

Supplementary

Figure 1. Flowchart of included patients

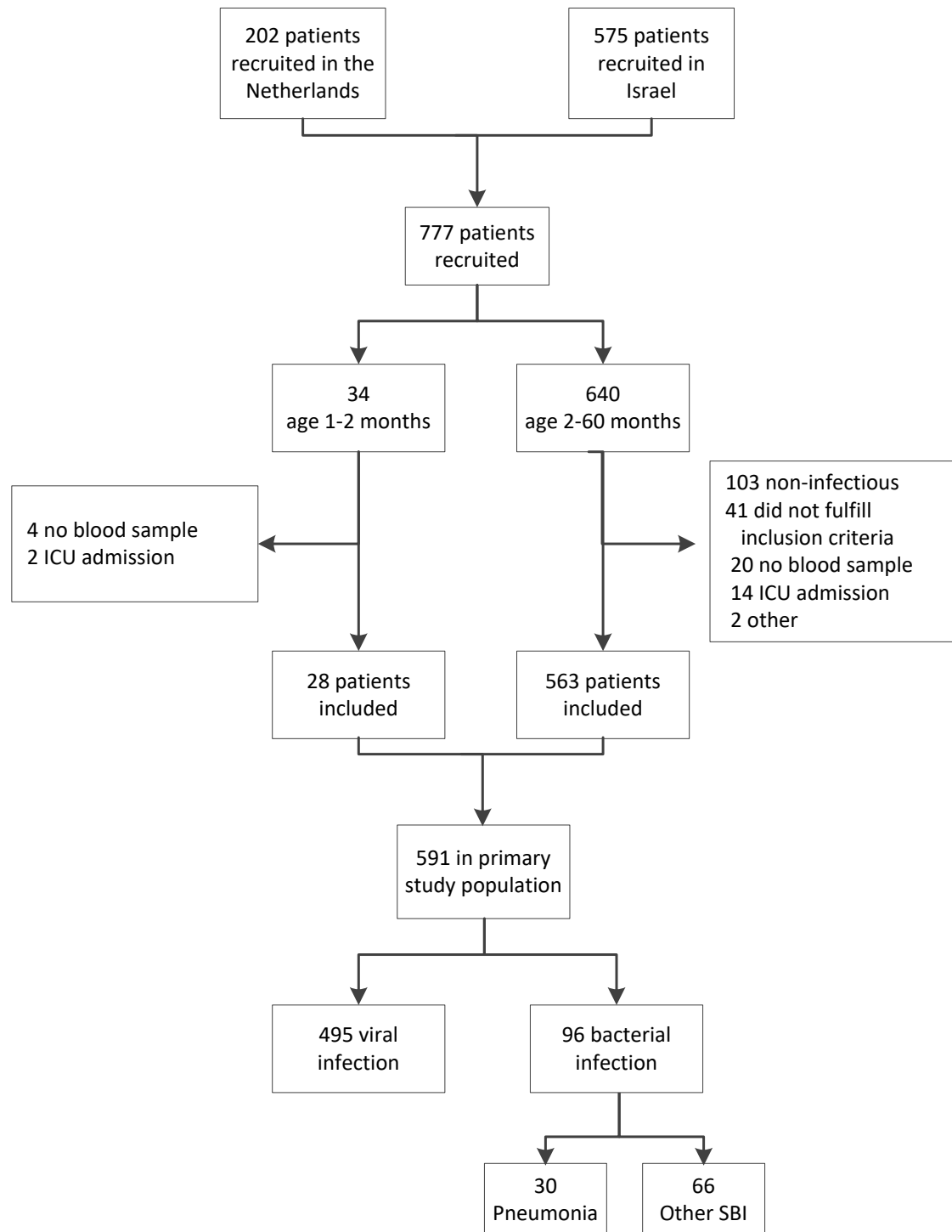


Figure 2. Receiver operating characteristics (ROC) curve of sensitivity versus specificity for the original and updated Feverkidstool.

Area under the receiving operating curve (c-statistic) for the original and for the updated Feverkidstool for pneumonia and other SBI are shown in the figure. The c-statistic difference for pneumonia is 0.09 and 0.05 for other SBI. FKT: Feverkidstool, SBI: serious bacterial infection.

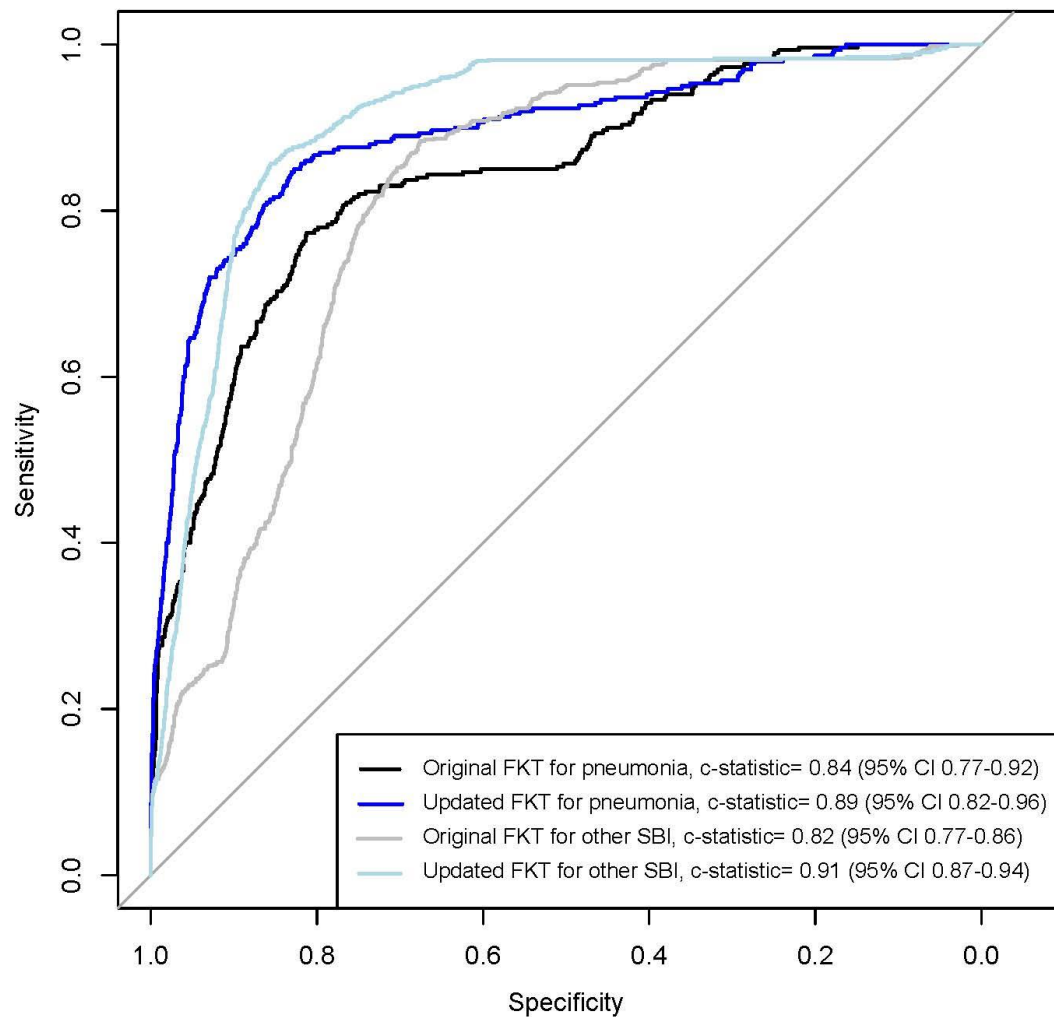


Table 1. Characteristics of patients with and without reference standard

Clinical syndrome was based on the diagnosis of the attending physician at discharge from the hospital. LRTI included pneumonia and bronchiolitis; URTI included laryngitis, pharyngitis, otitis media, sinusitis and tonsillitis. Baseline characteristics of excluded patients are shown in the supplementary material. *p-values of differences between bacterial and viral infections.

	Viral and bacterial reference standard diagnosis (n=520)	Inconclusive reference standard diagnosis (n=71)	p-value
Predictor variables			
Age (years), median (IQR)	1.2(0.6-2.4)	1.7(1.0-3.0)	0.01
Gender, male, n (%)	289(56%)	42(59%)	0.61
Duration of fever (days), median (IQR)	2(1-4)	2(1-4)	0.80
Temperature (°C), median (IQR)	38.5(37.7-39.2)	38.6(37.8-39.3)	0.49
Respiratory rate, mean (SD)	42(16)	39(12)	0.35
Tachypnea, n (%)	140(27%)	19(27%)	0.74
Heart rate, mean (SD)	152(24)	151(25)	0.92
Tachycardia, n(%)	248(48%)	34(48%)	0.77
Oxygen saturation %O ₂ , median (IQR)	98(97-100)	98(96-100)	0.41
Desaturation, <94%O ₂ , n (%)	25(5%)	0(0%)	0.10
Chest wall retractions, n (%)	67(13%)	3(4%)	0.045
Ill appearance, n (%)	153(29%)	26(37%)	0.22
C-reactive protein (mg/l), median (IQR)	18(7-46)	53(18-83)	<0.001
Assay score, median (IQR)	7(1-40)	35(5-88)	<0.001
Other variables			
Hospital admission n (%)	290(56%)	38(54%)	0.70
Hospitalization duration (days), median (IQR)	3(2-4)	3(2-5)	0.08
Antibiotic treatment prescribed n (%)	180(35%)	53(75%)	<0.001
Recruiting site			0.80
Secondary care centre, n (%)	487(94%)	66(93%)	
Tertiary care centre, n (%)	33(6%)	5(7%)	
Clinical syndrome			0.21
Bacteraemia /viraemia	10(2%)	1(1%)	
Central nervous system	9(2%)	0(0%)	
Fever without source	164(32%)	16(23%)	
Gastro-enteritis	19(4%)	1(1%)	
Lower respiratory tract infection	127(24%)	17(24%)	
Upper respiratory tract infection	127(24%)	23(32%)	
Urinary tract infection	22(4%)	2(3%)	
Other	42(8%)	11(16%)	

Table 2. Sensitivity analysis of the cohort without imputed reference standard diagnoses

Presented data are c-statistics and 95% confidence intervals

	Pneumonia	Other SBIs
Original Feverkidstool	0.87(0.79-0.95)	0.82(0.76-0.88)
Updated Feverkidstool	0.91(0.83-0.98)	0.91(0.86-0.95)

Table 3. Description of recalibration of the Feverkidstool and the updated model

Linear predictors for pneumonia and other SBI Feverkidstool are calculated as defined previously [1]:

*LP (pneumonia Feverkidstool) = -17.9 (Intercept) + 1.02 * Age (max 1 year, in years) + 0.01 * Age (if >1 year: age in years - 1) + 0.13 * Sex (female) + 0.29 * Temperature (°C) + 0.21 * Duration of fever (days) + 0.44 * Presence of tachypnoea - 0.04 * Presence of tachycardia + 1.59 * Oxygen saturation <94% - 0.18 * Capillary refill time (>3s) + 0.47 * Presence of chest wall retractions + 0.16 * ill appearance + 0.64 * Ln(CRP) (mg/l)*

*LP (other SBI Feverkidstool) = -4.7 (Intercept) - 1.73 * Age (max 1 year, in years) + 0.11 * Age (if >1 year: age in years - 1) + 0.70 * Sex (female) - 0.02 * Temperature (°C) - 0.03 * Duration of fever (days) - 0.11 * Presence of tachypnoea - 0.02 * Presence of tachycardia - 3.29 * Oxygen saturation <94% + 0.30 * Capillary refill time (>3s) - 3.78 * Presence of chest wall retractions + 0.27 * ill appearance + 1.14 * Ln(CRP) (mg/l)*

where LP refers to the linear predictor in a (polytomous) logistic regression model.

We used the fixed intercept and coefficients within the original Feverkidstool, but used the outcome as a linear predictor in our logistic recalibration model and in the updated model. This resulted in the following (polytomous) logistic regression models:

Recalibration of original Feverkidstool:

LP1 = -0.58 + 1.28 (LP pneumonia Feverkidstool)

LP2 = -0.02 + 0.54 (LP other SBI Feverkidstool)

Updated Feverkidstool, including combination assay:

LP3 = -4.19 + 0.59 (LP pneumonia Feverkidstool, with median CRP for all patients) + 0.05 (score Assay)

LP4 = -3.57 + 0.24 (LP other SBI Feverkidstool, with median CRP for all patients) + 0.05 (score Assay)

Probabilities of the outcomes are calculated with:

Original Feverkidstool Risk (pneumonia) = $e^{LP1} / (1 + e^{LP1} + e^{LP2})$

Original Feverkidstool Risk (other SBI) = $e^{LP2} / (1 + e^{LP1} + e^{LP2})$,

Updated Feverkidstool Risk (pneumonia) = $e^{LP3} / (1 + e^{LP3} + e^{LP4})$

Updated Feverkidstool Risk (other SBI) = $e^{LP4} / (1 + e^{LP3} + e^{LP4})$, [2, 3]

References

1. Nijman RG, Vergouwe Y, Thompson M, van Veen M, van Meurs AH, van der Lei J, et al. Clinical prediction model to aid emergency doctors managing febrile children at risk of serious bacterial infections: diagnostic study. *Bmj*. 2013;346:f1706.
2. Begg CB, Gray R. Calculation of polychotomous logistic-regression parameters using individualized regressions. *Biometrika*. 1984(71):11-8.
3. Wijesinha A, Begg CB, Funkenstein HH, McNeil BJ. Methodology for the differential diagnosis of a complex data set. A case study using data from routine CT scan examinations. *Medical decision making : an international journal of the Society for Medical Decision Making*. 1983;3(2):133-54.