Table 1. Figure 2 shows the distribution of antibiotic prescription by age, rectal temperature, and duration of fever.

TABLE 1 Characteristics of the study population

CHARACTERISTICS		
Age in years (median, IQR)	2.4	(1.1-4.7)
Male gender (N, %)	4601	(53)
Rectal temperature in °C (median, IQR)	38.4	(37.7-39.1)
Antibiotic prescription (N, %)	3167	(36.5)
Duration of fever in days[a] (median, IQR)	2.0	(0-3)

IQR: interquartile range.
[a] N = 6933 contacts.

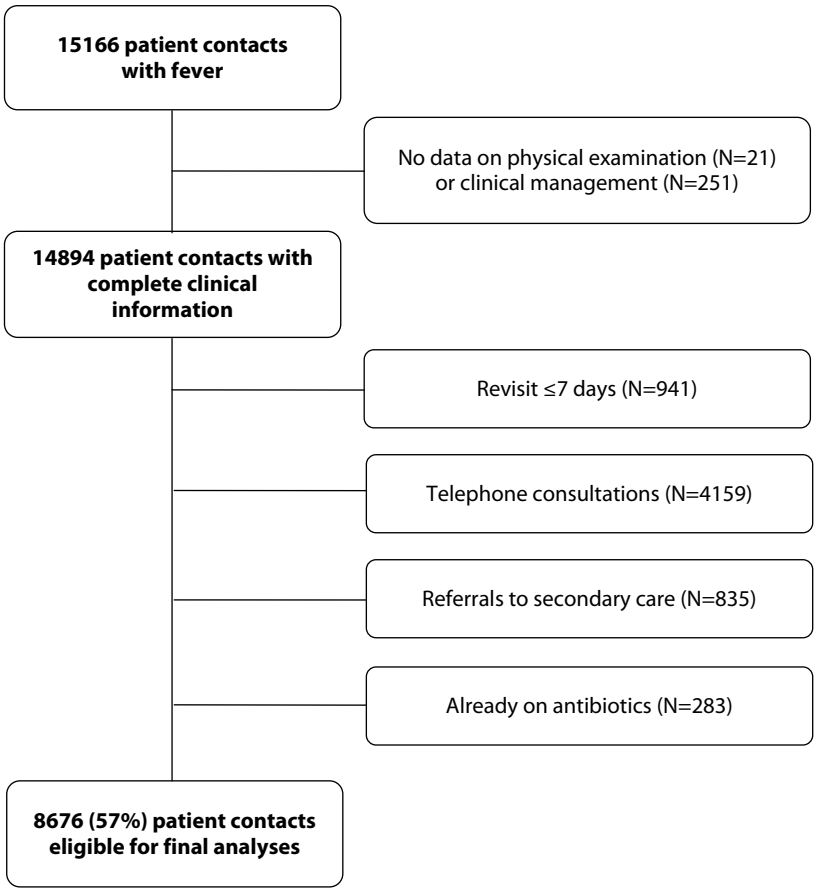

FIGURE 1 Selection of eligible patient contacts

Multivariate logistic regression

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

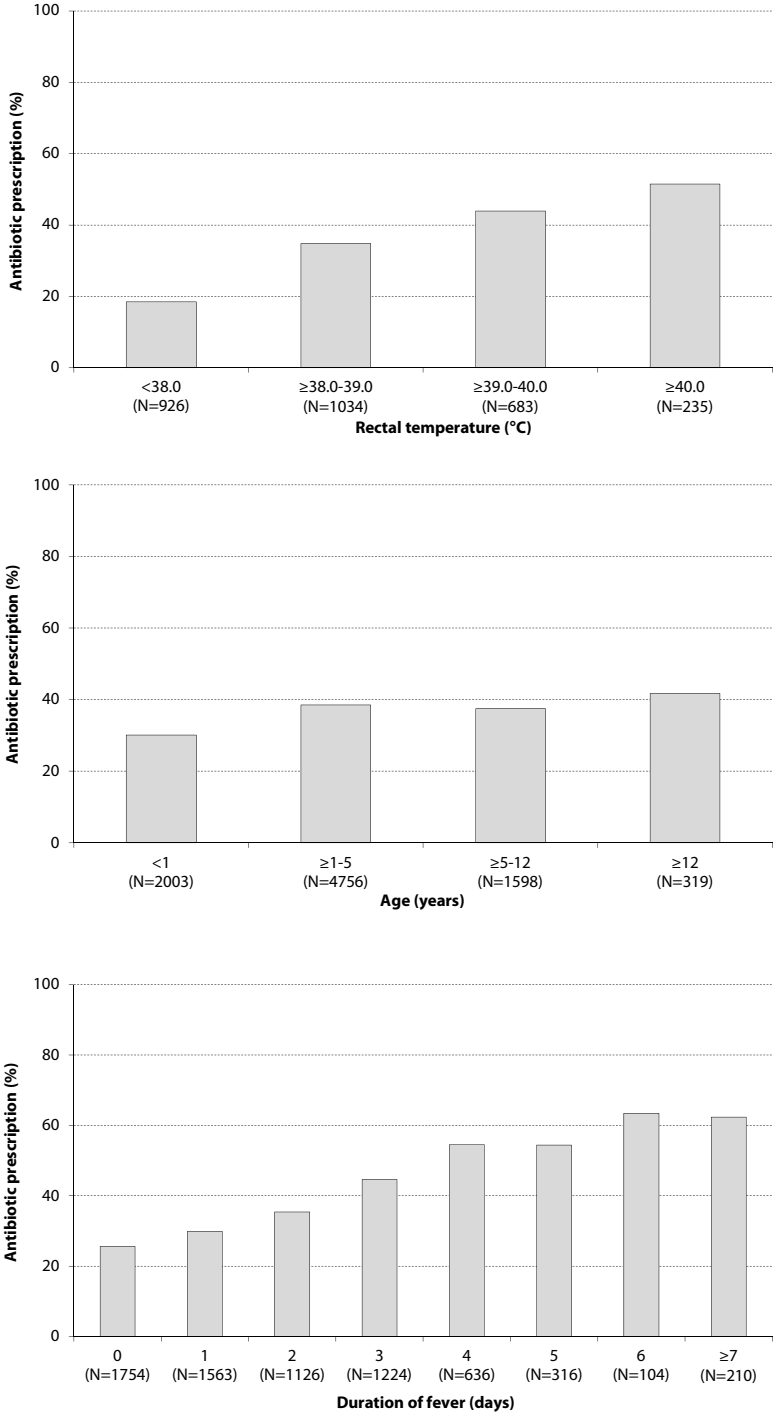

FIGURE 2 Distribution of percentage antibiotic prescription by age group, rectal temperature, and duration of fever

TABLE 2 Alarming signs and symptoms and prescribed antibiotics

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

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

TABLE 3 Multivariate analysis of alarming signs and symptoms that were significantly related to antibiotic prescription

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

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

DISCUSSION

Summary

This large study, evaluating 8,676 face-to-face contacts of febrile children presenting at five GP cooperatives, shows that antibiotics were prescribed in 36.5% of the patient contacts. Multivariate analysis revealed that several alarming signs and/or symptoms were significantly related to antibiotic prescription, suggesting that treating a potentially serious bacterial infection is a consideration of the GP. However, the relatively low explained variation (R^2 = 0.19) shows that other considerations, not included in the analysis, also made a substantial contribution.

Strengths and limitations

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

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

The GPs did not record the signs and symptoms in a fully structured way. Therefore, when a characteristic was not recorded, it is possible that the variable was absent and that the GP did not write it down, or that the GP did not look for that particular sign or symptom. This problem was discussed in a consensus meeting including specialists in family medicine and paediatrics. It seems legitimate to consider some signs (e.g. unconsciousness) as being absent when the GP did not report this, since if that sign had been present the GP would always notice and record it. This is especially so since the Dutch guideline specifically advises to look for the various alarming signs and/or symptoms when assessing a febrile child.[5]

Comparison with existing literature

In the present study, the amount of prescribed antibiotics (36.5%) is similar to the 36.3% prescribed in a previous study.[4] Although this latter study was performed in younger children, overall it is similar to the present one with regard to the setting, study population, and clinical guidelines used. When selecting the same age category in the present study, 35.0% of children aged 3 months to 6 years were prescribed antibiotics (2,629/7,514), that is, a rate very similar to the earlier report.

Surprisingly, increasing age was significantly related to antibiotic prescription. This was unexpected since younger children are more at risk for a serious infection, and therefore

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

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

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

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

The present study shows that only a small proportion of the antibiotic prescriptions is explained by the related alarming signs and symptoms. This is not surprising, since other clinical features may also contribute to considering whether to prescribe antibiotics (e.g. otorrhoea, bulging tympanic membrane).[25-28] Unfortunately, information on these clinical features was not available in this study, and could therefore not be included in the analyses. The explained variation of antibiotic prescriptions might have been higher, if these variables could have been added. This assumption was confirmed by the previous study in a similar setting, in which it was shown that variables like signs of throat infection or earache are also related to antibiotic prescription.[4] In that study, multivariate analysis explained 26% of the proportion of variation. Hypothetically, in the most positive perspective, 45% of the variation in antibiotic prescription is explained by the two studies; however, this is not actually the case, since there is some overlap in the signs and symptoms (e.g. ill appearance). This indicates that in ≥55% of the prescribed antibiotics other (unknown) factors contribute to the GP's decision to prescribe antibiotics. Earlier studies found that non-medically based considerations may also contribute to the GP's decision to prescribe antibiotics, e.g. assuming that the patient or the parents expect antibiotics.[29-31] However, these assumptions are not always valid,[32-34] and GPs may need to reconsider their management of febrile children.

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

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

Signs of UTI were significantly related to less antibiotic prescription; this is surprising because a UTI is a clear indication for antibiotics.[39] However, this result can be explained by the fact that this variable is composed of several signs, including pollakisuria, dysuria, and abdominal pain without diarrhoea or other focus of the fever (Appendix 1, see page 83). This may explain the lack of a significant relation between signs of UTI and antibiotic prescription. Another, more disturbing, explanation may be that GPs do not endorse the signs and/or symptoms of a possible UTI. Recognition and treatment of UTIs in children is important since they can cause transient or permanent kidney damage.[40,41]

Implications for research and pratice

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

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APPENDIX 1 Grouping alarming signs into composed determinants of serious infection

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

CHAPTER 6

The role of alarming signs in referral management of febrile children consulting primary out-of-hours care

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ABSTRACT

Background The diagnostic value of alarming signs of serious infections in low prevalence settings is unclear.

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

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

Method We performed logistic regression analyses to assess the association between alarming signs of serious infections (selected from two guidelines and one systematic review) and referral to the ED. Adherence to the guideline was explored by a 2x2 contingency table.

Results 794 (8.1%) of 9,794 eligible patients were referred to the ED. Alarming signs most strongly associated with referral were 'age <1 month', 'decreased consciousness', 'meningeal irritation', and 'signs of dehydration'. Nineteen percent of 3,424 children with a *positive* referral indication according to the guideline were referred to the ED. The majority of those not referred had only one or two alarming signs present. A *negative* referral indication was adhered to for the majority of children. Still, in 20% of referred children, alarming signs were absent.

Conclusion In the majority of consultations, GPs did not adhere to a positive referral advice by the guideline for febrile children, particularly not if only one or two alarming signs were present. Besides, in 20% of referred children alarming signs were absent. This suggests that other factors than alarming signs alone seem important in decisions on referral management.

INTRODUCTION

In primary care, general practitioners (GPs) frequently encounter febrile children, who are at risk of serious infections (e.g. meningitis, sepsis, pyelonephritis)[1,2], which can lead to morbidity and mortality.[3-5] The combined prevalence of serious infections in primary care is less than 1%.[6] GPs stand for the challenging task of distinguishing the large group of children with a low risk of serious infection from the minority at high risk and requiring further action.
Studies on identifying serious infections in low prevalence settings are scarce.[6-9] Current clinical guidelines supporting GPs in handling febrile children are predominantly based on consensus and evidence from hospital emergency care studies, which lack external validation in low-prevalence settings.[7,9] The International NICE guideline for children with feverish illness[10,11] proposes a traffic light system, which advises to refer a child for specialist consultation if either a 'red' (high risk) or 'orange' (intermediate risk) feature is present. Likewise, the Dutch national guideline for febrile children consulting primary care[12] also bases its referral advice on the presence of single alarming signs (all of which are also classified as 'red' or 'orange' features in the NICE guideline[10]). Recently, a systematic review of mainly hospital emergency care studies, identified many of these alarming signs as potentially useful in identifying children at high risk of serious infection.[13] Still, much debate is going on about the diagnostic value of these signs in low prevalence settings.[7,8,13]
In this study we aimed to explore to what extent alarming signs play a role in referral management of GPs, who face a febrile child in primary out-of-hours care.

METHODS

Study design

In this observational study, we collected semi-structured, routine clinical practice data of children with fever who had presented to GP out-of-hours care. We assessed how strongly alarming signs of serious infection were associated with referral management of GPs and to what extent GPs adhered to the national guideline's advice on referral.

Study settings and patient selection

Details on out-of-hours health care in the Netherlands and data collection of this study have been published previously.[14] In short, data were available for all patient contacts which had taken place at five GPCs of the Rotterdam Rijnmond-district between March 2008 and February 2009. We selected all contacts of children (<16 years), who had a physical consultation by the GP and fever (temperature >38.0ºC). We excluded revisits for the same problem within 7 days of the initial presentation (Figure 1).

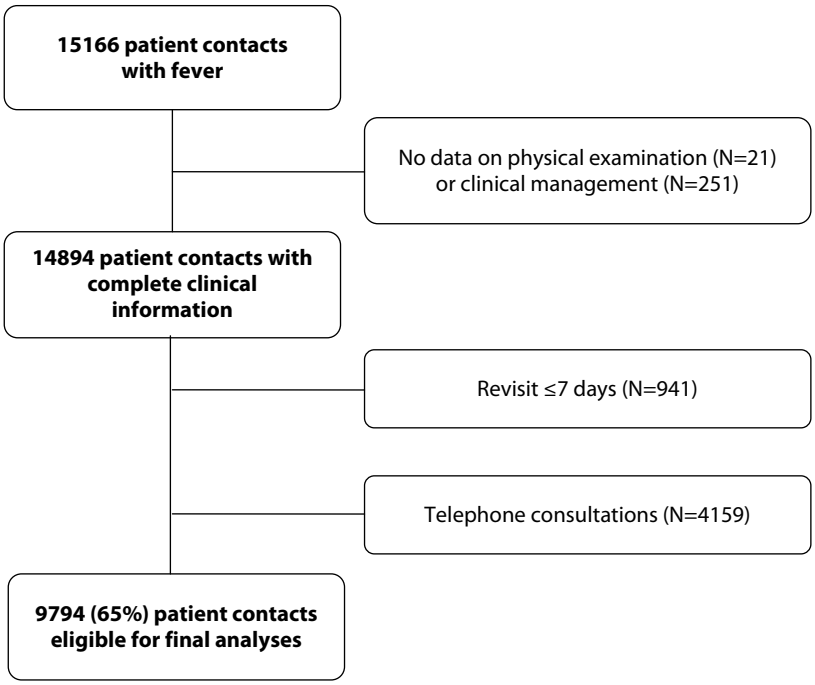

FIGURE 1 Selection of eligible contacts

Extraction of alarming signs of serious infections

Clinical features indicative for a serious infection were derived from (1) the Dutch national GP guideline for febrile children[12]; (2) the international NICE traffic light system for identifying febrile children at risk of a serious infection[10]; and (3) a systematic review, which summarized all evidence-based alarming signs for serious infections in children.[13] Details on selection of the clinical features included in the study were reported previously.[14] Selected, closely-related features were grouped into 18 alarming signs of serious infection (Appendix 1, see page 99). We manually recoded whether alarming signs were 'present', 'absent' or 'not mentioned' in the patient record, using a data-entry computer program (Embarcadero Delphi XE, Version 15.0, Embarcadero Technologies Inc. 2010). Clinical management by the GP was recoded as 'referral to ED (yes/no)'.

Statistical analyses

Missing data

Since clinical information was obtained from routine practice data, we had to deal with missing values (Table 1).[14] In short, we decided for the purpose of this study, to deal with missing values in two ways: (1) alarming signs were assumed to be so relevant that, if present, the GP would document them. Consequently, signs 'not mentioned' in the patient record were considered 'absent' (i.e. ill appearance, ABC instability, unconsciousness, drowsy, inconsolable, cyanosis, shortness of breath, meningeal irritation, neurological signs, vomiting and diarrhea, dehydration, extremity problems, and petechial rash); (2) for the remaining alarming signs we imputed missing values ten times using the MICE logarithm (R-Project) (i.e. abnormal circulation, signs of urinary tract infection, temperature ≥40°C, and duration of fever). The imputation model included gender, age, and all alarming signs included in the analyses (describing case-mix of the population) and the outcome variable 'referral to the ED'. Results of the imputation procedure are displayed in Appendix 2 (see page 100). Features which were not explicitly mentioned in the national guideline and which had a high percentage of missing values (>70%) were excluded from the analyses (i.e. parental concern and vital signs).

Association between alarming signs and referral management

Firstly, we focused on our national guideline[12], which advises to refer a febrile child to secondary care if at least one alarming sign is present. Guideline definitions of the alarming signs 'age below 1 month', 'abnormal circulation', 'meningeal irritation', 'petechial rash', and 'signs of dehydration' matched with those of our dataset. For the other guideline features, we had to combine alarming signs or use best proxies. We selected 'age between 1-3 months' as a proxy for the guideline feature 'age between 1-3 months and fever of unknown origin', 'ill appearance and/or inconsolable and/or ABC-instability' as a proxy for 'ill appearance', 'unconsciousness and/or drowsy' as a proxy for 'decreased consciousness', 'vomiting and diarrhea' as a proxy for 'persistent vomiting', and 'shortness of breath and/or cyanosis' as a proxy for 'severe shortness of breath'.

We performed logistic regression analyses to assess the association between the national guideline-specific alarming signs and referral to the ED. For the multivariable analyses, we used multiple imputed data, as much relevant clinical information would be lost by performing a complete case analyses only. Next, our regression analyses were extended by the addition of alarming signs selected from the NICE guideline[10] and a systematic review.[13]

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

TABLE 1 Characteristics of study population

BASIC CHARACTERISTICS			RANGE
Female gender (N (%))	4521	(46.2)	
Age in years (median, IQR)	2.3	(1.0 - 4.6)	0.02 - 16
Temperature at GPC in °C[a] (median, IQR)	38.5	(37.7 - 39.1)	35.5 - 41.3
ALARMING SIGNS	**PRESENT**		**ABSENT**
	N	**(%)**	**N (%)**
Parental concern[a]	1665	(17.0)	4 (<0.1)
Ill appearance	389	(4.0)	9405 (96.0)
ABC-instability	1	(<0.1)	9793 (>99.9)
Unconsciousness	8	(0.1)	9786 (99.9)
Drowsy	53	(0.5)	9741 (99.5)
Inconsolable	384	(3.9)	9410 (96.1)
Abnormal circulation[a]	162	(1.7)	2424 (24.7)
Cyanosis	46	(0.5)	9748 (99.5)
Shortness of breath	465	(4.7)	9329 (95.3)
Meningeal irritation	55	(0.6)	9739 (99.4)
Neurological signs	152	(1.6)	9642 (98.4)
Vomiting and diarrhoea	2073	(21.2)	7721 (78.8)
Dehydration	96	(1.0)	9698 (99.0)
Extremity problems	27	(0.3)	9767 (99.7)
Signs of UTI[a]	499	(5.1)	3467 (35.4)
Petechial rash	34	(0.3)	9760 (99.7)
Temperature ≥40°C[a]	2462	(25.1)	6093 (62.2)
Duration of fever[a]			
started today	2008	(24.9)	
1 day	1729	(21.4)	
2 days	1228	(15.2)	
3 days	1325	(16.4)	
4 days	700	(8.7)	
5 days	731	(9.1)	
6 days	120	(1.5)	
≥7 days	230	(2.8)	
OUTCOME MEASURE	**YES**		**NO**
	N	**(%)**	**N (%)**
Referral to ED	794	(8.1)	9000 (91.9)

N: number of contacts; IQR: interquartile range; GPC: general practitioner cooperative; ABC: airway, breathing, circulation; ED: emergency department.

[a] Missing values for: Temperature at GPC: 6426 (65.6%); Parental concern: 8125 (83.0%); Abnormal circulation: 7208 (73.6%); Signs of UTI: 5828 (59.5%); Temperature≥40°C: 1239 (12.7%); Duration of fever: 2073 (21.1%).

TABLE 2 Associations between the presence of alarming signs and referral by the GP

ALARMING SIGNS ACCORDING TO NATIONAL GUIDELINE		NICE TRAFFIC LIGHT SYSTEM[10]	POSITIVE LR >5 IN SYSTEMATIC REVIEW[12]	REFERRED (N=794)	NON-REFERRED (N=9000)	UNIVARIATE OR[a]	ADJUSTED OR[b,d]	ADJUSTED OR[b,e]
				N (%)	N (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Age < 1 month	yes	red	no	25 (3.1)	7 (0.1)	42 (18 - 97)	64 (26 - 161)	78 (30 - 205)
Age between 1-3 months	yes	red	no	74 (9.3)	98 (1.1)	9.4 (6.8 - 13)	11 (7.8 - 17)	15 (9.8 - 23)
Ill appearance	present	red	yes	255 (32)	463 (5.1)	8.7 (7.3 - 10)	6.8 (5.4 - 8.6)	7.7 (6.0 - 9.8)
Decreased consciousness	present	red	yes	53 (6.7)	4 (<0.1)	161 (58 - 446)	134 (45 - 399)	117 (37 - 369)
Abnormal circulation	present	red	yes	71 (25)	91 (4)	8.1 (5.7 - 11)	3.9 (2.4 - 6.4)	3.4 (1.9 - 5.8)
Persistent vomiting	present	red (if bile-stained)	no	231 (29)	1842 (21)	1.6 (1.4 - 1.9)	1.3 (1.1 - 1.7)	1.5 (1.2 - 1.9)
Petechial rash	present	red	yes	15 (1.9)	19 (0.2)	9.1 (4.6 - 18)	12 (5.3 - 28)	12 (4.9 - 28)
Meningeal irritation	present	red	yes	49 (6.2)	6 (0.1)	99 (42 - 231)	90 (36 - 229)	121 (47 - 315)
Severe shortness of breath	present	orange/red	yes	213 (27)	270 (3.0)	12 (9.7 - 15)	12 (8.9 - 15)	16 (12 - 21)
Signs of dehydration (all ages)	present	orange/red	no	78 (9.8)	18 (0.2)	54 (32 - 91)	41 (22 - 77)	58 (31 - 110)
OTHER EVIDENCE-BASED ALARMING SIGNS[c]								
Neurological signs	present	red	yes	43 (5.4)	109 (1.2)	4.7 (3.3 - 6.7)		7.2 (4.2 - 12)
Extremity problems	present	orange	N/A	17 (2.1)	10 (0.1)	20 (9.0 - 43)		56 (23 - 133)
Signs of UTI[a]	present	N/A	no	77 (22)	422 (12)	2.2 (1.7 - 2.9)		3.8 (2.6 - 5.4)
Temperature ≥ 40°C[a]	present	N/A	yes	188 (26)	2274 (29)	0.9 (0.7 - 1.0)		0.9 (0.7 - 1.2)
Duration of fever in days[a] (median, IQR)	per day	orange (if ≥5 days)	no	2 (0-3)	1 (0-3)	0.9 (0.9 - 1.0)		1.0 (0.9 - 1.1)

[a] Univariate analyses was performed on complete case analyses for 'abnormal circulation' (Ntot=2586); 'signs of UTI' (Ntot=3966) ; ' temperature≥40°C' (Ntot=8555) and 'duration of fever', truncated at the 97.5th percentile (= 7 days; Ntot=8071).
[b] Multivariate analyses was performed on the multiple (10x) imputed dataset (Ntot=9794).
[c] Other evidence-based alarming signs for serious infections were selected from Van den Bruel et al.[12] and the NICE Guideline for febrile children.[10]
[d] Nagelkerke's R^2 (median) = 0.40.
[e] Nagelkerke's R^2 (median) = 0.45.

RESULTS

Characteristics of the study population are displayed in Table 1. In total, 794 (8.1%) of 9,794 contacts were followed by a referral to the ED. Frequencies of individual alarming signs were generally higher among referred than non-referred children (Table 2). Among the alarming signs selected from the national guideline, 'age below 1 month', 'decreased consciousness', 'meningeal irritation', and 'signs of dehydration' were most strongly associated with referral. Together, the guideline-specific alarming signs explained 40% of the variability in referral by the GP. Among the alarming signs selected from the NICE guideline and the systematic review, 'extremity problems' were most strongly associated with referral to the ED.

Adherence to the guideline

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

Table 4 shows the number of alarming signs present in children with a *positive* referral indication. The majority of children for whom the GP overruled the guideline's advice (i.e. decided *not* to refer the child) had one or two alarming signs present. When ≥3 alarming signs were present, nearly all children were referred. Alarming signs that were predominantly overruled by GPs were 'vomiting', 'ill appearance', 'abnormal circulation' and 'shortness of breath'.

TABLE 3 GPs' referral management and guideline adherence

REFERRAL INDICATION ACCORDING TO THE NATIONAL GUIDELINE[a]	OBSERVED IN PRACTICE (N)		TOTAL (N)
	Referred	Non-referred	
Yes	633	2791	**3424**
No	161	6209	**6370**
Total (N)	**794**	**9000**	**9794**

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

TABLE 4 Alarming signs among febrile children *with* a referral indication according to the national guideline

TOTAL NUMBER OF ALARMING SIGNS PRESENT[a]	REFERRED (N=633)		NON-REFERRED (N=2791)	
	N	(%)	N	(%)
1	264	(42)	2456	(88)
2	214	(34)	304	(11)
3	118	(19)	29	(1.0)
4	33	(5.2)	2	(<0.1)
5	4	(0.6)	0	(0)
ALARMING SIGNS PRESENT				
Age < 1 month	25	(4.0)	7	(0.3)
Age between 1-3 months	74	(12)	98	(3.5)
Ill appearance	255	(40)	463	(17)
Decreased consciousness	53	(8.4)	4	(0.1)
Abnormal circulation	205	(32)	431	(15)
Vomiting	231	(37)	1842	(66)
Petechial rash	15	(2.4)	19	(0.7)
Meningeal irritation	49	(7.8)	6	(0.2)
Severe shortness of breath	213	(34)	270	(9.7)
Signs of dehydration	78	(12)	18	(0.6)

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

CONCLUSION

Summary

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

Strengths and limitations

By our best knowledge, this study is the first to give insight in associations between guideline and literature-based alarming signs and GP's referral management in primary out-of-hours care practice.

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

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

As prospective data collection in low prevalence settings is difficult, we made use of routine clinical practice data. Consequently, alarming signs 'not mentioned' in the patient record could either mean 'not present' or 'not looked at by the physician'. In a consensus meeting, we decided to use a multiple imputation strategy to limit the amount of clinical information lost and to best approximate true values. A sensitivity analyses on complete cases revealed no major differences in outcomes (data not shown).

GPs may have justified their referral decisions by more clearly documenting the alarming signs in the patient record of referred children (i.e. verification bias). This may have led to an overestimation of the reported associations. As alarming signs such as 'ill appearance' and 'abnormal circulation' were also frequently observed among non-referred children, we assume this bias to be limited.

Comparison with existing literature

Several individual alarming signs have been demonstrated to have potential value in identifying ('ruling-in') serious infections in children.[13] Their applicability, however, depends on the setting-specific prevalence of disease. Taking into account the low prior probability of serious infection in primary care (~1%), the majority of individual alarming signs will only raise the posterior probability to about 10% when present.[13] As these results were only based on a single primary care study, which lacks external validation, their generalizability to and diagnostic impact in other low prevalence populations may be questioned.[9,15]

Still, both our national guideline[12] and the international NICE guideline[10] base their referral advice on the presence of single alarming signs. From the safe-side perspective, this may seem a valid approach, however the disadvantage may be a considerable overload of children who present at the ED without a serious infection (i.e. false positives). In our study, we observed that if one should follow the national guideline, 35% of all children consulted should be referred.

Comparable results were reported by others, who validated our national guideline as well as the NICE guideline in low[16] and intermediate prevalence populations.[16,17] They also found that the vast majority of febrile children consulted, received a positive referral indication (range 16-99%). Consequently, this yielded high sensitivities (range: 81 to 100%), whereas specificities were dramatically low for some (range: 1 to 85%).

Luckily, in clinical practice, we observed that GPs only referred 19% of the patients with a positive referral indication, of whom the majority had three or more alarming signs present. 'Meningeal irritation' and 'decreased consciousness' were nearly ever neglected as alarming sign, whereas 'ill appearance' and 'abnormal circulation' were quite a few times overruled. This may suggest that some features have a broader clinical range in primary care as compared with high prevalence settings, where these signs were identified as important indicators of serious infection.[13] From these results, it seems that GPs already apply a certain threshold above which they feel their referral is grounded (i.e. they balanced the risk between false positive and false negative outcomes). Besides, they seem to share the opinion that combinations of alarming signs may do better in ruling-in serious infections than single signs alone. In line with this finding, others have recently reported on the diagnostic value of three or more 'red features' of the NICE traffic light system (personal communication, E. Kerkhof, August 2013, article submitted). Unfortunately, the posterior probability of disease was still unsatisfactorily raised to a maximum of about 10% in low prevalence settings specifically.

Should we then better shift our focus towards ruling-out serious infections in low-prevalence settings? Previous reports have indicated that individual alarming signs have insufficient rule-out value on their own.[6,7,13] Combinations of absent alarming signs may however significantly decrease the probability of disease.[13] For the majority of children without alarming signs present, the GPs in our study seemed quite confident about the absence of a serious infection. The difficulty, however, lies in determining the threshold of exactly how many signs must be absent to sufficiently rule-out serious febrile illness. Clinical prediction rules (CPRs) may, next to guidelines, help physicians identifying children at low risks of disease.[18-24] The only CPR developed for primary care specifically showed a promising high sensitivity and low negative likelihood ratio at derivation[6], however lacked generalizability on external validation in other low-prevalence populations.[16] In addition, we have shown that other CPRs developed for hospital emergency care were of limited use in the primary out-of-hours care setting as well (*Chapter 8*).

Lastly, our study demonstrated, that 20% of the referred children had no alarming sign present. This suggests that other reasons seem important in GPs' referral management. Even though beyond the scope of this article, one may speculate that for example the physician's gut feeling or a worried parent may be valid candidates[6], as well as an insufficient safety-net at home.

Implications for research and practice

Even though the exact harms and benefits of currently used clinical guidelines should be further elucidated, the question rises whether it is possible to develop a guideline with only clinical signs that sufficiently rules-in or rules-out serious infections in children consulting primary care. Future studies may answer this question by focusing on (1) the exploration of alternative reasons of GPs to refer a febrile child; (2) the potentially additive value of inflammatory marker point-of-care tests (e.g. CRP) to guidelines or clinical prediction rules, as these have shown promising results in adult primary care studies as well as studies performed at pediatric EDs[25-27]; and (3) exploration of disease course over time in longitudinal follow-up studies, to provide future guidelines with adequate safety-netting advices to fill the gap of insufficient rule-in or rule-out value reached by clinical alarming signs alone.

Conclusion

In contrast to the guideline's advice, GPs working in primary out-of-hours care seem more conservative in referring febrile children to the ED, especially if only one or two alarming signs of serious infection are present. Besides, in 20% of referred children, alarming signs were absent, which suggests that other factors may be important in decisions on referral of febrile children to the hospital ED.

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APPENDIX 1 Grouping of alarming signs for serious infection

GROUPED ALARMING SIGNS	TOTAL SELECTION OF ALARMING SIGNS
Parental concern	Parental concern
Ill appearance	Clinician's instinct something is wrong Clinically ill appearance
ABCD-instability	ABCD-instability
Unconsciousness	Unconsciousness
Drowsy	Child is drowsy Somnolence Reactivity/functional status (decreased) Hypotonia
Inconsolable	Child is inconsolable Irritability Changed crying pattern Child is moaning
Abnormal circulation	Abnormal skin color (pale, mottled, ashen) Capillary refill time >2 sec Tachycardia
Cyanosis	Cyanosis Oxygen saturation <95%
Shortness of breath	Shortness of breath Nasal flaring Rapid breathing Changed breathing pattern
Meningeal irritation	Meningeal irritation Neck stiffness Bulging fontanelle
Neurological signs	Focal neurological signs Paresis/paralysis Seizures/fits
Vomiting & diarrhoea	Vomiting (>2x in disease period) Diarrhea (>2x in disease period)
Dehydration	Dry mucous membranes Sunken eyes Decreased skin elasticity Reduced urine output Hypotension (APLS) Poor feeding
Extremity problems	Swelling of limb or joint Non-weight bearing limb Not using an extremity
Signs of urinary tract infection	Pollakisuria Dysuria Tummy ache (without other focus for fever)
Petechial rash	Petechial rash Purpura
Temperature ≥40°C	Measured at home or at GPC
Duration of fever	Duration of fever (>38.0°C) in days

APPENDIX 2 Results of the multiple imputation procedure

ALARMING SIGNS	PRESENT		ABSENT	
	N	(%)	N	(%)
Temperature at GPC in °C (mean, SE)	38.4	(0.02)		
Abnormal circulation	636	(6.5)	9158	(93.5)
Signs of UTI	1213	(12.4)	8581	(87.6)
Temperature ≥40°C	2811	(28.7)	6983	(71.3)
Duration of fever				
Started today	2560	(26.1)		
1 day	2199	(22.5)		
2 days	1543	(15.8)		
3 days	1669	(17.0)		
4 days	885	(9.0)		
5 days	451	(4.6)		
6 days	154	(1.6)		
≥7 days	333	(3.4)		

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

CHAPTER 7

Alarming signs in the Manchester Triage System: a tool to identify febrile children at risk of hospitalization

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ABSTRACT

Objectives To assess whether the flowcharts and discriminators of the Manchester Triage System (MTS) can be used as indicators of alarming signs of serious febrile illness to predict the risk of hospitalization for febrile children who present at the emergency department (ED).

Study design Observational study, which included 2,455 children (<16 years) who came to the ED of a university hospital with fever as their main complaint (May 2007 to July 2009). Alarming signs for serious febrile illness were matched with MTS flowcharts and discriminators. At triage, the percentage of alarming signs positive was calculated. The diagnostic ability of the percentage of alarming signs positive to identify children at risk of hospitalization was assessed by calculating positive and negative likelihood ratios.

Results Thirty percent of children had at least 1 alarming sign positive at triage. Twenty-three percent were hospitalized. Positive likelihood ratios of hospitalization were 5.0 (95% CI: 3.9 to 6.5) for children with >20% of alarming signs positive at triage and 12.0 (95% CI: 5.2 to 27.6) for those with >40% of alarming signs positive. Negative likelihood ratios were 0.8 (95% CI: 0.8 to 0.8) and 1.0 (95% CI: 0.9 to 1.0), respectively.

Conclusions By alternatively using the flowcharts and discriminators of the MTS as alarming signs, rather than urgency classifiers, the MTS can function as a simple, readily available tool to identify febrile children at risk of hospitalization early in the care process. This knowledge may help to improve ED throughput times as well as admission and discharge management at pediatric EDs.

INTRODUCTION

Pediatric emergency departments (EDs) are becoming more and more crowded.[1] Febrile children constitute one of the major patient groups at pediatric EDs and are at risk of serious illnesses, like meningitis, sepsis, or pneumonia.[2,3] Prevalence of such infections ranges from about 7 to 15%.[2-5] Early detection of serious febrile illnesses is important, because delaying or missing such diagnoses may lead to morbidity or even mortality and hospitalization is often required.[6-8] Recently, a systematic review has identified several alarming signs for serious illnesses in children with fever.[2]

Because the need for strategies to improve patient flows at pediatric EDs is growing, Asplin *et al*. have proposed a conceptual input-throughput-output model to find areas for improvement of ED work flows.[9] One of the model's suggestions is that if one can already predict whether a patient will likely be admitted during the intake-phase (e.g. triage), timeliness of admission to the ward or discharge management can be improved.[1,9]

The Manchester Triage System (MTS)[10,11] is implemented in a large scale and used to prioritize patients according to acuity.[3,12-16] The MTS contains flowcharts (presenting problem) and discriminators (other signs and symptoms) for triage of both adult and pediatric patients and collects clinical information at the moment of presentation at the ED.

This study aimed to assess whether the flowcharts and discriminators of the MTS can be used as indicators of alarming signs of serious febrile illness, rather than urgency classifiers alone, to predict the risk of hospitalization for febrile children who present at the ED.

PATIENTS AND METHODS

This observational study is part of an ongoing study on validation of the MTS, for which standardized clinical information is prospectively and electronically collected.[12,17] The institution's medical ethics committee approved the study and the requirement for informed consent was waived.

We included all children up to 16 years of age who had come to the ED of the Sophia Children's Hospital, Rotterdam, the Netherlands, from May 2007 to July 2009. This ED is part of the Erasmus University Medical Center and provides care to approximately 9,000 children annually (i.e. 50% general pediatrics, 40% surgery, 10% other specialties).[18] Eligible contacts were those who had general pediatric problems and: (1) fever as the reason for contact; (2) fever selected as triage discriminator; or (3) a rectal temperature ≥38.5°C measured at the ED. Revisits for the same complaint within 7 days were excluded, as were children who died at the ED.

All children who presented at the ED were routinely triaged with the MTS. The MTS consists of 49 flowchart-diagrams which represent main problems with which children present to the ED (e.g. 'crying baby' or 'shortness of breath'). Each flowchart is built up of a specific combination of discriminators (i.e. signs and symptoms which often go hand-in-hand with the presenting

problem). Within each flowchart, the discriminators are arranged from most urgent (U1, top) to least urgent (U5, bottom) (Figure 1). At triage, trained nurses first have to select the most appropriate flowchart for the child. Next, the patient's urgency level is assessed by selection of the most relevant discriminator, starting from the top of the flowchart moving downwards. For the purpose of this study, triage nurses also had to indicate whether the other discriminators within the flowchart were present or absent ('triage remaining items'). In our hospital, a modified version of the first edition of the MTS (official Dutch translation)[10] was used, which contained several adjustments for triage of febrile children.[19] Compliance with triage was 97% (7,311/7,573). Inter-rater agreement (agreement in triage urgency level if multiple nurses triage one patient) and intra-rater agreement (agreement in triage urgency level if one triage nurse triages one case scenario at different time points) have been shown to be good for the MTS, both at our own ED and other setting[20,21] and were not influenced by nurses' work experience.[21] Patient's characteristics, selected flowchart, selected discriminators, urgency category, and hospitalization were extracted from the computerized MTS. Medical records were checked manually for children who missed one or more triage remaining items (N = 262; 3.5%). For 47 (1.8%) patients some triage remaining items remained missing and were assumed to be absent. Among all evaluated in the ED, 0.5% left before being seen by a physician. These patients were not followed-up, because this number was very small and will not have influenced our results. We matched alarming signs for serious illness, as identified in a systematic review (positive likelihood ratio >5 or negative likelihood ratio <0.2),[2] with flowcharts and discriminators of the MTS. Three flowcharts and 20 discriminators were considered as valid proxies for 14 alarming signs (Table 1). The alarming signs 'child moaning', 'crackles', and 'decreased breathing sounds' could not be matched with any flowchart or discriminator. Two alarming signs were excluded from the analysis: 'decreased skin elasticity' was specific for only gastro-enteritis with subsequent dehydration and 'any abnormal finding in history or physical examination' we found too unspecific for triage purposes.

Because every flowchart contains a unique combination of discriminators, relevant for the presenting problem, the maximum number of alarming signs that could have been selected at triage of a child was depended on the assigned flowchart and ranged from 1 to 7. For example, in the flowchart 'Crying Baby' (Figure 1), 8 discriminators are valid proxies for 6 alarming signs in total. To correct for the difference in the maximum number of alarming signs between flowcharts, we calculated the percentage of alarming signs positive at triage as follows:

$$\text{Percentage of alarming signs positive} = \frac{\text{number of alarming signs present at triage, given the assigned flowchart}}{\text{maximum number of alarming signs available in the assigned flowchart}}$$

The primary outcome measure of this study was hospitalization. At our study ED, the admission policy was based on medical indications only: (1) abnormal or threatened vital signs; (2) requirement of intravenous (IV)-medication or IV-fluids; or (3) failure to ingest medication (e.g. need for a nasogastric tube). To validate our assumption that hospitalization could be used as a proxy for serious febrile illness, we evaluated the number of diagnostic and therapeutic interventions performed during hospital admission, and the definite diagnosis in a random subsample of admitted children (January 2008 to July 2009; N=356).

TABLE 1 Flowcharts and discriminators of the MTS as proxies for alarming signs for serious illness[2]

ALARMING SIGNS FOR SERIOUS ILLNESS*	FLOWCHART OR DISCRIMINATOR OF THE MTS
GLOBAL ASSESSMENT	
Parental concern	Flowchart 'Worried parent'
Child appears ill/Clinical impression/Clinician instinct something is wrong	Flowchart 'Unwell child' Flowchart 'Irritable child'
CHILD BEHAVIOUR	
Changed crying pattern/Inconsolable child	Prolonged or uninterrupted crying Inconsolable by parents Not distractable
Child drowsy	Altered conscious level Responds to voice or pain only Fails to react to parents
Child moaning	-
CIRCULATORY AND RESPIRATORY FEATURES	
Cyanosis	Very low SaO2 Low SaO2
Poor peripheral circulation/Hypotension	Shock
Crackles	-
Decreased breathing sounds	-
Shortness of breath/Rapid breathing	Inadequate breathing Stridor Increased work of breathing Unable to talk in sentences Wheeze
MISCELLANEOUS	
Meningeal irritation	Signs of meningism
Petechial rash	Non-blanching rash Purpura
Seizures	Currently fitting
Unconsciousness	Unresponsive child Unresponsive

SaO_2 percentage of available hemoglobin that is saturated with oxygen.
* Alarming signs 'decreased skin elasticity' (gastroenteritis only) and 'any abnormal finding in history or physical examination' (unspecific) are excluded from the Table.

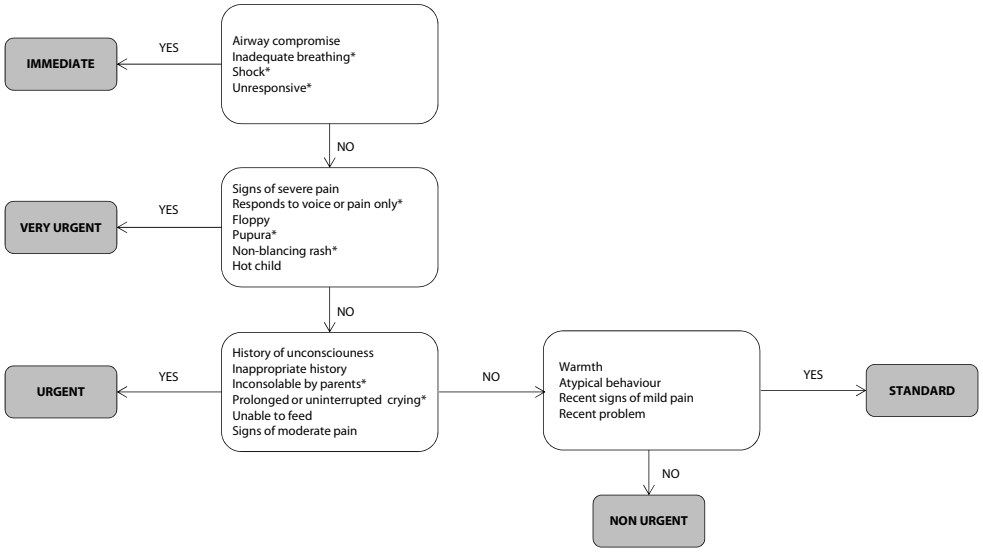

FIGURE 1 Example of the MTS-flowchart 'Crying Baby' with its specific discriminators
Example of the MTS flowchart 'Crying Baby'. Urgency categories and maximum waiting time: 'immediate': 0 minutes, 'very urgent': 10 minutes, 'urgent': 60 minutes, 'standard': 120 minutes, 'non urgent': 240 minutes. Eight discriminators (*) function as a proxy for 6 alarming signs for serious illness. Reprinted with permission from the BMJ Publishing Group (Mackway-Jones K, Manchester Triage Group. Emergency Triage, 1st edition. London: BMJ Publishing Group; 1997).

Statistical analyses

The majority of patients (77%) were assigned to flowcharts in which the maximum number of alarming signs that could be selected was 5 (flowcharts 'general', 'shortness of breath', and 'vomiting and diarrhea') or 7 (flowcharts 'worried parent' and 'fits'). In our analyses, we therefore categorized the percentage of alarming signs positive as such that for children assigned to these flowcharts the categories corresponded with 'no alarming signs positive at triage' (0%; 'none'), '1 alarming sign positive at triage' (≤20%, 'low'), '2 alarming signs positive at triage' (≤40%, 'intermediate'), and '3 or more alarming signs positive at triage' (>40%, 'high').

Two-by-two contingency tables were constructed to show the distribution of hospitalizations among the 4 percentage groups. To determine the diagnostic value of the percentage of alarming signs to assess the need for hospitalization, as if it were a diagnostic test, we calculated sensitivity, specificity, and positive and negative likelihood ratios with 95% CIs (VassarStats Clinical Calculator; http://vassarstats.net/clin1.html). To indicate a 'positive' and 'negative' test result, we dichotomized the percentage of alarming signs at the three cut-off points: (1) >0% vs. no alarming signs; (2) more than 20% of alarming signs positive (>20% vs. ≤20%); (3) more than 40% of alarming signs positive (>40% vs. ≤40%). For descriptive statistics we used SPSS PASW statistics software (v. 17.0.2; SPSS Inc., Chicago, IL, USA).

RESULTS

In total, 2,455 (32%) of 7,573 children were eligible for analyses (Figure 2). No differences in age, sex, temperature, and frequency of hospitalization were found between children included in the study and those with missing flowchart (N=262; data not shown). Patient's and triage characteristics of the study population are shown in Table 2. Hospitalization was required for 563 (23%) children. Main reasons for hospitalization were: (1) a diagnosis of serious bacterial infection (32%); (2) requirement of IV-medication/fluids or oxygen/dose-aerosol treatment (42%); (3) failure of therapy compliance at home (4%); (4) observation, awaiting diagnostic test results (14%); and (5) other reasons (7%). Eleven percent of children had a revisit for the same complaint within 7 days. Hospitalization after a revisit occurred in 77 (3%) of children.

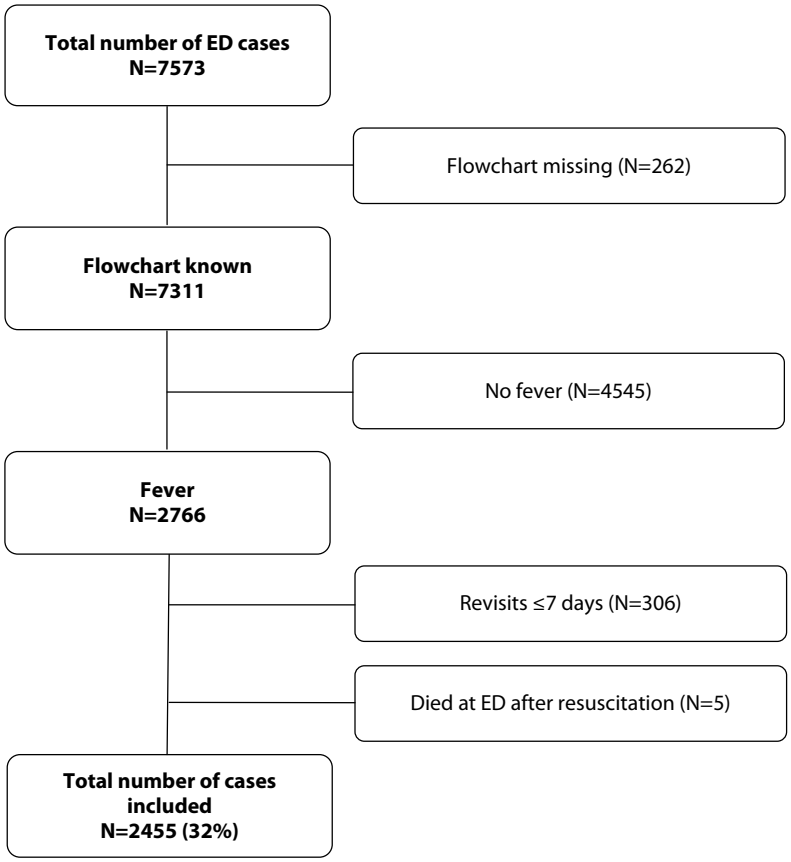

FIGURE 2 Selection of the study population

TABLE 2 Patients' and triage characteristics of the total study population

CHARACTERISTICS		
Male sex (N; %)	1423	(58)
Age in years (median; IQR)	2.2	(1.0 - 4.6)
Temperature in °C (median; IQR)	38.9	(38.1 - 39.5)
MTS urgency (N; %)		
Immediate	64	(3)
Very urgent	725	(30)
Urgent	1232	(50)
Standard	422	(17)
Non urgent	12	(1)
MTS flowchart (N; %)		
General	824	(34)
Shortness of breath in children	363	(15)
Worried parent	281	(11)
Vomiting & diarrhea	236	(10)
Fits	187	(8)
Urinary problems	78	(3)
Other flowcharts[a]	486	(20)
Hospitalization (N; %)	563	(23)

Sex: 1 missing value; Temparture: 83 missing values.
[a] Other flowcharts (n): abdominal pain in children (69), hematological disorder (61), rashes (60), unwell child (53), ear problems (50), throat ache (41), headache (41), crying baby (27), local infection/abscess (15), neck pain (14), astma (8), thoracic pain (8), irritable child (7), shortness of breath (6), limping child (5), extremity problems (5), nose problems (3), back pain (3), abdominal pain (2), foreign body (2), apparently drunk (2), strange behaviour (1), gastro-intestinal bleeding (1), severe trauma (1), unwell adult (1).

Alarming signs for serious illness and hospitalization

For 733 (30%) children at least 1 alarming sign was selected at triage. Among these, 544 (74%) had 1 alarming sign positive, 158 (22%) had 2, 20 (3%) had 3, 9 (1%) had 4, and 2 (0.3%) had 5. For children assigned to the 5 most commonly used flowcharts, the relation between the percentage of alarming signs positive and hospitalization is depicted in Figure 3.

Table 3 shows the diagnostic performance of the percentage of alarming signs positive, as if we would use it as a diagnostic tool. The presence of more than 20% alarming signs at triage showed a high specificity (>95%) for hospitalization. The positive likelihood ratios for patients with more than 20% and more than 40% of alarming signs positive at triage indicate that hospitalization is 5 and 12 times as likely to be required for children in these groups as compared with those who had lower percentages. Negative likelihood ratios were approximately one for all three cut-off levels.

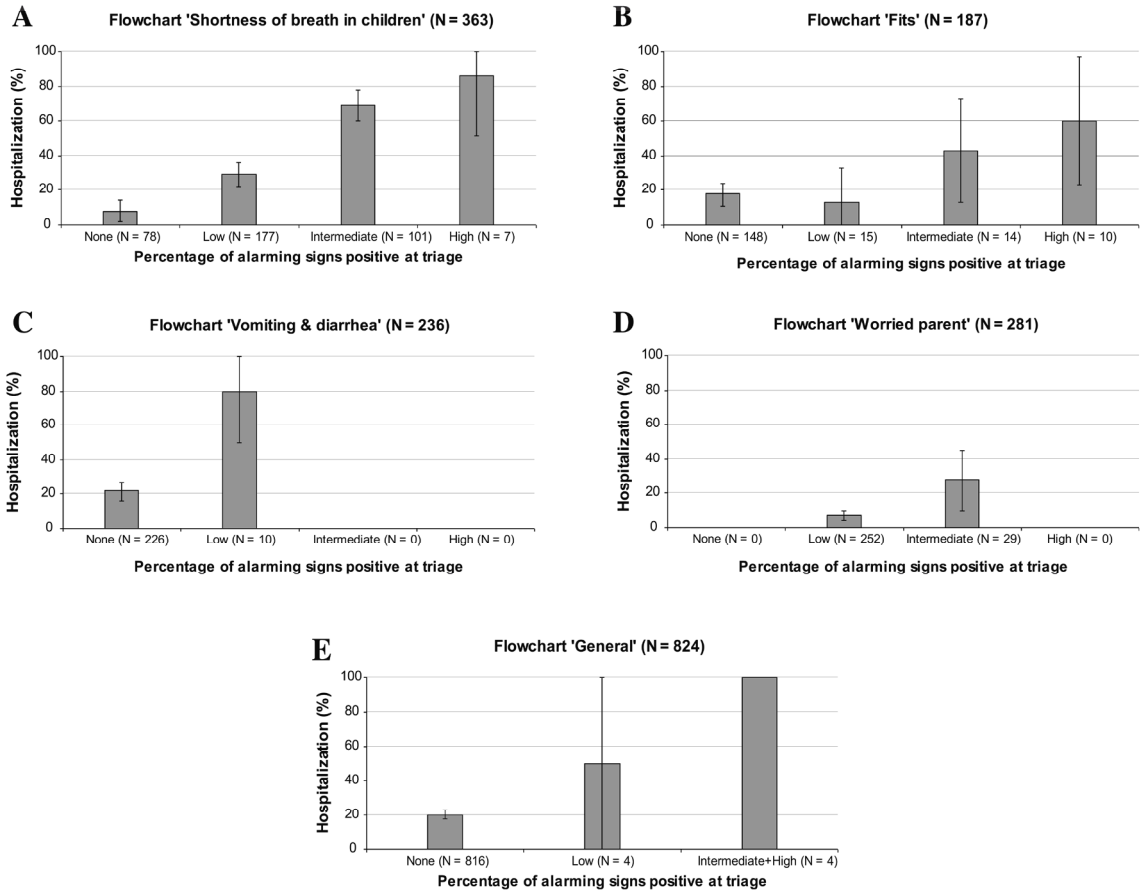

FIGURE 3 Hospitalization per percentage group of alarming signs positive at triage for the most commonly chosen flowcharts
Low: ≤20% of alarming signs positive at triage; Intermediate: >20% - ≤40% of alarming signs positive at triage; High: >40% of alarming signs positive at triage. Error bars represent 95% confidence intervals. For the flowchart 'General' the intermediate and high percentage groups are displayed as one group because of small group numbers.

TABLE 3 Diagnostic performance of alarming signs for serious illness positive at triage of febrile children

ALARMING SIGNS POSITIVE[a]	N (% of total population)	HOSPITALIZATION within group (%)	SENSITIVITY		SPECIFICITY		LR+		LR-	
			%	(95% CI)	%	(95% CI)	%	(95% CI)	%	(95% CI)
None	1722 (70)	335 (19)	-	-	-	-	-	-	-	-
> 0 - 20%	523 (21)	102 (20)	40.5	(36.4-44.7)	73.3	(71.2-75.3)	1.5	(1.3-1.7)	0.8	(0.8-0.9)
> 20 - 40%	178 (7)	101 (57)	22.4	(19.1-26.1)	95.6	(94.5-96.4)	5.0	(3.9-6.5)	0.8	(0.8-0.8)
> 40%	32 (1)	25 (78)	4.4	(3.0-6.6)	99.6	(99.2-99.8)	12.0	(5.2-27.6)	1.0	(0.9-1.0)

LR+: positive likelihood ratio, LR-: negative likelihood ratio

[a] Cut-off levels for a 'positive test' to calculate sensitivity, specificity and likelihood ratios: >0%: at least one alarming sign positive at triage versus none. >20%: >20% of alarming signs positive at triage versus ≤20%. >40%: >40% of alarming signs positive at triage versus ≤40%.

DISCUSSION

Over the past years, much effort has been put into finding alarming signs, which identify febrile children at risk of a serious illness.[2-4] This study showed that by alternatively using the flowcharts and discriminators of the MTS, as indicators of alarming signs rather than urgency classifiers, the system has the potential to identify children at risk of hospitalization early in the ED care process. We found the majority of alarming signs for serious illness to be represented as flowcharts or discriminators in the MTS. A percentage of alarming signs positive at triage above 20% was useful for 'ruling-in' hospitalization (high specificity and positive likelihood ratio). For children with more than 40% of alarming signs positive the likelihood of hospitalization was even higher, although this analysis was based on small numbers. On the contrary, a low percentage or absence of alarming signs was not helpful in excluding ('ruling-out') hospitalization, as shown by the low sensitivities and high negative likelihood ratios. These patients should still be assessed with caution and one should look for other clinical parameters to judge their risk of serious illness.

In principal, triage systems have been developed to prioritize patients according to their acuity upon arrival at the ED. Others have previously demonstrated that a high MTS urgency level could not well discriminate between children with or without serious bacterial infections.[3,5] Both authors explained this limited discriminative ability by the fact that assessing a patient's level of urgency is different from predicting severity of illness or diagnosing a disease.[3,5,22] In this study, we focused on the more specific and detailed information available in the MTS (i.e. the presence of alarming signs of serious febrile illness specifically instead of a high urgency classification only), which resulted in a higher diagnostic value to predict the need for hospitalization.

We certainly realize that the MTS may not be the most optimal tool for recognizing children at risk for hospitalization. However, more sophisticated tools, such as computerized decision support systems, often require additional clinical characteristics not available from the triage assessment.[23] Besides, such tools are scarce for general complaints such as fever, because their development and implementation is difficult and time-consuming.[23,24]

In practice, the percentage of alarming signs can be automatically calculated by the computerized MTS or by hand. Next, the observed likelihood ratios can be applied to Bayes' nomogram[25] to calculate the post-test probabilities of hospitalization for febrile children who present at comparable ED settings. For example, in a particular ED-setting with a pre-test probability of hospitalization of 15%, the probability of hospitalization will increase to 45% for a febrile child with >20% of alarming signs positive and 70% in case >40% of alarming signs are positive at triage (Figure 4).

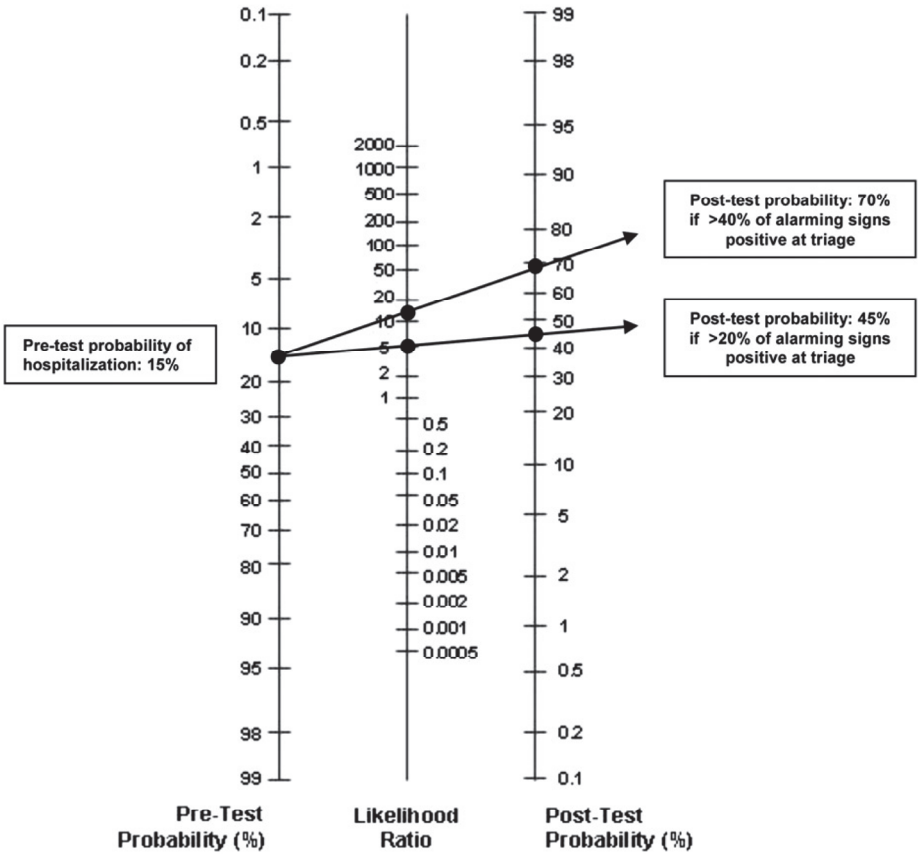

FIGURE 4 Example of the calculation of post-test probabilities of hospitalization using Bayes nomogram

Early identification of children at risk of hospitalization, as a proxy for serious illness, may be useful in further prioritizing patients at the ED, accelerating the application of diagnostic or therapeutic interventions, or deciding to perform interventions after the patient is first admitted to the in-hospital ward.[1,9] Before broad implementation in practice, our findings should be validated in other settings where the MTS is used for triage of febrile children. Subsequently, impact studies must evaluate the improvement of throughput and output flows of febrile children at the pediatric ED.

Our study population comprised a good case mix of nearly 2,500 children, selected from a multicultural, inner-city ED population. Even though in The Netherlands we have a well-preserved primary care system (general practitioners), which functions as a gatekeeper for specialist care, nearly one-half of our ED population was self-referred.[26]. Therefore, we think our results are likely to be generalizable to other Western pediatric EDs with a case mix

population of referred and nonreferred children. Besides, hospital admission was defined for medical indications only at our study ED. From this perspective, the choice of being admitted is independent of referral status or the prevalence of disease.

Selection bias seems unlikely, because compliance with triage was high and general patients' characteristics and hospitalization frequencies of children excluded due to missing flowcharts were comparable with those of children included in the study.

We only had information on revisits, which had taken place at our study ED, even though in practice patients may have visited other health care facilities subsequently. Because our study ED is the major pediatric emergency care facility of the Rotterdam district with 24/7 availability, we do not expect to have missed many revisits.

Selection of alarming signs at triage was restricted by the flowchart chosen. It might have been possible that additional alarming signs were present at triage, which could not have been selected because of the absence of these discriminators in that particular flowchart. Because we primarily focused on alternative use of the available content of the MTS, rather than the exact number of alarming signs present at triage, this will not have influenced our results and its clinical implications.

Lastly, some alarming signs were strongly associated with the outcome, e.g. abnormal vital signs, and mainly applied to children classified as 'immediate (U1)'. Analyses without this patient group resulted in comparable findings (data not shown), which indicates that inclusion of these children in our main analyses was of no major threat to the validity of our results.

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PART III

Clinical prediction rules for serious infections in primary out-of-hours care

CHAPTER 8

The diagnostic value of clinical prediction rules for febrile children in primary out-of-hours care: an observational cohort study

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ABSTRACT

Objective To assess the applicability and diagnostic value of published clinical prediction rules (CPRs) for serious infections in febrile children consulting the low-prevalence care setting.

Design Observational cohort study.

Setting General practitioner's out-of-hours care service.

Participants Children with fever aged below 16 years.

Methods Alarming signs of serious infections and clinical management by the general practitioner were available from routine clinical practice data and were manually recoded with a structured electronic data-entry program. Eight CPRs for serious infections were selected from literature. CPR-variables were matched with alarming signs and CPRs were applied to the primary care population. As outcome measure, we defined 'referral to the emergency department (ED)' as a proxy for 'serious infections'. CPR performance was assessed by sensitivity, specificity, calibration analyses and the area under the receiver operating characteristic (ROC)-curve.

Results 9,794 GPC-contacts were eligible, 54% were boys, median age was 2.3 years (interquartile range 1.0 to 4.6) and 8.1% were referred to the ED. Frequencies of CPR-variables varied from 0.5% to 25%. For CPRs which predicted a high or low risk of serious infection, sensitivities ranged from 42 to 54% and specificities from 68 to 89%. For CPRs which gave a continuous risk prediction, referral frequencies were generally low in the lower ends and higher in the upper ends of the predicted risk, however discrimination between the middle categories was limited. For three CPRs calibration-slopes were >1, indicating that predictor effects were larger in the primary care population. ROC-areas varied between 0.52 and 0.81.

Conclusion Published CPRs to identify children with serious infections performed only moderately well in the primary out-of-hours care setting and seem not directly applicable for use in clinical practice.

INTRODUCTION

The majority of children who present to primary (out-of-hours) care have fever as one of their main complaints.[1,2] Febrile children are at risk of serious infections, such as sepsis, meningitis or pneumonia, which are important causes of morbidity and mortality.[3-5] The prevalence of serious infections in primary care is low[6] and physicians stand for the challenging task to distinguish children at high risk of serious infections from those with self-limiting disease. Studies on identification of serious infections in primary care are scarce. Consequently, practice guidelines are mainly based on consensus of expert opinion and scientific evidence collected from secondary and tertiary emergency care studies.[7,8] To complement practice guidelines, clinical prediction rules (CPRs) may be powerful tools to improve clinical decision making on the basis of combinations of clinical signs and symptoms.[9] Unfortunately, most published CPRs for serious infections have also predominantly been developed at hospital emergency departments (EDs)[10-12] and lack of external validation in low-prevalence populations hampers their implementation in primary care practice.[10,12,13]
Our study aims to assess the applicability and diagnostic value of published CPRs for serious infections in febrile children consulting primary out-of-hours care.

METHODS

Study design

In this observational study, we prospectively collected, semi-structured, routine clinical practice data of children who had presented to out-of-hours primary care with fever. In this population, we assessed the diagnostic value of published CPRs for serious infections, defining 'referral to the ED' as our outcome measure. The institution's medical ethics committee reviewed the study and the requirement for informed consent was waived (MEC-2012-378).

Out-of-hours health care system in the Netherlands

In the Netherlands, out-of-hours primary care (5 p.m. to 8 a.m. daily and the entire weekend) is organised in general practitioner cooperatives (GPCs; out-of-hours primary care centers), in which general gractitioners (GPs) rotate shifts.[14,15] Similar large-scale cooperatives emerged in the United Kingdom, Scandinavia, and Australia.[16-18] In the Netherlands, referral to the ED is required for about 5% to 10% of all primary care consultations[14,19], which is similar to the United Kingdom, United States, and Canada.[20,21] In addition, patients can directly present to the ED on their own initiative (self-referral). Only in life-threatening situations patients are instructed to call the national emergency number for ambulance services.

Study setting and selection of patients

Data collection of this study has been published previously.[22] In short, we selected all contacts of children under the age of 16 years, which had taken place at five GPCs of the Rotterdam Rijnmond-district (collaboration of >250 GP-practices) between March 2008 and February 2009. Eligible contacts were those concerning children who had a face-to-face consultation with the GP and: (1) reported fever as the reason for contact; (2) had fever within 24 hours prior to contact; or (3) had a (rectal or tympanic) temperature >38°C measured at the GPC. We excluded recontacts for the same problem within 7 days of the initial presentation from our main analyses.

Extraction of relevant clinical signs

Clinical features indicative of serious infections were derived from one systematic review[11] and two published guidelines on management of febrile children.[7,8] We included features that: (1) had a high predictive value (positive likelihood ratio >5.0 or negative likelihood ratio <0.2); (2) were mentioned in at least two of the three data sources; (3) did not represent a diagnosis; and (4) were not prone to high inter-observer variability (e.g. auscultatory sounds).[23] The selected features were grouped into 18 'alarming signs' (Appendix 1, see page 135). For eligible contacts, we manually recoded whether alarming signs were 'present', 'absent' or 'not mentioned' in the patient record, using a data-entry computer program (Embarcadero Delphi XE, Version 15.0, Embarcadero Technologies Inc. 2010). Clinical management by the GP was recoded as 'referral to ED', 'control appointment', or 'no follow-up'.

Selection of CPRs and translation to the primary out-of-hours care population

Published CPRs for serious infections in children were identified from two systematic reviews[10,11], complemented by an additional literature search up to December 2011 (Appendix 2, see page 136). Selected CPRs were deemed to: (1) have clinical signs and symptoms as predictors; (2) have no more than one laboratory test as a predictor variable, because these are unavailable at the GPC; (3) have a composite outcome of serious infections; and (4) advise on management strategies or give a risk score. Eight of 32 CPRs extracted from literature were included in the final analyses (Table 1).[6,24-29] Variables of the selected CPRs were matched with the alarming signs in the GPC-dataset. In case alarming signs were not entirely identical to the original CPR variables, we used best proxy variables. When CPR variables were missing in the GPC-dataset, we assumed them absent (Table 3).

TABLE 1 Overview of selected clinical prediction rules

CLINICAL PREDICTION RULE	SETTING	MODEL	AGE	PATIENTS (N)	SERIOUS INFECTIONS (%)	CPR VARIABLES
HIGH/LOW RISK PREDICTION						
1. Van den Bruel et al. [6]	primary	CART	0-16yrs	3981	0.8	clinician's instinct something is wrong, dyspnoea, temperature, age, diarrhoea
2. Thompson et al. [24]	secondary	High/low	3mo – 16yrs	527	15	temperature, oxygen saturation ≤94%, tachypnoea, tachycardia
3. Pantell et al. [25]	pediatric practices/ secondary	CART	<3mo	3066	2.9	age, ill appearance, temperature
CONTINUOUS RISK PREDICTION						
4. Pantell et al. [25]	pediatric practices/ secondary	MLRM	<3mo	3066	2.9	age, ill appearance, temperature, abnormal cry, Medicaid insurance, ill family members, inner-city clinic, URTI diagnosed
5. Bleeker et al. [26]	secondary	MLRM	1 - 36mo	381	27	ill clinical appearance, poor peripheral circulation, chest wall retractions +/- tachypnea, duration of fever, history of vomiting
6. Berger et al. [27]	secondary	MLRM	2wk – 1yr	138	24	clinical impression, duration of fever >48hrs, history of diarrhoea, CRP
7. YICSSG et al. [28]	secondary (mimic primary care)	MLRM	<2mo	8889	7-70	cyanosis, temperature, prolonged capillary refill, movement on stimulation only, tachypnoea, severe chest indrawings, history of convulsions, stiff limbs, history of difficulty feeding, lethargic, grunting
8. Brent et al. [29]	secondary	MLRM	1mo – 15yrs	1951	4	state variation, temperature, capillary refill ≥2sec, hypoxia, tachypnoea, dehydration, history of developmental delay, risk factor for infection (co-morbidity)

MLRM: multivariate logistic regression model; CART: classification and regression tree; URTI: upper respiratory tract infection; CRP: C-reactive protein.

In primary care, identification of febrile children at risk of a serious infection (i.e. requiring specialist assessment), is often more important than confirming the exact diagnosis[13,30], which hampered the verification of outcome diagnoses in our routine clinical practice dataset. We therefore used 'referral to the ED (i.e. being at high risk)' as a proxy for 'serious infection'. We validated this proxy among a subset of GP-referred febrile children who presented to the ED of the nearby Sophia Children's Hospital during the out-of-hours period (January 2006 to July 2009; N=376).[19] We observed that 66% of these GP-referred children required some form of extensive diagnostic interventions (e.g blood culture or lumbar punction), extensive therapeutic interventions (e.g. intravenous (IV)-medication or aerosol treatment) or hospitalization, indicating the presence of a serious febrile illness. Besides, only 395 (4%) of 9,794 GPC-contacts were followed by a second contact for the same complaint within 7 days, of which 67 (0.7%) were referred to the ED. Figures were comparable for children who had or had not been prescribed antibiotics at first consultation.

Missing data

Since clinical information was obtained from routine practice data, missing values were present. A consensus-meeting with one general practitioner, two paediatricians and two residents (general practice and paediatrics) decided, for the purpose of this study, to deal with missing values in two ways: (1) we assumed all alarming signs for serious infections to be always documented when present. Consequently, when alarming signs were 'not mentioned' in the patient record, they were considered to be 'absent'; (2) for continuous variables (i.e. temperature and duration of fever) we replaced missing values by mean values.

Statistical analyses

Patient characteristics and frequencies of alarming signs were analysed using descriptive statistics. For some CPRs based on multivariable logistic regression models, two separate but closely related variables were combined into one alarming sign (e.g. 'tachypnoea' and 'chest wall retractions' into 'shortness of breath') or categorical variables (e.g. mild, moderate, severe) were dichotomised into 'present' or 'absent' for application in the GPC-population (Table 3). For such CPR variables we recalculated the beta coefficients as a weighted mean on the basis of the original beta coefficients and the number of patients with the variable present at derivation.

Selected CPRs were applied to the eligible GPC-population, within the age ranges the rules were originally derived for. For CPRs which predict a high or low risk of serious infection (CPRs 1 to 3), calibration was assessed by calculating the percentage of referral in the predicted high and low risk groups. For CPRs which gave a continuous risk prediction (CPRs 4 to 8), we first calculated the linear predictor, which is the sum product of regression coefficients of the rule and the variable values ($lp = \alpha + \beta_1 \cdot x_1 + \beta_2 \cdot x_2 + \ldots + \beta_i \cdot x_i$, in which α is the intercept and β_1-β_i are the regression coefficients of the variables x_1-x_i). Calibration was assessed by calculating the

observed frequency of referral among patient groups based on percentiles of the predicted risk (i.e. *lp*-outcome) and calculation of calibration slopes. Discriminative ability was assessed by calculating sensitivity, specificity, and likelihood ratios for CPRs 1 to 3 and areas under the receiver operating characteristic curve (ROC-area) for CPRs 4 to 8. Statistical analyses were performed with SPSS PASW Software version 17.0.2 (SPSS Inc., Chicago, IL, USA).

RESULTS

Description of the GPC-population

In total, 9,794 GPC-contacts were eligible for analyses (Figure 1). General patient characteristics and clinical features are shown in Table 2. Vital signs such as heart rate, respiratory rate and oxygen saturation were documented in only 2% of the patients (data not shown). Referral to the ED was required for 794 (8.1%) contacts.

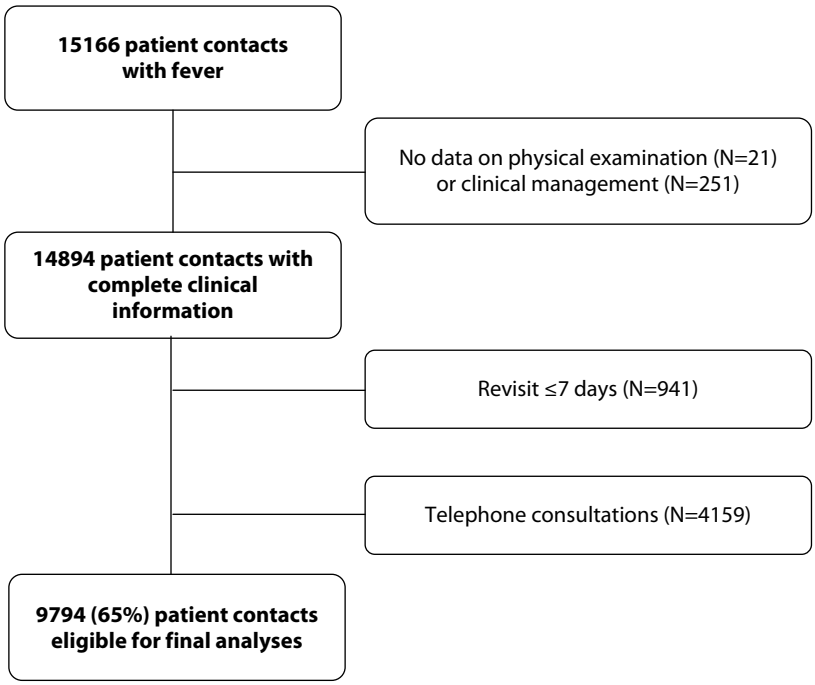

FIGURE 1 Selection of eligible contacts

TABLE 2 Characteristics of total study population

CHARACTERISTICS			RANGE
Male gender (N, %)	5273	(53.8)	
Age (median in years, IQR)	2.3	(1.0-4.6)	0.02-16
Consultation type (N, %)			
Physical at GPC	9719	(99.2)	
Home visit	75	(0.8)	
Temperature at GPC[a] (median in °C, IQR)	38.5	(37.7-39.1)	35.5-41.3
ALARMING SIGNS	**PRESENT**		
	N	**(%)**	
Parental concern	1665	(17.0)	
Ill appearance	389	(4.0)	
ABC instability	1	(<0.1)	
Unconsciousness	8	(0.1)	
Drowsy	53	(0.5)	
Inconsolable	384	(3.9)	
Abnormal circulation	162	(1.7)	
Cyanosis	46	(0.5)	
Shortness of breath	465	(4.7)	
Meningeal irritation	55	(0.6)	
Neurological signs	152	(1.6)	
Vomiting and diarrhoea	2073	(21.2)	
Dehydration	96	(1.0)	
Extremity problems	27	(0.3)	
Signs of UTI	499	(5.1)	
Petechial rash	34	(0.3)	
Temperature ≥40°C	2462	(25.1)	
DURATION OF FEVER[b]	**PRESENT**		
	N	**(%)**	
Started today	2008	(20.5)	
1 day	1729	(17.7)	
2 days	1228	(12.5)	
3 days	1325	(13.5)	
4 days	700	(7.1)	
>5 days	731	(7.5)	
REFERRAL/FOLLOW-UP	**PRESENT**		
	N	**(%)**	
Referral to ED	794	(8.1)	
Control appointment	770	(7.9)	
No follow-up	8230	(84.0)	

IQR: interquartile range; GPC: general practitioner cooperative; ABC: airway, breathing, circulation; ED: emergency department.

[a] Temperature was not measured for 57% of patients, in analyses replaced by mean temperature (N = 3368): 38.4°C (se 0.02).

[b] Duration of fever was unknown for 21% of patients, in analyses replaced by mean duration (N = 7721): 2.01 days (se 0.02).

Performance of CPRs applied to the GPC-population

Eight CPRs were applicable to the primary out-of-hours care setting (Table 1). Observed frequencies of CPR variables were generally low in the GPC-population and ranged from 0.5% (cyanosis/drowsy) to 25% (temperature ≥40ºC; Table 3). For CPRs 1 to 3, observed referral frequencies varied from 4% to 38% among the patients predicted as 'low-risk' and from 13% to 78% among those predicted as 'high-risk' (Table 4). For CPRs 4 to 8, the distribution of patients over the percentile groups of the predicted risk differed considerably per CPR, with the lowest percentile groups accounting for minimally 6% to maximally 44% of the total population (Table 5). The observed percentage of children referred to the ED was generally low for those in the lowest percentile groups (range: 0% to 20%). Observed referral frequencies of children in the upper percentile groups ranged from 17% (CPR 5) to 100% (CPR 7). Calibration slopes varied from 0.17 (CPR 6) to 2.05 (CPR 8), with 3 rules having a slope >1, which indicates that the effects of CPR variables were larger in the GPC-population than in the derivation-population (Table 5). Sensitivities of CPRs 1 to 3 ranged from 42% to 54%, and were lower than those reported in derivation-settings. In contrast, specificities of CPRs 2 and 3 were higher (>86% versus 39% and 35% at derivation), as were positive and negative likelihood ratios (Table 4). Discriminative abilities of CPRs 4 to 8 varied widely, but were to some extent comparable with ROC-areas reported in the derivation studies (Table 5). CPR 6 had the lowest ROC-area of 0.52, whereas the two rules developed for young children showed best discriminative abilities with ROC-areas of 0.77 (CPR 4) and 0.81 (CPR 7).

DISCUSSION

Summary of main results

This study demonstrates that published CPRs for serious infections, mainly derived at hospital EDs, performed only moderately well in the primary out-of-hours care setting. Most CPR variables were observed to be low frequent in the GPC-population and their predictive effects were stronger in the GPC-setting as compared with derivation. We found limited rule-out value for CPRs which classified children in high or low risk groups, as their sensitivities were low and negative likelihood ratios were high. Discriminative abilities of CPRs which gave a continuous risk prediction were to some extent comparable with derivation studies, however still too moderate to be directly applicable to clinical primary care practice.

TABLE 3 Model predictors used and their frequencies in the GPC-population

DERIVATION-POPULATION	STUDY POPULATION	
	Variables/proxies	Frequency of presence
1. VAN DEN BRUEL ET AL.		**(0-16yrs: N=9794)**
Clinician instinct something is wrong	Ill appearance	4.0%
Dyspnoea	Shortness of breath	4.7%
Temperature ≥39.95°C	Temperature ≥40°C	25.1%
Age between 1.18-2.42 yrs	Age between 1.18-2.42 yrs	22.4%
Diarrhoea	Vomiting & diarrhoea	21.2%
2. THOMPSON ET AL.		**(3mo-16yrs: N=9590)**
Temperature ≥39.0°C	Temperature	11.5%
Oxygen saturation ≤94%	Cyanosis	0.5%
Tachypnoea (APLS)	Shortness of breath	4.7%
Tachycardia (APLS)	Abnormal circulation	1.6%
3. PANTELL ET AL.		**(<3mo: N=204)**
Age<25 dys	Age <25 dys	12.3%
Ill appearance	Ill appearance	2.5%
Temperature ≥38.6°C	Temperature ≥38.6°C	14.7%
4. PANTELL ET AL.		**(<3mo: N=204)**
Age ≤30 days	Age ≤30 days	14.7%
Age 31-60 days	Age 31-60 days	39.2%
Ill appearance	Ill appearance	2.5%
Temperature 38.5-38.9 °C	Temperature 38.5-38.9 °C	10.8%
Temperature 39.0-39.4°C	Temperature 39.0-39.4°C	5.9%
Temperature ≥39.5°C	Temperature ≥39.5°C	1.0%
Abnormal cry	Inconsolable	22.5%
Medicaid insurance	N/A	N/A
Ill family members	N/A	N/A
Inner-city clinic	N/A	N/A
URTI diagnosed	N/A	N/A
5. BLEEKER ET AL.		**(1-36mo: N=5809)**
Ill clinical appearance	Ill appearance	3.8%
Poor peripheral circulation	Abnormal circulation	1.2%
Chest wall retractions +/- tachypnea	Shortness of breath	5.9%
Duration of fever (days)	Duration of fever (days)	2 dys (1.0-3.0)
History of vomiting	Vomiting & diarrhoea	22.8%
6. BERGER ET AL.		**(2wk-1yr: N=2382)**
Clinical impression	Ill appearance	2.9%
Duration of fever >48hrs	Duration of fever >48hrs	40.7%
History of diarrhoea	Vomiting and diarrhoea	24.8%
CRP	N/A	N/A
7. YICSSG ET AL.		**(<2mo: N=114)**
Cyanosis	Cyanosis	0.9%
Temperature <35.5 °C	Temperature <35.5 °C	0%
Temperature ≥37.5°C	Temperature ≥37.5°C	93.9%
Prolonged capillary refill	Abnormal circulation	6.1%

Movement on stimulation only	Drowsy	4.4%
Lethargic	Drowsy	
Tachypnea	Shortness of breath	9.6%
Severe chest indrawings	Shortness of breath	
History of convulsions	Neurological signs	0%
Stiff limbs	Neurological signs	
History of difficulty feeding	Dehydration	1.8%
Grunting	Inconsolable	25.4%
8. BRENT ET AL.		**(1mo-16yrs: N=9762)**
State variation category	Drowsy	0.5%
Temperature ≥37.5-38.4	Temperature ≥37.5-38.4	76.0%
Temperature ≥38.5	Temperature ≥38.5	17.6%
Capillary refill ≥2sec	Abnormal circulation	1.6%
Hypoxia category	Cyanosis	0.5%
Tachypnoea	Shortness of breath	4.7%
Dehydration category	Dehydration	1.0%
History of developmental delay	N/A	N/A
Risk factor for infection (co-morbidity)	N/A	N/A

GPC: general practitioner cooperative; N/A: alarming sign not present in GPC-dataset, assumed absent.

Explanation of findings and clinical implications

Primary care physicians, who generally work in low-prevalence settings, have to balance the risk of missing a serious infection versus unnecessary referral.[31] This difficulty particularly accounts for children in the 'grey area', that is, those with an unclear presentation[13], which has been demonstrated among children hospitalised for meningococcal disease.[32-35] Half of this group were not referred upon first consultation by a GP due to the lack of specific clinical features. Also paediatric malpractice lawsuits mainly involved infectious diagnoses with failures to consult or refer.[36,37] Clinical decision support by CPRs may be helpful in this diagnostic dilemma, however in the low prevalence setting, high rule-out value should be achieved in order to reduce the number of false-negative patients.[30,31] Unfortunately, the published CPRs which predicted a high or low risk of serious infection showed insufficient rule-out value (low sensitivities and high negative likelihood ratios) and therefore seem to be of limited use in the GPC-population. For CPRs which gave a continuous risk prediction, diagnostic performances ranged widely. Most CPRs could not well discriminate between the middle percentile-groups of the predicted risk and observed referral frequencies varied considerably (Appendix 3, see page 137), which may limit their ability to support clinical management of children in the 'grey area'.

TABLE 4 Performance of CPRs with a high/low risk prediction (CPRs 1-3)

CLINICAL PREDICTION RULE	SI/REFERRAL AMONG HIGH-RISK (%)	SI/REFERRAL AMONG LOW-RISK (%)	SENSITIVITY		SPECIFICITY		LR + (95% CI)		LR- (95% CI)	
			%	(95% CI)	%	(95% CI)				
1. VAN DEN BRUEL ET AL.										
Derivation-population (N=3981)	6	0.03	97	(83-100)	89	(88-90)	8.4	(7.6-9.4)	0.04	(0.01-0.2)
GPC-population (N=9794)	**13**	**6**	**54**	(50-57)	**68**	(67-69)	**1.7**	(1.6-1.8)	**0.7**	(0.6-0.7)
2. THOMPSON ET AL.										
Derivation-population (N=527)	54	31	80	(75-85)	39	(34-44)	1.3	(1.2-1.5)	0.5	(0.4-0.7)
GPC-population (N=9590)	**22**	**4**	**50**	(47-54)	**86**	(85-87)	**3.6**	(3.3-3.9)	**0.6**	(0.5-0.6)
3. PANTELL ET AL.										
Derivation-population (N=3066)	3	0.4	94	(84-98)	35	(33-37)	1.4	(1.3-1.5)	0.2	(0.1-0.5)
GPC-population (N=240)	**78**	**38**	**42**	(33-53)	**89**	(81-94)	**3.7**	(2.1-6.6)	**0.7**	(0.5-0.8)

SI: serious infection; *N*: number of contacts; LR+: positive likelihood ratio; LR-: negative likelihood ratio; CI: confidence interval; GPC: general practitioner cooperative.

TABLE 5 Performance of CPRs with continuous risk prediction (CPRs 4-8)

CLINICAL PREDICTION RULE	CALIBRATION SLOPE	ROC-AREA (95% CI)	
4. PANTELL ET AL.			
Derivation population (N=3066)		0.82	(N/A)
GPC-population (N=204)	**1.44**	**0.77**	**(0.71-0.84)**
5. BLEEKER ET AL.			
Derivation population (N=381)		0.69	(0.63-0.75)
GPC-population (N=5809)	**0.82**	**0.65**	**(0.62-0.67)**
6. BERGER ET AL.			
Derivation population (N=138)		N/A	N/A
GPC-population (N=2382)	**0.17**	**0.52**	**(0.49-0.56)**
7. YICSSG ET AL.			
Derivation population (N=8889)		N/A	N/A
GPC-population (N=114)	**2.00**	**0.81**	**(0.73-0.89)**
8. BRENT ET AL.			
Derivation population (N=1951)		0.77	(0.71-0.83)
GPC-population (N=9762)	**2.05**	**0.71**	**(0.69-0.73)**

GPC: general practitioner cooperative; ROC-area: area under the receiver operating characteristic curve; CI: confidence interval.

The two CPRs developed for very young children may potentially be supportive in structural documentation of alarming signs and may assist in quantifying a (change in) risk of serious illness (e.g. in case of a revisit) or further refinement of the diagnosis[31,38], as these showed best performances. The only CPR derived in primary care[6] showed no diagnostic value in our GPC-population. Previously, others had also demonstrated only marginal rule-out value for this CPR, as well as for the more specific YOS-score, a pneumonia rule, and a meningitis rule, on external validation in another primary care dataset[12,39], which underscores the importance of external validation before implementation in practice.[9,13]

Possible explanations for the moderate performance of CPRs in our GPC-population may be that: (1) observed frequencies of CPR variables were low; (2) vital signs were barely measured (as has been described previously in primary care)[40]; and (3) additional diagnostic tests (e.g. inflammatory markers) were unavailable. These issues reduced heterogeneity of the population and resulted in less spread of predicted risks, which may have decreased discriminative abilities. Besides, variable definitions were not always identical to the original dataset, as was our outcome measure, which approximates serious infection, by identifying children at high risk. Consequently, this may have affected the CPRs' performances in either a positive or negative way.[41] In this study, we particularly observed a stronger effect of CPR variables in the GPC-setting as compared with derivation (calibration slopes >1; Table 5).

Strengths and limitations

We are the first to assess the diagnostic value of several published CPRs for serious infections in an urban, multi-ethnic, out-of-hours primary care cohort of nearly 10,000 contacts of febrile children. We expect our results to be valuable to many other countries where primary care is provided by GPs (e.g. UK, Canada, Australia, and New Zealand) or out-of-hours care has similarly shifted towards large-scale cooperatives (e.g. United Kingdom and Australia).[42]

Since prospective studies on serious infections in low prevalence settings are challenging and time consuming, we used routine clinical practice data as a second best, which introduced some difficulties and limitations.[13,30] Firstly, we used 'referral to the ED' as a proxy outcome measure for 'serious infections'. We validated this proxy (as described in the Methods section), still some bias cannot be excluded, as for a small proportion of children clinical management might have been based on factors other than the presence of alarming signs only (e.g. parental concern).[22] On the other hand, for each of the selected CPRs, 'serious infection' has been defined differently. Since for primary care physicians, identifying children at high risk of serious infections (i.e. needing specialist consultation) is more important than knowing exact diagnoses, 'referral to ED' may be a valid outcome, which captures all of these different definitions of serious infections.

Secondly, we had to deal with a considerable number of missing ('not mentioned') values. Since assumptions on the mechanism of missingness may be diverse, we replaced missing values on the basis of clinical rationale for the purpose of this study. To evaluate potential bias arising from this approach, we performed sensitivity analyses with missing values imputed on the basis of correlations between missing values and available information of other variables. For CPRs 4 to 8, these secondary analyses showed similar ROC-areas but calibration slopes closer to 1 (i.e. better model fit). For CPRs 2 and 3, we observed in particular higher sensitivities (73% and 62% resp.) and lower negative likelihood ratios (0.4 and 0.6 resp.). Since, for the low-prevalence setting we are mainly interested in ruling-out-value, the analyses presented here may 'err' on the safe side by underestimating rather than overestimating.

Conclusion and future directions

Published CPRs to identify serious infections in febrile children performed only moderately well in the out-of-hours primary care population. Based on the moderate discriminative ability and ruling-out value, these CPRs seem not directly applicable to primary out-of-hours care practice. Future studies should focus on adjustment of existing CPRs (i.e. updating) to the primary care population or development of new CPRs for this setting specifically, including variables available in primary care practice.[43] Besides, the additional value of inflammatory marker point-of-care-tests (e.g. C-reactive protein) should be explored, as this has already been demonstrated to be valuable in adult primary care.[44,45]

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APPENDIX 1 Grouping of alarming signs for serious infection

GROUPED ALARMING SIGNS	TOTAL SELECTION OF ALARMING SIGNS
Parental concern	Parental concern
Ill appearance	Clinician's instinct something is wrong Clinically ill appearance
ABCD-instability	ABCD-instability
Unconsciousness	Unconsciousness
Drowsy	Child is drowsy Somnolence Reactivity/functional status (decreased) Hypotonia
Inconsolable	Child is inconsolable Irritability Changed crying pattern Child is moaning
Abnormal circulation	Abnormal skin color (pale, mottled, ashen) Capillary refill time > 2 sec Tachycardia
Cyanosis	Cyanosis Oxygen saturation <95%
Shortness of breath	Shortness of breath Nasal flaring Rapid breathing Changed breathing pattern
Meningeal irritation	Meningeal irritation Neck stiffness Bulging fontanelle
Neurological signs	Focal neurological signs Paresis/paralysis Seizures/fits
Vomiting & diarrhoea	Vomiting (>2x in disease period) Diarrhoea (>2x in disease period)
Dehydration	Dry mucous membranes Sunken eyes Decreased skin elasticity Reduced urine output Hypotension (APLS) Poor feeding
Extremity problems	Swelling of limb or joint Non-weight bearing limb Not using an extremity
Signs of urinary tract infection	Pollakisuria Dysuria Tummy ache (without other focus for fever)
Petechial rash	Petechial rash Purpura
Temperature ≥40°C	Measured at home or at GPC
Duration of fever	Duration of fever (>38.0°C) in days

APPENDIX 2 Electronic search strategy for clinical prediction rules

Pubmed

(Decision Trees[mesh] OR decision rule*[tw] OR decision tree*[tw] OR prediction rule*[tw] OR predictive rule*[tw] OR decision model*[tw] OR prediction model*[tw] OR predictive model*[tw] OR decision analysis model*[tw] OR risk score*[tw]) AND (child[mesh] OR child[tiab] OR children[tiab] OR pediatric*[tw] OR infant*[tw]) AND ("Arthritis, Infectious"[Mesh] OR "Bone Diseases, Infectious"[Mesh] OR "Community-Acquired Infections"[Mesh] OR "Respiratory Tract Infections"[Mesh] OR "Sepsis"[Mesh] OR "Skin Diseases, Infectious"[Mesh] OR "Soft Tissue Infections"[Mesh] OR "Urinary Tract Infections"[Mesh] OR "Meningitis"[Mesh] OR meningitis[tw] OR serious infection*[tw] OR serious bacterial infection*[tw] OR severe bacterial infection*[tw] OR severe infection*[tw] OR "Gastroenteritis"[Mesh])

Embase

('Decision Tree'/de OR ((decision* OR predict* OR risk*) NEAR/3 (rule* OR model* OR algorithm* OR aid OR score* OR tree*)):de,ab,ti) AND (child/exp OR (child* OR pediatric* OR infant*):de,ab,ti) AND ('infectious arthritis'/exp OR 'hematogenous osteomyelitis'/exp OR 'communicable disease'/exp OR 'respiratory tract infection'/exp OR 'sepsis'/exp OR 'skin infection'/exp OR 'soft tissue infection'/exp OR 'urinary tract infection'/exp OR 'meningitis'/exp OR 'gastroenteritis'/exp OR (serious* NEAR/3 infection*):de,ab,ti)

APPENDIX 3 **Distribution of contacts over the percentiles of the predicted risk and frequency of referral within groups**

PERCENTILES OF THE PREDICTED RISK	CPR4 PANTELL ET AL.		CPR 5 BLEEKER ET AL.		CPR 6 BERGER ET AL.		CPR 7 YICSSG ET AL.		CPR 8 BRENT ET AL.	
	N	Referral to ED	N	Referral to ED	N	Referral to ED	N	Referral to ED	N	Referral to ED
0-10th			893	6%			7	0%	610	6%
10-20th	65	20%	228	8%						
20-30th			744	5%	1052	12%				
30-40th	16	75%	281	7%			65	40%		
40-50th	6	67%	554	4%	29	45%			6,926	4%
50-60th	48	25%	811	9%	322	11%				
60-70th	7	86%	566	4%						
70-80th	20	65%	464	13%	685	10%	20	100%	291	34%
80-90th	24	92%	705	9%	35	46%	10	80%	1657	11%
90-100th	18	94%	563	26%	259	17%	12	100%	278	67%
Total	**204**	**49%**	**5809**	**9%**	**2382**	**13%**	**114**	**58%**	**9762**	**8%**

CPR: clinical prediction rule; ED: emergency department.

CHAPTER 9

General discussion and future research perspectives

GENERAL DISCUSSION

In the Netherlands, out-of-hours care is organized by general practitioner cooperatives (GPCs) and hospital emergency departments (EDs). Parents should initially contact the GPC, where the GP can decide to give the child a self-care advice, a treatment (e.g. antibiotics) or to refer the child to the ED for consultation by a paediatrician. Since not all parents stringently stick to this order of contact, a proportion of children are presented on their parents' initiative to the ED directly (i.e. self-referrals; Chapter 3).[1]

As a consequence of the different modes of entry, patient characteristics and disease prevalence differ between both the GPC and ED setting. In primary out-of-hours care, the main presenting complaints of children are fever, earache, vomiting, skin laceration, and respiratory problems.[1,2] The majority of complaints are low urgent and only 5% to 10% of children are referred to the hospital ED for specialist evaluation (Chapter 2).[1] Within the group of febrile children, clinical alarming features most frequently present are ill appearance, inconsolability, shortness of breath, and vomiting or diarrhoea (Chapter 4).[3] Prevalence of serious infections in primary care has been reported to be about 1%.[4] At the hospital ED, the major presenting complaints are injuries, fever, shortness of breath, abdominal pain with or without diarrhoea and vomiting, and seizures.[1,5,6] About one quarter of all children who present to the paediatric ED are classified as high urgent[6] and up to 30% require hospital admission (Chapter 2).[7] Among the group of febrile children, the most common accompanying complaints are respiratory problems (e.g. cough, dyspnoea), gastro-intestinal complaints (e.g. vomiting, diarrhoea, abdominal pain), and neurological symptoms (e.g. headache, irritability, fits; Chapter 3). About 15% to 20% of febrile children are diagnosed with a serious bacterial infection.[8,9]

Even though substantial differences between the GPC and ED exist, both settings closely interact together and should actually be considered as an integrated pathway for emergency care medicine (schematically represented in Figure 1). As fever is one of the most frequently encountered problems in primary care[2,10,11] and hospital emergency care[5-7,12], with potentially hazardous consequences (i.e. morbidity and mortality),[13-15] research in febrile children consulting both settings is requested. The results reported in this thesis have added further knowledge on characteristics of patient populations within the care pathway of febrile children as a whole and evaluated current management strategies to highlight gaps and new starting points for improvement of care in this specific patient group.

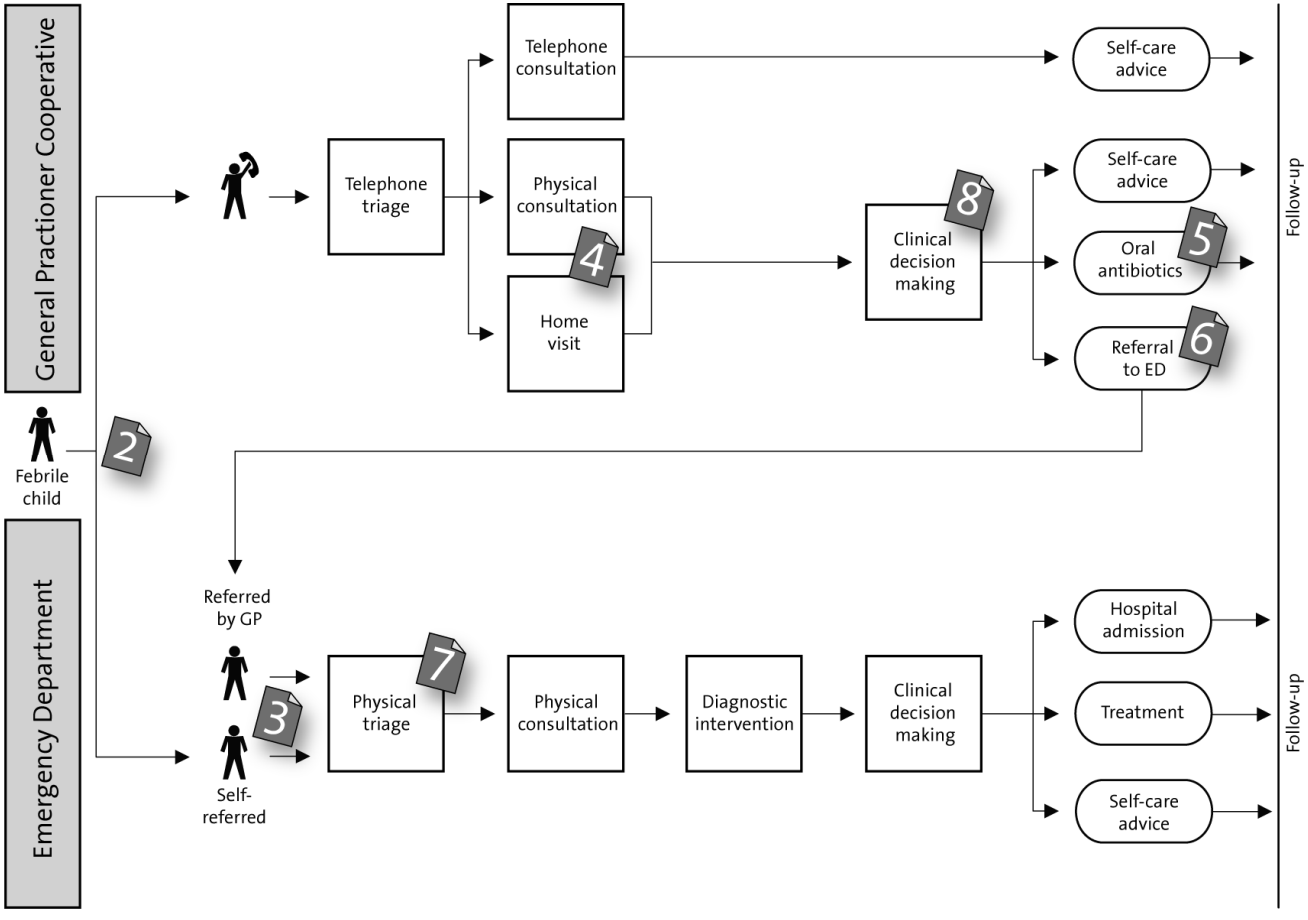

FIGURE 1 Schematic representation of the (simplified) out-of-hours care pathway of febrile children
Numbers indicate the chapters of this thesis.

Identification of children at risk of serious illness in the paediatric out-of-hours care pathway

Starting at the moment of presentation (see Figure 1, Chapter 2), both the GPC and the ED currently use their own triage systems to prioritize patients according to urgency.[16,17] We explored the validity of a uniform triage system, the Netherlands Triage System (NTS), for both telephone triage at the GPC and physical triage at the ED. Even though we concluded that uniform triage may be feasible, one may question whether we should aim to use a uniform algorithm, considering the different aims and consequences of triage at both settings.

Due to differences in clinical characteristics and severity of disease, 'high urgency' and 'low urgency' have a different meaning at both settings. At the GPC, telephone triage is primarily used to distinguish patients in need for consultation by the GP (or in a minority of the cases immediate referral to the ED) from those who can be given a telephone advice or who can wait until regular working hours. On the contrary, physical triage at the ED is not performed to assess *which* patients need to be seen by the physician, but in what order specialist attention is needed. As a consequence of the low prevalence of disease in primary care, the majority of GPC patients (~90%) are classified in the lower part of the urgency spectrum (urgency categories 3 to 5), whereas at the high-prevalence ED-setting, a quarter to one third of the patients are classified as high urgency (urgency categories 1 or 2; Chapter 2).

Secondly, the major challenge of triage systems is generally not the identification of patients with clear life-threatening conditions, but the identification of those who require urgent medical care, within the majority of patients who present with less specific complaints. This may especially be a problem in telephone triage, where the important role of visual cues available at physical triage is ignored and triagists must rely on only auditory history cues instead. The fact that this may influence urgency assessment has already been demonstrated by an agreement of urgency levels designated by telephone triage and physical triage of only 49% for non-critically ill patients presenting at the ED.[18] Telephone triage may be considered as one of the most complex and vulnerable parts of out-of-hours primary care[19-22], on average resulting in about 10% potentially unsafe contacts.[21]

Taken together, it seems impossible to incorporate enough setting-specific, discriminative features into a single triage system to provide a universal urgency classification, as telephone triage at the GPC and physical triage at the ED are two different entities.

Next, we identified that the role of alarming signs to discriminate serious infections may be different during consultation at the GPC as compared with the ED (see Figure 1, Chapter 4). Due to the low prevalence of disease[4], we found the majority of individual alarming signs to be reported in only less than 5% of the GPC consultations. Additionally, we observed that, with the exception of temperature, vital signs (i.e. heart rate, respiratory rate, and oxygen saturation), were barely measured by GPs (Chapter 8), a finding which was demonstrated previously.[23,24]

Consequently, these characteristics result in a different case-mix with less heterogeneity in the population as compared with ED settings, where besides a higher prevalence of disease, more alarming signs and extensive vital sign measurements are available. Additionally, at ED settings, diagnostic tests (e.g. inflammatory markers) can be applied to further differentiate between children with and without a serious infection.

The infrequent appearance of individual alarming signs may, on itself, limit their usefulness as 'red flags' in routine GPC consultations. Besides, it was demonstrated that most of these signs could only increase the prior probability of serious infection in primary care (~1%)[4] to a posterior probability of about 10%.[8] Even though this is already a 10-fold increased risk, this threshold still remains too low to actively base any treatment or referral decision on, as this will lead to a large number of false-positive patients (i.e. children not having a serious infection being treated with antibiotics or being referred to the hospital ED). On the contrary, none of the alarming features had enough rule-out value on its own to exclude the presence of a serious infection. This emphasizes that focusing on single alarming signs may not be enough and other safeguards should be put into place to avoid missing a serious diagnosis.[25]

Therefore, we also focused on the usefulness of combinations of alarming signs at GPC consultation. Until now, clinical prediction rules (CPRs) or diagnostic algorithms (which combine clinical features to predict the presence of serious infections) specifically designed for the low prevalence setting are scarce.[26,27] Therefore, we selected CPRs which were mainly developed at hospital emergency departments[28-33] and applied these to our GPC population (see Figure 1, Chapter 8). Unfortunately, all CPRs, including the only decision rule developed for the low prevalence setting specifically[4], showed moderate performance with limited discriminative value in the low prevalence population. Similar unsatisfactory results were reported by others, who also validated the low prevalence decision rule, as well as the YOS-score, a pneumonia rule and a meningitis rule.[34] From these results one may conclude that existing CPRs are not directly applicable to clinical primary care practice. Our calibration analyses demonstrated that some predictor variables seemed to have a stronger effect in the GPC setting than in the (original) ED setting (calibration slopes >1). This may be another indication that the impact of alarming signs in the GPC setting differs from that in the ED setting and rules should be adjusted to the low prevalence setting specifically.

After exploring the different value of alarming signs during consultation, we next evaluated how GPs use these alarming signs in their decisions on clinical management of febrile children during current routine practice (see Figure 1, Chapters 5 & 6). In Chapter 6 we demonstrated that GPs seem to agree that combinations of alarming signs may (at least) do better at ruling-in and ruling-out serious illness than single alarming signs alone. National[10] and international guidelines[12,35] available to guide physicians in management decisions still base their referral advice on the presence of single alarming signs, even though evidence grounding these

protocols is limited.[26,34,36,37] We observed that GPs adhered to a positive referral advice by the national guideline in only 19% of the consultations, among whom the majority had at least three alarming signs present. Some alarming features were nearly ever neglected (e.g. meningeal irritation and decreased consciousness), whereas others were overruled more frequently (e.g. ill appearance and abnormal circulation). This may suggest that some alarming signs have a broader clinical range and a different diagnostic value in the low prevalence setting as compared with ED settings, where these signs were identified as important predictors for serious bacterial infections.[8,38]

The presence of alarming signs seemed, however, not the only argument for GPs to base their clinical management decisions on. Among the children referred to the ED, 20% had no alarming sign present (Chapter 6) and only 19% of the variability in antibiotic prescriptions could be explained by alarming signs only (Chapter 5). This may not be very surprising, as we found antibiotics to be prescribed to one out of three children (not referred to the ED), whereas the prevalence of bacterial infections is of course much lower in this setting. The presence of clinical features indicating focal infections (e.g. sore throat, bulging tympanic membrane, or earache), which were not included in our analyses, may have accounted for some part of the prescriptions.[39-42] For the remaining part of the 'unexplained' prescriptions and referrals, one may speculate that decisions were based on other considerations, like the physician's gut feeling something is wrong[43], parental concern[4], the inability to provide an adequate safety net (as patients consulted during out-of-hours are generally not followed over time by the same GP)[25], or a (demanding) parent who expects to receive an antibiotic prescription or specialist consultation.[44-46] Further knowledge on these additional considerations will provide further clues for optimisation of clinical management.

The last step of the out-of-hours care pathway to discuss, is the moment of presentation at the hospital emergency department (see Figure 1, Chapter 3). Patients presenting to the ED are either referred by a GP or specialist, brought in by ambulance services after contacting the national emergency number, or present on their own initiative (i.e. self-referrals).[1] Generally, self-referred patients are regarded as nonurgent patients, equivalent to those who present to primary care settings.[47-49] However, among the group of febrile children, one in four parents properly judged and acted on their child's severity of illness by presenting to the ED on their own initiative. General measures to discourage self-referrals from presenting to the ED, such as redirection to primary care practices or governmental policies to self-payment of ED visit costs are undesirable, as these may potentially result in delayed or missed diagnoses.

Additionally, these findings discourage the incorporation of referral type in triage algorithms used at EDs, as has been previously suggested by others.[50] Alarming signs, on the contrary, may be more useful at triage to identify children with a serious infection (see Figure 1, Chapter 7). Previously, it was demonstrated that the urgency levels assigned by the Manchester Triage

System (MTS)[17] could not well discriminate between the presence or absence of a serious bacterial infection.[28,51] However, by alternatively using the content of the MTS (i.e. its flowcharts and discriminators) as indicators of alarming signs, rather than urgency classifiers, the system has the potential to identify febrile children at risk of hospitalization early in the care process. Potentially, this may improve patient throughput and output flows at the ED, as patients can be further prioritized and admissions can be accelerated in order to perform interventions at the in-hospital ward.[52] Still, febrile children without alarming signs should be assessed with caution, since the MTS could not exclude the need for hospitalization in these patients. Consequently, one should look for other clinical measures to judge their risks of serious illness, in order not to delay or miss serious diagnoses.

Methodological challenges of diagnostic research in low prevalence settings

While performing the studies reported in this thesis, we encountered several difficulties of diagnostic research in febrile children consulting the low prevalence setting.[26,36,53]

The first problem arose from the low prevalence of disease. Large patient cohorts of febrile children are needed to reach enough statistical power to identify reliable clinical predictors of serious infection.[53,54] This was for example demonstrated by the only prospective diagnostic accuracy study performed in a primary care setting[4], in which only 31 (0.78%) of 4,100 children with an acute illness were diagnosed with a serious infection. Presumably, only broad national or international collaborations can give rise to sufficiently large, prospective patient cohorts, with the drawback of being extremely costly and logistically challenging.

As an alternative approach, we selected our patients from a routine clinical practice database of febrile children who had presented to five collaborating GPCs, located in close proximity of one another (the district of Rotterdam Rijnmond). One of the major strengths of this practical approach is that we were able to collect data of nearly 15,000 febrile children during only a one year period at relatively low costs. Due to the large number of patients, lack of statistical power and chance findings are of no major concern. Besides, another strength of routine care data may be the generalizability to other out-of-hours primary care populations, as well as populations presenting to acute paediatric assessment units with a low prevalence of disease, since we only selected our eligible patients on the presence of an acute feverish illness instead of pre-specified specific complaints such as cough or meningeal irritation.

The second difficulty was the lack of verified outcome diagnoses, i.e. a serious (bacterial) infection. Ideally, a golden standard or reference test should be performed to objectify the presence or absence of a serious infection.[55] The most objective test would be a positive bacteriologic body fluid culture (e.g. blood, urine or spinal fluid) or the presence of nodular infiltrations or consolidations in the lung on chest radiographs.[38] At the GPC, however, several factors hinder this objectification. Firstly, the availability of diagnostic interventions is limited and diagnostic tests are generally performed at hospital EDs (after referral of the patient).

Secondly, about one third of the children who consult the GPC with fever receive an antibiotics prescription (Chapter 5),[56] whereas the underlying pathogen remains unknown. In theory, one may overcome these problems by performing invasive testing on all febrile children presenting to the GPC, however due to the low prior probability of serious infection this consideration is unethical and extremely costly. Alternatively, in the absence of a reference test, patient follow-up data may be validly used under the assumption that a serious infection will be absent if the patient recovers without treatment (good clinical course) and present if the patient returns with clear symptoms of a serious infection, shortly after the initial presentation.[57] Unfortunately, since GPCs only function as out-of-hours care services and information on disease course and follow-up visits are generally directed to the patient's own GP practice, data on the course of disease were not registered in the GPCs' medical information system. As a second best, we therefore selected a proxy variable to best approximate our true outcome of interest.[36,58] Since in the low prevalence setting the identification of children at high risk serious illness is more important than knowing exact diagnoses, we assumed 'referral to the ED' to be a valid proxy for 'being at risk of a serious infection'. We validated this proxy among a subset of febrile children referred to the ED after consultation at the GPC (Chapter 8). Still, some verification bias cannot be excluded, as for some children referral management by the GP may have been based on factors other than the presence of alarming signs only (e.g. demanding parents or the need for diagnostic certainty, i.e. false-positives). Additionally, others may for example have been adequately treated with antibiotics (instead of being referred, i.e. false-negatives), which makes it impossible to classify febrile children (not) having a serious infection in a 100% error-free way.

The third difficulty was the relatively unstructured documentation of clinical information in the routine care database. Even though GPs reported data on patient history, physical examination, working diagnosis, and treatment or referral in separate text boxes, they were not instructed to report clinical information in a fully standardized way. We observed that some signs were barely mentioned in the patient records (e.g. vital sign measurements), whereas others were nearly always documented (e.g. the appearance of the child). Consequently, we had to make several assumptions on the presence or absence of alarming signs in retrospect, on the basis of the prevalence of disease, clinical experience and common knowledge. Some signs we considered to be so relevant in assessing a febrile child that the GP would always document them when present (e.g. unconsciousness, cyanosis, meningeal irritation, or petechial rash). For other signs (e.g. signs of UTI, temperature ≥40°C, and duration of fever) we agreed that this assumption may not hold true and missing values were replaced by mean values or multiple imputation strategies were used to best approximate true frequencies. Still, some bias may have been present, as for example previously, it was noted that GPs make diagnostic transfers to working diagnoses that justify their antibiotic prescriptions.[59] Likewise, GPs may have documented the presence or absence of certain alarming signs more explicitly to support their medical

actions, which may have strengthened the associations between alarming signs and antibiotic prescriptions or referral to the ED. However, since alarming signs such as 'ill appearance' and 'abnormal circulation' were also frequently observed among non-referred children (Chapter 6), we assume this bias to be limited.

FUTURE RESEARCH PERSPECTIVES

So far, we have discussed several important findings of this thesis, as well as some methodological challenges and gaps remaining for diagnostic research in febrile children presenting to the continuum of out-of-hours care, ranging from primary out-of-hours care to the hospital ED. Arising from the above, several recommendations can be put forward for future diagnostic studies in low prevalence settings.

In order to improve diagnostic research in this setting, a prospective study would be most preferable, since this facilitates a pre-specified protocol to ensure that all relevant clinical information can be completely registered for each patient included in the study.[55] As the prevalence of serious infections is relatively low, effort should be put into setting up collaborating networks between different GPCs in the Netherlands or even comparable large-scale cooperatives abroad (e.g. the United Kingdom or Scandinavia) to reach enough statistical power.

As mentioned previously, the diagnosis of serious (bacterial) infections should ideally be established by a golden reference test.[55] As one must overcome the unethical and costly problem of applying invasive testing on all febrile children consulting, one may instead incorporate a follow-up period, e.g. a telephone call one week after the initial GP visit. The collection of information on the course of disease, repeat visits at the GP or the hospital, diagnostic interventions, treatments, and hospital admissions may be a valid alternative way to rule-in or rule-out a diagnosis of serious infection.[57] Retrieval of medical information can then be easily directed towards the GP or hospital of interest. The fact that one third of febrile children currently receive an antibiotics prescription after first consultation at the GPC may, however, negatively influence the use of follow-up as a proxy for disease by 'masking' the underlying pathogen. Therefore, one should simultaneously incorporate a more restricted antibiotics prescription management with, for example, scheduled revisits shortly after presentation at the GP (e.g. a safety netting protocol)[25] to overcome this difficulty and potentially reduce the number of antibiotic prescriptions in primary care practice simultaneously.

Next, we have demonstrated that alarming signs are low frequent in the low prevalence setting and their diagnostic value seems limited. With the exception of temperature, vital signs were also found to be scarcely measured in febrile children consulting primary care.[23,24] Since these are prone to a high inter-observer variability[60] and their ability to discriminate between children with and without a serious infection remains debatable[28,33,61,62], one may question their added value as indicators of serious infection in primary care practice.

More promising results come from the addition of inflammatory markers. Previously, C-reactive protein (CRP) was shown to be a strong predictor of serious bacterial infections.[9,63] Incorporation of CRP measurements in a clinical prediction model consisting of clinical signs and symptoms, significantly increased the model's diagnostic performance at the hospital ED.[38] The availability of CRP point-of-care tests, which require only a single drop of finger blood for an instant measurement, may facilitate easy collection of this information during GP consultation. Previously, CRP point-of-care tests were already demonstrated to be assistive in antibiotic prescriptions to adult primary care patients with acute cough and lower respiratory tract infections.[64-66] Future research in febrile children should therefore focus on the potential role of CRP in this patient group, to facilitate GPs' decisions on self-care advices, antibiotics prescription and referral to the ED.

Ultimately, one may want to evaluate the out-of-hours care chain as a continuum, since interventions applied to one setting will indisputably have impact on the other setting. This may be facilitated by storage of clinical data from GP practices, GPCs and hospitals in a regionally (or even nationally) organized electronic database. Such an integrated information system will enable following a certain patient over time with all clinical information available and facilitate further evaluations on harms, benefits and cost-effectiveness of novel management strategies within the out-of-hours care chain as a whole.

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CHAPTER 10

English summary/ Nederlandse samenvatting

ENGLISH SUMMARY

The general aim of this thesis was to improve the early recognition of febrile children at risk of serious infections and to support clinical management decisions for febrile children presenting to primary out-of-hours care and hospital emergency care settings.
In the Netherlands, different out-of-hours care facilities are available for patients who require medical attention outside regular working hours. Patients can either contact the general practitioner cooperative (GPC), which provides primary care by telephone advice or physical consultation by a general practitioner (GP) or they can visit the GPC or the hospital emergency department (ED) on their own initiative. In case of an emergent medical situation, the national emergency number is available, answered by the ambulance dispatch centre.

The first part of this thesis focused on the clinical characteristics of children with and without fever who consulted the GPC and the hospital ED. In **Chapter 2** we validated the Netherlands Triage System (NTS), which is a single five urgency level triage system specifically developed for both telephone triage at the GPC and physical triage at the ED. We defined surrogate urgency markers to best approximate a patient's true urgency. Among 3,207 ED-patients, we observed significant trends of increase in resource use, hospitalization and follow-up visits at the out-patient clinic towards the higher urgency categories. Nineteen percent of children were classified as high urgency (U1 or U2) and 15% were admitted to the hospital. For the GPC-patients who had received a telephone consultation (N=2,356), we observed a trend towards more referrals to the ED in the high NTS urgency levels and more self-care advices in the low NTS urgency levels. Among the GPC-patients who had received a physical consultation by the GP (N=4,312), we likewise observed a trend towards more ED-referrals among the high-urgent patients, whereas the association between urgency level and GP advice only (i.e. without referral or medication prescription) was less explicit. At the GPC, less than 10% of children were classified as high urgent and 5% were referred to the hospital ED. Our results suggest that the NTS as a single triage system for both physical and telephone triage seems feasible. However, we question, whether one should aim to use a uniform algorithm, considering the differences in patient characteristics, and aims and consequences of triage at both settings.
In **Chapter 3** we compared the severity of illness between 2,835 (62%) febrile children (<16 years) who were referred to an urban hospital ED by their parents (self-referred) and 1,774 (38%) febrile children referred by a GP. As illness-severity markers we used a high urgency classification by the Manchester Triage System (i.e. 'immediate' or 'very urgent' category), extensive diagnostic tests (i.e. extensive laboratory tests or a radiological examination), extensive therapeutic interventions (i.e. intravenous (IV)-fluids, IV-medication or aerosol treatment), and hospitalization. In both referral groups, the most common presenting problems accompanying the fever were dyspnoea, gastro-intestinal complaints, or neurological complaints. Nearly half

of all GP-referred and self-referred children were classified as 'high urgency'. The remaining illness severity markers were more frequently observed among GP-referred than self-referred patients. Taken together, 43% of GP-referred children needed extensive diagnostic tests, IV-medication or aerosol treatment, hospitalization, or a combination of these against 27% of self-referred children (odds ratio (OR): 2.0, 95% confidence interval (CI): 1.75 to 2.27). We concluded that even though self-referred children with fever were less severely ill than GP-referred children, a considerable number of parents properly judged and acted on their child's severity of illness by presenting their child to the ED on their own initiative.

The second part of this thesis focused on the presence of alarming signs of serious infections and their role in current and future clinical management of febrile children presenting to either the GPC or the hospital ED. In **Chapter 4** we explored the frequency of alarming signs of serious infection in febrile children (<16 years) consulting the GPC. In this observational cohort study, we used routine clinical practice data of more than 10,000 patient contacts from five GPCs (consisting of >250 GP-practices). Median age was 2.2 years (interquartile range (IQR): 1.0 to 4.5) and median temperature 38.5°C (IQR: 37.7 to 39.1°C). Alarming signs were selected from two practice guidelines for clinical assistance of febrile children and one systematic review. The presence of alarming signs was manually recoded for each eligible patient record using a data-entry computer program. Some signs, which were previously reported in literature to be related to serious infections, were poorly documented by GPs (e.g. parental concern, duration of fever, and body temperature) resulting in a considerable number of missing values (range 13% to 82%). Frequencies of documented alarming signs ranged from <0.1% to 21.1%, with the vast majority of signs being present in less than 5% of the consultations. For most alarming signs we observed a trend towards a higher frequency among the youngest children. When alarming signs were combined, 59.7% of children had at least one alarming sign present at presentation. Among these, only 6.7% had three or more alarming signs present.
In the same patient cohort, we examined in **Chapter 5**, whether alarming signs were related to antibiotics prescription by GPs working in primary out-of-hours care. Among the 8,676 eligible contacts (children already on antibiotics at the moment of presentation and children referred to the ED after consultation were excluded), 3,167 (36.5%) received an antibiotics prescription. Multivariate logistic regression analysis showed that signs positively related to antibiotic prescription were: increasing age, body temperature, ill appearance, inconsolable, shortness of breath, and duration of fever. A negative association was found for neurological signs, signs of urinary tract infection and vomiting and diarrhoea. Only 19% of the variation in antibiotic prescriptions could be explained by the presence of alarming signs only, which indicates that other considerations (not analysed in this study) make a substantial contribution to GPs' management decisions in primary out-of-hours care.

In **Chapter 6** we gave insight in the extent to which alarming signs play a role in referral management and assessed guideline adherence of GPs facing a febrile child in primary out-of-hours care practice. Among the 9,794 eligible contacts (only face-to-face consultations), 794 (8.1%) were referred to the ED. Multivariate logistic regression analyses revealed that alarming signs most strongly associated with referral were: age below one month, decreased consciousness, meningeal irritation, signs of dehydration, and extremity problems. For guideline adherence we focused on our national guideline for febrile children, which advises to refer a child to the ED, if at least one of ten guideline-specific alarming signs is present. As a result, 3,424 (35%) of 9,794 contacts had a positive referral indication, of which only 633 (19%) were consequently referred. The majority of cases for which the GP overruled the guideline's referral advice (N=2,791) had no more than 2 alarming signs present. A negative referral indication was agreed upon by GPs in 6,209 (97%) of 6,370 contacts, still 20% of children referred to the ED had no alarming sign present. From these results we concluded that GPs seem more conservative in referring febrile children to the ED than the national guideline proposes. Other factors than alarming signs for serious infections alone, seem important in GPs' decisions on referral management of children with fever.

At many European hospital EDs the Manchester Triage System (MTS) is used to prioritise patients according to urgency upon their presentation. For urgency level assignment, flowcharts (main presenting problem) and discriminators (symptoms that go hand-in-hand with the main problem) have to be selected. Several of these flowcharts and discriminators represent alarming signs of serious infection. In **Chapter 7** we studied whether we could use the content of the MTS as indicators of alarming signs rather than urgency classifiers alone, to predict hospitalization at the moment of presentation at the ED. For this observational cohort study, we included 2,455 febrile children who had presented to an urban hospital ED. All children were routinely triaged with the computerised MTS, in which the most appropriate flowchart and all applicable discriminators could be documented. Fourteen alarming signs of serious infection had a valid proxy as MTS flowchart or discriminator. For 733 (30%) children, at least one alarming sign was selected at triage (range 1 to 5). Hospitalization was required for 563 (23%) patients. As the maximum number of alarming signs that could be selected at triage differed by the flowchart chosen, for each patient, the percentage of alarming signs positive at triage was calculated. Positive likelihood ratios of hospitalization were 5.0 (95% CI: 3.9 to 6.5) for children with >20% of alarming signs positive at triage and 12.0 (95% CI: 5.2 to 27.6) if >40% of alarming signs were positive. Negative likelihood ratios were close to 1, indicating that a low percentage or absence of alarming signs could not rule-out hospitalization. By using the content of the MTS differently, i.e. as indicators of alarming signs of serious infection, the MTS may function as a readily available tool to identify children at risk of hospitalization early in the care process.

In the third part of this thesis we focused on clinical prediction rules (CPRs) as a different tool to identify febrile children at risk of serious illness. All (except one) currently published CPRs have been developed in hospital emergency care settings. In **Chapter 8** we assessed the diagnostic value of eight published CPRs in the primary out-of hours care population (N=9,794). As outcome measure we defined 'referral to the ED' as a proxy for 'serious infections'. Three CPRs predicted a high or low risk of serious infection. Among the children classified as low risk by these rules, 4% to 38% were referred to the ED, whereas among the high risk patients 13% to 78% were referred. Specificities ranged from 68% to 89% and sensitivities from 42% to 54%, which were lower than those reported in the derivation setting. For the five CPRs which gave a continuous risk prediction, referral frequencies were generally low in the lower ends of the predicted risk and high in the higher ends of the predicted risk. We assessed performance of these CPRs in different ways. Calibration slopes ranged from 0.17 (overestimation) to 2.05 (underestimation). Predictive effects of CPR variables were found to be larger in the GPC setting than the ED setting, as three rules had calibration slopes above 1. Discriminative abilities, measured as the area under the receiver operating characteristic curve (ROC-area), varied widely from 0.52 (none) to 0.81 (moderate), however, were to some extent comparable with ROC-areas reported in the derivation studies. Based on the overall moderate ruling-out value and moderate diagnostic performance, published CPRs for serious infections seem not directly applicable to primary out-of-hours care practice.

Finally, this thesis ends with a general discussion described in **Chapter 9**. Several important findings of this thesis are discussed in relation to each other and addressed in light of previously published studies. Methodological challenges and gaps remaining for diagnostic research in febrile children presenting to the low prevalence care setting are highlighted. Recommendations are made for future studies in this setting, in which focus should be directed towards setting up (national) collaborating networks for prospective data collection, follow-up data on the course of disease, and the additive value of inflammatory point-of-care tests (e.g. C-reactive protein). Ultimately, an integrated medical information system may facilitate evaluations of harms, benefits and cost-effectiveness of novel management strategies within the out-of-hours care chain as a whole.

NEDERLANDSE SAMENVATTING

Hoofdstuk 1 beschrijft de achtergrond en doelstellingen van de in dit proefschrift gepresenteerde studies. De hoofddoelen van dit proefschrift zijn: (1) een bijdrage leveren aan het vroegtijdig herkennen van kinderen met een ernstige infectie (leeftijd <16 jaar) en (2) het verbeteren van het medisch beleid voor kinderen met koorts die zich presenteren op de huisartsenpost (HAP) of spoedeisende hulp (SEH).
In Nederland zijn verschillende zorglocaties beschikbaar voor medische zorg buiten kantoortijden. Patiënten dienen, in principe, eerst telefonisch contact op te nemen met de HAP, waarna zij een telefonisch consult of fysiek consult ontvangen. Daarnaast kunnen zij ook op eigen initiatief de HAP of SEH van een ziekenhuis bezoeken. In geval van een spoedeisende situatie kan gebeld worden met het nationale alarmnummer 1-1-2.

In het eerste deel van dit proefschrift ligt de focus op het beschrijven van patiënt karakteristieken van kinderen met en zonder koorts die zich presenteren op de HAP of SEH. In **Hoofdstuk 2** wordt de validatie analyse van het Nederlands Triage Systeem (NTS) beschreven. Het NTS is een triage systeem dat speciaal ontwikkeld is voor zowel telefonische triage op de HAP als fysieke triage op de SEH. Surrogaat urgentie markers werden gedefinieerd om de werkelijke urgentie van de patiënt zo goed mogelijk te benaderen. Op de SEH analyseerden wij 3.207 patiënten. De NTS urgentie bleek significant geassocieerd met de mate van verrichte diagnostische interventies, opnames en herhaalbezoeken op de polikliniek. Van alle kinderen die zich presenteerden op de SEH werd 19% geclassificeerd als hoog urgent (U1 of U2) en 15% werd opgenomen in het ziekenhuis. Op de HAP analyseerden we 6.668 contacten. Hiervan ontvingen 2.356 patiënten een telefonisch consult. In deze groep observeerden we meer verwijzingen naar de SEH onder de hoog urgent geclassificeerde patiënten en meer zelfzorgadviezen onder de laag urgent geclassificeerde patiënten. Binnen de groep patiënten die op de HAP werden beoordeeld door de huisarts (fysiek consult; N=4.312) was de NTS urgentie significant geassocieerd met het aantal verwijzingen naar de SEH, maar werd geen duidelijke associatie gevonden tussen de hoogte van de NTS urgentie en de frequentie van een zelfzorgadvies gegeven door de huisarts. Van alle HAP contacten, bleek minder dan 10% geclassificeerd als hoog urgent (U1 of U2) en werd 5% verwezen naar de SEH. Onze resultaten suggereren dat een uniform triage systeem voor zowel fysieke als telefonische triage haalbaar zou kunnen zijn. Echter, het is de vraag of hier werkelijk naar gestreefd moet worden, gezien de verschillen in patiënt karakteristieken en doelstellingen van triage op beide zorglocaties.
In **Hoofdstuk 3** wordt een vergelijking gemaakt tussen de ziekte ernst van kinderen met koorts verwezen door de huisarts (N=1.774 (38%)) en kinderen die op eigen initiatief van hun ouders de SEH bezochten (zelfverwijzers; N=2.835 (62%)). Als markers voor ziekte ernst werden gebruikt: (1) een hoge urgentie-classificatie door het Manchester Triage Systeem (MTS; U1 of

U2); (2) uitgebreide diagnostische interventies (o.a. uitgebreid bloedonderzoek of radiologisch onderzoek); (3) uitgebreide therapeutische interventies (o.a. toediening van intraveneuze (IV) vloeistoffen/medicatie of een aerosol verneveling); en (4) ziekenhuis opname. In beide verwijsgroepen werden dyspneu, gastro-intestinale klachten en neurologische klachten het meest gerapporteerd. Bijna de helft van alle huisartsverwezen en zelfverwezen kinderen werd geclassificeerd als hoog urgent. Binnen de groep huisartsverwezen kinderen behoefde 43% enige vorm van uitgebreide diagnostische interventie, IV-medicatie/aerosol verneveling of opname, binnen de groep zelfverwezen kinderen was dit nodig voor 27% (odds ratio (OR): 2,0, 95% betrouwbaarheidsinterval (CI): 1,75 tot 2,27). Geconcludeerd werd dat zelfverwezen kinderen met koorts minder ernstig ziek zijn dan huisartsverwezen kinderen, maar dat een aanzienlijk deel van de ouders toch adequaat handelt door hun kind op eigen initiatief te presenteren op de SEH.

Het tweede deel van dit proefschrift beschrijft de aanwezigheid van alarmsymptomen van ernstige infecties en hun rol in huidige en toekomstige behandelstrategieën van kinderen met koorts die zich presenteren op de HAP of SEH. In **Hoofdstuk 4** wordt geëvalueerd in welke mate alarmsymptomen voorkomen bij kinderen die met koorts de HAP bezoeken. Voor deze observationele cohort studie werd gebruik gemaakt van routine praktijk gegevens van meer dan 10.000 kinderen afkomstig van vijf samenwerkende HAP's (samen meer dan 250 huisartsenpraktijken representerend). Achttien evidence-based alarmsymptomen werden geselecteerd uit een nationale en internationale richtlijn voor de evaluatie en behandeling van kinderen met koorts en een systematisch review. De aanwezigheid van alarmsymptomen werd voor elk HAP-contact handmatig en gestructureerd gecodeerd met behulp van een elektronisch data-invoer programma. Sommige alarmsymptomen, in de literatuur beschouwd als voorspellend voor ernstige infecties, bleken met enige regelmaat niet te worden gerapporteerd door huisartsen. Voorbeelden van dergelijke alarmsymptomen zijn onder andere ongerustheid bij ouders, duur van de koorts en de hoogte van de (gemeten) lichaamstemperatuur. Dit resulteerde in een aanzienlijk aantal missende waarden (13% tot 82%). De mediane leeftijd van de geïncludeerde contacten (N=10.476) bedroeg 2,2 jaar (interquartile range (IQR): 1,0 tot 4,5 jaar) en de mediane temperatuur was 38,5°C (IQR: 37,7 tot 39,1°C). De frequenties van voorkomen van de geselecteerde alarmsymptomen varieerden van <0,1% tot 21,1%, waarbij het overgrote deel van de alarmsymptomen in minder dan 5% van de contacten werden gerapporteerd. Over het algemeen, was de frequentie van gerapporteerde alarmsymptomen hoger, naarmate de patiënt jonger was. Indien alle alarmsymptomen samengenomen werden, bleek bij 59,7% van de patiënten ten minste één alarmsymptoom aanwezig te zijn. Bij slechts 6,7% van de patiënten waren drie of meer alarmsymptomen aanwezig ten tijde van presentatie.

In **Hoofdstuk 5** wordt de relatie tussen de aanwezigheid van alarmsymptomen en het voorschrijven van antibiotica door de huisarts geëvalueerd in hetzelfde HAP-cohort. In totaal werden de gegevens van 8.676 kinderen met koorts geanalyseerd. Kinderen die al antibiotica gebruikten op het moment van presentatie op de HAP en kinderen die na het HAP consult werden verwezen naar de tweede lijn werden geëxcludeerd. In totaal kregen 3.167 (36,5%) van de 8.676 kinderen met koorts een antibioticum voorgeschreven. Door middel van een multivariate logistische regressie analyse werd aangetoond dat (oplopende) leeftijd, lichaamstemperatuur, een zieke indruk, ontroostbaarheid, kortademigheid en de duur van de koorts positief geassocieerd waren met het voorschrijven van antibiotica. Een negatieve relatie met antibioticum voorschrift werd gevonden voor de alarmsymptomen neurologische klachten, teken van een urineweginfectie en braken of diarree. Slechts 19% van de variatie in het voorschrijven van antibiotica kon worden verklaard door de aanwezigheid van evidence-based alarmsymptomen. Hieruit werd geconcludeerd dat voor een aanzienlijk deel van de antibiotica voorschriften op de HAP, de huisarts andere overwegingen (niet geanalyseerd in deze studie) laat meespelen in zijn medisch handelen.

In **Hoofdstuk 6** wordt inzicht gegeven in de rol van evidence-based alarmsymptomen bij het verwijsbeleid van de huisarts buiten kantoortijden. Van de in totaal 9.794 kinderen met koorts geanalyseerd in deze studie (alleen fysieke contacten op de HAP) werden er 794 (8,1%) verwezen naar de SEH. Uit de multivariate logistische regressie analyse bleek dat van de tien alarmsymptomen vermeld in de huidige Nederlandse richtlijn, leeftijd <1 maand, verminderd bewustzijn, meningeale prikkeling, tekenen van dehydratie en extremiteitsproblemen het sterkst geassocieerd waren met verwijzing naar de SEH. Vervolgens werd geëvalueerd in hoeverre HAP-artsen het in de richtlijn voorgeschreven beleid opvolgden; te weten een kind dient verwezen te worden naar de SEH indien ten minste één van de tien alarmsymptomen aanwezig is. In totaal was bij 3.424 (35%) van de 9.794 kinderen minimaal één alarmsymptoom aanwezig. Binnen deze groep werden 633 (19%) kinderen daadwerkelijk verwezen naar de SEH. Binnen de groep kinderen waarbij de huisartsen het verwijsadvies van de richtlijn niet opvolgden (N=2.791), bleek bij de meerderheid maximaal twee alarmsymptomen aanwezig te zijn. Voor de 6.370 contacten die volgens de richtlijn niet voldeden aan de criteria voor verwijzing (dat wil zeggen kinderen zonder alarmsymptomen), stemden huisartsen in 97% van de gevallen in met dit advies. Echter, onder de verwezen contacten, werd 20% verwezen naar de SEH in afwezigheid van een in de richtlijn benoemd alarmsymptoom. Geconcludeerd kan worden dat huisartsen werkend op de HAP over het algemeen een conservatiever beleid voeren dan de huidige richtlijn voor kinderen met koorts voorschrijft. Naast de aanwezigheid van (over het algemeen meerdere) alarmsymptomen, blijken ook andere factoren een rol te spelen in het verwijsbeleid van de huisarts.

Op zowel Nederlandse als Europese SEH's wordt voor triage van patiënten die zich presenteren vaak gebruik gemaakt van het Manchester Triage Systeem. In dit systeem dienen per

patient een 'flowchart' (hoofdprobleem waarvoor de patiënt de SEH bezoekt) en relevante 'discriminatoren' (klachten en symptomen die gerelateerd zijn aan het hoofdprobleem) geselecteerd te worden om zo tot een urgentie-classificatie te komen. Een aantal van deze flowcharts en discriminatoren komt overeen met alarmsymptomen voor ernstige infecties. In **Hoofdstuk 7** wordt onderzocht of de flowcharts en discriminatoren van het MTS op een alternatieve manier gebruikt kunnen worden (als indicatoren van alarmsymptomen van ernstige infecties) om het risico op opname te voorspellen ten tijde van presentatie op de SEH. Voor deze observationele cohort studie werden 2.455 kinderen met koorts geïncludeerd, die zich presenteerden op de SEH van het Sophia Kinderziekenhuis te Rotterdam. Bij binnenkomst op de SEH werden alle kinderen routinematig getrieerd met het MTS, waarbij de geselecteerde flowchart en discriminatoren elektronisch werden opgeslagen. Veertien alarmsymptomen voor ernstige infecties kwamen overeen met een MTS flowchart of discriminator. Voor 733 (30%) kinderen werd ten minste één alarmsymptoom tijdens triage geselecteerd (range 1 tot 5). Ziekenhuisopname was geïndiceerd voor 563 (23%) patiënten. Daar het maximaal aantal te selecteren alarmsymptomen varieerde per geselecteerde flowchart, werd voor elke patiënt het percentage aanwezige alarmsymptomen tijdens triage berekend. De positieve likelihood ratio voor opname was 5,0 (95% CI 3,9 tot 6,5) voor kinderen met >20% alarmsymptomen aanwezig bij triage en 12,0 (95% CI 5,2 tot 27,6) indien >40% alarmsymptomen aanwezig waren. De hoge negatieve likelihood ratio's (~ 1) geven aan dat een laag percentage aanwezige alarmsymptomen de noodzaak tot opname niet uitsluit. Uit deze studie werd geconcludeerd dat het MTS zou kunnen functioneren als een eenvoudig voorhanden zijnde instrument om kinderen met een verhoogd risico op opname bij binnenkomst op de SEH te identificeren.

In het derde deel van dit proefschrift ligt de focus op het gebruik van klinische predictieregels om kinderen met koorts met een verhoogd risico op een ernstige infectie te identificeren. Nagenoeg alle tot op heden in de literatuur gepubliceerde predictieregels zijn ontwikkeld in een tweedelijns spoedeisende hulp setting. In **Hoofdstuk 8** wordt de diagnostische waarde van acht reeds gepubliceerde klinische predictieregels in de HAP-populatie geëvalueerd (N=9.794). Als uitkomstmaat werd 'verwijzing naar de SEH' gebruikt als proxy voor 'ernstige infecties'. Drie van de acht predictieregels geven een 'hoog' of 'laag' risico indicatie. Binnen de groep kinderen met een voorspeld laag risico op een ernstige infectie werd 4% tot 38% verwezen naar de SEH. Binnen de groep kinderen met een voorspeld hoog risico op een ernstige infectie werd 13% tot 78% verwezen naar de SEH. De specificiteit van deze predictieregels varieerde van 68% tot 89% en de sensitiviteit van 42% tot 54%; beiden bleken lager dan de waarden gerapporteerd in de derivatie populaties. De vijf overige predictieregels resulteerden in een continue risico voorspelling. Over het algemeen werden kinderen met een hoog voorspeld risico frequenter verwezen naar de SEH dan kinderen met een laag voorspeld risico. De prestatie van de predictieregels werd vervolgens op verschillende manieren

geanalyseerd. Een kalibratie analyse toonde waarden variërend van 0,17 tot 2,05. Voor drie predictieregels bleek de kalibratie waarde >1, wat betekent dat de voorspellende waarde van de predictoren uit de predictieregels over het algemeen groter is in de HAP-setting dan in de derivatie setting. Het discriminerend vermogen van de regels werd onderzocht door middel van een receiver operating characteristic curve (ROC-area). Deze varieerden sterk van 0,52 (geen) tot 0,81 (matig), maar waren tot op zekere hoogte vergelijkbaar met het discriminerend vermogen van de predictieregels toegepast in de derivatie setting. Vanwege de matige rule-out waarde en prestaties van de geselecteerde predictieregels, werd geconcludeerd dat de huidige beschikbare klinische predictieregels voor kinderen met koorts niet direct toepasbaar zijn in de huisartsenzorg buiten kantoortijden.

Dit proefschrift wordt afgesloten met een algemene discussie beschreven in **Hoofdstuk 9**. Hierin worden de belangrijkste resultaten uit dit proefschrift bediscussieerd in relatie tot elkaar en in het licht van eerdere wetenschappelijke publicaties. Tevens worden de methodologische uitdagingen en beperkingen van diagnostisch onderzoek bij kinderen met koorts die zich presenteren in een laag prevalente setting benadrukt. Er worden aanbevelingen gedaan voor toekomstig onderzoek, waarbij de focus zal moeten liggen bij het opzetten van (nationale) samenwerkingsverbanden voor prospectieve gegevensverzameling, longitudinaal vervolgonderzoek naar het beloop van ziekte en de toegevoegde waarde van sneltesten voor inflammatie markers, zoals het C-reactive protein (CRP). Wellicht kunnen, met behulp van een geïntegreerd medisch informatie systeem op de verschillende zorglocaties, de voordelen, nadelen en kosteneffectiviteit van nieuwe diagnose- en behandelstrategieën kunnen worden geëvalueerd, zonder daarbij de wisselwerking tussen de zorglocaties binnen de spoedzorgketen uit het oog te verliezen.

APPENDICES

I LIST OF ABBREVIATIONS

ADC	Ambulance dispatch centre
CI	Confidence interval
CPR	Clinical prediction rule
CRP	C-reactive protein
ED	Emergency department
GP	General practitioner
GPC	General practitioner cooperative
IQR	Interquartile range
IV	Intravenous
LR	Likelihood ratio
LSMA	National standard for dispatch centre ambulance care
NTG	National telephone guide of the Dutch College of General Practitioners
NTS	Netherlands Triage System
MTS	Manchester Triage System
OR	Odds ratio
ROC-area	Area under the receiver operating characteristic curve
U1	Triage urgency level 1

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III LIST OF PUBLICATIONS

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

2. **van Ierland Y**, Seiger N, van Veen M, Moll HA, Oostenbrink R. Alarming signs in the Manchester triage system: a tool to identify febrile children at risk of hospitalization. J Pediatr. 2013 Apr;162(4):862-866.

3. **van Ierland Y**, Seiger N, van Veen M, van Meurs AH, Ruige M, Oostenbrink R, Moll HA. Self-referral and serious illness in children with fever. Pediatrics. 2012 Mar;129(3):e643-51.

4. **van Ierland Y**, van Veen M, Huibers L, Giesen P, Moll HA. Validity of telephone and physical triage in emergency care: the Netherlands Triage System. Fam Pract. 2011 Jun;28(3):334-41.

5. **van Ierland Y**, de Beaufort AJ. Why does meconium cause meconium aspiration syndrome? Current concepts of MAS pathophysiology. Early Hum Dev. 2009 Oct;85(10):617-20.

6. **van Ierland Y**, de Boer M, de Beaufort AJ. Meconium-stained amniotic fluid: discharge vigorous newborns. Arch Dis Child Fetal Neonatal Ed. 2010 Jan;95(1):F69-71.

7. Jacobi CE, **van Ierland Y**, van Asperen CJ, Hallensleben E, Devilee P, Jan Fleuren G, Kenter GG. Prediction of BRCA1/2 mutation status in patients with ovarian cancer from a hospital-based cohort. Genet Med. 2007 Mar;9(3):173-9.

8. **van Ierland Y**, Elshout G, Moll HA, Nijman RG, Vergouwe Y, van der Lei J, Berger MY, Oostenbrink R. The role of alarming signs in referral management of febrile children consulting primary out-of-hours care. Submitted.

9. **van Ierland Y**, Elshout G, Berger MY, Vergouwe Y, de Wilde M, van der Lei J, Moll HA, Oostenbrink R. The diagnostic value of clinical prediction rules for febrile children in primary out-of-hours care: an observational cohort study. Submitted.

10. Elshout G*, **van Ierland Y***, Bohnen AM, de Wilde M, Moll HA, Oostenbrink R, Berger MY. Alarming signs and symptoms in febrile children in primary care: an observational cohort study. Submitted. **Both authors contibuted equally to this manuscript*

IV ABOUT THE AUTHOR

Yvette van Ierland was born on the 31st of December 1980 in Utrecht, the Netherlands. She was educated at the primary school 'Prins Willem Alexander school' in Beusichem and passed secondary school (Atheneum) at the 'Koningin Wilhelmina College' in Culemborg in 1999. In the same year she moved to Leiden to study Biomedical Sciences at the Leiden University. During her study she performed a research project, funded by the Dutch Kidney Foundation, entitled 'Phenotypic characterization of genes expressed by human tolerogenic dendritic cells' at the department of Nephrology of the Leiden University Medical Center (Dr. C. van Kooten and Dr. A.M. Woltman). For her graduation assignment (2005), she participated in a research project to develop a prediction model to identify the presence of a pathogenic BRCA1/2 mutation in women with ovarian cancer at the department of Human Genetics of the Leiden University Medical Center (Prof. dr. P. Devilee). Since Yvette has always wanted to become a medical doctor, she simultaneously obtained her medical degree at the Leiden University between 2001 and 2007. She started working as a resident in Paediatrics (ANIOS) at the Bronovo Hospital, The Hague (2007-2008) and the HAGA Hospital - Juliana Children's Hospital, The Hague (2008-2009). Between 2009 and 2013 she performed her PhD project on 'Alarming signs of serious infections in febrile children' under supervision of Prof. dr. H.A. Moll (promotor) and Dr. R. Oostenbrink (co-promotor) at the department of General Paediatrics of the Erasmus MC - Sophia Children's Hospital in Rotterdam. The general aim of this research project was to improve early recognition of febrile children at risk of serious infections and to support clinical management decisions for febrile children presenting to primary out-of-hours care and hospital emergency care settings. This project was performed in close collaboration with the departments of General Practice (Prof. dr. M.Y. Berger), Medical Informatics (Prof. dr. J. van der Lei) and the Center for Medical Decision Making (Prof. dr. E.W. Steyerberg) of the Erasmus MC, Rotterdam. During her PhD-period, Yvette also obtained her Master of Science degree in Clinical Epidemiology at the Netherlands Institute for Health Sciences in Rotterdam (2012). In September 2012 she started as a resident in Clinical Genetics (AIOS) at the Leiden University Medical Center (Prof. dr. C.J. van Asperen). In her spare time, Yvette likes to travel, sport, cook and spend time with family and friends. She is engaged to Peter Paul Bos, who works as a manager product management in logistics and together they live in Oegstgeest.

V PHD PORTFOLIO

Erasmus MC Department:	General Paediatrics
Research School:	Netherlands Institute for Health Sciences (NIHES)
PhD period:	July 2009 - September 2013
Promotor:	Prof. dr. Henriëtte A. Moll
Co-promotor:	Dr. Rianne Oostenbrink

1. PhD Training	**Year**	**Workload (ECTS)**
General academic skills		
- Workshop 'Methods of Patient-Bound Research and Grant Writing', Erasmus MC, Rotterdam	2010	0.5
- TULIPS Grant Writing Weekend, Bergen aan Zee	2010	2.0
- Biomedical English Writing and Communication, Erasmus MC, Rotterdam	2011	4.0
- KNMG-training *'Solliciteren naar een opleidingsplaats'*, Bronovo Hospital, The Hague	2012	1.0
Research skills		
- Internal Research Meetings, Department of General Paediatrics, Erasmus MC	2009-2012	2.0
- Joint Research Meetings, Departments of General Paediatrics, Medical Informatics, and Center for Medical Decision Making, Erasmus MC	2009-2012	1.0
- Joint Research Meetings, Departments of General Paediatrics and General Practice, Erasmus MC	2009-2012	0.5
- Introduction to Data-Analysis, Netherlands Institute for Health Sciences (NIHES), Rotterdam	2009	0.7
- Master of Science in Clinical Epidemiology, NIHES, Rotterdam	2010 - 2012	40.0
Core curriculum		
Classical Methods for Data-analysis		
Clinical Epidemiology		
Modern Statistical Methods		
Study Design		
Methodologic Topics in Epidemiologic Research		
In-depth courses		
Courses for the Quantitative Researcher		
Principles of Epidemiologic Data-analysis		
Regression Analysis for Clinicians		
Advanced Topics in Decision-making in Medicine		

Missing Values in Clinical Research

Summer programme courses

Introduction to Decision Making in Medicine

Principles of Research in Medicine

Clinical Decision Analysis

Methods of Public Health Research

Clinical Trials

Health Economics

Markers and Prognostic Research

Topics in Meta-analysis

Cohort Studies

Case-control Studies

Principles of Genetic Epidemiology

Social Epidemiology

The Practice of Epidemiologic Analysis

Seminars and workshops

- Congress on Emergency Care Medicine, Julius Center for Health Sciences and Primary Care, Utrecht	2009	1.0
- PhD-Day, Erasmus MC, Rotterdam	2010	1.0
- PhD-Day, Erasmus MC, Rotterdam	2011	1.0
- Research Masterclass, 29th Annual Meeting of the European Society of Paediatric Infectious Diseases, The Hague	2011	1.0
- Young Investigators Day, Congress of the Dutch Society for Paediatrics, Veldhoven	2011	1.0

National conferences - presentations

- Regional Conferences of the Netherlands Triage System, Sint Jansdal Hospital Harderwijk, Diakonessenhuis Zeist, Catharina Hospital Eindhoven [oral presentations]	2009	2.0
- National Study Day 'More Efficiency in Emergency Care', Amsterdam [oral presentation - invited speaker]	2009	1.0
- Sophia Scientific Research Organisation (SSWO), Erasmus MC [oral presentation]	2010	1.0
- Congress of the Dutch Society for Paediatrics, Veldhoven [oral presentations]	2010-2012	2.0
- Sophia Scientific Research Organisation (SSWO), Erasmus MC [poster presentation]	2011	1.0
- Congress of the Dutch College of General Practitioners, Maastricht [oral presentation]	2012	1.0

International conferences - presentations

- 28th Annual Meeting of the European Society of Paediatric Infectious Diseases (ESPID), Nice, France [poster presentation]	2010	1.0
- Research Masterclass, 28th Annual Meeting of the ESPID, Nice, France [oral presentation]	2010	1.0
- 29th Annual Meeting of the ESPID, The Hague [oral presentation]	2011	1.0
- 30th Annual Meeting of the ESPID, Thessaloniki, Greece [poster presentation]	2012	1.0
- 7th European Congress on Emergency Medicine - Antalya, Turkey [oral presentation]	2012	0.5

2. Teaching	**Year**	**Workload (ECTS)**
Supervising		
- Ms. F. Dijkstra, student iBMG, Erasmus University, Rotterdam.	2009	0.2
- Data-entry students (T. Kreçinic, Z. Gocmen, M. Hofhuis, M. Rotsteeg)	2011-2012	2.0

VI DANKWOORD

Ongelofelijk, maar waar, ik ben nu echt toegekomen aan het schrijven van de laatste pagina's van mijn proefschrift! Wat een vreemd, maar vooral ook trots gevoel! I did it! Maar de afgelopen jaren heb ik er zeker niet alleen voor gestaan en daarom wil ik me via deze laatste pagina's heel graag richten tot een aantal speciale mensen, die ieder op hun eigen wijze hebben bijgedragen aan mijn promotieonderzoek en zonder wie deze bijzondere, mooie, uitdagende, gezellige, soms frustrerende, maar vooral leerzame periode er niet zou zijn geweest!

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