Shock Index in the early assessment of febrile children at the emergency

Nienke N Hagedoorn,1 Joany M Zachariasse,2 Dorine Borensztajn,3 Elise Adriaansens,4 Ulrich von Both,4,5 Enitan D Carroll,6,7 Irini Eleftheriou,8 Marieke Emonts,9,10 Michiel van der Flier,11,12 Ronald de Groot,11,12 Jethro Adam Herberg,13 Benno Kohlmaier,14 Emma Lim,9,10 Ian Maconochie,15 Federico Martinón-Torres,16 Ruud Gerard Nijman,13 Marko Pokorn,17 Irene Rivero-Calle,18 Maria Tsolia,8 Dace Zavadskas,18 Werner Zenz,19 Michael Levin,13 Clementien Vermont,19 Henriette A Moll3 On behalf of the PERFORM consortium

ABSTRACT

Objective (1) To derive reference values for the Shock Index (heart rate/systolic blood pressure) based on a large emergency department (ED) population of febrile children and (2) to determine the diagnostic value of the Shock Index for serious illness in febrile children.


Patients Febrile children with measured blood pressure.

Main outcome measures Serious bacterial infection (SBI), invasive bacterial infection (IBI), immediate life-saving interventions (ILSIs) and intensive care unit (ICU) admission. The association between high Shock Index (>95th centile) and each outcome was determined by logistic regression adjusted for age, sex, referral, comorbidity and temperature. Additionally, we calculated sensitivity, specificity and negative/positive likelihood ratios (LRs).

Results Of 5622 children, 461 (8.2%) had SBI, 46 (0.8%) had IBI, 203 (3.6%) were treated with ILSI and 69 (1.2%) were ICU admitted. High Shock Index was associated with SBI (adjusted OR (aOR) 1.6 (95% CI 1.3 to 1.9)), ILSI (aOR 2.5 (95% CI 2.0 to 2.9)), ICU admission (aOR 2.2 (95% CI 1.4 to 2.9)) but not with IBI (aOR 1.5 (95% CI 0.6 to 2.4)). For the different outcomes, sensitivity for high Shock Index ranged from 0.10 to 0.15, specificity ranged from 0.95 to 0.95, negative LRs ranged from 0.90 to 0.95 and positive LRs ranged from 1.8 to 2.8.

Conclusions High Shock Index is associated with serious illness in febrile children. However, its rule-out value is insufficient which suggests that the Shock Index is not valuable as a screening tool for all febrile children at the ED.

BACKGROUND

Early recognition of serious illness is of critical importance in febrile children who attend the emergency department (ED). Correct identification enables timely treatment of children with serious bacterial infections (SBIs) and children in need of intensive care unit (ICU) admission which improves patient outcomes.1–4 A recent review has studied the Shock Index, heart rate divided by systolic blood pressure (BP), as haemodynamic marker to predict disease severity in children and adults at the ED.5 Shock Index in adults has been studied in specific disease groups including trauma and myocardial infarction, and in a large general ED study in which high Shock Index >1.3 at triage has been associated with hospital admission and in-hospital mortality.6 In paediatrics, evidence of the Shock Index is limited to children with trauma,7–10 children with septic shock11–13 and a single-centre general ED population.14 To our knowledge, the Shock Index as a potential non-invasive measure in the early assessment for recognition of serious illness, including need for immediate life-saving interventions (ILSIs) and SBI, has not yet been evaluated. In addition, the association of the Shock Index with ICU admission in febrile children in a multicentre cohort is still unknown.

Like other vital signs, the normal ranges of the Shock Index are age dependent. Population-based centiles for Shock Index have been published for healthy children >8 years.15 Since fever increases...
heart rate values, reference values based on healthy children may not be generalisable to acutely ill children with fever attending the ED. In order to facilitate interpretation for clinical practice, clinical cut-off values are needed to classify children with high Shock Index.

We aimed (1) to derive reference values for the Shock Index based on this large ED population and (2) to determine the diagnostic value of the Shock Index for serious illness in febrile children attending European EDs.

**METHODS**

**Study design**

This is a secondary analysis of the MOFICHE Study (Management and Outcome of Febrile children in Europe), embedded in the PERFORM Project (Personalized Risk assessment in Febrile illness to Optimize Real-life Management across the European Union). The MOFICHE Study is an observational multicentre study assessing the management and outcome of febrile children in Europe using routine data. Details of the study design are described previously.19

In short, children from 0 to 18 years presenting with fever (temperature ≥38.0°C) or with fever <72 hours before ED visit were included. Twelve EDs from eight European countries participated as part of the PERFORM Project: Austria, Germany, Greece, Latvia, the Netherlands (n=3), Spain, Slovenia and the UK (n=3). The participating hospitals were either university (n=9) or large teaching hospitals (n=3), and all were partners of the PERFORM consortium. Data were collected from January 2017 until April 2018 for at least 1 year. For the current study, we selected patients with routine BP measurement at the ED. For one ED (London, UK), BP measurements were not available and all visits from this ED were excluded.

Data collected were part of routine care and included sex, mode of referral (self-referral, general practitioner, private paediatrician, emergency medical services or other), comorbidity (chronic condition expected to last ≥1 year),20 alarming signs from the National Institute for Health and Care Excellence guideline on fever including consciousness (alert, voice, pain, unresponsive) and ill appearance as assessed by the physician, and vital signs: first measurement of temperature, heart rate, non-invasive systolic BP, capillary refill time. Heart rate was measured by pulse oximeters and systolic BP using oscillometric devices. In addition, we collected diagnostics (C reactive protein value (CRP) and blood cultures, cerebral spinal fluid cultures and other cultures) collected at the ED or first day of hospital admission. Further, we collected treatment with ILSI at the ED, defined as airway and breathing support (non-rebreathing mask, non-invasive ventilation, intubation), emergency procedures (chest needle decompression, pericardiotenises or open thoracotomy), haemodynamic support (fluid bolus (>10 mL/kg) or blood administration) or emergency medication (naloxone, dextrose, atropine, adenosine, epinephrine or vasopressors).21 In addition, we collected data of prescribed antibiotics and general ward admission >24 hours, or ICU admission following ED visit.

To classify cause of infection in routine ED practice, we used a consensus-based flow chart combining all clinical data and diagnostic results. We used this flow chart to define the presumed cause of infection for each patient (online supplemental appendix 1). The diagnosis ‘definite bacterial’ infection was assigned when pathogenic bacteria were identified by sterile site culture or PCR. Patients were defined as ‘probable bacterial’ when a bacterial syndrome was suspected, but no bacteria were identified and CRP level was above 60 mg/L.21

**Outcome measures**

Serious illness was defined using four different outcomes: SBI, invasive bacterial infection (IBI), ILSI and all visits requiring ICU admission. Definition of SBI was decided on in a consensus meeting of experts in paediatrics and paediatric infectious disease specialists (PERFORM partners). SBI was defined as patients with ‘definite bacterial’ or ‘probable bacterial’ with focus on infection from the gastrointestinal tract, lower respiratory tract, urinary tract, bone and joints, central nervous system or sepsis.24 25 IBI, a subset of SBI, was defined as positive bacterial culture or PCR detection of a single pathogenic bacterium in blood, cerebrospinal fluid or synovial fluid. All cultures that were treated as contaminant and cultures growing contaminants were considered non-IBI.26 In addition, cultures growing a single contaminant or candida were defined positive in patients with malignancy, immunodeficiency, immunosuppressive drugs or a central catheter, since antimicrobial treatment is recommended in these patient groups.27

**Data analysis**

We described the study population, and compared patients with and without BP measurement and focused the analysis on patients with BP measurement.

**Part 1: Shock Index reference values**

For the analysis on reference values, we excluded patients with immediate triage urgency as these patients are vitally compromised, and excluded children with missing heart rate values. First, we visualised heart rate and systolic BP by age using scatterplots. Second, we assessed the relation between heart rate and systolic BP using standardised z-scores calculated separately for different age groups: patients >1 year were grouped in 1-year age groups and patients <1 year were grouped in <3 months, 3–6 months and 6 months–1 year. Next, we calculated the Shock Index by dividing heart rate by systolic BP and calculated 95th centile Shock Index values in the different age groups.

**Part 2: diagnostic value of Shock Index for serious illness**

We evaluated the diagnostic value of the Shock Index using the following analyses: (1) the additional value of the Shock Index over systolic BP alone, (2) diagnostic performance of Shock Index above the 95th centile for each of the outcomes, and (3) stratified for age, we explored age-appropriate cut-off values of Shock Index for the different outcomes.

First, we assessed the additional value of the Shock Index to systolic BP by comparing a model with solely systolic BP to a model with both Shock Index and systolic BP (likelihood ratio test). Second, we used univariable logistic regression analysis to assess the association of Shock Index above the 95th centile with each of the outcomes. In multivariable analyses, we adjusted for age, sex, referral (referred vs self-referred), comorbidity and temperature. A previous study recommends to adjust for age besides the use of age-adjusted vital signs.28 Next, we calculated the diagnostic performance of Shock Index above the 95th centile for each of the outcomes using sensitivity, specificity, and negative and positive likelihood ratios (LRs). Negative LR <0.2 or positive LR >5 was defined as relevant.29 Furthermore, we described the ‘number needed to detect a disease’ which reflects the number needed to be examined in order to accurately detect on a person with the disease.30 Next, the discriminative ability of the Shock Index as continuous predictor for the outcomes was presented by area under the curve of receiver operating characteristics (AUROC) in different age groups. We

---

used the following age groups to ensure sufficient numbers of the different outcomes for analysis: <1 year, 1–5 years, 5–10 years and >10 years. We explored age-appropriate cut-off values of the Shock Index for the different outcomes with a high sensitivity. We determined the optimal cut-off as a sensitivity of at least 90% with maximum specificity.

**Missing values**

Patients with missing data for the outcomes (cause of infection, focus of infection, ICU admission) were excluded from analysis (n=26). Missing values for referral, comorbidity, temperature, heart rate, capillary refill time and consciousness were multiple imputed including all available information of the patients using the mice package which resulted in 20 imputation sets (details in online supplemental appendix 2). In a sensitivity analysis, using a different approach to deal with missing BP data, we selected all EDs with >20% BP measurements and imputed missing BP values. In this subset, we repeated all analyses from part 2. All data analyses were performed in R V.3.6.

**RESULTS**

**Study population**

Of 32,766 eligible patients, we included 5622 patients with BP measurement and complete outcome (2548 female (45.3%), median age 4.2 years (IQR 1.8–8.4)) (figure 1). Of those, 1338 (23.8%) patients had comorbidity and 2354 patients (41.9%) were referred to the ED. Regarding the outcomes, 461 patients with tachycardia or hypotension more often had Shock Index values above the 95th centile (293 of 1765, 16.6%) than children without tachycardia or hypotension (14 of 3744, 0.4%).

**Part 1: Shock Index reference values**

In our cohort of febrile children, systolic BP values increased with age, whereas heart rate and Shock Index values decreased with age (figure 2A–D, online supplemental appendix 5). The 95th centile for Shock Index was 2.61 for children <3 months and decreased to 1.21 for children aged 17–18 years. Overall, Shock Index values were higher in children with tachycardia or hypotension than in children without tachycardia or hypotension (p<0.001). Children with tachycardia or hypotension more often had Shock Index values above the 95th centile (293 of 1765, 16.6%) than children without tachycardia or hypotension (14 of 3744, 0.4%).

**Part 2: diagnostic value of Shock Index for serious illness**

Overall, 5.5% (310 of 5622) of patients had Shock Index values >95th centile. In patients with SBI, IBI, ILSI or ICU admission, high Shock Index >95th centile occurred in 9.5% (44 of 461), 13.0% (6 of 46), 14.3% (29 of 203) and 11.6% (8 of 69), respectively (table 1).

Addition of Shock Index to the model with only systolic BP led to a significant improved model for each of the outcomes (p<0.05). As a sole predictor, the 95th centile cut-off of Shock Index was associated with SBI (OR 1.9 (95% CI 1.6 to 2.3)), IBI (OR 2.6 (95% CI 1.7 to 3.4)), ILSI (OR 3.1 (95% CI 2.7 to 3.5)) and ICU admission (OR 2.6 (95% CI 1.9 to 3.3)). For SBI, patients with ILSI, 30 (17.8%) were admitted to the ICU. Patients with BP measurement had more often one of the outcomes of serious illness than patients without BP measurement (details in online supplemental appendix 4).
ILSI and ICU paediatric life support; ED, emergency department; IBI, invasive bacterial infection; ICU, intensive care unit; ILSI, immediate life-saving intervention; SBI, serious bacterial infection.

In adults, Shock Index values of >0.9 are related to hospital admission and mortality.\(^5\,6\) In children, reference values and accurate cut-off values for Shock Index are yet unclear. Rappaport et al.\(^6\) have provided reference values of the Shock Index for healthy subjects aged >8 years based on auscultatory BP measurements. Gupta and Alam\(^6\) reported Shock Index values in a small study of children with sepsis for the outcome mortality. In this study, we provide reference values of the Shock Index for febrile children attending EDs. These values could be used as a

**DISCUSSION**

In this large European multicentre study, we provided reference values for Shock Index in febrile children attending the ED. In addition, we evaluated the diagnostic value of Shock Index for serious illness defined as SBI, IBI, ILSI and ICU admission. High Shock Index showed an association with serious illness, but its rule-out value was poor.

Tachycardia and delayed capillary refill are early haemodynamic markers of shock, while hypotension is considered a late sign. The Shock Index combines the properties of heart rate and systolic BP and could potentially improve identification of acutely ill children at the ED. Previous studies in paediatrics have been studying the role of Shock Index in trauma, septic shock, and hospital and ICU admission.\(^5\,7\,8\,10–14\,32\,33\) In our previous single-centre study, we found an association of high Shock Index for hospital and ICU admission in children with different presentations at the ED.\(^14\) Although this previous study included both febrile and non-febrile children, our study confirms an association of high Shock Index with SBI, ILSI and ICU admission in febrile children.

Table 1  Clinical characteristics of the study population and for the different outcomes

<table>
<thead>
<tr>
<th>Study population, n=5622</th>
<th>Missing SBI, n=461</th>
<th>IBI, n=46</th>
<th>ILSI, n=203</th>
<th>ICU admission, n=69</th>
</tr>
</thead>
<tbody>
<tr>
<td>General characteristics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age in years, median (IQR)</td>
<td>4.2 (1.8–8.5)</td>
<td>5.3 (1.8–12.0)</td>
<td>4.8 (1.3–9.1)</td>
<td>4.1 (1.5–9.2)</td>
</tr>
<tr>
<td>Female</td>
<td>2548 (45.3)</td>
<td>228 (49.5)</td>
<td>21 (45.7)</td>
<td>89 (43.8)</td>
</tr>
<tr>
<td>Comorbidity</td>
<td>1338 (23.8)</td>
<td>91 (167.32)</td>
<td>29 (63.0)</td>
<td>92 (45.3)</td>
</tr>
<tr>
<td>Complex comorbidity</td>
<td>530 (9.4)</td>
<td>85 (18.4)</td>
<td>21 (45.7)</td>
<td>53 (26.1)</td>
</tr>
<tr>
<td>Referred</td>
<td>2354 (41.9)</td>
<td>110 (293.63)</td>
<td>35 (76.1)</td>
<td>152 (74.9)</td>
</tr>
<tr>
<td>Triage urgency</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low: standard, non-urgent</td>
<td>1746 (31.1)</td>
<td>184 (39.9)</td>
<td>6 (13.0)</td>
<td>23 (11.3)</td>
</tr>
<tr>
<td>High: immediate, very urgent, intermediate</td>
<td>3612 (64.2)</td>
<td>224 (48.6)</td>
<td>37 (80.4)</td>
<td>159 (78.3)</td>
</tr>
<tr>
<td>Clinical symptoms</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fever duration in days, median (IQR)</td>
<td>1.5 (0.5–3)</td>
<td>1.5 (0.5–3)</td>
<td>0.5 (0.5–3)</td>
<td>0.5 (0.5–1.5)</td>
</tr>
<tr>
<td>Ill appearance</td>
<td>868 (15.4)</td>
<td>620 (173.75)</td>
<td>22 (47.8)</td>
<td>106 (52.2)</td>
</tr>
<tr>
<td>Decreased consciousness</td>
<td>82 (1.5)</td>
<td>90 (10.2)</td>
<td>5 (10.9)</td>
<td>42 (20.7)</td>
</tr>
<tr>
<td>Vital signs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Temperature in °C, median (IQR)</td>
<td>37.6 (36.8–38.4)</td>
<td>37.9 (37.1–38.7)</td>
<td>38.4 (37.7–39.2)</td>
<td>38.2 (37.3–39)</td>
</tr>
<tr>
<td>Temperature in °C, median (IQR)</td>
<td>37.6 (36.8–38.4)</td>
<td>37.9 (37.1–38.7)</td>
<td>38.4 (37.7–39.2)</td>
<td>38.2 (37.3–39)</td>
</tr>
<tr>
<td>Temperature in °C, median (IQR)</td>
<td>37.6 (36.8–38.4)</td>
<td>37.9 (37.1–38.7)</td>
<td>38.4 (37.7–39.2)</td>
<td>38.2 (37.3–39)</td>
</tr>
<tr>
<td>Temperature in °C, median (IQR)</td>
<td>37.6 (36.8–38.4)</td>
<td>37.9 (37.1–38.7)</td>
<td>38.4 (37.7–39.2)</td>
<td>38.2 (37.3–39)</td>
</tr>
<tr>
<td>Temperature in °C, median (IQR)</td>
<td>37.6 (36.8–38.4)</td>
<td>37.9 (37.1–38.7)</td>
<td>38.4 (37.7–39.2)</td>
<td>38.2 (37.3–39)</td>
</tr>
<tr>
<td>Prolonged capillary refill (&gt;3 s)</td>
<td>105 (1.9)</td>
<td>866 (24.5)</td>
<td>3 (6.5)</td>
<td>39 (19.2)</td>
</tr>
<tr>
<td>Tachycardia (APLS)</td>
<td>1667 (29.7)</td>
<td>55 (199.43)</td>
<td>27 (58.7)</td>
<td>113 (55.7)</td>
</tr>
<tr>
<td>Hypotension (APLS)</td>
<td>209 (3.7)</td>
<td>38 (8.2)</td>
<td>3 (6.5)</td>
<td>22 (10.8)</td>
</tr>
<tr>
<td>Shock Index, median (IQR)</td>
<td>1.2 (1.0–1.4)</td>
<td>55 (1.2–1.0–1.5)</td>
<td>1.3 (1.9–1.6)</td>
<td>1.3 (1.1–1.6)</td>
</tr>
<tr>
<td>Shock Index, &gt;95th centile for age</td>
<td>310 (5.5)</td>
<td>55 (44.9)</td>
<td>6 (13.0)</td>
<td>29 (14.3)</td>
</tr>
<tr>
<td>Diagnostics and treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C reactive protein in mg/L, median (IQR)</td>
<td>20 (5–61)</td>
<td>3378 (91–154)</td>
<td>58 (17–147)</td>
<td>20 (5–75)</td>
</tr>
<tr>
<td>Blood cultures performed</td>
<td>967 (17.2)</td>
<td>243 (52.7)</td>
<td>46 (100)</td>
<td>118 (58.1)</td>
</tr>
<tr>
<td>Cerebrospinal fluid performed</td>
<td>140 (2.5)</td>
<td>34 (7.4)</td>
<td>8 (17.4)</td>
<td>28 (13.8)</td>
</tr>
<tr>
<td>Admission to the ward &gt;24 hours</td>
<td>1159 (20.6)</td>
<td>137 (281.61)</td>
<td>34 (73.9)</td>
<td>109 (53.7)</td>
</tr>
<tr>
<td>Admission to the ICU</td>
<td>69 (1.2)</td>
<td>19 (4.1)</td>
<td>7 (15.2)</td>
<td>43 (21.2)</td>
</tr>
<tr>
<td>Antibiotic treatment following ED visit</td>
<td>1983 (35.3)</td>
<td>55 (407.88)</td>
<td>44 (95.7)</td>
<td>151 (74.4)</td>
</tr>
</tbody>
</table>

APLS, advanced paediatric life support; ED, emergency department; IBI, invasive bacterial infection; ILSI, immediate life-saving intervention; SBI, serious bacterial infection.
reference value for clinical practice or further studies, although generalisability of these values to all febrile children or other populations may be limited.

In our sample of patients with measured BP, Shock Index values above the 95th centile cut-off value were associated with SBI, ILSI and ICU admission adjusted for age, sex, referral, comorbidity and temperature. In this multivariate analysis, Shock Index 95th centile was not significantly associated with IBI although the trend was similar. High Shock Index had high specificity and moderate positive LRs, but had poor rule-out value with low sensitivity and poor negative LRs. Its poor rule-out value makes the Shock Index not a valuable screening tool at the ED. Although we identified age-specific cut-off values with high sensitivity, none had adequate specificity and therefore leading to high number of false positives. Although this was not the focus of our study, the Shock Index may have additional value in specific high-risk patients or as repeated measurement for monitoring disease course or treatment effect.

Physiologically based scores have been developed for the early recognition of disease severity in children including scores as quick Sequential Organ Failure Assessment (qSOFA), quick Paediatric Logistic Organ Dysfunction-2 (qPELOD-2) and Liverpool qSOFA (LqSOFA).34–37 In previous ED studies, these scores showed high specificity but low sensitivity for serious illness.36 37 LqSOFA is based on heart rate and capillary refill time as haemodynamic parameters, whereas qSOFA and qPELOD-2 both require BP measurement. Since heart rate and capillary refill time are easy to assess in children, LqSOFA could be more easily implemented than scores that need BP measurement. The low sensitivity of these scores, however, makes them of limited clinical value for routine use at the ED.

Systolic BP measurement is also required for the Shock Index. The National Institute for Health and Care Excellence does not advise routine BP measurement in febrile children attending the ED,21 but recommends BP measurement in children with abnormal heart rate or prolonged capillary refill. In our cohort, BP measurement was performed in 1799 of 7804 (23%) of children with abnormal heart rate or capillary refill. This poor adherence to recommendations agrees with findings of moderate adherence to other vital sign measurements in febrile children in different European EDs.38

Strengths of this study include the participation of different EDs in Europe, the detailed data collection and the evaluation of the Shock Index for different definitions of serious illness:

![Figure 2](A) Scatterplots of heart rate for age; (B) systolic blood pressure (BP) for age; (C) step chart of reference values of Shock Index (mean and 95th centile); (D) scatterplot of age-adjusted z-scores of systolic BP for age-adjusted z-scores of heart rate.

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Diagnostic value of high Shock Index &gt;95th centile for serious illness, n=5622</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBI, n=461</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>1.9 (1.6 to 2.3)</td>
<td>1.6 (1.3 to 1.9)</td>
</tr>
<tr>
<td>IBI, n=46</td>
<td>2.6 (1.7 to 3.4)</td>
</tr>
<tr>
<td>ILSI, n=203</td>
<td>3.1 (2.7 to 3.5)</td>
</tr>
<tr>
<td>ICU admission, n=69</td>
<td>2.6 (1.9 to 3.3)</td>
</tr>
</tbody>
</table>

*Adjusted for age, sex, referral, comorbidity and temperature.
aOR, adjusted OR; IBI, invasive bacterial infection; ICU, intensive care unit; ILSI, immediate life-saving intervention; LR, likelihood ratio; SBI, serious bacterial infection.
SBI, IBI, ILSI and ICU admittance, and adjustment for age, sex, referral, comorbidity and temperature. Our study has limitations. First, the selection of patients with BP measurement could have led to selection bias. Due to the limited number of BP measurements in our cohort, multiple imputation of systolic BP in all patients was not possible. In a sensitivity analysis, we imputed systolic BP in all visits of febrile children at the five EDs with >20%BP measurement and found similar results. This suggests that the selection of patients with BP measurement did not influence our results. The low proportion of BP measurement in our study reflects clinical practice where guidelines do not advise routine BP measurement in febrile children.21 38 Patients with BP measurement, however, likely reflect the group in which the Shock Index would potentially be used in clinical practice.

Second, we focused our analysis on high Shock Index since in febrile children we expect the combination of tachycardia and hypotension to be valuable. However, we recognise that hypotension without compensatory high heart rate is a relevant sign of shock which could result in normal Shock Index values. Lastly, the presence of hypotension or tachycardia may have influenced decisions to initiate treatment with ILSI or paediatric ICU admission. We acknowledge that Shock Index might not be a complete independent variable for these outcomes.

Conclusions

In this large observational study of 11 European EDs, we provide reference values for Shock Index for febrile children at the ED. High Shock Index was associated with serious illness like SBI, IBI, ILSI and ICU admission. For serious illness, the rule-out value of high Shock Index was not sufficient. Our results suggest that the Shock Index is not valuable as a routine screening tool in the early assessment of febrile children at the ED.

Table 3  Discriminative value of Shock Index (continuous) for serious illness, stratified for age n=5622

<table>
<thead>
<tr>
<th>Shock Index (continuous) stratified for age</th>
<th>SBI</th>
<th>IBI</th>
<th>ILSI</th>
<th>ICU admission</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC (95% CI) AUC (95% CI) AUC (95% CI) AUC (95% CI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1 year, n=801</td>
<td>0.66 (0.60 to 0.72)</td>
<td>0.71 (0.56 to 0.85)</td>
<td>0.70 (0.60 to 0.80)</td>
<td>0.73 (0.59 to 0.87)</td>
</tr>
<tr>
<td>1–5 years, n=2395</td>
<td>0.54 (0.49 to 0.59)</td>
<td>0.56 (0.42 to 0.70)</td>
<td>0.57 (0.51 to 0.64)</td>
<td>0.58 (0.47 to 0.68)</td>
</tr>
<tr>
<td>5–10 years, n=1330</td>
<td>0.56 (0.50 to 0.62)</td>
<td>0.68 (0.50 to 0.86)</td>
<td>0.61 (0.52 to 0.69)</td>
<td>0.52 (0.36 to 0.69)</td>
</tr>
<tr>
<td>&gt;10 years, n=1096</td>
<td>0.55 (0.50 to 0.60)</td>
<td>0.74 (0.63 to 0.85)</td>
<td>0.71 (0.64 to 0.79)</td>
<td>0.72 (0.45 to 0.98)</td>
</tr>
</tbody>
</table>

AUC, area under the curve; IBI, invasive bacterial infection; ICU, intensive care unit; ILSI, immediate life-saving intervention; SBI, serious bacterial infection.

Acknowledgements  Members of PERFORM consortium are listed in online supplemental appendix B.


Funding  This work was supported by the European Union’s Horizon 2020 research and innovation programme (grant agreement no. 668303), by the National Institute for Health Research (NIHR) Biomedical Research Centres at Imperial College London, Newcastle Hospitals NHS Foundation Trust and Newcastle University, and by NIHR Academic Clinical Fellowship award (ACL-2018-21-00 to RN).

Disclaimer  The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health.

Competing interests  None declared.

Patient consent for publication  Not required.

Ethics approval  The study was approved by all the participating hospitals. No informed consent was needed for this study. Austria (Ethikkommission Medizinische Universität Graz, ID: 28-518 ex 15/16); Germany (Ethikkommission Bei Der LMU München, ID: 699-16); Greece (ethics committee, ID: 9683/2015.07.2016); Latvia (Centrālā medicīnas etikas komiteja, ID: 14.07.2016, No. II 16-07-14); Slovenia (Public of Slovenia National Medical Ethics Committee, ID: 0120-483(2016-3); Spain (Comité Autonómico de Ética de la Investigación de Galicia, ID: 2016/331)); the Netherlands (Commissie Mensegrenden onderzoek, ID: NLSB103.091.16); the UK (ethics committee, ID: 16L01684, IRAS application no. 209035, confidentiality advisory group reference: 16/CAG/0136). In the UK, an ‘opt-out’ procedure was used for this study.

Provenance and peer review  Not commissioned; externally peer reviewed.

Data availability statement  Data are available in a public, open access repository. A data set containing individual participant data will be made available in a public data repository containing a specific DOI. The data will be anonymised and will not contain any identifiable data. The data manager of the PERFORM consortium can be contacted for inquiries (fishtas.de@imperial.ac.uk).

Supplemental material  This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability
REFERENCES

18. PERFORM consortium. Personalised risk assessment in febrile illness to optimise real-life management (PERFORM); 2019.
Appendix 1: Flowchart to classify presumed cause of infection

Presumed cause of infection: categorisation based on clinical data

**Presumed bacterial**
- Sterile-site pathogenic bacteria, match syndrome
- No CRP = No
- CRP > 50 mg/L = Definite Bacterial
- CRP < 50 mg/L = Probable Bacterial

**Presumed viral**
- Unknown bacterial / viral
- CRP > 50 mg/L = No
- CRP < 50 mg/L = Probable Viral
- Virus identified that matches syndrome
- Virus identified but no virus identified
- Mix: Illness or insufficient clinical information
- Other infection
- Unclear features: Infection or inflammatory
- Other

**Unknown bacterial / viral**
- Bacterial syndrome: but no bacteria identified
- Unclear features: OR microbiology does not fit syndrome
- Other

CRP, c-reactive protein; LRTI, lower respiratory tract infection; URTI, upper respiratory tract infection.
*Patients could have identified viral co-infection. (1)*

References
Appendix 2. Additional methods: multiple imputation

Missing data

For the main analysis, we excluded patients without systolic blood pressure (BP) measurement. We used multiple imputation by chained equations using the MICE package in R to impute referral, comorbidity, temperature, heart rate, capillary refill time and consciousness. We included hospital, all outcome measures and other auxiliary variables influencing case-mix and disease severity in the imputation model. Multiple imputation was performed on all patients (n=32,766). For the statistical analysis where we used the multiple imputation data, results were pooled for a final result. For the main analysis, patients with missing systolic BP measurement were excluded leading to 5648 eligible visits.

For the sensitivity analysis, we used a different approach to deal with missing BP data. We selected the five EDs with >20% BP measurements (n=12,385), and imputed missing BP values in this subset. In this subset we repeated all analysis from part 2. Proportion of missingness of variables are provided in Table 1 and Appendix 5.

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>Ill appearance</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>Work of breathing</td>
<td>Capillary refill time</td>
<td>Blood culture performed</td>
<td>Antibiotic prescription type</td>
<td>Serious bacterial infection</td>
</tr>
<tr>
<td>Previous medical care (yes, primary care / yes, this ED / yes other secondary care)</td>
<td>Consciousness</td>
<td>Oxygen saturation</td>
<td>Cerebrospinal fluid performed</td>
<td>Antibiotic prescription mode</td>
<td>Invasive bacterial infection</td>
</tr>
<tr>
<td>Season</td>
<td>Meningeal signs</td>
<td>Non-invasive systolic blood pressure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Comorbidity</td>
<td>Focal neurology</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complex comorbidity</td>
<td>Non-blanching rash</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dehydration</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Seizures</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Appendix 3. Further details of serious bacterial infections (n=461), invasive bacterial infections (n=46) and immediate-lifesaving interventions (n=203)

<table>
<thead>
<tr>
<th>Infection focus of serious bacterial infections (n=461)</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary tract</td>
<td>153 (33.2%)</td>
</tr>
<tr>
<td>Lower respiratory tract infection</td>
<td>139 (30.2%)</td>
</tr>
<tr>
<td>Gastro intestinal or surgical abdomen</td>
<td>93 (20.2%)</td>
</tr>
<tr>
<td>Sepsis</td>
<td>37 (8.0%)</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>15 (3.3%)</td>
</tr>
<tr>
<td>Meningitis / CNS infection</td>
<td>10 (2.2%)</td>
</tr>
<tr>
<td>Other</td>
<td>14 (3.0%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Invasive bacterial infections (n=46)</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacteraemia*</td>
<td>40 (87%)</td>
</tr>
<tr>
<td>Bacterial meningitis*</td>
<td>6 (13%)</td>
</tr>
<tr>
<td>Bone and joint</td>
<td>2 (4.3%)</td>
</tr>
</tbody>
</table>

*Two patients had both bacteraemia and bacterial meningitis

<table>
<thead>
<tr>
<th>Immediate life-saving interventions (n=203)*</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Airway/breathing interventions</td>
<td>100 (49.3%)</td>
</tr>
<tr>
<td>Haemodynamic interventions</td>
<td>112 (55.2%)</td>
</tr>
<tr>
<td>Emergency medications</td>
<td>52 (26.6%)</td>
</tr>
</tbody>
</table>

*Multiple categories per patients possible
### Appendix 4. Patient characteristics of patients with blood pressure measurement and patients without blood pressure measurement

<table>
<thead>
<tr>
<th></th>
<th>Blood pressure measured (n=5622)</th>
<th>No blood pressure measured (n=26841)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>General characteristics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age in years, median (IQR)</td>
<td>4.2 (1.8-8.5)</td>
<td>2.6 (1.3-5.2)</td>
</tr>
<tr>
<td>Female</td>
<td>2548 (45.3)</td>
<td>12172 (45.3)</td>
</tr>
<tr>
<td>Comorbidity</td>
<td>1338 (23.8)</td>
<td>3831 (14.3)</td>
</tr>
<tr>
<td>Complex comorbidity</td>
<td>530 (9.4)</td>
<td>931 (3.5)</td>
</tr>
<tr>
<td>Referred</td>
<td>2354 (41.9)</td>
<td>11028 (41.1)</td>
</tr>
<tr>
<td>Triage urgency</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low: standard, non-urgent</td>
<td>3612 (64.2)</td>
<td>18670 (69.6)</td>
</tr>
<tr>
<td>High: immediate, very urgent, intermediate</td>
<td>1746 (31.1)</td>
<td>7292 (27.2)</td>
</tr>
<tr>
<td><strong>Clinical symptoms</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fever duration in days, median (IQR)</td>
<td>1.5 (0.5-3)</td>
<td>1.5 (0.5-3)</td>
</tr>
<tr>
<td>Ill appearance</td>
<td>868 (15.4)</td>
<td>4855 (18.1)</td>
</tr>
<tr>
<td>Decreased consciousness</td>
<td>82 (1.5)</td>
<td>87 (0.3)</td>
</tr>
<tr>
<td><strong>Vital signs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Temperature in °C, median (IQR)</td>
<td>37.6 (36.8-38.4)</td>
<td>37.7 (37.0-38.4)</td>
</tr>
<tr>
<td>Hypoxia &lt;95%</td>
<td>2920(5.2)</td>
<td>935 (3.5)</td>
</tr>
<tr>
<td>Prolonged capillary refill (&gt;3 sec)</td>
<td>105 (1.9)</td>
<td>254 (0.9)</td>
</tr>
<tr>
<td>Tachycardia (APLS)</td>
<td>1667 (29.7)</td>
<td>5537 (20.6)</td>
</tr>
<tr>
<td><strong>Diagnostics and treatment</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRP in mg/L, median (IQR)</td>
<td>20 (5-61)</td>
<td>17 (5-47)</td>
</tr>
<tr>
<td>Blood cultures performed</td>
<td>967 (17.2)</td>
<td>1798 (6.7)</td>
</tr>
<tr>
<td>Cerebrospinal fluid performed</td>
<td>140 (2.5)</td>
<td>198 (0.7)</td>
</tr>
<tr>
<td>Antibiotic treatment following ED visit</td>
<td>1983 (35.2)</td>
<td>8305 (30.9)</td>
</tr>
<tr>
<td>Admission to the ward &gt;24 hours</td>
<td>1159 (20.6)</td>
<td>5415 (20.2)</td>
</tr>
<tr>
<td><strong>Serious illness</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serious bacterial infection</td>
<td>461 (8.2)</td>
<td>1683 (6.5)</td>
</tr>
<tr>
<td>Invasive bacterial infection</td>
<td>46 (0.8)</td>
<td>82 (0.3)</td>
</tr>
<tr>
<td>Admission to the ICU</td>
<td>69 (1.2)</td>
<td>76 (0.3)</td>
</tr>
<tr>
<td>Immediate life-saving interventions</td>
<td>203 (3.6)</td>
<td>212 (0.8)</td>
</tr>
</tbody>
</table>

APLS, advanced paediatric life support; CRP, C-reactive protein; ICU, intensive care unit; IQR, interquartile range; NA, not applicable
Appendix 5. Shock Index reference values according to age, n=5509

<table>
<thead>
<tr>
<th>Age group</th>
<th>N</th>
<th>Shock Index Mean (SD)</th>
<th>Shock Index 95th centile</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;3m</td>
<td>181</td>
<td>1.83 (0.48)</td>
<td>2.62</td>
</tr>
<tr>
<td>3-6m</td>
<td>163</td>
<td>1.63 (0.34)</td>
<td>2.19</td>
</tr>
<tr>
<td>6m-1y</td>
<td>430</td>
<td>1.54 (0.29)</td>
<td>2.02</td>
</tr>
<tr>
<td>1-2y</td>
<td>753</td>
<td>1.45 (0.29)</td>
<td>1.96</td>
</tr>
<tr>
<td>2-3y</td>
<td>574</td>
<td>1.36 (0.25)</td>
<td>1.88</td>
</tr>
<tr>
<td>3-4y</td>
<td>549</td>
<td>1.28 (0.22)</td>
<td>1.77</td>
</tr>
<tr>
<td>4-5y</td>
<td>462</td>
<td>1.24 (0.23)</td>
<td>1.64</td>
</tr>
<tr>
<td>5-6y</td>
<td>406</td>
<td>1.18 (0.21)</td>
<td>1.62</td>
</tr>
<tr>
<td>6-7y</td>
<td>276</td>
<td>1.13 (0.21)</td>
<td>1.53</td>
</tr>
<tr>
<td>7-8y</td>
<td>234</td>
<td>1.09 (0.21)</td>
<td>1.47</td>
</tr>
<tr>
<td>8-9y</td>
<td>196</td>
<td>1.05 (0.22)</td>
<td>1.44</td>
</tr>
<tr>
<td>9-10y</td>
<td>185</td>
<td>1.01 (0.20)</td>
<td>1.41</td>
</tr>
<tr>
<td>10-11y</td>
<td>166</td>
<td>1.00 (0.20)</td>
<td>1.35</td>
</tr>
<tr>
<td>11-12y</td>
<td>157</td>
<td>0.98 (0.21)</td>
<td>1.34</td>
</tr>
<tr>
<td>12-13y</td>
<td>139</td>
<td>0.90 (0.19)</td>
<td>1.33</td>
</tr>
<tr>
<td>13-14y</td>
<td>127</td>
<td>0.93 (0.24)</td>
<td>1.21</td>
</tr>
<tr>
<td>14-15y</td>
<td>159</td>
<td>0.92 (0.21)</td>
<td>1.32</td>
</tr>
<tr>
<td>15-16y</td>
<td>122</td>
<td>0.92 (0.21)</td>
<td>1.26</td>
</tr>
<tr>
<td>16-17y</td>
<td>99</td>
<td>0.85 (0.21)</td>
<td>1.26</td>
</tr>
<tr>
<td>17-18y</td>
<td>131</td>
<td>0.87 (0.23)</td>
<td>1.21</td>
</tr>
</tbody>
</table>

SD, standard deviation; m, months; y, year
Appendix 6. Shock Index cut-off values for the different outcomes, stratified for age groups

<table>
<thead>
<tr>
<th>Serious bacterial infection</th>
<th>Shock Index cut-off value*</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Negative LR</th>
<th>Positive LR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &lt;1 year</td>
<td>1.37</td>
<td>0.91</td>
<td>0.24</td>
<td>0.37</td>
<td>1.20</td>
</tr>
<tr>
<td>Age 1-5 year</td>
<td>1.12</td>
<td>0.90</td>
<td>0.18</td>
<td>0.54</td>
<td>1.10</td>
</tr>
<tr>
<td>Age 5-10 year</td>
<td>0.81</td>
<td>0.91</td>
<td>0.08</td>
<td>1.21</td>
<td>0.98</td>
</tr>
<tr>
<td>Age &gt;10 year</td>
<td>0.67</td>
<td>0.90</td>
<td>0.11</td>
<td>0.88</td>
<td>1.02</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Invasive bacterial infection</th>
<th>Shock Index cut-off value*</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Negative LR</th>
<th>Positive LR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &lt;1 year</td>
<td>1.43</td>
<td>1.00</td>
<td>0.31</td>
<td>0.00</td>
<td>1.45</td>
</tr>
<tr>
<td>Age 1-5 year</td>
<td>1.19</td>
<td>0.92</td>
<td>0.29</td>
<td>0.29</td>
<td>1.28</td>
</tr>
<tr>
<td>Age 5-10 year</td>
<td>0.79</td>
<td>0.92</td>
<td>0.07</td>
<td>1.26</td>
<td>0.98</td>
</tr>
<tr>
<td>Age &gt;10 year</td>
<td>0.93</td>
<td>0.91</td>
<td>0.54</td>
<td>0.17</td>
<td>1.98</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Immediate life-saving intervention</th>
<th>Shock Index cut-off value*</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Negative LR</th>
<th>Positive LR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &lt;1 year</td>
<td>1.40</td>
<td>0.91</td>
<td>0.27</td>
<td>0.34</td>
<td>1.24</td>
</tr>
<tr>
<td>Age 1-5 year</td>
<td>1.06</td>
<td>0.91</td>
<td>0.12</td>
<td>0.78</td>
<td>1.03</td>
</tr>
<tr>
<td>Age 5-10 year</td>
<td>0.96</td>
<td>0.92</td>
<td>0.25</td>
<td>0.33</td>
<td>1.22</td>
</tr>
<tr>
<td>Age &gt;10 year</td>
<td>0.79</td>
<td>0.92</td>
<td>0.29</td>
<td>0.29</td>
<td>1.29</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ICU admission</th>
<th>Shock Index cut-off value*</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Negative LR</th>
<th>Positive LR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &lt;1 year</td>
<td>1.32</td>
<td>0.94</td>
<td>0.18</td>
<td>0.33</td>
<td>1.14</td>
</tr>
<tr>
<td>Age 1-5 year</td>
<td>1.11</td>
<td>0.90</td>
<td>0.17</td>
<td>0.56</td>
<td>1.09</td>
</tr>
<tr>
<td>Age 5-10 year</td>
<td>0.68</td>
<td>0.93</td>
<td>0.02</td>
<td>4.25</td>
<td>0.94</td>
</tr>
<tr>
<td>Age &gt;10 year</td>
<td>0.53</td>
<td>1.00</td>
<td>0.01</td>
<td>0.00</td>
<td>1.01</td>
</tr>
</tbody>
</table>

* minimal sensitivity >=90% and maximal specificity
Appendix 7. Sensitivity analysis for febrile children in 5 EDs with >20% SBP measurement (n=12347)

<table>
<thead>
<tr>
<th>Shock Index &gt;95th centile value</th>
<th>OR (95% CI)</th>
<th>Adj. OR (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBI n=643</td>
<td>1.7 (1.2-2.4)</td>
<td>1.4 (1.0-2.0)</td>
</tr>
<tr>
<td>IBI n=81</td>
<td>2.0 (0.8-4.8)</td>
<td>1.7 (0.7-4.1)</td>
</tr>
<tr>
<td>ILSI n=336</td>
<td>2.6 (1.8-3.8)</td>
<td>2.4 (1.6-3.6)</td>
</tr>
<tr>
<td>ICU admission n=90</td>
<td>2.9 (1.5-5.5)</td>
<td>3.0 (1.5-5.8)</td>
</tr>
</tbody>
</table>

*Adjusted for age, sex, referral (y/n), comorbidity (y/n), temperature
Adj, adjusted; CI, confidence interval; ICU, intensive care unit; OR, odds ratio

Diagnostic performance of high Shock Index >95th centile for serious illness (n=12347)

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
<th>Positive LR (95% CI)</th>
<th>Negative LR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBI</td>
<td>0.08 (0.06-0.10)</td>
<td>0.97 (0.96-0.97)</td>
<td>2.4 (1.8-3.2)</td>
<td>0.95 (0.93-0.97)</td>
</tr>
<tr>
<td>IBI</td>
<td>0.10 (0.04-0.19)</td>
<td>0.97 (0.96-0.97)</td>
<td>2.9 (1.5-5.7)</td>
<td>0.93 (0.87-1.00)</td>
</tr>
<tr>
<td>ILSI</td>
<td>0.13 (0.09-0.17)</td>
<td>0.97 (0.96-0.97)</td>
<td>3.9 (2.9-5.3)</td>
<td>0.90 (0.87-0.94)</td>
</tr>
<tr>
<td>ICU admission</td>
<td>0.14 (0.08-0.23)</td>
<td>0.97 (0.96-0.97)</td>
<td>4.3 (2.6-7.20)</td>
<td>0.89 (0.81-0.96)</td>
</tr>
</tbody>
</table>

Discriminative value of Shock Index (continuous) for serious illness, stratified for age n=12347

<table>
<thead>
<tr>
<th>Shock Index (continuous) stratified for age</th>
<th>SBI AUC (95% CI)</th>
<th>IBI AUC (95% CI)</th>
<th>ILSI AUC (95% CI)</th>
<th>ICU admission AUC (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1 year, n=2337</td>
<td>0.63 (0.57-0.68)</td>
<td>0.71 (0.58-0.84)</td>
<td>0.69 (0.61-0.77)</td>
<td>0.71 (0.59-0.83)</td>
</tr>
<tr>
<td>1-5 year, n=6064</td>
<td>0.55 (0.51-0.60)</td>
<td>0.56 (0.42-0.69)</td>
<td>0.59 (0.54-0.65)</td>
<td>0.57 (0.46-0.67)</td>
</tr>
<tr>
<td>5-10 year, n=2484</td>
<td>0.53 (0.46-0.59)</td>
<td>0.65 (0.50-0.81)</td>
<td>0.56 (0.48-0.64)</td>
<td>0.53 (0.36-0.69)</td>
</tr>
<tr>
<td>&gt;10 year, n=1462</td>
<td>0.59 (0.53-0.65)</td>
<td>0.63 (0.46-0.80)</td>
<td>0.66 (0.59-0.74)</td>
<td>0.73 (0.48-0.98)</td>
</tr>
</tbody>
</table>

AUC, area under the curve; CI, confidence interval; IBI, invasive bacterial infection; ICU, intensive care unit; ILSI, immediate life-saving intervention; SBI, serious bacterial infection
Appendix 8: Members of PERFORM Consortium V6.0

PERFORM Consortium
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 Habgood-Coote; Shea Hamilton;
Clive Hoggart; Sara Hourmat; Heather Jackson; Ian Maconochie; Stephanie Menikou; Naomi Lin; Samuel Nichols; Ruud Nijman; Ivonne Pena Paz; Priyen Shah; Ching-Fen Shen; 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-Torres¹
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 Cebeý-López¹, María José Curras-Tual¹,², Carlos Durán Suárez¹, Luisa García Vicente¹, Alberto Gómez-Carballa¹,², Jose Gómez Rial¹, Pilar Leboráns Iglesias¹, Federico Martínón-Torres¹, Nazareth Martinón-Torres¹, José María Martínón Sánchez¹, Belén Mosquera Pérez¹, Jacobo Pardo-Seco¹,², Lidia Piñeiro Rodríguez¹, Sara Pishedda¹,², Sara Rey Vázquez¹, Irene Rivero Calle¹, Carmen Rodríguez-Tenneiro¹, 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.gevni.org), Instituto de Investigación Sanitaria de Santiago, Universidad de Santiago de Compostela, Galicia, Spain.
² Unidade de Xenética, Departamento de Anatomía Patológica 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.
³ Fundación Pública Galega de Medicina Xenómica, Servizo Galego de Saúde (SERGAS), Instituto de Investigaciones Sanitarias (IDIS), and Grupo de Medicina Xenómica, Centro de Investigación Biomédica en Red de Enfermedades Raras (CIBERER), Universidade de Santiago de Compostela (USC), Santiago de Compostela, Spain.

RSU Partner (Latvia)

Principal Investigator
Dace Zavadska¹,²

Other RSU group authors (in alphabetical order):
Anda Balode¹,², Arta Bārzdina¹,², Dārta Deksne¹,², Dace Gardovska¹,², Dagne Grāvele², Ilze Grope¹,², Anija Meiere¹,², Ieva Nokalna¹,², Jana Pavāre¹,², Zanda Pučuka¹,², Katrīna Selecka¹,², Aleksandra Sidorova¹,², Dace Svile², Urzula Nora Urbāne¹,².

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 Rocalsatou Sarr
Momodou Saidykhan
Saffiatou Darboe
Samba Ceesay
Umberto D’alessandro

Medical Research Council Unit The Gambia at LSHTM
P O Box 273,
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 Zachariaasse ¹

Additional investigator
W Dik ³

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, MD 1, Luregn J Schlapbach, MD, FCICM 2,3, Eric Giannoni, MD 4,5, Martin Stocker, MD 6, Klara M Posfay-Barbe, MD 7, Ulrich Heininger, MD 8, Sara Bernhard-Stirnemann, MD 9, Anita Niederer-Loher, MD 10, Christian Kahlert, MD 10, Giancarlo Natalucci, MD 11, Christa Relly, MD 12, Thomas Riedel, MD 13, Christoph Aebi, MD 1, Christoph Berger, MD 12 for the Swiss Pediatric Sepsis Study

Affiliations:

1 Department of Pediatrics, Inselspital, Bern University Hospital, University of Bern, Switzerland
2 Neonatal and Pediatric Intensive Care Unit, Children’s Research Center, University Children’s Hospital Zurich, University of Zurich, Zurich, Switzerland
3 Child Health Research Centre, University of Queensland, and Queensland Children’s Hospital, Brisbane, Australia
4 Clinic of Neonatology, Department Mother-Woman-Child, Lausanne University Hospital and University of Lausanne, Switzerland
5 Infectious Diseases Service, Department of Medicine, Lausanne University Hospital and University of Lausanne, Switzerland
6 Department of Pediatrics, Children’s Hospital Lucerne, Lucerne, Switzerland
7 Pediatric Infectious Diseases Unit, Children’s Hospital of Geneva, University Hospitals of Geneva, Geneva, Switzerland
8 Infectious Diseases and Vaccinology, University of Basel Children’s Hospital, Basel, Switzerland
9 Children’s Hospital Aarau, Aarau, Switzerland
10 Division of Infectious Diseases and Hospital Epidemiology, Children’s Hospital of Eastern Switzerland St. Gallen, St. Gallen, Switzerland
11 Department of Neonatology, University Hospital Zurich, Zurich, Switzerland
12 Division of Infectious Diseases and Hospital Epidemiology, and Children’s Research Center, University Children’s Hospital Zurich, Switzerland
13 Children’s Hospital Chur, Chur, Switzerland

Liverpool Partner

Principal Investigators

Enitan D Carroll 1,2,3
Stéphane Paulus 1

Research Group (in alphabetical order):

BMJ Publishing Group Limited (BMJ) disclaims all liability and responsibility arising from any reliance
Supplemental material placed on this supplemental material which has been supplied by the author(s) Arch Dis Child
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 Levadas

Goudi, Athens

Micropathology Ltd:

Dr Marie Voice  Post doc scientist

Professor Colin Fink , Clinical Microbiologist

Additional investigators

Dr Marie Voice, Post doc scientist

Dr. Leo Calvo-Bado, Post doc scientist
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 Hude¹, Markus Keldorfer⁵, Larissa Krenn⁴, Heidemarie Pilch⁵, Andreas Pfleger², Klaus Pfurtscheller⁴, Gudrun Nordberg⁵, Tobias Niedrist⁸, Siegfried Rödl⁴, Andrea Skrabl-Baumgartner¹, Matthias Sperl⁷, Laura Stampfer⁵, Volker Strenger³, Holger Till⁶, Andreas Trobisch⁵, Sabine Löffler⁴

Author Affiliations:

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

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

³ Department of Pediatric Hematooncoloy, Medical University of Graz, Graz, Austria
Paediatric Intensive Care Unit, Medical University of Graz, Graz, Austria

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

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

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

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

London School of Hygiene and Tropical Medicine

WP S/WP1

Principal Investigator:

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

Research Group

Dr Juan Emmanuel Dewez1 MD, DTM&H, MSc

Mr David Bath2 MSc, MAppFin, BA(Hons)

Dr Alec Miners2 BA(Hons), MSc, PhD

Dr Ruud Nijman3 PhD MSc MD MRCPCH

Dr Catherine Wedderburn1 BA, MBChB, DTM&H, MSc, MRCPCH

Ms Anne Meierford1 MSc, BMedSc, BMBS

Dr Baptiste Leurent4, 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 Groot1, Michiel van der Flier1,2,3, Marien I. de Jonge1

Co-investigators Radboud University Medical Center (in alphabetical order):

Koen van Aerde1,2, Wynand Alkema1, Bryan van den Broek1, Jolein Gloerich1, Alain J. van Gool1, Stefanie Henriet1,2, Martijn Huijnen1, Ria Philipsen1, Esther Willems1
Investigators PeDBIG PERFORM DUTCH CLINICAL NETWORK (in alphabetical order):
G.P.J.M. Gerrits, M. van Leur, J. Heidema, L. de Haan, C.J. Miedema, C. Neeleman, C.C. Obihara,
G.A. Tramper-Stranders

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)

Principal Investigators
Andrew J. Pollard, Rama Kandasamy, Stéphane Paulus

Additional Investigators
Michael J. Carter, Daniel O'Connor, Sagida Bibi, Dominic F. Kelly, Meeru Gurung, Stephen Thorson,
Imran Ansari, David R. Murdoch, Shrijana Shrestha.

Author Affiliations:
1. Oxford Vaccine Group, Department of Paediatrics, University of Oxford, Oxford, United Kingdom.
2. NIHR Oxford Biomedical Research Centre, Oxford, United Kingdom.
3. Paediatric Research Unit, Patan Academy of Health Sciences, Kathmandu, Nepal.
4. Department of Pathology, University of Otago, Christchurch, New Zealand.

Newcastle University, Newcastle upon Tyne, (UK)

Principal Investigator:
Marieke Emonts (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{6}

Christine Mackerness\textsuperscript{8}

Students MOFICHE

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

Students/medical staff PERFORM

Tasnim Araf\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}

Engagement work/ethics/cost effectiveness

Mike Martin\textsuperscript{6}, 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.
5Great North Children’s Hospital, Research Unit, Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne, United Kingdom.

6Great North Children’s Hospital, Paediatric Oncology, Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne, United Kingdom.

7Population 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.

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 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 Mallet\textsuperscript{1,2, 3}

Research Group:
Karen Brengel-Pesce\textsuperscript{1,2, 3}
Alexandre Pachot\textsuperscript{1}
Marine Mommert\textsuperscript{1,2}

\textsuperscript{1}Open Innovation & Partnerships (OIP), bioMérieux S.A., Marcy l’Etoile, France
\textsuperscript{2}Joint research unit Hospice Civils de Lyon - bioMérieux, Centre Hospitalier Lyon Sud, 165 Chemin du Grand Revoyet, 69310 Pierre-Bénite, France
\textsuperscript{3}EA 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 Pokorn\textsuperscript{1,2, 3} MD, PhD

Research Group:
Mojca Kolnik\textsuperscript{1} MD, Katarina Vincek\textsuperscript{1} MD, Tina Plankar Srovin\textsuperscript{1} MD, PhD, Natalija Bahovec\textsuperscript{1} MD, Petra Prunk\textsuperscript{1} MD, Veronika Osterman\textsuperscript{1} MD, Tanja Avramoska\textsuperscript{1} MD

Affiliations:
\textsuperscript{1}Department of Infectious Diseases, University Medical Centre Ljubljana, Japljeva 2, SI-1525 Ljubljana, Slovenia
\textsuperscript{2}University Childrens’ Hospital, University Medical Centre Ljubljana, Ljubljana, Slovenia
\textsuperscript{3}Department of Infectious Diseases and Epidemiology, Faculty of Medicine, University of Ljubljana, Slovenia

Amsterdam, Academic Medical Hospital & Sanquin Research Institute (NL)

Principal Investigator:
Taco Kuijpers\textsuperscript{1,2}

Co-investigators
Ilse Jongerius \textsuperscript{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)