External validation of a multivariable prediction model for identification of pneumonia and other serious bacterial infections in febrile immunocompromised children

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Abstract

Objective

To externally validate and update the *Feverkids* tool clinical prediction model for differentiating bacterial pneumonia and other serious bacterial infections (SBIs) from non-SBI causes of fever in immunocompromised children.

Design

International, multicentre, prospective observational study embedded in PErsonalised Risk assessment in Febrile illness to Optimise Real-life Management across the European Union (PERFORM).

Setting

Fifteen teaching hospitals in nine European countries.

Participants

Febrile immunocompromised children aged 0-18 years.

Methods

The *Feverkids* clinical prediction model predicted the probability of bacterial pneumonia, other SBI or no SBI. Model discrimination, calibration and diagnostic performance at different risk thresholds were assessed. The model was then re-fitted and updated.

Results

Of 558 episodes, 21 had bacterial pneumonia, 104 other SBI, and 433 no SBI. Discrimination was 0.83 (95%CI 0.71-0.90) for bacterial pneumonia, with moderate calibration and 0.67 (0.61-0.72) for other SBIs, with poor calibration. After model re-fitting, discrimination improved to 0.88 (0.79-0.96) and 0.71 (0.65-0.76) and calibration improved. Predicted risk <1% ruled out bacterial pneumonia with sensitivity 0.95 (0.86-1.00) and negative likelihood ratio (LR) 0.09 (0.00-0.32). Predicted risk >10% ruled in bacterial pneumonia with specificity 0.91 (0.88-0.94) and positive LR 6.51 (3.71-10.3). Predicted risk <10% ruled out other SBIs with sensitivity 0.92 (0.87-0.97) and negative LR 0.32 (0.13-0.57). Predicted risk >30% ruled in other SBIs with specificity 0.89 (0.86-0.92) and positive LR 2.86 (1.91-4.25).

Conclusion

Discrimination and calibration were good for bacterial pneumonia but poorer for other SBIs. The rule-out thresholds have the potential to reduce unnecessary investigations and antibiotics in this high-risk group.

Introduction

Children with immunocompromising conditions, including primary immunodeficiencies (PID) or immunodeficiencies secondary to malignancy, transplantation, chemotherapy and immunosuppressive drugs, are at high risk (HR) of serious bacterial infections (SBI) [1-3]. They may present with atypical features [4] and fever may be the only sign of infection [5]. They may also develop fever due to viral, fungal and non-infectious causes [6].

Differentiating between causes of fever in immunocompromised children is a challenge which results in frequent usage of empirical broad-spectrum antibiotics, which has reduced mortality but contributes to antimicrobial drug resistance [7]. There is a need for clinical prediction tools for SBI in this high-risk population.

Clinical prediction models have been developed for the emergency department setting to assist in identifying the small number of children with SBIs [8-10]. However, these studies largely excluded children with immunocompromise, as do UK guidelines [11]. While prediction models have been derived [12-18] and validated [19] for children with febrile neutropenia, these are not in routine clinical use and they do not address fever in non-neutropenic immunocompromised patients.

The *Feverkids* tool multivariate clinical prediction model uses clinical variables available at presentation and admission C-reactive protein (CRP) to predict the risk of bacterial pneumonia and other serious bacterial infections (SBI) versus no SBI [8]. SBI is a heterogeneous group composed of several types of bacterial infection, with clinical signs contributing differently to diagnosis and with distinct diagnostic approaches and management. The division of SBIs into bacterial pneumonia and other SBIs in this multivariate model allows prediction of the risk of these SBIs separately.

The model was derived in two populations of febrile children presenting to ED in the Netherlands and externally validated in the UK [8]. It has since been further externally validated [20] and assessed for impact [21, 22]. Patients with immunocompromise were excluded during development, although a recent predictive model for invasive bacterial infection (IBI) based on *Feverkids* variables included children with comorbidities including immunocompromise [23].

This study externally validates the *Feverkids* tool clinical prediction model in immunocompromised children.

Methods

This prospective, international, multicentre, observational study is embedded within the Personalised Risk assessment in Febrile illness to Optimise Real-life Management across the European Union (PERFORM) study [24]. Reporting is in accordance with the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) guidelines (Appendix 1).

Participants

Recruitment was between 2nd June 2016 and 31st December 2019. Children <18 years old were eligible for inclusion if they had an immunocompromising condition and presented to a participating hospital's emergency department, ward or intensive care unit with fever ≥38.0°C, history of fever within 72 hours, or suspicion of infection, and had a clinical indication for blood investigations. Participants could have multiple episodes a minimum of two weeks apart.

Immunocompromising conditions included primary immunodeficiency or secondary immunodeficiency, haematological or solid organ malignancy, human immunodeficiency virus (HIV), haematopoietic or solid organ transplant, or receipt of immunosuppressive medications within the last two weeks. Medications which qualified a patient for inclusion in this study included systemic anticancer chemotherapy, oral or intravenous steroids, methotrexate, tacrolimus, ciclosporin, colchicine, defibrotide, immunoglobulin, biologic agents, and other immunosuppressants. No specific steroid dose or duration was defined for inclusion, however almost all participants either received steroids in conjunction with other immunosuppressants, were receiving high doses intravenously, or were on lower doses long term.

Participants were recruited from fifteen tertiary centres in nine countries: four sites in the United Kingdom and the Netherlands and one site in Austria, Germany, Greece, Latvia, Slovenia, Spain, and Switzerland. Eight patients recruited to a site in The Gambia were excluded. Participant involvement lasted for the illness episode plus 28 days.

Outcome measures

Diagnosis was made by experienced paediatricians following a reference standard [25]. This classifies episodes into one of eleven phenotypes: definite bacterial, probable bacterial, bacterial syndrome, unknown bacterial/viral, viral syndrome, probable viral, definite viral, trivial illness, other infection, uncertain infection/inflammation, or inflammatory syndrome. All centres had training in applying the reference standard and difficult classifications were discussed with consortium experts.

To compare with the original model study [8], these phenotypes were further grouped into three categories: bacterial pneumonia, other serious bacterial infections (other SBIs) and no SBI.

Bacterial pneumonia was diagnosed in PERFORM 'definite/probable bacterial/bacterial syndrome' cases where there were clinical symptoms compatible with acute respiratory infection and radiological evidence of bacterial pneumonia.

Other SBIs were diagnosed in PERFORM 'definite/probable bacterial/bacterial syndrome' cases where there was a positive blood, urine or cerebrospinal fluid culture, or localising features of infection indicative of a serious bacterial infection (e.g. sepsis [26], cellulitis, meningitis, abscess, urinary tract infection, bacterial upper respiratory tract infection, osteomyelitis, or infectious diarrhoea with a pathogenic stool organism). Uncomplicated pharyngitis, cystitis, and soft tissue infection without systemic features were not included as other SBIs.

'No SBI' was diagnosed in the absence of bacterial pneumonia or other SBI. This included probable or definite viral illness, a non-infectious cause, or an uncertain diagnosis. Episodes of febrile neutropenia without a positive sterile-site culture, sepsis syndrome or localising symptoms of bacterial infection were classified as having no SBI. Patients with parasitic infection were excluded.

Details of the underlying causes of immunocompromise, immunosuppressing medications, and the clinical phenotypes of the PERFORM HR cohort are described in van der Velden et al. [27].

Predictor variables

The *Feverkids* clinical prediction model uses eleven predictor variables which are available at the time of presentation: age, sex, temperature, duration of fever, tachycardia, tachypnoea, ill appearance, chest

wall retractions, prolonged capillary refill time (>3 seconds), oxygen saturation <94%, and C-reactive protein [8] (Appendix 2). The prediction model was applied to calculate the predicted risk of bacterial pneumonia and of other SBIs as a group.

Statistical analysis

Statistical analysis was performed in R 4.0.5. The required sample size to validate the model was calculated at n=59 cases for bacterial pneumonia and n=71 for other SBIs [28]. Missing values were imputed 10 times using Multiple Imputation by Chained Equations [29]. The imputation model included all predictor variables, diagnostic outcome, recruitment site, category of immunosuppressive condition and whether the patient was receiving immunosuppressive drugs/chemotherapy, had neutropenia with neutrophils <0.5 x 10^9/L or had any NICE red traffic light features (neurological symptoms, non-blanching rash) [11]. A complete case analysis was also performed.

Discrimination plots were used to compare the predicted risks for bacterial pneumonia and for other SBIs for each outcome category [30].

To quantify the ability to discriminate between bacterial pneumonia, other SBIs and no SBI, the pairwise C-statistic (equal to the area under the receiver operating curve AUC) was calculated for pairs of outcomes (pneumonia and no SBI, and other SBI and no SBI) [30]. The polytomous discrimination index (PDI) was calculated. The PDI assess discriminative ability, considering all possible outcome categories n, where the value indicating a non-informative test is $1/n$ and a value of 1 indicates a perfect discriminating test. The PDI is the average of category-specific polytomous discrimination indices, each of which separately reflects the ability to predict a case better than non-cases for all outcome categories of interest [31, 32].

Model calibration, which describes the agreement between the predicted risks and observed number of events, is important for models intended to inform decision-making. To assess calibration, the predicted risks of pneumonia were compared with the observed proportions of pneumonia and the predicted risks of other SBIs were compared with the observed proportions of other SBIs. Calibration intercept (ideally 0) and slope (ideally 1) were reported and flexible calibration curves were plotted [33].

Diagnostic performance (sensitivity, specificity, positive and negative predictive values, and positive and negative likelihood ratios) was assessed for risk thresholds between 1% and 30% for children with bacterial pneumonia compared with all others (children with other SBIs and with no SBI) and for children with other SBIs compared with all others (children with pneumonia and with no SBI). No established risk thresholds for determining whether to request additional diagnostic tests or initiate antibiotic therapy exist in this population. The thresholds were chosen to facilitate comparison with the original *Feverkids* study and to encompass possible high- and low-risk cut-offs.

Model update

The model was updated by re-fitting a polytomous multivariable prediction model to this cohort using the *Feverkids* variables (Appendix 2). The model was then further developed by incorporating other variables of clinical interest: neutropenia with neutrophils $<0.5 \times 10^9$/L and NICE red traffic light features (neurological symptoms, non-blanching rash) [11] and by exploring the effect of restricting other SBIs to only those with invasive bacterial infection (IBI), those with isolation of pathogenic bacteria from blood, cerebrospinal fluid, or synovial fluid [23].

Results

Population characteristics

Of 592 episodes, 31 episodes were excluded as they did not have a minimum of two clinical model predictor variables and three patients with a final diagnosis of a parasitic infection were also excluded. 558 episodes were included following imputation of missing values. There were 21 cases of bacterial pneumonia (3.8%), 104 cases of other SBI (18.8%) and 433 cases of no SBI.

Table 1 describes the participant characteristics. Table 2 details the source of other SBIs.

The most common cause of other SBI was central line associated blood stream infection (CLABSI, n=34) followed by bacteraemia due to any other cause (n=13). 59 participants had invasive bacterial infection (IBI). This group was comprised of the 59 participants with CLABSI and 13 with other causes of bacteraemia, plus one participant with a cerebrospinal fluid culture positive for *Neisseria meningitidis* without demonstrated bacteraemia.

Of 433 patients with no SBI, 70 had a probable viral illness and 55 had a definite viral illness confirmed with a positive viral PCR. Non-infectious causes of illness included adverse effects of treatment for malignancy or haematopoietic transplant and inflammatory conditions. 116 (27%) of those with no SBI had a chest radiograph and 349 (81%) received empirical antibiotics.

Validation of the original prediction model

Figure 1 shows discrimination plots comparing the predicted risks of (a) bacterial pneumonia and (b) other SBI for each outcome category. The *Feverkids* tool showed good external validity for prediction of bacterial pneumonia, with area under the curve (AUC) 0.83 (95% CI: 0.74-0.93) (Figure 2a). The AUC for other SBI prediction was 0.67 (0.61-0.72) (Figure 2b). The polytomous discrimination index of the model was 0.55 (0.48-0.63).

An analysis of complete cases (n=323) showed AUC for bacterial pneumonia prediction (n=16) was 0.81 (0.68-0.95) and the AUC for other SBI prediction (n=64) was 0.63 (0.56-0.71).

Model calibration

Calibration curves for the prediction of bacterial pneumonia and other SBIs are shown in Figure 3. The calibration for bacterial pneumonia was good, with slope 0.93 (95% CI 0.59-1.27) and intercept -0.54 (95% CI -1.01-0.08). Calibration for prediction of other SBIs was poorer, with slope 0.36 (0.23-0.49) and intercept 1.00 (0.75-1.25).

Model update

The re-fitted model (Appendix 2) showed improved AUC for bacterial pneumonia of 0.88 (95% CI 0.79-0.96) and 0.71 (0.65-0.76) for other SBIs (Figure 4). The PDI improved to 0.65 (0.59-0.76) and calibration of both models improved (Figure 5).

The addition of the variables neutropenia ($<0.5 \times 10^9$/L), neurological signs and non-blanching rash did not significantly improve the AUC for bacterial pneumonia (0.88 (0.75-0.95)) or other SBIs (0.72 (0.67-0.78)). Restricting the other SBI category to only those with IBI (n=59) resulted in a model with similar performance, with AUC for prediction of pneumonia of 0.88 (0.76-0.95) and for other IBIs of 0.69 (0.62-0.75).

Diagnostic thresholds

The dichotomous diagnostic performance measures for bacterial pneumonia and other SBIs at different risk thresholds for the re-fitted model are detailed in Table 3.

Low-risk rule-out thresholds were identified, where a clinician might reasonably stop diagnostic workup. 49% of participants had a predicted risk of bacterial pneumonia ≤1%. This low-risk threshold ruled out bacterial pneumonia with sensitivity of 0.95 (95% CI 0.86-1.00) and negative likelihood ratio (LR) of 0.09 (0.00-0.32).

22% of participants had a predicted risk of SBI of ≤10%. This low-risk threshold ruled out other SBIs with sensitivity of 0.92 (0.87-0.97) and negative LR of 0.32 (0.13-0.57).

11% of participants were above a high-risk threshold of 10% for bacterial pneumonia, which identified bacterial pneumonia with specificity of 0.91 (0.88-0.94) and positive LR of 6.51 (3.71-10.3). 15% of participants were above a high-risk threshold of 30% for other SBIs, which identified other SBIs with specificity 0.89 (0.86-0.92) and positive LR of 2.86 (1.91-4.25).

Discussion

Interpretation and clinical implications

This study assesses the external validity of the *Feverkids* tool in a heterogeneous group of immunocompromised children.

The discriminative ability of the model to predict bacterial pneumonia in this cohort was good, with performance comparable to the derivation and external validation cohorts of healthy children [8] and with adequate calibration.

The discriminative ability of the model to predict other SBIs in this study was poorer than in the derivation cohort (AUC 0.86) but comparable to the external validation cohort (AUC 0.69) [8]. This may be due to differences in case mix: bacterial pneumonia and UTI were the most common SBIs in the original study, and in this cohort, central line-associated bloodstream infection (CLABSI) was the most common cause of SBI. This population also has a higher incidence of non-SBI conditions causing

severe illness, such as inflammatory conditions and invasive fungal disease, which contribute to the poorer performance of the predictive tool for other SBIs.

Importantly, the higher rate of SBI in this cohort limits the utility of the model, as it systematically under-estimated the risk of other SBIs. This improved with re-fitting.

Concerns about missing SBIs in immunocompromised children may contribute to over-investigation and treatment. The identification of low-risk thresholds adds to work on using the *Feverkids* tool to limit unnecessary clinical investigations and antimicrobial overuse [32, 34]. For example, in the no SBI group, 116 participants had a chest radiograph. If clinicians did not perform a chest radiograph in participants with <1% bacterial pneumonia risk, 49 fewer participants with no SBI would have been X-rayed, a reduction of 42%.

Estimating the reduction in empirical antibiotic usage is more challenging as it depends on understanding the rationale for initiating antibiotic treatment in each patient. 66 cases of no SBI had a predicted risk below both the rule-out threshold of <1% for bacterial pneumonia and <10% for other SBI, of which 37 were prescribed antibiotics. The model could have guided improved antibiotic prescribing in this group.

The calibrated low-risk threshold for other SBIs in this study (10%) is significantly higher than in the original study (<2.5%) [8], however no established risk thresholds exist in this population, and a 10% low-risk threshold is in keeping with another study in febrile neutropenia [19].

Strengths and Limitations

This is the largest cohort of its kind to date, with well-characterised cases representing diverse underlying causes for immunodeficiency, recruited from multiple centres and countries across Europe. However, the study has fewer than the recommended number of cases of bacterial pneumonia to update the *Feverkids* prediction model, which demonstrates the challenge of gathering large cohorts of patients of this type. Multiple imputation of missing values improved the study precision [35]. While real-time imputation of missing predictor values has been proposed to allow clinicians to use prediction models with incomplete data [9], this was not explored in this study. However, the complete case analysis

showed similar results to the imputed dataset, which suggests that including imputed values did not impact the prediction performance significantly. Further, it is anticipated that most children with immunocompromise presenting with fever or infection symptoms would have the clinical data for the tool available and most would undergo blood tests including CRP.

The heterogeneity of the study population reflects the case mix across Europe and permits wider application and generalisability of the results. Participants were only recruited at academic/tertiary care hospitals, nonetheless this reflects that most care provided to this population is supported with specialist guidance. There was insufficient power to undertake site-specific analyses. This study uses the original study's classification into three outcome categories and does not assess the ability to predict specific SBIs, although the exploratory model for IBI performed similarly. Some important SBIs such as meningitis have characteristic features but have a low incidence, which makes the development of a model which treats them separately challenging [8]. The heterogeneity of other SBIs in this study may have limited the predictive ability of the model.

Further work

The utility of the predictive model in targeting further investigations (chest x-rays, urine samples, blood cultures) and guiding antibiotic management may be explored in future studies.

Immunocompromised children may present with severe illness with or without a bacterial aetiology, therefore predictive tools may be limited in their ability to distinguish serious bacterial infections by clinical features alone. The prediction model uses CRP as the only laboratory variable. Future predictive models may benefit from using biomarkers such as interleukin-6, interleukin-8, interleukin-10, and TNFα [36] in conjunction with clinical features. Further, the ongoing DIAMONDS (Diagnosis and Management of Febrile Illness using RNA Personalised Molecular Signature Diagnosis) study will explore the utility of a multiclass RNA-based test for SBIs [37].

Conclusions

This study validates a prediction model using clinical features and CRP for identification of bacterial pneumonia and other SBI in children with immunodeficiency presenting with febrile illness or

suspected infection. The model shows good discrimination and calibration for bacterial pneumonia and poorer discrimination and calibration for other SBIs. There is a need for predictive tools to identify serious bacterial infections in immunocompromised children. Tools combining clinical features, established markers of infection and novel biomarkers are needed to improve the diagnosis of serious bacterial infection in this group.

Post-conclusions text:

Authors' contributions

AJM wrote the original manuscript, performed the statistical analysis and contributed to preparing the database and recruitment. FvdV reviewed the manuscript and was responsible for the study dataset and data quality control. GdV was involved in the preparation of the database and patient recruitment. UvB, MT, WZ, CV, LK, EL, MP, DZ, FMT, IRC, NH, EU, LS, TK, AP, SY, CF, MV, EC, PA, AK, SP, JH, ML, MvdF, RdG, RN and ME were responsible for the conduct of the PERFORM study and patient recruitment for their respective sites. TD was responsible for the digital database system and its maintenance. RN and ME supervised the project. All authors reviewed and approved the final manuscript.

Ethical approval

Ethical approval was obtained in all participating countries via their national ethics committees (for the UK: IRAS: 209035, REC: 16/LO/1684). Informed consent was obtained from all participants or their legal guardians with assent from older children.

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What is already known on this topic:

1. Most febrile children without pre-existing comorbidities have viral illnesses, however immunocompromised children are at an increased risk of serious bacterial infections.
2. Existing clinical prediction tools to identify serious bacterial infections have mostly been developed in children without immunocompromising conditions.
3. No established risk thresholds for determining whether to request additional diagnostic tests or initiate antibiotic therapy exist in immunocompromised children.

What this study adds:

1. This study is a validation of the *Feverkids* clinical prediction tool for bacterial pneumonia and other serious bacterial infections in a population of immunocompromised children.
2. The tool, combining clinical features and CRP, had good discrimination and calibration for bacterial pneumonia, however discrimination and calibration for other SBIs was poorer.

How this study might affect research, practice or policy:

1. The study can help researchers and clinicians understand how the *Feverkids* tool performs at different risk thresholds in this high-risk group.
2. The identification of low-risk thresholds may be able to guide clinicians in the use of chest radiographs for suspected bacterial pneumonia in this group.
3. The study will help inform future work combining clinical features and novel biomarkers for the prediction of serious bacterial infections in immunocompromised children.

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Table 1 - Participant characteristics for 558 episodes of suspected infection assessed by *Feverkids*: Predictor variables, underlying diagnosis causing immunocompromise, other characteristics and interventions and outcome for each group

	Bacterial pneumonia (n=21)	Other SBI (n=104)	No SBI (n=433)	Missing values n (%)
Predictor variables				
Age (years)	7.4 (4.9-12.8)	9.0 (4.0-13.7)	7.8 (4.4-12.7)	0 (0%)
Male sex	16 (76%)	61 (59%)	250 (58%)	0 (0%)
Temperature on admission (ºC)	37.4 (37.1-37.9)	38.3 (37.1-39.1)	38.0 (37.2-38.4)	8 (1.4%)
Tachycardia	12 (57%)	55 (53%)	200 (47%)	31 (5.6%)
Tachypnoea	14 (67%)	24 (23%)	134 (31%)	118 (21%)
Oxygen saturations <94%	6 (33%)	0 (0%)	31 (8.6%)	84 (15%)
Capillary refill >3 seconds	2 (10%)	5 (6%)	7 (2%)	115 (21%)
Ill appearance	11 (55%)	49 (48%)	106 (27%)	42 (7.5%)
Chest wall recessions	6 (29%)	2 (2%)	20 (5%)	0 (0%)
Duration of illness (days)	2 (0-3)	0 (0-1)	0 (0-2)	0 (0%)
C-reactive protein (mg/L)	182 (47-225)	36 (16-88)	21 (6-53)	11 (2.0%)
Underlying diagnosis n (%)				
Haematological malignancy	4 (20%)	35 (34%)	168 (39%)	-
Central nervous system malignancy	0 (0%)	7 (7%)	26 (6%)	-
Other solid organ malignancy	2 (10%)	12 (12%)	72 (17%)	-
Non-malignant haematological disease	8 (38%)	8 (8%)	52 (12%)	-
Inflammatory syndrome	1 (5%)	5 (5%)	41 (9%)	-
Primary immunodeficiency	1 (5%)	6 (6%)	39 (9%)	-
Cystic fibrosis	1 (5%)	1 (1%)	3 (0.7%)	-
Solid organ transplant	3 (14%)	14 (13%)	13 (3%)	-
Human immunodeficiency virus infection	0 (0%)	5 (5%)	1 (0.2%)	-
Nephrotic syndrome	0 (0%)	3 (3%)	3 (0.7%)	-
Short bowel syndrome	0 (0%)	2 (2%)	2 (0.5%)	-
Other conditions	1 (5%)	6 (6%)	13 (3%)	-
Other characteristics				
Receiving chemotherapy	5 (24%)	48 (46%)	242 (56%)	-
Receiving other immunosuppressant drugs	12 (57%)	59 (57%)	233 (54%)	-
Neutropenia <0.5 x 10^9/L	4 (19%)	38 (37%)	188 (43%)	-
Interventions and outcome				
Empirical antibiotics started	20 (95%)	102 (98%)	349 (81%)	-
Admitted to PICU	10 (48%)	10 (10%)	31 (7%)	-
Died	2 (10%)	1 (1%)	8 (2%)	-

Data are presented as n (%) or median (IQR). SBI: Serious Bacterial Infection. PICU: Paediatric Intensive Care Unit. The number and percentage of missing values are reported for variables which were imputed.

Table 2 - Source of other serious bacterial infections in children with immune compromise assessed with the *Feverkids* tool

Source of other SBIs	n=104 (%)
Bacteraemia (CLABSI)	34 (33%)
Bacteraemia (other)	13 (13%)
Cellulitis	7 (7%)
Gastroenteritis/colitis	6 (%)
Meningitis	5 (5%)
Surgical (intra-abdominal, abscess, wound infection)	13 (13%)
URTI	5 (5%)
UTI/pyelonephritis	18 (17%)
Other, including sepsis without an identified source	3 (2%)

CLABSI: Central line associated blood stream infection SSI: Surgical site infection URTI: Upper respiratory tract infection UTI: Urinary tract infection

Table 3 – Dichotomous diagnostic performance measures for pneumonia and other SBIs at different risk thresholds in immune compromised children in the re-fitted *Feverkids* model

	% above/below threshold	Sensitivity (95% CI)	Specificity (95% CI)	Predictive value (95% CI)		Likelihood ratio (95% CI)	
				Positive	Negative	Positive	Negative
Pneumonia							
1.0% *	51/49	0.95 (0.86-1.00)	0.53 (0.48-0.58)	0.09 (0.08-0.10)	1.00 (0.99-1.00)	2.00 (1.71-2.27)	0.09 0.00-0.32
2.5%	31/69	0.86 (0.67-1.00)	0.71 (0.67-0.76)	0.13 (0.10-0.15)	0.99 (0.98-1.00)	2.99 (2.27-3.67)	0.20 0.02-0.45
5%	17/83	0.71 (0.52-0.90)	0.85 (0.82-0.88)	0.19 (0.13-0.25)	0.98 (0.97-0.99)	4.75 (3.18-6.62)	0.34 0.12-0.58
10%**	11/89	0.57 (0.38-0.76)	0.91 (0.88-0.94)	0.24 (0.16-0.33)	0.98 (0.97-0.99)	6.51 (3.71-10.3)	0.47 0.25-0.71
15%	6/94	0.57 (0.38-0.76)	0.96 (0.94-0.97)	0.39 (0.26-0.54)	0.98 (0.97-0.99)	13.0 (7.01-23.8)	0.45 0.24-0.67
Other SBI							
2.5%	97/3	1.00 (1.00-1.00)	0.03 (0.01-0.04)	0.20 (0.20-0.20)	1.00 (1.00-1.00)	1.02 (1.00-1.04)	0.00 (0.00-1.23)
5%	92/8	0.99 (0.97-1.00)	0.09 (0.07-0.12)	0.21 (0.20-0.21)	0.98 (0.92-1.00)	1.09 (1.05-1.13)	0.10 (0.00-0.40)
10%*	78/22	0.92 (0.87-0.97)	0.24 (0.20-0.28)	0.23 (0.21-0.24)	0.93 (0.88-0.97)	1.22 (1.12-1.31)	0.32 (0.13-0.57)
15%	59/41	0.84 (0.76-0.90)	0.45 (0.40-0.50)	0.27 (0.24-0.29)	0.92 (0.89-0.95)	1.52 (1.34-1.71)	0.36 (0.21-0.54)
30%**	15/85	0.32 (0.23-0.40)	0.89 (0.86-0.92)	0.41 (0.31-0.50)	0.84 (0.83-0.86)	2.86 (1.91-4.25)	0.77 (0.66-0.87)

*Possible rule-out threshold ** Possible rule-in threshold