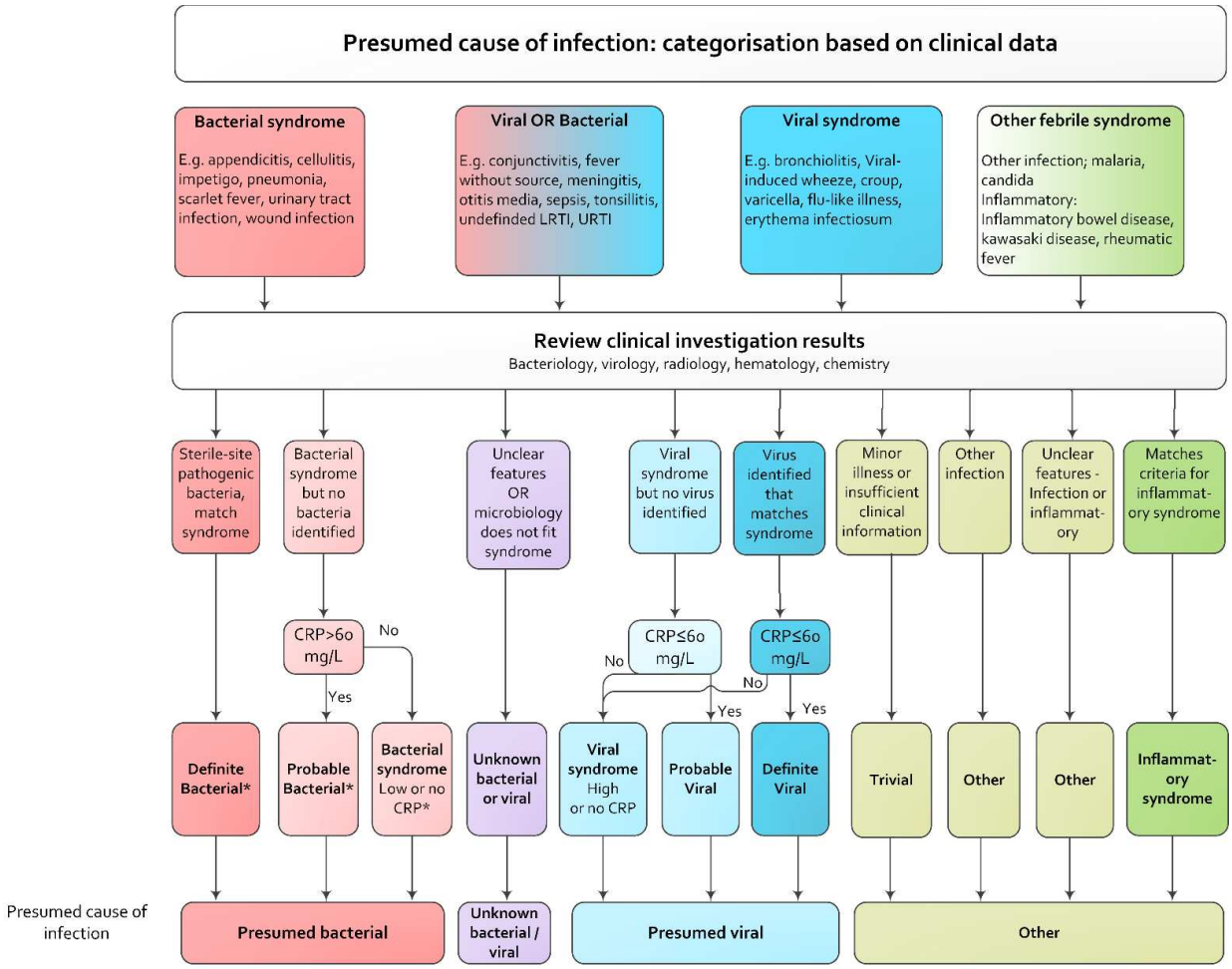
Appendix 1: Flowchart to classify presumed cause of infection



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
Complex comorbidity	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 95th 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 >=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 >95th 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

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