Supplemental information
Appendix 1: Statistical analysis plan

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

SAP version 1.0 date 14th July 2019

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:
1 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 as 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>Cerebrospinal fluid performed</td>
<td>Antibiotic prescription mode</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**

Dehydration

**Seizures**

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.

Drafted by: Nienke N. Hagedoorn
Statistician: Daan Nieboer
Supervision: Dr. Clementien Vermont, Prof. Henriette A. Moll
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. The LASSO was applied to a stacked dataset containing all imputed data. 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, we considered predefined variables with predictive value for IBI: 1) variables in the Feverkidstool (age, sex, temperature, fever duration, tachypnea and tachycardia defined by Advanced Pediatric Life Support), 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) and 3) complex chronic condition (condition in ≥2 body systems, malignancy or immunocompromised).

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). This approach aims to reduce the degree of overfitting by shrinking large regression coefficients and performs variable selection. 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). 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. 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 casemix 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). 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
- **Model B** - developed on all patients excluding patients from London, UK
- **Model C** - developed on all patients excluding patients from Nijmegen UMC, NL
- **Model D** - developed on all patients excluding patients from Rotterdam, NL
- **Model E** - developed on all patients excluding patients from 8 EDs with <10 cases

Validation of **model A** on patients from Ljubljana, Slovenia
Validation of **model B** on patients from London, UK
Validation of **model C** on patients from Nijmegen UMC, NL
Validation of **model D** on patients from Rotterdam, NL
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</th>
<th>IBIs N (% of study population per ED)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Graz, Austria</td>
<td>13698</td>
<td>53 (0.4%)</td>
</tr>
<tr>
<td>Athens, Greece</td>
<td>2570</td>
<td>82 (3.2%)</td>
</tr>
<tr>
<td>Riga, Latvia</td>
<td>12 (6.5%)</td>
<td></td>
</tr>
<tr>
<td>Munich, Germany</td>
<td>61 (1.9%)</td>
<td></td>
</tr>
<tr>
<td>Nijmegen, CWZ, the Netherlands</td>
<td>12 (6.5%)</td>
<td></td>
</tr>
<tr>
<td>Ljubljana, Slovenia</td>
<td>61 (1.9%)</td>
<td></td>
</tr>
<tr>
<td>Liverpool, UK</td>
<td>76 (16.2%)</td>
<td></td>
</tr>
<tr>
<td>Newcastle, UK</td>
<td>41 (8.6%)</td>
<td></td>
</tr>
<tr>
<td>London, UK</td>
<td>184 (17.6%)</td>
<td></td>
</tr>
<tr>
<td>Santiago de Compostela, Spain</td>
<td>9 (3.2%)</td>
<td></td>
</tr>
<tr>
<td>Rotterdam, the Netherlands</td>
<td>369 (40.1%)</td>
<td></td>
</tr>
<tr>
<td>Nijmegen, UMC, the Netherlands</td>
<td>135 (42.1%)</td>
<td></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=21,267)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>General characteristics</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>Previous chronic condition</td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>3332 (19.4)</td>
</tr>
<tr>
<td>Complex</td>
<td>1138 (6.6)</td>
</tr>
<tr>
<td>Referred</td>
<td>9287 (53.9)</td>
</tr>
<tr>
<td>Triage urgency</td>
<td>9794 (56.9)</td>
</tr>
<tr>
<td>Fever kidstoool</td>
<td></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>6001 (34.9)</td>
</tr>
<tr>
<td>Tachycardia (APLS)</td>
<td>54.9</td>
</tr>
<tr>
<td>Hypoxia &lt;95%</td>
<td>762 (4.4)</td>
</tr>
<tr>
<td>Prolonged capillary refill (&gt;3 sec)</td>
<td>339 (1.9)</td>
</tr>
<tr>
<td>Work of breathing</td>
<td>913 (5.3)</td>
</tr>
<tr>
<td>Ill appearance</td>
<td>4742 (27.5)</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>Meningeal signs</td>
<td>126 (0.7)</td>
</tr>
<tr>
<td>Focal neurology</td>
<td>102 (0.6)</td>
</tr>
<tr>
<td>Status epilepticus</td>
<td>51 (0.3)</td>
</tr>
<tr>
<td>Rash: petechiae/non blanching</td>
<td>664 (3.9)</td>
</tr>
<tr>
<td>Blood cultures performed</td>
<td>3478 (20.2)</td>
</tr>
<tr>
<td>CSF performed</td>
<td>444 (2.6)</td>
</tr>
<tr>
<td>Admission to the ward &gt;24 hours</td>
<td>6590 (38.3)</td>
</tr>
<tr>
<td>Admission to the ICU</td>
<td>135 (0.8)</td>
</tr>
<tr>
<td>Antibiotic treatment following ED visit</td>
<td>6795 (39.5)</td>
</tr>
<tr>
<td>Lifesaving interventions: airway, breathing or hemodynamic support</td>
<td>371 (2.2)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>935 (5.4)</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

Identified pathogen stratified for complex chronic comorbidity

<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></td>
<td>9 (18%)</td>
</tr>
<tr>
<td>Candida species</td>
<td></td>
<td>4 (8%)</td>
</tr>
<tr>
<td>Viridans streptococci</td>
<td></td>
<td>4 (8%)</td>
</tr>
<tr>
<td>Klebsiella spp</td>
<td></td>
<td>3 (6%)</td>
</tr>
<tr>
<td>Enterococcus spp</td>
<td></td>
<td>3 (6%)</td>
</tr>
<tr>
<td>Moraxella spp</td>
<td></td>
<td>1 (2%)</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><strong>Feverkidstool</strong></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**                |              |
| Status epilepticus                     | No cases     |
| Reduced level of consciousness         | 4.70 (2.04-10.83)* |
| Focal neurology                        | 2.30 (0.54-9.71) |
| Meningeal signs                        | 9.20 (4.54-18.62)* |
| Abnormal neurology: decreased level of consciousness, presence of meningeal signs or focal neurology | 4.81 (2.61-8.91) |
| Non-blanching rash                     | 2.31 (1.21-4.41)* |

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

*Significant, p<0.05

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

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

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

Model specification of multivariate logistic model for IBI, model 2 with the addition of variable low/high IBI incidence ED

<table>
<thead>
<tr>
<th></th>
<th>Coefficients</th>
<th>OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Intercept)</td>
<td>-6.13</td>
<td>0.00</td>
</tr>
<tr>
<td>Male</td>
<td>-0.16</td>
<td>0.85</td>
</tr>
<tr>
<td>Age &lt; 1 year*</td>
<td>-2.22</td>
<td>0.11</td>
</tr>
<tr>
<td>Age ≥ 1 year*</td>
<td>0.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Temperature</td>
<td>-0.16</td>
<td>0.85</td>
</tr>
<tr>
<td>Fever duration in days</td>
<td>-0.15</td>
<td>0.86</td>
</tr>
<tr>
<td>Tachypnea</td>
<td>-0.47</td>
<td>0.62</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>0.66</td>
<td>1.94</td>
</tr>
<tr>
<td>Hypoxia</td>
<td>-0.81</td>
<td>0.44</td>
</tr>
<tr>
<td>Prolonged capillary refill</td>
<td>-0.31</td>
<td>0.74</td>
</tr>
<tr>
<td>Increased work of breathing</td>
<td>-0.47</td>
<td>0.62</td>
</tr>
<tr>
<td>Ill appearance</td>
<td>1.18</td>
<td>3.26</td>
</tr>
<tr>
<td>Ln CRP</td>
<td>0.75</td>
<td>2.11</td>
</tr>
<tr>
<td>Abnormal neurology</td>
<td>1.10</td>
<td>3.01</td>
</tr>
<tr>
<td>Non-blanching rash</td>
<td>1.06</td>
<td>2.89</td>
</tr>
<tr>
<td>Complex chronic condition</td>
<td>1.56</td>
<td>4.78</td>
</tr>
<tr>
<td>ED with high IBI incidence (&gt;2%)</td>
<td>1.98</td>
<td>7.26</td>
</tr>
</tbody>
</table>

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

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

![Calibration plot: apparent calibration for model 2 for IBI (addition of variable ED with low IBI incidence (<2%) / ED with high incidence (≥2%)](image-url)
Appendix 10: Performance of the prediction model (model 1)

Decision curve analysis

![Decision curve analysis graph]

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%)

![Post-test probability graph]
Appendix 11: Sensitivity analysis: model development on population with imputed CRP-level (n=37093)

Model specification of multivariate logistic model for IBI based 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 0.00</td>
</tr>
<tr>
<td>Male</td>
<td>-0.19 0.83</td>
</tr>
<tr>
<td>Age &lt; 1 year*</td>
<td>-2.58 0.08</td>
</tr>
<tr>
<td>Age &gt; 1 year*</td>
<td>0.00 1.00</td>
</tr>
<tr>
<td>Temperature</td>
<td>-0.05 0.95</td>
</tr>
<tr>
<td>Fever duration in days</td>
<td>-0.15 0.86</td>
</tr>
<tr>
<td>Tachypnea</td>
<td>-0.43 0.65</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>0.71 2.03</td>
</tr>
<tr>
<td>Hypoxia</td>
<td>-0.86 0.42</td>
</tr>
<tr>
<td>Prolonged capillary refill</td>
<td>0.02 1.02</td>
</tr>
<tr>
<td>Increased work of breathing</td>
<td>-0.34 0.71</td>
</tr>
<tr>
<td>Ill appearance</td>
<td>0.94 2.55</td>
</tr>
<tr>
<td>Ln CRP</td>
<td>0.78 2.17</td>
</tr>
<tr>
<td>Abnormal neurology</td>
<td>1.54 4.66</td>
</tr>
<tr>
<td>Non-blanching rash</td>
<td>1.40 4.04</td>
</tr>
<tr>
<td>Complex chronic condition</td>
<td>2.43 11.3</td>
</tr>
</tbody>
</table>

*The risk of children aged < 1 year was calculated: β(age <1 year)×age in years. The risk of children aged < 1 year was calculated: β(age <1 year)×age in years. The risk of children aged >1 years was calculated with: β(age <1 year)×1+β(age ≥1 year)×(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.
References


PARTNER: IMPERIAL COLLEGE (UK)
Chief investigator/PERFORM coordinator:

Michael Levin

Principal and co-investigators; work package leads (alphabetical order)

Aubrey Cunnington (grant application)
Tisham De (work package lead)
Jethro Herberg (Principle Investigator, Deputy Coordinator, grant application)
Myrsini Kaforou (grant application, work package lead)
Victoria Wright (grant application, Scientific Coordinator)

Research Group (alphabetical order)

Lucas Baumard; Evangelos Bellos; Giselle D’Souza; Rachel Galassini; Dominic Hapgood-Coote; Shea Hamilton; Clive Hoggart; Sara Hourmat; Heather Jackson; Ian Macnochie; Stephanie Menikou; Naomi Lin; Samuel Nichols; Ruud Nijman; Ivonne Pena Paz; Priyen Shah; Ching-Fen Shen; Ortensia Vito; Clare Wilson

Clinical recruitment at Imperial College Healthcare NHS Trust (alphabetical order))

Amina Abdulla; Ladan Ali; Sarah Darnell; Rikke Jorgensen; Sobia Mustafa; Salina Persand

Imperial College Faculty of Engineering

Molly Stevens (co-investigator), Eunjung Kim (research group); Benjamin Pierce (research group)
Clinical recruitment at Brighton and Sussex University Hospitals

Katy Fidler (Principle Investigator)
Julia Dudley (Clinical Research Registrar)
Research nurses: Vivien Richmond, Emma Tavliavini

Clinical recruitment at National Cheng Kung University Hospital

Ching-Fen Shen (Principal Investigator); Ching-Chuan Liu (Co-investigator); Shih-Min Wang (Co-investigator), funded by the Center of Clinical Medicine Research, National Cheng Kung University

SERGAS Partner (Spain)
Principal Investigators
Federico Martinón-Torres 1
Antonio Salas1,2

GENVIP RESEARCH GROUP (in alphabetical order):
Fernando Álvez González1, Cristina Balo Farto1, Ruth Barral-Arca1,2, María Barreiro Castro1, Xabier Bello1,2, Mirian Ben García1, Sandra Carnota1, Miriam Cebev-López1, María José Curras-Tualal1,2, Carlos Durán Suárez1, Luisa García Vicente1, Alberto Gómez-Carballal1,2, Jose Gómez Rial1, Pilar Leboráns Iglesias1, Federico Martinón-Torres1, Nazareth Martinón-Torres1, José María Martinón Sánchez1, Belén Mosquera Pérez1, Jacobo Pardo-Secol1,2, Lidia Piñeiro Rodríguez1, Sara Pischedda1,2, Sara Rey Vázquez1, Irene Rivero Calle1, Carmen Rodríguez-Tenreiro1, Lorenzo Redondo-Collazo1, Miguel Sadiki Ora1, Antonio Salas1,2, Sonia Serén Fernández1, Cristina Serén Trasorras1, Marisol Vilas Iglesias1.

1 Translational Pediatrics and Infectious Diseases, Pediatrics Department, Hospital Clínico Universitario de Santiago, Santiago de Compostela, Spain, and GENVIP Research Group (www.genvip.org), Instituto de Investigación Sanitaria de Santiago, Universidad de Santiago de Compostela, Galicia, Spain.
2 Unidade de Xenética, Departamento de Anatomía Patolóxica e Ciencias Forenses, Instituto de Ciencias Forenses, Facultade de Medicina, Universidade de Santiago de Compostela, and GenPop Research Group, Instituto de Investigaciones Sanitarias (IDIS), Hospital Clínico Universitario de Santiago, Galicia, Spain.
RSU Partner (Latvia)
Principal Investigator
Dace Zavadska

Other RSU group authors (in alphabetical order):

1 Riga Stradins university, Riga, Latvia.
2 Children clinical university hospital, Riga, Latvia.

Medical Research Council Unit The Gambia (MRCG) at LSHTM Partner
Principal Investigator
Effua Usuf

Additional Investigators
Kalifa Bojang
Syed M. A. Zaman
Fatou Secka
Suzanne Anderson
Anna Roca-Isatou Sarr
Momodou Saidykhan
Saffiatou Darboe
Samba Ceesay
Umberto D’alessandro

Medical Research Council Unit The Gambia at LSHTM
P O Box 273,
Version: 6.1 September 2020

Fajara, The Gambia

**ERASMUS MC-Sophia Children’s Hospital**  
**Principal Investigator**  
Henriëtte A. Moll¹

**Research group**  
Dorine M. Borensztajn¹, Nienke N. Hagedoorn, Chantal Tan¹,¹, Clementien L. Vermont², Joany Zachariasse¹

**Additional investigator**  
W Dik³

¹ Erasmus MC-Sophia Children’s Hospital, Department of General Paediatrics, Rotterdam, the Netherlands  
² Erasmus MC-Sophia Children’s Hospital, Department of Paediatric Infectious Diseases & Immunology, Rotterdam, the Netherlands  
³ Erasmus MC, Department of immunology, Rotterdam, the Netherlands

---

**Swiss Pediatric Sepsis Study**

**Principal Investigators:**

Philipp Agyeman, MD¹ (ORCID 0000-0002-8339-5444), Luregn J Schlapbach, MD, FCICM²,³ (ORCID 0000-0003-2281-2598)

**Clinical recruitment at University Children’s Hospital Bern for PERFORM:**

Christoph Aebi¹, Verena Wyss¹, Mariama Usman¹

**Principal and co-investigators for the Swiss Pediatric Sepsis Study:**

Philipp Agyeman, MD¹, Luregn J Schlapbach, MD, FCICM²,³, Eric Giannoni, MD⁴,⁵, Martin Stocker, MD⁶, Klara M Posfay-Barbe, MD⁷, Ulrich Heininger, MD⁸, Sara Bernhard-Stirnemann, MD⁹, Anita Niederer-Loher, MD¹⁰, Christian Kahlert, MD¹⁰, Giancarlo Natalucci, MD¹¹, Christa Relly, MD¹², Thomas Riedel, MD¹³, Christoph Aebi, MD¹, Christoph Berger, MD¹² **for the Swiss Pediatric Sepsis Study**

**Affiliations:**

¹ Department of Pediatrics, Inselspital, Bern University Hospital, University of Bern, Switzerland
Neonatal and Pediatric Intensive Care Unit, Children’s Research Center, University Children’s Hospital Zurich, University of Zurich, Zurich, Switzerland

Child Health Research Centre, University of Queensland, and Queensland Children’s Hospital, Brisbane, Australia

Clinic of Neonatology, Department Mother-Woman-Child, Lausanne University Hospital and University of Lausanne, Switzerland

Infectious Diseases Service, Department of Medicine, Lausanne University Hospital and University of Lausanne, Switzerland

Department of Pediatrics, Children’s Hospital Lucerne, Lucerne, Switzerland

Pediatric Infectious Diseases Unit, Children’s Hospital of Geneva, University Hospitals of Geneva, Geneva, Switzerland

Infectious Diseases and Vaccinology, University of Basel Children’s Hospital, Basel, Switzerland

Children’s Hospital Aarau, Aarau, Switzerland

Division of Infectious Diseases and Hospital Epidemiology, Children’s Hospital of Eastern Switzerland St. Gallen, St. Gallen, Switzerland

Department of Neonatology, University Hospital Zurich, Zurich, Switzerland

Division of Infectious Diseases and Hospital Epidemiology, and Children’s Research Center, University Children’s Hospital Zurich, Switzerland

Children’s Hospital Chur, Chur, Switzerland

Liverpool Partner

Principal Investigators

Enitan D Carrol1,2,3

Stéphane Paulus 1.

Research Group (in alphabetical order):

Elizabeth Cocklin1, Rebecca Jennings4, Joanne Johnston4, Simon Leigh1, Karen Newall4, Sam Romaine1
Version: 6.1 September 2020

1 Department of Clinical Infection, Microbiology and Immunology, University of Liverpool Institute of Infection and Global Health, Liverpool, England
2 Alder Hey Children’s Hospital, Department of Infectious Diseases, Eaton Road, Liverpool, L12 2AP
3 Liverpool Health Partners, 1st Floor, Liverpool Science Park, 131 Mount Pleasant, Liverpool, L3 5TF
4 Alder Hey Children’s Hospital, Clinical Research Business Unit, Eaton Road, Liverpool, L12 2AP

NKUA Partner (Greece)

Principal investigator: Professor Maria Tsolia (all activities)

Investigator/Research fellow: Irini Eleftheriou (all activities)

Additional investigators:

Recruitment: Maria Tambouratzi

Lab: Antonis Marmarinos (Quality Manager)

Lab: Marietta Xagorari

Kelly Syggelou

2nd Department of Pediatrics, National and Kapodistrian University of Athens,

“P. and A. Kyriakou” Children’s Hospital

Thivon and Levadias

Goudi, Athens

Micropathology Ltd:

Principal Investigator:

Professor Colin Fink, Clinical Microbiologist

Additional investigators

Dr Marie Voice, Post doc scientist
Dr. Leo Calvo-Bado¹, Post doc scientist

¹ Micropathology Ltd, The Venture Center, University of Warwick Science Park, Sir William Lyons Road, Coventry, CV4 7EZ.

Medical University of Graz, Austria (MUG)

Principal Investigator:

Werner Zenz¹ (all activities)

Co-investigators (in alphabetical order)

Benno Kohlmaier¹ (all activities)

Nina A. Schweintzger¹ (all activities)

Manfred G. Sagmeister¹ (study design, consortium wide sample management)

Research team

Daniela S. Kohlfürst¹ (study design)

Christoph Zurl¹ (BIVA PIC)

Alexander Binder¹ (grant application)

Recruitment team, data managers, (in alphabetical order):

Susanne Hösele¹, Manuel Leitner¹, Lena Pölz¹, Glorija Rajic¹,

Clinical recruitment partners (in alphabetical order):

Sebastian Bauchinger¹, Hinrich Baumgart⁴, Martin Benesch³, Astrid Ceolotto¹, Ernst Eber², Siegfried Gallistl¹, Gunther Gores⁵, Harald Haidl¹, Almuthe Hauer¹, Christa Hude³, Markus Keldorfer⁵, Larissa Krenn⁴, Heidemarie Pilch⁵, Andreas Pfleger², Klaus Pfurtscheller⁴, Gudrun
Nordberg⁵, Tobias Niedrist⁸, Siegfried Rödl⁶, Andrea Skrabl-Baumgartner¹, Matthias Sperl⁷, Laura Stampfer⁵, Volker Strenger³, Holger Till⁶, Andreas Trobisch⁵, Sabine Löffler⁵

Author Affiliations:

¹Department of Pediatrics and Adolescent Medicine, Division of General Pediatrics, Medical University of Graz, Graz, Austria

²Department of Pediatric Pulmonology, Medical University of Graz, Graz, Austria

³Department of Pediatric Hematooncoloy, Medical University of Graz, Graz, Austria

⁴Paediatric Intensive Care Unit, Medical University of Graz, Graz, Austria

⁵University Clinic of Paediatrics and Adolescent Medicine Graz, Medical University Graz, Graz,Austria

⁶Department of Paediatric and Adolescence Surgery, Medical University Graz, Graz, Austria

⁷Department of Pediatric Orthopedics, Medical University Graz, Graz, Austria

⁸Clinical Institute of Medical and Chemical Laboratory Diagnostics, Medical University Graz, Graz, Austria

London School of Hygiene and Tropical Medicine

WP 1 WP2, WP5

Principal Investigator:

Dr Shunmay Yeung¹,²,³ PhD, MBBS, FRCPC, MRCP, DTM&H

Research Group

Dr Juan Emmanuel Dewez¹ MD, DTM&H, MSc

Prof Martin Hibberd¹ BSc, PhD

Mr David Bath² MSc, MAppFin, BA(Hons)

Dr Alec Miners² BA(Hons), MSc, PhD

Dr Ruud Nijman³ PhD MSc MD MRCPC

Dr Catherine Wedderburn² BA, MBChB, DTM&H, MSc, MRCPC
Ms Anne Meierford\textsuperscript{1} MSc, BMedSc, BMBS

Dr Baptiste Leurent\textsuperscript{4}, PhD, MSc

1. Faculty of Infectious and Tropical Disease, London School of Hygiene and Tropical Medicine, London, UK
2. Faculty of Public Health and Policy, London School of Hygiene and Tropical Medicine, London, UK
3. Department of Paediatrics, St. Mary’s Hospital Imperial College Hospital, London, UK
4. Faculty of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, London, UK

Radboud University Medical Center (RUMC), The Netherlands

Principal Investigators:
Ronald de Groot\textsuperscript{1}, Michiel van der Flier\textsuperscript{1,2,3}, Marien I. de Jonge\textsuperscript{1}

Co-investigators Radboud University Medical Center (in alphabetical order):
Koen van Aerde\textsuperscript{1,2}, Wynand Alkema\textsuperscript{1}, Bryan van den Broek\textsuperscript{1}, Jolein Gloerich\textsuperscript{1}, Alain J. van Gool\textsuperscript{1}, Stefanie Henriet\textsuperscript{1,2}, Martijn Huijnen\textsuperscript{1}, Ria Philipsen\textsuperscript{1}, Esther Willems\textsuperscript{1}

Investigators PeDBiG PERFORM DUTCH CLINICAL NETWORK (in alphabetical order):
G.P.J.M. Gerrits\textsuperscript{8}, M. van Leur\textsuperscript{8}, J. Heidema\textsuperscript{4}, L. de Haan\textsuperscript{1,2}, C.J. Miedema\textsuperscript{5}, C. Neeleman\textsuperscript{1} C.C. Obihara\textsuperscript{6}, G.A. Tramper-Stranders\textsuperscript{7}

1. Radboud University Medical Center, Nijmegen, The Netherlands
2. Amalia Children’s Hospital, Nijmegen, The Netherlands
3. Wilhelmina Children’s Hospital, University Medical Center Utrecht, Utrecht, The Netherlands
4. St. Antonius Hospital, Nieuwegein, The Netherlands
5. Catharina Hospital, Eindhoven, The Netherlands
6. ETZ Elisabeth, Tilburg, The Netherlands
7. Franciscus Gasthuis, Rotterdam, The Netherlands
8. Canisius Wilhelmina Hospital, Nijmegen, The Netherlands

Oxford team (UK)
Version: 6.1 September 2020

Principal Investigators

Andrew J. Pollard\textsuperscript{1,2}, Rama Kandasamy\textsuperscript{1,2}, Stéphane Paulus \textsuperscript{1,2}

Additional Investigators

Michael J. Carter\textsuperscript{1,2}, Daniel O’Connor\textsuperscript{1,2}, Sagida Bibi\textsuperscript{1,2}, Dominic F. Kelly\textsuperscript{1,2}, Meeru Gurung\textsuperscript{3}, Stephen Thorson\textsuperscript{3}, Imran Ansari\textsuperscript{3}, David R. Murdoch\textsuperscript{4}, Shrijana Shrestha\textsuperscript{3}, Zoe Oliver\textsuperscript{5}

Author Affiliations:

\textsuperscript{1}Oxford Vaccine Group, Department of Paediatrics, University of Oxford, Oxford, United Kingdom.

\textsuperscript{2}NIHR Oxford Biomedical Research Centre, Oxford, United Kingdom.

\textsuperscript{3}Paediatric Research Unit, Patan Academy of Health Sciences, Kathmandu, Nepal.

\textsuperscript{4}Department of Pathology, University of Otago, Christchurch, New Zealand.

\textsuperscript{5}Department of Paediatrics, University of Oxford.

\textbf{Newcastle University, Newcastle upon Tyne, (UK)}

Principal Investigator:

Marieke Emonts \textsuperscript{1,2,3} (all activities)

Co-investigators

Emma Lim\textsuperscript{2,3,7} (all activities)

Lucille Valentine\textsuperscript{4}

Recruitment team (alphabetical), data-managers, and GNCH Research unit:
Karen Allen\textsuperscript{5}, Kathryn Bell\textsuperscript{5}, Adora Chan\textsuperscript{5}, Stephen Crulley\textsuperscript{5}, Kirsty Devine\textsuperscript{5}, Daniel Fabian\textsuperscript{5}, Sharon King\textsuperscript{5}, Paul McAlinden\textsuperscript{5}, Sam McDonald\textsuperscript{5}, Anne McDonnell\textsuperscript{2,5}, Ailsa Pickering\textsuperscript{2,5}, Evelyn Thomson\textsuperscript{5}, Amanda Wood\textsuperscript{5}, Diane Wallia\textsuperscript{5}, Phil Woodsford\textsuperscript{5},

Sample processing: Frances Baxter\textsuperscript{5}, Ashley Bell\textsuperscript{5}, Mathew Rhodes\textsuperscript{5}

PICU recruitment
Rachel Agbeko\textsuperscript{8}
Christine Mackerness\textsuperscript{8}

Students MOFICHE
Bryan Baas\textsuperscript{2}, Lieke Kloosterhuis\textsuperscript{2}, Wilma Oosthoek\textsuperscript{2}

Students/medical staff PERFORM
Tasnim Arif\textsuperscript{6}, Joshua Bennet\textsuperscript{2}, Kalvin Collings\textsuperscript{2}, Ilona van der Giessen\textsuperscript{2}, Alex Martin\textsuperscript{2}, Aqeela Rashid\textsuperscript{6}, Emily Rowlands\textsuperscript{2}, Gabriella de Vries\textsuperscript{2}, Fabian van der Velden\textsuperscript{2}

Engagement work/ethics/cost effectiveness
Lucille Valentine\textsuperscript{4}, Mike Martin\textsuperscript{9}, Ravi Mistry\textsuperscript{2}, Lucille Valentine\textsuperscript{4}

Author Affiliations:
\textsuperscript{1} Translational and Clinical Research Institute, Newcastle University, Newcastle upon Tyne UK
\textsuperscript{2} Great North Children’s Hospital, Paediatric Immunology, Infectious Diseases & Allergy, Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne, United Kingdom.
\textsuperscript{3} NIHR Newcastle Biomedical Research Centre based at Newcastle upon Tyne Hospitals NHS Trust and Newcastle University, Westgate Rd, Newcastle upon Tyne NE4 5PL, United Kingdom
\textsuperscript{4} Newcastle University Business School, Centre for Knowledge, Innovation, Technology and Enterprise (KITE), Newcastle upon Tyne, United Kingdom
\textsuperscript{5} Great North Children’s Hospital, Research Unit, Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne, United Kingdom.
\textsuperscript{6} Great North Children’s Hospital, Paediatric Oncology, Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne, United Kingdom.
1Population Health Sciences Institute, Newcastle University, Newcastle upon Tyne, UK

8Great North Children’s Hospital, Paediatric Intensive Care Unit, Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne, United Kingdom.

9Northumbria University, Newcastle upon Tyne, United Kingdom.

LMU Munich Partner (Germany)

Principal Investigator:

Ulrich von Both¹ 2 MD, FRCPCH (all activities)

Research group:

Laura Kolberg¹ MSc (all activities)

Manuela Zwerenz¹ MSc, Judith Buschbeck¹ PhD

Clinical recruitment partners (in alphabetical order):

Christoph Bidlingmaier³, Vera Binder⁴, Katharina Danhauser⁵, Nikolaus Haas¹⁰, Matthias Griese⁶, Tobias Feuchtinger⁴, Julia Keil⁹, Matthias Kappler⁶, Eberhard Lurz⁷, Georg Muench⁸, Karl Reiter⁹, Carola Schoen⁹

Author Affiliations:

¹Div. Paediatric Infectious Diseases, Hauner Children’s Hospital, University Hospital, Ludwig Maximilians University (LMU), Munich, Germany

²German Center for Infection Research (DZIF), Partner Site Munich, Munich, Germany

³Div. of General Paediatrics, ⁴Div. Paediatric Haematology & Oncology, ⁵Div. of Paediatric Rheumatology, ⁶Div. of Paediatric Pulmonology, ⁷Div. of Paediatric Gastroenterology, ⁸Neonatal Intensive Care Unit, ⁹Paediatric Intensive Care Unit Hauner Children’s Hospital, University
Version: 6.1 September 2020

Hospital, Ludwig Maximilians University (LMU), Munich, Germany, 10Department Pediatric Cardiology and Pediatric Intensive Care, University Hospital, Ludwig Maximilians University (LMU), Munich, Germany

bioMérieux, France

Principal Investigator:
François Mallet1,2, 3

Research Group:
Karen Brengel-Pesce1,2, 3
Alexandre Pachot1
Marine Mommert1,2

1Open Innovation & Partnerships (OIP), bioMérieux S.A., Marcy l’Etoile, France
2Joint research unit Hospice Civils de Lyon - bioMérieux, Centre Hospitalier Lyon Sud, 165 Chemin du Grand Revoyet, 69310 Pierre-Bénite, France
3EA 7426 Pathophysiology of Injury-induced Immunosuppression, University of Lyon1-Hospices Civils de Lyon-bioMérieux, Hôpital Edouard Herriot, 5 Place d’Arsonval, 69437 Lyon Cedex 3, France

Department of Infectious Diseases, University Medical Centre Ljubljana, Slovenia

Principal Investigator:
Marko Pokorn1,2, 3 MD, PhD

Research Group:
Mojca Kolnik1 MD, Katarina Vincek1 MD, Tina Plankar Srovin1 MD, PhD, Natalija Bahovec1 MD, Petra Prunk1 MD, Veronika Osterman1 MD, Tanja Avramoska1 MD

Affiliations:
1Department of Infectious Diseases, University Medical Centre Ljubljana, Japljeva 2, SI-1525 Ljubljana, Slovenia
2University Childrens’ Hospital, University Medical Centre Ljubljana, Ljubljana, Slovenia
3Department of Infectious Diseases and Epidemiology, Faculty of Medicine, University of Ljubljana, Slovenia
Amsterdam, Academic Medical Hospital & Sanquin Research Institute (NL)

Principal Investigator:
Taco Kuijpers 1,2

Co-investigators
Ilse Jongerius 2

Recruitment team (EUCLIDS, PERFORM):
J.M. van den Berg1, D. Schonenberg1, A.M. Barendregt1, D. Pajkrt1, M. van der Kuip1,3, A.M. van Furth1,3

Students PERFORM
Evelien Sprenkeler 2, Judith Zandstra 2,

Technical support PERFORM
G. van Mierlo 2, J. Geissler 2

Author Affiliations:

1 Amsterdam University Medical Center (Amsterdam UMC), location Academic Medical Center (AMC), Dept of Pediatric Immunology, Rheumatology and Infectious Diseases, University of Amsterdam, Amsterdam, the Netherlands

2 Sanquin Research Institute, & Landsteiner Laboratory at the AMC, University of Amsterdam, Amsterdam, the Netherlands.

3 Amsterdam University Medical Center (Amsterdam UMC), location Vrije Universiteit Medical Center (VUMC), Dept of Pediatric Infectious Diseases and Immunology, Free University (VU), Amsterdam, the Netherlands (former affiliation)