Supplemental information
Appendix 1: Statistical analysis plan

Statistical Analysis Plan
Prediction of invasive bacterial infections in febrile children presenting to Emergency Departments in Europe

Background
Still today children die on treatable infectious diseases due to delayed or missed diagnosis presented at the Emergency Department (ED) or primary care.(1-3) On the other hand, antibiotics are prescribed for viral infections and infection with an unknown bacterial or viral cause in order not to miss one child with an invasive bacterial infection.(4)

The distinction between invasive bacterial infections and viral infections on only clinical signs and symptoms is difficult. Biomarkers as C-reactive protein and procalcitonin are currently used in febrile children to detect bacterial infections and to target appropriate antibiotic prescribing. However, these markers measure non-specific inflammation and immunologic responses. Recent research focuses on finding new discriminators of bacterial and viral infections using novel, sophisticated techniques (genomic, proteomic and transcriptomic approaches).(5-7) It is yet unclear which patients would benefit from potential new biomarkers. It is not feasible to apply new biomarkers to all febrile children. Therefore, decision models need to be developed which can identify these patients.

We searched PUBMED from 1st January 2009 to 1st July 2019 for published studies covering clinical prediction models for bacterial infections in children using keywords “child”, “fever”, “bacterial infection” and “clinical prediction” and checked references for relevant articles. The existing literature on clinical prediction models for bacterial infections focuses on young infants (< 3 months) and healthy children in particular. For older children, the Feverkidstool (Nijman et al.) is an extensively validated clinical prediction model for prediction of pneumonia and other serious bacterial infections which includes bacteraemia and meningitis but also infections of the urinary tract, gastro-intestinal tract and soft tissue. We could not identify a clinical prediction model for the outcome invasive bacterial infections including older children or children with chronic conditions.

Objectives
1. To update an existing clinical prediction model to identify invasive bacterial infections in febrile children at the ED
2. Can we target patients who can benefit from a new biomarker based on risk-prediction by this model?

Methods
Study design:
Prospective observational study
This study is a prospectively planned analysis in the MOFICHE study (Management and Outcome of Febrile Illness in Children) which is part of the PERFORM project. MOFICHE is a prospective observational study using routine data. The need for informed consent was waived.

Setting:
12 Emergency Departments (EDs) in 8 countries

Population:
Children 0-18 years with fever (temperature >38.0 C) measured at ED or history of fever (<72 hours) before ED visit. For this analysis, we will exclude children with working diagnosis of urinary tract infections after ED visit. For diagnosis of urinary tract infections, easy available diagnostics are already available at the ED. Therefore, a clinical prediction model has limited additional value in this group. Furthermore, we will focus our analysis on patients with CRP measurement since these are patients with diagnostic uncertainty after initial assessment by the physician.

Inclusion period:
I January 2017 – 1 April 2018, at least 12 months per study site.

**Primary outcomes:**
Invasive bacterial infections (IBI): bacteraemia, bacterial meningitis and bacterial bone and joint infections. Infections were defined positive growth of a single pathogenic bacterium in blood, cerebrospinal fluid or synovial fluid from cultures collected at ED visit or the first 24 hours from hospital admission.

Cultures growing contaminants (coagulase-negative staphylococci, alpha-haemolytic streptococci, *Micrococcus* species or *Propionibacterium* species are defined negative (8)

In children who are immunocompromised, malignancies or with a central line, these contaminants are still relevant invasive bacterial infections that need antibiotic treatment. In these patient groups, cultures with a single contaminant are defined positive.

All patients were entered in the electronic case record form (eCRF) by the local team. We will check all the positive cultures to ensure consistency and validity of coding.

**Missing data**
For this analysis, we will exclude patients with no CRP value and exclude patients with working diagnosis of urinary tract infection. We will use multiple imputation by chained equations using the MICE package in R to impute all missing predictor variables. We will assume the variables to be ‘missing at random’ where missingness can be explained by other variables in the data. We will incorporate hospital, all predictor variables, outcome measures and other auxiliary variables in the imputation model. Multiple imputation will be performed on all patients (n=38480).

**Variables in the multiple imputation model:**

<table>
<thead>
<tr>
<th>General characteristics</th>
<th>Markers of disease severity</th>
<th>Vital signs</th>
<th>Diagnostics</th>
<th>Treatment</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital</td>
<td>Triage urgency</td>
<td>Heart rate</td>
<td>CRP-level</td>
<td>Immediate life-saving interventions</td>
<td>Disposition</td>
</tr>
<tr>
<td>Age</td>
<td>Fever duration</td>
<td>Respiratory rate</td>
<td>Chest X-ray categories</td>
<td>Oxygen treatment</td>
<td>Final diagnosis</td>
</tr>
<tr>
<td>Sex</td>
<td>Capillary refill time</td>
<td>Temperature</td>
<td>Urinalysis categories</td>
<td>Inhalation medication</td>
<td>Focus of infection</td>
</tr>
<tr>
<td>Referral type (self / GP / emergency services / other)</td>
<td>Ill appearance</td>
<td>Oxygen saturation</td>
<td>Blood culture performed</td>
<td>Antibiotic prescription type</td>
<td></td>
</tr>
<tr>
<td>Previous medical care (yes, primary care / yes, this ED / yes other secondary care)</td>
<td>Work of breathing</td>
<td></td>
<td>Cerebrospinal fluid performed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Season</td>
<td>Meningeal signs</td>
<td></td>
<td></td>
<td>Previous antibiotic treatment</td>
<td></td>
</tr>
<tr>
<td>Arrival hours (morning / evening / night)</td>
<td>Focal neurology</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Comorbidity</td>
<td>Non-blanching rash</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Dehydration
Seizures

**Descriptive analysis**
We will perform descriptive analysis for children with and without IBI. We will use frequencies, mean and standard deviation for normally distributed data, median and interquartile range for normally distributed data. In addition, we will compare patients with CRP measurement and patients without CRP measurement.

**Predictor variables**
We will include predictor variables chosen a-priori that have predictive value for bacterial infection. We will perform univariate logistic regression analysis for these predictor variables:

**Predictor variables included in the Feverkidstool (9):**
- Age
- Sex
- Temperature
- Fever duration in days
- Tachypnea: defined by Advanced Paediatric Life Support (10)
- Tachycardia: defined by Advanced Paediatric Life Support (10)
- Hypoxia: oxygen saturation <94%
- Prolonged capillary refill time: >3 seconds
- Increased work of breathing: chest wall retractions, nasal flaring, grunting or apnoea
- Ill appearance: ill, moderately ill, irritable or uncomfortable
- C-reactive protein value

**NICE red warning signs for serious illness (11):**
- Abnormal consciousness: responsive to verbal stimulation, responsive to pain or unresponsive
- Presence of meningeal signs: presence of Kernig, Brudzinski, tripod phenomenon, neck stiffness or bulging fontanelle
- Focal neurological signs
- Status epilepticus: seizures for >=30 minutes
- Non-blanching rash: petechiae or other non-blanching rash

**Complex chronic condition (12):**
- Chronic condition in ≥2 body systems that is expected to last at least 1 year or malignancy or immunocompromised

We will use 10 events per variable to include predictor variables in model development. If not enough events are available, we will combine abnormal consciousness, presence of meningeal signs and focal neurological signs in a composite variable. Linearity of continuous variables will be assessed using restricted cubic splines. Outliers for continuous variables will be truncated at the 0.01 percentile and the 0.99 centile.

**Model development**
We will perform variable selection by least absolute shrinkage and selection operator (LASSO). Using LASSO, we perform variable selection and reduce degree of overfitting by shrinking large regression coefficients.(13) We will estimate the lambda using 10 times 10-fold-cross validation. To note, variable selection will not be based on significance in univariate logistic regression analysis.

**Model validation**
The model will be validated using internal-external cross-validation. In this method, the model is repeatedly derived on all EDs except one, and validated on the remaining ED.(14, 15)

**Model performance**
Model performance will be assessed by
- Discrimination of the model by concordance (c)-statistic.
- Calibration, the agreement between predicted risks and observed outcome will be visualized using calibration plots.\(^{(16)}\)
- Diagnostic performance at different risk-threshold for the probability of IBI using sensitivity, specificity and negative and positive likelihood ratios. We will focus on cut-offs that can be used to rule-out (negative LR \(<0.2\)) or rule-in IBI (positive LR\(>5\)).\(^{(17)}\)

**Sensitivity analysis**
A sensitivity analysis will be performed in the population where missing CRP values will be imputed.
Appendix 2: Definition of contaminants

Appendix 3: Definition of contaminants

Micrococcus
Coagulase-negative staphylococci
Propionibacterium species
Alpha-haemolytic streptococci (except pneumococcus)
Corynebacterium species (diphteroids)
Bacillus species
Pseudomonas (except P. aeruginosa)
Other environmental non-fermenting gram-negative rods
Appendix 3: Additional methods on data analysis

Multiple imputation
Missing data were multiple imputed using the MICE package in R v3.4. The imputation model included the outcome variable IBI, all considered predictors, ED and other auxiliary variables related to casemix and disease severity (specific details of the multiple imputation model are proved in the Statistical Analysis Plan). The imputation process resulted in 20 imputation sets. For all the statistical analysis, apart from the model development in LASSO (least absolute shrinkage and selection operator), results were pooled for a final result.(18) The LASSO was applied to a stacked dataset containing all imputed data.(19) To adjust for the inflated sample size we assigned each record a weight of 1/20 (20 is number of imputed datasets).

Model development and internal-external cross-validation
For model development (20, 21), we considered predefined variables with predictive value for IBI: 1) variables in the Feverkidstool(9) (age, sex, temperature, fever duration, tachypnea and tachycardia defined by Advanced Pediatric Life Support(10), oxygen saturation <94%, capillary refill >=3 seconds, work of breathing, ill appearance and CRP value), 2) NICE warnings signs which were not included in the Feverkidstool (consciousness, meningeal signs, focal neurology, status epilepticus, non-blanching rash)(11) and 3) complex chronic condition (condition in ≥2 body systems, malignancy or immunocompromised).(12) Level of consciousness, meningeal signs and focal neurology were combined into a composite variable abnormal neurology. Linearity of continuous variables was assessed using restricted cubic splines. As in the Feverkidstool, age was modelled linear piecewise for children <1 year and children >1 year and a logarithmic transformation for CRP was used. Outliers were truncated at the 0.01 percentile for temperature (35.7 °Celsius) and the 0.99 percentile for CRP (215 mg/L) and fever duration (8 days).

Variable selection was not influenced by the results of the univariate logistic regression analysis, but was performed using least absolute shrinkage and selection operator (LASSO).(13, 22) This approach aims to reduce the degree of overfitting by shrinking large regression coefficients and performs variable selection.(13) The lambda to derive the final model was estimated using 10 times 10-fold cross-validation. We used internal-external cross-validation in EDs with >10 IBI cases (four EDs) and EDs with <10 IBI cases (eight EDs) were combined in one group leading to five ED groups (appendix 5). In internal-external cross-validation The model was repeatedly derived on all ED groups except one, and validated on the remaining ED group (see figure A below).(14) Unlike splitting data in a derivation and validation set, this method uses all available data for the model development and uses cross-validation to validate the model five times. This cross-validation determines model performance most accurately but also provides information on the heterogeneity of performance across different settings. This internal-external cross-validation is therefore superior to a single external validation.(14, 15) We assessed the discriminative ability by the area under the receiver operating curve (AUC), and calibration, the agreement between predicted risks and observed cases., was evaluated by calibration plots. We explored the impact of difference in case-mix heterogeneity on the discriminative ability of the model in the internal-external cross-validation. Sensitivity, specificity, negative and positive likelihood ratios (LR) were evaluated at different cut-offs for the individual probability of IBI according to the model. We explored cut-offs for ruling-out (negative LR <0.2) or ruling-in IBI (positive LR >5).(17) Missing values for the covariates were multiple imputed (MICE). Sensitivity analysis was performed in the population where missing CRP values were imputed. All analyses were performed in R v3.6.
Figure A

Model adaptation

**Final model** – Model developed on all patients of 12 EDs

**Cross-validation**

- **Model A** - developed on all patients excluding patients from Ljubljana, Slovenia
  - Validation of model A on patients from Ljubljana, Slovenia

- **Model B** - developed on all patients excluding patients from London, UK
  - Validation of model B on patients from London, UK

- **Model C** - developed on all patients excluding patients from Nijmegen UMC, NL
  - Validation of model C on patients from Nijmegen UMC, NL

- **Model D** - developed on all patients excluding patients from Rotterdam, NL
  - Validation of model D on patients from Rotterdam, NL

- **Model E** - developed on all patients excluding patients from 8 EDs with <10 cases
  - Validation of model E on patients from 8 EDs with <10 cases

5 cross-validations - Pooled using random-effects model
Appendix 4: EDs - classification of EDs with low (<2%) and high incidence (>2%) for IBI based on proportion of invasive bacterial infection, and proportion of chronic complex comorbidity per ED

<table>
<thead>
<tr>
<th>ED</th>
<th>N total included patients</th>
<th>N study population</th>
<th>IBIs N (% of study population per ED)</th>
<th>Chronic complex comorbidity N (% of study population per ED)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Graz, Austria</td>
<td>2241</td>
<td>1987</td>
<td>1 (0.1%)</td>
<td>73 (3.7%)</td>
</tr>
<tr>
<td>Athens, Greece</td>
<td>4548</td>
<td>1450</td>
<td>1 (0.1%)</td>
<td>19 (1.3%)</td>
</tr>
<tr>
<td>Riga, Latvia</td>
<td>9000</td>
<td>5495</td>
<td>9 (0.2%)</td>
<td>60 (1.1%)</td>
</tr>
<tr>
<td>Munich, Germany</td>
<td>1173</td>
<td>456</td>
<td>1 (0.2%)</td>
<td>19 (4.2%)</td>
</tr>
<tr>
<td>Nijmegen, CWZ, the Netherlands</td>
<td>423</td>
<td>184</td>
<td>1 (0.5%)</td>
<td>12 (6.5%)</td>
</tr>
<tr>
<td>Ljubljana, Slovenia</td>
<td>3667</td>
<td>3183</td>
<td>23 (0.7%)</td>
<td>61 (1.9%)</td>
</tr>
<tr>
<td>Liverpool, UK</td>
<td>1623</td>
<td>468</td>
<td>8 (1.7%)</td>
<td>76 (16.2%)</td>
</tr>
<tr>
<td>Newcastle, UK</td>
<td>3854</td>
<td>475</td>
<td>9 (1.9%)</td>
<td>41 (8.6%)</td>
</tr>
<tr>
<td>London, UK</td>
<td>5714</td>
<td>1047</td>
<td>22 (2.1%)</td>
<td>184 (17.6%)</td>
</tr>
<tr>
<td>Santiago de Compostela, Spain</td>
<td>3877</td>
<td>281</td>
<td>6 (2.1%)</td>
<td>9 (3.2%)</td>
</tr>
<tr>
<td>Rotterdam, the Netherlands</td>
<td>1683</td>
<td>921</td>
<td>36 (3.9%)</td>
<td>369 (40.1%)</td>
</tr>
<tr>
<td>Nijmegen, UMC, the Netherlands</td>
<td>677</td>
<td>321</td>
<td>18 (5.6%)</td>
<td>135 (42.1%)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>38480</strong></td>
<td><strong>16268</strong></td>
<td><strong>135</strong></td>
<td><strong>1058</strong></td>
</tr>
</tbody>
</table>

EDs with low incidence for IBI (<2%)

<table>
<thead>
<tr>
<th>ED</th>
<th>N total included patients</th>
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</tr>
<tr>
<td>Rotterdam, the Netherlands</td>
<td>1683</td>
<td>921</td>
<td>36 (3.9%)</td>
<td>369 (40.1%)</td>
</tr>
<tr>
<td>Nijmegen, UMC, the Netherlands</td>
<td>677</td>
<td>321</td>
<td>18 (5.6%)</td>
<td>135 (42.1%)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>13698</strong></td>
<td><strong>53</strong></td>
<td><strong>53 (0.4%)</strong></td>
<td><strong>367 (2.7%)</strong></td>
</tr>
</tbody>
</table>

ED, emergency department; IBI, invasive bacterial infection; UK, United Kingdom; UMC, university medical centre; CWZ, Canisius Wilhelmina Hospital
Appendix 5: Patient characteristics of patients with CRP measurement and patients without CRP measurement

<table>
<thead>
<tr>
<th>CRP measured (n=17,213)</th>
<th>No CRP measured (n=21267)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>General characteristics</strong></td>
<td></td>
</tr>
<tr>
<td>Age in years, median (IQR)</td>
<td>2.77 (1.29-6.02)</td>
</tr>
<tr>
<td>Male</td>
<td>9305 (54.1)</td>
</tr>
<tr>
<td></td>
<td>49.6-62.0</td>
</tr>
<tr>
<td>Previous chronic condition</td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>3332 (19.4)</td>
</tr>
<tr>
<td></td>
<td>7.8-71.8</td>
</tr>
<tr>
<td>Complex</td>
<td>1138 (6.6)</td>
</tr>
<tr>
<td></td>
<td>1.1-41.3</td>
</tr>
<tr>
<td>Referred</td>
<td>9287 (53.9)</td>
</tr>
<tr>
<td></td>
<td>6.9-99.2</td>
</tr>
<tr>
<td>Triage urgency</td>
<td>9794 (56.9)</td>
</tr>
<tr>
<td></td>
<td>10.9-86.5</td>
</tr>
<tr>
<td>Feverkidstool</td>
<td>334 (19.4)</td>
</tr>
<tr>
<td>Temperature in °C, median (IQR)</td>
<td>37.8 (37-38.5)</td>
</tr>
<tr>
<td>Fever duration in days, median (IQR)</td>
<td>1.5 (0.5-3)</td>
</tr>
<tr>
<td>Tachypnea (APLS)</td>
<td>3585 (20.8)</td>
</tr>
<tr>
<td></td>
<td>5.9-45.8</td>
</tr>
<tr>
<td>Tachycardia (APLS)</td>
<td>6001 (34.9)</td>
</tr>
<tr>
<td></td>
<td>11.0-887</td>
</tr>
<tr>
<td>Hypoxia &lt;95%</td>
<td>762 (4.4)</td>
</tr>
<tr>
<td></td>
<td>1.3-9.2</td>
</tr>
<tr>
<td>Prolonged capillary refill (&gt;3 sec)</td>
<td>339 (1.9)</td>
</tr>
<tr>
<td></td>
<td>0.2-7.0</td>
</tr>
<tr>
<td>Work of breathing</td>
<td>913 (5.3)</td>
</tr>
<tr>
<td></td>
<td>0.5-13.2</td>
</tr>
<tr>
<td>Ill appearance</td>
<td>4742 (27.5)</td>
</tr>
<tr>
<td></td>
<td>1.9-52.6</td>
</tr>
<tr>
<td>CRP in mg/L, median (IQR)</td>
<td>17 (5-49)</td>
</tr>
<tr>
<td>NICE Warning signs</td>
<td></td>
</tr>
<tr>
<td>Decreased consciousness</td>
<td>148 (0.9)</td>
</tr>
<tr>
<td></td>
<td>0.1-5.4</td>
</tr>
<tr>
<td>Meningeal signs</td>
<td>126 (0.7)</td>
</tr>
<tr>
<td></td>
<td>0.1-3.7</td>
</tr>
<tr>
<td>Focal neurology</td>
<td>102 (0.6)</td>
</tr>
<tr>
<td></td>
<td>0.0-3.7</td>
</tr>
<tr>
<td>Status epilepticus</td>
<td>51 (0.3)</td>
</tr>
<tr>
<td></td>
<td>0.0-2.3</td>
</tr>
<tr>
<td>Rash: petechiae/non blanching</td>
<td>664 (3.9)</td>
</tr>
<tr>
<td></td>
<td>1.1-18.0</td>
</tr>
<tr>
<td>Blood cultures performed</td>
<td></td>
</tr>
<tr>
<td>Admission to the ward &gt;24 hours</td>
<td>3478 (20.2)</td>
</tr>
<tr>
<td>CSF performed</td>
<td>444 (2.6)</td>
</tr>
<tr>
<td>Admission to the ICU</td>
<td>6590 (38.3)</td>
</tr>
<tr>
<td>Antibiotic treatment following ED visit</td>
<td>135 (0.8)</td>
</tr>
<tr>
<td>Lifesaving interventions: airway, breathing or hemodynamic support</td>
<td>6795 (39.5)</td>
</tr>
<tr>
<td></td>
<td>27.9-211</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>371 (2.2)</td>
</tr>
<tr>
<td></td>
<td>0.0-11.5</td>
</tr>
<tr>
<td></td>
<td>3.2-9.7</td>
</tr>
</tbody>
</table>

APLS, advanced paediatric life support; CRP, C-reactive protein; CSF, cerebrospinal fluid; ED, emergency department; ICU, intensive care unit; IQR, interquartile range; NA, not applicable
Appendix 6: Details of patients with complex chronic conditions

<table>
<thead>
<tr>
<th>Identified pathogen</th>
<th>No complex chronic condition, n=85</th>
<th>Complex chronic condition, n=50</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strep. pneumoniae</td>
<td>23 (27.1%)</td>
<td>5 (10%)</td>
</tr>
<tr>
<td>Staph. aureus</td>
<td>15 (17.6%)</td>
<td>10 (20%)</td>
</tr>
<tr>
<td>E. coli</td>
<td>9 (10.6%)</td>
<td>4 (8%)</td>
</tr>
<tr>
<td>Neisseria meningitidis</td>
<td>9 (10.6%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Kingella kingae</td>
<td>7 (8.2%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Group B streptococcus</td>
<td>6 (7.1%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Group A streptococcus</td>
<td>5 (5.9%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Salmonella spp</td>
<td>4 (4.7%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Haemophilus influenzae</td>
<td>4 (4.7%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Enterobacter spp</td>
<td>2 (2.4%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Coagulase-negative staphylococci (CoNS)</td>
<td>9 (18%)</td>
<td></td>
</tr>
<tr>
<td>Candida species</td>
<td>4 (8%)</td>
<td></td>
</tr>
<tr>
<td>Viridans streptococci</td>
<td>4 (8%)</td>
<td></td>
</tr>
<tr>
<td>Klebsiella spp</td>
<td>3 (6%)</td>
<td></td>
</tr>
<tr>
<td>Enterococcus spp</td>
<td>3 (6%)</td>
<td></td>
</tr>
<tr>
<td>Moraxella spp</td>
<td>1 (2%)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>1 (1.2%)</td>
<td>3 (6%)</td>
</tr>
</tbody>
</table>

C-reactive protein level in immunocompromised patients for no IBI (A) vs IBI (B) for IBI risk categories

A n=341

B n=24
# Appendix 7: Univariate logistic regression analysis for invasive bacterial infection.

## Supplementary file 5:
Univariate logistic regression analysis for invasive bacterial infection.

N=16268, IBI cases N=135

<table>
<thead>
<tr>
<th>Variables</th>
<th>OR (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feverkidstool</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1.04 (0.74-1.46)</td>
</tr>
<tr>
<td>Age &lt;1 year±</td>
<td>0.25 (0.14-0.43)*</td>
</tr>
<tr>
<td>Age &gt;1 year±</td>
<td>1.01 (0.97-1.05)</td>
</tr>
<tr>
<td>Temperature in °C</td>
<td>1.34 (1.13-1.59)*</td>
</tr>
<tr>
<td>Fever duration in days</td>
<td>0.89 (0.80-0.99)*</td>
</tr>
<tr>
<td>Tachypnea (APLS)</td>
<td>1.50 (1.03-2.18)*</td>
</tr>
<tr>
<td>Tachycardia (APLS)</td>
<td>2.84 (2.01-4.01)*</td>
</tr>
<tr>
<td>o2 saturation &lt;94%</td>
<td>0.65 (0.24-1.75)</td>
</tr>
<tr>
<td>Prolonged capillary refill time (&gt;3 sec)</td>
<td>2.62 (1.24-5.56)*</td>
</tr>
<tr>
<td>Presence of work of breathing</td>
<td>1.62 (0.90-2.93)</td>
</tr>
<tr>
<td>Ill appearance</td>
<td>2.51 (1.76-3.58)*</td>
</tr>
<tr>
<td>Ln CRP</td>
<td>1.89 (1.63-2.19)*</td>
</tr>
</tbody>
</table>

### NICE alarming signs

<table>
<thead>
<tr>
<th>Variables</th>
<th>OR (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Status epilepticus</td>
<td>No cases</td>
</tr>
<tr>
<td>Reduced level of consciousness</td>
<td>4.70 (2.04-10.83)*</td>
</tr>
<tr>
<td>Focal neurology</td>
<td>2.30 (0.54-9.71)</td>
</tr>
<tr>
<td>Meningeal signs</td>
<td>9.20 (4.54-18.62)*</td>
</tr>
<tr>
<td>Abnormal neurology; decreased level of consciousness, presence of meningeal signs or focal neurology</td>
<td>4.81 (2.61-8.91)</td>
</tr>
<tr>
<td>Non-blanching rash</td>
<td>2.31 (1.21-4.41)*</td>
</tr>
</tbody>
</table>

### Chronic condition

| Complex chronic condition                     | 8.83 (6.19-12.59)* |

*Significant, p<0.05

±The risk of children aged < 1 year was calculated: $\beta_{(\text{age <1 year})}\times$age in years.
The risk of children aged >1 years was calculated with: $\beta_{(\text{age <1 year})}\times1+\beta_{(\text{age ≥1 year})}\times($age in years−1).

APLS, Advanced Paediatric Life Support; CRP, C-reactive protein; ln, natural log
Appendix 8: Calibration plot: observed proportion vs predicted probability of the clinical prediction model for 5 internal-external cross-validations.

The solid red line with a slope of 1 and intercept of 0 represents ideal prediction accuracy. The dotted lines indicate the 95% confidence interval.

A. Model developed on leave-out EDs with <10 cases, validated on EDs with <10 cases
B. Model developed on leave-out Ljubljana (Slovenia), validated on Ljubljana (Slovenia)
C. Model developed on leave-out London (UK), validated on London (UK)
D. Model developed on leave-out Nijmegen (the Netherlands), validated on Nijmegen, UMC (the Netherlands)
E. Model developed on leave-out Rotterdam (the Netherlands), validated on Rotterdam (the Netherlands)

Legend: ED, emergency department; UK, united kingdom; UMC, University Medical Centre
Appendix 9: Model 2 – model specification and performance

In model 2 the variable ED with low/high IBI incidence is added to the model.

Model 2 – model specification

<table>
<thead>
<tr>
<th>Coefficient</th>
<th>OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Intercept)</td>
<td>-6.13</td>
</tr>
<tr>
<td>Male</td>
<td>-0.16</td>
</tr>
<tr>
<td>Age &lt; 1 year*</td>
<td>-2.22</td>
</tr>
<tr>
<td>Age ≥ 1 year*</td>
<td>0.00</td>
</tr>
<tr>
<td>Temperature</td>
<td>-0.16</td>
</tr>
<tr>
<td>Fever duration in days</td>
<td>-0.15</td>
</tr>
<tr>
<td>Tachypnea</td>
<td>-0.47</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>0.66</td>
</tr>
<tr>
<td>Hypoxia</td>
<td>-0.81</td>
</tr>
<tr>
<td>Prolonged capillary refill</td>
<td>-0.31</td>
</tr>
<tr>
<td>Increased work of breathing</td>
<td>-0.47</td>
</tr>
<tr>
<td>Ill appearance</td>
<td>1.18</td>
</tr>
<tr>
<td>Ln CRP</td>
<td>0.75</td>
</tr>
<tr>
<td>Abnormal neurology</td>
<td>1.10</td>
</tr>
<tr>
<td>Non-blanching rash</td>
<td>1.06</td>
</tr>
<tr>
<td>Complex chronic condition</td>
<td>1.56</td>
</tr>
<tr>
<td>ED with high IBI incidence (&gt;2%)</td>
<td>1.98</td>
</tr>
</tbody>
</table>

*Age <1 year and age ≥ 1 year were calculated linear-piecewise:
The risk of children aged < 1 year was calculated: \( \beta_{(age <1 \text{ year})} \times \text{age in years} \).
The risk of children age ≥ 1 year was calculated: \( \beta_{(age <1 \text{ year})} \times 1 + (\text{age in years}-1) \times \beta_{(age \geq 1 \text{ in years})} \).

CRP, C-reactive protein; IBI, invasive bacterial infection; ln, natural log.
Model 2 - performance

Discrimination:
Development model 2: C-statistic 0.88 (95%CI 0.85-0.90)

Calibration:
Apparent calibration for model 2 for IBI (addition of variable ED with low IBI incidence (<2%) / ED with high IBI incidence (>=2%)). Risk predictions are calculated on the developed model using all data (n=16268). These risk predictions are calibrated in the two groups: EDs with low IBI incidence (A) and EDs with high IBI incidence (B). ED, emergency department; IBI, invasive bacterial infection
Appendix 10: Performance of the prediction model (model 1)

Decision curve analysis

Post-test probability for varying pre-test probabilities for invasive bacterial infection (IBI)

Negative test for the low-risk threshold (0.1%) and positive test for the high-risk threshold (2.0%)
**Appendix 11: Sensitivity analysis: model development on population with imputed CRP-level (n=37093)**

<table>
<thead>
<tr>
<th>Coefficients</th>
<th>OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Intercept)</td>
<td>-9.67</td>
</tr>
<tr>
<td>Male</td>
<td>-0.19</td>
</tr>
<tr>
<td>Age &lt; 1 year*</td>
<td>-2.58</td>
</tr>
<tr>
<td>Age &gt; 1 year*</td>
<td>0.00</td>
</tr>
<tr>
<td>Temperature</td>
<td>-0.05</td>
</tr>
<tr>
<td>Fever duration in days</td>
<td>-0.15</td>
</tr>
<tr>
<td>Tachypnea</td>
<td>-0.43</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>0.71</td>
</tr>
<tr>
<td>Hypoxia</td>
<td>-0.86</td>
</tr>
<tr>
<td>Prolonged capillary refill</td>
<td>0.02</td>
</tr>
<tr>
<td>Increased work of breathing</td>
<td>-0.34</td>
</tr>
<tr>
<td>Ill appearance</td>
<td>0.94</td>
</tr>
<tr>
<td>Ln CRP</td>
<td>0.78</td>
</tr>
<tr>
<td>Abnormal neurology</td>
<td>1.54</td>
</tr>
<tr>
<td>Non-blanching rash</td>
<td>1.40</td>
</tr>
<tr>
<td>Complex chronic condition</td>
<td>2.43</td>
</tr>
</tbody>
</table>

*The risk of children aged < 1 year was calculated: \( \beta(\text{age <1 year}) \times \text{age in years.} \)

The risk of children aged >1 years was calculated with: \( \beta(\text{age <1 year}) \times 1 + \beta(\text{age ≥1 year}) \times (\text{age in years−1}). \)

CRP, C-reactive protein; ln, natural log
Appendix 12: Clinical case examples

Case 1:
A previously healthy, 4 year old boy presents with fever since 1.5 day. At the ED he has a temperature of 38.9 degrees, heart rate of 160/min, respiratory rate of 45/min, oxygen saturation of 99% and normal capillary refill time. He is ill-appearing, has increased work of breathing and a normal neurological exam. CRP-level = 10 mg/L.

Risk-prediction:
The patient is at intermediate-risk (>0.1% and <2%) for an invasive bacterial infection.

Case 2:
A previously healthy neonate of 2 months presents with fever since 12 hours. She has temperature of 38.8 degrees, heart rate of 170/min, respiratory rate of 35/min, normal oxygen saturation and normal capillary refill time. She is ill-appearing and has no increased work of breathing. Neurological exam is normal. CRP-level = 5 mg/L.

Risk-prediction:
The patient is at high-risk (>2%) for an invasive bacterial infection.
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