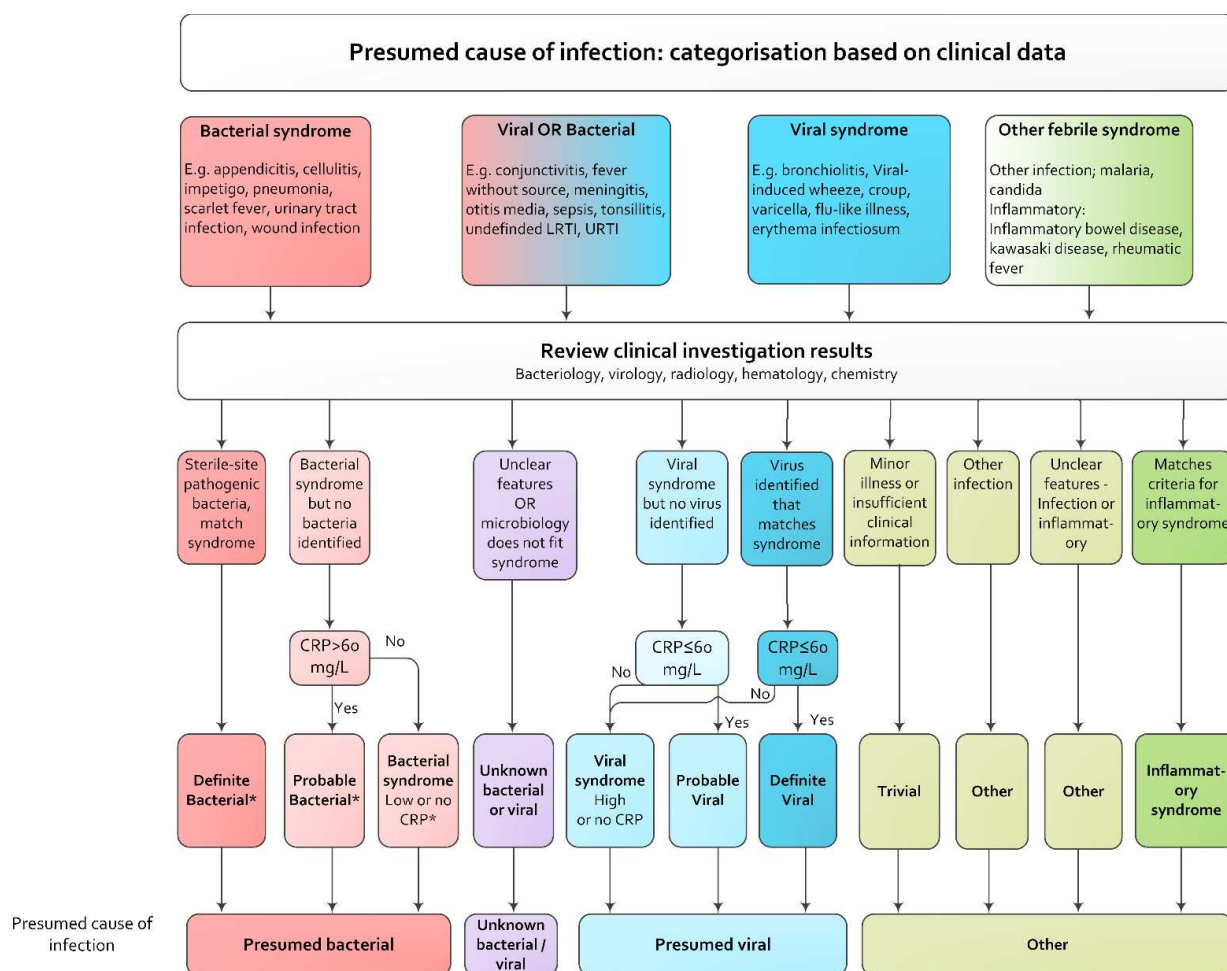


Appendix 1: Flowchart to classify presumed cause of infection

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

References

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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:

| General characteristics | Markers of disease severity | Vital signs | Diagnostics | Treatment | Outcomes |
|---|-----------------------------|--------------------------------------|-------------------------------|-------------------------------------|------------------------------|
| Hospital | Triage urgency | Heart rate | CRP-level | Immediate life-saving interventions | Disposition |
| Age | Fever duration | Respiratory rate | Chest X-ray categories | Oxygen treatment | Final diagnosis |
| Sex | Ill appearance | Temperature | Urinalysis categories | Inhalation medication | Focus of infection |
| Referral type (self / GP / emergency services / other) | Work of breathing | Capillary refill time | Blood culture performed | Antibiotic prescription type | Serious bacterial infection |
| Previous medical care (yes, primary care / yes, this ED / yes other secondary care) | Consciousness | Oxygen saturation | Cerebrospinal fluid performed | Antibiotic prescription mode | Invasive bacterial infection |
| Season | Meningeal signs | Non-invasive systolic blood pressure | | | |
| Comorbidity | Focal neurology | | | | |
| Complex comorbidity | Non-blanching rash | | | | |
| | Dehydration | | | | |
| | Seizures | | | | |

Appendix 3. Further details of serious bacterial infections (n=461), invasive bacterial infections (n=46) and immediate-lifesaving interventions (n=203)

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

| Invasive bacterial infections (n=46) | N (%) |
|--------------------------------------|----------|
| Bacteraemia* | 40 (87%) |
| Bacterial meningitis* | 6 (13%) |
| Bone and joint | 2 (4.3%) |

*Two patients had both bacteraemia and bacterial meningitis

| Immediate life-saving interventions (n=203)* | N (%) |
|--|-------------|
| Airway/breathing interventions | 100 (49.3%) |
| Haemodynamic interventions | 112 (55.2%) |
| Emergency medications | 52 (26.6%) |

*Multiple categories per patients possible

Appendix 4. Patient characteristics of patients with blood pressure measurement and patients without blood pressure measurement

| | Blood pressure measured (n=5622) | | No blood pressure measured (n=26841) | |
|--|-------------------------------------|---------|---|---------|
| | n (%) | Missing | n (%) | Missing |
| General characteristics | | | | |
| Age in years, median (IQR) | 4.2 (1.8-8.5) | | 2.6 (1.3-5.2) | |
| Female | 2548 (45.3) | | 12172 (45.3) | |
| Comorbidity | 1338 (23.8) | 91 | 3831 (14.3) | 182 |
| <i>Complex comorbidity</i> | 530 (9.4) | 91 | 931 (3.5) | 182 |
| Referred | 2354 (41.9) | 110 | 11028 (41.1) | 1044 |
| Triage urgency | | 264 | | 879 |
| Low: standard, non-urgent | 3612 (64.2) | | 18670 (69.6) | |
| High: immediate, very urgent, intermediate | 1746 (31.1) | | 7292 (27.2) | |
| Clinical symptoms | | | | |
| Fever duration in days, median (IQR) | 1.5 (0.5-3) | 704 | 1.5 (0.5-3) | 1676 |
| Ill appearance | 868 (15.4) | 621 | 4855 (18.1) | 1040 |
| Decreased consciousness | 82 (1.5) | 90 | 87 (0.3) | 210 |
| Vital signs | | | | |
| Temperature in °C, median (IQR) | 37.6 (36.8-38.4) | 480 | 37.7 (37.0-38.4) | 2432 |
| Hypoxia <95% | 2920(5.2) | 211 | 935 (3.5) | 5204 |
| Prolonged capillary refill (>3 sec) | 105 (1.9) | 866 | 254 (0.9) | 3004 |
| Tachycardia (APLS) | 1667 (29.7) | 55 | 5537 (20.6) | 3372 |
| Diagnostics and treatment | | | | |
| CRP in mg/L, median (IQR) | 20 (5-61) | 3378 | 17 (5-47) | 13021 |
| Blood cultures performed | 967 (17.2) | | 1798 (6.7) | |
| Cerebrospinal fluid performed | 140 (2.5) | | 198 (0.7) | |
| Antibiotic treatment following ED visit | 1983 (35.2) | 55 | 8305 (30.9) | 398 |
| Admission to the ward >24 hours | 1159 (20.6) | 137 | 5415 (20.2) | 328 |
| Serious illness | | | | |
| Serious bacterial infection | 461 (8.2) | | 1683 (6.3) | |
| Invasive bacterial infection | 46 (0.8) | | 82 (0.3) | |
| Admission to the ICU | 69 (1.2) | | 76 (0.3) | |
| Immediate life-saving interventions | 203 (3.6) | | 212 (0.8) | |

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

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

SD, standard deviation; m, months; y, year

Appendix 6. Shock Index cut-off values for the different outcomes, stratified for age groups

| Serious bacterial infection | Shock Index cut-off value* | Sensitivity | Specificity | Negative LR | Positive LR |
|------------------------------------|-----------------------------------|--------------------|--------------------|--------------------|--------------------|
| Age <1 year | 1.37 | 0.91 | 0.24 | 0.37 | 1.20 |
| Age 1-5 year | 1.12 | 0.90 | 0.18 | 0.54 | 1.10 |
| Age 5-10 year | 0.81 | 0.91 | 0.08 | 1.21 | 0.98 |
| Age >10 year | 0.67 | 0.90 | 0.11 | 0.88 | 1.02 |

| Invasive bacterial infection | Shock Index cut-off value* | Sensitivity | Specificity | Negative LR | Positive LR |
|-------------------------------------|-----------------------------------|--------------------|--------------------|--------------------|--------------------|
| Age <1 year | 1.43 | 1.00 | 0.31 | 0.00 | 1.45 |
| Age 1-5 year | 1.19 | 0.92 | 0.29 | 0.29 | 1.28 |
| Age 5-10 year | 0.79 | 0.92 | 0.07 | 1.26 | 0.98 |
| Age >10 year | 0.93 | 0.91 | 0.54 | 0.17 | 1.98 |

| Immediate life-saving intervention | Shock Index cut-off value* | Sensitivity | Specificity | Negative LR | Positive LR |
|---|-----------------------------------|--------------------|--------------------|--------------------|--------------------|
| Age <1 year | 1.40 | 0.91 | 0.27 | 0.34 | 1.24 |
| Age 1-5 year | 1.06 | 0.91 | 0.12 | 0.78 | 1.03 |
| Age 5-10 year | 0.96 | 0.92 | 0.25 | 0.33 | 1.22 |
| Age >10 year | 0.79 | 0.92 | 0.29 | 0.29 | 1.29 |

| ICU admission | Shock Index cut-off value* | Sensitivity | Specificity | Negative LR | Positive LR |
|----------------------|-----------------------------------|--------------------|--------------------|--------------------|--------------------|
| Age <1 year | 1.32 | 0.94 | 0.18 | 0.33 | 1.14 |
| Age 1-5 year | 1.11 | 0.90 | 0.17 | 0.56 | 1.09 |
| Age 5-10 year | 0.68 | 0.93 | 0.02 | 4.25 | 0.94 |
| Age >10 year | 0.53 | 1.00 | 0.01 | 0.00 | 1.01 |

* minimal sensitivity $\geq 90\%$ and maximal specificity

Appendix 7. Sensitivity analysis for febrile children in 5 EDs with >20% SBP measurement (n=12347)

Univariate and multivariate analysis of Shock Index >95th centile values for serious illness (n=12347)

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

*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)

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

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

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

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



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