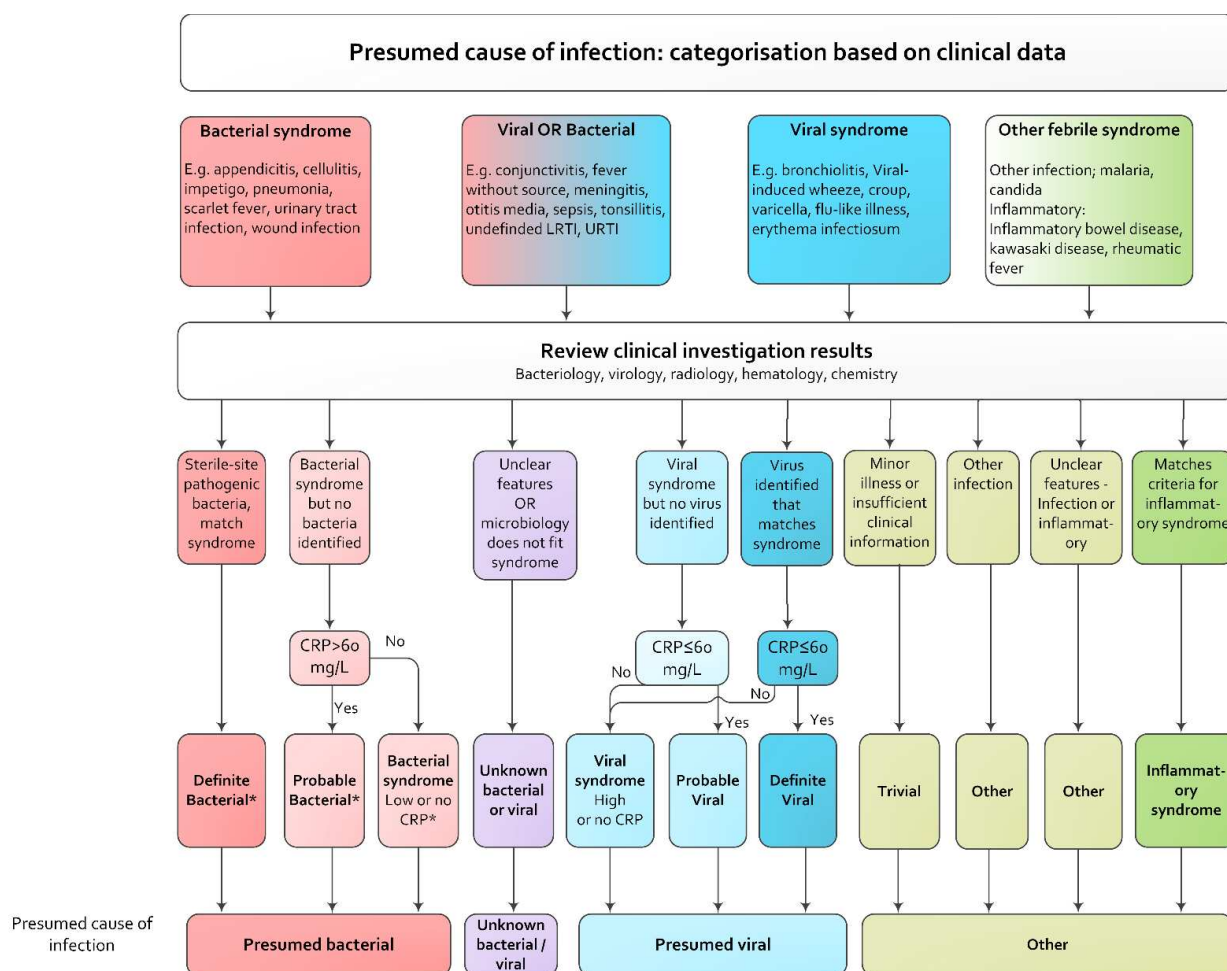


**Appendix 1: Flowchart to classify presumed cause of infection**

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
<b>General characteristics</b>				
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)	
<b>Clinical symptoms</b>				
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
<b>Vital signs</b>				
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
<b>Diagnostics and treatment</b>				
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
<b>Serious illness</b>				
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 <sup>th</sup> 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

<b>Serious bacterial infection</b>	<b>Shock Index cut-off value*</b>	<b>Sensitivity</b>	<b>Specificity</b>	<b>Negative LR</b>	<b>Positive LR</b>
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

<b>Invasive bacterial infection</b>	<b>Shock Index cut-off value*</b>	<b>Sensitivity</b>	<b>Specificity</b>	<b>Negative LR</b>	<b>Positive LR</b>
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

<b>Immediate life-saving intervention</b>	<b>Shock Index cut-off value*</b>	<b>Sensitivity</b>	<b>Specificity</b>	<b>Negative LR</b>	<b>Positive LR</b>
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

<b>ICU admission</b>	<b>Shock Index cut-off value*</b>	<b>Sensitivity</b>	<b>Specificity</b>	<b>Negative LR</b>	<b>Positive LR</b>
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 >95<sup>th</sup> centile values for serious illness (n=12347)

	Shock Index >95 <sup>th</sup> centile value	
	OR (95% CI)	Adj. OR (95% CI)*
<b>SBI</b> n=643	1.7 (1.2-2.4)	1.4 (1.0-2.0)
<b>IBI</b> n=81	2.0 (0.8-4.8)	1.7 (0.7-4.1)
<b>ILSI</b> n=336	2.6 (1.8-3.8)	2.4 (1.6-3.6)
<b>ICU admission</b> 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 >95<sup>th</sup> centile for serious illness (n=12347)

	Sensitivity (95% CI)	Specificity (95% CI)	Positive LR (95% CI)	Negative LR (95% CI)
<b>SBI</b>	0.08 (0.06-0.10)	0.97 (0.96-0.97)	2.4 (1.8-3.2)	0.95 (0.93-0.97)
<b>IBI</b>	0.10 (0.04-0.19)	0.97 (0.96-0.97)	2.9 (1.5-5.7)	0.93 (0.87-1.00)
<b>ILSI</b>	0.13 (0.09-0.17)	0.97 (0.96-0.97)	3.9 (2.9-5.3)	0.90 (0.87-0.94)
<b>ICU admission</b>	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)
<b>Shock Index (continuous) stratified for age</b>				
<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

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