Supplemental information

Appendix 1: Statistical analysis plan

Statistical Analysis Plan

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

SAP version 1.0 date 14th July 2019

Background

Still today children die on treatable infectious diseases due to delayed or missed diagnosis presented at the Emergency Department (ED) or primary care.(1-3) On the other hand, antibiotics are prescribed for viral infections and infection with an unknown bacterial or viral cause in order not to miss one child with an invasive bacterial infection.(4)

The distinction between invasive bacterial infections and viral infections on only clinical signs and symptoms is difficult. Biomarkers as C-reactive protein and procalcitonin are currently used in febrile children to detect bacterial infections and to target appropriate antibiotic prescribing. However, these markers measure non-specific inflammation and immunologic responses. Recent research focuses on finding new discriminators of bacterial and viral infections using novel, sophisticated techniques (genomic, proteomic and transcriptomic approaches).(5-7) It is yet unclear which patients would benefit from potential new biomarkers. It is not feasible to apply new biomarkers to all febrile children. Therefore, decision models need to be developed which can identify these patients.

We searched PUBMED from 1st January 2009 to 1st July 2019 for published studies covering clinical prediction models for bacterial infections in children using keywords "child", "fever", "bacterial infection" and "clinical prediction" and checked references for relevant articles. The existing literature on clinical prediction models for bacterial infections focuses on young infants (< 3 months) and healthy children in particular. For older children, the Feverkidstool (Nijman et al.) is an extensively validated clinical prediction model for prediction of pneumonia and other serious bacterial infections which includes bacteraemia and meningitis but also infections of the urinary tract, gastro-intestinal tract and soft tissue. We could not identify a clinical prediction model for the outcome invasive bacterial infections including older children or children with chronic conditions.

Objectives

1. To update an existing clinical prediction model to identify invasive bacterial infections in febrile children at the ED
2. Can we target patients who can benefit from a new biomarker based on risk-prediction by this model?

Methods

Study design:
Prospective observational study
This study is a prospectively planned analysis in the MOFICHE study (Management and Outcome of Febrile Illness in Children) which is part of the PERFORM project. MOFICHE is a prospective observational study using routine data. The need for informed consent was waived.

Setting:
12 Emergency Departments (EDs) in 8 countries

Population:
Children 0-18 years with fever (temperature >38.0 C) measured at ED or history of fever (<72 hours) before ED visit. For this analysis, we will exclude children with working diagnosis of urinary tract infections after ED visit. For diagnosis of urinary tract infections, easy available diagnostics are already available at the ED. Therefore, a clinical prediction model has limited additional value in this group. Furthermore, we will focus our analysis on patients with CRP measurement since these are patients with diagnostic uncertainty after initial assessment by the physician.

Inclusion period:

1 January 2017 – 1 April 2018, at least 12 months per study site.

Primary outcomes:
Invasive bacterial infections (IBI): bacteraemia, bacterial meningitis and bacterial bone and join infections. Infections were defined positive growth of a single pathogenic bacterium in blood, cerebrospinal fluid or synovial fluid from cultures collected at ED visit or the first 24 hours from hospital admission.

Cultures growing contaminants (coagulase-negative staphylococci, alpha-haemolytic streptococci, *Micrococcus* species or *Propionibacterium* species are defined negative (8)

In children who are immunocompromised, malignancies or with a central line, these contaminants are still relevant invasive bacterial infections that need antibiotic treatment. In these patient groups, cultures with a single contaminant are defined positive.

All patients were entered in the electronic case record form (eCRF) by the local team. We will check all the positive cultures to ensure consistency and validity of coding.

Missing data
For this analysis, we will exclude patients with no CRP value and exclude patients with working diagnosis of urinary tract infection. We will use multiple imputation by chained equations using the MICE package in R to impute all missing predictor variables. We will assume the variables to be 'missing at random' where missingness can be explained by other variables in the data. We will incorporate hospital, all predictor variables, outcome measures and other auxiliary variables in the imputation model.
Multiple imputation will be performed on all patients (n=38480).

Variables in the multiple imputation model:

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	Capillary refill time	Temperature	Urinalysis categories	Inhalation medication	Focus of infection
Referral type (self / GP / emergency services / other)	Ill appearance	Oxygen saturation	Blood culture performed	Antibiotic prescription type	
Previous medical care (yes, primary care / yes, this ED / yes other secondary care)	Work of breathing		Cerebrospinal fluid performed	Antibiotic prescription mode	
Season	Meningeal signs			Previous antibiotic treatment	
Arrival hours (morning / evening / night)	Focal neurology				
Comorbidity	Non-blanching rash				

	Dehydration				
	Seizures				

Descriptive analysis
We will perform descriptive analysis for children with and without IBI. We will use frequencies, mean and standard deviation for normally distributed data, median and interquartile range for normally distributed data. In addition, we will compare patients with CRP measurement and patients without CRP measurement.

Predictor variables
We will include predictor variables chosen a-priori that have predictive value for bacterial infection. We will perform univariate logistic regression analysis for these predictor variables:

Predictor variables included in the Feverkidstool (9):
- Age
- Sex
- Temperature
- Fever duration in days
- Tachypnea: defined by Advanced Paediatric Life Support (10)
- Tachycardia: defined by Advanced Paediatric Life Support (10)
- Hypoxia: oxygen saturation <94%
- Prolonged capillary refill time: >3 seconds
- Increased work of breathing: chest wall retractions, nasal flaring, grunting or apnoea
- Ill appearance: ill, moderately ill, irritable or uncomfortable
- C-reactive protein value

NICE red warning signs for serious illness (11):
- Abnormal consciousness: responsive to verbal stimulation, responsive to pain or unresponsive
- Presence of meningeal signs: presence of Kernig, Brudzinski, tripod phenomenon, neck stiffness or bulging fontanelle
- Focal neurological signs
- Status epilepticus: seizures for >=30 minutes
- Non-blanching rash: petechiae or other non-blanching rash

Complex chronic condition (12)
- Chronic condition in ≥2 body systems that is expected to last at least 1 year or malignancy or immunocompromised

We will use 10 events per variable to include predictor variables in model development. If not enough events are available, we will combine abnormal consciousness, presence of meningeal signs and focal neurological signs in a composite variable.
Linearity of continuous variables will be assessed using restricted cubic splines. Outliers for continuous variables will be truncated at the 0.01 percentile and the 0.99 centile.

Model development
We will perform variable selection by least absolute shrinkage and selection operator (LASSO). Using LASSO, we perform variable selection and reduce degree of overfitting by shrinking large regression coefficients.(13) We will estimate the lambda using 10 times 10-fold-cross validation. To note, variable selection will not be based on significance in univariate logistic regression analysis.

Model validation
The model will be validated using internal-external cross-validation. In this method, the model is repeatedly derived on all EDs except one, and validated on the remaining ED.(14, 15)

Model performance
Model performance will be assessed by

- Discrimination of the model by concordance (c)-statistic.
- Calibration, the agreement between predicted risks and observed outcome will be visualized using calibration plots.(16)
- Diagnostic performance at different risk-threshold for the probability of IBI using sensitivity, specificity and negative and positive likelihood ratios. We will focus on cut-offs that can be used to rule-out (negative LR <0.2) or rule-in IBI (positive LR>5).(17)

Sensitivity analysis
A sensitivity analysis will be performed in the population where missing CRP values will be imputed.

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Appendix 2: Definition of contaminants

Appendix 3: Definition of contaminants
Micrococcus
Coagulase-negative staphylococci
Propionibacterium species
Alpha-haemolytic streptococci (except pneumococcus)
Corynebacterium species (diphteroids)
Bacillus species
Pseudomonas (except P. aeruginosa)
Other environmental non-fermenting gram-negative rods

Appendix 3: Additional methods on data analysis

Multiple imputation

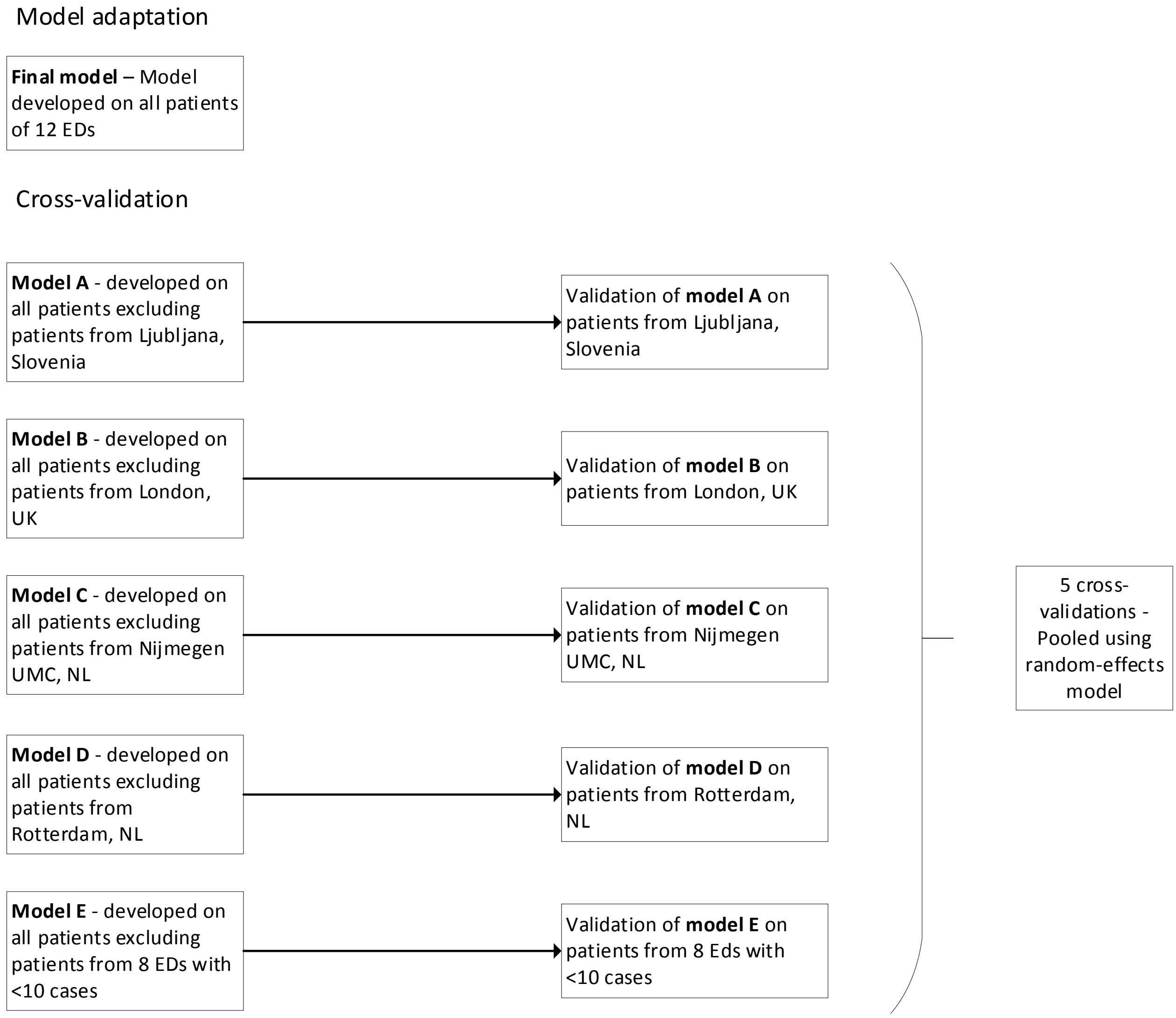
Missing data were multiple imputed using the MICE package in R v3.4. The imputation model included the outcome variable IBI, all considered predictors, ED and other auxiliary variables related to casemix and disease severity (specific details of the multiple imputation model are proved in the Statistical Analysis Plan). The imputation process resulted in 20 imputation sets. For all the statistical analysis, apart from the model development in LASSO (least absolute shrinkage and selection operator), results were pooled for a final result.(18) The LASSO was applied to a stacked dataset containing all imputed data.(19) To adjust for the inflated sample size we assigned each record a weight of 1/20 (20 is number of imputed datasets).

Model development and internal-external cross-validation

For model development (20, 21), we considered predefined variables with predictive value for IBI: 1) variables in the Feverkidstool(9) (age, sex, temperature, fever duration, tachypnea and tachycardia defined by Advanced Pediatric Life Support(10), oxygen saturation <94%, capillary refill >=3 seconds, work of breathing, ill appearance and CRP value), 2) NICE warnings signs which were not included in the Feverkidstool (consciousness, meningeal signs, focal neurology, status epilepticus, non-blanching rash)(11) and 3) complex chronic condition (condition in ≥2 body systems, malignancy or immunocompromised).(12) Level of consciousness, meningeal signs and focal neurology were combined into a composite variable abnormal neurology. Linearity of continuous variables was assessed using restricted cubic splines. As in the Feverkidstool, age was modelled linear piecewise for children <1 year and children >1 year and a logarithmic transformation for CRP was used. Outliers were truncated at the 0.01 percentile for temperature (35.7 °Celsius) and the 0.99 percentile for CRP (215 mg/L) and fever duration (8 days).

Variable selection was not influenced by the results of the univariate logistic regression analysis, but was performed using least absolute shrinkage and selection operator (LASSO).(13, 22) This approach aims to reduce the degree of overfitting by shrinking large regression coefficients and performs variable selection.(13) The lambda to derive the final model was estimated using 10 times 10-fold cross-validation. We used internal-external cross-validation in EDs with >10 IBI cases (four EDs) and EDs with <10 IBI cases (eight EDs) were combined in one group leading to five ED groups (appendix 5). In internal-external cross-validation The model was repeatedly derived on all ED groups except one, and validated on the remaining ED group (see figure A below).(14) Unlike splitting data in a derivation and validation set, this method uses all available data for the model development and uses cross-validation to validate the model five times. This cross-validation determines model performance most accurately but also provides information on the heterogeneity of performance across different settings. This internal-external cross-validation is therefore superior to a single external validation.(14, 15) We assessed the discriminative ability by the area under the receiver operating curve (AUC), and calibration, the agreement between predicted risks and observed cases., was evaluated by calibration plots. We explored the impact of difference in case-mix heterogeneity on the discriminative ability of the model in the internal-external cross-validation. Sensitivity, specificity, negative and positive likelihood ratios (LR) were evaluated at different cut-offs for the individual probability of IBI according to the model. We explored cut-offs for ruling-out (negative LR <0.2) or ruling-in IBI (positive LR >5).(17) Missing values for the covariates were multiple imputed (MICE). Sensitivity analysis was performed in the population where missing CRP values were imputed. All analyses were performed in R v3.6.

Figure A


Model adaptation
Final model – Model developed on all patients of 12 EDs
Cross-validation
Model A - developed on all patients excluding patients from Ljubljana, Slovenia
Validation of model A on patients from Ljubljana, Slovenia
Model B - developed on all patients excluding patients from London, UK
Validation of model B on patients from London, UK
Model C - developed on all patients excluding patients from Nijmegen UMC, NL
Validation of model C on patients from Nijmegen UMC, NL
Model D - developed on all patients excluding patients from Rotterdam, NL
Validation of model D on patients from Rotterdam, NL
Model E - developed on all patients excluding patients from 8 EDs with <10 cases
Validation of model E on patients from 8 Eds with <10 cases
5 cross-validations - Pooled using random-effects model

Appendix 4: EDs - classification of EDs with low (<2%) and high incidence (>2%) for IBI based on proportion of invasive bacterial infection, and proportion of chronic complex comorbidity per ED

ED	N total included patients	N study population	IBIs N (% of study population per ED)	Chronic complex comorbidity N (% of study population per ED)
Graz, Austria	2241	1987	1 (0.1%)	73 (3.7%)
Athens, Greece	4548	1450	1 (0.1%)	19 (1.3%)
Riga, Latvia	9000	5495	9 (0.2%)	60 (1.1%)
Munich, Germany	1173	456	1 (0.2%)	19 (4.2%)
Nijmegen, CWZ, the Netherlands	423	184	1 (0.5%)	12 (6.5%)
Ljubljana, Slovenia	3667	3183	23 (0.7%)	61 (1.9%)
Liverpool, UK	1623	468	8 (1.7%)	76 (16.2%)
Newcastle, UK	3854	475	9 (1.9%)	41 (8.6%)
London, UK	5714	1047	22 (2.1%)	184 (17.6%)
Santiago de Compostela, Spain	3877	281	6 (2.1%)	9 (3.2%)
Rotterdam, the Netherlands	1683	921	36 (3.9%)	369 (40.1%)
Nijmegen, UMC, the Netherlands	677	321	18 (5.6%)	135 (42.1%)
Total	**38480**	**16268**	**135**	**1058**
EDs with low incidence for IBI (<2%)		13698	53 (0.4%)	367 (2.7%)
EDs with high incidence for IBI (>2%)		2570	82 (3.2%)	364 (14.2%)

ED, emergency department; IBI, invasive bacterial infection; UK, United Kingdom; UMC, university medical centre; CWZ, Canisius Wilhelmina Hospital

Appendix 5: Patient characteristics of patients with CRP measurement and patients without CRP measurement

	CRP measured (n=17,213)			No CRP measured (n=21267)		
	n (%)	Range EDs	Missing	n (%)	Range EDs	Missing
General characteristics						
Age in years, median (IQR)	2.77 (1.29-6.02)			2.74 (1.31-5.28)		
Male	9305 (54.1)	49.6-62.0		11805 (55.5)	52.4-62.4	1
Previous chronic condition			97			273
Any	3332 (19.4)	7.8-71.8		3162 (14.9)	3.9-61.6	
Complex	1138 (6.6)	1.1-41.3		729 (3.4)	0.0-32.6	
Referred	9287 (53.9)	6.9-99.2	980	6789 (31.9)	3.9-99.3	185
Triage urgency			529			647
Low: standard, non-urgent	9794 (56.9)	10.9-86.5		14291 (67.2)	8.8-93.9	
High: immediate, very urgent, intermediate	6890 (40.0)	13.5-86.8		6329 (29.8)	6.1-89.9	
Feverkidstool						
Temperature in °C, median (IQR)	37.8 (37-38.5)		809	37.7 (36.9-38.4)		2211
Fever duration in days, median (IQR)	1.5 (0.5-3)		875	1.5 (0.5-3.0)		1900
Tachypnea (APLS)	3585 (20.8)	5.9-45.8	4186	4942 (23.2)	2.4-48.3	4607
Tachycardia (APLS)	6001 (34.9)	11.0-54.9	887	6854 (32.2)	11.4-49.4	2620
Hypoxia <95%	762 (4.4)	1.3-9.2	2538	733 (3.4)	0.3-12.9	3043
Prolonged capillary refill (>3 sec)	339 (1.9)	0.2-7.0	2503	84 (0.4)	0.0-2.6	1928
Work of breathing	913 (5.3)	0.5-13.2	2315	1732 (8.1)	0.0-35.6	3176
Ill appearance	4742 (27.5)	1.9-52.6	664	1265 (5.9)	0.4-43.3	1057
CRP in mg/L, median (IQR)	17 (5-49)		7	NA		
NICE Warning signs						
Decreased consciousness	148 (0.9)	0.1-5.4	150	53 (0.2)	0.0-1.8	240
Meningeal signs	126 (0.7)	0.1-3.7	943	11 (0.1)	0.0-0.1	1101
Focal neurology	102 (0.6)	0.0-3.7	1376	31 (0.1)	0.0-1.8	1081
Status epilepticus	51 (0.3)	0.0-2.3	940	15 (0.1)	0.0-1.2	201
Rash: petechiae/non blanching	664 (3.9)	1.1-18.0	1307	448 (2.1)	0.4-4.1	3106
Blood cultures performed	3478 (20.2)	0.5-73.7		88 (0.4)	0.0-2.0	
CSF performed	444 (2.6)	0.2-13.5		8 (0.0)	0.0-0.2	
Admission to the ward >24 hours	6590 (38.3)	18.0-63.8	175	668 (3.1)	0.9-29.6	347
Admission to the ICU	135 (0.8)	0.3-5.4	21	23 (0.1)	0.0-2.4	35
Antibiotic treatment following ED visit	6795 (39.5)	27.9-70.8	211	5504 (25.9)	16.9-43.0	273
Lifesaving interventions: airway, breathing or hemodynamic support	371 (2.2)	0.0-11.5		112 (0.5)	0.0-3.0	
Urinary tract infection	935 (5.4)	3.2-9.7	4	418 (1.9)	0.9-3.8	23

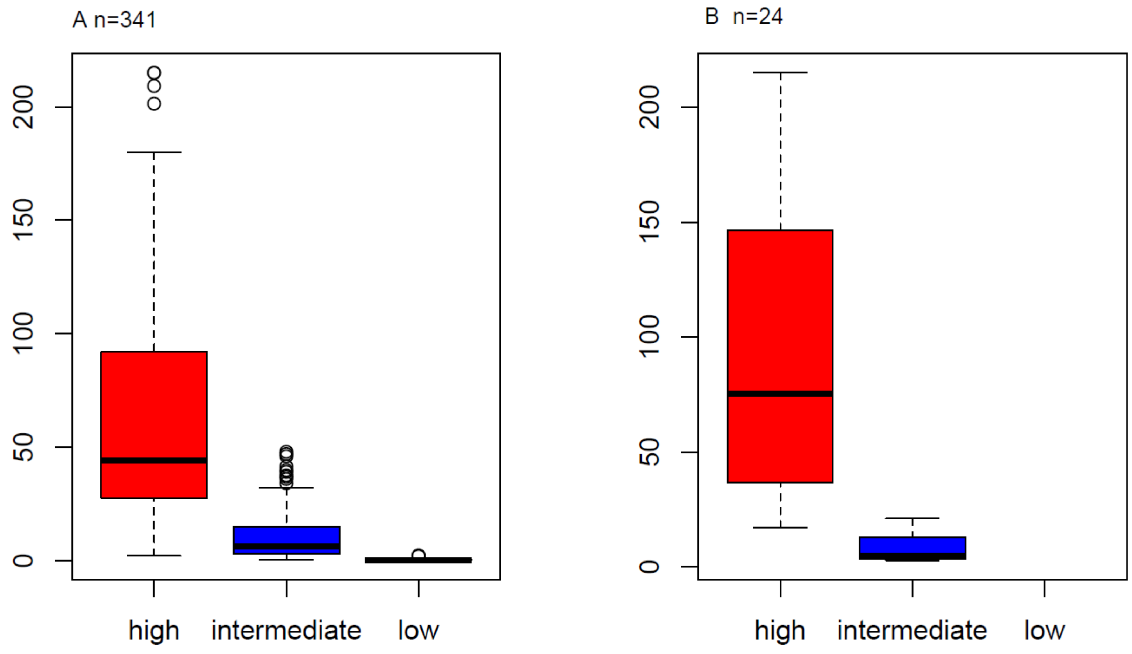
APLS, advanced paediatric life support; CRP, C-reactive protein; CSF, cerebrospinal fluid; ED, emergency department; ICU, intensive care unit; IQR, interquartile range; NA, not applicable

Appendix 6: Details of patients with complex chronic conditions

Identified pathogen stratified for complex chronic comorbidity

Identified pathogen	No complex chronic condition , n=85 n (%)	Complex chronic condition , n=50 n (%)
Strep. pneumoniae	23 (27.1%)	5 (10%)
Staph. aureus	15 (17.6%)	10 (20%)
E. coli	9 (10.6%)	4 (8%)
Neisseria meningitidis	9 (10.6%)	1 (2%)
Kingella kingae	7 (8.2%)	0 (0%)
Group B streptococcus	6 (7.1%)	0 (0%)
Group A streptococcus	5 (5.9%)	1 (2%)
Salmonella spp	4 (4.7%)	1 (2%)
Haemophilus influenzae	4 (4.7%)	0 (0%)
Enterobacter spp	2 (2.4%)	1 (2%)
Coagulase-negative staphylococci (CoNS)		9 (18%)
Candida species		4 (8%)
Viridans streptococci		4 (8%)
Klebsiella spp		3 (6%)
Enterococcus spp		3 (6%)
Moraxella spp		1 (2%)
Other	1 (1.2%)	3 (6%)

C-reactive protein level in immunocompromised patients for no IBI (A) vs IBI (B) for IBI risk categories



Appendix 7: Univariate logistic regression analysis for invasive bacterial infection.

Supplementary file 5:
Univariate logistic regression analysis for invasive bacterial infection.
N=16268, IBI cases N=135

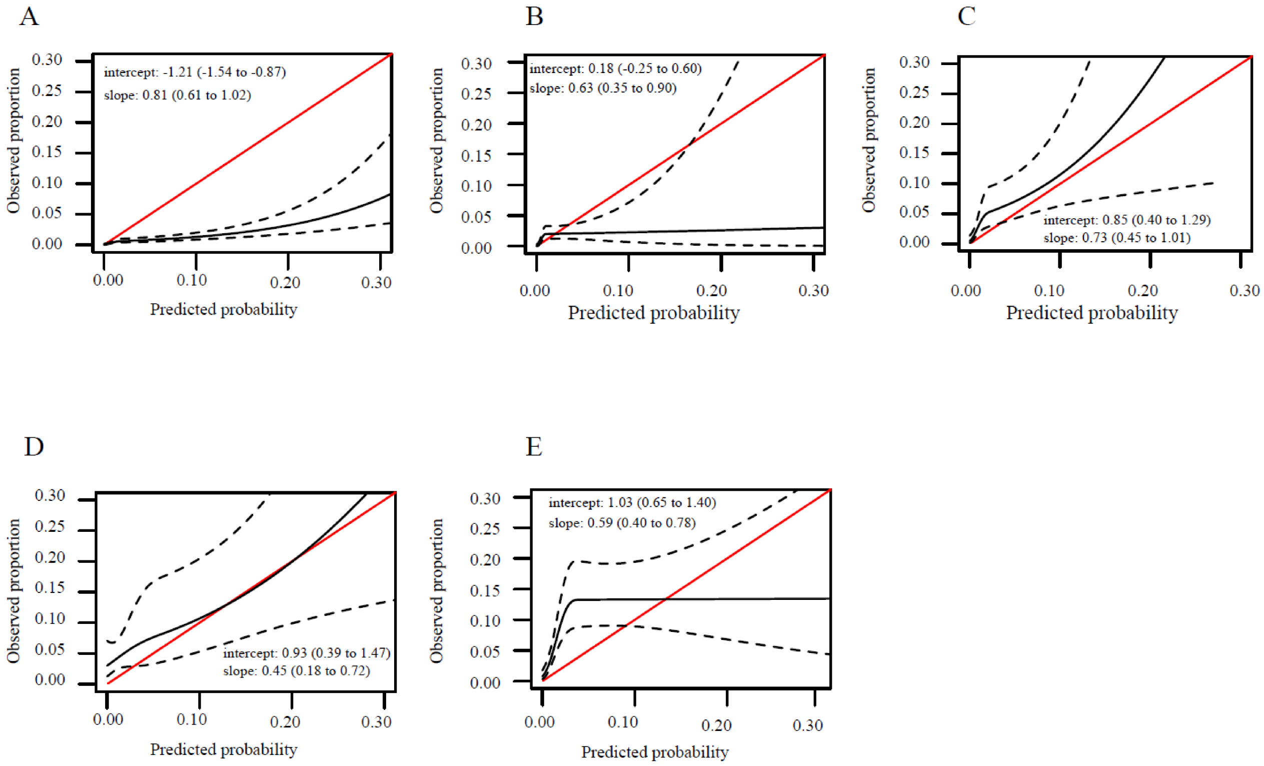
Variables	**OR (95%CI)***
Feverkidstool	
Male	1.04 (0.74-1.46)
Age <1 year±	0.25 (0.14-0.43)*
Age >1 year±	1.01 (0.97-1.05)
Temperature in °C	1.34 (1.13-1.59)*
Fever duration in days	0.89 (0.80-0.99)*
Tachypnea (APLS)	1.50 (1.03-2.18)*
Tachycardia (APLS)	2.84 (2.01-4.01)*
o2 saturation <94%	0.65 (0.24-1.75)
Prolonged capillary refill time (>3 sec)	2.62 (1.24-5.56)*
Presence of work of breathing	1.62 (0.90-2.93)
Ill appearance	2.51 (1.76-3.58)*
Ln CRP	1.89 (1.63-2.19)*
NICE alarming signs	
Status epilepticus	No cases
Reduced level of consciousness	4.70 (2.04-10.83)*
Focal neurology	2.30 (0.54-9.71)
Meningeal signs	9.20 (4.54-18.62)*
Abnormal neurology: decreased level of consciousness, presence of meningeal signs or focal neurology	4.81 (2.61-8.91)
Non-blanching rash	2.31 (1.21-4.41)*
Chronic condition	
Complex chronic condition	8.83 (6.19-12.59)*

*Significant, p<0.05

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

APLS, Advanced Paediatric Life Support; CRP, C-reactive protein; ln, natural log

Appendix 8: **Calibration plot: observed proportion vs predicted probability of the clinical prediction model for 5 internal-external cross-validations.**



The solid red line with a slope of 1 and intercept of 0 represents ideal prediction accuracy. The dotted lines indicate the 95% confidence interval.

A, Model developed on leave-out EDs with <10 cases, validated on EDs with <10 cases
B, Model developed on leave-out Ljubljana (Slovenia), validated on Ljubljana (Slovenia)

C, Model developed on leave-out London (UK), validated on London (UK)

D, Model developed on leave-out Nijmegen (the Netherlands), validated on Nijmegen, UMC (the Netherlands)

E, Model developed on leave-out Rotterdam (the Netherlands), validated on Rotterdam (the Netherlands)

Legend: ED, emergency department; UK, united kingdom; UMC, University Medical Centre

Appendix 9: Model 2 – model specification and performance

In model 2 the variable ED with low/high IBI incidence is added to the model.

Model 2 – model specification

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

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

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

CRP, C-reactive protein; IBI, invasive bacterial infection; ln, natural log

Model 2 - performance

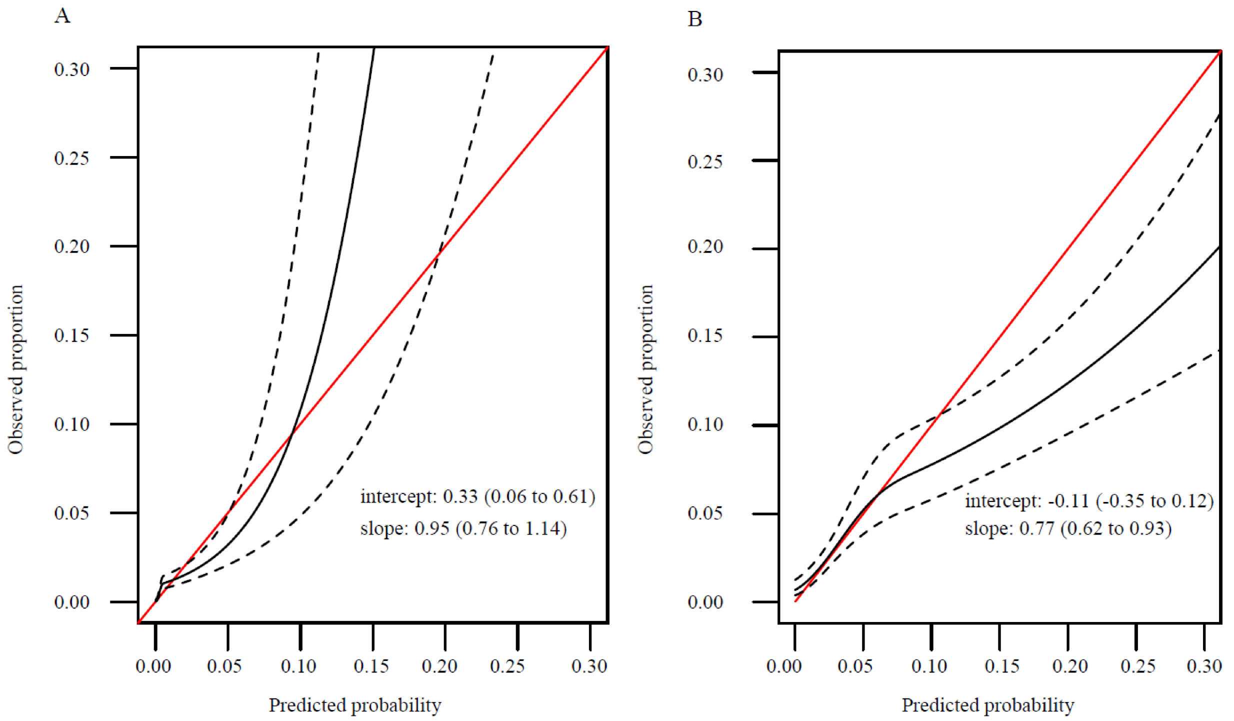
Discrimination:

Development model 2: C-statistic 0.88 (95%CI 0.85-0.90)

Calibration:

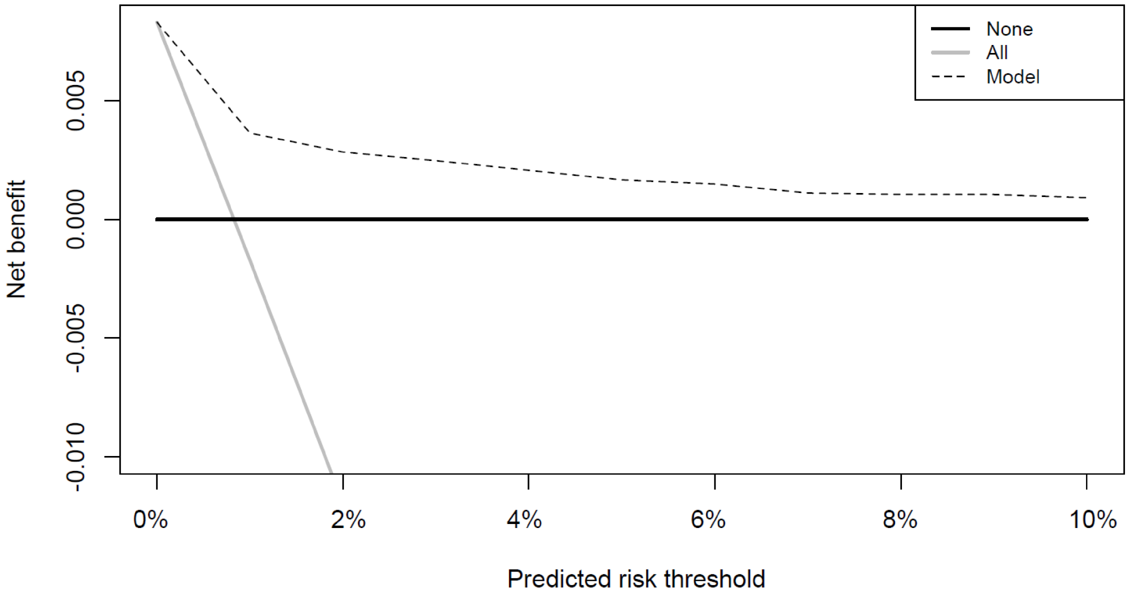
Apparent calibration for model 2 for IBI (addition of variable ED with low IBI incidence (<2%) / ED with high IBI incidence (>=2%)). Risk predictions are calculated on the developed model using all data (n=16268). These risk predictions are calibrated in the two groups: EDs with low IBI incidence (A) and EDs with high IBI incidence (B). ED, emergency department; IBI, invasive bacterial infection

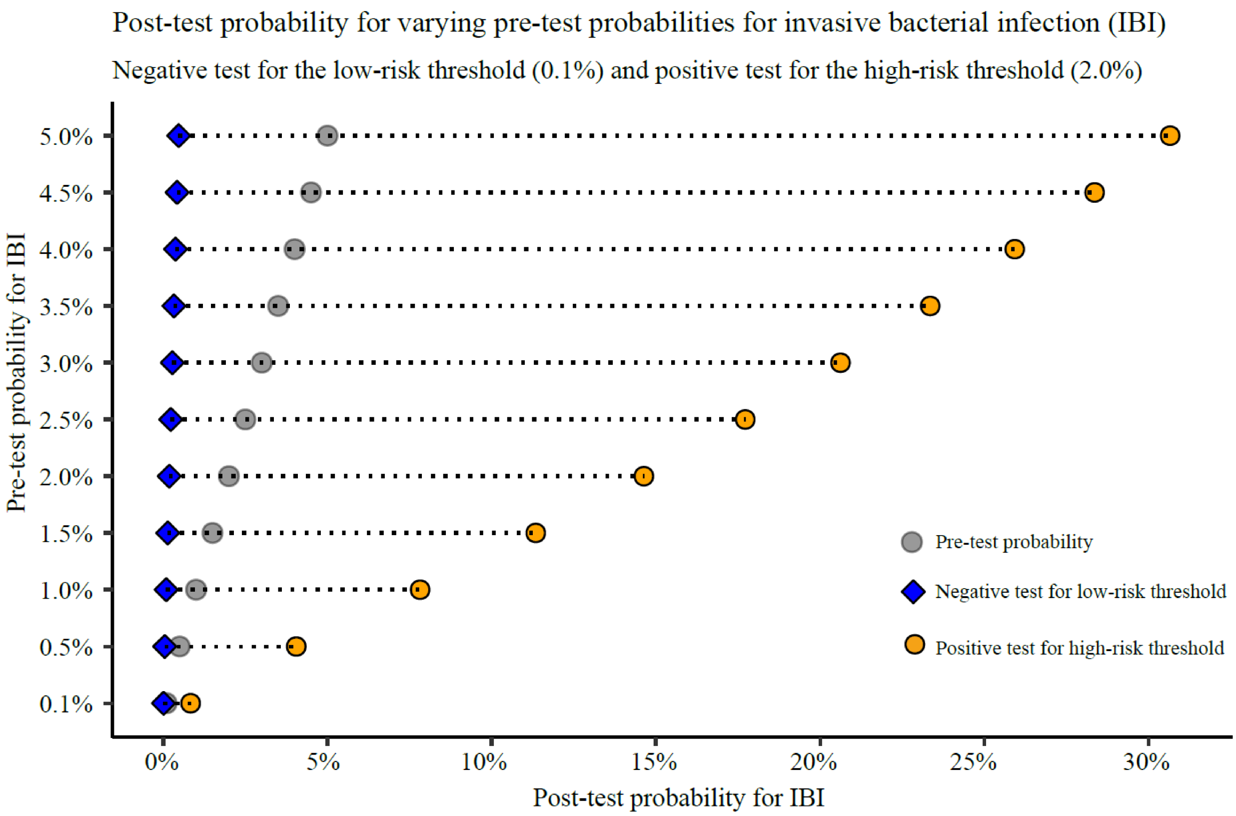
Calibration plot: apparent calibration for model 2 for IBI (addition of variable ED with low IBI incidence (<2%) / ED with high incidence (>=2%)



Appendix 10: Performance of the prediction model (model 1)

Decision curve analysis





Appendix 11: Sensitivity analysis: model development on population with imputed CRP-level (n=37093)

Model specification of multivariate logistic model for IBI based on population with imputed CRP-level (n=37093)

		Coefficients	OR
	(Intercept)	-9.67	0.00
Feverkidstool	Male	-0.19	0.83
	Age < 1 year*	-2.58	0.08
	Age >1 year*	0.00	1.00
	Temperature	-0.05	0.95
	Fever duration in days	-0.15	0.86
	Tachypnea	-0.43	0.65
	Tachycardia	0.71	2.03
	Hypoxia	-0.86	0.42
	Prolonged capillary refill	0.02	1.02
	Increased work of breathing	-0.34	0.71
	Ill appearance	0.94	2.55
	Ln CRP	0.78	2.17
NICE warning signs	Abnormal neurology	1.54	4.66
	Non-blanching rash	1.40	4.04
Comorbidity	Complex chronic condition	2.43	11.3

*The risk of children aged < 1 year was calculated: $\beta_{(age <1 year)}$×age in years. The risk of children aged < 1 year was calculated: β(age <1 year)×age in years.
The risk of children aged >1 years was calculated with: β(age <1 year)×1+β(age ≥1 year)×(age in years−1).

CRP, C-reactive protein; ln, natural log

Appendix 12: Clinical case examples

Case 1:
A previously healthy, 4 year old boy presents with fever since 1.5 day.
At the ED he has a temperature of 38.9 degrees, heart rate of 160/min, respiratory rate of 45/min, oxygen saturation of 99% and normal capillary refill time. He is ill-appearing, has increased work of breathing and a normal neurological exam.
CRP-level = 10 mg/L.

Risk-prediction:
The patient is at intermediate-risk (>0.1% and <2%) for an invasive bacterial infection.

Case 2:
A previously healthy neonate of 2 months presents with fever since 12 hours.
She has temperature of 38.8 degrees, heart rate of 170/min, respiratory rate of 35/min, normal oxygen saturation and normal capillary refill time. She is ill-appearing and has no increased work of breathing.
Neurological exam is normal.
CRP-level = 5 mg/L.

Risk-prediction:
The patient is at high-risk (>2%) for an invasive bacterial infection.

Hagedoorn NN, *et al. Arch Dis Child* 2020;0:1–7. doi: 10.1136/archdischild-2020-319794

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