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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

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Table of Contents

Abbreviations used in the Thesis

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
ED	Emergency department
ICU	Intensive Care Unit
LR (–)	Negative likelihood ratio
LR (+)	Positive likelihood ratio
NICE	National Institute for Health and Clinical Excellence
NPV	Negative predictive value
OR	Odds ratio
PERFORM	Personalised Risk Assessment in Febrile Illness to Optimise Real-life Management across the European Union
POTCs	Point-of-care tests
PPV	Positive predictive value
ROC	Receiver operating characteristic
SBI	Serious bacterial infection
W	Wilcoxon statistic
χ^2	Chi-squared test

Introduction

Febrile illness in a child is one of the most common reasons for seeking medical assistance. 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 [1–5]. In 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 [6, 7] to between 4 % and 15 % of all febrile children presenting to paediatric emergency departments [8–11] (up to 27 % in very young children with fever without source [12, 13]).

SBI, defined by most studies as a range of infections including bacteraemia, sepsis, pneumonia, bacterial meningitis, complicated urinary tract infection, acute osteomyelitis, and septic arthritis, and others [6, 8, 10, 13–15], may result in adverse outcomes, patient deterioration, even death unless recognized early [16, 17]. Due to multitude of febrile children visiting ED, timely discrimination between children with a high or low risk for SBI is very challenging. The high costs of investigation [18], and dissatisfaction in parents caused by long waiting times and painful procedures [19] increase the pressure on clinicians even further.

Through previous research in paediatrics, several clinical signs and symptoms associated with serious illness in febrile children have been identified [20], 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 [21–25], of which arguably the best known is the “Traffic light” system developed in United Kingdom by National Institute for Health and Clinical Excellence (NICE) [21]. 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 [7, 11, 26].

To estimate the probability of SBI in febrile children in various clinical settings, numerous clinical prediction rules have been created [6, 9–13, 25, 27–32]. 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 [27, 33, 34] than models based on clinical variables only [6, 8, 11, 13]. 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 non-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 [35], but also “gut feeling” of something wrong, even if alarm signs are absent [6, 36, 37]. This “sense of alarm” has been associated with increased likelihood of SBI in children in primary care settings [6, 37], and it has proven to be useful in other fields of medicine, such as recognition of cancer in primary care [38, 39]. Similarly, parental concern that “this illness is different” has been identified among parents of children with SBI [40] and associated with an increased likelihood of developing SBI in a prospective study in primary care [6]. 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 [41], is still present nowadays despite widely available information on proper management of fever in children [42–46], and one of the main causes of non-urgent visits to ED [44, 47]. 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 [46, 48, 49]. 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 the 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 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 Materials and methods

1.1 Setting

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

1.1.1 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 [50].

1.1.2 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

Liepāja Regional Hospital, Daugavpils Regional Hospital, Vidzeme Hospital, Jēkabpils Regional Hospital, North Kurzeme Regional Hospital, Association of Balvi and Gulbene Hospitals. 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.

1.2 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.

1.3 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 1.1.

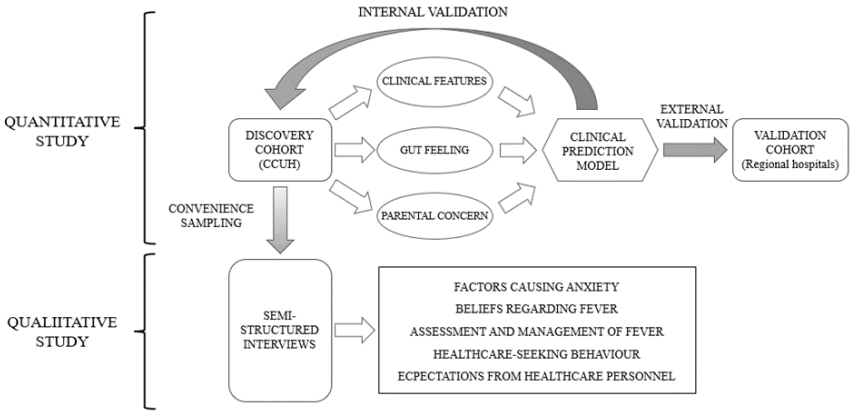

Figure 1.1 **Study design**

1.3.1 Quantitative study

The quantitative part of the 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) [51]. 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. 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 [20], included in popular clinical practice guidelines and assessment scores [21, 22, 52–54], 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 [22, 55]. Poor peripheral circulation was defined as cold hands and feet, and / or prolonged capillary refill time [56]. 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) [57], 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. 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 [6, 37], as well as "Sense of reassurance", defined as an intuitive feeling that the child has a self-limiting illness [58] 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. Parental concern was defined as an impression that this episode of illness is different / more severe than the child's previous febrile episodes [6, 40], 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 on the child's previous illnesses.

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 [8, 10, 14, 59–62]. For this study, SBI was defined as any of the infections displayed in Table 1.1 requiring hospitalization (for at least 24 hours).

Table 1.1

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 magnetic resonance imaging

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 was estimated [63]. 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 and 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 0.9to 0.99 indicates a perfect model [64]. 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.

1.3.2 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, while some interviews were postponed to a later time within 72 hours of admission.

Enrolment was considered complete when no new information emerged from the interviews and data saturation had been reached [65]. 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 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 [66]. 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.

1.4 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 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 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.

2 Results

2.1 Demographic data

2.1.1 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 the enrolled patients, 18.1 % (n = 34) were younger than 12 months, and 81.4 % of patients (n = 153) were younger than 5 years.

2.1.2 Clinicians

In CCUH, the questionnaire on “gut feeling” and “sense of reassurance” was completed in 356 cases of the enrolled patients. 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).

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 most cases (86.7 %, n = 163) the clinician had more than 10 years of clinical work experience.

2.1.3 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. Half of the participants (50.8 %) were parents of two children, 35.2 % had one child, and 14.0 % had 3 or more children.

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, aged 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. Most of the participants had either one (34.3 %) or two (39.3 %) children, while 26.4 % had three or more children.

2.2 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 2.1. 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 (range < 24 hours to 25 days).

In validation population, 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 2.1

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 %)

2.3 Analysis of predictor variables in discovery cohort

Data on thirty potential predictor variables were collected from patients enrolled in CCUH. The selected clinical variables (except for cyanosis) can be viewed in Table 2.2. 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.

Due to failure to complete questionnaires within the specified time, data on the non-analytical variables, "gut feeling" of something being wrong, and "sense of reassurance" were missing in 161 and 162 cases, respectively, and data on parental concern was missing in 250 cases.

2.3.1 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 2.2.

Table 2.2

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	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 2.2 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	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	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	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	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 consciousnes	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*
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

* 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.

2.3.2 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 2.3.

Table 2.3

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–	0.69 (0.49–	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 2.4.

Table 2.4

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)	98.0 (87.5–99.7)	< 0.001
"Sense of reassurance" of licensed paediatricians							
40.2 (31.4–49.4)	97.7 (87.7–99.9)	8.81 (3.45–22.49)	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)	98.0 (87.5–99.7)	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 2.5. 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 2.5

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

Table 2.5 continued

Clinical features	OR (95 % CI)	*p* value
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.

2.3.3 Parental concern

Parental concern ("different illness") was significantly more commonly expressed by parents of children who developed SBI (as reflected in Table 2.6), 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 2.6

Diagnostic value (95 % CI) of parental concern in discovery cohort

Parental concern (different / more severe illness)							
Sensitivity (%)	**Specificity (%)**	**OR**	**LR (+)**	**LR (–)**	**PPV (%)**	**NPV (%)**	***p* value**
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

2.4 Clinical prediction models

2.4.1 Selection of predictor variables

All clinical and non–analytical variables 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, parental concern was not included. 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 2.7.

Table 2.7

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 2.8 reflects the variables selected for CPM 2.

Table 2.8

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.

2.4.2 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 2.1.

The ROC AUC 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 2.2 displays the ROC curves of CPM 2 in derivation and validation populations.

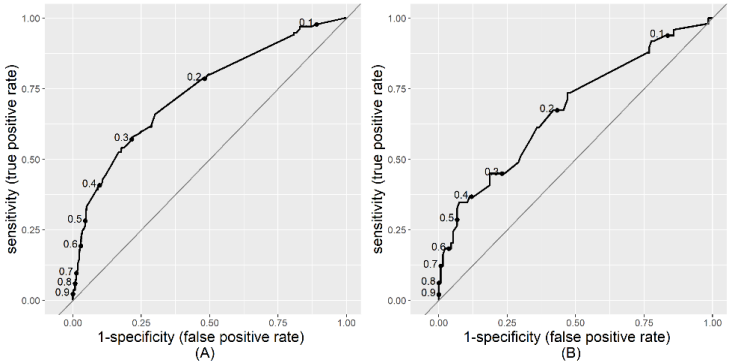

Figure 2.1 **Receiver operating characteristic curves of clinical prediction model 1(CPM 1) for risk of serious bacterial infections (SBIs) in derivation (A) and validation (B) populations***

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

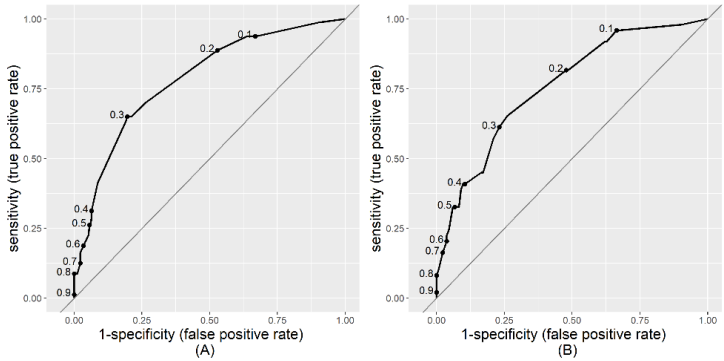

Figure 2.2 **Receiver operating characteristic curves of clinical prediction model 2 (CPM 2) for risk of serious bacterial infections (SBIs) in derivation (A) and validation (B) populations***

* 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)).

2.4.3 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 2.3 and 2.4 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.

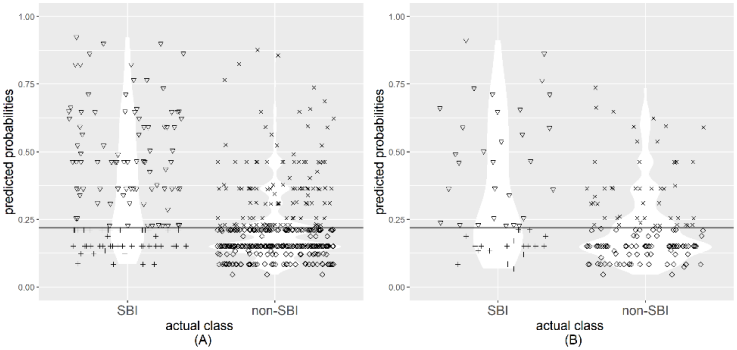

Figure 2.3 **Confusion matrix for discrimination between subjects with SBI and without SBI by CPM 1 in research (A) and validation (B) populations with the chosen cut-off value of 0.219**

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

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.

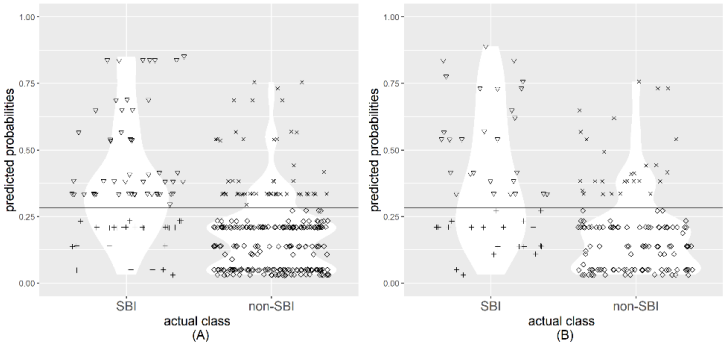

Figure 2.4 **Confusion matrix for discrimination between subjects with SBI and without SBI by clinical prediction model 2 (CPM 2) in research (A) and validation (B) populations with the chosen cut-off value of 0.283**

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

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 calculation of sensitivity, specificity, PPV and NPV, LR (+) and LR (–) at different risk threshold levels for both models resulted in 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 (sensitivity (95 % CI) = 94 % (86 %–98 %), LR (–) (95 % CI) = 0.19 (0.08–0.45), while a cut-off 0.6 (specificity (95 %CI) = 98 %

(95 %–99 %), LR (+) (95 % CI) = 7.18 (2.28–18.27) was optimal for ruling-in SBI, and yielded similar sensitivities and specificities in both cohorts.

2.4.4 Assessment score based on CPM 2

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 2.9.

Table 2.9

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 applied to both derivation and validation cohorts. The sensitivities, specificities, PPV and NPV, and (LR (+) and LR (–) at different score cut-off values are reflected in Table 2.10.

Table 2.10

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)
≥ 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)

Table 2.10 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)						
≥ 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 analysis of performance of the scoring system at different cut-off points, patients with score value of 3 points or less were stratified in a low-risk category for SBI, while patients with 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 a result, most 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. Figure 2.5 illustrates the distribution of patients with and without SBI between the different risk categories in derivation and validation cohorts.

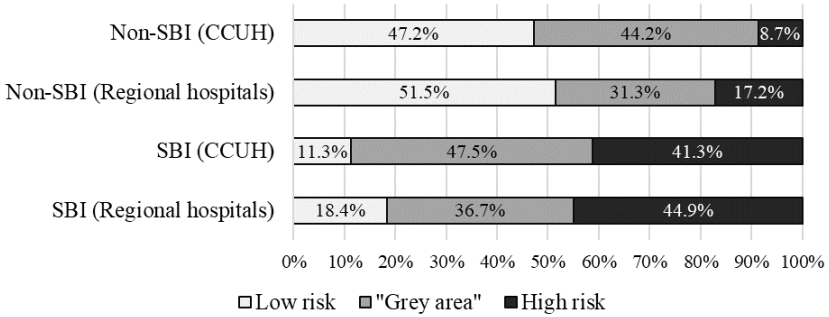

Figure 2.5 **Categorization of patients with and without serious bacterial infection (SBI) in derivation and validation cohorts according to scoring system based on CPM 2**

2.5 Analysis of parental perception of fever

2.5.1 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.

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 at which parents usually administered antipyretics ranged from 37.0 °C to 40 °C, (median 38 °C). Nearly half of the respondents (48.5 %) reported giving antipyretics at a body temperature 38.0 °C–38.4 °C,

while 35.5 % gave medication at 38.5 °C–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 % reduce 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 one (median 38 °C), the difference was statistically significant (W (Wilcoxon statistic) = 23532, $p < 0.001$).

The median temperature that parents evaluated as high fever in CCUH, and regional hospitals alike was 39 °C (37.0 °C–42.0 °C). Most respondents (92.5 %, n = 382) believed that the child's body temperature 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 (37.0 °C–42.0 °C). 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 2.6.

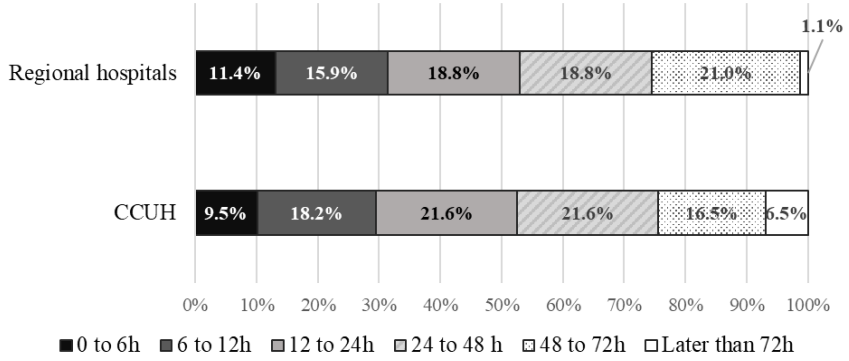

Figure 2.6 **Time after the onset of febrile illness in their child at which parents usually seek medical attention**

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.

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.

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.

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 2.7.

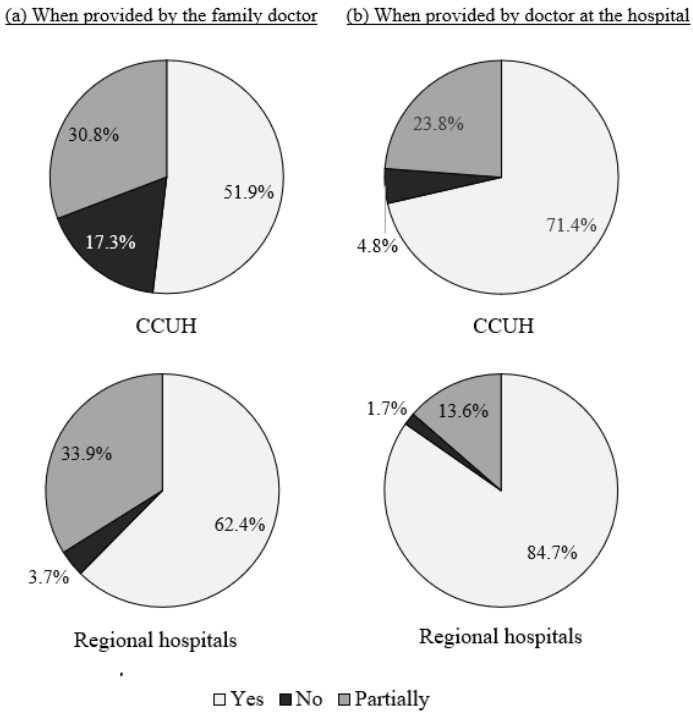

Figure 2.7 **Answer to the question: "Was the explanation on the nature of illness and reasons for fever satisfactory?"**

The majority (67.3 %, n = 278) of all participants stated that they felt 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 ($w = 24130$, $p < 0.001$). 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 who turned to the ambulance or the ED of a hospital.

2.5.2 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 each interview was between 5 minutes and 19 seconds to 22 minutes and 5 seconds, (median 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).

Main themes

Six main themes 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.

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 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. 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. Two parents were alarmed by witnessing seizure-like activities. Some patients got concerned when noticing respiratory symptoms in their febrile child, such as cough, runny nose, rapid breathing, difficulty breathing, "choking", and cyanosis. 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. 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. Some parents agreed that fever is helping the organism to fight against the pathogens and is an excellent indicator that the body is fighting an infection. However, in most cases the parents believed that fever is beneficial to fighting infection only to some extent, up to a certain temperature (38 °C or 39 °C), after which the effects are rather negative, requiring extra effort from the child to cope with illness. Some other parents believed that fever reduces the ability to fight infection due to dehydration and overheating. 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.

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 to evaluate the effects of antipyretics, though the monitoring 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. Other parents measured their child's temperature according to a schedule, mostly around one hour after giving antipyretics, and later the frequency of re-assessment varied from once in six hours to once in every 15 minutes.

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.

Fever management practices

Ibuprofen and Paracetamol were used by almost all the parents to reduce the temperature in their child, with no preference to either. 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.

Alternative ways to reduce body temperature were used by most of the participants, which included undressing the child, applications with wet towel or cloth, rubbing with alcohol, lemon water, or diluted vinegar, and cold bath. Only one respondent saw these methods as unacceptable and only relied on medication. One parent used homeopathic medicine along with antipyretics.

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

The reasons for seeking medical help were similar to the features that caused anxiety in the parents - 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. The amount of time the parents chose to wait before consulting a medic varied amongst the participants. A few would consult a doctor immediately, while most parents would observe the child at home for several days, waiting for two to three days, or even three to five days before seeing a doctor.

Expectations from healthcare personnel

Parents expected medical personnel to meet their child's medical needs, their own informational needs, and their emotional needs.

With regards to the child's medical needs, 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, while 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.

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, or when their concerns about the child were disregarded.

3 Discussion

The 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.

3.1 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.

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. Strong association between ill appearance and serious illness has been found in studies in both primary care [37] and hospital EDs [10, 27, 31, 67].

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 [6, 11, 61], though in studies of populations with higher prevalence of SBI it provides little diagnostic value [61]. 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 [62], where poor feeding and restlessness were associated with increased risk for SBI. The study 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 [50], 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.

The study showed that combining clinical features together in clinical prediction models was more effective in recognizing SBI than considering their diagnostic value separately.

3.2 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, while "sense of reassurance" was significantly predictive of absence of SBI, both when analysed separately and when integrated in a clinical prediction model.

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 [20, 61] and clinical guidelines [21, 22]. 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 [20]. While the classic definition of "gut feeling" implies that the clinician may be unsure of the reasons they are experiencing a "sense of alarm" [37, 68], 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 [68–73]. 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 [71, 72, 74, 75].

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 [6, 37], in which it has shown high predictive value for SBI. The diagnostic value of "gut feeling" in this study was significantly lower than 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 [39, 69, 73]. The level of experience improved the accuracy of the non-analytical reasoning of the clinician, which is consistent with most studies [36, 69, 70, 75–77] but contradicts the findings of one Belgian primary care study [37].

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", it was evident that experience of clinician affected the diagnostic accuracy of this variable.

3.3 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 also required data on fewer clinical variables. Both models showed slight, but acceptable decrease in performance in validation population. As application of both models to

derivation and validation populations still resulted in an overlap of patients with and without SBI, 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, from which models including laboratory markers have superior performance [10, 12, 27, 29, 33, 34, 78]. Not surprisingly, the diagnostic value of these prediction models was also superior to CPM 1 and CPM 2, which did not include laboratory variables. When compared to other prediction rules for serious infection in febrile children that are based on clinical parameters alone [6, 8, 11, 13], CPM 1 and CPM 2 show similar diagnostic performance in derivation cohort, and better performance when prospectively validated externally [27, 33, 79].

3.4 Role of parental concern and fever-related anxiety

In this study, the rule-in value of parental concern for diagnosis of SBI was poor. This contradicts the findings of studies in primary care [6, 20], where parental concern was strongly predictive of SBI. 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 [40] and may not be applicable to emergency departments, 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 the general opinion was that high fever is very dangerous to the child.

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 [43, 47, 49, 80–86], and have prevailed for decades [41, 42, 80].

Fever is one of the main reasons for seeking healthcare specialists after hours [42, 87], 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 behaviour of the study participants–parents who believed that lower temperatures are dangerous to a child were more likely to contact a doctor earlier. 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 university education less frequently automatically associated fever with serious illness. This correlates with findings in other studies, where low educational and socioeconomic status was associated with higher levels of fever phobia [43, 85, 88, 89], though some studies have found higher anxiety among parents with high education level [49] or no influence of education level at all [90]. This study showed that the number of children in the family affected the urge to seek help early, while use of antipyretics and general beliefs about fever were unaffected by the size of the family. In previous studies, having more than one child has been reported to decrease fever–related anxiety and increase the accuracy of perception of fever [49, 81, 91, 92].

Though parents were generally more satisfied with the explanatory work provided by doctors at the hospital than what they previously received at their family doctors, and generally felt safer at the hospital, satisfaction levels of parents in CCUH and regional hospitals with provided information were not 100 % after visiting either specialist, which indicates that communication with parents, including education on nature and management of febrile illness, needs improvement in both primary care and hospitals.

The expectations from the healthcare personnel revealed by the respondents were similar to the findings of other studies [81, 89, 93, 94], 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 [94, 95], 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.

3.5 Limitations

This study is not without limitations, which are the following. As informed consent of a parent or guardian was required for participation in the study, consecutive enrolment was not possible, and the study samples are relatively small. Due to missing data, the number of complete cases from which CPM 2 was derived was lower than a preferred sample size.

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 [9, 10].

3.6 Implications in clinical practice and future research

3.6.1 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.

As a high proportion of patients classified as “high risk” according to the scoring system based on CPM 2 were diagnosed with SBI, 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 [20, 96], should also be considered.

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.

3.6.2 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 [69, 70, 73, 74]. "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 [70, 73]. 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 [69–72, 74, 97]. 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 [37, 98]. The results of the Thesis also suggest that the intuitive part of assessment enhances the analytical reasoning of the clinician. Therefore, doctors should be enabled to request further diagnostic tests on the basis of "gut feeling", even if other "red flag" signs are absent [38].

Intuitive feelings should not, however, replace following diagnostic guidelines for specific illnesses, or use of internationally accepted assessment scores [99]. Studies show that combined use of clinical scores and "gut feeling" results in the best diagnostic performance [100, 101].

3.6.3 Consideration of parental concern and fever-related anxiety

Parental concern was not significantly predictive of SBI in this study. However, 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. 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 [89, 102] 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 [44, 103–108]. 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.

Conclusions

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, 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 the 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. https://doi.org/10.3390/medicina55070398

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/10.2478/prolas-2019-0019

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, pp. 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.

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