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RĪGA STRADIŅŠ UNIVERSITY

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# Diagnostic Value of Clinical Presentation, Parental Concern, and Clinician's Non-Analytical Reasoning in Identifying Serious Bacterial Infections in Febrile Children

Doctoral Thesis for obtaining a doctoral degree
"Doctor of Science (*Ph.D.*)"

Sector – Clinical Medicine
Sub-Sector – Paediatrics

Riga, 2022

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# Anotācija


**Klīnisko pazīmju kopuma, vecāku un ārstu intuitīvā novērtējuma nozīme smagu bakteriālu infekciju diagnostikā bērniem ar drudzi**

Drudzis bērniem ir viens no biežākajiem palīdzības meklēšanas iemesliem Neatliekamās palīdzības nodaļā. Lai gan visbiežāk drudzi izraisa pašlimitējošas vīrusu infekcijas, 4 līdz 25 % gadījumos bērniem, kuri vērsušies Neatliekamās palīdzības nodaļā ar drudzi, tiek diagnosticētas smagas bakteriālas infekcijas (SBI), kas joprojām ir viens no biežākajiem bērnu mirstības cēloņiem arī attīstītajās valstīs. Ātra febrilu pacientu ar iespējamu SBI atpazīšana ir nozīmīgs izaicinājums klīnicistiem lielās pacientu plūsmas Neatliekamās palīdzības nodaļā dēļ.

Šī pētījuma mērķis bija uzlabot agrīnu SBI atpazīšanu bērniem ar drudzi, kuri vēršas pēc palīdzības Neatliekamās palīdzības nodaļā, izvērtējot dažādu klīnisko pazīmju, klīnicista intuitīvā novērtējuma ("*gut feeling*") par iespējamu smagu saslimšanu, klīnicista intuitīvā novērtējuma par iespējamu pašlimitējošu saslimšanu ("*sense of reassurance*"), kā arī vecāku bažu par atšķirīgi / smagāk noritošu saslimšanu bērnam (*parental concern*) diagnostisko vērtību. Balstoties uz minētajiem faktoriem kā mainīgajiem, tika izveidoti un validēti divi klīniskie paredzēšanas modeļi. Modeļa, kurā iekļauti tikai klīniskie parametri, efektivitāte tika salīdzināta ar otra modeļa, kurā tika iekļauti klīnicista instinktu raksturojošie parametri, efektivitāti SBI atpazīšanā. Modeļi tika izveidoti, balsoties uz 517 prospektīvi iekļautu pacientu klīnisko informāciju, kuri pēc palīdzības vērsās Bērnu klīniskās universitātes slimnīcas (BKUS) Neatliekamās palīdzības nodaļā. Rezultāti tika validēti balstoties uz datiem, kas iegūti no 188 prospektīvi iekļautu pacientu populācijas, kuri pēc palīdzības bija vērsušies sešās Latvijas reģionālajās slimnīcās.

Lai gan klīnicista intuitīvā novērtējuma ("*gut feeling*") par iespējamu smagu saslimšanu prognostiskā vērtība SBI atpazīšanā bija ierobežota, klīnicista intuitīvais novērtējums par iespējamu pašlimitējošu saslimšanu "*sense of reassurance*" bija nozīmīgs prognostisks rādītājs SBI neesamībai. Modelis, kurā klīnicista instinktu raksturojošie mainīgie tika integrēti kopā ar klīniskajām pazīmēm, efektīvāk atpazina SBI gan izveides (*receiver operating characteristic curve* (ROC) *area under curve* (AUC) 0,783, 95 % ticamības intervāls (TI) 0,727–0,839), gan validācijas populācijās (ROC AUC 0,752, 95 % TI 0,674–0,830), salīdzinot ar modeli, kurā tika iekļauti tikai klīniskie parametri (ROC AUC izveides populācijā – 0,738, 95 % TI 0,688–0,788, validācijas populācijā – 0,677, 95 % TI 0,586–0,767). Abiem modeļiem bija mērena efektivitāte SBI atpazīšanā drudža pacientiem, kuri vērsās pēc palīdzības Neatliekamās palīdzības nodaļā. Pamatojoties uz efektīvāko modeli, tika izveidota uz punktiem balstīta drudža pacientu vērtēšanas sistēma, kas vienkāršoja pacientu ar augstu vai zemu SBI risku atpazīšanu, kā arī

nodalīja daļu pacientu tā sauktajā diagnostikas “pelēkajā zonā”, kurā SBI un vieglāk noritošu infekciju klīnisko izpausmju smagums bija līdzīgs.

Atšķirībā no citu Eiropas valstu pētījumu rezultātiem primārās aprūpes līmenī, vecāku bažu par atšķirīgi / smagāk noritošu saslimšanu prognostiskā vērtība SBI atpazīšanā pētījuma populācijā bija zema. Vecāku bažu līmeni ietekmēja satraukums, ko izraisīja drudzis bērnam jeb tā dēvētā “drudža fobija”, kas savukārt mudināja vecākus drudža gadījumā bērnam vērsties pēc palīdzības agrīni. Kvalitatīvā pētījumā, balstoties uz 34 vecāku intervijām, kuru bērni tika iekļauti BKUS kohortā, tika noskaidrots, ka vecāku starpā pastāv mīti par drudža iespējamu kaitīgu ietekmi uz bērna organismu. Šo nepareizo, uz pierādījumiem nebalstīto pieņēmumu saglabāšanos nereti veicināja nepietiekams klīnicistu skaidrojums par bērnu ar drudzi aprūpi, kā arī emocionālā atbalsta trūkums no medicīnas personāla puses, vecākiem rūpējoties par ar drudzi slimu bērnu. Pētījums parāda, ka “drudža fobijas” mazināšanai un vecāku bažu kā klīniskā rādītāja precizitātes uzlabošanai nepieciešama plašāka vecāku izglītošana par to, kā izvērtēt un aprūpēt bērnu ar drudzi.

**Atslēgvārdi:** drudzis, smaga bakteriala infekcija, klīnicista intuitīvais novērtējums, vecāku bažas, drudža fobija.

## Abstract

Fever is one of the main reasons for visits to paediatric emergency departments (ED). Although in most cases the underlying cause is self-limiting viral infections, 4 to 25 % of children visiting ED with fever develop serious bacterial infections (SBI), which are significant causes of childhood mortality, even in developed countries. Due to high number of patients visiting ED with febrile illness, rapid discrimination between children with and without possible SBI is challenging.

This study aimed to improve early recognition of SBI in children who present to ED by assessing the diagnostic value of clinical signs at presentation, clinician's non-analytical reasoning, defined as "gut feeling" of serious illness and "sense of reassurance", and parental concern of different / more severe illness. Based on these variables, derivation and external validation of two clinical prediction models (CPMs) for SBI was performed, and the performance of a CPM based on clinical variables alone was compared to a model integrating clinical features together with variables of non-analytical reasoning. The models were derived from a dataset of 517 febrile patients presenting to the ED of Children's Clinical University Hospital (CCUH) in Riga, and externally validated in a dataset of 188 patients prospectively enrolled in six regional hospitals in Latvia.

While the prognostic value of clinician's "gut feeling" as an independent variable for diagnosing SBI was limited, "sense of reassurance" was significantly predictive of absence of SBI, and the performance of the CPM 2 integrating the non-analytical variables with clinical features was superior in both derivation (*Receiver Operating Characteristic curve* (ROC) *Area Under Curve* (AUC) 0.783, 95 % confidence interval (CI) 0.727–0.839) and validation cohorts (ROC AUC 0.752, 95 % CI 0.674–0.830), when compared to the performance of the CPM 1, which was based solely on clinical variables (ROC AUC in derivation population 0.738, 95 % CI 0.688–0.788, in validation population 0.677, 95 % CI 0.586–0.767). Both CPMs had moderate ability to predict SBI in febrile children presenting to ED and acceptable performance in the validation cohort. A scoring system based on the superior prediction model was created to distinguish between patients with high or low risk of SBI, as well as to identify patients in diagnostic "grey area", in which the severity of manifestations of SBI and mild infections overlapped.

Contrary to studies in primary care performed in other European countries, parental concern was not significantly predictive of SBI. Elements of fever-related anxiety were identified as factors influencig the level of parental concern and urging parents to present to healthcare early. A qualitative interview study including 34 parents of patients enrolled in derivation cohort revealed existing misconceptions regarding the possible negative effects of

fever, which often were a result of unfulfilled educational and emotional needs when caring for a febrile child. This study suggests that educational intervention is necessary to reduce “fever phobia” in parents and to improve the diagnostic reliability of parental concern.

**Key words:** fever, serious bacterial infection, gut feeling, parental concern, fever phobia.

# Table of Contents

# Abbreviations

| | |
|---|---|
| AIC | Akaike information criterion |
| AUC | Area under curve |
| CCUH | Children's Clinical University Hospital |
| CFU | Colony forming units |
| CI | Confidence interval |
| CPM | Clinical prediction model |
| CRP | C-reactive protein |
| CRT | Capillary refill time |
| CSF | Cerebrospinal fluid |
| ED | Emergency department |
| FUO | Fever of unknown origin |
| ICU | Intensive Care Unit |
| IFN | Interferon |
| IL-1 | Interleukin-1 |
| LR (–) | Negative likelihood ratio |
| LR (+) | Positive likelihood ratio |
| MRI | Magnetic resonance imaging |
| MTS | Manchester Triage System |
| NICE | National Institute for Health and Clinical Excellence |
| NPV | Negative predictive value |
| OR | Odds ratio |
| PAU | Paediatric assessment unit |
| PCR | Polymerase chain reaction |
| PECARN | Paediatric Emergency Care Applied Research Network |
| PERFORM | Personalised Risk assessment in febrile illness to optimise Real-life Management across the European Union |
| POPs | Paediatric Observation Priority Score |
| POTCs | Point-of-care tests |
| PPV | Positive predictive value |
| qSOFA | Quick Sequential Organ Failure Assessment |
| ROC | Receiver operating characteristic |
| $SaO_2$ | Oxygen saturation |
| SBI | Serious bacterial infection |
| SE | Standard error |
| SIRS | Systemic inflammatory response syndrome |

| | |
|---|---|
| SOFA | Sequential Organ Failure Assessment |
| TNF-α | Tumour necrosis factor alpha |
| UTI | Urinary tract infection |
| W | Wilcoxon statistic |
| WBC | White blood cells |
| YOS | Yale observation scale |
| $\chi^2$ | Chi-squared test |

# Introduction

Febrile illness in a child is one of the most common reasons for seeking medical assistance. In developed countries, close to 40 % of children aged 6 months or younger, and over 60 % of children aged 6 months to 5 years have had a febrile episode at least once in their lives [1, 2]. Most febrile children present to primary care, where fever is the reason behind up to 30 % of paediatric visits [3, 4]. Fever is one of the leading reasons for visiting paediatric emergency departments (ED), where it constitutes for 7.5 % to nearly a quarter of all consultations, and up to 30 % of non-surgical cases [5–9]. In the vast majority of cases fever caused by self-limiting viral infections, and, after introduction of comprehensive immunization programmes in developed countries, the rate of serious bacterial infections (SBI) ranges from less than 1 % in primary care [10, 11] to between 4 % and 15 % of all febrile children presenting to paediatric emergency departments [12–15] (up to 27 % in very young children with fever without source [16, 17]).

Children with febrile illness create a challenge for healthcare workers, especially doctors working at paediatric EDs – on one hand, the probability of serious illness is relatively low, therefore taking precautions such as antibiotic prescription or extensive, often invasive investigation may prove to be unnecessary, yet lead to increased costs, prolonged stay at the ED, and decreased patient satisfaction [18, 19]. On the other hand, a small portion of these children may have a serious illness, in which case failure to recognize and treat the infection early may result in adverse outcomes, patient deterioration, even death [20, 21]. Through previous research in paediatrics, several clinical signs and symptoms associated with serious illness in febrile children have been identified [22], which can aid the diagnostic process. Recognition of these signs serve as a foundation for national and international guidelines for clinical evaluation of febrile children [2, 23–26], of which arguably the best known is the "Traffic light" system developed in United Kingdom by National Institute for Health and Clinical Excellence (NICE) [2]. And yet, studies have shown that recognition of "red" and "amber" clinical features in febrile children still failed to identify a significant proportion of children with serious illness [11, 15, 27].

To estimate the probability of SBI in febrile children in various clinical settings, numerous clinical prediction rules have been created [10, 13–17, 26, 28–33]. These models often include a limited number of clinical variables, making rapid assessment and triage of patients more convenient. Prediction models that include laboratory results in addition to clinical parameters perform far better when validated in other populations [28, 34, 35] than models based on clinical variables only [10, 12, 15, 17]. Despite the added reliability, assessment of laboratory variables in large patient populations may be problematic in settings

where rapid point-of-care tests (POTCs) are unavailable and obtaining laboratory results requires additional time and personnel.

Another problem in clinical evaluation of children with febrile illness is that sometimes, especially when presenting early in disease, the “red flag” symptoms may not have developed yet, and clinical signs may be subtle and son-specific to either serious or self-limiting illness. It is evident that not only presence or absence of “alarm” signs in the febrile child play a role in the decision of a primary care physician to refer the child to secondary care or ED [36], but also “gut feeling” of something wrong, even if alarm signs are absent [10, 37, 38]. This “sense of alarm” has been associated with increased likelihood of SBI in children in primary care settings [10, 38], and it has proven to be useful in other fields of medicine, such as recognition of cancer in primary care [39, 40]. Similarly, parental concern that “this illness is different” has been identified among parents of children with SBI [41] and associated with an increased likelihood of developing SBI in a prospective study in primary care [10]. Though the results of studies in primary care are promising, the diagnostic value of “sense of alarm” when expressed by either parents or clinicians is yet to be fully assessed in secondary and tertiary healthcare, such as paediatric emergency departments.

Furthermore, it is important to clarify the factors causing parental anxiety during febrile illness in their child. While it may be the case that the main reason behind parental concerns is the seriousness of the child’s condition, lack of understanding of the role of fever during an infection, or unfounded fear of its effects also plays a significant role. “Fever phobia” by parents, first described decades ago [42], is still present nowadays despite widely available information on proper management of fever in children [43–47], and one of the main causes of non-urgent visits to ED [45, 48]. Recognition of this anxiety and exploration of the triggers for it is the key for improvement of communication with the caregivers, and would enable clinicians to construct educational measures to reduce the concern raised by fever itself and empower parents to manage their child’s fever properly and with confidence [47, 49, 50]. Moreover, it would help clinicians to distinguish between fever phobia and genuine concern that the child’s condition is more serious during this particular febrile episode, which can significantly improve the evaluation and diagnostic process.

This research focuses on integrating clinical variables, clinician’s “gut feeling” of something being wrong, and parental concern into a diagnostic tool for recognition of serious bacterial infections in children presenting to paediatric emergency department with a febrile illness.

**Aim of the Thesis**

The aim of this thesis is to assess the diagnostic value of objective variables – clinical signs and symptoms at presentation – separately and in combination, as well as of non-analytical variables – clinician's "gut feeling" of something wrong and "sense of reassurance", and parental concern, in early recognition of serious bacterial infection in febrile children who present to Emergency department.

**Objectives of the Thesis**

1. To identify clinical features at presentation with high prognostic value for SBI in children with fever.
2. To evaluate the diagnostic significance of clinician's "gut feeling" of something being wrong, also defined as "sense of alarm", and "sense of reassurance" in recognition of SBI in febrile children who present to ED.
3. To assess the prognostic value of parental concern ("different / more severe illness") in diagnosis of SBI in febrile children who present to ED.
4. To explore reasons that raise parental concern while caring for a child with a febrile illness.
5. To analyse parental beliefs regarding fever and to identify, if present, elements of fever phobia.
6. To develop and prospectively validate a diagnostic tool for predicting serious bacterial infections in children with fever, based on combination of objective variables (clinical features) and non-analytical variables ("gut feeling" of something being wrong, "sense of reassurance", and parental concern).

**Hypotheses of the Thesis**

1. "Gut feeling" of something wrong and "Parental concern" are significant prognostic factors of SBI in children with fever, as is "sense of reassurance" for absence of SBI.
2. Addition of non-analytical variables ("gut feeling" of something wrong, "sense of reassurance", and parental concern) to a combination of clinical features in a prediction model can improve the performance of the diagnostic tool in recognizing serious bacterial infection.

**Research question of the Thesis**

How do parents experience taking care of a child with febrile illness – what causes anxiety and urge to look for help, and what kind of help is expected from healthcare personnel?

**Scientific novelty of the Thesis**

This study adds to understanding of how serious bacterial infection can be predicted in febrile children prior to availability of diagnostic investigation results, by integrating clinical features at presentation together with variables describing clinician's non-analytical reasoning in an internally and externally validated clinical prediction model. The study is so far the first among the published studies to investigate the diagnostic value of clinician's non-analytical reasoning in tertiary care paediatrics. Though there is evidence for high diagnostic value of "gut feeling" of something being wrong in primary care studies, research on its significance in Emergency Department settings is lacking. The diagnostic value of "sense of reassurance" in ruling out serious infection in paediatrics is so far unknown. Similarly, there are no published studies on diagnostic value of parental concern in recognition of SBI in children presenting to Emergency Departments. In addition to assessing its prognostic value, this study aims to clarify the reasons for parental concern when caring for a febrile child, and to examine the role of fever-related anxiety.

# 1 Literature Review

## 1.1 Concept of fever

Despite the widespread prevalence of the phenomenon, the understanding and interpretation of the concept of fever varies between healthcare specialists, physiologists, and laypersons, such as patients or their parents. Historically, medical views of fever have gone through stages of accepting it as an essential component in fighting illness (the yellow bile as "fire" that cooks out the infection – understanding based in Hippocratic doctrine of humour theory) to almost direct association with severe, even mortal disease in the Enlightenment era, as a result of erroneous conclusions from physiological experiments [42, 51, 52]. Through meticulous research in immunology and neurophysiology, the role of fever as physiological reaction to threat to the organism has been clarified [51].

Nowadays, clinical sources and medical literature define fever as elevation of body temperature above the normal daily variations [53–57]. The rise of body temperature during fever is a regulated process, which occurs as a host reaction to infection, inflammation, trauma, or neoplastic processes, of which invasion or infection with foreign microorganisms (viruses, bacteria, protozoa) is the most common trigger. Microbial products or cytokines secreted by the host during inflammatory response act as pyrogenic substances to increase the hypothalamic set point, to which the body temperature is subsequently adjusted through increased heat production and decreasing heat loss [54–59]. Fever must be distinguished from hyperthermia, an unregulated increase in body temperature which results from increased exposure to heat or abnormal heat production in excess of heat loss, while the hypothalamic set point is unchanged [54, 60, 61]. Hyperthermia may arise from increased environmental heat exposure; abnormal thermoregulation due to central nervous system injury of the hypothalamus, thyrotoxicosis, status epilepticus, or genetic conditions affecting thermoregulation; or increased heat production caused by hyperthermia-inducing drug intoxication [54, 62].

The margins of variations of normal body temperature are less clear. Normal body temperature was first defined by Carl Reinhold August Wunderlich as axillary temperature range of 36.6 to 37. 4 °C [63, 64], the average temperature of 37.0 °C was accepted as the defined norm [56, 65, 66]. However, there are significant variations in body temperature depending on age, sex, race, time of day, time of year, and other factors such as comorbidities [64–68]. The variability of body temperature is greater in younger people, as is the body temperature itself, when compared to older adults and elderly [67–70]. Normal body temperature in infants younger than 3 months can be especially high and reach a level considered as fever in older children and adults [71]. Site of measurement is another important

aspect to consider when defining normal body temperature and fever. Several organizations define fever as increase in core (rectal) temperature above 38 °C [2, 57], and it is known that measurements taken in other sites will register lower temperatures – axillary temperature is 0.5–0.7 °C lower, oral temperature may differ by negative 0.4 °C, and readings of tympanic temperature may be 0.3 °C lower [2, 66, 69, 72]. Nevertheless, the cut-off values for fever and choice of sites for temperature measurement differ significantly between studies regarding febrile illness in children. While some adhere to the "gold standard" of measuring rectal temperature [14, 16, 73, 74], others accept use of less invasive measurement methods [10, 12, 13]. Body temperature considered as fever is mostly set at 38 °C, varying slightly between 37.9 °C and 38.3 °C.

Fever is viewed as an adaptive response to infection developed by many animal species through evolution [56]. There is prevailing evidence of beneficial role of fever by promoting chemotaxis of neutrophils to the site of inflammation [75, 76], amplifying the protective effects of interferon (IFN), tumour necrosis factor alpha (TNF-α), or Interleukin-1 (IL-1) [56, 76–78], and by induction of stress responses in microorganisms [79]. Furthermore, fever suppression with antipyretics can supress the immune response of the host by impairing adherence of immune cells to endothelium, suppressing migration of leukocytes, and by inhibition of production of inflammatory cytokines [58], though there is no evidence that antipyretics prolong the duration of illness [80]. As fever is physiologically regulated, the body temperature rarely rises above 42 °C, except in cases of underlying thyrotoxicosis, malignant hyperthermia, or under hyperthermic environmental conditions. Also, an increase in body temperature above 41 °C is rarely associated with infection [54, 81, 82].

## 1.2 Aetiology of fever in children in developed countries

### 1.2.1 Infectious causes of fever

Infection is the main cause of fever in children, accounting for 95 % of cases in febrile illness lasting for up to 7 days [83]. The aetiology of fever is most commonly viral (upper respiratory tract infections, viral gastroenteritis, etc.), followed by uncomplicated bacterial infection (otitis media, tonsillitis, pharyngitis, sinusitis etc) [2, 62, 84, 85]. Parasitic infections such as malaria are less common causes of fever in countries outside the endemic areas, though should be ruled out in returning travellers with febrile illness [86, 87].

In contrast to self-limiting infection, serious bacterial infection (SBI) may result in significant adverse outcomes, morbidity, and mortality if left untreated [20, 21, 88]. In otherwise healthy children without immunosuppression, the prevalence of SBI among febrile

episodes is rare. The overall rate of SBI varies from less than 1 % in children who present to primary care [10, 11], to anywhere between 4 % and 15 % of all febrile children presenting to paediatric emergency departments [12–15], and higher in very young infants presenting to ED with fever without source, when it can reach up to 27 % [16, 17]. Only a small proportion of children presenting to ED with fever are diagnosed with culture-positive invasive bacterial infections, with the estimated incidence less than 1 % [32].

The risk of SBI also depends on the age of the child. The prevalence of SBI in infants younger than 3 months with febrile illness can reach 5 to 14 %, and it is even higher in febrile neonates (up to 28 days old), from which 10 to 20 % are diagnosed with SBI [62, 85, 88, 89]. After introduction of vaccination against microorganisms such as *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Neisseria meningitidis*, the prevalence of SBI in febrile children older than 3 months has decreased significantly, down to 0.34 to 1 % [62, 85, 90].

**Serious bacterial infections**

Most studies define serious bacterial infections as bacteraemia, sepsis, pneumonia, complicated urinary tract infection [13, 91], bacterial meningitis [15, 30, 31, 73, 92, 93], acute osteomyelitis, and septic arthritis [10, 12, 14, 16, 17, 27, 28, 38, 94–101]. Other studies also include deep abscesses [12, 15, 92, 98], cellulitis [10, 14, 38, 96, 99], acute bacterial gastroenteritis [10, 14, 17, 28, 38, 95, 96, 99, 100, 102, 103], acute appendicitis [15, 92, 99], toxic shock syndrome [92], mastoiditis [12, 15], ethmoiditis [14, 28], and other infections in their definition SBI. While most studies on serious bacterial infection in febrile children have been conducted in emergency departments, admission to hospital was required for any of these infections to qualify as SBI in studies based on primary care cohorts [10, 38, 99]. There are also sight variations to the reference standards for the different SBIs applied to different research populations, which are reflected in Table 1.1.

Some studies and evaluation algorithms of acutely ill / febrile children include non-bacterial infection in their outcome definition of serious illness [10, 38, 95, 99, 100, 102, 103], such as aseptic meningitis [10, 15, 31, 38, 95, 99], lower respiratory tract infection (bronchiolitis) with hypoxia [100, 102, 103], gastroenteritis with abnormal electrolyte levels [100, 102, 103], Kawasaki disease [15], etc.

Table 1.1

**Most common serious bacterial infections and their reference standards**

| Infection | Prevalence among SBIs | Reference standards |
|---|---|---|
| Bacteraemia | 3.5 % (in febrile children up to 16 years in primary care [99]) to 37.5 % (in children aged 1 to 36 months with fever without source [93]) | Isolation of a [single] bacterial pathogen from blood culture [10, 12, 14, 17, 28, 30, 38, 73, 74, 93–107] |
| | | Detection of a single pathogenic bacterium in blood via culture or PCR [32] |
| | | Definite bacteraemia – detection of a single pathogenic microorganism on blood culture or PCR.<br>Probable bacteraemia – growth of two or more types of organism (one not a contaminant); growth of *Streptococci viridans* or other common contaminant in case of endocarditis [13, 27, 91] |
| Pneumonia | 6.9 % (lobar pneumonia in children aged 7 days to 36 months) [98] to 70.3 % (in children aged 1 month to 15 years) [12]. | Infiltrate [10, 12, 17, 28, 38, 95, 96, 99, 101–103] / consolidation [100] in a chest radiograph confirmed by radiologist |
| | | Lobar consolidation in a chest radiograph confirmed by a radiologist [94, 97, 98, 106] |
| | | Respiratory difficulty with consolidation in a chest radiograph [92] |
| | | Focal parenchymal density [74] / consolidation [13, 27, 91, 93] in a chest radiograph together with a pathogenic microorganism found on blood culture [13, 27, 73, 91] / pleural fluid [13, 27, 73, 91, 93] / positive serology for *Mycoplasma pneumoniae* [13, 27, 91]. |
| | | Nodular infiltrate or consolidation in chest radiograph assessed by two radiologists [14] |
| Urinary tract infection / acute pyelonephritis | 16.1 % (children younger than 17 years presenting to primary care) [10] to 85 % in children younger than 90 days presenting to ED [30]. | Isolation of at least $10^3$ [30, 95, 107–109] / colony forming units (CFU) of a single urinary tract pathogen in 1 ml of suprapubic aspirate urine sample<br>OR $10^3$ [95] / $10^4$ [30, 74, 92, 101] / $5 \times 10^4$ [104, 106–109] / $10^7$ [13, 27, 91]/ CFU /ml of catheterized sample<br>OR growth of $10^5$ [74, 92]/ $10^8$ [13, 27, 91] CFU/ml in a clean catch sample<br>OR $10^4$ to $5 \times 10^4$ CFU/ml in catheterized [107, 108] / clean catch sample [104, 109] plus abnormal urine analysis [104, 107–109] |
| | | Isolation of at least $10^5$ CFU/ml of a single urinary tract pathogen in urine culture [93, 97, 98] / two consecutive urine samples [94] AND cortical defect in renal cortical scintigraphy [93, 94, 97, 98] |
| | | Isolation of at least $10^5$ CFU/ml of a single urinary tract pathogen in urine culture PLUS white blood cells in urine AND serum C-reactive protein (CRP) elevation [10, 38] |
| | | Isolation of $10^4$ [73] / $10^5$ [96, 99] CFU/ml of a single organism in urine culture / Bacterial pathogen isolated from urine [12, 14, 17, 28, 100, 102, 103, 105] |

Table 1.1 continued

| Infection | Prevalence among SBIs | Reference standards |
|---|---|---|
| Bacterial meningitis | 0 % – 25 % | Bacterial pathogen isolated in cerebrospinal fluid (CSF) [14, 30, 32, 73, 74, 93–96, 100, 104–107, 109] |
| | | Pleocytosis and a bacterial pathogen isolated in CSF [10, 97–99] |
| | | Clinical meningitis plus a cerebrospinal fluid polymorphonuclear leucocytosis [12, 15] |
| Acute osteomyelitis / septic arthritis | 0 % – 6.7 % [32] | Pathogenic bacteria isolated from bone / joint aspirate [10, 12, 14, 32, 38, 95, 96] |
| | | Pathogenic bacteria isolated from bone / joint aspirate OR blood culture [94] |
| | | Pathogenic bacteria isolated from bone / joint aspirate OR MRI or bone scintigraphy suggestive for osteomyelitis [99] |
| Deep abscess / cellulitis | 0 % – 18.2 % [96] | Bacterial growth in specimen culture from soft tissue [14, 96, 102, 103, 106] |
| | | Identification of deep abscess assessed by computed tomography scan [92, 98] and surgical exploration [98] |
| | | Cellulitis [15] / deep collection [12] requiring admission or intravenous antibiotics [15] / surgical drainage [12] |
| | | Acute, suppurative inflammation of the subcutaneous tissues [10, 38, 99] |
| Bacterial gastroenteritis | 0 % – 6.9 % [12, 92] | Isolation of bacterial pathogen in stool [10, 14, 38, 74, 95, 100, 102–104, 106] |
| | | Isolation of Salmonella, Shigella or Campylobacter species in stool [96] |
| | | Isolation of bacterial pathogen in stool AND dehydration [99] |

### 1.2.2 Non-infectious causes

In acute febrile illness (lasting less than 7 days), non-infectious causes account for less than 5 % of cases [83], therefore they are usually considered when fever lasts longer and the cause of fever is unclear after a week of investigations, which is characteristic to fever of unknown origin (FUO). Even then, infection is one of the main reasons for fever, discovered in 19 to 59 % of cases of FUO in children [110–113]. Second most common reasons for FUO in children are autoimmune or inflammatory diseases, such as systemic lupus erythematosus, systemic juvenile idiopathic arthritis, Kawasaki disease, vasculitis, etc [112, 113]. Malignancies are a rare cause of fever in children, identified in 2 to 6.4 % of cases of FUO [112–114]. In up to a quarter of cases of FUO in children, the cause is never identified [112, 115].

## 1.3 Assessment of probability of serious bacterial infection in febrile children

### 1.3.1 Symptoms associated with serious bacterial infections

Several signs and symptoms have been included in assessment scores intended for patient triage and early recognition of serious illness in children who present to healthcare [2, 116–119]. Most of these clinical signs can be categorized in one of the following groups: vital signs, activity, signs of respiratory distress, skin symptoms, and hydration level. Though the scores, such as the NICE "Traffic light" system, Paediatric Early Warning Scores, and Manchester Triage system are widely used, the diagnostic value of the clinical signs selected as the most alarming features in these scores may be limited [11]. The following chapter discusses these clinical signs and their performance in recognition of SBI in studies including febrile children.

**Vital signs**

Vital signs include body temperature, heart rate, respiratory rate, oxygen saturation, capillary refill time, and blood pressure [15]. These parameters serve as basis for paediatric assessment scores such as SIRS (Systemic inflammatory response syndrome) criteria [120], modified and adapted SOFA and qSOFA (quick Sequential Organ Failure Assessment) scores [118, 120], NICE sepsis stratification tool [23], and as "amber" features in NICE "Traffic light" system [2], though reference ranges vary slightly among different assessment tools. While some studies have found association between abnormalities in specific vital signs or their combinations with serious infection in children, others have found little to no association when the correlation between abnormal vital signs and SBI have been analysed.

**Tachycardia**

Tachycardia (increased heart rate according to normal values for specific age) has been associated with increased likelihood of serious infection and intermediate infection in a prospective cohort study conducted in ED in United Kingdom [15], and has been included in several prediction models for SBI derived from ED cohorts in UK [12], Australia [13], and other research sites in Europe [32]. It must be noted that the positive likelihood ratio (LR (+)) for tachycardia was less than 5, and negative likelihood ratio was above 0.2 in these studies, which makes them of limited value for confirming or ruling-out SBI. Other studies conducted in ED in the Netherlands, UK [14], and Singapore [121] found no association between tachycardia and SBI. Interpretation of the relationship between tachycardia and SBI in febrile children is complicated by fever-related increase in temperature by approximately 10 beats per

minute with increase in body temperature by each degree Celsius, which is characteristic to children and infants older than 2 months [122, 123].

**Tachypnoea**

Tachypnoea / rapid breathing has been strongly associated with increased likelihood of SBI in two studies performed in primary care settings (LR (+) ≥ 5), though its rule-out value was limited (LR (–) = 0.70) [10, 99]. These studies included children aged 0 to 16 years, and tachypnoea was defined as breathing rate either above 40 breaths per minute [10], or above 50 breaths per minute [99]. Another study on children younger than 2 years presenting to ED found association between tachypnoea ( > 59 breaths per minute in infants younger than 6 months, > 52/min between 6 and 11 months, and > 42/min for children between 1 and 2 years) with pneumonia, though with less significant rule-in value (LR (+) = 3.08) [22, 124]. Other studies conducted in a paediatric assessment units or EDs have found association between tachypnoea and serious infection [15], pneumonia [13, 14], and urinary tract infection [13], though also yielding a LR (+) less than five. Tachypnoea has been included in several prediction models for SBI [12, 14, 28, 32, 33], though not all of them found significant association between tachypnoea and SBI when analysing the variable separately [12, 33], and different reference values for tachypnoea were used. Also, increase in respiratory rate related to elevated body temperature has been noted in several studies [123, 125], suggesting that adjustment of reference values for respiratory rate with regards to not only age, but the body temperature of the child [125]. Furthermore, tachypnoea may be equally associated with pneumonia and other, non-bacterial lower respiratory tract infections [125].

**Decreased oxygen saturation**

Hypoxia, or decreased oxygen saturation ($SaO_2$), has been associated with SBI [12, 15] or pneumonia [14, 126] in ED studies in UK, the Netherlands, and Australia (OR > 1, LR (+) < 5), but no association between decreased $SaO_2$ and SBI was found in one primary care study in Belgium [99] and a study in ED in Singapore [121]. Decreased oxygen saturation (SaO2 below 95 % [12], 94 % [14, 32] or 90/92 % [12, 126]) has been included in some prediction models for SBI [12, 14], moderate / severe pneumonia [126], or invasive bacterial infections [32].

**Prolonged capillary refill time**

Assessment of capillary refill time (CRT) is included in routine assessment of paediatric patients by several guidelines and screening tools [2, 118, 127, 128], though its diagnostic value for serious infection is inconclusive. In a systematic literature review published in 2010 [22], poor peripheral circulation [22, 28, 129] (defined as prolonged CRT [10, 15]) was identified as a warning sign (LR (+) (95 % CI) > 5) for SBI [10, 15, 28] or bacterial meningitis [129]. However, subsequent studies of children presenting to ED with fever or acute illness have failed to replicate these results. A large cohort study of children under 5 years presenting to an ED in Australia showed a modest association (odds ratio (OR) (95 % CI) > 1) between CRT 2 to 3 seconds and pneumonia, and no significant association with urinary tract infection or bacteraemia [13]. No significant association between prolonged CRT and the presence of SBI was found in three other prospective studies on febrile children presenting to ER in the Netherlands [14, 130] and the UK [14, 131]. The cut-off for normal versus prolonged CRT varies between studies – while some studies define prolonged CRT as that exceeding 2 seconds [15, 130], use 3 seconds as the cut-off [10, 14, 131]. A systematic review published in 2014 defines the upper limit of CRT as 4 seconds when assessed on the chest or foot, and 2 seconds when measured on a finger, suggesting that CRT above 3 seconds when measured on a finger should be considered abnormal. No significant effect of body temperature on CRT was found. Use of stopwatch is recommended for obtaining more accurate results and decreasing inter-observer variability [132]. Another systematic review on the diagnostic value of prolonged CRT in recognition of serious illness in children suggests that it should be considered as a "red flag" due to high specificity for serious outcomes such as severe illness, meningitis, sepsis, and death, though normal CRT should not be considered as reassuring as the sensitivity of prolonged CRT for these outcomes is low [133].

**Arterial hypotension**

Arterial hypotension (blood pressure below the $5^{th}$ percentile, or minus 2 standard deviations) in a child with infection is considered a sign of septic shock [134, 135] and prognostic of severe outcomes, such as acute kidney injury [136], and mortality [137]. However, in paediatric population, due to increased cardiovascular adaptive mechanisms such as increase in heart rate, normal blood pressure is maintained for much longer. Therefore, diagnosis of septic shock should be based on tachycardia, tachypnoea, and prolonged capillary refill, and altered mental state, with hypotension being a delayed sign [23].

**Very high fever**

More cautious approach to children, especially very young infants, with high fever (39 °C or more) is advised in several guidelines [2, 138], and the level of body temperature is included in several prediction rules for SBI [10, 12–15, 28, 30, 32, 96]. And yet very few studies independently associate the level of increase in body temperature with significantly higher likelihood for SBI. One study performed in primary care in Belgium including children 0 to 16 years (prevalence of SBI 0.78 %) showed high diagnostic accuracy for fever above 40 °C (LR (+) > 5), with high specificity (96.5 %) but lower sensitivity (20.7 %). Having fever above 40 °C increased the likelihood of serious infection from 0.8 % to 5.0 % [10]. However, a validation study performed in similar primary care settings showed much lower diagnostic accuracy (LR (+) (95 % CI) = 2.2 (0.6–7.6)) [99]. Another study on young infants (1 to 26 weeks) showed significant predictive value (LR (+) > 5) for body temperatures above 38.9 °C or below 36.4 °C and serious illness, though the definition of serious illness included non-bacterial illnesses such as bronchiolitis, intussusception, and gastroesophageal reflux [100]. Slightly increased likelihood (LR (+) = 2.8) of SBI in very young infants with body temperature 38.5 °C was identified in another study in Japan [139]. Some studies performed in paediatric assessment units and EDs show mild association between high fever (above 38.5 °C [12] / 39.0 °C [15] / 39.5 [92]) and SBI, though with lower diagnostic accuracy (LR (+) < 5), while others have found mild association between higher temperatures and pneumonia [13, 14] or urinary tract infection [13], but not bacteraemia [13] or other SBIs [14]. A systematic review and meta-analysis based on 11 studies found that body temperature above 40 °C increased the risk for SBI in infants but not in older children [140]. A few other studies have found no significant association between the degree of fever and increased likelihood of SBI [73, 91, 96, 97].

**Activity**

Evaluation of the child's behaviour and activity level is one of the most significant components in many assessment scores for febrile children [2, 14, 103, 141, 142]. An ill-appearing child with altered or no response to social cues, drowsiness, or lethargy, and changed crying pattern is categorized as high risk, while normal activity level and response to social cues are seen as reassuring [2, 103]. Changes in the child's behaviour are one of the key observations made by parents of seriously ill children [41], whereas clinician's assessment of ill appearance in the child is one of the strongest predictors of SBI [10, 14, 22, 32, 38, 99].

**Ill appearance**

The definition of ill appearance varies between studies. Some define it simply as "child appears (seriously) ill to the healthcare personnel" [10, 11, 13, 14, 73, 99, 143], while others use a more complex definition based on a complication of several factors, such as the child's activity, reaction to social stimuli, quality of cry, changes in skin colour, and hydration [14, 96, 103]. Another study defines "clinical impression" of serious illness as "a subjective observation that the illness is serious on the basis of the history, observation, and clinical examination" [38]. The highest reported diagnostic (rule-in) value for ill appearance in detecting SBI comes from primary care studies (LR (+) > 5) [10, 22, 99]. In hospital EDs, ill appearance has also associated with SBI, though with more limited diagnostic accuracy (OR > 1; LR (+) < 5) [11–14, 28, 32]. Two studies [96, 129] found no association between ill appearance / clinical impression and SBI.

A suggested limitation to ill appearance may be inter-rater variability in classifying children as "ill appearing" or "not ill appearing", however studies suggest that the inter-rater reliability for ill appearance is clinically adequate and not significantly affected by the level of experience of the clinician [38, 144].

**Changes in behaviour**

Other changes during child's behaviour associated with increased likelihood of serious illness are drowsiness [10, 99, 100, 129], changed crying pattern [10, 22], moaning [10, 22, 99], and reduced consciousness [10, 12, 99]. Inconsolability has been found to increase the likelihood of SBI in one primary care study [10], while no significant association was found in a validation study in similar settings [99]. The same study associated weak or high-pitched cry with SBI [10], though the association is very weak or insignificant in populations with high prevalence of SBI [11, 15, 28, 129]. The diagnostic ability of changed response to social cues, an important "red flag" sign in NICE "Traffic light" assessment score [2] and Yale observation scale (YOS) [103], for SBI has been found to be limited [10, 129] or poor [11, 12, 145]. According to studies in both high and low prevalence settings, the association between restlessness or irritability and SBI is insignificant [10, 92, 99]. Poor feeding (decreased eating or drinking) has been associated with increased likelihood of serious illness (also including conditions without bacterial aetiology) in one study with young infants (0 to 26 weeks) [100], while in other studies this observation has limited to no diagnostic value [10, 92, 99].

**Respiratory symptoms**

Assessment of respiratory symptoms is another component of the NICE "Traffic light" system of children under 5 years of age. According to this assessment tool, nasal flaring and crackles in the chest are associated with intermediate risk for serious illness, whereas grunting and chest recessions – with a high risk.

**Use of accessory breathing muscles**

Evidence on the association between chest recessions and significantly increased risk for serious illness (LR (+) > 5 has been found in two studies in general practice settings with low prevalence of SBI (3 % or less) [10, 99]. Association of equal strength was found in one study conducted paediatric ED including infants aged 1 to 26 weeks [100], though it also included non-bacterial illnesses in the outcome of serious illness, such as bronchiolitis. Other studies conducted in intermediate or high prevalence settings have found significant but limited diagnostic value for chest retractions with regards to SBI [17, 28] or pneumonia [14, 146, 147], and some have found no significant association [11, 13, 33, 121]. While only attributed intermediate risk for serious illness according to NICE "Traffic light" tool, nasal flaring has been strongly associated with SBI in a study in primary care settings [99], and has been significantly associated with pneumonia in several other studies [146–148], though with lesser diagnostic accuracy.

**Grunting**

Grunting has been found to be significantly predictive of SBI in one study in paediatric ED [11, 12]. Elsewhere it has showed limited but significant diagnostic value (LR (+) < 5, OR > 1) in infants aged 1 to 26 weeks recruited in paediatric ED in Australia [100], while in another study, grunting was associated with SBI in children older than 3 months, or children at all ages who had a chronic disease, however no association between grunting and SBI was found in previously healthy infants below the age of 3 months [105].

**Abnormal breathing sounds**

Abnormal auscultative sounds have variable diagnostic value for SBI. The strongest diagnostic accuracy (LR (+) > 5) for crackles (crepitations) found in a primary care study [10], while other studies both in primary care [99] and hospitals report significant but weaker association, mostly with pneumonia [13, 146, 147]. Limited [99] or no significant predictive value for SBI has been detected for rhonchi or wheezing [13, 33, 146, 147, 149], or stridor [13]. Decreased breathing sounds have been associated with SBI in primary care studies [10, 99] and

with pneumonia in studies in ED [13, 33, 146, 148], while other studies report no significant diagnostic value [147].

**Skin**

A section of febrile child assessment in both NICE "Traffic light" system and Yale observation scale is dedicated to evaluation of any changes in the colour of the skin, lips, and tongue [2, 103]. Both associate pale, ashen, mottled, or cyanotic colour with high risk for serious illness. Non-blanching, or haemorrhagic, rash such as petechiae or purpura is also associated with high risk in the NICE guidelines, especially with regards to meningococcal infection or sepsis [2].

**Changes in skin colour**

Of all changes in skin colour, Cyanosis has the most evidential support for significantly increased likelihood for SBI (LR (+) > 5), coming from studies in both primary care [10, 99] and EDs [129]. Pallor has variable reported diagnostic accuracy for SBI – from high in infants up to 26 weeks [100] and children with suspected meningococcal disease [150] to significant but limited in children up to 16 years presenting to primary care [99]. Mottled colour has been significantly associated with SBI in study including infants up to 3 months of age presenting to ED [121]. When all mentioned abnormal skin colour changes (pale / ashen / mottled / blue) have been studied together, the predictive value for SBI varies from high (in low prevalence settings) [10] to significant, but limited (LR (+) < 5, OR > 1) [11, 12, 15, 28, 96, 129].

**Non-blanching rash**

Non-blanching rash along with fever has been considered as one of the most significant "red flag signs" for serious illness requiring immediate screening for sepsis and meningococcal disease, and administration of antibacterial therapy without delay [2, 151]. Indeed, significantly increased likelihood for SBI in febrile children with petechial rash has been confirmed by many studies with varying prevalence of SBI [10, 11, 32, 92, 93, 99, 129, 152, 153]. However, studies suggest that only a small proportion (around 2 to 23 %) of children with haemorrhagic rash are eventually diagnosed with meningococcal disease or sepsis [150, 152–156]. These studies observed that febrile children with petechiae were more likely to have meningococcal disease or sepsis if they were ill-appearing, irritable or lethargic, and had disseminated haemorrhagic rash, nuchal rigidity, prolonged capillary refill time, or hypotension [152–155], while the probability of sepsis in well-appearing infants and children with petechiae was small [154, 157]. Many children with haemorrhagic rash and fever are diagnosed with self-limiting viral

infections that do not require hospital admission or antibiotics [150, 152, 155]. Therefore, revised guidance suggests a tailored approach to febrile children with petechiae with regards to referral to EDs and initiation of antimicrobial therapy [150, 152, 156, 158].

**Hydration**

Assessment of child's hydration status during febrile illness is one of the main aspects that may affect the decision to refer a child from primary care to ED [159], and some signs of dehydration have been associated with intermediate or high risk of serious illness in paediatric assessment [2, 102]. Yet whether signs of dehydration are truly suggestive of SBI is inconclusive.

The analysis of the association between signs of dehydration and SBI is complicated by the fact that fever itself increases the metabolic rate of the affected individual [160–162], thus affecting both caloric and fluid requirement, and the changes in body temperature facilitate fluid loss due to increased respiration and sweating [163]. Though these effects may contribute to need for intervention due to dehydration, they are physiological manifestations of fever regardless of the cause [162].

**Sings of dehydration**

Decreased skin turgor is considered a high-risk feature according to the NICE "Traffic light" system [2]. While there are studies in both ED settings [11, 12, 129] and primary care [99] that confirm the strong prognostic value, data from other studies show limited [28] diagnostic value or even no significant association between reduced skin turgor and serious illness [10, 11, 15]. Some association has been found between dry mucous membranes or other signs of dehydration and serious illness, though the diagnostic value has been limited (LR (+) < 5) [10, 12].

**Decreased urine output**

On the relationship between decreased urine output and serious illness, the data are contradictory. One study on young infants up to 26 weeks presenting to ED found that decreased urine output (less than four nappies per day) was significantly associated with serious illness (LR (+) > 5) [100], however it has to be noted that the study included non-bacterial illnesses in their definition of serious illness, such as gastroenteritis (also non-bacterial), bronchiolitis, pyloric stenosis, and others. Significant but limited association between reduced urine output reported by parents, and SBI (OR > 1, LR (+) < 5) was found in one primary study on febrile

children up to 16 years [99]. In contrast, another study on febrile children aged one to 36 months found that history of poor voiding was associated with decreased likelihood of SBI [17].

### Other signs and symptoms

#### Duration of fever

Most studies have found that the mean duration of fever prior to presentation was significantly longer in febrile children who are diagnosed with SBI compared to children without SBI [14, 17, 73, 97, 98] and that children with prolonged fever (for more than 48 hours) were diagnosed with SBI more frequently than others [10, 96, 99]. Duration of fever as a predictor variable has been included in several prediction models for SBI [14, 28, 32, 96]. However it may not been selected as an independent "red flag" sign for SBI because of the limited rule-in value (LR (+) < 5) [10, 22, 28, 74, 96, 99].

#### Shivering

Shivering or rigors is an intermediate risk ("amber") sign in the NICE Traffic light system [2]. However, a recent systematic review on the diagnostic value of shivering [164] with regards to SBI has found that, while significantly associated with serious infection in children with known malignancies (LR (+) (95 % CI) = 3.47 (2.58–4.36), shivering has poor diagnostic value in children with no malignancies [165–168].

#### Positive meningeal signs

The presence of meningeal signs, such as nuchal rigidity, Brudzinski's sign, Kernig's sign, significantly increases the likelihood that the child will be diagnosed with serious illness in a systematic review published in 2010 and in later studies [10, 22, 99, 129, 152, 169, 170], though some of these studies included aseptic meningitis in their outcome definition along with bacterial meningitis [10, 99]. Even so, there is evidence that signs of meningeal irritation are markedly more common in febrile children with bacterial meningitis compared to those with aseptic meningitis [171, 172], with Kernig's sign having the highest specificity and positive likelihood ratio for prediction of bacterial meningitis [170]. Bacterial meningitis is diagnosed in close to 40 % of cases with positive meningeal signs [171].

However, the absence of meningeal signs does not rule out bacterial meningitis, especially in infants and neonates [173]. In infants, bacterial meningitis more commonly manifests with non-specific symptoms like irritability or lethargy, poor feeding, vomiting, and other symptoms such as seizures, bulging fontanel, etc [171, 172, 174]. In very young infants and neonates, bacterial meningitis should be considered in case of fever, ill appearance, and

absence of criteria for low risk of SBI [107, 173]. In addition, use of antibiotics prior to presentation is known to alter the clinical manifestations of bacterial meningitis [175, 176].

### Seizures

Status epilepticus and focal seizures have been listed among the high-risk ("red") features in the NICE traffic light system [2]. Indeed, seizures and status epilepticus are reportedly associated with bacterial meningitis [10, 22, 100, 129, 169, 177, 178]. However, differentiation between complex and simple febrile seizures is important, as the incidence of bacterial meningitis in the latter is low, even in infants [179–182]. Therefore, the necessity of performing a lumbar puncture in children living in developed countries with simple febrile seizure should be carefully considered or decided against [181–183], except in case of other important circumstances, such as previous antibiotic use, which could alter the natural manifestations of the disease [176].

### Pain and swelling of a limb

Swelling of limb or joint as well as non-weight bearing or not using an extremity are considered as intermediate risk factors ("amber") for SBI [2]. While studies analysing these symptoms as predictor variables for SBI are scarce [13, 99], they are known as possible symptoms of acute osteomyelitis, septic arthritis [184, 185] and other serious conditions like erysipelas, cellulitis, deep vein thrombosis, or malignancy [186–188]. In any case when these symptoms are present, an extensive workup is necessary for clarification of their cause.

### Other factors

### Age

Febrile children younger than 3 months are generally considered at higher risk of serious infection [189], and much more cautious approach is applied to very young infants when compared to older children. As fever may be the only sign of SBI at this age, clinical evaluation may fail to identify children with higher likelihood of infection [95, 190, 191], therefore these infants are mostly hospitalized and undergo an in-depth investigation, including blood culture, biomarkers, and lumbar punctures. In addition, broad spectrum antibiotics are often initiated [107]. To avoid overuse of antibiotics and invasive investigation (lumbar puncture), several assessment scores for very young infants have been proposed, such as Philadelphia criteria [142], Rochester criteria [141], Boston criteria [192], and PECARN (Pediatric Emergency Care Applied Research Network) rule [107]. These prediction rules include both clinical assessment (ill appearance vs well appearance), and some basic investigation results.

Indeed, many studies performed in population of febrile infants show higher prevalence (up to 30 %) of SBI [95, 96, 100, 121] compared to studies in similar clinical settings involving children of wider age range [12–15], though studies showing lower (10 % or less) prevalence of SBI in very young infants presenting to ED [30, 73] also exist. However, whether very young age is predictive of SBI in febrile children is not very clear. While fever in infants under one month has been found significantly associated with SBI [96], some studies indicate that the incidence of SBI in febrile children aged 2 to 3 months is similar to that in other children up to 6 months [73] 3 years of age [97]. A study on children with hyperpyrexia presenting to an ED in the United States found that the incidence of SBI was significantly lower in children older than 36 months compared to younger children and infants [74], whereas other studies on febrile children presenting to an ED found no diagnostic value of age as predictor variable in either of these age groups [12, 13]. A systematic review on the diagnostic value of clinical signs concluded that age is of limited value in confirming or ruling-out SBI in febrile children [22]. Nevertheless, it is included as a predictor variable in a few prediction models or decision trees for SBI [10, 14, 32].

**Sex**

Most studies show that the prevalence of SBI is similar in males and females [10, 12–14, 73, 96, 106]. Two studies on very young febrile infants presenting to an ED showed significantly higher prevalence of SBI in males, largely due to urinary tract infections [121, 193]. Another study found out that all of the included infants (age < 60 days) who were misclassified as low risk by PECARN rule were males [109]. Other studies on SBI in young infants either showed similar risk for SBI in both sexes [73, 104, 106], or did not analyse differences in sex [30, 31, 95, 100, 107, 194]. Some studies report lower rates for urinary tract infection in circumcised males [73, 193, 195]. After young infancy, the incidence of urinary tract infection is known to be higher in females [13, 195, 196].

**Underlying medical condition**

Analysing the impact of chronic underlying medical condition on the risk for SBI in children is complicated since these children are excluded from most studies [22]. This also means that most of the diagnostic tools designed for recognition of SBI in febrile children are not applicable to children with chronic comorbidities [32]. While some conditions like congenital or acquired immunodeficiencies and illnesses requiring use of immunosuppressive medication are known to increase the risk for SBI, the impact of other conditions such as neurological deficit is less understood. Of the few studies that have included children with

chronic conditions, chronic disease is found to increase the likelihood of SBI [12, 13, 32, 74]. However more studies are necessary for full understanding on how chronic conditions affect the clinical presentation of febrile illness and the likelihood of SBI.

### 1.3.2 Assessment scores for febrile children

Although recognition of "red flag" signs in febrile children is essential in detection of potential SBI, these clinical features usually have low sensitivities when analysed independently. Several assessment scores including combination of alarming clinical features have been introduced, often leading to higher sensitivity and accuracy in recognizing serious illness. Arguably the best known and widely used clinical scores for identification of children with higher risk for serious infection, sepsis, or other severe outcomes are Manchester Triage System (MTS) [197], NICE "Traffic light" tool [2], NICE Sepsis stratification tool [74], Yale Observation Scale (YOS) [103], Paediatric Observation Priority Score (POPs) [117], Systemic Inflammatory Response Syndrome (SIRS) criteria [198], and Paediatric Sequential Organ Failure Assessment Score (pSOFA) [199].

In addition to high-risk scores, several tools have been designed to predict non-serious illness and safe discharge, especially for very young infants, with the goal to limit the use of invasive investigation and unnecessary hospitalization. While some of the high-risk scores can be used for this purpose by ruling out alarming symptoms, other tools, such as the Rochester criteria [141], Philadelphia criteria [142], Boston criteria [192], and the PECARN tool [107] have been created to recognize low risk for SBI. Along with clinical features, these assessment tools include some laboratory values.

As pre-laboratory stage of assessment of febrile children by clinicians at the emergency department is the primary emphasis of this thesis, the diagnostic performance of the clinical assessment scores for prediction of serious illness in these settings, namely Yale Observation Scale and NICE "Traffic light" tool will be discussed further in detail.

#### Yale observation scale

In 1982, McCarthy et al introduced an assessment scale for febrile children, originally younger than 24 months, to detect serious illness [103]. The scale consists of six items: quality of cry, reaction to parent stimulation, state variation, changes in skin colour, hydration, and response to social stimuli (see Table 1.2.). A total score above 10 was determined to indicate ill appearance. In the original study, less than 3 % of patients with YOS equal or below 10 had serious illness, compared to 92.7 % with score 16 points or above [103].

Table 1.2

**Yale Observation Scale**

| Observation item | Normal (Score = 1) | Moderate Impairment (Score = 3) | Severe Impairment (Score = 5) |
|---|---|---|---|
| 1. Quality of cry | Strong with normal tone OR Content and not crying | Whimpering OR Sobbing | Weak OR Moaning OR High pitched |
| 2. Reaction to parent stimulation | Cries briefly then stops OR Content and not crying | Cries off and on | Continual cry OR Hardly responds |
| 3. State variation | If awake → Stays awake OR If asleep and stimulated → wakes up quickly | Eyes close briefly awake OR awakes up with prolonged stimulation | Falls to sleep OR Does not wake up |
| 4. Colour | Pink | Pale extremities OR Acrocyanosis | Pale OR Cyanotic OR Mottled OR Ashen |
| 5. Hydration | Skin normal, eyes normal AND Mucous membranes moist | Skin, eyes – normal AND Mouth slightly dry | Skin doughy / tented AND Dry mucous membranes AND/OR Sunken eyes |
| 6. Response (talk, smile) to social overtures | Smiles OR Alerts (< 2 mo) | Brief smile OR Alerts briefly (< 2 mo) | No smile, Face anxious / dull / expressionless OR No alerting (< 2 mo) |

The diagnostic value of the scale has been assessed in numerous validation studies including very young infants or children up to 3 years of age. And yet, most of the validation studies have yielded disappointing results. While the sensitivities and specificities of ill appearance according to YOS (score above 10 points) are highly variable, only one study with 219 participants reports high ability to recognize bacteraemia in febrile children [200]. In other studies, YOS has provided limited value in recognizing SBI (LR (+) < 5). Some studies show little difference in YOS results between children with or without SBI [191, 201–203], and missing a significant proportion of patients with SBI as they are evaluated as “well-appearing” [73, 95, 191]. The sensitivities, specificities, positive and negative likelihood ratios of YOS > 10 in validation studies are listed in Table 1.3.

Table 1.3

**Diagnostic performance of Yale Observation Scale above 10 points in validation studies**

| Study | Type, inclusion criteria | Outcomes | Prevalence of outcome | Sensitivity, % (95 % CI) | Specificity, % (95 % CI) | LR (+) (95 % CI) | LR (–) (95 % CI) |
|---|---|---|---|---|---|---|---|
| Baker et al, 1990 [95] | Prospective, consecutive. Infants 29 to 56 days old, rectal temperature ≥ 38.2 °C presenting to ED in USA | Serious illness (SBI + aseptic meningitis | 29.4 % | 46.0 (29.5–63.1) | 79.8 (69.9–87.6) | 2.27 (1.32–3.90) | 0.68 (0.49–0.93) |
| | | SBI | 15.1 % | 33.3 (9.9–65.1) | 72.8 (63.7–80.7) | 1.23 (0.52–2.88) | 0.92 (0.60–1.39) |
| Teach et al, 1995 [201] | Retrospective analysis, multicentre (8 EDs in USA), 90 days to 36 months of age, temperature ≥ 39.0 °C, non-focal illness | Bacteraemia | 2.9 % | 5.2 (2.5–9.4) | 96.7 (96.3–97.2) | 1.59 (0.86–2.95) | 0.98 (0.95–1.01) |
| Jamuna et al, 2000 [204] | Prospective; outpatient department and ED, India Age 3 to 36 months, Temperature > 99 °F, no localized signs of infection | Bacteraemia | 4 % | 100 | 41.6 | 1.71 | 0 |
| Galetto-Lacour et al, 2001 [97] | Prospective; ED, Switzerland; Age 7 days to 36 months; Temperature (rectal) > 38.0 °C; no local signs of infection | SBI | 22.6 % | 20 (3–56) | 86 (76–93) | 1.43 | 0.93 |
| Galetto-Lacour et al, 2003 [98] | Prospective; ED, Switzerland; Age 7 days to 36 months; Temperature (rectal) > 38.0 °C; no local signs of infection | SBI | 29.3 % | 23 (5–54) | 82 (67–92) | 1.28 | 0.94 |
| Andreola et al, 2007 [94] | Prospective, consecutive, ED, Italy. Fever with unknown source. Age 7 days to 3 months with temperature > 38.0 °C, age 3 to 36 months with temperature > 39.5°C | SBI | 23 % | 38.3 (28.5–48.9) | 67.8 (62.4–73.0) | 1.19 | 0.91 |

| Study | Type, inclusion criteria | Outcomes | Prevalence of outcome | Sensitivity, % (95 % CI) | Specificity, % (95 % CI) | LR (+) (95 % CI) | LR (–) (95 % CI) |
|---|---|---|---|---|---|---|---|
| Bang et al, 2009 [200] | Prospective, children 3 to 36 months with rectal temperature 38.0 °C presenting to rural hospital in India | Bacteraemia | 28 % | 87.9 (71.0–92.8) | 83.8 (73.0–87.3) | 5.42 (3.71–7.92) | 0.14 (0.07–0.29) |
| Verbakel et al, 2013 [205] | 7 datasets of febrile children presenting to primary care and ED in UK, Netherlands, Belgium, each with different age range and inclusion criteria. | Serious infection | Low prevalence – 4.0 % (Monteny et al)[206] | 23.1 (5.04–53.8) | 93.2 (90.5–95.3) | 3.38 (1.19–9.64) | 0.83 (0.61–1.11) |
| | | | Intermediate prevalence – 5.3 % (Brent et al) [12] | 22.3 (15.9–29.9) | 94.5 (93.6–95.3) | 4.05 (2.88–5.69) | 0.82 (0.75–0.90) |
| | | | High prevalence – 37.7 % (Thompson et al) [15] | 19.5 (14.7–25.1) | 88.6 (85.2–91.5) | 1.71 (1.18–2.48) | 0.91 (0.85–0.98) |
| Kansakar et al, 2014 [207] | Cross-sectional, children aged 1 to 36 months presenting to hospital in Nepal with fever ≤ 7 days | SBI | 33 % | 45.5 (28.1–63.5) | 88.1 (77.8–94.7) | 3.81 (1.80–8.06) | 0.62 (0.45–0.86) |
| Florin, 2021 [208] | Convenience sample, 26 EDs participating in PECARN. infants 60 days or younger, rectal temperature ≥ 38°C | Definite pneumonia | 2.7 % | 28.3 (16.0–43.5) | 86.4 (84.7–88.0) | 2.08 (1.29–3.35) | 0.83 (0.69–1.00) |

Table 1.3 continued

**NICE "Traffic light" system**

The "Traffic light" system is a part of UK's National guidance "Feverish illness in children: assessment and initial management in children younger than 5 years" issued first in 2007 and revised in 2013 by National Collaborating Centre for Women's and Children's Health, and commissioned by National Institute for Health and Care Excellence (NICE) [2]. The tool is partially based on the features of Yale Observation Scale, with addition of other alarming features, and were discussed, and approved by, wide range of clinical specialists including nurses, general practitioners, paediatric registrars, and consultants in paediatrics, infectious diseases, and emergency medicine [209]. The updated 2013 version of "Traffic light" tool [2, 210] is illustrated in Table 1.4.

Table 1.4

**NICE "Traffic light" system**

| | **Green – low risk** | **Amber – intermediate risk** | **Red – high risk** |
|---|---|---|---|
| Colour (of skin, lips, or tongue) | • Normal colour | • Pallor reported by parent / carer | • Pale / mottled / ashen / blue |
| Activity | • Responds normally to social cues<br>• Content / smiles<br>• Stays awake or awakens quickly<br>• Strong normal cry / not crying | • Not responding normally to social cues<br>• No smile<br>• Wakes only with prolonged stimulation<br>• Decreased activity | • No response to social cues<br>• Appears ill to the healthcare professional<br>• Does not wake or if roused does not stay awake<br>• Weak, high-pitched, continuous cry |
| Respiratory | • | • Nasal flaring<br>• Tachypnoea: respiratory rate<br>• >50 breaths / minute age 6–12 months<br>• >40 breaths / minute, age >12 months<br>• Oxygen saturation ≤ 95 %<br>• Crackles in the chest | • Grunting<br>• Tachypnoea: respiratory rate > 60 breaths / minute<br>• Moderate or severe chest indrawing |
| Circulation and hydration | • Normal skin and eyes<br>• Moist mucous membranes | • Tachycardia:<br>• > 160 beats / minute, age < 12 months<br>• >150 beats / minute, age 12–24 months<br>• > 140 beats / minute, age 2–5 years<br>• Capillary refill time ≥ 3 seconds<br>• Dry mucous membranes<br>• Poor feeding in infants<br>• Reduced urine output | • Reduced skin turgor |

Table 1.4 continued

| | Green – low risk | Amber – intermediate risk | Red – high risk |
|---|---|---|---|
| Other | • None of the amber or red symptoms or signs | • Age 3–6 months, temperature ≥ 39 °C<br>• Fever for 5 days or longer<br>• Rigors<br>• Swelling of a limb or joint<br>• Non-weight bearing limb / not using an extremity | • Age < 3 months, temperature ≥ 38 °C<br>• Non-blanching rash<br>• Bulging fontanelle<br>• Neck stiffness<br>• Status epilepticus<br>• Focal neurological signs<br>• Focal seizures |

The diagnostic accuracy of the NICE "Traffic light" system or its selected alarming features has been assessed in two prospective [15, 211] and four retrospective studies [11, 27, 205, 212]. Four of these studies [15, 27, 205, 211] were conducted prior to the revision in 2013. The 2013 update in the "Traffic light" system included adding the features "tachycardia" and "rigors" to "amber" risk factor column, removal of features "a new lump larger than 2 centimetres" and "bile-stained vomiting", and moving "temperature ≥ 39 °C in a child aged 3 to 6 months" from the "red" to "amber" category [213].

An analysis of the diagnostic performance of the "red" features in the updated tool in a combination of datasets from various clinical settings [11] showed that some of the "red" features failed to show a high rule-in value (LR(+) > 5), and the diagnostic performance of other features varied among settings of different prevalence of serious infection. The diagnostic performance of the "red flag" signs in most of the datasets was limited (LR (+) < 5) even when three or more of them were present.

In assessment of the predictive value of presence of any of the "red" or "amber" features of the NICE "Traffic light" system, all validation studies yielded relatively high sensitivities (ranging from 85 to 100 %), but low specificities (0.12 to 29 %) and relatively low positive likelihood ratios, which were lower than 5. Studies report that some cases of SBI, mainly urinary tract infections, are missed by the sole use of the "Traffic light" tool [15, 27], but the diagnostic performance is improved by addition of urine analysis [27, 214], which is recommended by the NICE guidance for febrile children who fall into the "low-risk" category [2]. One study reported presence of at least one of the "red" or "amber" features in three-quarters of patients with mild infection [15].The sensitivities, specificities, positive and negative likelihood ratios are reflected in Table 1.5.

**Diagnostic performance of presence of any of the "red" and "amber" features of NICE "Traffic light" system**

| Study | Type, inclusion criteria | Outcomes | Prevalence of outcome | Sensitivity, % (95 % CI) | Specificity, % (95 % CI) | LR (+) (95 % CI) | LR (–) (95 % CI) |
|---|---|---|---|---|---|---|---|
| Thompson et al, 2009 [15] | Prospective, Children aged 3 months to 16 years with suspected acute infection | Serious infection, Intermediate infection VS Minor infection, No infection | 15.4 % (serious infection) 29.3 % (intermediate infection) | 85 (81–89) | 29 (25–34) | 1.2 (1.1–1.3) | 0.5 (0.4–0.7) |
| De et al, 2013 [27] | Retrospective, febrile children under 5 years presenting to ED | SBI | 7.1 % | 85.8 (83.6–87.7) | 28.5 (27.8–29.3) | 1.2 | 0.5 |
| Yao et al, 2019[212] | Retrospective, febrile infants ≤ 3 months presenting to ED | Serious illness | 30.8 % | 93.3 (90.0–95.7) | 14.1 (11.7–16.8) | 1.09 (1.0–1.1) | 0.48 (0.3–0.7) |
| Verbakel et al, 2014 [211] | Prospective, acutely ill children up to 16 years admitted to hospital | Sepsis, meningitis | 0.47 % | 100 (92.9–100) | 0.12 (0.00–0.69) | 0.99 (0.97–1.02) | 5.28 (0.22–1.28) |
| Verbakel et al, 2013 [205] | 7 datasets of febrile children presenting to primary care and ED in UK, Netherlands, Belgium, each with different age range and inclusion criteria | SBI | Low prevalence –4.0 % (Monteny et al) [206] | 100 (83.2–100) | 1.03 (0.34–2.38) | 0.99 (0.92–1.06) | 2.11 (0.12–36.9) |
| | | | Intermediate prevalence – 5.3 % (Brent et al) [12] | 97.3 (93.2–99.3) | 26.7 (25.1–28.5) | 1.33 (1.28–1.38) | 0.10 (0.04–0.27) |
| | | | High prevalence – 43.8 % (Oostenbrink et al) [215] | 90.9 (86.8–94.1) | 25.7 (21.6–30.1) | 1.22 (1.14–1.31) | 0.35 (0.23–0.54) |

### 1.3.3 Clinical prediction models for SBI in febrile children

Relying on presence or absence of individual clinical signs in assessment of children during febrile illness may be complicated due to low sensitivities and possible lack of manifestation of these signs early in illness, while assessment scores that categorize clinical parameters in different risk categories are partially consensus-based and often fail to show high accuracy in clinical studies. Clinical prediction rules derived from prospectively acquired data use statistical methods to select a combination of variables that can effectively estimate the probability for the patient to have serious infection.

Many clinical prediction models (CPMs) for serious infection in children with fever or acute illness have been derived in the last two decades. Some are based on clinical features alone [10, 13, 15, 216], while some require inflammatory markers, such as leukocyte count, urine analysis, or CRP [14, 28, 30, 32, 96]. Some models are derived to predict the probability of serious infection in young infants [30, 96, 217], while others are applicable to children of variable age range [10, 12, 14, 15, 32]. The clinical prediction models for SBI are described in detail in Table 1.6.

Table 1.6

**Description of clinical prediction models**

| Authors, year | Country, Setting | Inclusion criteria | Age range | Sample / prevalence of SBI | CPM variables |
|---|---|---|---|---|---|
| **High / Low risk prediction** | | | | | |
| Bachur and Harper, 2001[30] | ED, USA, retrospective | Rectal temperature ≥ 38.0°C | ≤ 90 days | 5279/7.1 % | Positive urine analysis; WBC > 20.000 or Temperature > 39.6 °C, WBC < 4.100, Age < 13 days |
| Van den Bruel et al, 2007 [10] | GP, ED (self-referred), Belgium, prospective, consecutive | Acute illness for maximum 5 days | 0–16 years | 3901/0.78 % | Clinician's instinct something is wrong), Dyspnoea, Temperature ≥ 39.95 °C Diarrhoea Age ≥ 2.42 years Age ≤ 1.18 years |
| Thompson et al, 2009 [15] | UK, PAU, prospective | Suspicion of acute infection | 3 months to 16 years | 700/15.4 % serious infection, 29.3 % intermediate infection | Temperature ≥ 39.0 °C Tachypnoea Tachycardia CRT > 2 seconds $O_2$ saturation ≤ 94 % |

Table 1.6 continued

| Authors, year | Country, Setting | Inclusion criteria | Age range | Sample / prevalence of SBI | CPM variables |
|---|---|---|---|---|---|
| **Continuous risk prediction** | | | | | |
| Berger et al, 1996 [96] | Netherlands, ED, prospective, consecutive | Rectal temperature ≥ 38.0 °C | 2 weeks to one year | 138/23.9 % | Duration of fever<br>Standardised clinical impression score<br>Diarrhoea<br>Focal signs<br>of infection CRP |
| Bleeker et al, 2007 [28] | Netherlands, ED, prospective, consecutive | Temperature ≥ 38.0°C<br>Fever without source | 1 to 36 months | 381/25.1 % | Ill appearance<br>Poor peripheral circulation<br>Chest wall retractions + tachypnoea<br>Duration of fever (days)<br>History of vomiting<br>(Clinical + laboratory model also includes CRP, leukocyte count, positive urine analysis) |
| Craig et al, 2010 [13] | Australia, ED, prospective, consecutive | Fever (axillary / reported temperature ≥ 38.0 °C), "child felt hot" | 0 to 5 years | 15781/7.2 % (UTI 3.4 %, Pneumonia 3.4 %, bacteraemia 0.4 %) | 26 variables |
| Brent et al, 2011[12] | UK, ED, prospective, consecutive | Suspected acute infection | 1 month to 16 years | 1951/3.8 % | History of developmental delay<br>Risk factor for infection<br>State variation<br>Temperature category<br>Capillary refill time<br>Dehydration category<br>Tachypnoea<br>Hypoxia category |
| Nijman et al, 2013 [14] | Netherlands (validation UK), ED, prospective, consecutive | Temperature ≥ 38.0 °C | 1 month to 15 years | 2717/12.6 % | Age Female sex<br>Duration of fever (days) Temperature<br>Tachypnoea<br>Tachycardia<br>Oxygen saturation < 94 % Capillary refill time > 3 sec.<br>Chest wall retractions<br>Ill appearance CRP |

Table 1.6 continued

| Authors, year | Country, Setting | Inclusion criteria | Age range | Sample / prevalence of SBI | CPM variables |
|---|---|---|---|---|---|
| **Continuous risk prediction** | | | | | |
| Hagedoorn et al, 2020 [32] | 12 EDs in 9 European countries, prospective | temperature ≥ 38.0 °C or fever < 72 hours before ED visit | 0 to 18 years | 16268/0.8 % (invasive bacterial infections) | Sex<br>Age<br>Temperature<br>Duration of fever<br>Tachypnoea<br>Tachycardia<br>Hypoxia<br>Increased work of breathing<br>Ill appearance<br>Non-blanching rash<br>Abnormal neurology<br>CRP |
| Yaeger et al, 2021 [217] | ED, USA Cross-sectional, retrospective | Temperature ≤ 38.0 °C (documented or reported) | ≤ 90 days | 877/7.6 % | Sex<br>Insurance<br>Chronic medical condition<br>Age<br>Gestational age<br>Ill appearance<br>Maximum temperature<br>Duration of illness<br>Cough status<br>Urinary tract inflammation |

The performance of CPMs in derivation and validation populations are variable. The only CPM that includes "gut feeling" of something wrong, which is also the only model derived from a primary care cohort [10], has showed markedly lower diagnostic performance in patient cohorts from studies in emergency departments [14, 28, 34, 129, 145, 216, 218, 219]. Models including laboratory values in addition to clinical features [14, 28, 30, 32, 96] outperform models based only on clinical variables in validation studies. The performance of CPMs predicting serious infection in derivation and validation studies are shown in Tables 1.7 and 1.8.

Table 1.7

**Diagnostic performance of clinical prediction models with high / low risk prediction**

| CPM | SBI prevalence, % | Sensitivity, % (95 % CI) | Specificity, % (95 % CI) | AUC | LR (+) (95 % CI) | LR (–) (95 % CI) |
|---|---|---|---|---|---|---|
| **Bachur and Harper, 2001** [30] | | | | | | |
| Derivation cohort | 7.1 | 82.2 (78.0–86.0) | 76.4 (75.2–77.6) | 0.79 | 3.48 (3.25–3.73) | 0.23 (0.19–0.29) |
| V1: Spain, 2148 infants < 3 months [34, 220] | 16.4 | 94 (90–96) | 80 (78–82) | 0.87 | 4.65 (4.22–5.12) | 0.08 (0.05–0.12) |
| V2: France, ED, 2204 infants < 3 months [34, 219] | 17.2 | 59 (54–64) | 86 (85–88) | 0.73 | 4.35 (3.77–5.02) | 0.47 (0.42–0.53) |
| V3: Netherlands 159 infants < 3 months [14, 34] | 15.1 | 71 (51–85) | 83 (76–89) | 0.77 | 4.23 (2.68–6.67) | 0.35 (0.19–0.66) |
| V4: Netherlands 766 infants 3–12 months [14, 34] | 9.8 | 82 (72–089) | 78 (75–80) | 0.80 | 3.68 (3.14–4.31) | 3.68 (3.14–4.31) |
| **Van den Bruel et al, 2007** [10] | | | | | | |
| Derivation cohort: | 0.78 | 96.8 (83.3–99.9) | 88.5 (87.5–89.5) | – | 8.4 (7.6–9.4) | 0.04 (0.01–0.2) |
| V1: Oostenbrink et al, 2001 ED, 593 children 1 month to 15 years [129, 145] | 44.4 | 64.4 (58.2–70.2) | 27.1 (22.4–32.2) | – | 0.88 (0.79–0.99) | 1.31 (1.03–1.67) |
| V2: Roukema et al, 2006, ED, 1750 children < 16 years [145, 218] | 13.0 | 88.4 (82.7–92.8) | 41.4 (39.0–43.9) | – | 1.51 (1.41–1.62) | 0.28 (0.18–4.23) |
| V3: Bleeker et al, 2007, ED, 595 children 1–36 months [28] | 23.5 | 88.6 (82.1–93.3) | 32.3 (28–36.8) | – | 1.31 (1.20–1.43) | 0.35 (0.22–0.57) |
| V4: Monteny et al, 2008. Primary care, 506 children 3 months – 6 years [205, 206] | 4.0 | 90.0 (68.3–98.8) | 43.6 (39.2–48.2) | – | 1.60 (1.35–1.88) | 0.23 (0.06–0.86) |
| V5: Thompson et al, 2009, PAU, 700 children 3 months to 16 years [15, 145] | 44.7 | 20.3 (16.0–25.2) | 85.4 (81.5–88.7) | – | 1.39 (1.00–1.93) | 0.93 (0.87–1.00) |

Table 1.7 continued

| CPM | SBI prevalence, % | Sensitivity, % (95 % CI) | Specificity, % (95 % CI) | AUC | LR (+) (95 % CI) | LR (–) (95 % CI) |
|---|---|---|---|---|---|---|
| V6: Brent et al, 2011 ED, 2762 children 1 month – 15 years [12, 145] | 13.4 | 99.7 (98.5–100) | 2.09 (1.56–2.75) | – | 1.02 (1.01–1.03) | 0.13 (0.02–0.92) |
| V7: Verbakel et al, 2015 [99] | All – 3.3 | 74.2 (68.7–79.2) | 65.8 (64.6–66.6) | – | 2.2 (2.0–2.3) | 0.4 (0.3–0.5) |
| | GP setting – 0.3 | 100 (71.5–100) | 77.7 (76.2–79.1) | – | 4.3 (3.8–4.9) | 0.1 (0.0–0.8) |
| | Paediatric out-patients – 2.6 | 82.7 (72.2–90.4) | 60.5 (58.7–62.3) | – | 2.1 (1.9–2.3) | 0.3 (0.2–0.5) |
| | ED setting – 7.5 | 69.5 (62.6–75.9) | 56.0 (54.0–58.0) | – | 1.6 (1.4–1.8) | 0.5 (0.4–0.7) |
| V8: Ierland et al, 2015, Primary care, Netherlands 0 to 16 years (n = 9794) [221] | Outcome – referral to ED | 54 (50–57) | 68 (67–69) | – | 1.7 (1.6–1.8) | 0.7 (0.6–0.7) |
| V9: Spain, 2148 infants < 3 months [34, 220] | 16.4 | 11 (8–14) | 94 (93–95) | 0.53 | 1.77 (1.25–2.52) | 0.95 (0.92–0.99) |
| V10: France, ED, 2204 infants < 3 months [34, 219] | 17.2 | 48 (43–53) | 63 (61–65) | 0.56 | 1.31 (1.16–1.47) | 0.82 (0.74–0.91) |
| V11: Netherlands ED, 159 infants < 3 months [14, 34] | 15.1 | 46 (28–65) | 64 (56–72) | 0.55 | 0.84 (0.57–1.24) | 0.84 (0.57–1.24) |
| V12: Netherlands ED, 766 infants 3–12 months [14, 34] | 9.8 | 53 (42–64) | 56 (52–59) | 0.55 | 1.21 (0.97–1.52) | 0.83 (0.65–1.07) |
| **Thompson et al, 2009** [15] | | | | | | |
| Derivation cohort | 44.7<br>15.4 (serious infection),<br>29.3 (inter-mediate infection) | 80 (75–85) | 39 (34–44) | – | 1.3 (1.2–1.5) | 0.5 (0.4–0.7) |
| V1: Ierland et al, 2015, Primary care, Netherlands 3 months to 16 years (n = 9590) [221] | Outcome – referral to ED | 50 (47–54) | 86 (85–87) | – | 3.6 (3.3–3.9) | 0.6 (0.5–0.6) |
| V2: France, ED, 2204 infants < 3 months [34, 219] | 17.2 | 61 (56–66) | 44 (42–46) | 0.53 | 1.09 (1.00–1.20) | 0.88 (0.77–1.01) |

| CPM | SBI prevalence, % | Sensitivity, % (95 % CI) | Specificity, % (95 % CI) | AUC | LR (+) (95 % CI) | LR (–) (95 % CI) |
|---|---|---|---|---|---|---|
| **Thompson et al, 2009** [15] | | | | | | |
| V3: Netherlands ED, 159 infants < 3 months [14, 34] | 15.1 | 58 (0.39–0.76) | 48 (0.40–0.57) | 0.53 | 1.12 (0.77–1.64) | 0.87 (0.52–1.43) |
| V4: Netherlands ED, 766 infants 3 to 12 months [14, 34] | 9.8 | 63 (51–73) | 47 (44–51) | 0.55 | 1.19 (0.99–1.44) | 0.79 (0.58–1.07) |

Table 1.8

**Diagnostic performance of clinical prediction models with continuous risk prediction**

| Population | Prevalence of SBI / outcome | Calibration slope (SE) | AUC (95 % CI) |
|---|---|---|---|
| **Berger et al, 1996** [96] | | | |
| Derivation population | 23.8 % | NA | NA |
| V1 [221]: Ierland et al, 2015, Primary care, Netherlands, 2 weeks to one year (n = 2383) | (outcome – referral to ED) 13 % | 0.17 | 0.52 (0.49–0.56) |
| **Bleeker et al, 2007** [28] | | | |
| Derivation population | 25.1 % | NA | Clinical prediction model 0.69 (0.63–0.75) |
| | | | Clinical + laboratory 0.86 (0.82–0.90) |
| V1: Roukema et al, 2008, ED, Netherlands, 1 to 36 months (n = 390)[222] | 12.1 % | – | Clinical prediction model: 0.56 (0.48–0.65) |
| V2: Ierland et al, 2015, Primary care, Netherlands, 1 to 36 months (n = 5809) [221] | (outcome–referral to ED) 9.0 % | 0.82 | Clinical prediction model: 0.65 (0.62–0.67) |
| V3: Spain, 2148 infants < 3 months [34, 220] | 16.4 % | 2.95 (2.81–3.09) | Clinical + laboratory model: 0.94 (0.93–0.96) |
| V4: France, ED, 2204 infants < 3 months [34, 219] | 17.2 % | 1.15 (0.07) | Clinical + laboratory model: 0.80 (0.77–0.82) |
| V5: Netherlands, ED, 159 infants < 3 months [14, 34] | 15.1 % | 0.97 (0.48–1.46) | Clinical + laboratory model: 0.78 (0.69–0.87) |
| V6: Netherlands, ED, 766 infants 3 to 12 months [14, 34] | 9.8 % | 1.09 (0.84–1.34) | Clinical + laboratory model: 0.82 (0.77 to 0.87) |
| **Craig et al, 2010** [13] | | | |
| Derivation population | UTI 3.4 % | NA | 0.80 (0.78–0.82) |
| | Pneumonia 3.4 % | NA | 0.84 (0.83–0.86) |
| | Bacteraemia 0.4 % | NA | 0.88 (0.84–0.92) |

Table 1.8 continued

| Population | Prevalence of SBI / outcome | Calibration slope (SE) | AUC (95 % CI) |
|---|---|---|---|
| **Craig et al, 2010** [13] | | | |
| V1: Validation sample, ED, Australia, 5584 children aged 0 to 5 years [13] | UTI 4.0 % | – | 0.78 (0.74–0.81) |
| | Pneumonia 3.5 % | – | 0.84 (0.82–0.87) |
| | Bacteraemia 0.6 % | – | 0.74 (0.66–0.82) |
| V2: France, ED, 2204 infants < 3 months [34, 219] | UTI 14.5 % | −0.00 (0.00) | 0.47 (0.44–0.51) |
| | Pneumonia 2.0 % | 0.74 (0.12) | 0.74 (0.67–0.82) |
| | Bacteraemia 0.7 % | 0.30 (0.20) | 0.60 (0.46–0.75) |
| **Brent et al, 2011** [12] | | | |
| Derivation population | 3.8 % | NA | 0.77 (0.71–0.83) |
| V1: Ierland et al, 2015, Primary care, Netherlands, 1 month to 16 years (n = 9762) | (outcome – referral to ED) 8.0 % | 2.05 | 0.71 (0.69–0.73) |
| V2: France, ED, 2204 infants < 3 months [34, 219] | 17.2 % | 0.35 (0.11) | 0.56 (0.53–0.59) |
| V3: Netherlands, ED, 159 infants < 3 months [14, 34] | 15.1 % | 0.45 (0.13–1.02) | 0.59 (0.46–0.72) |
| V4: Netherlands, ED, 766 infants 3 to 12 months [14, 34] | 9.8 % | 0.08 (0.18–0.34) | 0.53 (0.46–0.60) |
| **Feverkidstool – Nijman et al, 2013** [14] | | | |
| Derivation population | Pneumonia 6.3 % | NA | 0.81 (0.73–0.88) |
| | Other SBI 6.3 % | NA | 0.86 (0.79–0.92) |
| V1: PAU, UK, prospective, 1 month to 15 years [14] | Pneumonia 12.1 % | NA | 0.81 (0.69–0.93) |
| | Other SBI 13.3 % | – | 0.69 (0.53–0.86) |
| V2: de Vos-Kerkhof et al, 2015, randomised controlled trial, ED, Netherlands, 439 children aged 1 month to 16 years [35] | Pneumonia 13.2 % | – | 0.83 (0.75–0.90) |
| | Other SBI 8.8 % | – | 0.81 (0.72–0.90) |
| V3: Irwin et al, 2017, ED, UK, prospective, 1101 children aged 0 to 16 years [223] | Pneumonia 9.8 % | – | 0.85 (0.81–0.90) |
| | Other SBI 14.2 % | – | 0.76 (0.71–0.80) |
| V4: Nijman et al, 2018, Netherlands, ED, prospective, consecutive, 1085 children 1 month to 16 years [224] | Pneumonia 6.7 % | – | 0.84 (0.74–0.94) |
| | Other SBI 9.0 % | – | 0.82 (0.73–0.91) |
| V5: France, ED, 2204 infants < 3 months [34, 219] | Pneumonia 2.0 % | 0.92 (0.18) | 0.72 (0.65–0.79) |
| | Other SBI 15.2 % | 0.86 (0.08) | 0.77 (0.74–0.80) |
| V6: Netherlands, ED, 159 infants < 3 months [14, 34] | Pneumonia 2.5 % | 1.50 (0.35–2.65) | 0.86 (0.67–1.00) |
| | Other SBI 12.5 % | 0.56 (0.19–0.93) | 0.68 (0.55–0.80) |

Table 1.8 continued

| Population | Prevalence of SBI / outcome | Calibration slope (SE) | AUC (95 % CI) |
|---|---|---|---|
| **Feverkidstool – Nijman et al, 2013** [14] | | | |
| V7: Netherlands, ED, 766 infants 3 to 12 months [14, 34] | Pneumonia 2.1 % | 1.38 (0.89–1.87) | 0.89 (0.83–0.95) |
| | Other SBI 7.7 % | 0.84 (0.61–1.07) | 0.82 (0.76–0.87) |
| **Hagedoorn et al, 2020** [32] | | | |
| Derivation population (12 EDs in 9 countries) | 0.8 % (outcome – invasive bacterial infection) | NA | 0.84 (0.81–0.88) |
| Cross-validation (5 ED groups) | | 0.45–0.81 | 0.78 (0.74–0.82) |
| **Yaeger et al, 2021**[217] | | | |
| Derivation population (not externally validated) | 7.6 % | NA | Regression CPM: 0.945 (0.913–0.977) |
| | | NA | Super learner model: 0.956 (0.935–0.975) |

As these prediction rules are mostly targeted to improve rapid discrimination between patients with and without serious illness / SBI, impact studies of these models on the management of febrile patients in different settings are necessary, and yet there are few. A prospective observational study in out-of-hours primary care centres in the Netherlands showed that most prediction models had only moderate performance for predicting referral to emergency departments [221].

A randomized controlled trial assessing the impact of the model by Nijman et al (Feverkidstool) [14] showed to reduce the number of full blood counts performed at the ED but did not affect antibiotic prescription, hospitalization, or revisits, while another study of the Nijman model for pneumonia showed reduction in antibiotic prescription in children with suspected lower respiratory tract infections [225]. Overall, models with effective prediction of bacterial pneumonia also require biomarkers, as does Feverkidstool [226].

### 1.3.4 Clinician's "gut feeling" and its diagnostic value

At the age of evidence-based medicine, it may be assumed that clinician's intuition should play little role in clinical decision-making, putting more emphasis on application of high-quality scientific information and evidence extracted from rigorous studies and systematic literature reviews [227–229]. It is, however, necessary to understand that the complexity of medical reasoning, which involves analytical and non-analytical processes alike.

Research in cognitive psychology suggests that reasoning involves two cognitive systems or processes [230–237]. One of them, described as "non-analytical", "intuitive", "tacit", "automatic", "experiential", or "system 1" is associative, intuitive, and fast, enabling the clinician to make rapid decisions in complex or time-restricted situations. The other, called

"analytical", "rational", "controlled", or "system 2" process, involves conscious and effortful application of the learned information and rules, and use of diagnostic tools.

While very different, these processes are not mutually exclusive in medical problem-solving and decision-making [229, 230, 235, 238]. Having a "sense of alarm" about a clinical situation, even if unfounded by supporting clinical "red flags", may prompt the initiation of a thorough investigation process, in which analytical reasoning will be applied [238, 239]. In situations when decisions must be made without delay, the initial rapid response may be intuitive, while the analytical system monitors the validity of this response and tests for potential inconsistencies or bias [230, 240]. Thus, both cognitive processes contribute to the improvement of medical decisions.

The significant role of skilled intuition and non-analytical reasoning has been recognized in several medical specialties, including nursing, midwifery, dentistry, general practice, paediatrics, and several other medical specialties [38, 40, 231, 232, 237, 241–251]. Cross-cultural studies show that clinicians are aware of the role and significance of the intuitive part of their reasoning in everyday practice, and that two types of intuitive feelings – "sense of alarm" and "sense of reassurance" are well-established concepts [243, 252–255]. An agreement on the necessity of inclusion of recognition and awareness of "gut feeling" in medical education is also prevalent amongst European clinicians [230, 235, 239, 243, 256].

**Sense of alarm / gut feeling that "something is wrong"**

The "sense of alarm" has been described as an uneasy feeling in clinicians, when something in the clinical situation "does not add up", or, in other words, "does not fit", which is understood as a concern for a potential adverse outcome, even if there are no clear indications [228, 243, 247, 252–254, 257]. Other studies use a similar term, "gut feeling" that "something is wrong", even if the doctor is unable to explain why [10, 38].

A "sense of alarm" is often the grounds for initiation of more in-depth investigation process. However, doctors have sometimes described experiencing doubts on relying on this subjective feeling, and feeling they have to rationalize their uneasiness by finding objective clinical evidence [228, 243, 247, 253, 258, 259]. Despite these doubts, the necessity to act out on these intuitive feelings has been emphasized in some guidelines [260], as studies show evidence on missed cases of serious illness as a result on not pursuing further investigation in case of "gut feeling" of something being wrong, even if other "red flags" are absent [38, 261].

Furthermore, studies show that "sense of alarm" / "gut feeling" that something is wrong provides added value in diagnosis of serious infections in children [10, 38], as well as gastro-intestinal bleeding [249], cancer [40, 262], and other life- or limb-threatening conditions [237,

250, 263, 264]. In paediatrics, it has been associated with significantly increased risk for serious illness in febrile children presenting to primary care [38], and also identified as a key variable in a CPM derived from a primary care cohort (LR (+) (95 % CI) = 23.48 (16.85–32.71)) [10].

**Triggers for sense of alarm / "gut feeling" that something is wrong**

While the definition of "sense of alarm" or "gut feeling" of seething wrong implies that there may be no clinical findings to justify the concerns of the physician, several triggers have been identified. An important trigger is the case "falling out of a pattern" – an existing difference between what is seen and what is expected in a clinical situation of a kind [228, 231, 265, 266].

More specifically, factors initiating "sense of alarm" / "gut feeling" that something is wrong listed by doctors are behavioural changes in a patient, changes in appearance, gestures, and body language [243]. Patients who visit their general practitioner less frequently, or seek help during the night, are also more likely to raise "sense of alarm" [243, 267]. Naturally, some of the well-established clinical "red flag" signs have also been associated with "sense of alarm", such as seizures, ill appearance, changed breathing pattern, drowsiness, fatigue, weight loss, symptoms of urinary tract infection, crackles, crepitations, etc [37, 38, 262, 267].

**Sense of reassurance**

"Sense of reassurance" has been described as feeling sure about the prognosis or course of the illness of the patient, even when not knowing the precise diagnosis ("everything fits in") [239, 243, 252, 253, 257]. "Sense of reassurance" is said to be helpful in coping with the high workload of seeing many patients, by adopting "watchful wating" instead of aggressive testing and treatment strategies [239, 243]. However, some clinicians also felt they still needed to stay on their guard even in case they felt "sense of reassurance", to avoid missing any serious cases [253]. While several studies on diagnostic value of "sense of alarm" have been conducted, showing promising results, research in the validity of "sense of reassurance" is lacking.

**Factors affecting intuitive reasoning**

The use and diagnostic value of skilled intuition is affected by several clinician-related factors. One of the variables may be the state of the individual clinician – it has been suggested that lack of time, involvement of several cases at once, sleep deprivation, fatigue, and distraction negatively affect their non-analytical reasoning, [230], in either overuse, underuse, or lack of accuracy. However, other studies show that burn-out does not affect the use of "gut

feeling" [268], and that clinicians could experience "gut feeling" even in the middle of a busy day [243].

Another factor affecting intuitive reasoning is the level of experience of the clinician. In several studies, experienced doctors, nurses, and midwifes had more confidence in their intuition than their less-experienced colleagues [37, 241, 243, 247, 266], and a prospective cohort study has shown increasing predictive value of "gut feeling" for cancer with every additional year of experience [267]. Nevertheless, the junior colleagues should not be discouraged to use their "gut feeling". A prospective study on recognition of serious illness in children shows contrasting results – with every year of experience, clinicians were less likely to experience "gut feeling", which may indicate diagnostic uncertainty, however the diagnostic power of "gut feeling" was similar to that of more senior doctors [38].

The patient-clinician relationship may have one of the most significant influences on the non-analytical reasoning of the clinician. Continuity of care and prior knowledge of the patient is said to be a determining factor of being able to recognize that "something does not fit in" [40, 239, 243] and could sometimes enable the clinician to experience "gut feeling" when assessing the patient remotely [243]. By contrast, one study reports that, with increased knowledge of the patient, general practitioners were less likely to use their "gut feeling" for diagnosing cancer [269].

The type of medical specialty also affects "gut feeling". A focus group study on use of "gut feelings" among different specialists revealed that, the more general the specialty, for example, general practice and paediatrics, where patients present with large variety of conditions, the more likely the doctor was to use and rely on "gut feelings" [247].

**Integration of the concept of "gut feeling" in medical education**

In most studies clinicians agree that "gut feeling" can be taught, though the task may prove to be a difficult one [230, 235, 239, 243, 256]. Several strategies have been proposed to induce intuitive thinking in medical education, of which there is most agreement on exposure to varied clinical cases, and feedback provided by the tutors during clinical problem-solving, including encouragement for intuitive reasoning and expression of the student's or junior clinician's intuitive thoughts [228, 230, 236, 238, 243, 256, 270].

Due to variability of clinical presentation, it is not adequate to see just one example of a specific disease during the learning process. It is advised to expose the trainees to cases with typical manifestations of a condition first, then followed by more complex situations [230]. This is also true about development of skilled intuition. As gut feeling often implies recognition that a case "does not fit", seeing numerous cases with benign or poor outcomes will aid the

development of the ability to sometimes distinguish between the two automatically, before the analytical part of reasoning is applied [230, 231, 243]. In addition to focusing to signs and symptoms, trainees should be stimulate to focus on the behaviour and other non-verbal cues of the patient to develop a more holistic approach, and to be aware of their own intuitive feelings during the assessment [239].

Analysis of many clinical cases will not, however, compensate for insufficient feedback from the tutors or traineeship supervisors. In addition to discussion of differential diagnoses and extensive clinical examination, students or trainees should be encouraged to express their intuitive hypotheses early on during the investigation process and receive feedback on their thoughts [228, 230]. Discussing the reasons behind the decisions made by trainees also enables the recognition of potential cognitive bias [231]. The emphasis should be placed on how intuition can be integrated with the analytical process of medical diagnostic reasoning [230, 236, 238, 256], which, as evidence suggests, will result in a more effective clinical practice.

### 1.3.5 Diagnostic value of parental concern

Attentive consideration of parental concern as a factor indicating serious illness or sepsis in a child is recommended in a systematic literature review [22] and by NICE Sepsis stratification tool [23]. The evidence for the diagnostic value of parental concern mainly comes from primary care studies, while the evidence from patients presenting to EDs is scarce [271].

A qualitative study published in 2005 reported that, among children who had experienced serious infection, a common finding was parental concern at an early stage of the illness, expressed as a feeling that this time, the "illness is different" [41]. Another statement in a qualitative study on recognition of meningitis in children by general practitioners stated that, sometimes maternal instinct that their child "isn't quite right" is the only clue that the child is seriously ill [272]. The diagnostic value of parental concern was assessed in a prospective multi-centre study in primary care [10], where it was significantly associated with increased likelihood of serious illness (LR (+) (95 % CI) = 14.35 (9.30–22.15)), and was one of the key variables in decision trees to foe prediction of serious infection, pneumonia, or sepsis / meningitis. In another study, parental concern was identified as one of the main triggers for clinician's "gut feeling" [38].

However, factors other than the severity of the child's condition or observed changes in the child's behaviour can affect the level of parental anxiety. Particularly, it can be affected by parental beliefs on the possible harmful effects of fever [43, 273, 274], as well as the effectiveness of communication with healthcare personnel, in terms of provided information and support [275, 276]. The reasons for parental worries, and the possibility of "fever phobia"

in parents should be clarified before considering parental concern as a variable suggesting serious illness.

### 1.4 Fever phobia

Fever in a child can cause significant anxiety in the parents. Often the reason for this concern are the misconceptions on harmful effects on fever. Studies report that negative effects attributed to fever (if left untreated) by parents include dehydration, vomiting, serious illness, delirium, coma, seizures, blindness, deafness, brain damage, and even death [42, 43, 48, 50, 273, 277–283], and the body temperature associated with these adverse effects can be as low as 38 °C, or even lower [281]. Another misconception suggests that, unless medication is given, the body temperature can increase to uncontrollable hights such as 43.3 °C [283, 284]. These irrational beliefs, also labelled as "fever phobia" [42], have been observed in parents of various socioeconomic and education levels and in different parts of the world [46, 50, 282, 285]. The misconceptions about fever have remained relatively unchanged throughout the last four decades, despite decline in childhood mortality due to illness, and availability of evidence-based materials for guidance for management of fever [44, 47, 282].

Parental anxiety over febrile illness in their child often lead to aggressive management strategies, such as frequent temperature measurements, overuse of medication, and application of non-evidence-based practices such as cold sponging, rubbing the child with alcohol, etc [43, 46, 273, 277, 281, 283]. In addition, concern about the child's fever leads to unwarranted use of emergency healthcare services [48, 286].

While lack of knowledge on the pathophysiology and management of fever is one of the main reasons behind these misconceptions and malpractices by parents, it may come as a result of their experience of ineffective communication with healthcare workers [45, 275, 287, 288]. When the parent perceives fever as a threat to their child's health and wellbeing, they feel an overwhelming sense of responsibility to protect their child, and, if their worries are dismissed as irrelevant and questions are not answered properly, the frustration and anxiety increase even further [275, 276, 287–289]. While trying to receive information on the management of fever in their child and on proper use of antipyretics, parents sometimes receive conflicting information from different healthcare specialists they visit [287]. It is also important for the parent to understand the cause of the illness in their child, and phrases like "it is nothing" or "it is just a virus", probably intended for reassurance, instead added to their worries and decreased their trust in the healthcare professional [45, 275, 287, 288]. Clinicians also may fail to meet the emotional needs for support, encouragement and reassurance expressed by the parents [276, 287].

Several interventions are necessary to decrease fever phobia in parents. First of all, parents should be provided with a clear, reliable, and consistent information on how to assess the severity of illness in their child, when to seek help, and how to manage fever at home [49, 287, 290]. This could be done by providing clear and written instructions during visit, handouts or other audio-visual aids [45, 290–293]. Not less importantly, possible anxiety related to fever in a child, as well as other concerns, should be addressed during visits to healthcare, and parents should be provided with the necessary reassurance and emotional support [276, 287].

# 2 Materials and Methods

## 2.1 Setting

The study included two cohorts – the discovery cohort, and the validation cohort.

### 2.1.1 Discovery cohort

The discovery cohort consisted of patients presenting to Emergency Department of Children's Clinical University Hospital (CCUH) in Riga, Latvia, between 1st of April 2017 and 31st of December 2018. CCUH is the only hospital in Latvia providing tertiary level of care exclusively for children. CCUH is a university hospital and serves as the main clinical setting for training of medical students and residents in paediatrics and its various subspecialties. The ED of CCUH is attended by children younger than 18 years, and the main reasons for presentation are problems related to childhood illness, trauma, foreign bodies, or other emergencies. The number of annual visits to ED is approximately sixty-five thousand, around nine thousand of which are febrile episodes. Around half of the febrile visits to the ED in CCUH are self-referred, over 41 % are delivered to ED by an ambulance, and less than 5 % are referred by a family doctor or another specialist. Though 51 % of patients are classified as non-urgent, 70 % of febrile patients undergo laboratory or other investigations at the ED, and close to 30 % remain at the ED for a prolonged observation for up to 24 hours. Around 27 % of febrile children who present to the ED are eventually hospitalized [294].

### 2.1.2 Validation cohort

The validation cohort included patients who presented to the Emergency departments of one out of six regional hospitals in Latvia, between 1st of January 2019 and 31st of March 2019. The hospitals that took part in the study were Liepājas Reģionālā slimnīca, Daugavpils Reģionālā slimnīca, Vidzemes Slimnīca, Jēkabpils Reģionālā slimnīca, Ziemeļkurzemes Reģionālā slimnīca, Balvu un Gulbenes Slimnīcu apvienība. These hospitals provide secondary level of healthcare services for people of all age groups and have a Paediatric department. The Emergency departments of these hospitals are visited by children and adults alike, who present with various accidents and emergencies.

## 2.2 Inclusion and exclusion criteria

All children aged one month up to 18 years (not including) who presented to ED within the study period with fever (body temperature above 38.0 °C reported by carers or assessed at the ED with axillary thermometer) or history of fever within the previous 3 days were considered eligible to the study if none of the following exclusion criteria were present:

- Chronic comorbidities that increase the risk for infection (primary or secondary immunodeficiency, history of splenectomy, etc.)
- Chronic use of immunosuppressing medication (chemotherapy, glucocorticoids, disease-modifying antirheumatic drugs, etc.)
- Referral from primary care, another hospital or specialist with an already established diagnosis
- Patient / carer refuses to participate in the study.

Written informed consent to participate in the study was required from the parents / carers of the patient, or the patient themselves if aged 14 years or older.

## 2.3 Study design

The study was conducted as a mixed methods study and consisted of two parts: quantitative and qualitative study. The study process is illustrated in Figure 2.1.

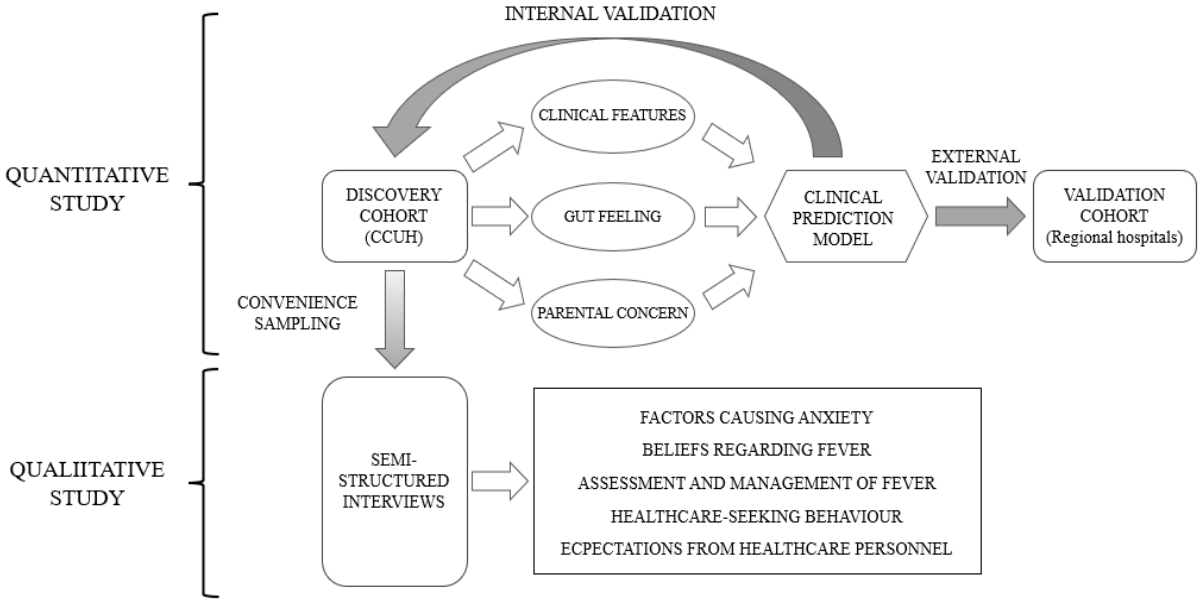


Figure. 2.1 **Study design**

### 2.3.1 Quantitative study

The quantitative part of this thesis was a prospective, observational cohort study. At the first stage of the study, patients were prospectively enrolled in the discovery cohort. Data collected from the discovery cohort were used for analysis of the diagnostic value of clinical variables, "gut feeling", and parental concern, as well as for derivation of clinical prediction models (CPMs). A small sample of derivation cohort was also included in a qualitative interview study. The derived and internally validated CPMs were subsequently validated externally by application to the validation cohort.

#### Patient enrolment

In CCUH, patients were approached by the researcher on selected days distributed evenly within the study period, the recruitment lasted for around 4 to 6 hours each day. During the time of recruitment, all eligible patients who were observed at the ED were approached, and patients whose carers provided an informed written consent were recruited.

The majority of patients in the discovery cohort were recruits to European Union (EU) Horizon 2020 project "Personalised Risk assessment in febrile illness to optimise Real-life Management across the European Union" (PERFORM) [295]. The main goal of the PERFORM project was to improve diagnosis and management of febrile patients, by identification and validation of promising new discriminators of bacterial and viral infection including transcriptomic and clinical phenotypic markers. However, no new laboratory diagnostic markers were analysed for this thesis.

#### Data collection

#### Clinical features

Data collected for the study included date and time of presentation, age and gender of the patient, clinical features at presentation, the diagnosis, and relevant clinical data supporting the diagnosis. The data were recorded in a standardised case report form, which can be viewed in the Appendices as Appendix 1 (case report form in English) and Appendix 2 (Case Report Form in Latvian). The clinical features included vital signs as well as several clinical features, which were selected based on alarming features identified by a previously published systematic review [22], included in popular clinical practice guidelines and assessment scores [2, 23, 103, 117, 296], and other relevant studies on serious bacterial infection or serious illness in children. In total, 27 clinical variables were assessed.

The body temperature at presentation was measured via axillary liquid-in-glass thermometer, in addition to recording parent-reported peak body temperature during the episode prior to presentation. Vital signs (heart rate, blood pressure, oxygen saturation) were assessed by an electronic monitor, and respiratory rate was evaluated by the clinician during physical examination. Assessed heart rate and respiratory rate were evaluated according to age [23, 297]. Poor peripheral circulation was defined as cold hands and feet, and / or prolonged capillary refill time [298]. Clinical impression of "ill / toxic appearance", defined as child appearing pale, mottled, or cyanotic, lethargic or inconsolable, or showing signs of respiratory distress (tachypnoea, chest retractions, etc) [299], was also noted.

Clinical signs and symptoms were recorded in the standardised case report form, where the clinician noted the signs that were present, the signs and symptoms that were not noted were considered as absent by the research team.

**"Gut feeling" of something being wrong / "sense of reassurance"**

For the assessment of clinician's "gut feeling" of something being wrong and "sense of reassurance", the doctors were given a short questionnaire to be completed after the physical examination of the child, before any laboratory, imaging or other investigation results became available. The questionnaire was developed in collaboration with the Department of Public Health and Epidemiology of Rīga Stradiņš University, and its contents were discussed with experienced paediatricians, after which no changes were made. The full questionnaire can be viewed in the Appendices as Appendix 3 (Clinician's questionnaire in English) and Appendix 4 (Clinician's questionnaire in Latvian). Introduction on completion of Clinicians' questionnaire was provided to clinicians working at the ED of CCUH as well as the regional hospitals prior to the study. The "Gut feeling" of something being wrong, defined as an intuitive feeling that the child may have a serious illness [10, 38], as well as "Sense of reassurance", defined as an intuitive feeling that the child has a self-limiting illness [300] were noted. Both "gut feeling" of something being wrong and "sense of reassurance" were evaluated as "present", "not sure", or "absent" in case the clinician stated in the questionnaire that they did not experience "gut feeling" that something is wrong. In the statistical analyses coded as binary, "present" or "absent" / "not sure" was used.

The clinicians were also asked to name (if they could) the possible triggers of this impression. On the other side of the questionnaire sheet, the physicians stated their opinion on the presence of any of the listed SBIs and marked the presence of any alarming signs and symptoms.

The questionnaire was considered as an extension to the main case report form for assessment of variables “gut feeling” and “sense of reassurance”, therefore no validation procedures were performed.

**Parental concern**

The parents of enrolled patients were approached and asked to fill a questionnaire evaluating their concern about the child during the particular episode of illness. The questionnaire was developed in collaboration with the Department of Public Health and Epidemiology of Rīga Stradiņš University, and subsequently piloted in a small cohort of 26 patients, after which some alterations were made in questions unrelated to parental concern. The parental questionnaire can be viewed in the Appendices as Appendix 5 (Parental questionnaire in English) and Appendix 6 (Parental concern in Latvian). Parental concern was defined as an impression that this episode of illness is different / more severe than the child’s previous febrile episodes [10, 41], and was evaluated according to a 7-point Likert scale, where “definitely yes”, “most likely yes”, and “more likely yes than no” was interpreted as present, “difficult to say” was regarded as neutral, while “more likely no than yes”, “most likely no”, “definitely no” were interpreted as absent. In statistical analysis, the evaluation “difficult to say” was coded equal to “absent”.

The questionnaire also included questions on the behavioural changes observed during the febrile episode, and additional questions on their beliefs on the management and effects of fever. Information on the age and education of the parents, number of children in the family, and the child’s previous illnesses was also collected.

The parental questionnaire was considered as an extension to the main case report form for assessment of variable “parental concern”, and no validation procedures were performed.

**Outcomes**

The defined primary outcomes of the study were presence or absence of SBI. The diagnoses classified as SBI were chosen according to most commonly used definitions of SBI in other clinical studies (illustrated in Table 1.1). For this study, SBI was defined as any of the infections displayed in Table 2.1 requiring hospitalization (for at least 24 hours).

Table 2.1

**Definitions and reference standards for SBI used in the study**

| No. | Type of infection | Reference standards |
|---|---|---|
| 1 | Bacteraemia | A single bacterial pathogen identified in a blood culture |
| 2 | Bacterial meningitis | Polymorphonuclear leucocytosis and bacterial pathogen identified in cerebrospinal fluid |
| 3 | Pneumonia | An infiltrate on a chest X-ray identified by a paediatric radiologist |
| 4 | Urinary tract infection | Positive urine culture ($10^5$ colony forming units (CFU) per ml of a single bacterial pathogen in a midstream urine sample or $10^4$ CFU/ml in a catheterized sample) |
| 5 | Bacterial soft tissue infections | Cellulitis / phlegmon / erysipelas / deep pus collection or abscess requiring hospitalization and systemic antibacterial therapy |
| 6 | Bacterial gastroenteritis with dehydration | Bacterial pathogen identified in a stool sample of a patient with symptoms of acute gastroenteritis requiring hospitalization and intravenous rehydration |
| 7 | Acute complicated appendicitis | Acute appendicitis with necrosis / perforation / peritonitis |
| 8 | Acute osteomyelitis / septic arthritis | Pathogenic bacteria isolated from bone / joint aspirate OR osteomyelitis identified in MRI |

Secondary outcomes were hospitalization, antibacterial treatment, and admission to paediatric Intensive Care Unit (ICU).

**Follow-up**

The patients were followed up until discharge of the hospital and further for up to 28 days from presenting to ED, to rule out or confirm development of SBI, initiation of antibiotics, or readmission to the hospital. For patients discharged from the hospital before day 28, the follow-up was arranged via telephone close to day 28 (on a working day, during working hours). Two call attempts were made by a member of the research team to contact the patient / guardians, after which no further attempts were made. If the research team failed to contact a patient, the possibility of readmission was ruled out by researching the patient on the hospital record system (for patients enrolled in regional hospitals, hospitalization in CCUH as the reference hospital was also ruled out). As the diagnosis of SBI for this study required hospitalization for at least 24 hours due to one of infections meeting criteria for SBI, no patient without SBI was reclassified as SBI unless there was a readmission.

**Statistical analysis and derivation of clinical prediction models**

The bivariate analysis of association between each of the clinical variables, “gut feeling”, “sense of reassurance”, parental concern and SBI was performed by constructing 2 × 2 contingency tables. The Chi-squared test or Fisher’s exact test were performed, as appropriate. A *p* value of less that 0.05 was considered significant. For each variable, odds ratio (OR), positive (LR (+)) and negative likelihood ratios (LR (–)), positive predictive value (PPV)

and negative predictive value (NPV) were calculated to assess the diagnostic value with regards to SBI. Variables with OR 1 or more were considered as associated with SBI, while variables with LR (+) of 5 or more were considered significantly predictive of SBI (high rule-in value). Associations between parent-reported behavioural changes and detection of SBI, and between alarming signs and "gut feeling" were also evaluated.

Variable selection for the clinical prediction model was performed using stepwise logistic regression (forward, backward, and bidirectional). A sample size of 500 subjects is recommended for derivation of CPMs via logistic regression of unknown number of variables for observational studies with large populations [301], another equation to estimate the sample size is $100 + 50i$, where $i$ refers to the number of independent variables selected for the final model.

No data imputation for missing values was performed, and only cases with no missing data were used in logistic regression (complete case analysis). The aim of this study was to create a short, simple screening model; therefore, Akaike information criterion (AIC) was used to penalize for too many parameters.

Two clinical prediction models were created – one with clinical parameters (signs and symptoms) alone, and another, in which "gut feeling" and "sense of reassurance" was also included. For each of the two models, Likelihood Ratio (LR), Wald, and Conditional selection criteria were used to assess the variety of regression models. Models were similar in all cases and did not give significant improvement. The performance of the models was assessed by constructing a receiver operating characteristic (ROC) curve assessing the area under curve (AUC). A model with AUC close to 0.5 is evaluated as useless, AUC between 0.51 and 0.69 indicates a poor test, values between 0.7 and 0.79 are considered moderate, between 0.8 and 0.89 – good, and 0.9 to 0.99 indicates a perfect model [302]. The statistical significance of the difference between the AUCs of the models was assessed by DeLong's test for two ROC curves. The optimal cut-off points for the models were chosen according to Youden's index, while calculation of sensitivity, specificity, positive and negative predictive values, and positive and negative likelihood ratios at different cut-off points in both derivation and validation cohorts were also performed.

The statistical analysis was performed by using MS Excel, SPSS version 26, and RStudio software version 1.4.1103.

**Validation**

Bootstrapping was used for assessment of the model's internal validity and correction for overoptimism by applying the model to 100 000 bootstrap samples of the data. For external validation, the model was tested for prediction of SBI in a separate dataset of patients presenting to one of six regional hospitals.

**Assessment of beliefs, practices and health care seeking behaviour of parents regarding fever in children**

The data on parental beliefs regarding fever, administration of antipyretics, healthcare-seeking behaviour, both when dealing with fever in their children in general and during the ongoing episode, and experience in communication with health care workers were collected via the parental questionnaire, in addition to assessment of parental concern. In addition, demographic data (age and level of education of parents or legal guardians, number of children in the family, age and gender of the patient admitted to ED) were also collected and analysed.

Statistical analysis was performed using MS Excel, SPSS version 26, and R studio version 1.4.1103 data analysis software. The statistical significance of the differences between categorical variables was estimated by applying Pearson's Chi-squared test. Wilcoxon rank-sum test was used for comparison of two independent groups of nonparametric continuous data. A significance level of $p < 0.05$ was applied.

### 2.3.2 Qualitative study

To assess the reasons for parental concern during febrile illness, and to explore on any possible misconceptions about fever that may lead to fever phobia, an applied research design study was conducted in a form of qualitative interview study in addition to the parental questionnaires with quantitative data.

**Recruitment of participants**

A convenience sample of parents / carers of patients from validation cohort was recruited for participation in qualitative, semi-structured interviews. Parents from different educational backgrounds, as well as with varying number of children, were selected to achieve maximum variation. Most interviews took place during the child's observation at the ED, though some interviews were postponed to a later time within 72 hours of admission, after the patient's immediate medical needs were addressed and the mental and psychological condition of the parents was adequate for them to participate in the interview.

Enrolment was considered complete when no new information emerged from the interviews and data saturation had been reached [303]. Recruitment of participants for the interview study took place between October 2017 and April 2018.

**Data collection and analysis**

The data for the qualitative study were collected via semi-structured qualitative interviews. The topic guide for the interviews was developed basing on rigorous study of existing literature as well as professional opinions. The interviewer's guideline on the questions to be asked during the interview can be viewed in the Appendices as Appendix 7. The interviewer was instructed to cover all the listed topics, but not necessarily in the same order as shown in the guideline, to allow a natural flow of conversation. Before the study, the interviews were piloted by two parents, who suggested no major corrections. The topics discussed in the interview included:

- signs and symptoms causing increasing concern,
- ways of assessing and monitoring fever,
- opinion and beliefs on the positive effects of fever,
- opinion and beliefs on the possible side effects and dangers of fever,
- practices of management of fever,
- seeking for help in case of fever in their child,
- expectations from healthcare professionals when dealing with febrile illness in their child,
- experience in communication with doctors regarding febrile illness in their child.

All interviews were audio recorded and transcribed verbatim for data analysis. Participants were not asked to verify their transcripts.

Inductive thematic analysis was used to analyse the data of all transcripts [304]. Key themes were identified through a step-by-step process, including:

1) familiarization with all data through repeated listening to the records and reading of the transcripts,
2) descriptive coding of repeated patterns and themes,
3) linking, grouping, and categorization of the themes and subthemes.

## 2.3 Ethics statement

The study was conducted in accordance with the Helsinki declaration and guidelines for good clinical practice.

Enrolment of CCUH patients in the PERFORM (Personalised Risk assessment in febrile illness to optimise Real-life Management across the European Union) project was approved by the Central Medical Ethics Committee of the Republic of Latvia (Decision No 1/16-07-14; approval date 26.05.2016.).

The inclusion of additional cohort of CCUH patients and collection of clinical data, the data from the clinician's and parental questionnaires, as well as recording of the interviews was approved by the ethics committee of Rīga Stradiņš University (Decision no. 13/05.10.2017.). The ethics committee of Rīga Stradiņš University also approved of enrolment of patients of regional hospitals in the validation cohort (Decision No.6-3/27, approval date 25.10.2018.), after obtaining consent for the study from the Institutional Review Board of Children's Clinical University Hospital, as well as from the designated officials in the Regional hospitals.

Written informed consent was obtained from each caregiver / patient (if aged 14 years or older) for participation in the study as well as for the analysis and publication of collected data. The carers who participated in the qualitative study provided written informed consent for audio recording of the interviews.

# 3 Results

## 3.1 Demographic data

### 3.1.1 Patients

In total, 517 patients presenting to the ED of CCUH were enrolled. 385 patients consented to participation in the PERFORM project, and additional 132 patients agreed to participation outside the PERFORM project. 54 % (n = 279) of the patients were boys. The age of the patients ranged from one month to 17 years and 11 months, the median age was 58 months. 47 patients (9.1 %) were younger than one year, 261 children (50.5 %) were younger than 5 years.

In regional hospitals, 188 patients were enrolled for validation of created CPMs. 48.9 % (n = 92) were boys. The median age of patients in validation cohort was 28 months (range one month to 16 years and 4 months). Of all enrolled patients, 18.1 % (n = 34) were younger than 12 months, and 81.4 % of patients (n = 153) were younger than 5 years.

### 3.1.2 Clinicians

**Discovery cohort**

The questionnaire on "gut feeling" and "sense of reassurance" was completed in 356 cases among patients enrolled in CCUH. For the rest of the discovery cohort the data were missing, mostly due to inability of the clinicians to complete the questionnaire within the specified time frame (before investigation results became available). In one hundred and sixty-five of the cases (46.3 %), the clinicians were licensed paediatricians with clinical experience ranging from five to fifty-three years (median six years), in 46 cases (27.9 %) the licensed paediatrician had work experience 10 years or more as a doctor. The rest of the enrolled patients were seen by paediatric residents with one to four years of medical work experience (median three years).

**Validation cohort**

In regional hospitals, the clinician's questionnaire was completed for all 188 of enrolled patients. Most of the patients (89.4 %, n = 186) were seen by licensed paediatricians with five to forty-one years of experience (median 28 years), in the majority of cases (86.7 %, n = 163) the clinician had more than 10 years of clinical work experience.

### 3.1.3 Parents and guardians

**Parents enrolled in CCUH**

In CCUH, 273 parents took part in the questionnaire. Data on parental concern (different / more severe illness) were given by parents of 267 (51.6 %) of the enrolled patients. Six more parents had completed some parts of the questionnaire but omitted the questions specifying their concern about the child's condition. The part on beliefs regarding fever and healthcare-seeking behaviour was completed by 235 parents.

Most of the participants (89.0 %, n = 243) were mothers aged 21 to 56 years (median age 34 years), 49.6 % (n = 120) had a university degree. The questionnaire was completed also by 23 fathers aged 23 to 52 years (median 34), 56.5 % (n = 13) of them had a university degree. Seven of the participants were other legal guardians, mostly grandparents.

Of participants who completed the data on beliefs regarding fever and healthcare-seeking behaviour, 206 (87.6 %) were mothers, 49.3 % (n = 100) with a university degree, and 9.3 % (n = 22) were fathers, of whom 54.5 % (n = 12) had a university degree. The number of children in the families participating in the questionnaire on beliefs on fever is displayed in figure 3.1.3.

The reasons for failure to obtain a completed questionnaire from the rest of the parents in discovery cohort (n = 250) were refusal to take part in it, failure to complete it within the specified time frame, or discharge prior to completion of the questionnaire.

**Parents enrolled in regional hospitals**

In regional hospitals, 178 parents participated in the study on parental concern and beliefs regarding fever, while one of them had left questions on parental concern unanswered. Again, the overwhelming majority (92.1 %, n = 164) of participants were mothers with age range between 18 and 48 years (median 31 years), 38.4 % (n = 63) out of whom had a university degree. The number of fathers enrolled in the study was 12, their age ranged from 29 to 43 years (median 35 years), and 33.3 % of the fathers (n = 4) had a university degree. The rest of the participants were two grandparents. The number of children in families recruited in regional hospitals is shown in figure 3.1.

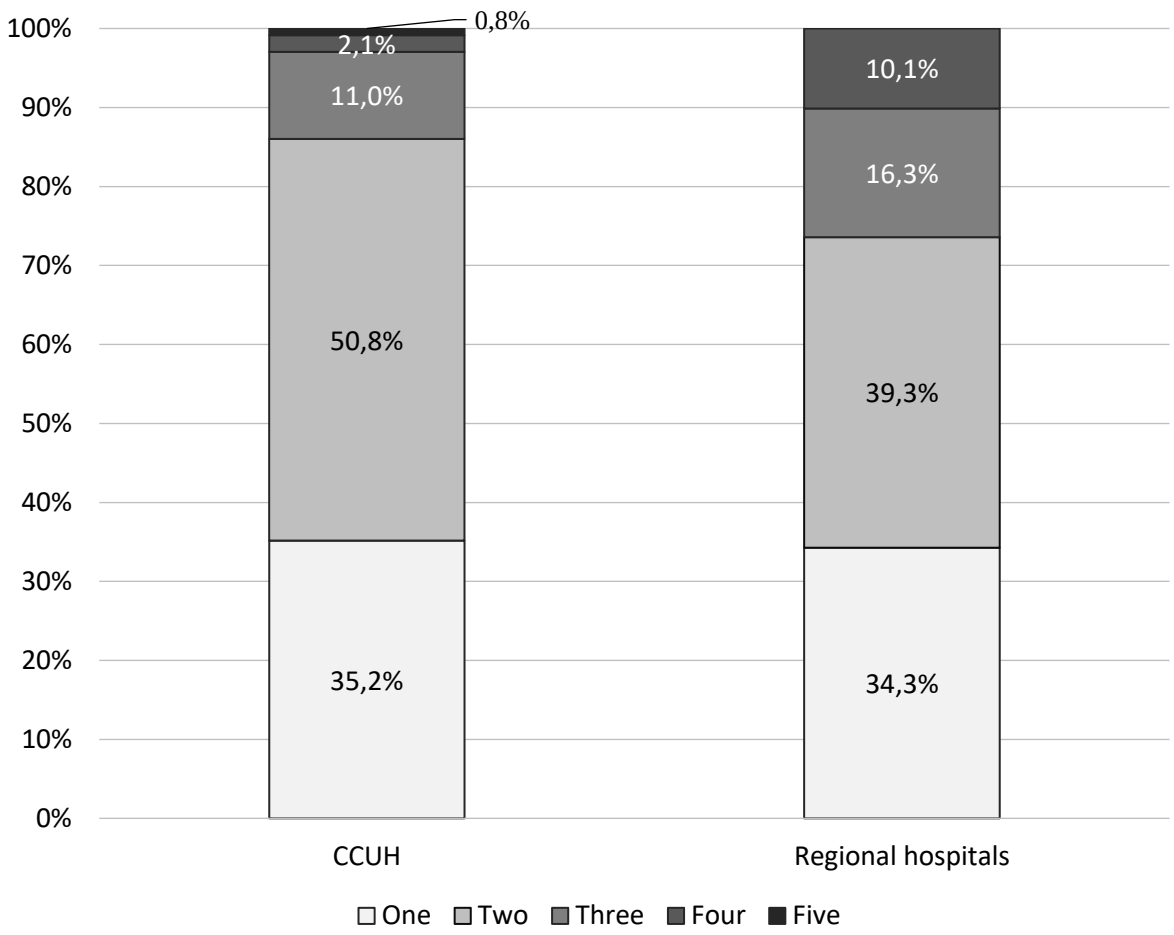


Figure 3.1 **Number of children in families of the participants in parental questionnaire**

## 3.2 Outcomes

Of all patients enrolled in the discovery cohort, 26.7 % (n = 138) were diagnosed with SBI. The final diagnoses of the patients are summarized in Table 3.1. All patients with SBI were hospitalized for at least 24 hours and received antibiotics, 31 of these patients were hospitalized in the ICU. The duration of hospitalization in patients with SBI ranged from 1 to 44 days (median 5 days).

Of the 379 patients who did not develop SBI, 191 (50.4 %) received or were prescribed antibiotics, 228 (60.2 %) were hospitalized, and five patients were hospitalized in ICU. The median duration of hospitalization among patients without SBI was 2 days, ranging from less than 24 hours to 25 days.

In validation population consisting of 188 patients from regional hospitals, 26.6 % of patients (n = 50) developed SBI. All patients with SBI underwent laboratory investigations and received antibiotics, none were hospitalized in ICU. Of patients without SBI (72.4 %, n = 138), all underwent laboratory tests, 89.1 (n = 123) were hospitalized (none in ICU), and 49.3 % (n = 68) were prescribed antibiotics.

Table 3.1

**Final diagnoses in discovery cohort (CCUH) and validation cohort (Regional hospitals)**

| Diagnosis | CCUH N (percentage) | Regional hospitals N (percentage) |
|---|---|---|
| SBI present | 138 (26.7 %) | 50 (26.6 %) |
| Pneumonia | 68 (13.2 %) | 34 (18.1 %) |
| Urinary tract infection | 22 (4.3 %) | 14 (7.4 %) |
| Acute complicated appendicitis, peritonitis | 9 (1.7 %) | 0 (0 %) |
| Frontitis, orbital cellulitis, mastoiditis | 3 (0.6 %) | 0 (0 %) |
| Invasive soft tissue infection (phlegmon, cellulitis, abscess) | 8 (1.5 %) | 0 (0 %) |
| Acute osteomyelitis / septic arthritis | 10 (1.9 %) | 0 (0 %) |
| Bacterial gastroenteritis | 7 (1.4 %) | 2 (1.1 %) |
| Bacterial meningitis (incl. meningococcal) | 4 (0.8 %) | 0 (0 %) |
| Meningococcal sepsis | 2 (0.4 %) | 0 (0 %) |
| Bacteraemia with shock or multiorgan injury | 2 (0.4 %) | 0 (0 %) |
| Other bacteraemia | 3 (0.6 %) | 0 (0 %) |
| SBI absent | 379 (73.3 %) | 138 (73.4 %) |
| Upper respiratory tract infections (incl. nasopharyngitis, conjunctivitis, stomatitis, gingivitis, non-specific) | 69 (13.3 %) | 29 (15.4 %) |
| Tonsillitis / Pharyngitis | 75 (14.5 %) | 25 (13.3 %) |
| Acute laryngitis (croup) | 2 (0.4 %) | 4 (2.1 %) |
| Acute otitis media | 9 (1.7 %) | 5 (2.7 %) |
| Parotitis | 3 (0.6 %) | 0 (0 %) |
| Infectious mononucleosis | 7 (1.4 %) | 2 (1.1 %) |
| Influenza | 29 (5.6 %) | 24 (12.8 %) |
| Lower respiratory tract infection (bronchitis / bronchiolitis) | 37 (7.2 %) | 36 (19.1 %) |
| Scarlet fever | 5 (1.0 %) | 1 (0.5 %) |
| Acute gastroenteritis | 41 (7.9 %) | 6 (3.2 %) |
| Acute uncomplicated appendicitis | 8 (1.5 %) | 0 (0 %) |
| Aseptic meningitis, encephalitis | 11 (2.1 %) | 0 (0 %) |
| Viral syndrome | 27 (5.2 %) | 3 (1.6 %) |
| Unspecified uncomplicated bacterial infection | 33 (6.4 %) | 2 (1.1 %) |
| Inflammatory / autoimmune | 4 (0.8 %) | 1 (0.5 %) |
| Unspecified diagnosis (non-infectious) | 10 (1.9 %) | 0 (0 %) |
| Other | 9 (1.7 %) | 0 (0 %) |

## 3.3 Analysis of predictor variables in discovery cohort

### 3.3.1 Frequency of the selected predictor variables

Data on thirty potential predictor variables were collected from patients enrolled in CCUH, which can be seen in Table 3.2. Data on the highest temperature during the episode of illness was missing in 70 cases, and seven cases did not include data on the duration of fever, the data on heart rate was missing in 4 cases.

Table 3.2

**Frequency of predictor variables in research population**

| Variable | Present (%) | Present in SBI (%) | Present in non-SBI (%) | Missing |
|---|---|---|---|---|
| T ≥ 40 °C (reported by parents) | 115 (22.2 %) | 37 (26.8 %) | 78 (20.6 %) | 70 |
| Fever ≥ 3 days | 206 (39.8 %) | 68 (49.3 %) | 138 (36.4 %) | 7 |
| Tachycardia | 135 (26.1 %) | 38 (27.5 %) | 97 (25.6 %) | 4 |
| Ill / toxic appearance | 140 (27.1 %) | 68 (49.3 %) | 72 (19.0 %) | 0 |
| Drowsiness | 138 (26.7 %) | 49 (35.5 %) | 89 (23.5 %) | 0 |
| Lethargy | 21 (4.1 %) | 11 (8.0 %) | 10 (2.6 %) | 0 |
| Irritability | 43 (8.3 %) | 11 (8.0 %) | 32 (8.4 %) | 0 |
| Grunting | 21 (4.1 %) | 10 (7.2 %) | 11 (2.9 %) | 0 |
| Inconsolable crying | 20 (3.9 %) | 7 (5.1 %) | 13 (3.4 %) | 0 |
| Reduced appetite | 258 (49.9 %) | 71 (51.4 %) | 187 (49.3 %) | 0 |
| Refusal of food | 101 (19.5 %) | 29 (21.0 %) | 72 (19.0 %) | 0 |
| Refusal to drink | 115 (22.2 %) | 23 (16.7 %) | 92 (24.3 %) | 0 |
| Reduced urine output | 98 (19.0 %) | 30 (21.7 %) | 68 (17.9 %) | 0 |
| Reduced skin turgor | 63 (12.2 %) | 19 (13.8 %) | 44 (11.6 %) | 0 |
| Cyanosis | 0 (0.0 %) | 0 (0.0 %) | 0 (0.0 %) | 0 |
| Tachypnoea | 78 (15.1 %) | 38 (27.5 %) | 40 (10.6 %) | 0 |
| Abnormal breath sounds | 76 (14.7 %) | 35 (25.4 %) | 41 (10.8 %) | 0 |
| Reduced breath sounds | 28 (5.4 %) | 17 (12.3 %) | 11 (2.9 %) | 0 |
| Shortness of breath | 22 (4.3 %) | 10 (7.2 %) | 12 (3.2 %) | 0 |
| Chest retractions | 25 (4.8 %) | 15 (10.9 %) | 10 (2.6 %) | 0 |
| Poor peripheral circulation | 32 (6.2 %) | 20 (14.5 %) | 12 (3.2 %) | 0 |
| Meningeal signs | 15 (2.9 %) | 4 (2.9 %) | 11 (2.9 %) | 0 |
| Non-blanching rash | 24 (4.6 %) | 8 (5.8 %) | 16 (4.2 %) | 0 |
| Seizures | 7 (1.4 %) | 2 (1.4 %) | 5 (1.3 %) | 0 |
| Hypotension | 6 (1.2 %) | 4 (2.9 %) | 2 (0.5 %) | 0 |
| Loss of consciousness | 4 (0.8 %) | 2 (1.4 %) | 2 (0.5 %) | 0 |
| Hypothermia | 1 (0.2 %) | 1 (0.7 %) | 0 (0.0 %) | 0 |
| “Gut feeling” of something wrong | 104 (20.1 %) | 46 (33.3 %) | 58 (15.3 %) | 161 |
| Sense of reassurance | 102 (19.7 %) | 5 (3.6 %) | 97 (25.6 %) | 162 |
| Parental concern | 171 (33.1 %) | 47 (34.1 %) | 124 (32.7 %) | 250 |

### 3.3.2 Bivariate analysis of diagnostic value of clinical signs and symptoms

Of all analysed clinical variables, only hypotension was significantly predictive of SBI (LR (+) > 5), however with an only 2.9 % sensitivity. Other symptoms with significant association with SBI (OR > 1; $p < 0.05$) but limited diagnostic rule-in value (LR (+) < 5) were poor peripheral circulation, reduced breathing sounds, chest retractions, lethargy, tachypnoea, toxic appearance, grunting, abnormal breathing sounds, shortness of breath, drowsiness, and duration of fever for more than 3 days.

No significant association between other alarming signs, such as positive meningeal signs, non-blanching rash, seizures, and SBI was found due to the low prevalence of these symptoms in the discovery population. Cyanosis was excluded from bivariate analysis as it was not noted in any of the patients in discovery cohort, and hypothermia was also excluded, as it was found in only one patient, who had SBI.

The sensitivities, specificities, OR, LR (+), LR (–), PPV and NPV of the clinical variables, and their respective confidence intervals are displayed in Table 3.3.

Table 3.3

**Diagnostic value of clinical variables in discovery cohort**

| Variable | Sensitivity (%) (95 % CI) | Specificity (%) (95 % CI | OR (95 % CI) | LR (+) (95 % CI) | LR (–) (95 % CI) | PPV %) (95 %CI) | NPV (%) (95 % CI) | *p* value |
|---|---|---|---|---|---|---|---|---|
| T ≥ 40 °C (reported by parents) | 32.2 (23.8–41.5) | 76.5 (71.6–81.0) | 1.55 (0.97–2.46) | 1.55 (0.97–2.46) | 1.55 (0.97–2.46) | 1.55 (0.97–2.46) | 76.5 (73.9–78.9) | 0.066 |
| Fever ≥ 3 days | 49.6 (40.1–58.3) | 63.0 (57.9–67.9) | 63.0 (57.9–67.9) | 1.34 (1.08–1.66) | 1.34 (1.08–1.66) | 1.34 (1.08–1.66) | 77.3 (73.9–80.4) | 0.010 |
| Tachycardia | 27.9 (20.6–36.2) | 74.3 (69.6–78.6) | 74.3 (69.6–78.6) | 1.09 (0.79–1.50) | 0.97 (0.86–1.09) | 28.2 (22.2–35.0) | 74.1 (71.7–76.3) | 0.616 |
| Ill / toxic appearance | 49.3 (40.7–57.9) | 81.0 (76.7–84.8) | 81.0 (76.7–84.8) | 81.0 (76.7–84.8) | 81.0 (76.7–84.8) | 81.0 (76.7–84.8) | 81.4 (78.7–83.9) | < 0.001 |
| Drowsiness | 35.5 (27.6–44.1) | 76.5 (71.9–80.7) | 76.5 (71.9–80.7) | 1.51 (1.13–2.02) | 0.84 (0.74–0.97) | 35.5 (29.2–42.4) | 76.5 (74.0–78.9) | 0.006 |
| Lethargy | 8.0 (4.1–13.9) | 97.4 (95.2–98.7) | 3.21 (1.33–7.75) | 3.04 (1.32–6.99) | 0.94 (0.90–1.00) | 52.4 (32.3–71.7) | 74.5 (73.5–75.5) | 0.006 |
| Irritability | 8.0 (4.1–13.8) | 91.6 (88.3–94.2) | 0.94 (0.46–1.92) | 0.94 (0.49–1.82) | 1.01 (0.95–1.07) | 25.6 (15.1–39.9) | 73.2 (72.0–74.3) | 0.863 |
| Grunting | 7.3 (3.5–12.9) | 97.1 (94.9–98.5) | 97.1 (94.9–98.5) | 2.50 (1.08–5.75) | 0.96 (0.91–1.00) | 47.6 (28.3–67.7) | 74.2 (73.2–75.1) | 0.027 |
| Inconsolable crying | 5.1 (2.1–10.2) | 96.6 (94.2–98.2) | 1.50 (0.59–3.85) | 1.48 (0.60–3.63) | 0.98 (0.94–1.03) | 35.0 (18.0–56.9) | 73.6 (72.8–74.5) | 0.392 |
| Reduced appetite | 51.5 (42.8–60.0) | 50.7 (45.5–55.8) | 1.09 (0.74–1.61) | 1.04 (0.86–1.26) | 0.96 (0.79–1.17) | 27.5 (23.9–30.7) | 74.1 (70.2–77.8) | 0.671 |
| Refusal of food | 21.0 (14.6–28.8) | 81.0 (76.7–84.8) | 1.13 (0.70–1.84) | 1.11 (0.75–1.62) | 0.98 (0.88–1.08) | 28.7 (21.5–37.2) | 73.8 (71.8–75.7) | 0.609 |
| Refusal to drink | 16.7 (10.9–24.0) | 75.7 (71.1–80.0) | 0.62 (0.38–1.03) | 0.69 (0.45–1.04) | 1.10 (1.00–1.21) | 20.0 (14.2–27.4) | 71.4 (69.4–73.3) | 0.066 |
| Reduced urine output | 21.7 (15.2–29.6) | 82.0 (77.8–85.8) | 1.27 (0.78–2.06) | 1.21 (0.83–1.78) | 0.95 (0.86–1.05) | 30.6 (23.1–39.3) | 74.2 (72.3–76.1) | 0.330 |

Table 3.3 continued

| Variable | Sensitivity (%) (95 % CI) | Specificity (%) (95 % CI | OR (95 % CI) | LR (+) (95 % CI) | LR (–) (95 % CI) | PPV %) (95 %CI) | NPV (%) (95 % CI) | *p* value |
|---|---|---|---|---|---|---|---|---|
| Reduced skin turgor | 13.8 (8.5–20.7) | 88.4 (84.7–91.4) | 1.22 (0.68–2.17) | 1.19 (0.72–1.96) | 0.98 (0.90–1.05) | 30.2 (20.7–41.6) | 73.8 (72.3–75.2) | 0.507 |
| Tachypnoea | 27.5 (20.3–35.8) | 89.5 (85.9–92.4) | 3.22 (1.96–5.29) | 2.61 (1.75–3.89) | 0.81 (0.73–0.90) | 48.7 (38.9–58.6) | 77.2 (75.3–79.1) | < 0.001 |
| Abnormal breathing sounds | 25.4 (18.4–33.5) | 89.2 (85.6–92.1) | 2.80 (1.70–4.63) | 2.34 (1.56–3.52) | 0.84 (0.75–0.93) | 46.1 (36.2–56.2) | 76.6 (74.7–78.4) | < 0.001 |
| Reduced breathing sounds | 12.3 (7.3–19.0) | 97.1 (94.9–98.5) | 4.70 (2.14–10.31) | 4.24 (2.04–8.83) | 0.90 (0.85–0.96) | 60.7 (42.6–76.3) | 75.3 (74.0–76.4) | < 0.001 |
| Shortness of breath | 7.3 (3.5–12.9) | 96.8 (94.5–98.4) | 2.39 (1.01–5.66) | 2.29 (1.01–5.18) | 0.96 (0.91–1.01) | 74.1 (73.2–75.1) | 74.1 (73.2–75.1) | 0.042 |
| Chest retractions | 10.9 (6.2–17.3) | 97.4 (95.2–98.7) | 4.50 (1.97–10.28) | 4.12 (1.90–8.95) | 0.92 (0.86–0.97) | 60.0 (40.8–76.5) | 75.0 (73.9–76.1) | < 0.001 |
| Poor peripheral circulation | 14.5 (9.1–21.5) | 96.8 (94.5–98.4) | 5.18 (2.46–10.92) | 4.58 (2.30–9.11) | 0.88 (0.82–095) | 62.5 (45.6–76.8) | 75.7 (74.3–77.0) | < 0.001 |
| Meningeal signs | 2.9 (0.8–7.3) | 97.1 (94.9–98.5) | 0.999 (0.31–3.19) | 1.00 (0.32–3.08) | 1.00 (0.97–1.03) | 26.7 (10.5–52.9) | 73.3 (72.6–74.0) | 1.000* |
| Non-blanching rash | 5.8 (2.5–11.1) | 95.8 (93.2–97.6) | 1.40 (0.58–3.34) | 1.37 (0.60–3.14) | 0.98 (0.94–1.03) | 33.3 (18.0–53.3) | 73.6 (72.7–74.5) | 0.451 |
| Seizures | 1.5 (0.2–5.1) | 98.7 (97.0–99.6) | 1.10 (0.21–5.74) | 1.10 (0.22–5.60) | 1.00 (0.98–1.02) | 28.6 (7.3–67.1) | 73.3 (72.9–73.8) | 1.000* |
| Hypotension | 2.9 (0.8–7.3) | 99.5 (98.1–99.9) | 5.63 (1.02–31.07) | 5.49 (1.02–29.65) | 0.98 (095–1.01) | 66.7 (27.0–91.5) | 73.8 (73.2–74.3) | 0.046* |
| Loss of consciousness | 1.5 (0.2–5.1) | 99.5 (98.1–99.9) | 2.77 (0.39–19.87) | 2.75 (0.39–19.31) | 0.99 (0.97–1.01) | 50.0 (12.5–87.6) | 73.5 (73.1–73.9) | 0.290* |

* Fisher's exact test was applied when the number of subjects in one of the cells in the 2 × 2 contingency table was less than 5

### 3.3.3 The diagnostic values of "Gut feeling" of something wrong and "sense of reassurance"

Clinician's "gut feeling" of something being wrong was significantly associated with increased likelihood of SBI, though its diagnostic value was limited (OR > 1, LR (+) < 5). The diagnostic value of "gut feeling" of something wrong expressed by a licensed paediatrician was higher than that of paediatric residents. The diagnostic values of "gut feeling" of something being wrong are reflected in Table 3.4.

Table 3.4

**Diagnostic value of "gut feeling" of something being wrong for prediction of SBI in discovery cohort**

| Sensitivity (%) (95 % CI) | Specificity (%) (95 % CI) | OR (95 % CI) | LR (+) (95 % CI) | LR (–) (95 % CI) | PPV (%) (95 %CI) | NPV (%) (95 % CI) | *p* value |
|---|---|---|---|---|---|---|---|
| **"Gut feeling" of something being wrong, expressed by all clinicians** | | | | | | | |
| 54.8 (43.5–65.7) | 78.7 (73.3–83.4) | 4.47 (2.66–7.50) | 2.57 (1.90–3.47) | 0.57 (0.45–0.73) | 44.2 (37.0–51.7) | 84.9 (81.5–87.8) | < 0.001 |
| **"Gut feeling" of something being wrong, expressed by licensed paediatricians** | | | | | | | |
| 58.1 (42.1–73.0) | 84.4 (76.8–90.4) | 7.52 (3.46–16.41) | 3.73 (2.30–6.06) | 0.50 (0.35–0.71) | 56.8 (44.8–68.1) | 85.1 (80.0–89.1) | < 0.001 |
| **"Gut feeling" of something being wrong, expressed by paediatric residents** | | | | | | | |
| 50.0 (33.4–66.6) | 72.3 (64.2–79.5) | 2.62 (1.25–5.46) | 1.82 (1.19–2.74) | 0.69 (0.49–0.97) | 32.8 (24.3–42.5) | 84.3 (79.4–88.2) | 0.009 |

Clinician's "Sense of reassurance" was significantly predictive of absence of SBI in discovery cohort (LR (+) (95 % CI) = 6.01(2.53–14.28), $p < 0.001$. Again, the association was stronger when the intuitive feeling was expressed by the licensed paediatricians than when compared to their junior colleagues. The diagnostic value of "sense of reassurance" for predicting absence of SBI is shown in Table 3.5.

Table 3.5

**Diagnostic value of "sense of reassurance" in predicting absence of SBI in discovery cohort**

| Sensitivity (%) (95 % CI) | Specificity (%) (95 % CI) | OR (95 % CI) | LR (+) (95 % CI) | LR (–) (95 % CI) | PPV (%) (95 %CI) | NPV (%) (95 % CI) | *p* value |
|---|---|---|---|---|---|---|---|
| **"Sense of reassurance" of all clinicians** | | | | | | | |
| 35.8 (30.1–41.8) | 94.1 (86.7–98.0) | 8.81 (3.45–22.49) | 6.01 (2.53–14.28) | 0.68 (0.62–0.76) | 95.1 (89.1–97.9) | 31.2 (29.0–33.5) | < 0.001 |
| **"Sense of reassurance" of licensed paediatricians** | | | | | | | |
| 40.2 (31.4–49.4) | 97.7 (87.7–99.9) | 28.19 (3.76–211.65) | 17.27 (2.46–121.20) | 0.61 (0.53–0.71) | 98.0 (87.5–99.7) | 36.5 (33.1–40.1) | < 0.001 |
| **"Sense of reassurance" of paediatric residents** | | | | | | | |
| 31.4 (23.9–39.8) | 92.1 (78.6–98.3) | 5.35 (1.56–18.33) | 3.98 (1.31–12.12) | 0.74 (0.64–0.86) | 93.6 (82.8–97.8) | 26.7 (24.0–29.7) | 0.004 |

Among the cases in which the clinicians stated that they did not experience "gut feeling" of something wrong (n = 116), 77 reported "sense of reassurance", 23 were unsure about "sense of reassurance", and 16 experienced neither of these intuitive feelings. Similarly, in cases where "sense of reassurance" was stated as absent (n = 141), "gut feeling" of something wrong was reported as positive in 84 cases, "unsure" – in 41 cases, and absent in 16 cases. In 69 cases, clinicians were unsure about either "gut feeling" of something wrong, or "sense of reassurance". The correlation between the two variables was low (Pearson correlation coefficient –0.397).

Thirteen variables were found to be associated with "gut feeling" of something being wrong in bivariate analysis, the strongest were ill / toxic appearance, poor peripheral circulation, lethargy, reduced breath sounds, and shortness of breath. All clinical features associated with "gut feeling" can be viewed in Table 3.6. Variables with no association to "gut feeling" of something wrong were tachycardia, irritability, grunting, inconsolable crying, reduced appetite, refusal to drink, decreased urine output, decreased skin turgor, petechiae, seizures, hypothermia, and a body temperature, either on admission or registered within episode, above the thresholds of 39.0 °C, 39.5 °C, or 40.0 °C.

Table 3.6

**Clinical features associated with "gut feeling" of something being wrong (bivariate analysis)**

| Clinical features | OR (95 % CI) | *p* value |
|---|---|---|
| Ill / Toxic appearance | 10.49 (6.06–18.15) | < 0.001 |
| Poor peripheral circulation | 8.86 (2.82–27.84) | 0.000* |
| Lethargy | 7.92 (2.10–29.87) | 0.001* |
| Reduced breath sounds | 6.38 (2.38–17.10) | < 0.001 |
| Shortness of breath | 5.87 (1.77–19.53) | 0.003* |
| Chest retractions | 4.85 (1.74–13.49) | 0.003* |
| Abnormal breath sounds | 3.35 (1.84–6.09) | < 0.001 |
| Tachypnoea | 2.61 (1.42–4.80) | 0.002 |
| Drowsiness | 2.19 (1.33–3.59) | 0.002 |
| Refusal of food | 2.18 (1.29–3.66) | 0.003 |
| Parental concern | 1.90 (1.03–3.51) | 0.040 |
| Positive meningeal signs | N/A | 0.002* |
| Arterial hypotension | N/A | 0.002* |

* Fisher's exact test was applied when the number of subjects in one of the cells in the 2 × 2 contingency table was less than 5

### 3.3.4 Parental concern

Parental concern ("different illness") was significantly more commonly expressed by parents of children who developed SBI (as reflected in Table 3.7), however its value in predicting SBI in children with fever was limited. Parental observation of rapid and more superficial breathing was associated with parental concern (OR (95 % CI) = 1.77 (1.06–2.93), $p = 0.027$), as was observation of decrease in urine output (OR (95 % CI) = 2.16 (1.21–3.87),

and highest observed body temperature 39.0 °C (OR (95 % CI) = 2.09 (1.14–3.83). None of the other parent-reported symptoms and behavioural changes listed in the questionnaire (grunting, moaning, rejection of favourite toys or activities, inconsolable crying, screaming, irritability, drowsiness, refusal of food or drinks) had a significant association with parental concern.

Table 3.7

**Diagnostic value of parental concern in discovery cohort**

| **Sensitivity (%) (95 % CI)** | **Specificity (%) (95 % CI)** | **OR (95 % CI)** | **LR (+) (95 % CI)** | **LR (–) (95 % CI)** | **PPV (%) (95 %CI)** | **NPV (%) (95 % CI)** | ***p* value** |
|---|---|---|---|---|---|---|---|
| **Parental concern (different / more severe illness)** | | | | | | | |
| 74.6 (62.1–84.7) | 39.2 (32.5–46.3) | 1.90 (1.01–3.57) | 1.23 (1.02–1.47) | 0.65 (0.41–1.02) | 27.5 (24.0–31.2) | 83.3 (76.0–88.8) | 0.046 |

## 3.4 Clinical prediction models

### 3.4.1 Selection of variables included in clinical prediction models

All variables listed in Tables 3.2 and 3.3 were provisionally considered as eligible for entering in the logistic regression procedures and variable selection for the clinical prediction models (CPMs). However, due to the large number of missing data and limited diagnostic value, inclusion of parental concern was decided against. Highest body temperature was also not entered in logistic regression, as data were missing in 70 cases. Prior to exclusion, the relevance of body temperature as a predictor variable was ruled out by entering several thresholds (above 39.0 °C, above 39.5 °C, and above 40.0 °C) separately in logistic regression analysis. In none of the cases the body temperature was selected as a variable, nor did it change the other selected variables. Variables “cyanosis”, “hypotension”, “loss of consciousness”, and “hypothermia” were further excluded as they were present in 1 % of population or less. The remaining variables were considered for derivation of the model.

Two CPMs were created. The first model (CPM 1) did not include the variables “gut feeling” of something being wrong and “sense of reassurance” and was based on clinical signs and symptoms alone, while the second model (CPM 2) included these variables. Due to missing data, the derivation of CPM 1 was based on 511complete cases of the CCUH patients (26.4 % of whom had SBI), while CPM 2 was based on 345 complete cases (with 23.1 % prevalence of SBI) in whom all the necessary variables were noted.

Assessment of variety of possible models in each case yielded similar results and did not provide significant improvement. The variables selected for the best model according to AIC criteria for CPM 1 are reflected in Table 3.8.

Table 3.8

**Variables of Clinical Prediction Model 1**

| Variables | Coefficient | Standard error | Odds ratio (95 % CI) |
|---|---|---|---|
| Ill / toxic appearance | 1.17 | 0.25 | 3.22 (2.01–5.44) |
| Irritability | −0.64 | 0.55 | 0.53 (0.19–1.65) |
| Refusal to drink | −0.66 | 0.31 | 0.51 (0.28–0.95) |
| Tachypnoea | 0.65 | 0.32 | 1.92 (1.06–3.65) |
| Abnormal breath sounds | 0.52 | 0.32 | 1.68 (0.92–3.23) |
| Reduced breath sounds | 0.82 | 0.51 | 2.26 (0.86–6.38) |
| Poor peripheral circulation | 1.18 | 0.54 | 3.25 (1.18–9.71) |
| Fever ≥ 3 days | 0.41 | 0.23 | 1.51 (0.96–2.41) |

In CPM 1, ill / toxic appearance, tachypnoea, abnormal breath sounds, reduced breath sounds, poor peripheral circulation, and fever lasting 3 days or more increased the likelihood of SBI, while irritability and refusal to drink decreased the odds to develop SBI.

Inclusion of variables “gut feeling” of something being wrong and “sense of reassurance” resulted in a different selection of variables in CPM 2. Table 3.9 reflects the variables selected according to AIC criteria as best for CPM 2.

Table 3.9

**Variables of Clinical Prediction Model 2**

| Variables | Coefficient | Standard Error | Odds ratio (95 % CI) |
|---|---|---|---|
| Refusal to drink | −0.51 | 0.36 | 0.60 (0.30–1.24) |
| Tachypnoea | 0.85 | 0.39 | 2.34 (1.14–5.19) |
| Reduced breath sounds | 1.48 | 1.00 | 4.37 (1.27–15.91) |
| Poor peripheral circulation | 0.96 | 0.85 | 2.61 (0.65–11.02) |
| “Gut feeling” | 0.64 | 0.32 | 1.90 (1.04–3.68) |
| “Sense of reassurance” | −1.63 | 1.41 | 0.20 (0.06–0.66) |

In CPM 2, tachypnoea, reduced breath sounds, poor peripheral circulation, and “gut feeling” increased the odds for SBI, while refusal to drink and “sense of reassurance’ lowered the odds for being diagnosed with SBI.

### 3.4.2 Performance in research and validation populations

The area under curve (AUC) for the Receiver operating characteristic (ROC) curve of CPM 1 was 0.738 (95 % CI 0.688–0.788) which is considered as moderate. In validation population, the AUC for CPM 1 was 0.677 (95 % CI 0.586–0.767), which is an acceptable difference (less than 10 %). The ROC curves of CPM 1 in both derivation and validation populations are shown in Figure 3.1.

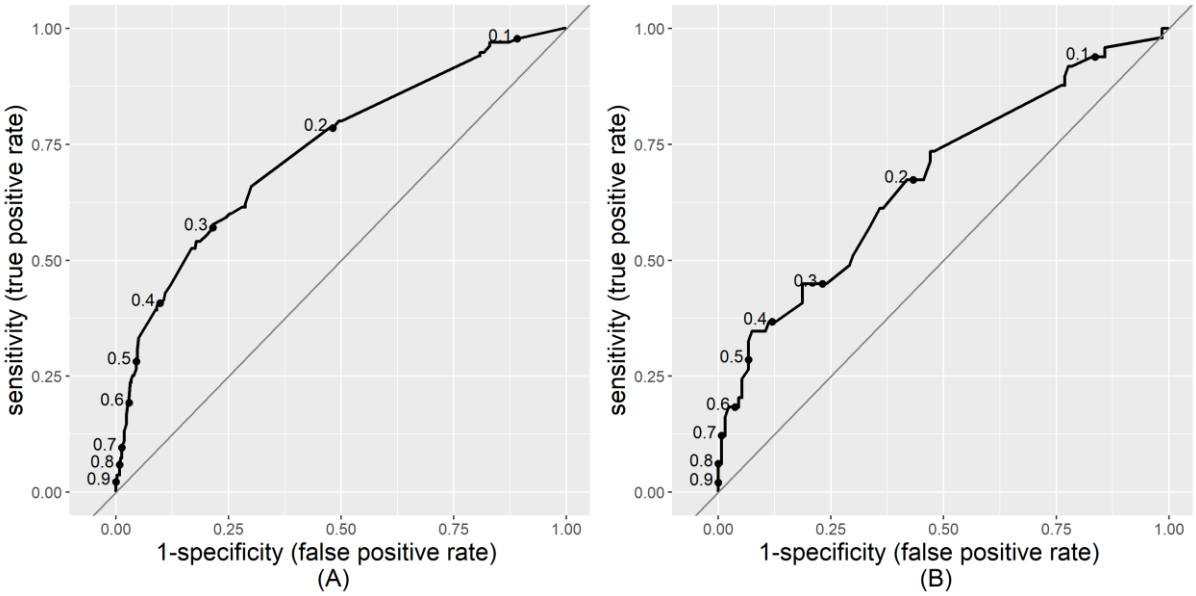


Figure 3.1 **Receiver operating characteristic curves of clinical prediction model 1(CPM 1) for risk of serious bacterial infections (SBIs) in derivation (A) and validation (B) populations***

* The dots on the curves represent sensitivity and specificity at different cut-off points

The ROC area under curve for CPM 2 was 0.783 (95 % CI 0.727–0.839), which is also moderate, but surpasses that of CPM 1. In validation population, the AUC was slightly lower than in research population – 0.752 (95 % CI 0.674–0.830), which is also an acceptable difference. Figure 3.2 displays the ROC curves of CPM 2 in derivation and validation populations.

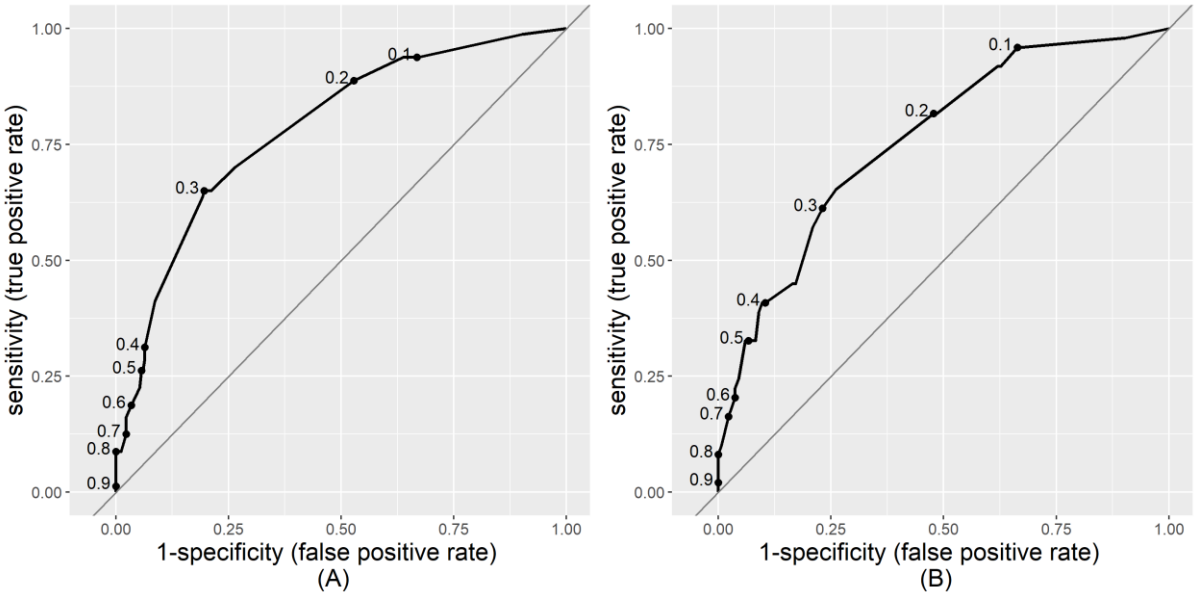


Figure 3.2 **Receiver operating characteristic curves of clinical prediction model 2 (CPM 2) for risk of serious bacterial infections (SBIs) in derivation (A) and validation (B) populations***

* The dots on the curves represent sensitivity and specificity at different cut-off points

According to DeLong's test for two ROC curves, the improvement of AUC of CPM2 in validation population over that of CPM1 was statistically significant ($p = 0.020$, 95 % CI (−0.150; −0.013)).

### 3.4.3 Interpretation of the clinical prediction models

The choice of a single best cut-off point values proved to be problematic for both CPMs. A cut-off point value of 0.219 to discriminate between the two groups (SBI and non-SBI) was set for CPM 1 based on Youden's index to provide highest possible sensitivity and specificity, and cut-off value 0.283 was set for CPM 2. Figures 3.3 and 3.4 illustrate the results of application of CPM1 and CPM2, respectively, to both derivation and validation cohorts, showing the distribution of patients with and without SBI around the estimated cut-off line.

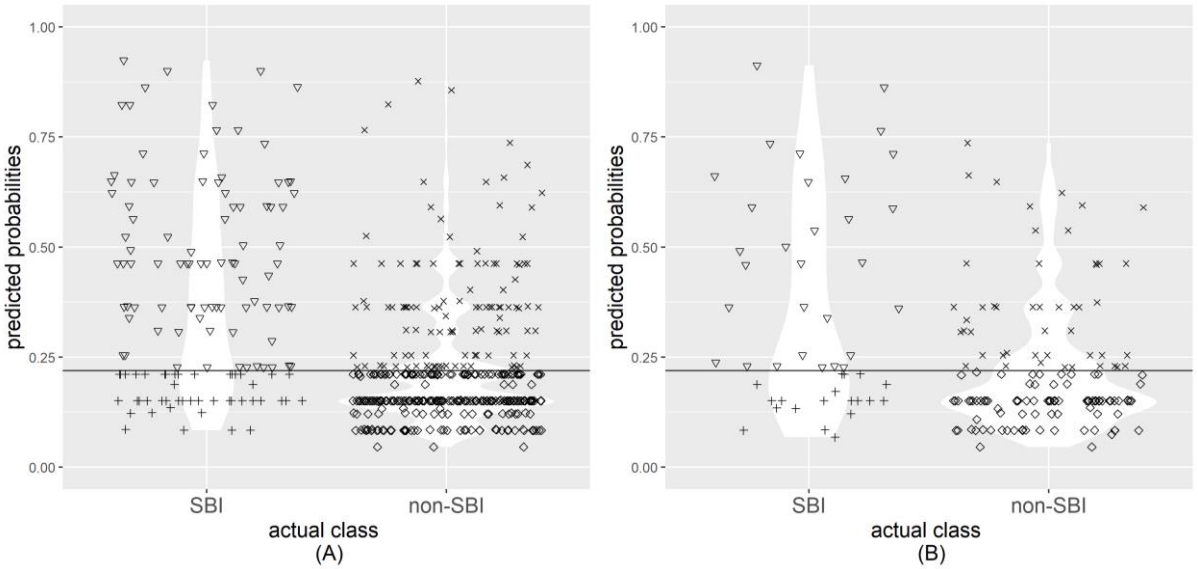


Figure 3.3 **Confusion matrix for discrimination between subjects with SBI and without SBI by clinical prediction model 1 (CPM 1) in research (A) and validation (B) populations with the chosen cut-off value of 0.219**

* Symbols: ▼ true positives; + false negatives; x false positives; ◊ true negatives.
The horizontal line represents the cut-off value

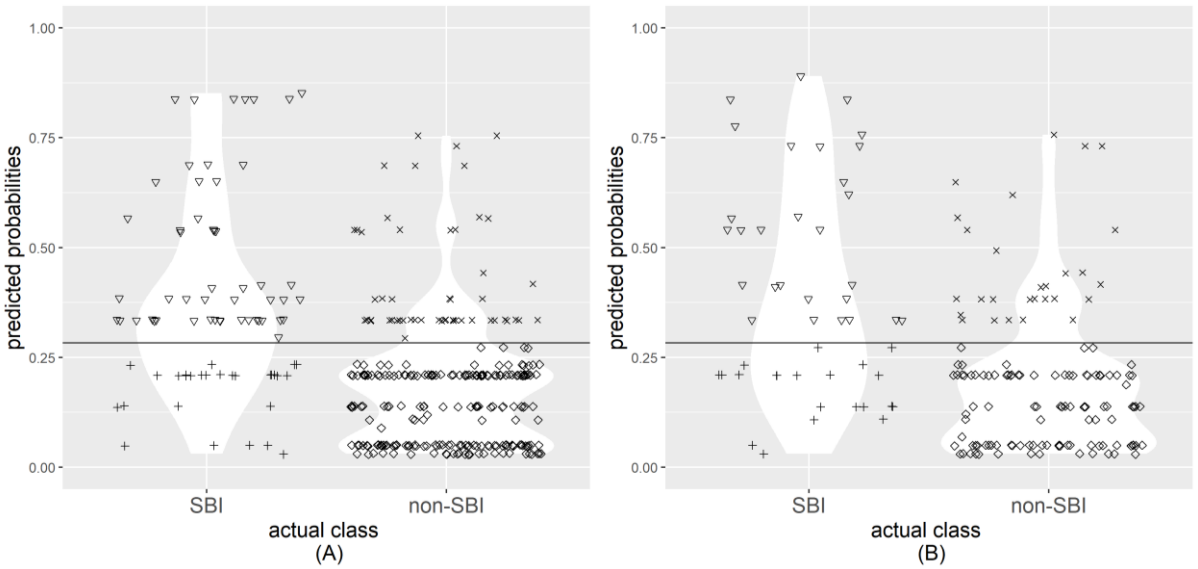


Figure 3.4 **Confusion matrix for discrimination between subjects with SBI and without SBI by clinical prediction model 2 (CPM 2) in research (A) and validation (B) populations with the chosen cut-off value of 0.283**

* Symbols: ▼ true positives; + false negatives; x false positives; ◊ true negatives.
The horizontal line represents the cut-off value

It was evident that choice of a single cut-off point, even with best possible sensitivity and specificity, resulted in a high concentration of patients near the cut-off points who were falsely predicted as either SBI or non-SBI.

The sensitivity of CPM 1 in research cohort at this chosen cut-off level was 65.9 % (95 % CI 57.2–73.9 %), the specificity was 69.9 % (95 % CI 65.0–74.5 %), and the accuracy of the model was 68.9 %. The model missed 46 (34.1 %) cases with SBI, which were instead predicted as non-SBI. In validation cohort, the model (at the chosen cut-off level) had 61.2 % sensitivity (95 % CI 46.2–74.8 %), 64.2 % specificity (95 % CI 55.4–72.3 %), and 63.4 % accuracy. Nineteen (38.8 %) patients with SBI were falsely predicted as non-SBI by the model.

Likewise, application of the chosen cut-off level to CPM 2 yielded a sensitivity of 65.0 % (95 % CI 53.5–75.3 %), specificity 80.4 % (95 % CI 75.0–85.0 %), and accuracy of 76.8 % in research population. Twenty-eight (35.0 %) cases with SBI were falsely identified as non-SBI. In validation population, use of the cut-off resulted in a sensitivity of 56.2 % (95 % CI 41.2–70.5 %), 79 % specificity (95 % CI 71.0–85.5 %), and 72.9 % accuracy, though 21 (43.8 %) of patients with SBI were falsely identified as non-SBI.

The performance of CPM 1 (sensitivity, specificity, positive and negative predictive values, positive and negative likelihood ratios) in derivation and validation populations are shown in Table 3.10, while the performance of CPM 2 is reflected in Table 3.11.

Table 3.10

**Diagnostic performance of CPM 1 at different cut-off points in derivation and validation cohorts**

| Cut-off | Sensitivity (95 % CI) | Specificity (95 % CI) | PPV (95 % CI) | NPV (95 % CI) | LR (+) (95 % CI) | LR (–) (95 % CI) |
|---|---|---|---|---|---|---|
| **Derivation cohort (CCUH)** | | | | | | |
| 0.10 | 0.97 (0.93–0.99) | 0.13 (0.10–0.17) | 0.29 (0.24–0.33) | 0.92 (0.81–0.98) | 1.11 (1.06–1.17) | 0.23 (0.09–0.63) |
| 0.20 | 0.79 (0.71–0.85) | 0.52 (0.47–0.57) | 0.37 (0.31–0.43) | 0.87 (0.82–0.91) | 1.63 (1.42–1.87) | 0.41 (0.30–0.58) |
| 0.30 | 0.57 (0.48–0.66) | 0.78 (0.74–0.83) | 0.49 (0.41–0.57) | 0.84 (0.79–0.87) | 2.65 (2.08–3.37) | 0.55 (0.45–0.67) |
| 0.40 | 0.41 (0.32–0.50) | 0.90 (0.87–0.93) | 0.60 (0.49–0.70) | 0.81 (0.77–0.85) | 4.14 (2.87–5.98) | 0.66 (0.57–0.76) |
| 0.50 | 0.28 (0.21–0.37) | 0.95 (0.93–0.97) | 0.69 (0.55–0.81) | 0.79 (0.75–0.82) | 6.23 (3.64–10.65) | 0.75 (0.68–0.84) |
| 0.60 | 0.19 (0.13–0.27) | 0.97 (0.95–0.99) | 0.72 (0.55–0.86) | 0.77 (0.73–0.81) | 7.24 (3.59–14.62) | 0.83 (0.76–0.90) |
| 0.70 | 0.10 (0.05–0.16) | 0.99 (0.97–1.00) | 0.72 (0.47–0.90) | 0.75 (0.71–0.79) | 7.24 (2.63–19.93) | 0.92 (0.87–0.97) |
| **Validation cohort (Regional hospitals)** | | | | | | |
| 0.10 | 0.94 (0.83–0.99) | 0.16 (0.11–0.24) | 0.29 (0.22–0.37) | 0.88 (0.69–0.97) | 1.12 (1.01–1.25) | 0.37 (0.12–1.19) |
| 0.20 | 0.67 (0.52–0.80) | 0.57 (0.48–0.65) | 0.36 (0.26–0.47) | 0.83 (0.73–0.90) | 1.56 (1.18–2.05) | 0.58 (0.38–0.88) |
| 0.30 | 0.45 (0.31–0.60) | 0.77 (0.69–0.84) | 0.42 (0.28–0.56) | 0.79 (0.71–0.86) | 1.94 (1.25–3.01) | 0.72 (0.55–0.94) |
| 0.40 | 0.37 (0.23–0.52) | 0.89 (0.82–0.94) | 0.55 (0.36–0.72) | 0.79 (0.72–0.86) | 3.28 (1.80–5.99) | 0.71 (0.57–0.89) |
| 0.50 | 0.29 (0.17–0.43) | 0.93 (0.88–0.97) | 0.61 (0.39–0.80) | 0.78 (0.71–0.84) | 4.25 (1.97–9.20) | 0.77 (0.64–0.92) |
| 0.60 | 0.18 (0.09–0.32) | 0.97 (0.93–0.99) | 0.69 (0.39–0.91) | 0.76 (0.69–0.83) | 6.15 (1.98–19.07) | 0.84 (0.73–0.96) |
| 0.70 | 0.12 (0.05–0.25) | 0.99 (0.96–1.00) | 0.86 (0.42–1.00) | 0.76 (0.69–0.82) | 6.41 (2.03–132.87) | 0.88 (0.80–0.98) |

Table 3.11

**Diagnostic performance of CPM 2 at different cut-off points in derivation and validation cohorts**

| Cut-off | Sensitivity (95 % CI) | Specificity (95 % CI) | PPV (95 % CI) | NPV (95 % CI) | LR (+) (95 % CI) | LR (–) (95 % CI) |
|---|---|---|---|---|---|---|
| **Derivation cohort (CCUH)** | | | | | | |
| 0.10 | 0.94 (0.86–0.98) | 0.33 (0.28–0.39) | 0.30 (0.24–0.36) | 0.95 (0.88–0.98) | 1.40 (1.27–1.55) | 0.19 (0.08–0.45) |
| 0.20 | 0.89 (0.80–0.95) | 0.47 (0.41–0.53) | 0.34 (0.27–0.40) | 0.93 (0.88–0.97) | 1.68 (1.46–1.93) | 0.24 (0.13–0.45) |
| 0.30 | 0.64 (0.52–0.74) | 0.81 (0.75–0.85) | 0.50 (0.40–0.60) | 0.88 (0.83–0.92) | 3.31 (2.46–4.46) | 0.45 (0.33–0.60) |
| 0.40 | 0.31 (0.21–0.43) | 0.94 (0.90–0.96) | 0.60 (0.43–0.74) | 0.82 (0.77–0.86) | 4.87 (2.77–8.55) | 0.73 (0.63–0.85) |
| 0.50 | 0.26 (0.17–0.37) | 0.94 (0.91–0.97) | 0.58 (0.41–0.74) | 0.81 (0.76–0.85) | 4.64 (2.51–8.57) | 0.78 (0.68–0.89) |

Table 3.11 continued

| Cut-off | Sensitivity (95 % CI) | Specificity (95 % CI) | PPV (95 % CI) | NPV (95 % CI) | LR (+) (95 % CI) | LR (–) (95 % CI) |
|---|---|---|---|---|---|---|
| **Derivation cohort (CCUH)** | | | | | | |
| 0.60 | 0.16 (0.09–0.26) | 0.98 (0.95–0.99) | 0.68 (0.43–0.87) | 0.79 (0.75–0.84) | 7.18 (2.82–18.27) | 0.86 (0.78–0.95) |
| 0.70 | 0.09 (0.04–0.17) | 0.99 (0.97–1.00) | 0.70 (0.35–0.93) | 0.78 (0.73–0.83) | 7.73 (2.05–29.20) | 0.92 (0.86–0.99) |
| **Validation cohort (Regional hospitals)** | | | | | | |
| 0.10 | 0.96 (0.86–1.00) | 0.34 (0.26–0.42) | 0.35 (0.27–0.43) | 0.96 (0.85–0.99) | 1.44 (1.26–1.65) | 0.12 (0.03–0.48) |
| 0.20 | 0.82 (0.68–0.91) | 0.52 (0.43–0.61) | 0.38 (0.29–0.49) | 0.89 (0.79–0.95) | 1.71 (1.37–2.13) | 0.35 (0.19–0.65) |
| 0.30 | 0.57 (0.42–0.71) | 0.79 (0.71–0.86) | 0.50 (0.36–0.64) | 0.83 (0.76–0.89) | 2.73 (1.82–4.12) | 0.54 (0.39–0.76) |
| 0.40 | 0.41 (0.27–0.56) | 0.90 (0.83–0.94) | 0.59 (0.41–0.75) | 0.81 (0.73–0.87) | 3.91 (2.15–7.11) | 0.66 (0.52–0.84) |
| 0.50 | 0.33 (0.20–0.48) | 0.94 (0.89–0.97) | 0.67 (0.45–0.84) | 0.79 (0.72–0.85) | 5.47 (2.50–11.97) | 0.72 (0.59–0.87) |
| 0.60 | 0.20 (0.10–0.34) | 0.96 (0.92–0.99) | 0.67 (0.38–0.88) | 0.77 (0.70–0.83) | 5.47 (1.97–15.20) | 0.83 (0.71–0.96) |
| 0.70 | 0.16 (0.07–0.30) | 0.98 (0.94–1.00) | 0.73 (0.39–0.94) | 0.76 (0.69–0.82) | 7.29 (2.02–26.38) | 0.86 (0.75–0.97) |

There was a significant gap between the risk thresholds with an optimal rule-in and rule-out values for SBI. For CPM 1, a 10 % risk threshold had a sensitivity of 97 % (95 % CI 93–99 %) and negative likelihood ratio 0.23 (95 %CI 0.09–0.63) in derivation population, while the positive likelihood ratio was low. By contrast, a cut-off of 0.5 was sufficient for ruling-in SBI (LR (+) (95 %CI) = 6.23 (3.64–10.65), specificity (95 % CI) = 95 % (93–97 %)), though with a low sensitivity of 28 % (95 % CI 21–37 %). The sensitivity and specificity at the low- and high-risk thresholds, respectively, were similar in validation population. Similar gap was evident for CPM 2, in which the recommended cut-off for ruling out SBI was 0.1, while a cut-off 0.6 was optimal for ruling-in SBI, which yielded similar sensitivities and specificities in both cohorts.

### 3.4.4 Assessment score based on CPM2

To simplify the clinical applicability of the derived CPMs, CPM 2 was chosen as the superior model according to its AUC in both derivation and validation populations, and a clinical score was created. The number of points in the score attributed to each variable was proportional to the regression coefficient, meaning that variables with negative regression coefficients were given negative points. To avoid negative total result, four points were added to the total sum of points, thus creating a range of zero to twelve possible points. The variables and their attributed points in the score are reflected in Table 3.12.

Table 3.12

**Clinical score to assess the risk for serious bacterial infection**

| Variables | Coefficient | Points if present | Points if absent |
|---|---|---|---|
| Refusal to drink | −0.51 | −1 | 0 |
| Tachypnoea | 0.85 | 2 | 0 |
| Reduced breath sounds | 1.48 | 3 | 0 |
| Poor peripheral circulation | 0.96 | 2 | 0 |
| "Gut feeling" | 0.64 | 1 | 0 |
| "Sense of reassurance" | −1.63 | −3 | 0 |
| Total | – | **Sum of points +4*** | |

* Four points are added to the total sum of points to avoid negative result

The scoring system was subsequently applied to the derivation population and its performance assessed in validation cohort. The sensitivities, specificities, positive and negative predictive values, and positive and negative likelihoods at different score cut-off values are reflected in Table 3.13.

Table 3.13

**Diagnostic performance of scoring system based on CPM 2 at different cut-off score values in derivation and validation cohorts**

| Cut-off | Sensitivity (95 % CI) | Specificity (95 % CI) | PPV (95 % CI) | NPV (95 % CI) | LR (+) (95 % CI) | LR (–) (95 % CI) |
|---|---|---|---|---|---|---|
| **Derivation cohort (CCUH)** | | | | | | |
| ≥ 1 point | 0.99 (0.93–1.00) | 0.10 (0.065–0.14) | 0.28 (0.24–0.26) | 0.96 (0.78–1.00) | 1.09 (1.04–1.15) | 0.13 (0.02–0.92) |
| ≥ 2 points | 0.94 (0.86–0.98) | 0.33 (0.27–0.39) | 0.30 (0.28–0.32) | 0.95 (0.88–0.98) | 1.40 (1.26–1.54) | 0.19 (0.08–0.45) |
| ≥ 3 points | 0.94 (0.86–0.98) | 0.33 (0.28–0.39) | 0.30 (0.28–0.32) | 0.95 (0.88–0.98) | 1.40 (1.27–1.55) | 0.19 (0.08–0.45) |
| ≥ 4 points | 0.89 (0.80–0.95) | 0.47 (0.41–0.53) | 0.34 (0.31–0.37) | 0.93 (0.88–0.96) | 1.68 (1.46–1.93) | 0.24 (0.13–0.45) |
| ≥ 5 points | 0.65 (0.54–0.75) | 0.79 (0.73–0.84) | 0.48 (0.41–0.55) | 0.88 (0.85–0.91) | 3.08 (2.32–4.08) | 0.44 (0.33–0.60) |
| ≥ 6 points | 0.41 (0.30–0.53) | 0.91 (0.87–0.94) | 0.60 (0.47–0.70) | 0.84 (0.81–0.86) | 4.75 (2.97–7.60) | 0.64 (0.53–0.78) |
| ≥ 7 points | 0.26 (0.17–0.37) | 0.94 (0.91–0.97) | 0.58 (0.43–0.72) | 0.81 (0.79–0.83) | 4.64 (2.51–8.57) | 0.78 (0.68–0.89) |
| ≥ 8 points | 0.16 (0.09–0.26) | 0.98 (0.95–0.99) | 0.68 (0.46–0.85) | 0.80 (0.79–0.81) | 7.18 (2.82–18.27) | 0.86 (0.78–0.95) |
| ≥ 9 points | 0.09 (0.04–0.17) | 0.99 (0.97–1.00) | 0.70 (0.38–0.90) | 0.78 (0.77–0.79) | 7.73 (2.05–29.20) | 0.92 (0.86–0.99) |
| **Validation cohort (Regional hospitals)** | | | | | | |
| ≥ 1 point | 0.98 (0.89–1.00) | 0.10 (0.05–0.16) | 0.28 (0.27–0.30) | 0.93 (0.64–0.99) | 1.08 (1.01–1.16) | 0.21 (0.03–1.57) |
| ≥ 2 points | 0.96 (0.86–1.00) | 0.33 (0.25–0.41) | 0.34 (0.31–0.37) | 0.96 (0.85–0.99) | 1.43 (1.25–1.63) | 0.12 (0.03–0.49) |
| ≥ 3 points | 0.96 (0.86–1.00) | 0.34 (0.26–0.42) | 0.35 (0.32–0.38) | 0.98 (0.85–0.99) | 1.44 (1.26–1.65) | 0.12 (0.03–0.48) |

Table 3.13 continued

| Cut-off | Sensitivity (95 % CI) | Specificity (95 % CI) | PPV (95 % CI) | NPV (95 % CI) | LR (+) (95 % CI) | LR (–) (95 % CI) |
|---|---|---|---|---|---|---|
| **Validation cohort (Regional hospitals)** | | | | | | |
| ≥ 4 points | 0.82 (0.68–0.91) | 0.51 (0.43–0.60) | 0.38 (0.33–0.43) | 0.89 (0.81–0.93) | 1.68 (1.35–2.10) | 0.36 (0.19–0.66) |
| ≥ 5 points | 0.61 (0.46–0.75) | 0.77 (0.69–0.84) | 0.49 (0.40–0.59) | 0.84 (0.79–0.89) | 2.65 (1.81–3.87) | 0.50 (0.35–0.73) |
| ≥ 6 points | 0.45 (0.31–0.60) | 0.83 (0.75–0.89) | 0.49 (0.37–0.61) | 0.80 (0.76–0.84) | 2.62 (1.61–4.25) | 0.67 (0.51–0.87) |
| ≥ 7 points | 0.33 (0.20–0.48) | 0.93 (0.88–0.97) | 0.64 (0.46–0.79) | 0.79 (0.76–0.82) | 4.86 (2.30–10.27) | 0.72 (0.59–0.88) |
| ≥ 8 points | 0.20 (0.10–0.34) | 0.96 (0.92–0.99) | 0.67 (0.42–0.85) | 0.77 (0.74–0.79) | 5.47 (1.97–15.20) | 0.83 (0.71–0.96) |
| ≥ 9 points | 0.16 (0.07–0.30) | 0.98 (0.94–1.00) | 0.73 (0.42–0.91) | 0.76 (0.74–0.78) | 7.29 (2.02–26.39) | 0.86 (0.75–0.97) |

Basing on the sensitivity, specificity, positive and negative likelihood ratio in derivation cohort, patients with score value of 3 points or less were stratified in a low-risk category for SBI, while patients who were assessed as reaching 6 or more points – into high-risk category. Patients with 4 or 5 points were classified as belonging to the "grey area". This interpretation of the score had adequate performance in validation population as well, with equal rule-out values for low-risk categories, while rule-in threshold for high-risk category in validation population was higher than in derivation cohort. Considering the goal for the model of reducing the number of missed cases of SBI, this was viewed as optimal.

As a result, the majority of patients with SBI in derivation cohort were categorized in either high risk or "grey area" categories, with the expense of missing 11.3 % of SBI patients (n = 9). In validation cohort, 18.5 % of patients with SBI (n = 9) were missed. Approximately half of the patients without SBI were categorized as low risk in both cohorts, while 8.7 % (n = 23) and 17.2 % (n = 23) of non-SBI patients were assessed as high-risk in derivation and validation cohorts, respectively. The categorization of patients of derivation and validation cohorts according to the scoring system is reflected in Table 3.14.

Table 3.14

**Interpretation of the clinical score according to outcomes in research and validation populations.**

| Points | Interpretation | Research cohort (CCUH) | | Validation cohort Regional hospitals | | Total* | |
|---|---|---|---|---|---|---|---|
| | | Non-SBI N** (%) | SBI N (%) | Non-SBI N (%) | SBI N (%) | Non-SBI N (%) | SBI N (%) |
| 0 | Low risk | 26 (9.8 %) | 1 (1.3 %) | 13 (9.7 %) | 1 (2.0 %) | 39 (9.8 %) | 2 (1.6 %) |
| 1 | | 61 (23.0 %) | 4 (5.0 %) | 31 (23.1 %) | 1 (2.0 %) | 92 (23.1 %) | 5 (3.9 %) |
| 2 | | 1 (0.4 %) | 0 (0.0 %) | 1 (0.7 %) | 0 (0.0 %) | 2 (0.5 %) | 0 (0.0 %) |
| 3 | | 37 (14.0 %) | 4 (5.0 %) | 24 (17.9 %) | 7 (14.3 %) | 61 (15.3 %) | 11 (8.5 %) |

Table 3.14 continued

| Points | Interpretation | Research cohort (CCUH) | | Validation cohort Regional hospitals | | Total* | |
|---|---|---|---|---|---|---|---|
| | | Non-SBI N** (%) | SBI N (%) | Non-SBI N (%) | SBI N (%) | Non-SBI N (%) | SBI N (%) |
| 4 | "Grey area" | 84 (31.7 %) | 19 (23.8 %) | 34 (25.4 %) | 10 (20.4 %) | 118 (29.6 %) | 29 (22.5 %) |
| 5 | | 33 (12.5 %) | 19 (23.8 %) | 8 (6.0 %) | 8 (16.3 %) | 41 (10.3 %) | 27 (20.9 %) |
| 6 | High risk | 8 (3.0 %) | 12 (15.0 %) | 14 (10.4 %) | 6 (12.2 %) | 22 (5.5 %) | 18 (14.0 %) |
| 7 | | 9 (3.4 %) | 8 (10.0 %) | 4 (3.0 %) | 6 (12.2. %) | 13 (3.3 %) | 14 (10.9 %) |
| 8 | | 3 (1.1 %) | 6 (7.5 %) | 2 (1.5 %) | 2 (4.1 %) | 5 (1.3 %) | 8 (6.2 %) |
| 9 | | 3 (1.1 %) | 0 (0.0 %) | 3 (2.2 %) | 5 (10.2 %) | 6 (1.5 %) | 5 (3.9 %) |
| 10 | | 0 (0.0 %) | 7 (8.8 %) | 0 (0.0 %) | 2 (4.1 %) | 0 (0.0 %) | 9 (7.0 %) |
| 11 | | 0 (0.0 %) | 0 (0.0 %) | 0 (0.0 %) | 1 (2.0 %) | 0 (0.0 %) | 1 (0.8 %) |

* The total number of patients represents the combination of patients in research and validation cohorts.
** Patients with missing values in any of the parameters are excluded from analysis in this Table.

Figure 3.5 illustrates the distribution of patients with and without SBI between the different risk categories in derivation and validation cohorts. The composition of low risk, "grey area" and high-risk categories in each cohort is shown in Figure 3.6.

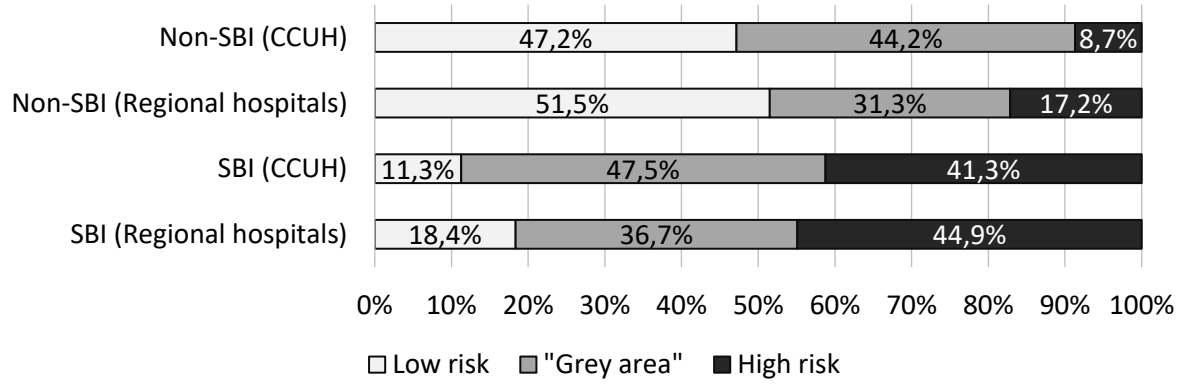


Figure 3.5 **Categorization of patients with and without serious bacterial infection (SBI) in derivation and validation cohorts according to scoring system based on CPM 2**

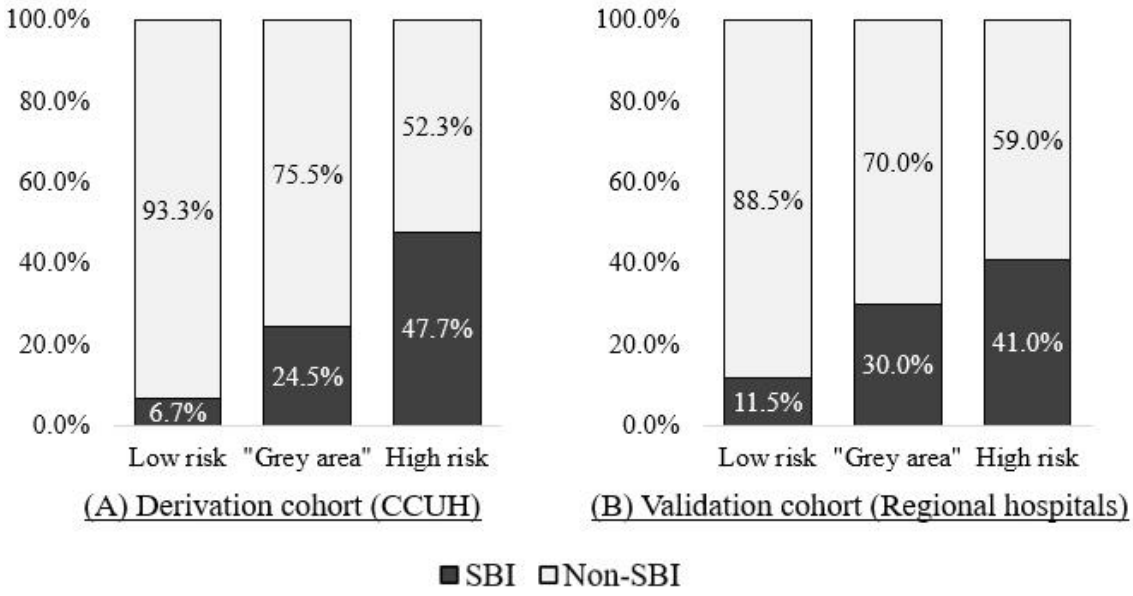


Figure 3.6 **Composition of patients with and without serious bacterial infection (SBI) within low risk, "grey area", and high-risk categories in derivation and validation cohorts**

## 3.5 Analysis of parental perception of fever

### 3.5.1 Results of the parental questionnaire

**Beliefs regarding fever and its management**

The question of whether fever itself indicates that the illness is serious was answered by 408 participants (233 in CCUH and 173 in regional hospitals). More than a half of the participants in both cohorts (56.6 %, n = 231) expressed an opinion that fever itself is indicative of a serious illness, while 29.7 % (n = 121) of parents stated that other symptoms should be considered as well. Only 9.1 % of participants (n = 37) thought that fever alone is not indicative of severity of illness, while 4.3 % (n = 19) stated that they don't know the answer. The differences between the opinions stated by participants enrolled in CCUH and regional hospitals can be viewed in Figure 3.7.

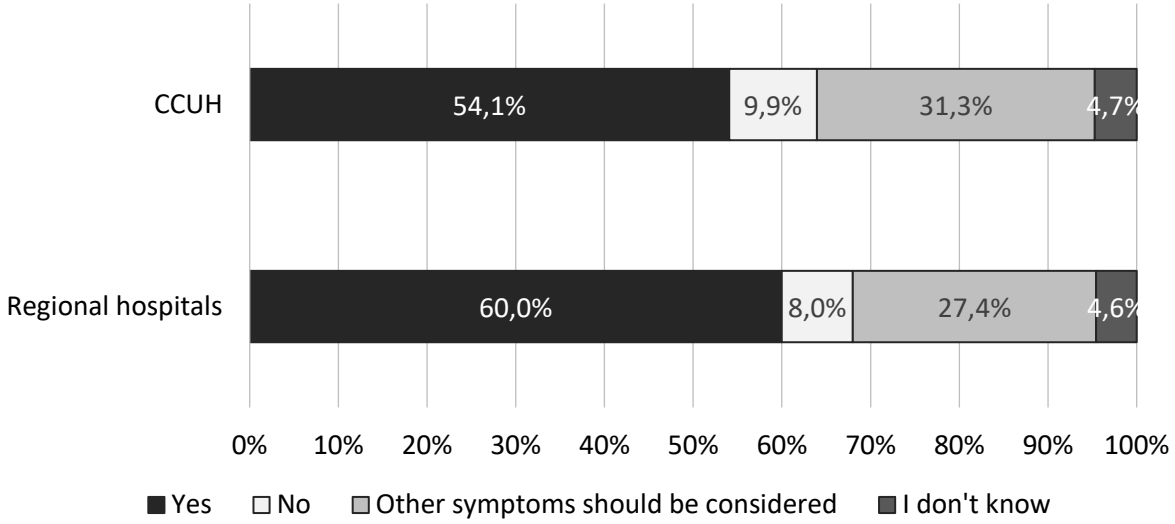


Figure 3.7 **Parental response to the question: "Does fever itself indicate that the illness is serious?"**

Participants in CCUH more frequently thought that fever does not indicate that the illness is serious and were more likely to consider other symptoms than participants in regional hospitals, though the difference was not statistically significant. While number of children in the family did not significantly affect parental opinion on the question, respondents with a university degree were less likely to automatically associate fever with serious illness than respondents without one (OR (95 % CI) = 0.62 (0.42–0.93)), $p = 0.02$.

The body temperature of the child at which parents usually administered antipyretics ranged from 37.0 °C to 40 °C, with median of 38 °C. Nearly half of the respondents (48.5 %) reported giving antipyretics at a body temperature between 38.0 °C and 38.4 °C, while 35.5 % were giving medication at temperature between 38.5 °C and 38.9 °C and 4.7 % – at 39.0 °C. Only seven respondents (1.7 %) would allow the temperature to rise above 39 °C, while 9.6 % stated that they start reducing the child's body temperature before it reaches 38.0 °C. Respondents with a university degree would give medication to reduce fever at a higher temperature (median 38.5 °C) than parents without higher education (median 38 °C), the difference was statistically significant (W (Wilcoxon statistic) = 23532, $p < 0.001$). The number of children in the family (one or multiple) did not significantly affect the temperature at which antipyretics were given, and the practices between respondents in CCUH and regional hospitals were similar.

The median temperature that parents evaluated as high fever in CCUH, and regional hospitals alike was 39 °C (range 37.0 °C to 42.0 °C). Most respondents (92.5 %, n = 382) believed that the child's body temperature during febrile illness can increase up to a level that is dangerous to the child's life. The median temperature believed to be dangerous to the child

by all respondents together was 39.8 °C (range 37.0 °C to 42.0 °C), though there were differences between the study sites. While among respondents in CCUH, median temperature associated with adverse effects was 39.5 °C, parents in regional hospitals mostly regarded fever above 40 °C as threatening, though the difference was not statistically significant ($p$ = 0.37). Neither level of education nor the size of the family did not affect parental beliefs on temperatures regarded as high fever or dangerous to the child ($p$ > 0.05).

**Healthcare-seeking behaviour in case of febrile illness in a child**

Slightly more than a half of the participants (56.1 %, n = 232) admitted that they seek medical attention within the first 24 hours after their children become ill with fever (54.4 % of participants in CCUH (n = 128) and 58.4 % of respondents in regional hospitals (n = 104)). The time after the onset of febrile illness when parents usually sought help is reflected in Figure 3.8.

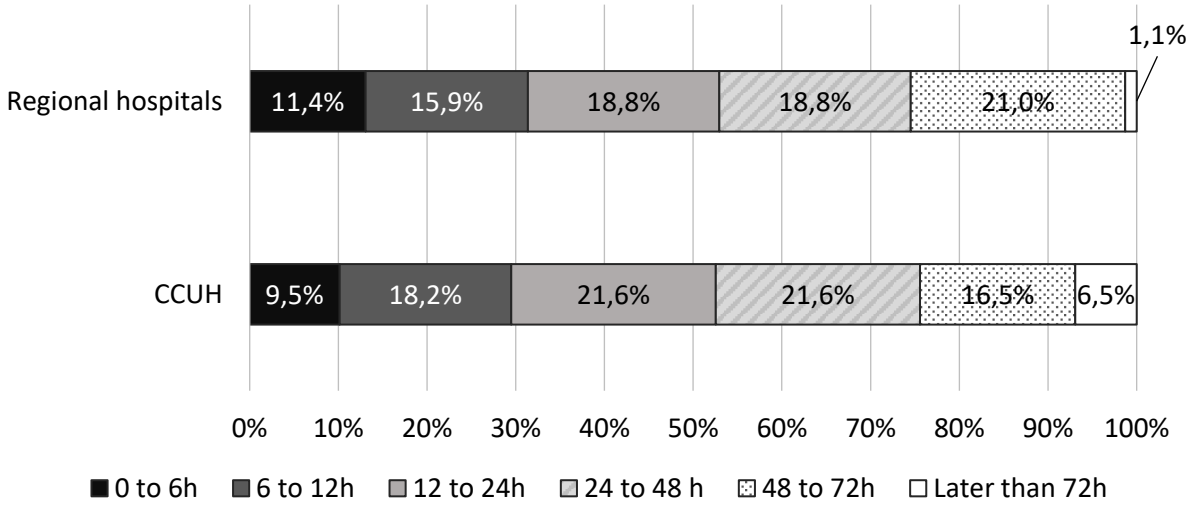


Figure 3.8 **Time after the onset of febrile illness in their child at which parents usually seek medical attention**

Parents of a single child were slightly more likely to seek medical attention within the first 24 hours than parents of multiple children (65.0 % vs 52.7 %), and the difference was statistically significant (OR (95 % CI) = 1.67 (1.10 – 2.55); $\chi^2$ = 5.804; $p$ = 0.016). The median temperature believed to dangerous was significantly lower for parents seeking help within the first 24 hours (median 39.5 °C) than for parents who would seek help later (median 40 °C), (W = 14630, $p$ = 0.016). Similarly, parents who usually sought help on the first day of illness were also giving their children antipyretics at a lower body temperature (median 38 °C) than parents who delayed contacting or visiting a doctor (median 38.3 °C) (W = 17381, $p$ = 0.025). The education level of respondents did not affect the time at which they usually sought help when their child had fever.

When asked when they first contacted a doctor during the current febrile episode of the patient enrolled in the study, 48.6 % of participants (n = 201) did so within the first 24 hours after the onset of symptoms, and the number of children in the family did not affect the timing of seeking help, nor did the education level of the parents. The body temperature associated with adverse effects was lower (median 39.5 °C) among parents who sought help on the first day than among those who did so later (median 40 °C) ($W = 10027$, $p < 0.001$).

The first doctor visited or contacted during the ongoing febrile episode by majority of participants in both cohorts (67.3 %, n = 278) was a primary care specialist (in 58.6 % of cases it was the family doctor, 7.7 % contacted the out-of-hours family doctor telephone service, while 1.0 % of participants visited an out-of-hours primary care doctor). Participants enrolled in CCUH more commonly were first seen by an ambulance doctor or physician at the hospital (32.3 %, n = 76) than respondents in regional hospitals, whose children in only 23.6 % of cases (n = 42) were first examined by these specialists. More details can be viewed in Figure 3.9.

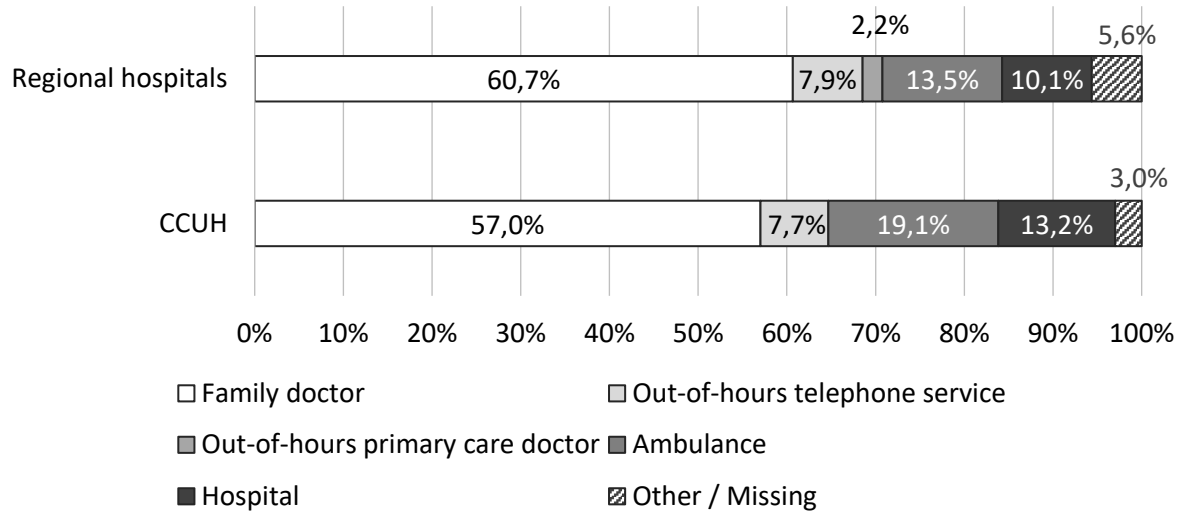


Figure 3.9 **First doctor visited or contacted after the onset of symptoms of the ongoing febrile episode**

Of all participants, 387 provided details on timing of their first contact with the doctor during the current illness of their child (221 participants in CCUH, and 166 in regional hospitals). In most cases (64.0 %, n = 248), the first attempt of seeking medical attention within the ongoing episode was made within the normal working hours (8 a.m. to 5 p.m.). In regional hospitals, 39.8 % of participants (n = 66) first visited or called a doctor outside the normal working ours, compared to 33.0 % of parents (n = 73) enrolled in CCUH.

The median temperature believed to be dangerous by participants who sought help outside the working hours was lower (39.5 °C) than that believed to be harmful by those who first visited or called the doctor within the working hours (median 39.9 °C), though this difference was not statistically significant (p = 0.07).

Of all parents who first sought help outside primary care (by calling an ambulance or visiting hospital), 33.0 % did so within the normal working hours (42.1 % in CCUH and 16.7 % in regional hospitals). Among parents who first sought help within the normal working hours, 15.7 % (n = 39) chose to call an ambulance or visit a hospital instead of contacting their family doctors. However, there were marked differences between the cohorts – among parents enrolled in CCUH, 21.6 % had sought help outside primary care within normal working hours, compared to only 7.0 % of parents recruited in regional hospitals. The median temperature believed to be dangerous by parents who sought help outside primary care within normal working hours was higher (39.65 °C) than that of parents who contacted primary care (39.95 °C), but the difference was not statistically significant (p > 0.05).

**Satisfaction with provided care**

Out of patients who first consulted their family doctor prior to visiting hospital ED, satisfaction with the provided explanation on the nature of illness provided by the doctor at the ED was higher than with that given by the family doctor in CCUH (OR (95 % CI) = 2.26 (1.02–5.00; $\chi^2$ = 4.100; $p$ = 0.043) and Regional hospital (OR (95 % CI) = 3.60 (1.11–11.66); $\chi^2$ = 4.980; $p$ = 0.026) cohorts alike. Respondents in regional hospitals were more satisfied with the information provided at the ED when compared with parents seeking help at CCUH (OR (95 % CI) = 2.21 (1.34–3.64); $\chi^2$ = 9.919; $p$ = 0.002); while the difference in satisfaction with information provided by family doctor between both cohorts was not statistically significant ($p$ > 0.05). The satisfaction with the provided explanation by family doctors or hospital specialists in each cohort is shown in Figure 3.10.

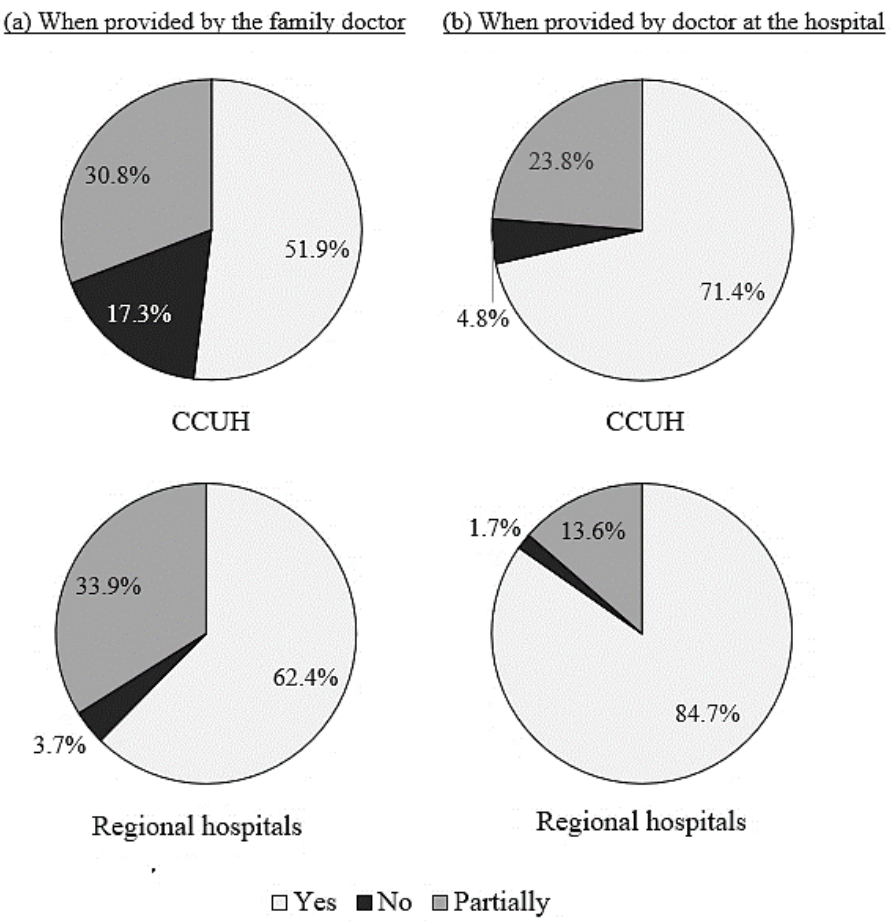


Figure 3.10 **Answer to the question: "Was the explanation on the nature of illness and reasons for fever satisfactory?"**

Similarly, out of parents having consulted family doctors before visiting ED, parental concern was reduced more effectively after a consultation with the physician at the emergency department than after the visit or call to the family doctor in CCUH cohort (OR (95 % CI) = 4.63 (1.92–11.13); $\chi^2 = 12.731$; $p < 0.001$), while the difference between the effect of a consultation by family doctor and of one received at the ED on the level of parental concern among parents recruited in Regional hospitals was not statistically significant ($p > 0.05$). Participants at the regional hospitals evaluated the effect of consultation provided by the family doctor (OR (95 % CI) = 1.71 (1.03–2.90); $\chi^2 = 4.368$; $p = 0.037$), as well as at ED (OR (95 % CI) = 1.75 (1.12–2.73); $\chi^2 = 6.051$; $p = 0.014$) on their level of concern more positively than the CCUH cohort. The effect of the consultation on reducing parental anxiety is shown in Figure 3.11.

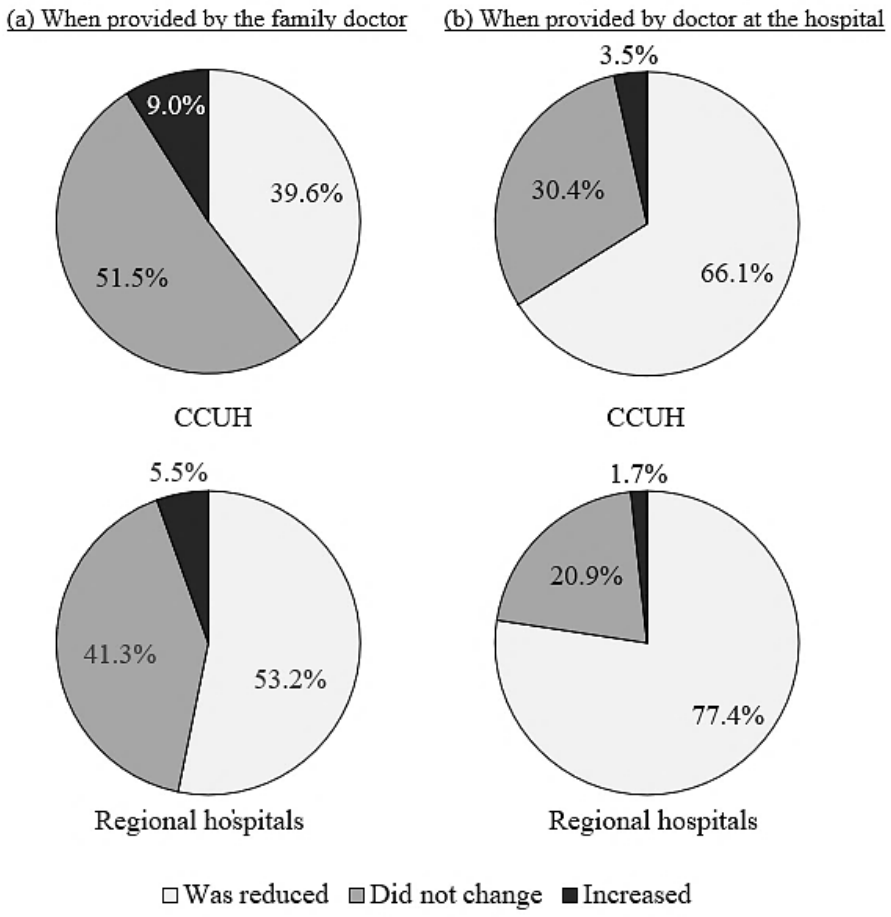


Figure 3.11 **Answer to the question: "How did the information provided by the doctor affect your level of concern about the illness of your child?"**

The majority (67.3 %, n = 278) of all participants stated that, when dealing with febrile illness in their child, they feel safer if the child was brought to the hospital instead of remaining under the care of their family doctor, 29.4 % (n = 121) were unsure, and only 2.4 % (n = 10) felt safer when treated by the family doctor (four respondents did not provide an answer to this question).

Most participants (64.4 %, n = 266) evaluated the availability of their family doctor as "good" or "very good". The satisfaction was significantly higher among participants in regional hospitals, where 75.2 % (n = 134) assessed the availability as "good" or "very good", in contrast to only 56.2 % (n = 132) when evaluated by the respondents in CCUH ($w = 24130$, $p < 0.001$). Of those who sought medical assessment within the working hours, this evaluation was given by 62.9 %, while among those who visited or called a doctor outside normal working hours it was 66.1 %. There was no statistically significant difference in satisfaction with the availability of family doctor between respondents who first contacted a primary care specialist and those whose children were assessed for the first time by the clinicians at the ambulance or at the emergency department of the hospital.

### 3.5.2 Results of the qualitative study

**Participants**

Data saturation for the study was reached after 30 interviews and confirmed after the next four interviews. The duration of the interview was between 5 minutes and 19 seconds to 22 minutes and 5 seconds, the median duration was 10 minutes. In total, the parents of 34 patients were enrolled, among them were twenty-nine mothers, three fathers, one grandmother, and in one case both father and mother participated in the interview. The age of the participants ranged from 22 to 63, the median age was 34 years. Twelve participants were parents of an only child, eighteen had two children in the family, and four participants had three children. Most of the participants had higher education (either bachelor's or master's degree). The age of the febrile children with whom the parents had sought help at the Emergency department ranged from two months to fifteen and a half years.

**Main themes**

Six main themes (Figure 3.12) emerged from the study, which were: signs causing concern; beliefs regarding fever; assessment and monitoring of fever; fever management practices; help-seeking behaviour; and expectations from the healthcare personnel.

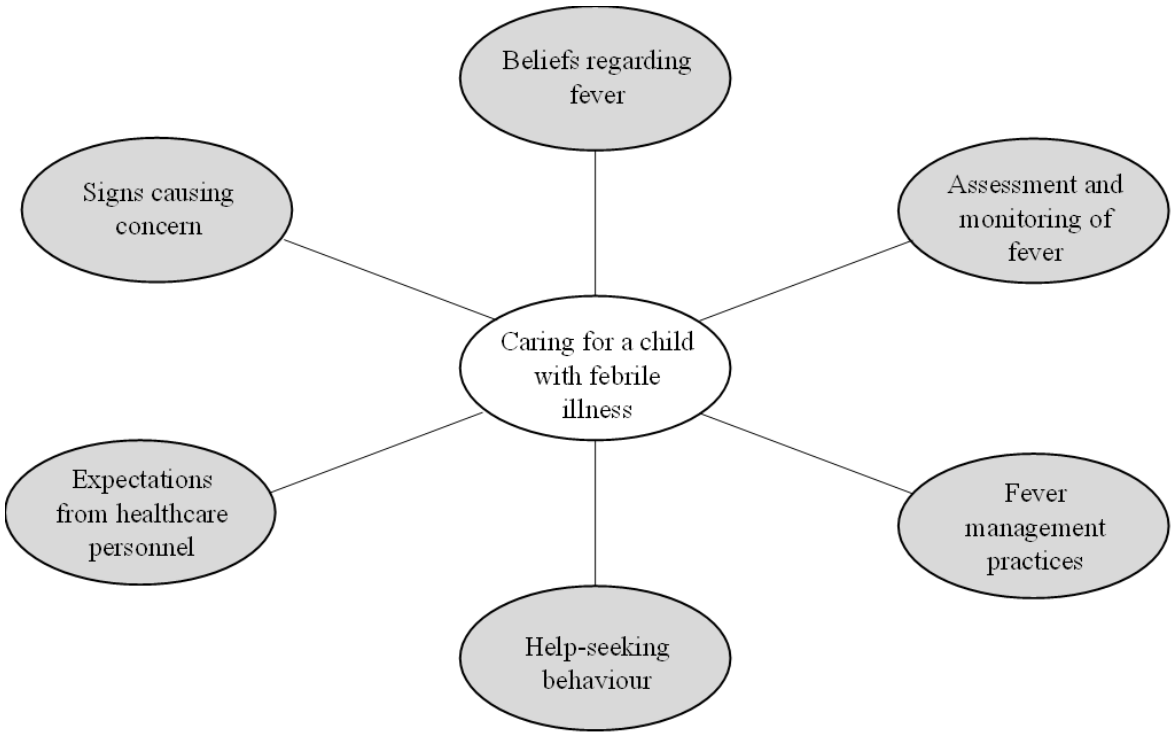


Figure 3.12 **Main themes emerging from semi-structured interviews**

**Signs causing concern**

The main factors that raised anxiety and lead to seeking medical help were fever itself, behavioural changes associated with fever, respiratory symptoms, and pain. The subtheme is further illustrated in Figure 3.13.

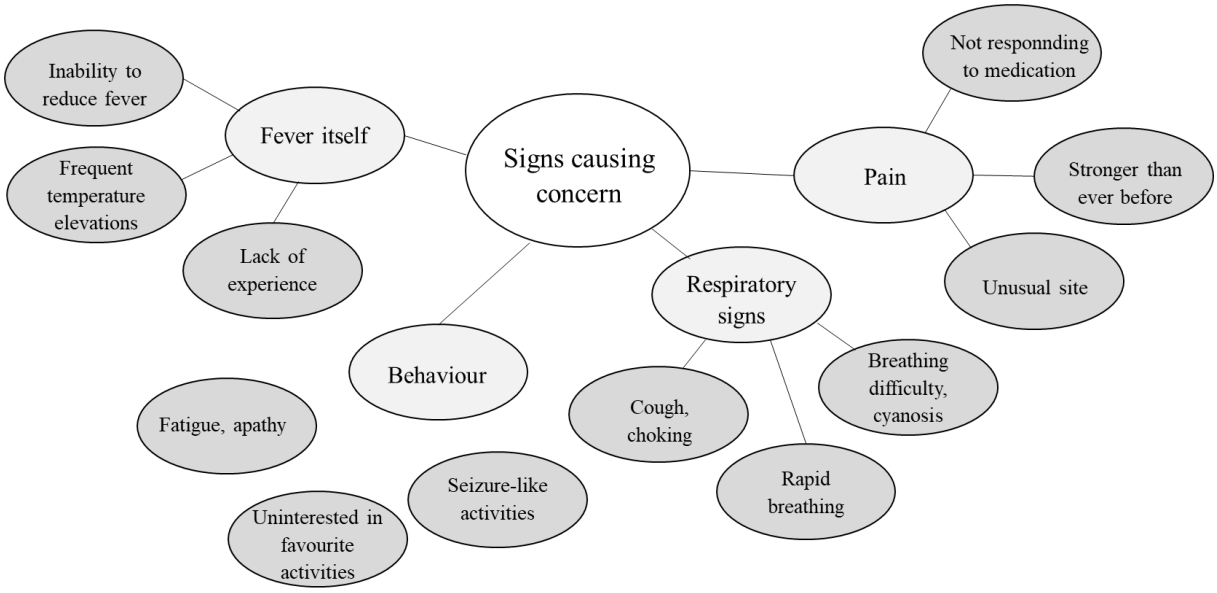


Figure 3.13 **Thematic map of subtheme: Signs causing parental concern**

The presence of elevated body temperature and fever was emphasized over other symptoms as the main reason for parental concern in one third of the cases (n = 11). These parents mostly expressed an overwhelming sense of duty to reduce the child's temperature and expressed anxiety when were not successful (Table 3.15).

Table 3.15

**Fever as the cause of parental concern**

| | |
|---|---|
| **Anxiety over inability to reduce fever** | Interview No 27: "*She was shivering [..] The temperature was just getting higher and higher. I was already tired, I could not go on keeping her cool. I understood I would not be able to handle that for the second night in a row.*" |
| **Anxiety over frequent elevations in body temperature** | Interview No 26: "*In her case I feel anxious when her temperature is above 38 °C. If the temperature reaches that every 8 hours, I am very anxious, but if it happens every 6 hours then I am panicking.*" |
| **Inexperience with febrile illness in a child** | Interview No 18: "*This is my first child, his first illness. The culmination of everything was when his temperature reached 38.8 degrees. That is when I understood that we need to go to the hospital.*" |

Behavioural changes, such as fatigue, apathy, not getting up from the bed, refusal to drink, loss of interest in favourite activities, crying, were identified as the main cause for concern in about one third of parents (Table 3.16). Two parents were alarmed by witnessing seizure-like activities.

Table 3.16

**Behavioural changes during fever causing parental anxiety**

| | |
|---|---|
| **Fatigue, apathy** | Interview No 7: "*He was just lying in bed and did not want to do anything. He started to complain about feeling very unwell.*"<br>Interview No 12: "*She became very tired, did not want to do anything, started to cry. She was not active and was drinking less than usual.*" |
| **Loss of interest in favourite activities** | Interview No 30: "*She was lying in bed the whole time, was not playing. She was unable to go to bathroom as she was not strong enough. She didn't want to watch cartoons…*" |
| **Seizure-like activities** | Interview No 19: "*His arm started to shake, and one of the eyes closed…"*<br>Interview No 31: "*His body was jerking for a moment, the eyes seemed to roll to the other side…"* |

Some patients got concerned when noticing respiratory symptoms in their febrile child, such as cough, runny nose, rapid breathing, difficulty breathing, "choking", and cyanosis (Table 3.17).

Table 3.17

**Most common respiratory signs causing parental anxiety**

| | |
|---|---|
| **Cough, choking** | Interview No 6: "*His nose was very runny, even from the mouth… He was coughing horribly. I think, when there is cough and high temperature, it means inflammation.*"<br>Interview No 1: "*She had an awful cough, I thought she was choking…*" |
| **Rapid breathing** | Interview No 25: "*…even during sleep, his heart rate and breathing was changed…*" |
| **Breathing difficulty, cyanosis** | Interview No 8: "*He was breathing unevenly, his lips got blue when the temperature got high.*" |

Pain was the most alarming sign noted by six of the participants. The concern of these parents was raised by pain that did not respond to medication, pain that was stronger than in the child's previous experience, and when child had pain in an unusual site (Table 3.18).

Table 3.18

**Pain as the reason for parental concern**

| | |
|---|---|
| **Pain not responding to medication** | Interview No 34: "*My child was screaming from pain; her tummy was aching. We gave some medicine, but it didn't get better, it only got worse.*" |
| **Pain stronger than ever before** | Interview No 22: "*He has had headache before, but not this strong, and not at just 37 °C…*"<br>Interview No 20: "*I thought I could not wait any longer, her condition seemed very serious…she did not want to eat, did not want to drink, she was just complaining that her leg hurts, with tears in her eyes.*" |
| **Pain at an unusual site** | Interview No 30: "*My daughter had been complaining about stomach ache for a couple of days, I thought she had just eaten something [wrong], and just gave her some medicine. But a couple of days later she developed high temperature. Her back was aching so that she could not sit up.*" |

Other signs that were mentioned by a few parents as the main concerns were sudden swelling of one of the extremities, vomiting, diarrhoea, skin rash, and fever with no apparent cause.

**Beliefs regarding fever**

The study participants expressed diverse opinions on whether fever was protective of or facilitating the progress of the illness. Main parental opinions are illustrated in Figure 3.14.

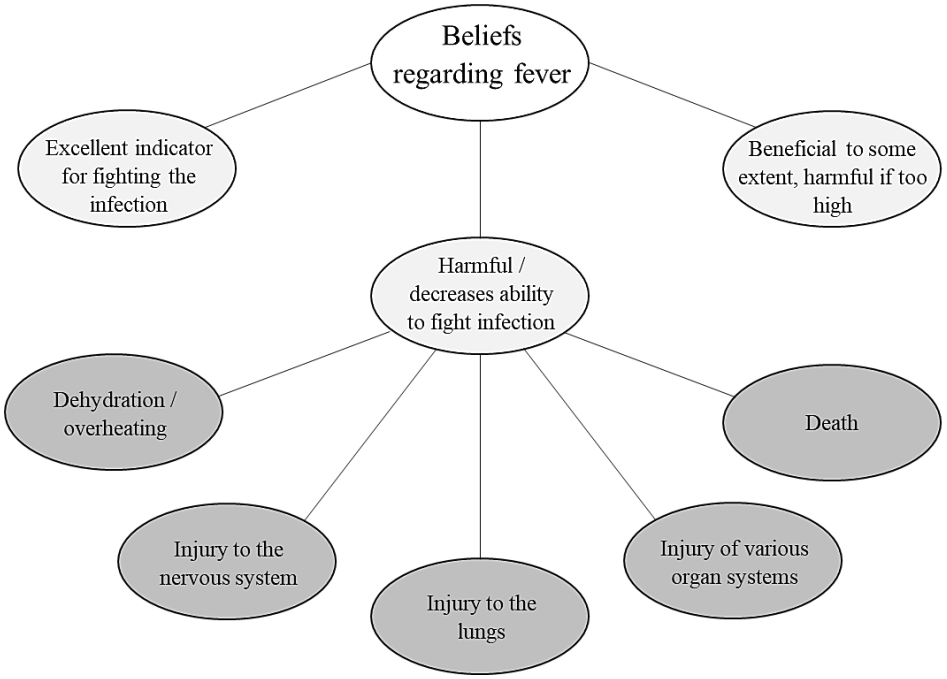


Figure 3.14 **Thematic map of subtheme: Parental beliefs regarding fever**

Some parents agreed that fever is helping the organism to fight against the pathogens:

Interview No 27:

"[*Fever] is an excellent indicator that the body is fighting, that the immune system is fighting the infection, the virus. The change in body temperature shows if the body can handle the infection on its own, or if help from outside is needed."*

However, in most cases the parents believed that fever is beneficial to fighting infection only to some extent:

Interview No 15: "*Elevated temperature is a sign that the organism is fighting the infection, either a virus or something else. But if it is higher than 38 °C, the body cannot deal with it. The organs can't function at such a high temperature, it's just extra work...*"

Interview No 22: "*At 37 to 38 °C the body fights viruses and bacteria. But if it is above 39 °C, the body can't handle it on its own.*"

In contrast, some other parents believed that fever reduces the ability to fight infection due to dehydration and overheating:

Interview No 6: "*Because of high temperature, the water disappears from the body. Just like when you heat water in a teapot. Then the person urinates less. The less urine, the less microorganisms are excreted from the body. Fever above 38.5 °C is dangerous.*"

Interview No 16: "*Immunity rapidly worsens. It is dangerous for the organs, for the brain. They can burn, cease to work. As I understand, it is very dangerous.*".

Plenty of harmful effects were attributed to fever by almost all respondents. Along with dehydration and possibility of seizures, it was believed to cause injuries to nervous system, kidneys, the brain, other internal organs, and some parents even believed it could lead to death (Table 3.19).

Table 3.19

**Detrimental effects attributed to fever**

| | |
|---|---|
| **Injury to the nervous system** | Interview No 13: *"...brain cells die. There can be seizures, irreversible effects on the body. I know it is dangerous...*" |
| **Injury to the lungs** | Interview No 32: "*Those little lungs just burn [..] there is a risk for a stroke...*". |
| **Injury to multiple organ systems** | Interview No 11: "*I don't ever let the temperature to get above 38 °C. I am scared of the complications. High temperature can cause loss of consciousness, the breathing can stop, there can be skin rash, diarrhoea, dehydration…"* |
| **Death** | Interview No 25: "*The water disappears. It can lead to death of the child. I have had experience, when, wrapped and bundled, the child just burns. Heart rate and breathing rate increases. Oxygen loss is possible. High temperature is a side effect of an illness. It fights it when it is around 37 to 38 °C. When it is higher than 42 °C, the child dies.*" |

**Assessment and monitoring fever**

The most common assessment and monitoring strategies emerging from parental interviews are illustrated in Figure 3.15.

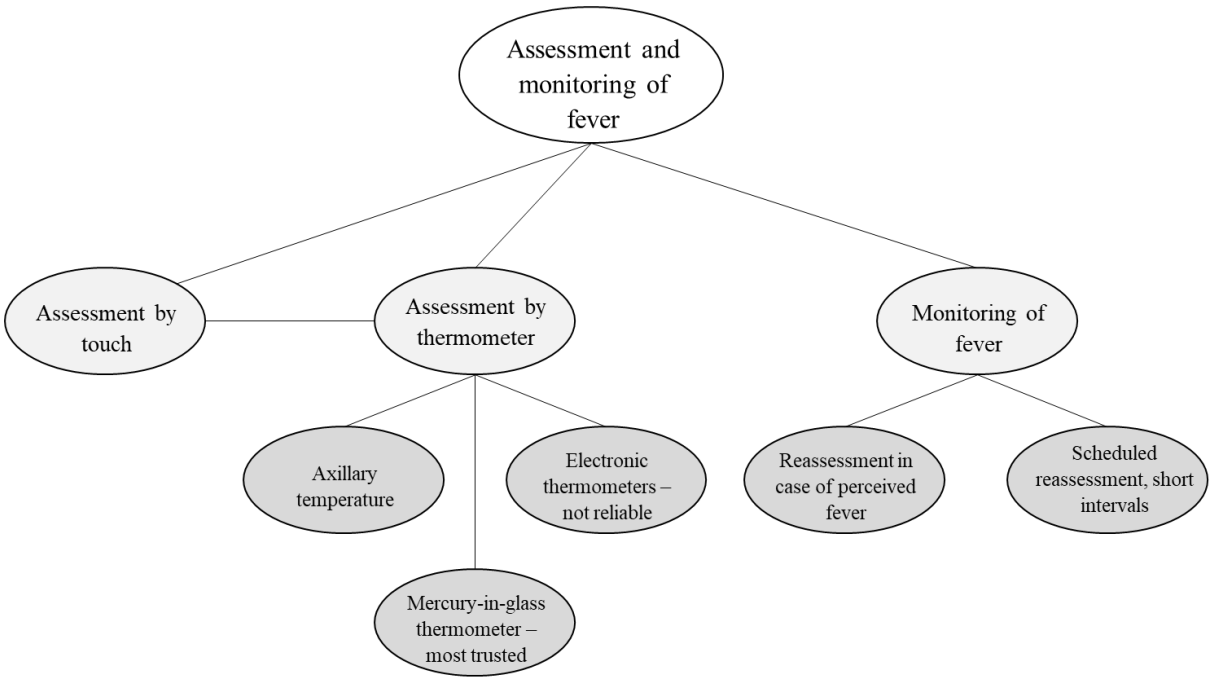


Figure 3.15 **Thematic map of subtheme: Assessment and monitoring of fever**

Most of the participants measured their child's temperature for the first time in a febrile episode whenever the child felt hot to touch. Later, when assessing the child again, most commonly in order to evaluate the effects of antipyretics, the strategies varied.

Around one third of parents (n = 12) went on to reassess the temperature of the child only when they subjectively felt that the child has a high temperature again:

Interview No 1: "*You can feel everything when you take a child in your lap. Especially if it is a baby. You can feel the fever when the child is hot*."

Interview No 17: "*I can already see when the child has a fever. After I gave medication, four hours later my daughter said she was feeling cold. I remeasured the temperature, it was high. My doctor told me to measure the temperature every 4 hours. If I feel the temperature is rising, I measure it, if not, I don't.*".

Other parents measured their child's temperature according to some sort of schedule. Mostly they reassessed the temperature around one hour after antipyretics, and later according to the frequency of re-evaluation varied from once in six hours to once in every 15 minutes.

Interview No 19: "*After giving medication, I measure the temperature every 30 minutes. When the temperature gets lower, I measure every 2 to 3 hours.*".

Interview No 14: "*At the beginning I measure it every 20 minutes. If the temperature is high, I measure every 10 to 15 minutes the whole day. When it gets lower, I measure it every hour*."

Most commonly, axillary temperature was measured by using either alcohol or mercury-in-glass thermometers, from which the later was more popular. Some parents used electronic thermometers to measure the temperature on the forehead or behind the ear, but generally they were not trusted as much as the axillary thermometers:

Interview No 10: "*We have a digital thermometer to check the temperature on the forehead. But I don t trust it very much. That is why I sometimes recheck it with a mercury thermometer*."

**Fever management practices**

The main findings in fever management practices among the interviewed parents are summarized in Figure 3.16.

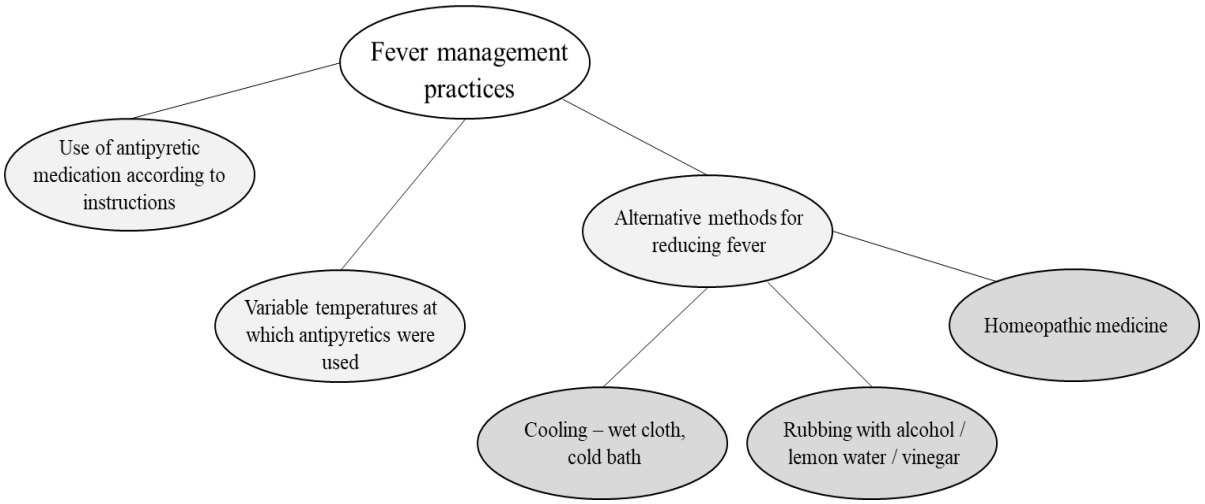


Figure 3.16 **Thematic map of subtheme: Fever management practices**

Ibuprofen and Paracetamol were used by almost all the parents to reduce the temperature in their child. There seemed to be no preference to either one of these. The parents generally followed the instructions on the packaging as well as those given by their doctors. None of the parents gave both drugs simultaneously, and 4-to-6-hour breaks between medication were almost always observed. If one of the antipyretic agents seemed to be ineffective and the temperature rose before 4 to 6 hours, the other agent was used.

Eighteen respondents gave medication when the temperature of the child was between 38 and 38.4 °C, and nine parents gave it when the temperature was between 38.5 and 38.9 °C. Only two parents allowed the temperature to rise above 39 °C. There were five parents who administered antipyretics when the temperature was just 37.2 to 37.9 degrees high.

Interview No 4: "*Usually I give Paracetamol, if the temperature is very high, also at night, so that he would sleep better. Even if the temperature is just 37.5 °C. During the day if the temperature is higher than 38 °C…*"

Alternative ways to reduce body temperature were used by most of the participants, which included undressing the child, application with wet towel or cloth, rubbing with alcohol, lemon water, or diluted vinegar, and cold bath.

Interview No 5: "*Wet towels on the forehead, on the belly, groins, and under knees. Rub with lemon water. I know that rubbing with alcohol or diluted vinegar is not allowed.*"

Interview No 9: "*I undress my child and then rub him with diluted vinegar.*"

Interview No 12: "*I apply a wet cloth (from cold water) on the forehead and the right side of the tummy. Some are helped by rubbing vodka on the skin*."

Only one respondent saw these methods as unacceptable and only relied on medication. One parent used homeopathic medicine along with antipyretics.

**Help-seeking behaviour**

Figure 3.17 summarizes the main parental views on seeking help during a febrile illness in their child.

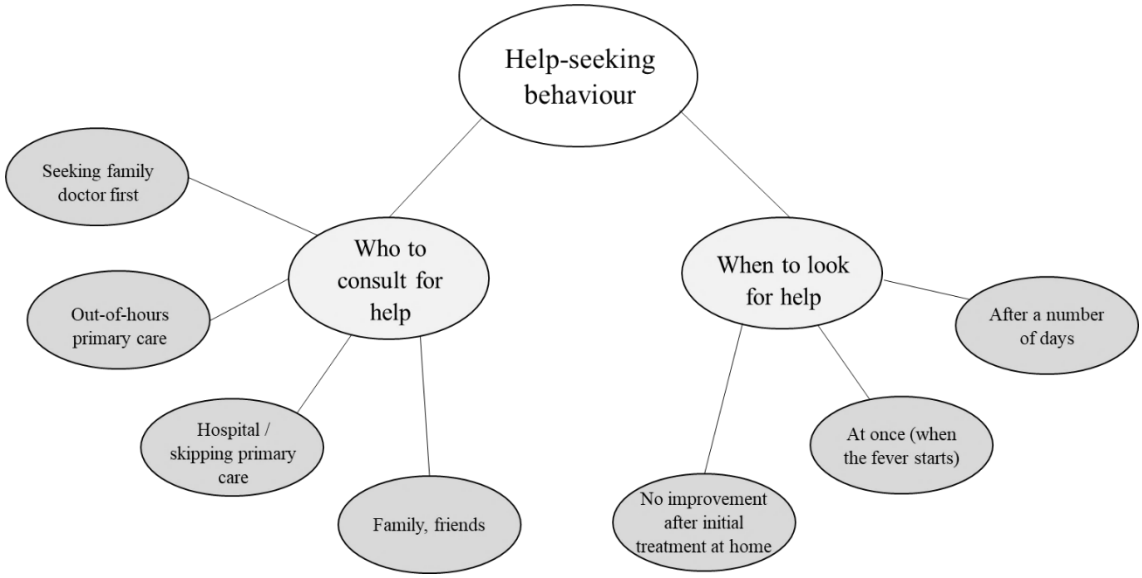


Figure 3.17 **Thematic map of subtheme: Help-seeking behaviour**

When needing advice on how to manage the child's illness, most parents first turned to their family doctors. If the family doctors were unavailable, some consulted the out-of-hours family doctor call centre, but some parents admitted they would skip the family doctor and go to the hospital as it was more convenient:

Interview No 8: "*At the beginning, we try to deal with it on our own. If we can't, we go to the hospital. We always have to wait for the visit to our family doctor, like four days for an appointment. We could go during the "acute hour", but then there are many sick children there and my child might catch something new...*"

Some parents would consult their family members, friends, and acquaintances with medical education for advice before seeking help at their dedicated family doctor:

Interview No 1: "*Usually I see what I can do myself, I've got some experience. Then my wife would call her mother, to get advice from her point of view. The family doctor won't tell anything new...*"

Interview No 27: "*At first I would seek the advice of my relatives who have some connection with medicine. We have a very good homeopathy specialist, sometimes we turn to him. Our family doctor would be the last one to consult, in my opinion that's just paperwork.*"

The reasons for seeking medical help were similar to the features that caused anxiety in the parents, which were high fever, behavioural changes, severe cough, and other sighs, such as changes in skin colour, vomiting, blood in stool, etc. Many parents sought help when they found it hard to reduce the temperature of the child, or saw no improvement after initial treatment at home:

Interview No 15: *"[we seek help] when the child has high temperature that won't get down. When the child has difficulty breathing, weak, changed behaviour that does not improve after giving medication.*"

The amount of time the parents chose to wait before consulting a medic varied amongst the participants. A few would consult a doctor straight away:

Interview No 13: "*If my child has temperature, I call the doctor straight away. I try to do that as soon as I can. He needs to come and take a look. He sees what I can't see!*"

Most parents would wait for a number of days and then decide if they need medical help from a doctor:

Interview No 22: "*If the temperature is under control, I usually wait for two to three days...*"

While some felt very confident and would wait for longer:

Interview No 27: "*Actually I am quite a tough mother, in my opinion. 38 to 38.5 °C is nothing, I think. I would not consult a doctor for at least 3 to 5 days. I have gathered quite a lot of information, if something is not typical, then I would seek help…*"

**Expectations from healthcare personnel**

Parents expected medical personnel to meet their child's medical needs, their own informational needs, and their emotional needs (see Figure 3.18).

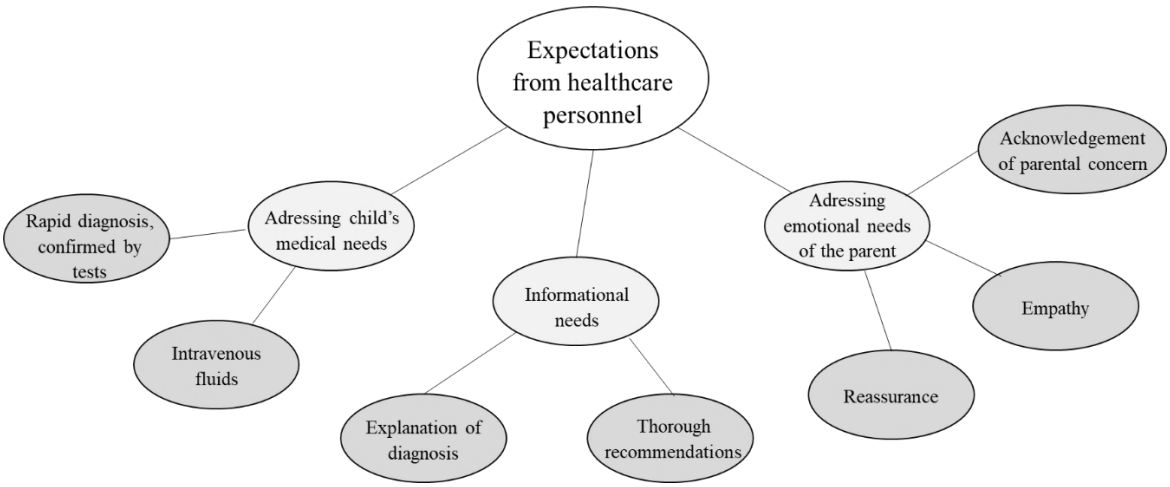


Figure 3.18 **Thematic map of subtheme: Expectations from healthcare personnel**

The general expectations from the medical personnel were usually the same by all parents, which were: accurate diagnosis, rapid medical help, and stabilization of the condition of the child, prescription of medication that would help. None of the parents expected prescription of antibiotics regardless of diagnosis, one parent expressed dissatisfaction when she felt her doctor prescribed antibiotics just because she felt the doctor didn't know what to do. Six parents emphasized the necessity of performing blood tests and other tests to confirm the diagnosis:

Interview No 22: "*I want to know the diagnosis, what we are treating my child for. But blood tests must also be taken. The same goes to the family doctor, because, of course, full diagnostics will be performed in the hospital, all blood tests will be taken*."

Interview No 24: "*If I'm in a hospital, I want investigations, blood tests [for my child], to be 100 % sure that she is going to be ok.*"

Three parents emphasized the need for intravenous fluids as they believed it would help to reduce fever and improve the condition of the child.

Meeting the emotional and information needs of the parents were emphasized as equally important to meeting the child's medical needs. Parents wanted to know the precise diagnosis, to understand why the child had the symptoms they had, how to manage their child's illness at home, and what to look for to decide if the condition has become more serious.

Interview No 12: "*Our family doctor explains things very well. She gives logical explanations, and even draws schemes if necessary. I am very satisfied*."

Interview No 14: "*If they tell me the diagnosis, they have my trust. But not that it's just a virus, that doesn't calm me down at all…*"

Parents expressed the need for the doctor to provide emotional support, to show empathy and understand their concerns, and take their opinion into account. The respondents exhibited appreciation when the doctor had provided that, but disapproval when their emotional needs were not met:

Interview No 32: "*I expect not only management of the consequences, but also insight in the depth of the problem. Emotional support, to calm me down. I haven't exactly cried, but sometimes my hands were shaking when I have been very anxious... for somebody to come and tell me that everything is going to be all right…*"

Interview No 25: "*In that moment I am hurting for my child, I feel his pain. I want the doctor to understand me, to see my child as their own…*"

One parent shared a previous experience when she was concerned for the child, but her concerns were not adequately considered:

Interview No 17: "*Once my eldest daughter had cough, her face was grey, and it was difficult for her to breathe. I called the ambulance, they told me it's nothing, but I said: I feel that it is very difficult for her to breathe. We came to the hospital, and it turned out she had bilateral pneumonia, we spent three weeks there…*"

Overall, the prevailing beliefs about fever and the resulting management practices show that there is a need for proactive parental education programmes to clarify the misconceptions about fever and provide information on how to evaluate the condition of their child, when to give antipyretics, and when the intervention of medical professionals is necessary.

# 4 Discussion

Pre-laboratory recognition of serious bacterial infection in case of febrile illness is a challenge to healthcare professionals. Over the last two decades, several research studies have been dedicated to identifying clinical features strongly associated with SBI, as well as derivation of prediction models, with varying success in different patient populations ranging from primary care to emergency departments. This thesis describes the first study so far that, in addition to clinical features, assesses the value of "gut feeling" and parental concern for prediction of SBI in febrile children presenting to ED. Furthermore, one of the derived and validated clinical prediction models is the first to integrate clinical features with variables of non-analytical reasoning for use in ED.

While some of the results in this thesis resemble the findings of previous studies in the field, some key differences were identified in terms of clinical features associated with SBI, as well as the prognostic value of "gut feeling" and parental concern in ED compared to primary care.

## 4.1 Clinical features associated with SBI

The study showed limited diagnostic power of clinical features when analysed separately. Only one of the assessed clinical variables, arterial hypotension, had a sufficient rule-in value for SBI. This finding is supported by other studies that identify hypotension as a potential "red flag" for serious illness or septic shock [22, 134, 135, 153]. However, in paediatric population, hypotension is considered a delayed sign for severe sepsis or septic shock, [23], thus the assessment of possible sepsis should be based on tachycardia, tachypnoea, prolonged capillary refill, and altered mental state instead. These latter variables were not significantly predictive of SBI in this study (LR (+) < 5) when analysed separately, though tachypnoea and poor peripheral circulation were selected as useful variables for both derived CPMs. No strong association between tachycardia on admission and SBI was found, which is contrary to other studies [15, 216].

Clinical impression of ill / toxic appearance was not significantly predictive of SBI in bivariate analysis, though it was identified as the key variable in CPM 1. It was also found to be the strongest variable triggering "gut feeling". Strong association between ill appearance and serious illness has been found in studies in both primary care [38] and hospital EDs [14, 28, 32, 143].

The study did not find an association between fever above 40 °C and SBI. Very high body temperature has been identified as one of the red flags in other prediction models [10, 15, 145], though in studies of populations with higher prevalence of SBI it provides little diagnostic value [145]. Increased body temperature was identified as a trigger for parental concern, while no association with eliciting "gut feeling" was found.

Surprisingly, refusal to drink and irritability decreased the likelihood of SBI, both when analysed separately and when included in CPMs. This contradicts the findings of another study of febrile children presenting to ED in North of England [92], where poor feeding and restlessness were associated with increased risk for SBI. The study included patients with similar age range (0 to 16 years) but had a broader definition of serious illness, also including aseptic meningitis, and the study period excluded winter / spring months, which is the peak period for several viral illnesses such as influenza. It may be speculated that, as around half of febrile patients in CCUH are self-referred [294], this factor may have been one of the reasons for presenting to hospital even for a child with a self-limiting illness, due to availability of intravenous rehydration. However, the role of selection bias in these findings should not be underestimated, as the parents of children requiring prolonged observation and treatment, including intravenous rehydration, were more prone to consent to participation in this study.

The study showed that combining clinical features together in clinical prediction models, especially when integrated with variables of non-analytical reasoning, was more effective in recognizing children with potential SBI than considering their diagnostic value separately.

## 4.2 Non-analytical diagnostic reasoning

In accordance with the second hypothesis of this thesis, the variables of non-analytical reasoning, defined as "gut feeling" of something being wrong, or "sense of reassurance" in the study, provided added value in diagnosis of SBI in febrile children, as "gut feeling" of serious illness was associated with SBI and replaced the impression of "ill / toxic appearance" in CPM 2, which had a superior performance to the model without the non-analytical variables. However, the rule-in value of "gut feeling" as a separate variable was limited, which is contrary to the first hypothesis of thesis, while "sense of reassurance" was significantly predictive of absence of SBI, both when analysed separately and when integrated in a clinical prediction model.

Though "ill / toxic" appearance was one of the main triggers for "gut feeling" of something being wrong, the latter had higher sensitivity, and, when expressed by more experienced paediatrician, it had higher specificity as well. The superiority of "gut feeling" over

clinical impression in predicting SBI in children is supported by another study in primary care, in which the specificity of "gut feeling" was markedly higher than clinical impression of ill appearance [38]. Contrary to the findings of a study in primary care [38], parental concern was not the strongest factor eliciting "gut feeling" in clinicians in derivation cohort, though an association between parental concern and "gut feeling" was found.

Many of the other identified triggers for "gut feeling" in this study were clinical features that have been identified as "red flags" for SBI in previous systematic reviews [22, 145] and clinical guidelines [2, 23]. In a systematic review published in 2010, the diagnostic value of "gut feeling" (assessed in primary care) was superior to that of many of other identified "red flag" signs [22]. This suggests that "gut feeling", though an intuitive process, may be based on subconscious integration of objective variables, together with other factors such as changed behaviour, which, as a result, allows the clinician to perceive the clinical situation, as described by Gestalt theory, as "an organized whole, which is more than a sum of its parts" [231]. While the classic definition of "gut feeling" implies that the clinician may be unsure of the reasons they are experiencing a "sense of alarm" [38, 252], qualitative studies in primary care and hospital settings show awareness of healthcare specialists that their intuitive feelings arise from the combination of appearance, behaviour, as well as clinical signs shown by the patient, and, with time, these experiences become automatic rather than systematic [228, 239, 243, 247, 252, 258, 305]. These studies show that "gut feeling" often arises when a clinical situation "falls out of a pattern" between what is seen in a patient and what is expected [228, 253, 258, 266, 305].

The diagnostic value of "gut feeling" for SBI in acutely ill children prior to this study has only been assessed in studies in primary care [10, 38], in which it has shown high predictive value for SBI and was identified as the most important variable in a decision tree for detection of SBI. The diagnostic value of "gut feeling" in this study was significantly lower than what was found in these primary care studies. This may be affected by lack of continuity of care, which makes it impossible to distinguish abnormal behaviour or appearance from the one natural for the patient in a state of well-being or non-serious illness. Continuity of care and prior knowledge of the patient is said to be a determining factor of being able to recognize that "something does not fit in" [40, 239, 243]. However, more factors could affect the difference in diagnostic value of "gut feeling" in hospital environment and emergency departments, therefore more studies in this field are necessary.

Contrary to the findings of the Belgian primary care study [38] in which level of experience did not significantly affect the diagnostic value of "gut feeling", this study showed higher accuracy of both "gut feeling" for prediction of SBI and "sense of reassurance" for prediction of absence of SBI when these intuitive feelings were expressed by more experienced

paediatricians. However, another study on the ability to recognize cancer in primary care showed increased diagnostic performance with more experience [267], and several qualitative studies show that clinicians with longer work experience show higher confidence in their intuition [37, 241, 243, 247, 266].

This is by far the first study to assess the predictive role of "sense of reassurance", which was found to be significantly predictive of absence of SBI, and markedly decreased the probability of SBI when integrated in CPM 2 and the clinical score based on the model. Similarly, to "gut feeling" of something being wrong, it was evident that experience of clinician affected the diagnostic accuracy of this variable.

### 4.3 Performance of clinical prediction models

The CPMs derived in the study had moderate ability to predict SBI in febrile children presenting to ED. The performance of CPM 2, which included the clinician's intuitive "gut feeling" and "sense of reassurance", was superior to CPM 1, which was based on clinical features alone. CPM 2 required data on fewer clinical variables, and at a cut-off with the highest possible sensitivity and specificity set by Youden index could accurately predict the outcome in more than three quarters of cases. Both models showed slight, but acceptable decrease in performance in validation population.

Application of both models to derivation and validation populations still resulted in an overlap of patients with and without SBI near the cut-off with the highest possible sensitivity and specificity. Therefore, a scoring system from CPM 2, the superior model, was derived, leading to better identification of patients in the "grey area" and reduced the number of patients who would otherwise be segregated into a low-risk category.

Several clinical prediction models for recognition of SBI in febrile children have been proposed. The models with the most accurate ability to distinguish between SBI and non-SBI and with the best performance in validation studies are those containing laboratory markers in addition to clinical signs and symptoms [14, 16, 28, 30, 34, 35, 224]. Not surprisingly, the diagnostic value of these prediction models was also superior to CPM 1 and CPM 2, which did not include laboratory variables. Nevertheless, the main goal of the study was to create a screening tool for selecting patients with increased risk of SBI and thus requiring further investigation. Therefore, we a priori decided to exclude any laboratory variables from our CPMs.

When compared to other prediction rules for serious infection in febrile children that are based on clinical parameters alone [10, 12, 15, 17], CPM 1 and CPM 2 show similar diagnostic performance in derivation cohort, and better performance when prospectively validated

externally. A clinical prediction rule for SBI in young children with fever without source presenting to ED developed by *Bleeker et al* [17] including variables such as duration of fever, temperature above 40 °C or below 36.7 °C, vomiting, age above one year, chest wall retractions and / or tachypnoea, and poor peripheral circulation, and absence of poor micturition had a ROC area under curve of 0.75 (0.68–0.83), which is similar to that of CPM 1 and CPM 2. However, the clinical model did not perform equally well when externally validated, yielding AUC of only 0.60 (0.49–0.70) in validation cohort [28]. An updated version including ill clinical appearance increased the AUC to 0.69 (0.63–0.75) in derivation population, and to 0.65 (0.62–0.67) when validated in an external dataset, though in primary care [221]. Similarly, another clinical score developed by Brent et al [12] based on 8 clinical variables showing moderate ability to predict SBI (AUC 0.77 (0.71–0.83)) did not perform equally well when validated in external datasets [34].

There have also been attempts to validate prediction models derived from primary care to settings similar to ED, for example, decision tree developed by van den Bruel et al [10], derived from a prospective study in primary care, including "gut feeling" that "something is wrong", dyspnoea, temperature above 39.95 °C, diarrhoea, and age, showed high sensitivity (96.8 %) and specificity (88.5 %). However, validation studies of the decision tree revealed poorer performance in ED settings [34, 99], with AUC ranging between 0.53 and 0.56 in febrile infants [34].

### 4.4 Role of parental concern and fever-related anxiety

In this study, the rule-in value of parental concern for diagnosis of SBI was poor, though it was more commonly expressed by the parents of children who were diagnosed with SBI. This contradicts the findings of studies in primary care [10, 22], where parental concern was strongly predictive of SBI, and was an important variable in decision trees for prediction of pneumonia, sepsis / meningitis, and other SBIs. This can be due to the definition of parental concern as the illness being different (more severe) than the child's previous illnesses. This definition was derived from a qualitative study in primary care [41] and may not be applicable to emergency departments and tertiary hospitals, to which the child is referred to in cases of more severe illnesses than have been managed in primary care.

Though both interview study and questionnaire results showed that parental concern was affected by behavioural, respiratory, and other signs in their child during febrile illness, the anxiety related to fever played an important role in their level of concern. Increased body temperature was identified as one of the main triggers for parental concern. The interview study showed that, although some parents saw mild fever as beneficial to fighting the infection, the

general opinion was that high fever is very dangerous to the child. According to the questionnaire results, most parents believed that fever itself is indicative of serious illness, and that the child's body temperature can increase to a level that could possibly endanger the child's life.

Several misconceptions regarding the possible negative effects of fever were found among the participants in the interviews, such as seizures, injury to the brain, kidneys, lungs, other organs, and even death. Very similar beliefs have been described as characteristic to parents across different countries and cultures [44, 48, 50, 273, 277, 278, 280, 283, 284, 306–308], and have prevailed for decades [42, 43, 273]. The median temperatures considered dangerous were relatively high in the study population, which is similar to findings of other studies [309, 310], though, not uniquely [287], some parents regarded temperature as low as 38.0 °C, or even lower, as dangerous to the child.

Due to the perceived threat caused by fever, the participants in the interview study and questionnaire showed similar sense of urgency to reduce fever and seek medical attention as described elsewhere [48, 276, 289]. Many studies show that fever phobia leads to overly aggressive management practices, including frequent assessment of body temperature, and uncontrolled administration of antipyretics [42, 43, 273, 277, 281, 283, 310]. Some participants in the interview study admitted measuring their child's temperature as often as once in 10 to 15 minutes. No parents, however, admitted to waking their child to measure temperature or give antipyretics, though one parent confessed of giving antipyretics prophylactically before sleep.

Attempts to reduce the child's body temperature as soon as it reached 38 °C were common among the study participants. Some parents (9.6 %) would even give antipyretics before the temperature reached 38.0 °C. These practices contradict the advice given in several evidence-based guidelines [24, 25, 210, 311], which state that antipyretics are not always necessary in case of fever and should be reserved for cases when the child is feeling significant discomfort. However, the low threshold of giving medication to reduce fever is not unique to parents in Latvia, as other studies in the United States, Israel, Australia, Italy [43, 48, 310, 312–314], where the proportion of parents giving antipyretics before the temperature reached 38 °C ranged from 2 % to more than a half. Non-pharmaceutical methods for reducing fever like applications of cold towels, cold bath, rubbing with alcohol, etc, were also reported by participants in the interviews. These practices, although still observed worldwide [45, 50, 273, 280, 281, 284, 315], are not recommended [2].

Fever is one of the main reasons for seeking healthcare specialists after hours [43, 286], even though many of these consultations are non-urgent and should be managed in primary care. The study confirmed that beliefs on fever affected the healthcare seeking behavior of the

study participants – parents who believed that lower temperatures are dangerous to a child were more likely to contact a doctor earlier and outside normal working hours. Also, parents who usually sought help within the first 24 hours of the onset of febrile illness were used to giving antipyretics at a lower body temperature than those who believed that a consultation by a healthcare specialist could be delayed until later.

The study showed that university education was protective against administration of antipyretics at lower body temperatures, and respondents with higher education less commonly thought that fever is automatically associated with serious illness. This correlates with findings in other studies, where low educational and socioeconomic status was associated with higher levels of fever phobia [44, 288, 307, 310], though some studies have found higher anxiety among parents with high education level [50] or no influence of education level at all [279]. However, the height of temperature perceived as dangerous was not affected by the level of education of parents, nor was the timing for seeking medical attention. In previous studies, having more than one child has been reported to decrease fever-related anxiety and increase the accuracy of perception of fever [50, 277, 278, 316]. In this study, parents of a single child were more likely to seek help within the first 24 hours of the illness, whereas no influence of the size of the family was observed over beliefs regarding fever and temperature at which antipyretics were administered by parents.

It was evident that the respondents of the questionnaire were generally more satisfied with explanatory work by doctors at the hospital than what they previously received at their family doctors. The majority also felt safer in the hospital than under the care of their family doctors. Approximately two thirds of the participants had sought help in primary care during the ongoing episode of child's illness, but sought help at the ED, nevertheless. Though the study only included patients who eventually visited the ED of a hospital and did not assess the opinion of patients who were only treated in primary care, this shows that incomplete success of reducing parental concern on a febrile illness in their child in primary care may lead to them seeking help elsewhere. Similarly, another study conducted in Tel Aviv revealed that many parents still had misconceptions about fever despite visiting the general practitioner within 2 days before seeking help at the ED, and the anxiety caused by fever in their child was not lower than in parents who had not been consulted in primary care prior the visit to ED [48].

The satisfaction levels of parents in CCUH and regional hospitals with provided information and reassurance were not 100 % after visiting either the family doctor or the specialist working at the ED, which indicates that communication with parents, including education on nature and management of febrile illness, needs improvement in both primary care and hospitals. Previous studies indicate that fever-related anxiety may not be relieved

effectively even if the primary source of information regarding fever is a healthcare specialist [273, 277, 317], due to inconsistent and sometimes conflicting information given by clinicians [273, 287, 317], or perceived disregard for their observations and worries [275, 277, 287, 318].

The expectations from the healthcare personnel revealed by the respondents were similar to the findings of other studies [275, 277, 288, 319], and showed that providing medical care and meeting parental informational and emotional needs were equally important to them. There was no pressure to prescribe antibiotics as described elsewhere [275, 320], instead some parents felt that blood tests are necessary for establishment of accurate diagnosis, and some other parents wanted intravenous fluids due to their perceived benefits.

There were marked differences between the study cohorts regarding seeking medical attention. The participants recruited in regional hospitals were less likely to skip primary care within normal working hours than the CCUH cohort, their satisfaction with the availability of family doctor was higher, as was their contentment with provided information and the ability of the family doctor to reduce their anxiety. Parents in regional hospitals also attributed adverse effects to higher temperatures than the CCUH, though the habits of administering antipyretics were similar. Whereas among the parents enrolled CCUH, the evaluation of the availability of the family doctor was not as high as among parents in regional hospitals, and more parents turned to ambulance or emergency department without consulting primary care first. Of those who contacted the family doctor before going to hospital, the evaluation of the communication with the physician was lower than in the other cohort. The reasons behind this were not investigated via the short questionnaire, however it can be concluded that, with the aim of increasing parental confidence and reducing the number of patients visiting the ED for febrile illness, more emphasis must be placed on improving the quality of support provided in primary care.

## 4.5 Strengths and limitations

The main strengths of this study are prospective enrolment of both derivation and validation cohorts, and application of uniform case report forms, which enabled the researchers to collect information on all variables with trustworthy accuracy, without a necessity for proxy variables. Parental questionnaires and interviews were conducted within a relatively short time frame from admission to ED, which enabled the parents to closely recall their observations and feelings regarding the child's illness. The follow-up strategy maintained throughout the study prevented loss of significant data, such as patient discharged as non-SBI representing for developed SBI within the illness episode.

The models derived in the study were validated internally and externally. There was a slight decrease in diagnostic performance of both CPM 1 and CPM 2 when applied to validation cohorts, however a decrease of this magnitude can be expected and does not indicate overfitting of the model. The models had moderate ability to predict SBI in both derivation and validation cohorts, even though they were drawn from settings with different level of care (tertiary vs secondary). It must be noted that patients at increased risk for infection due to comorbidities (who are more likely to present to tertiary care) were excluded.

This study is not without limitations, which are the following. As informed consent form a parent or guardian was required for participation in the study, consecutive enrolment was not possible, and the study samples are relatively small. The number of complete cases from which CPM 1 was derived met the preferred sample size, while the large number of missing variables for CPM 2 caused the number of complete cases to be lower than a preferred sample size. No data were imputed to replace the missing variables, as "gut feeling" and "sense of reassurance" are based on the intuitive and non-analytical interpretation of the clinical situation by the doctor, thus replacing the missing values with software-generated imputations was considered as inappropriate. The prevalence of SBI though is similar in the cohorts used to develop both models, and the performance of CPM 2 in an independent validation cohort is close to that in derivation cohort.

In derivation of the clinical prediction models, the level of experience of the clinician was not taken into account due to complexity in inclusion of such variable in a CPM, though the bivariate analyses revealed that the diagnostic value of "gut feeling" and "sense of reassurance" was higher when expressed by senior clinicians as opposed to medical residents.

A selection bias towards sicker children is evident due to requirement by the PERFORM project to collect blood samples for purposes not related to this particular study, and because parents spending longer time at the ED were more likely to provide informed consent and ensure participation of parents in the questionnaire on parental concern. The selection bias is reflected by the high prevalence of SBI in both cohorts.

The main outcome of the study was presence of SBI, which implies that non-bacterial serious illnesses such as aseptic meningitis, viral gastroenteritis with dehydration, severe bronchiolitis with respiratory insufficiency were classified as non-SBI, together with other, milder illnesses. This was done due to prioritizing screening for patients who might benefit from early initiation of antimicrobial treatment, while the treatment for the viral serious illnesses is mostly symptomatic. However, it also means that the model cannot be applied for screening of all serious illnesses.

The heterogeneity of the main outcomes of the study (presence or absence of SBI) is another limitation of this study, though it is shared with other studies on recognition of serious illness in febrile / acutely ill children. The infections included in the selected definitions of SBI affect different organ systems and could manifest with a large spectrum of signs and symptoms, some more typical in one condition than in another, thus selection of clinical variables that are useful for identification of all SBIs may be perceived as unreasonable. On the other hand, focusing on ruling out each one of the outcomes separately is contradictory to the main purpose of this study, which was to create a single, easily applicable screening model for further guidance in management of a wide range of patients presenting to ED with fever. It must be noted though that splitting the outcomes into different subtype categories of SBI, such as pneumonia, urinary tract infections, bacteraemia, and others, may have resulted in higher diagnostic accuracy [13, 14].

Assessment of parental beliefs regarding fever and healthcare-seeking behaviour via the parental questionnaire was also not without limitations. Only patients visiting the emergency department were enrolled in the study, thus limiting the applicability of the results on the general population, in which many febrile children are successfully treated in primary care. Hospital settings were selected with the aim of recruiting patients originating from the capital and various other regions in Latvia, and to get insight in the reasons why parents choose to visit the ED in case of febrile illness in their children. Also, the overwhelming majority of the respondents were mothers, which limits the applicability of the results to fathers and other guardians. To limit the length of the questionnaire, specific details on the factors associated with parental anxiety in case of fever in children, as well as on parental experience in communication with healthcare workers, were omitted. This information was clarified in the qualitative interviews, though with much more limited study population.

The interview study, as all qualitative interview studies with convenience sampling, is subject to selection bias. However, as data saturation was reached and confirmed, we believe that all significant information has been considered.

## 4.6 Implication in clinical practice and future research

### 4.6.1 Application and interpretation of clinical prediction models

This study introduces CPM 1 and CPM 2 as externally validated tools to aid paediatricians and paediatric residents in initial assessment of febrile children presenting to emergency departments. Like other prediction models, the CPMs derived in this study may help to recognize patients with a high probability of SBI, and, with the aid of the scoring system

based on CPM2, to identify patients who are in the uncertain "grey area", in which SBI and non-SBI are equally likely. This may be especially useful in directing a more purposeful investigation process and administration of antibacterial therapy in cases when patients present at early stages of illness, when any "red flag" signs for a specific illness may be absent. The advantage of CPM1 and CPM2 is that no laboratory values are required for the risk assessment, which is convenient for settings with high flow of patients where rapid point-of-care tests are unavailable.

As a high proportion of patients classified as "high risk" according to the scoring system based on CPM 2 were diagnosed with SBI, we propose that patients who fall into this section should receive early antibacterial therapy while waiting for the investigation results to confirm the diagnosis. Approximately one third of patients with SBI fell in the "grey area", therefore additional diagnostic interventions such as laboratory tests, diagnostic imaging, and / or repeated clinical assessment at a later stage of the disease should be performed to clarify the diagnosis in patients who are classified in this category, while "watchful waiting" could be applied to patients whose assessed risk for SBI is low. The CPMs do not overrule any guidelines for assessment and management of febrile patients in paediatric settings. Other signs and symptoms associated with SBI and listed as "red" features in NICE "Traffic light system for identifying risk for serious illness" but not included in the CPMs due to low incidence in research population, such as cyanosis, petechial rash, meningeal signs, or focal seizures [22, 210], should also be considered.

In summary, this study adds to understanding of how clinician's subjective review together with clinical signs can improve recognition of serious illness in paediatric emergency department. CPM 2 is so far the first prediction rule for SBI in febrile patients presenting to ED to include variables based on clinician's non-analytical reasoning. Another example is Paediatric Observation Priority Score (POPS), a triage tool based on physiological signs and clinician's gut feeling intended for assessment of severity of a child's condition and need for specialist review / admission when presenting to healthcare with acute illness of infectious or non-infectious origin [117, 260, 321].

Both CPMs developed in this study have so far only been validated in a small population of patients presenting to the EDs in hospitals of the same country. External validation in EDs in different countries, preferably in large patient populations with consecutive enrolment, and in settings with lower prevalence of SBIs, such as secondary or primary care, should be performed for reliable assessment of the applicability of the models to various patient populations.

### 4.6.2 Clinical relevance of "gut feeling" of something being wrong and "sense of reassurance"

Though specialists tend to be cautious with relying on their intuitive feelings in medical practice, the role of intuition in diagnostic reasoning has been recognized by clinicians working in general practice and hospitals alike, especially in scenarios with little time for analytic reasoning [239, 243, 247, 253]. "Sense of alarm", term similar to "gut feeling" of something being wrong used in this study, has been regarded as valuable source of judgement, which leads to closer evaluation and investigation [239, 247]. However, the perceived stigma on use of intuition at the age of evidence-based medicine sometimes creates a perceived necessity to give objective evidence before acting out on these intuitive feelings [228, 243, 247, 253, 258, 259]. On the other hand, evidence from previous studies shows that failure to consider "gut feeling" and not pursuing further investigation may result of missed cases of serious illness [38, 261]. Therefore, doctors should be enabled to request further diagnostic tests on the basis of "gut feeling", even if other "red flag" signs are absent [39].

The approach to "sense of reassurance" seems less straightforward. The reassuring intuitive feeling may be of a significant aid in discriminating between mild and serious illnesses in circumstances with high flow of patients, and limit the unnecessary use of invasive diagnostic tests [243]. However, clinicians feel more cautious towards it compared to "sense of alarm", suggesting that even if the initial feeling is reassuring, they should still be on their guard not to underestimate the situation, and review it if any doubts arise [247]. This study reveals "sense of reassurance" as the strongest variable to rule out SBI, and the non-analytic part of assessment is balanced by assessment of objective signs and symptoms in CPM 2. Other studies on prognostic value of "sense of reassurance" are necessary to examine the generalizability of its diagnostic application.

The results of this thesis suggest that the intuitive part of assessment enhances the analytical reasoning of the clinician. Therefore, it can be safely suggested that, during clinical evaluation of the patient, clinicians should examine their intuitive feelings, and consider them when deciding on the management of each case. Intuitive feelings should not, however, replace following diagnostic guidelines for specific illnesses, or use of internationally accepted assessment scores [322]. Studies show that combined use of clinical scores and "gut feeling" results in the best diagnostic performance [249, 250].

Increasing awareness of intuitive reasoning would provide significant input in education of junior clinicians. The higher diagnostic value of intuitive reasoning by senior colleagues shows that younger doctors could benefit from education on how skilled intuition should be developed. The currently proposed strategies for enhancing the non-analytical reasoning

include exposure to multiple real-life clinical cases, and effective feedback on the intuitive feelings expressed by the trainees [228, 230, 236, 238, 243, 256, 270]. Furthermore, the clinicians should be taught about the most common cognitive biases that occur in clinical reasoning, such as confirmation bias (only looking for information that supports the perceived diagnosis), framing effect (basing decisions on the positive / negative way the situation is presented), overconfidence bias (overestimation of one's diagnostic ability and intuition), self-satisfying bias ("the "eureka!" moment that stops all further thought"), and others [231]. It must be noted that these biases could affect one's diagnostic reasoning regardless of whether they are aware and / or considerate of the non-analytical part of the diagnostic process.

### 4.6.3 Consideration of parental concern and fever-related anxiety

Parental concern was not significantly predictive of SBI in this study, though it was more commonly expressed by parents whose children were eventually diagnosed with SBI. It must be noted that this study was focused on assessing the diagnostic value of parental concern in recognizing serious bacterial illness, however, viral infections with moderate to severe course are also common in ED and were present among the study population, such as viral meningitis, bronchiolitis with respiratory insufficiency, or viral gastroenteritis with dehydration. As parental concern and gut feeling of a possible serious illness are not discriminative between viral and bacterial infections, the false positive responses cannot always be associated with poor ability to identify serious illness. Therefore, parental concern should still be considered when discriminating between mild and serious illness in children presenting to ED.

A large part of parental anxiety, however, could be linked with their concern about perceived negative effects of fever. This indicates that in case the parent expresses increased concern about their child's illness, the clinician should inquire for reasons for the concern, and identify the elements of fever phobia. The small number of participants in the parental questionnaire make the assessment of parental concern, corrected for fever phobia, complicated due to low statistic power, therefore further studies on the subject with larger sample size are recommended.

As elements of fever-related anxiety and aggressive management of fever were evident among the enrolled parents, it is necessary to provide parents with both informational and emotional support when caring for a febrile child. Systematic reviews show that parents are in a need of clear, reliable, and consistent information on assessment of a child with fever, when and where to seek help, and how to manage febrile illness at home [288, 323] while, in reality, the available information is sometimes difficult to understand for all parents, and there are inconsistencies between information sources. Studies show that the best results are achieved

when the information is provided via different modalities, such as information provided during consultation with a healthcare specialist in oral and written form, handouts, audio-visual material, simulation-based education, and reliable websites [45, 290–293, 324–329]. Similar measures must be taken for educating the parents in Latvia, this could be achieved by creation of a universal guidance including evidence-based and easily understandable information, which could be distributed by doctors in primary care as well as emergency departments, and also made available online. In addition to information on fever and its management, the information needs on the current episode of febrile illness, such as the cause of fever, seriousness of the disease, and the potential dangers of fever should be satisfied [275, 277, 330].

Addressing the emotional needs of parents during febrile illness in their child is equally important. Studies show that dismissing the worries of parents as irrelevant, and shaming them for unwarranted visits to emergency department result in decreased confidence, confusion, and anxiety while addressing all concerns expressed by parents and reassurance that they are doing everything appropriately encourages the parents and empowers them to feel confident when caring for their febrile child [45, 275, 277, 287].

# Conclusion

1. Both derived clinical prediction models had moderate ability to predict serious bacterial infection in children presenting to emergency department with febrile illness. The models had acceptable performance in validation population.
2. Inclusion of variables of clinician's non-analytical reasoning, defined as "gut feeling" of serious illness, and "sense of reassurance", improved the performance of the derived clinical prediction model for serious bacterial infection in febrile children presenting to emergency department, thus confirming the added value of non-analytical reasoning suggested by the hypothesis.
3. Clinician's "Gut feeling" of serious illness was not significantly predictive of serious bacterial infection as an independent variable, which is contradict the hypothesis of the study. Clinician's "sense of reassurance" was significantly predictive for absence of serious bacterial infection.
4. Parental concern, defined as feeling that the illness is different / more severe, was not significantly predictive of serious bacterial in the study population, which contradicts the hypothesis of the study.
5. The study identified elements of fever-related anxiety in parents, including misconceptions regarding the negative effects of fever, frequent temperature measurements, use of antipyretics at low body temperature, and urge to present to healthcare early and outside normal working hours, evaluating hospital care as safer for their child.
6. The study gained insight on the educational, information and emotional needs of parents when caring for a febrile child.

# Approbation of the study – publications and thesis

## Doctoral thesis is based on following SCI publications:

1. **Urbane**, U. N. Petrosina, E., Zavadska, D., & Pavare, J. (2022) Integrating clinical signs at presentation and clinician's non-analytical reasoning in prediction models for serious bacterial infection in febrile children presenting to emergency department. Frontiers in Pediatrics, (10), 225. https://doi.org/10.3389/fped.2022.786795
2. **Urbane**, U. N., Gaidule-Logina, D., Gardovska, D., & Pavare, J. (2019). Value of parental concern and clinician's gut feeling in recognition of serious bacterial infections: a prospective observational study. BMC pediatrics, 19(1), 1–8. doi: 10.1186/s12887-019-1591-7
3. **Urbane**, U. N., Likopa, Z., Gardovska, D., & Pavare, J. (2019). Beliefs, practices and health care seeking behavior of parents regarding fever in children. Medicina, 55(7), 398. https://doi.org/10.3390/medicina55070398
4. **Urbane**, U.N., Gaidule-Logina, D., Gardovska, D., & Pavāre, J. (2019). Coping with febrile illness in children: a qualitative interview study of parents. In Proceedings of the Latvian Academy of Sciences (Vol. 73, No 2, 117–124). De Gruyter Poland. https://doi.org/10.2478/prolas-2019-0019
5. Thingsaker, E. E., **Urbane**, U. N., & Pavare, J. (2021). A Comparison of the Epidemiology, Clinical Features, and Treatment of Acute Osteomyelitis in Hospitalized Children in Latvia and Norway. Medicina, 57(1), 36. doi: 10.3390/medicina57010036

## Publications in Latvian peer-reviewed scientific journals:

1. **Urbāne**, U.N., Gaidule-Logina, D., Zavadska, D., Grope, I., Gardovska, D., Pavare, J. Vecāku novērojumu nozīme smagu bakteriālu infekciju savlaicīgā atpazīšanā bērniem ar drudzi. RSU zinātniskie raksti, 2017, 57–66.
2. Petruhina, J., **Urbane**, U. N., Petersons, A., & Pavare, J. (2017). Epidemiology and Antibacterial Treatment of Acute Hematogenous Osteomyelitis in Patients Hospitalized at Children's Clinical University Hospital in Riga, Latvia. Acta Chirurgica Latviensis, 17(2), 29–34.
3. **Urbāne**, U. N., Zavadska, D., Grope, I., Gardovska, D., Čaplinska, I., Erts, R., Pavare, J. Agrīnas diagnostikas iespējas bērniem ar smagām bakteriālām infekcijām slimnīcas neatliekamās palīdzības nodaļā. RSU zinātniskie raksti, 2016, 20–32.
4. Gardovska, D., Pavare, J., Grope, I., Balmaks, R., Tretjakovs, P., Zavadska, D., Ņikuļšins, S., Smane, L., Laizāne, G., Ziemele, I., Čirko, A., **Urbāne**, U.N., Rautiainena, L;, Višņevska, M., Troka, E., Kazāks, A., Gersone, G., Jurka, A., Grāvele, D. (2018). Dzīvībai bīstamo un sabiedrībai nozīmīgo infekcijas slimību izpēte bērniem Latvijā" The Latvian National Research Programme BIOMEDICINE FOR PUBLIC HEALTH, 61–73.

## Results are reported in the following international conferences:

1. **Urbane**, U.N., Petrosina, E., Zavadska, D., Pavare, J. Predictive model for serious bacterial infections in children with fever presenting to emergency department. Knowledge for Use in Practice – RSU Research week 2021, Riga, Latvia, 26th of March 2021, Book of abstracts p. 61.
2. **Urbane**, U.N., Petrosina, E., Zavadska, D., Pavare, J. Integrating clinical signs at presentation and clinician's "gut feeling" in prediction models for serious bacterial infection in children with fever. International Pediatrics Conference for Medical Students, online event organized by Vilnius University and Latvian Paediatrics association, 8th of May 2021.
3. **Urbane**, U.N. Value of "gut feeling" and parental concern in recognition of serious bacterial infection in febrile children presenting to emergency department. Fever phobia in parents. DIAMONDS and PERFORM General Assembly Meeting, 16–20 November 2020.

4. **Urbane**, U.N., Kavare, M., Marcuks, M., Gaidule-Logina, D., Grope, I., Zavadska, D., Gardovska, D., Pavare, J. Role of clinical signs, gut feeling and parental concern in recognizing serious bacterial infections. 4th Baltic Paediatric Congress 2019, Vilnius, Lithuania, 18th of May 2019.
5. **Urbane**, U.N., Likopa, Z., Kravale, I., Silova, A., Gardovska, D., Pavare, J. Precautionary level system in assessing children with febrile illness visiting Emergency Department. 4th Baltic Paediatric Congress 2019, Vilnius, Lithuania, 18th of May 2019.
6. **Urbane**, U.N., Gaidule-Logina, D., Marcuks, M., Katvare, M. Gardovska, D., Pavare, J. Coping with febrile illness in children: a qualitative interview study of parents" 4th Baltic Paediatric Congress 2019, Vilnius, Lithuania, 18th of May 2019.
7. **Urbane**, U.N., Likopa, Z., Kravale, I., Silova, A., Gardovska, D., Pavare, J. Assessment of children with febrile illness visiting Emergency Department according to "precautionary level" system. RSU International Research Conference on Medical and Health Sciences "Knowledge for Use in Practice", Riga, Latvia, April 1–3, 2019. Book of abstracts p. 134.
8. **Urbane**, U.N., Marcuks, M., Katvare, M., Gaidule-Logina, D., Zavadska, D., Gardovska, D., Pavare, J. Diagnostic values of parental concern and clinician's "gut feeling" in identifying serious bacterial infections in children with fever. RSU International Research Conference on Medical and Health Sciences "Knowledge for Use in Practice", Riga, Latvia, April 1–3, 2019. Book of abstracts p. 135.
9. **Urbane**, U.N., Gaidule-Logina, D., Katvare, M., Marcuks, M., Gardovska, D., Pavare, J. Diagnostic value of parental concern and clinician's gut feeling in recognition of serious bacterial infections in children with fever attending paediatric emergency department. The 7th Congress of the European Academy of Paediatric Societies (EAPS 2018) October 30 – November 3, 2018, Paris, France.
10. Gaidule-Logina, D., **Urbane**, U.N., Marcuks, M., Katvare, M., Pavare, J. Parental perspectives on evaluation and management of fever in children, and healthcare seeking behaviours in Latvia. Is there "fever phobia"? 36th Annual Meeting of the European Society for Paediatric Infectious Diseases (ESPID), May 28 – June 2, 2018, Malmo, Sweden.
11. **Urbane**, U.N., Gaidule-Logina, D., Zavadska, D., Grope. I. Role of parental observations in early diagnosis of serious bacterial infections in children with fever admitted to the hospital: a semi-qualitative pilot study. The 35th Annual Meeting of the European Society for Paediatric Infectious Diseases (ESPID), May 23–27, 2017, Madrid, Spain.
12. Pavare, J., Gardovska, D., **Urbane**, U.N. Measurement of immature granulocytes (ig) percentage to recognize severe bacterial infections as a cause of sepsis. The 28th Annual Meeting of the European Society of Paediatric and Neonatal Intensive Care (ESPNIC 2017), June 6–9, 2017, Lisbon, Portugal.

### Results are reported in following local conferences:

1. **Urbane**, U.N., Gaidule-Logina, D., Marčuks, M., Katvare, M., Zavadska, D., Gardovska, D., Pavare, J. Vecāku paradumi, meklējot palīdzību ar drudzi slimam bērnam. RSU Zinātniskā konference 2018, March 22–23, 2018 Riga, Latvia. Book of abstracts, p. 52.
2. **Urbane**, U.N., Gaidule-Logina, D., Marcuks, M., Katvare, M., Zavadska, D., Gardovska, D., Pavare, J. Smagu bakteriālu infekciju agrīna atpazīšana bērniem ar drudzi neatliekamās palīdzības nodaļā pirmslaboratorajā etapā. RSU Zinātniskā konference 2018, March 22–23, 2018 Riga, Latvia. Book of abstracts, p. 50.
3. Gaidule-Logina, D., **Urbane**, U.N., Marcuks, M., Katvare, M., Pavare. J. Bērnu ar drudzi novērtēšanas un palīdzības meklēšanas paradumi vecākiem Latvijā: vai pastāv "drudža fobija"? RSU Zinātniskā konference 2018, March 22–23, 2018 Riga, Latvia. Book of abstracts, p. 41.
4. Marcuks, M., **Urbane**, U.N., Gaidule-Logina, D., Katvare, M., Pavare, J. Diagnostic values of clinical features at presentation, parental concern and clinician's "gut feeling" in identifying

serious bacterial infections in children with fever. Children's Health Day 2018., November 2, 2018, Riga, Latvia.

5. **Urbane**, U.N., Gaidule-Logina, D., Zavadska, D., Grope, I., Gardovska, D., Pavare, J. Vecāku novērojumu loma smagu bakteriālu infekciju atpazīšanā bērniem: pilotpētījums. 2017. gada RSU zinātniskā konference, April 6–7, 2017, Riga, Latvia. Book of abstracts, p. 82.
6. **Urbane**, U.N. Klīnisko pazīmju kopuma, vecāku un ārstu izvērtējuma nozīme agrīnā smagu bakteriālu infekciju diagnostikā bērniem – rezultātu apkopojums Rīgā un reģionos. "Aktualitātes pediatrijā", conference organized by RSU Faculty of Continuing Education, June 6, 2019.
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# Appendices

**Diagnostic value of clinical presentation, parental concern and clinicians' gut feeling in identifying serious bacterial infections in febrile children**

## Clinical history and investigations

1. Age of patient (years + months) _____
2. Gender of the patient _____
3. Date of onset of symptoms _____
4. Date of the onset of fever _____
5. Date and time when seen at the ED _____
6. Highest body temperature during this episode, °C _____
7. Triage code _____
8. Vital signs on admission:
   a. Body temperature _____
   b. Heatt rate _____
   c. Respiratry rate _____
   d. Oxygen saturation _____ (□ in air / □ with O2 supplement)
   e. Systolic blood pressure_____
   f. Calpillary refill time _____
   g. Consciousness (GCS) _____
   h. Ill appearance (□ Yes / □No)
9. On antibiotics before admission (during this episode)?
   a. □ Yes
      i. (medication 1 _____ Date when started _____)
      ii. (medication 2 _____ Date when started _____)
   b. □ No
10. Comorbidities:
    a. □ None or unknown
    b. □ Malignancy (please specify _____)
    c. □ Pulmonary (please specify _____)
    d. □ Prematurity (time of gestation _____)
    e. □ Gastrointestinal (please specify _____)
    f. □ Neurologic disorders (please specify_____)
    g. □ Cardiovascular (please specify _____)
    h. □ Recent surgery (please specify _____)
    i. □ Immunodeficiency (incl. iatrogenic _____)
    j. □ Foreign body (e.g. catheter, specify _____)
    k. □ Allergic disease (please specify _____)

l. □ Endocrine (please specify _____)

m. □ Genetic (please specify _____)

n. □ Consanguinity (please specify _____)

o. □ Organ transplant (please specify _____)

p. □ History of sepsis / serious illness (please specify _____)

11. Does comorbidityincrease infection risk? (□ yes / □No)
12. Routinely used medication: _____
13. Does medication increase infection risk? (□ yes / □No)
14. Initial working diagnosis: _____
15. Please fill the following (Tick the appropriate)

1) Quality of cry:

| | |
|---|---|
| | a) Strong with normal tone OR Content and not crying |
| | b) Whimpering OR Sobbing |
| | c) Weak OR Moaning OR High pitched |

2) Reaction to parent stimulation

| | |
|---|---|
| | a) Cries briefly then stops OR Content and not crying |
| | b) Cries off and on |
| | c) Continual cry OR hardly responds |

3) State variation

| | |
|---|---|
| | a) If awake, stays awake OR If asleep and stimulated, wakes up quickly |
| | b) Eyes close briefly, awakes up with prolonged stimulation |
| | c) Awake OR Falls to sleep OR Does not wake up |

4) Skin colour:

| | |
|---|---|
| | a) Pink (or appropriate to ethnicity) |
| | b) Pale extremities or acrocyanosis |
| | c) Pale OR Cyanotic OR Mottled OR Ashen |

5) Hydration

| | |
|---|---|
| | a) Skin normal, eyes normal AND mucous membranes moist |
| | b) Skin, eyes normal AND Mouth slightly dry |
| | c) Skin doughy / tented AND Dry mucous membranes AND/OR sunken eyes |

6) Reaction (talk, smile) to social overtures

| | |
|---|---|
| | a) Smiles or alerts (< = 2 mo) |
| | b) Brief smile OR alerts briefly (< = 2 mo) |
| | c) No smile, face anxious / dull / expressionless OR no alerting (< = 2 mo) |

16. Which of the following features are present in the child's physical examination data or history of this episode? (tick the appropriate)

| | |
|---|---|
| ☐ | 1) Ill appearance |
| ☐ | 2) Drowsiness |
| ☐ | 3) Lethargy |
| ☐ | 4) Irritability |
| ☐ | 5) Grunting |
| ☐ | 6) Inconcolable crying |
| ☐ | 7) Decreased appetite |
| ☐ | 8) Refusal of any kind of food |
| ☐ | 9) Refusal of any kind of drink |
| ☐ | 10) Decreased urine output |
| ☐ | 11) Decreased skin turgor |
| ☐ | 12) Cyanosis |
| ☐ | 13) Tachypnoea |
| ☐ | 14) Crackles (type) _____ |
| ☐ | 15) Decreased breathing sounds |
| ☐ | 16) Shortness of breath |
| ☐ | 17) Chest retractions |
| ☐ | 18) Poor peripheral circulation |
| ☐ | 19) Positive meningeal signs |
| ☐ | 20) Non-blanching rash |
| ☐ | 21) Seizures |
| ☐ | 22) Hypotension |
| ☐ | 23) Unconsciousness |
| ☐ | 24) Hypothermia |
| ☐ | 25) Parental concern |

**Radiology results:**

| *Scoring of chest X-rays* | yes | no |
|---|---|---|
| Had CXR? | ☐ | ☐ |
| Normal | ☐ | ☐ |
| Infiltrates | ☐ | ☐ |
| Pneumonia with consolidation | ☐ | ☐ |
| Pleural effusion | ☐ | ☐ |
| Other: …… | ☐ | ☐ |

| *Other diagnostic radiology* | **Result** |
|---|---|
| MRI | …… |
| CT | …… |
| Ultrasound | …… |
| Other | …… |

**Blood tests (on admission** ……

| | Units | Results |
|---|---|---|
| **DATE:** | dd/mm/yy | |
| **Time:** | hh:mm | |
| Leu | $10^9$/L | |
| Neu | $10^9$/L | |
| Ly | $10^9$/L | |
| CRP | mg/L | |

***Maximum CRP during this episode (mg/L):***
……

***Maximum Leu/Neutrophil count during this ep ($10^9$/L):***
……

**SURGICAL OPERATIONS DURING THIS ADMISSION**

| **Date** | **Description** |
|---|---|
| **D D / M M / Y Y** | …… |
| **D D / M M / Y Y** | …… |

## VIROLOGY & BACTERIOLOGY

| *Test* | *Date(s) (ddmmyy)* | *Results* |
|---|---|---|
| Blood culture | ☐ | Central line ☐ Peripheral ☐ All negative ☐ |
| Blood PCR, rapid antigen (bacteriology) | ☐ | RAg ☐ PCR ☐ All negative ☐ |
| Blood PCR (virology) | ☐ | PCR ☐ Negative ☐ |
| CSF metrics | ☐ | White cells ..... Neutrophils %/abs ...../..... Lymphocytes %/abs ...../..... Protein ..... CSF & blood Glucose ...../..... CSF lactate ..... |
| CSF bacterial | ☐ | culture ☐ RAg/IF ☐ PCR ☐ All negative ☐ |
| CSF virology | ☐ | PCR ☐ Negative ☐ |
| Urinalysis | ☐ | Dipstix results (nitrites, leukocytes) Microscopy (epithelial & white cells) |
| Urine organism | ☐ | culture ☐ RAg ☐ PCR ☐ All negative ☐ |
| Nose, throat swab | ☐ | culture ☐ RAg/IF ☐ PCR ☐ All negative ☐ |
| Nasopharyngeal aspirate | ☐ | culture ☐ RAg/IF ☐ PCR ☐ All negative ☐ |
| Stool bacteriology | ☐ | culture ☐ RAg/IF ☐ PCR ☐ All negative ☐ |
| Stool virology | ☐ | RAg/IF ☐ PCR ☐ All negative |
| BAL | ☐ | Negative ☐ |
| ETT Aspirate | ☐ | Negative ☐ |
| Wound swab | ☐ | Negative ☐ |
| Skin swab | ☐ | Negative ☐ |
| Serology results | ☐ | Negative ☐ |
| TB investigations | ☐ | Culture ☐ Microscopy ☐ PCR ☐ IGRA ☐ All negative ☐ |
| *Other test* | | |
| *Other test* | | |

17. Was antimicrobial treatment prescribed?
    a. ☐ Yes
        i. (medication 1 _____date_____ Duration of treatment (days) _____)
        ii. (medication 2 _____date_____ Duration of treatment (days) _____)
    b. ☐ No

    Date and time of discharge_____

    Date when the patient had fever above 38 °C for the last time _____

    Final diagnosis _____

**Klīnisko pazīmju kopuma, vecāku un ārstu izvērtējuma nozīme bērnu ar drudzi izmeklēšanā un ārstēšanā, kā arī smagu bakteriālu infekciju agrīnā atpazīšanā**

**Anamnēzes dati un klīniskās pazīmes**

1. Pacienta vecums (gadi + mēneši) _____
2. Pacienta dzimums _____
3. Klīnisko simptomu sākšanās datums _____
4. Drudža sākšanās datums _____
5. Iestāšanās datums, laiks _____
6. Augstākā ķermeņa T saslimšanas epizodē _____
7. Vitālās pazīmes iestājoties:
   a. Ķermeņa temperatūra _____
   b. Sirdsdarbības frekvence _____
   c. Elpošanas frekvence _____
   d. Skābekļa saturācija _____(□ istabas gaisā / □ ar O2 padevi)
   e. Asinsspiediens _____
   f. Rekapilarizācijas laiks _____
   g. Apziņa (GKS balles) _____
   h. Bērns izskatās slims (□ Jā / □ Nē)
8. Vai saņēmis antibakteriālo terapiju pirms iestāšanās (epizodes ietvaros)
   a. □ Jā
      i. (medikaments 1 _____ Uzsākšanas datums _____)
      ii. (medikaments 1 _____ Uzsākšanas datums _____)
   b. □ Nē
9. Blakusslimības:
   a. □ Nav vai nav zināmas
   b. □ Malignitāte (precizēt _____)
   c. □ Plaušu saslimšanas (precizēt _____)
   d. □ Priekšlaikus dzimis (gestācijas nedēļa _____)
   e. □ Kuņģa-zarnu trakta saslimšanas (precizēt _____)
   f. □ Neiroloģiskas saslimšanas (precizēt _____)
   g. □ Sirdskaites (precizēt _____)
   h. □ Nesena operācija (precizēt _____)
   i. □ Imūndeficīts (ieskaitot jatrogēnu imūnsupresiju _____)
   j. □ Svešķermenis (piem., zonde, Porta kateters u.c. _____)
   k. □ Alerģiskas saslimšanas (precizēt _____)
   l. □ Endokrīnas saslimšanas (precizēt _____)

m. □ Ģenētiskas saslimšanas (precizēt _____)

n. □ Bērns no radniecīgas laulības / savienības (precizēt _____)

o. □ Orgānu transplantācija (precizēt _____)

p. □ Smaga saslimšana anamnēzē (precizēt _____)

10. Vai esošās blakusslimības palielina infekciju risku? (□ Jā / □ Nē)
11. Pastāvīgi lietotie medikamenti:_____
12. Vai pastāvīgi lietotie medikamenti palielina infekciju risku? (□ Jā / □ Nē)
13. Sākotnējā diagnoze: _____
14. Lūdzu aizpildīt sekojošo (vajadzīgo atzīmēt)

1) Raudāšanas veids:

| | |
|---|---|
| | a) Bērns neraud (ir apmierināts) vai spēcīgs kliedziens |
| | b) Šņukst |
| | c) Vājš kliedziens / stenēšana / spalgi kliedzieni |

2) Izturēšanās vecāku klātbūtnē

| | |
|---|---|
| | a) Apmierināts vai raud īslaicīgi |
| | b) Ik pa laikam raud |
| | c) Nepārtraukti raud, nav nomierināms |

3) Apziņa

| | |
|---|---|
| | a) Nomodā vai viegli pamodināms |
| | b) Miegains |
| | c) Nav pamodināms |

4) Ādas krāsa:

| | |
|---|---|
| | a) Sārta (vai atbilstoša etniskajai piederībai) |
| | b) Bālas ekstremitātes vai akrocianoze |
| | c) Pelēcīga / marmorizēta / cianotiska / bāla |

5) Hidratācija

| | |
|---|---|
| | a) Gļotādas valgas, turgors neizmainīts |
| | b) Sausa mutes gļotāda |
| | c) Sausas gļotādas / iekritušas acis |

6) Reakcija uz sociāliem stimuliem

| | |
|---|---|
| | a) Atsmaida (< 2 mēn. – pamostas, reaģē) |
| | b) Īslaicīgi smaida (< 2mēn. - īslaicīgi pamostas, reaģē) |
| | c) Nesmaida / uztraukts / bez izteiksmes (< 2 mēn. – nereaģē) |

15. Vai bērna šīs saslimšanas epizodes laikā anamnēzē un fizikālās izmeklēšanas datos sastopams kāds no sekojošajiem (atzīmēt esošo):

| | |
|---|---|
| ☐ | 1) Toksisks izskats / bērns izskatās smagi slims |
| ☐ | 2) Miegainība |
| ☐ | 3) Letarģija |
| ☐ | 4) Viegla uzbudināmība |
| ☐ | 5) Stenēšana |
| ☐ | 6) Nepārtraukta raudāšana |
| ☐ | 7) Samazināta apetīte |
| ☐ | 8) Atteikšanās ēst |
| ☐ | 9) Atteikšanās no šķidruma |
| ☐ | 10) Samazināta urinācija |
| ☐ | 11) Samazinās audu turgors |
| ☐ | 12) Cianoze |
| ☐ | 13) Tahipnoe |
| ☐ | 14) Trokšņi plaušās (kādi) _____ |
| ☐ | 15) Novājināta elpošana |
| ☐ | 16) Elpas trūkums |
| ☐ | 17) Elpošana ar palīgmuskulatūras līdzdalību |
| ☐ | 18) Mikrocirkulācijas traucējumi |
| ☐ | 19) Pozitīvi meningeālie simptomi |
| ☐ | 20) Petehiāli izsitumi |
| ☐ | 21) Krampji |
| ☐ | 22) Arteriāla hipotensija |
| ☐ | 23) Bezsamaņa |
| ☐ | 24) Hipotermija |
| ☐ | 25) Vecāki ļoti satraukti par bērna veselības stāvokli |

**Radioloģiskie izmeklējumi:**

| ***Krūškurvja rentgenogramma*** | **jā** | **nē** |
|---|---|---|
| Vai tika vekts krūškurvja RTG? | ☐ | ☐ |
| Bez patoloģijas | ☐ | ☐ |
| Infiltrāti | ☐ | ☐ |
| Pneimonija ar konsolidāciju | ☐ | ☐ |
| Izsvīdums pleirā | ☐ | ☐ |
| Cits: ..... | ☐ | ☐ |

| ***Citi attēldiagnostikas izmeklējumi*** | **Rezultāti** |
|---|---|
| MRI | ..... |
| CT | ..... |
| USG | ..... |
| Citi: | ..... |

**Operācijas epizodes laikā**

| **Datums** | **Apraksts** |
|---|---|
| D D / M M / GG | ..... |
| D D / M M / GG | |

**Izmeklējumi (iestājoties): asinsaina + bioķīmija** .....

| | **Vienības** | **Rezultāts** |
|---|---|---|
| **DATUMS:** | dd/mm/yy | |
| **Laiks:** | hh:mm | |
| Leikocīti | $10^9$/L | |
| Neitrofilie leikocīti | $10^9$/L | |
| Limfocīti | $10^9$/L | |
| CRO | mg/L | |

***Maksimālā CRO vērtība saslimšanas laikā (mg/L):*** .....

***Maksimālais leikocītu skaits saslimšanas laik ($10^9$/L):*** .....

**Virusoloģiskie un bakterioloģiskie izmeklējumi (ja tādi veikti)**

| *Izmeklējumi* | *Datums (ddmmyy)* | *Rezultāti* |
|---|---|---|
| Asins kultūra | ☐ | Centrālā vēna ☐ Perifērā vēna ☐ Negatīvs ☐ |
| Baktēriju PĶR un antigēnu noteikšanas testi | ☐ | Reksprestests ☐ PĶR ☐ Negatīvs ☐ |
| Vīrusu PĶR testi | ☐ | PĶR ☐ Negatīvs ☐ |
| Likvora izmeklējumi | ☐ | Leu Neu%/abs ...../... Ly %/abs ...../..... Olbaltums ..... glikoze asinīs un likvorā ...../..... laktāts ..... |
| Likvora bakterioloģija | ☐ | Kultūra ☐ Eksprestest/IF ☐ PĶR ☐ Negatīvs ☐ |
| Likvora virusoloģija | ☐ | PĶR ☐ Negatīvs ☐ |
| Urīna analīze | ☐ | Ar stripu (nitrīti, leu) Mikroskopija (epiteliālās š., leu) |
| Urīna uzsējums | ☐ | Kultūra ☐ Eksprestests ☐ PĶR ☐ Negatīvs ☐ |
| Nazofaringeālā iztriepe | ☐ | Kultūra ☐ Eksprestests ☐ PĶR ☐ Negatīvs ☐ |
| Nazofaringeālais aspirāts | ☐ | Kultūra ☐ Eksprestests ☐ PĶR ☐ Negatīvs ☐ |
| Fēču bakterioloģija | ☐ | Kultūra ☐ Eksprestests ☐ PĶR ☐ Negatīvs ☐ |
| Fēču virusoloģija | ☐ | Eksprestests/IF ☐ PĶR ☐ Negatīvs ☐ |
| Iztriepe no brūces | ☐ | Negatīvs ☐ |
| Ādas iztriepe | ☐ | Negatīvs ☐ |
| Seroloģija | ☐ | Negatīvs ☐ |
| TB izmeklējumi | ☐ | Kultūra ☐ Mikroskopija ☐ PĶR ☐ IGRA ☐ Negatīvs ☐ |
| *Cits* | | |
| *Cits* | | |

16. Vai pacientam tika nozīmēta antibakteriālā terapija?
    a. ☐ Jā
        i. (medikaments 1 _____datums _____ Terapijas ilgums (dienas) ____)
        ii. (medikaments 1 _____datums _____ Terapijas ilgums (dienas) ____)
    b. ☐ Nē

    Datums, kurā pacientam pēdējo reizi bijis T pacēlums virs 38 °C _____

    Izrakstīšanās datums, laiks ____ _____

    Izrakstīšanās diagnoze _____

**Diagnostic value of clinical presentation, parental concern and clinicians' gut feeling in identifying serious bacterial infections in febrile children**

**Clinician's questionnaire**

1. What is your evaluation of the overall condition of the child after initial examination?
   a) Mild illness / normal
   b) Moderate
   c) Severe
   d) Critical / life threatening
2. After the examination of the child, do you have an impression / intuitive feeling that the child has a serious illness?
   a) Yes

      For what reason:

      i. Am able to explain_____
      ii. Am not able to explain
   b) The possibility cannot be excluded
   c) No
3. After the examination of the child, do you have an impression / intuitive feeling that the child has a mild or self – limiting illness?
   a) Yes

      For what reason:

      i. Am able to explain_____
      ii. Am not able to explain
   b) Am not sure
   c) No
4. Based on the examination data, circle the possible primary diagnoses:
   a) Skin and soft tissue infection
   b) Urinary tract infection
   c) Pneumonia
   d) Bacterial gastroenteritis
   e) Bacterial meningitis
   f) Acute osteomyelitis
   g) Purulent arthritis
   h) Bacterial infection of unspecified site
   i) Sepsis
   j) None of the above

5. Which of the following features are present in the child's physical examination data or history of this episode? (Circle the appropriate)
    a) Ill appearance
    b) Lethargy / drowsiness
    c) Grunting
    d) Inconsolable crying
    e) Cyanosis
    f) Tachypnoea
    g) Shortness of breath
    h) Poor peripheral perfusion
    i) Positive meningeal signs
    j) Non-blanching rash / petechiae
    k) Seizures
    l) Hypotension
    m) Unconsciousness
6. Respondent data:
    a) Licensed doctor: work experience as a doctor (years) _____
    b) Medical resident: year of training _____

**Klīnisko pazīmju kopuma, vecāku un ārstu izvērtējuma nozīme bērnu ar drudzi izmeklēšanā un ārstēšanā, kā arī smagu bakteriālu infekciju agrīnā atpazīšanā**.

**Ārsta anketa**

1. Kāds ir jūsu vērtējums par bērna vispārējo stāvokli pēc pirmās apskates?
   a) Viegls
   b) Vidēji smags
   c) Smags
   d) Ļoti smags / kritisks
2. Vai pēc bērna pirmās apskates jums palika iespaids / intuitīva sajūta, ka bērnam ir smaga saslimšana?
   a) Jā

      Kāpēc:

      i. Varu precizēt _____
      ii. Nevaru precizēt
   b) Nav izslēgts
   c) Nē
3. Vai pēc bērna apskates jums palicis iespaids / intuitīva sajūta, ka bērnam ir pašlimitējoša saslimšana?
   a) Jā

      Kāpēc:

      i. Varu precizēt _____
      ii. Nevaru precizēt
   b) Neesmu pārliecināts(-a)
   c) Nē
4. Balstoties uz anamnēzes un objektīvās izmeklēšanas datiem, lūdzu atzīmēt saslimšanas, kas varētu būt bērnam šajā saslimšanas epizodē:
   a) Ādas un mīksto audu infekcija
   b) Akūta urīnceļu infekcija
   c) Pneimonija
   d) Bakteriāls gastroenterīts
   e) Bakteriāls meningīts
   f) Akūts osteomielīts
   g) Septisks artrīts
   h) Neprecizēta bakteriāla infekcija
   i) Sepse
   j) Nekas no minētā

5. Vai bērna anamnēzē un fizikālās izmeklēšanas datos sastopams kāds no sekojošajiem? (atzīmēt esošo)
   a) Toksisks izskats / bērns izskatās smagi slims
   b) Miegainība
   c) Stenēšana
   d) Nepārtraukta raudāšana
   e) Cianoze
   f) Tahipnoe
   g) Elpas trūkums
   h) Mikrocirkulācijas traucējumi
   i) Pozitīvi meningeālie simptomi
   j) Petehiāli izsitumi
   k) Krampji
   l) Arteriāla hipotensija
   m) Bezsamaņa
6. Anketu aizpilda:
   a) Sertificēts ārsts: darba stāžs (gados) _____
   b) Ārsts – rezidents: gads _____

**Questionnaire of the view of parents / guardians on their child's illness**

Dear parents / guardians,

We are very grateful for your participation in this questionnaire. The purpose of this questionnaire is to clarify your observations and feelings concerning febrile illness in your child. By gathering your answers and those of other participants, we aim to assess the value of the information provided by parents in early recognition of serious infections in children, so that parental opinion could be taken into consideration to a greater extent when evaluating children with fever in future. The completion of the questionnaire will not take longer than 15 minutes.

The survey will include questions regarding the ongoing episode of your child's illness, as well as questions on your general beliefs about fever in children.

Your consent or refusal to participate in this questionnaire will affect neither the management of your child's illness in the hospital nor the attitude of the healthcare personnel towards you or your child. You have the right to refuse further participation at any moment, as well as to demand the withdrawal of already given data from being analysed for the study. In that case, please inform any of the healthcare personnel, or the research team about your decision.

**Participant of the survey (circle the appropriate)** Mother, Father, Other_____

**No of children in the family / household: _____**

**Order of birth (**first / second / third**) of the child that is our patient _____**

**Age of the mother (carer)**: _____

**Level of education of the mother (carer) (circle the appropriate)**

1) Middle school
2) High school
3) Professional _____
4) Incomplete higher education
5) Higher education (level of degree): _____
6) Other _____

**Age of the father (carer)**: _____

**Level of education of the father (carer) (circle the appropriate)**

1) Middle school
2) High school
3) Professional _____
4) Incomplete higher education
5) Higher education (level of degree): _____
6) Other _____

**1. How many times has your child been ill over the last 12 months?**

_____

**2. How many times over the last 12 months have you sought help from your family doctor due to increased body temperature of this child?**

_____

**3. How many times has your child been hospitalized for longer than 24 hours?**

_____

**4. Has your child previously had any of the following infectious diseases, during which antibiotics were prescribed? (Mark the appropriate with X)**

| | **Once** | **Repeatedly** |
|---|---|---|
| 1) The child has had none of these infections | | |
| 2) Sinusiti | | |
| 3) Tonsillitis with use of antibiotics | | |
| 4) Pneumonia | | |
| 5) Bronchitis with use of antibiotics | | |
| 6) Urinary tract infection | | |
| 7) Gastrointestinal infection with use of antibiotics | | |
| 8) Bacterial meningitis | | |
| 9) Acute osteomyelitis | | |
| 10) Septic arthritis | | |
| 11) Sepsis | | |
| 12) Other illness with use of antibiotics _____ | | |

**5. Have you observed any of the following in your child during this episode of illness?**

| | |
|---|---|
| 1) The child was breathing shallower or faster | |
| 2) The child was grunting / moaning | |
| 3) The child had a changed skin color (greyish / pale) | |
| 4) The child was unwilling to play with his / her favourite toys | |
| 5) The child was crying the whole time and it was hard to calm him / her down | |
| 6) The child had an atypical cry | |
| 7) The child was screaming | |
| 8) The child was irritated and restless | |
| 9) The child slept longer than normally, was very sleepy | |

10) The child was eating less or refused food ☐
11) The child was drinking less or refused to drink ☐
12) The child had decreased urination ☐
13) The child's urine had an unusual smell ☐
14) Other observed changes _____ ☐

**6. Did the child feel better after you gave him / her medication to reduce the temperature? (Choose one)**

1) Yes, the child became active as usual ☐
2) The child felt better but his behaviour was still not as usual ☐
3) The child did not feel better ☐
4) The temperature did not go down ☐
5) The child got worse and worse ☐
6) I did not give my child such medication ☐

**7. When this episode if child's illness started, did you have a feeling that this time is different / more severe than other times when your child has had fever? (Choose one)**

1) Definitely yes ☐
2) Most likely yes ☐
3) More likely yes than no ☐
4) Difficult to say ☐
5) More likely no than yes ☐
6) Most likely no ☐
7) Definitely no ☐

**8. Did you have a feeling that this tie your child needed medical help more urgently than other times when she / he has had a fever?**

1) Yes ☐
2) No ☐
3) Difficult to say ☐

**9. For how long had your child been ill before you sought medical help for the first time?**

1) 0–6 hours ☐
2) 6–12 hours ☐
3) 12–24 hours ☐

4) 24–8 hours (2 days) ☐
5) 48–72 hours (3 days) ☐
6) Longer _____ ☐

**10. Day of the week (*for example, Sunday*), when your child got ill: _____**

**11. Day of the week and time when you first sought help for your child (day, hh:mm)**

_____

**12. How would you evaluate your level of concern when your child got ill this time?**

1) I was very concerned, unlike any other time ☐
2) I was concerned more than other times when she / he has been ill ☐
3) I was not concerned more than other times when she / he has been ill ☐
4) I was concerned not as much as other times when she / he has been ill ☐
5) I was not concerned at all ☐

**13. Where did you seek help first during this episode of the child's illness?**

1) Family doctor's appointment ☐
2) Consultation over the phone ☐
3) Out-of-hours healthcare service ☐
4) Ambulance ☐
5) Hospital ☐
6) Other _____ ☐

**14. Did the healthcare professional mentioned above provide a sufficient explanation of what was going on and of the reasons for the fever?**

1) Yes ☐
2) No ☐
3) Partially ☐

**15. Did the conversation with the healthcare professional mentioned above help to reduce your anxiety about your child's illness?**

1) Yes ☐
2) My anxiety did not change ☐
3) My anxiety increased ☐

**16. Did the healthcare professional you were seen by at this hospital sufficient explanation of what was going on and of the reasons for the fever?**

1) Yes ☐
2) No ☐
3) Partially ☐

**17. Did the conversation with the healthcare professional you were seen by in this hospital help to reduce your anxiety about your child's illness?**

1) Yes ☐
2) My anxiety did not change ☐
3) My anxiety increased ☐

**Thank you for your answers on this illness of your child! From this point on we would like to ask you about your beliefs on the management of fever in general.**

**18. What is a very high temperature, in your opinion? _____ °C**

**19. At what temperature would you give your child medication to reduce it?** Above ..... **°C**

**20. What medication would you give your child to reduce fever?**

1) Ibuprofen (Nurofen, Ibustar, Ibumetin, Ibufen) ☐
2) Paracetamol (Panadol, Efferalgan, calpol) ☐
3) Other (which one.....) ☐

**21. How would you choose the dosage of medication?**

1) As the doctor recommended ☐
2) As the packaging says ☐
3) Whatever I feel like, depends on the temperature ☐
4) Other ☐

**22. In your opinion, is there such thing as a dangerous level of body temperature?**

1) Yes (Above ..... °C) ☐
2) No ☐
3) I don't know ☐

**23. IS fever itself a sign of a serious and potentially dangerous illness?**

1) yes ☐
2) No ☐
3) Other symptoms must be present as well ☐
4) I don't know' ☐

**24. How soon after any of your children develops fever would you seek for medical help?**

1) 0–6 hours
2) 6–12 hours
3) 12–24 hours
4) 24–48 hours (2nd day)
5) 48–72 hours (3rd day)
6) Later (when) _____

**25. Does being treated in the hospital setting give you a better feeling of safety than care at home under supervision of your family doctor?**

1) Yes
2) No
3) Partially

**26. How would you evaluate the availability of your family doctor?**

1) Very good
2) Good
3) More likely good than bad
4) Normal
5) More likely bad than good
6) Bad
7) Very bad

**Vecāku / aizbildņu aptauja par bērna saslimšanu**

Cienījamie vecāki / aizbildņi!

Izsakām Jums lielu pateicību par piedalīšanos šajā aptaujā. Šīs aptaujas mērķis ir noskaidrot Jūsu novērojumus un izjūtas par Jūsu bērna saslimšanu. Apkopojot Jūsu un citu bērnu vecāku atbildes, paredzēts izzināt vecāku sniegtās informācijas vērtību agrīnā smagu infekciju atpazīšanā bērniem, lai nākotnē palielinātu vecāku lomu šo infekciju agrīnā diagnostikā un ārstēšanā bērniem. Aptaujas aizpildīšana aizņems aptuveni 15 minūtes.

Pēc šīs aptaujas, ja tam piekritīsiet, būsim ļoti pateicīgi, ja piedalīsieties detalizētākā sarunā (ilgums aptuveni 15–30 minūtes) ar pētniecības komandas pārstāvi, kuras laikā Jums tiks uzdoti plašāki jautājumi par Jūsu izjūtām un novērojumiem sakarā ar šo sava bērna saslimšanas reizi. Sarunas laikā tiks veikts tās audioieraksts, kas būs anonīms (identifikācijā tiks izmantots Jūsu bērna reģistrācijas numurs pētījumā). Intervijas saturs būs zināms tikai pētniecības komandai un netiks atklāts trešajām personām.

Jūsu piekrišana vai atteikšanās piedalīties šajā aptaujā un detalizētākajā sarunā neietekmēs Jūsu bērna ārstēšanas procesu vai attiecības ar bērna ārstēšanā iesaistīto medicīnisko personālu. Jums ir tiesības jebkurā mirklī pārtraukt dalību aptaujā vai sarunā, kā arī atteikties no sniegto datu izmantošanas pētījumā, šādā gadījumā informējot ārstniecības personālu vai kādu no pētniecības komandas locekļiem.

**Aptaujā piedalās (vajadzīgo apvilkt):** Māte, Tēvs, Cits_____

**Bērnu skaits ģimenē: _____**

**Kurš pēc kārtas (**pirmais / otrais / trešais**) jūsu ģimenē ir pašreiz saslimušais bērns? _____**

**Bērna mātes (aizbildnes) vecums gados**: _____

**Bērna mātes (aizbildnes) izglītības līmenis (vajadzīgo pasvītrot**):

1) Pamata
2) Vidējā
3) Profesionālā (kāda) _____
4) Nepabeigta augstākā
5) Augstākā (grāds): _____
6) Cita (kāda) _____

**Bērna tēva (aizbildņa) vecums gados**: _____

**Bērna tēva (aizbildņa) izglītības līmenis (vajadzīgo pasvītrot):**

1) Pamata
2) Vidējā
3) Profesionālā (kāda)_____
4) Nepabeigta augstākā
5) Augstākā (grāds): _____
6) Cita (kāda) _____

**1. Cik bieži jūsu bērns ir slimojis pēdējo 12 mēnešu laikā?**

_____

**2. Cik bieži pēdējo 12 mēnešu laikā esat vērsušies pēc palīdzības pie ārsta sakarā ar to, ka bērnam bijusi paaugstināta temperatūra?**

_____

**3. Cik reizes dzīves laikā Jūsu bērns bijis stacionēts slimnīcā ilgāk par 24 stundām?**

_____

**4. Vai jūsu bērnam iepriekš bijušas kādas no sekojošām infekcijas saslimšanām, kuru laikā lietotas antibiotikas? (atbilstošos variantus atzīmēt ar X)**

| | **Vienreiz** | **Atkārtoti** |
|---|---|---|
| 1) Bērnam nav bijušas šādas infekcijas | | |
| 2) Deguna blakusdobumu iekaisums | | |
| 3) Angīna, kuras ārstēšanā lietotas antibiotikas | | |
| 4) Plaušu karsonis | | |
| 5) Bronhīts, kura ārstēšanā lietotas antibiotikas | | |
| 6) Urīnceļu infekcija | | |
| 7) Kunģa un zarnu trakta saslimšana, kuras ārstēšanai lietotas antibiotikas | | |
| 8) Bakteriāls meningīts | | |
| 9) Akūts osteomielīt | | |
| 10) Septisks artrīts | | |
| 11) Sepse | | |
| 12) | | |

**5. Vai šajā bērna saslimšanas reizē esat novērojis/usi kādu no šīm pazīmēm?**

| | |
|---|---|
| 1) Bērns elpo seklāk vai biežāk | |
| 2) Bērns sten, vaid | |
| 3) Bērnam ir izmainīta ādas krāsa (pelēcīga / bāla) | |
| 4) Bērns atsakās no iemīļotajām aktivitātēm un rotaļlietām | |
| 5) Bērns ir raudulīgs, grūti nomierināms | |
| 6) Bērnam ir izmainīts raudāšanas veids | |
| 7) Bērns kliedz | |
| 8) Bērns izteikti satraukts un uzbudināts | |
| 9) Bērns guļ vairāk nekā parasti, ir miegains | |
| 10) Bērns mazāk ēd vai atsakās no ēdiena | |

11) Bērns mazāk dzer vai atsakās no dzēriena ☐
12) Bērnam samazināts urīna daudzums ☐
13) Bērnam izmainīta urīna smarža ☐
14) Citas īpašas pazīmes (kādas)_____ ☐

**6. Vai tad, kad bērnam iedevāt temperatūru pazeminošus līdzekļus, bērna pašsajūta uzlabojās (atzīmēt vienu)?**

1) Jā, bērns kļuva aktīvs kā ierasts ☐
2) Bērna pašsajūta uzlabojās, bet saglabājās izmainīta uzvedība ☐
3) Bērna pašsajūta neuzlabojās ☐
4) Temperatūra nemazinājās ☐
5) Bērnam palika arvien sliktāk ☐
6) Temperatūru pazeminošus līdzekļus bērnam nedevu. ☐

**7. Vai, sākoties pašreizējai saslimšanai, Jums bija sajūta, ka šoreiz bērns saslimis smagāk kā iepriekšējās reizes (atzīmēt vienu)?**

1) Noteikti jā ☐
2) Visticamāk jā ☐
3) Drīzāk jā nekā nē ☐
4) Grūti pateikt ☐
5) Drīzāk nē nekā jā ☐
6) Visticamāk nē ☐
7) Noteikti nē ☐

**8. Vai Jums bija sajūta, ka šoreiz bērnam medicīniskā palīdzība nepieciešama steidzamāk kā citas reizes, kad bērns slimojis ar paaugstinātu temperatūru?**

1) Jā ☐
2) Nē ☐
3) Grūti pateikt ☐

**9. Cik ilgi Jūsu bērnam jau bija slimības pazīmes, pirms meklējāt medicīnisko palīdzību?**

1) 0–6 stundas ☐
2) 6–12 stundas ☐
3) 12–24 stundas ☐
4) 24–48 stundas (2. diennakts) ☐
5) 48–72 stundas (3. diennakts) ☐
6) Ilgāk (cik) _____ ☐

**10. Nedēļas diena (*piem. svētdiena*), kad bērns saslima: _____**

**11. Nedēļas diena un laiks (hh:mm) (*piem. pirmdiena, 13.00*), kad pirmo reizi meklējāt palīdzību**

**_____**

**12. Kā Jūs vērtējat savu satraukumu par bērna saslimšanu?**

1) Biju ļoti satraukts/ta, kā nekad agrāk ☐
2) Biju satraukts/ta vairāk nekā citas reizes, kad bērns slimojis ☐
3) Nebiju satraukts/ta vairāk nekā citas reizes, kad bērns slimojis ☐
4) Biju satraukts/ta mazāk nekā citas reizes, kad bērns slimojis ☐
5) Nebiju satraukts/ta nemaz ☐

**13. Pie kā vērsāties pēc medicīniskās palīdzības pirmo reizi sakarā ar šo sava bērna saslimšanas reizi?**

1) Ģimenes ārsts ☐
2) Ģimenes ārstu konsultatīvais tālrunis ☐
3) Rajona dežūrārsts ☐
4) Ātrā palīdzība ☐
5) Slimnīca ☐
6) Cits _____ ☐

**14. Vai no iepriekš minētā medicīnas darbinieka saņēmāt pietiekamu izskaidrojumu par visu notiekošo, par paaugstinātas temperatūras iemesliem?**

1) Jā ☐
2) Nē ☐
3) Daļēji ☐

**15. Vai Jūsu satraukums par bērna saslimšanu mazinājās pēc sarunas ar iepriekš minēto medicīnas darbinieku?**

1) Jā ☐
2) Satraukums nemainījās ☐
3) Satraukums pieauga ☐

**16. Vai no Bērnu klīniskās universitātes slimnīcas mediķiem saņēmāt pietiekamu izskaidrojumu par visu notiekošo, par paaugstinātas temperatūras iemesliem?**

1) Jā ☐
2) Nē ☐
3) Daļēji ☐

**17. Vai Jūsu satraukums par bērna saslimšanu mazinājās pēc tam, kad bērnu apskatīja Bērnu klīniskās universitātes slimnīcas ārsti?**

1) Jā ☐
2) Satraukums nemainījās ☐
3) Satraukums pieauga ☐

**Pateicamies par Jūsu atbildēm par bērna saslimšanu! Tālāk vēlamies izzināt Jūsu uzskatus par ārstēšanas un aprūpes taktiku gadījumā, ja bērns slimo ar paaugstinātu temperatūru!**

**18. Kāda, pēc Jūsu domām, ir ļoti augsta temperatūra? _____ °C**

**19. Pie kāda temperatūras pacēluma Jūs saviem bērniem dodat temperatūru pazeminošos līdzekļus?** Virs ..... **°C**

**20. Kādus medikamentus Jūs dodat saviem bērniem, lai samazinātu temperatūru?**

1) Ibuprofēns ☐
2) Paracetamols ☐
3) Cits (lūdzu ierakstiet ..... **°C**) ☐

**21. Cik lielu medikamenta devu Jūs dodat saviem bērniem, lai samazinātu temperatūru?**

1) Kā ārsts rekomendējis ☐
2) Kā rakstīts uz iepakojuma ☐
3) Pēc sajūtām atkarībā no temperatūras ☐
4) Cits ☐

**22. Vai, jūsuprāt, eksistē bīstams temperatūras pacēlums?**

1) Jā (Virs ..... **°C**) ☐
2) Nē ☐
3) Nezinu ☐

**23. Vai paaugstināta temperatūra pati par sevi norāda uz bīstamu un nopietnu saslimšanu?**

1) Jā ☐
2) Nē ☐
3) Jābūt vēl citiem simptomiem ☐
4) Nezinu ☐

**24. Cik ilgi pēc temperatūras paaugstināšanās saviem bērniem jūs parasti meklējat medicīnisko palīdzību?**

1) 0–6 stundas
2) 6–12 stundas
3) 12–24 stundas
4) 24–48 stundas (2. diennakts)
5) 48–72 stundas (3. diennakts)
6) Vēlāk (kad) _____

**25. Vai atrašanās stacionārā Jums dod lielāku drošības sajūtu kā ārstēšanās ģimenes ārsta uzraudzībā?**

1) Jā
2) Nē
3) Daļēji

**26. Kā Jūs vērtējat sava ģimenes ārsta pieejamību?**

1) Ļoti laba
2) Laba
3) Vairāk laba nekā slikta
4) Normāla
5) Vairāk slikta nekā laba
6) Slikta (minēt iemeslu) _____
7) Ļoti slikta (minēt iemeslu) _____

Appendix 7. Questions asked in the semi-structured interviews*

| No. | Topic and the questions asked |
|---|---|
| 1. | Signs and symptoms causing increasing concern<br>At what moment of your child's illness did you start to feel worried?<br>What were the signs in the child's behaviour that caused the most concern? |
| 2. | Ways of assessing and monitoring fever<br>How do you assess your child's temperature during illness?<br>What thermometers do you use?<br>How often do you measure the child's temperature during illness? |
| 3. | Opinion and beliefs on the positive effects of fever<br>Do you think that elevated body temperature / fever has any positive effects on the child's body during illness? If yes, what are they? |
| 4. | Opinion and beliefs on the possible side effects and dangers of fever<br>Do you believe that fever is dangerous to the child? If yes, why is it dangerous?<br>What negative effects can fever have on the child's body? |
| 5. | Practices of management of fever<br>How do you manage your child's fever when she / he gets ill?<br>What medication do you use?<br>How do you choose the dose of medication?<br>At what temperature do you give medication to reduce fever?<br>How often do you give medication to reduce fever?<br>Do you use any additional methods to reduce fever? What are they? |
| 6. | Seeking for help in case of fever in their child<br>Who is the first (and then second) person you turn to for help in when your child has fever?<br>What signs during your child's illness urge you to seek help from others?<br>How long after your child develops fever do you usually seek help? |
| 7. | Expectations from healthcare professionals when dealing with febrile illness in their child<br>What do you expect from the healthcare professionals when you turn to them for help in case your child has a high temperature? |
| 8. | Experience in communication with doctors regarding febrile illness in their child<br>How would you describe your previous experience in communication with healthcare professionals when your child has had fever?<br>What explanation does your family doctor usually provide for your child's illness when he or she has a fever? Are you satisfied with it? |

* The questions were asked in this approximate order; however, the interviewer was able to alter the sequence of the questions if directed by the trajectory of the conversation. If the parent had already covered the information while elaborating on another question, some questions were omitted. The interviewer was able to ask some additional questions to clarify the answers with more details.

**Ethics Approval**

# Centrālā medicīnas ētikas komiteja

Brīvības iela 72, Rīga, LV-1011 • Tālr. 67876182 • Fakss 67876071 • E-pasts: vm@vm.gov.lv

Rīgā

14.07.2016. Nr.1/16-07-14

Rīgas Stradiņa Universitātei

*Atzinums par pētījuma pieteikumu „PERFORM (Personalised Risk assessment in Febrile illness to Optimise Real-life Management across the European Union – Personalizēts risku novērtējums saslimšanām ar drudzi, ar mērķi optimizēt to ārstēšanu Eiropas Savienībā)"*

Centrālā medicīnas ētikas komiteja 2016.gada 26.maijā ir izskatījusi Rīgas Stradiņa Universitātes iesniegto pētījuma pieteikumu *„PERFORM (Personalised Risk assessment in Febrile illness to Optimise Real-life Management across the European Union – Personalizēts risku novērtējums saslimšanām ar drudzi, ar mērķi optimizēt to ārstēšanu Eiropas Savienībā)"*.

Pamatojoties uz Centrālās medicīnas ētikas komitejas 2016.gada 26.maija sēdes protokola Nr.2016-3 punktu Nr.3 un iesniegtajiem pētījuma pieteikuma pildinājumiem, tiek izsniegts atzinums, ka Rīgas Stradiņa Universitātes pētījums *„PERFORM (Personalised Risk assessment in Febrile illness to Optimise Real-life Management across the European Union – Personalizēts risku novērtējums saslimšanām ar drudzi, ar mērķi optimizēt to ārstēšanu Eiropas Savienībā)"* nav pretrunā ar bioētikas normām.

Centrālās medicīnas ētikas komitejas priekšsēdētāja E.Pole

Strautiņš, 67876190
Edgars.Strautins@vm.gov.lv

Veidlapa Nr. E-9 (2)

RSU ĒTIKAS KOMITEJAS LĒMUMS NR. 13 / 05.10.2017.

Rīga, Dzirciema iela 16, LV-1007
Tel. 67061596

| | Komitejas sastāvs | Kvalifikācija | Nodarbošanās |
|---|---|---|---|
| 1. | Profesors Olafs Brūvers | Dr.theo. | teologs |
| 2. | Profesore Vija Sīle | Dr.phil. | filozofs |
| 3. | Asoc.prof. Santa Purviņa | Dr.med. | farmakologs |
| 4. | Asoc.prof. Voldemārs Arnis | Dr.biol. | rehabilitologs |
| 5. | Profesore Regīna Kleina | Dr.med. | patalogs |
| 6. | Profesors Guntars Pupelis | Dr.med. | ķirurgs |
| 7. | Asoc.prof. Viesturs Liguts | Dr.med. | toksikologs |
| 8. | Docente Iveta Jankovska | Dr.med. | |
| 9. | Docents Kristaps Circenis | Dr.med. | |

**Pieteikuma iesniedzējs:** **Urzula Nora Urbāne**
Medicīnas fakultāte, Doktorantūras nodaļa

**Pētījuma nosaukums:** "Klīnisko pazīmju kopuma, vecāku un ārstu izvērtējum nozīme bērnu ar drudzi izmeklēšanā un ārstēšanā, kā arī smagu bakteriālu infekciju agrīnā atpazīšanā."

**Iesniegšanas datums:** 25.09.2017.

**Pētījuma protokols:** Izskatot augstāk minētā pētījuma pieteikuma materiālus (protokolu) ir redzams, ka pētījuma mērķis tiek sasniegts veicot pacientu medicīniskās dokumentācijas (slimības vēstures-klīnisko pazīmju kopums) izpēti, bērnu vecāku un ārstu aptauju-anketēšanu, iegūto datu apstrādi un analīzi, kā arī izsakot priekšlikumus. Personu (pacientu, dalībnieku) datu aizsardzība, brīvprātīga informēta piekrišana piedalīties pētījumā un konfidencialitāte tiek nodrošināta. Līdz ar to pieteikums atbilst pētījuma ētikas prasībām.

**Izskaidrošanas formulārs:** ir

**Piekrišana piedalīties pētījumā:** ir

**Komitejas lēmums:** **piekrist** pētījumam

Komitejas priekšsēdētājs Olafs Brūvers Tituls: Dr. miss., prof.

Paraksts

LIGAS STRADIŅA UNIVERSITĀTE ĒTIKAS KOMITEJA

Ētikas komitejas sēdes datums: 05.10.2017.

Veidlapa Nr. E-9(3)
APSTIPRINĀTA
ar Rīgas Stradiņa universitātes rektora
2018. gada 26. septembra rīkojumu Nr. 5-1/238/2018

Rīgas Stradiņa universitātes
Pētījumu ētikas komitejas
**LĒMUMS**
Rīgā

25.10.2018. Nr.6-3/ 27

| | Komitejas sastāvs | Kvalifikācija | Nodarbošanās |
|---|---|---|---|
| 1. | Profesors Olafs Brūvers | Dr.theo. | teologs |
| 2. | Asoc.prof. Santa Purviņa | Dr.med. | farmakologs |
| 3. | Asoc.prof. Voldemārs Arnis | Dr.biol. | rehabilitologs |
| 4. | Profesore Regīna Kleina | Dr.med. | patologs |
| 5. | Profesors Guntars Pupelis | Dr.med. | ķirurgs |
| 6. | Asoc.prof. Viesturs Liguts | Dr.med. | toksikologs |
| 7. | Docente Iveta Jankovska | Dr.med. | ortodonts |
| 8. | Docents Kristaps Circenis | Dr.med. | docētājs |
| 9. | Lektore Ilvija Razgale | Mg.soc.d. | docētājs |

**Pieteikuma iesniedzējs/i:** **Urzula Nora Urbāne, 3. studiju gada doktorante Medicīnas fakultāte, doktorantūras nodaļa**

**Pētījuma / pētnieciskā darba nosaukums:** "Klīnisko pazīmju kopuma, vecāku un ārstu izvērtējuma nozīme bērnu ar drudzi izmeklēšanā un ārstēšanā, kā arī smagu bakteriālu infekciju agrīnā atpazīšanā – validācijas pētījums"

**Iesniegšanas datums:** 22.10.2018.

**Pētījuma protokols:** Izskatot augstāk minētā pētījuma pieteikuma materiālus (protokolu) ir redzams, ka pētījuma mērķis tiek sasniegts veicot bērnu vecāku aptauju-anketēšanu, ārstu aptauju-anketēšanu un ievācot klīniskos datus (anketa), iegūto datu apstrādi un analīzi, kā arī izsakot priekšlikumus. Personu (dalībnieku) datu apstrāde, aizsardzība, glabāšana, informēta brīvprātīga piedalīšanās un konfidencialitāte ir ievērota un nodrošināta. Līdz ar to pieteikums atbilst pētījuma ētikas prasībām.

**Komitejas lēmums:** **piekrist pētījumam**

Komitejas priekšsēdētājs Olafs Brūvers Tituls Dr. miss., prof.

Paraksts

RIGAS STRADIŅA UNIVERSITĀTE ĒTIKAS KOMITEJA

I Bērnu
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