Predictors of 'unlikely bacterial pneumonia' and 'adverse pneumonia outcome' in children admitted to hospital in central Vietnam

Phuong TK Nguyen, MD[1,2], Hoang T Tran, PhD[2], Thach S Tran, PhD[3], Dominic A Fitzgerald, Prof[1,4], Stephen M Graham, Prof[5], Ben J Marais, Prof[1]

[1]Discipline of Child and Adolescent Health, Sydney Medical School, The Children's Hospital at Westmead, The University of Sydney, Australia; [2]Da Nang Hospital for Women and Children, Vietnam; [3]Clinical Studies and Epidemiology, Bone Biology Division, Garvan Institute of Medical Research; [4]Respiratory Medicine, The Children's Hospital at Westmead, The University of Sydney, Australia; [5]Centre for International Child Health, University of Melbourne and Murdoch Children's Research Institute, Royal Children's Hospital, Melbourne, Australia

Corresponding author: Dr. Phuong TK Nguyen

Respiratory Department, Da Nang Hospital for Women and Children; 402 Le Van Hien Street, Ngu Hanh Son District, Da Nang, Vietnam

Tel: +84 905 561 593; Email: thng5150@uni.sydney.edu.au

Main point: We developed an algorithm to guide the management of children presenting to hospital with respiratory symptoms, in order to improve rational antibiotic use and reduce unnecessary hospital admission in Vietnam. Its clinical utility requires validation in a prospective study.

ABSTRACT

Background: Pneumonia is the leading cause of antibiotic use and hospitalisation in Vietnam. There is a need for better prediction of 1) ‘unlikely bacterial pneumonia’ to improve rational antibiotic use and 2) ‘adverse pneumonia outcome’ to guide hospital admission.

Methods: Prospective enrolment of all children under five admitted with ‘pneumonia’ (per clinician assessment) to the Da Nang Hospital for Women and Children over a one-year period. Children were classified as having ‘likely or ‘unlikely’ bacterial pneumonia and followed for outcome assessment. A Bayesian Model Averaging (BMA) approach was used to identify predictors of ‘unlikely bacterial pneumonia’ and ‘adverse pneumonia outcome’, which guided the development of a pragmatic management algorithm.

Results: Of 3,817 patients assessed, 2,199 (57.6%) met World Health Organisation (WHO) pneumonia criteria. In total, 1594 (41.7%) children were classified as ‘unlikely’ and 129 (3.4%) as ‘likely’ bacterial pneumonia. The remainder (2,399; 62.9%) were considered to have disease of ‘uncertain aetiology’. Factors predictive of ‘unlikely bacterial pneumonia’ were ‘no fever’, ‘no consolidation on chest radiograph’ and ‘absolute neutrophil count $<5x10^9$/L’ at presentation, which had a negative predictive value (NPV) for ‘likely bacterial pneumonia’ of 99.0%. Among those meeting WHO pneumonia criteria 8.6% (189/2,199) experienced an adverse outcome. Not having ‘any WHO danger sign’ or ‘consolidation on chest radiograph’ had a NPV of 96.8% for ‘adverse pneumonia outcome’.

Conclusion: An algorithm that screens for predictors of ‘likely bacterial pneumonia’ and ‘adverse pneumonia outcome’ could reduce unnecessary antibiotic use and hospital admission, but its clinical utility requires validation in a prospective study.

Keywords: childhood, pneumonia, predictor, adverse outcome, antibiotic use

Introduction

Pneumonia is a major contributor to childhood mortality with more than 90% of pneumonia deaths in children under five years old occurring in developing countries [1]. Bacterial pneumonia is generally considered to be the main culprit [2], although the establishment of an accurate aetiological diagnosis remains a major challenge [3, 4]. Bacterial blood cultures have low yield, while more sensitive polymerase chain reaction (PCR) based tests are limited by low sensitivity in blood and poor specificity in respiratory specimens [5]. Viral aetiologies may be underestimated in settings with limited diagnostic facilities that adopt syndromic approaches or rely on chest radiograph (CXR) findings. Results from the multi-centre Pneumonia Etiology Research for Child Health (PERCH) project found that respiratory syncytial virus (RSV) accounted for >30% of CXR confirmed pneumonia in children under five [5].

The use of antibiotics in children with viral pneumonia has come under scrutiny, given global concerns about rising rates of antimicrobial resistance and unnecessary antibiotic use [6]. In Vietnam, as in other East Asian settings, pneumonia is the main driver of paediatric hospitalisation and antibiotic use [7, 8]. There is a need for better recognition of bacterial pneumonia in children who are likely to benefit from antibiotic treatment, and consideration of 'rule out' approaches that restrict antibiotic use in those with 'unlikely bacterial pneumonia'. The PERCH study found that elevated C-reactive protein (CRP $\geq$40 mg/L) was positively associated with confirmed bacterial pneumonia (especially those with *Streptococcus pneumoniae* and *Haemophilus influenzae*) and negatively associated with RSV [9]. A recent study in Vietnam demonstrated that a point-of-care CRP test, using a cut-off of $\geq$50 mg/L, safely reduced unnecessary antibiotic use in children with an acute respiratory infection presenting to the local primary healthcare centres [10].

Given the limited availability and suboptimal performance of advanced diagnostic tests, the World Health Organization (WHO) pneumonia case management approach focuses on basic clinical signs and symptoms [11]. Despite good uptake of this approach and evidence of its value in sub-Saharan Africa and the Indian sub-continent [12], its use remains limited in east Asian countries like Vietnam

[13]. A retrospective analysis of admission data demonstrated that most children admitted with pneumonia in Vietnam did not meet WHO case management criteria, with only a small percentage meeting criteria for 'severe pneumonia' that generally indicate a need for hospital admission [14, 15]. Paediatricians in Vietnam feel uncomfortable with the high bar set for hospital admission by the WHO case management approach, which does not take account of CXR or laboratory findings. In the absence of local data to guide safe practice, most paediatricians prefer to err on the side of caution and adopt observed practice among senior clinicians or perceived practice in developed country settings.

Improving rational antibiotic use and reducing unnecessary hospital admissions, which increases health care cost and poses a risk of nosocomial infection, are top priorities for more effective pneumonia case management in Vietnam. The primary aim of our study was to identify predictors of 'unlikely bacterial pneumonia' among children presenting to hospital with respiratory symptoms; acknowledging that accurate aetiological diagnosis is unattainable in a large number of children. We also aimed to identify predictors of 'adverse pneumonia outcome' and combined the insight gained from predictive models with existing guidance to suggest a potential pragmatic algorithm to reduce unnecessary antibiotic use and hospitalization.

Methods

We conducted a prospective descriptive study of children under five years of age admitted with 'pneumonia' over a one-year period (July 01, 2017 to June 30, 2018). Written approval for the study was obtained from the Ethics Committee of the Da Nang Hospital for Women and Children (approved on January 13, 2017).

Study setting

The Da Nang Hospital for Women and Children is a provincial referral hospital in central Viet Nam, with 150 paediatric beds allocated for respiratory admissions. Severe respiratory infections are usually admitted directly to the intensive care unit (ICU), while non-severe infections are admitted to the respiratory ward or to a private fee-paying ward (with mild disease only). Patients come directly from home or are referred from district hospitals in Da Nang city and surrounding areas.

Study population

All children aged 2 - 59 months admitted to the respiratory ward or ICU, with a primary or secondary diagnosis of 'pneumonia' were enrolled. Researchers performed daily recruitment rounds to enroll patients, interview caregivers and document respiratory signs and symptoms on admission (see supplementary material for data collection form). All data were recorded by research personnel not involved in clinical patient care. Additional clinical, laboratory, and radiological findings, as well as pneumonia outcomes, were finalized and captured on hospital discharge. Children transferred in from district or provincial hospitals were excluded, since the study focused on symptoms and signs documented at hospital presentation. For 'adverse pneumonia outcome' we excluded children who did not meet revised WHO pneumonia criteria.

Pneumonia classification and outcome definitions

Children were classified as 'WHO no pneumonia' and 'WHO pneumonia' based on revised WHO pneumonia criteria [11]. Table 1 provides a detailed overview of all the relevant definitions and classifications used. For study classification purposes 'no pneumonia' was defined as 'WHO no pneumonia' plus a normal CXR. Assigned pneumonia aetiology was classified based on CRP, with CRP <10mg/L identifying 'likely viral pneumonia' and CRP ≥50 mg/L identifying 'likely bacterial pneumonia'. All other cases (CRP 10 to 49 mg/L or CRP not done) were regarded as 'uncertain'. 'Unlikely bacterial pneumonia' was defined as a combination of 'no pneumonia' and 'likely viral pneumonia'. 'Adverse pneumonia outcome' was defined as death or ICU admission in a child with 'WHO pneumonia' on admission.

Data management and statistical analysis

Data were entered into an Epi Data database (V4.4.3.1). Initial data were entered within a day of admission with final data entry and checking completed on hospital discharge. Data were checked for inconsistencies and corrections made by referring to the original patient record. We focussed our analyses on children with ‘no pneumonia’, ‘likely viral pneumonia’, and ‘likely bacterial pneumonia’ as defined. Children in the ‘uncertain’ category were excluded from the likely aetiology analysis. Relevant clinical and laboratory variables were summarized using descriptive statistics. All statistical analyses were performed using R version 3.5.2 [16].

Factors evaluated included gender, antibiotic use before admission, recent (during the past 2 weeks) admission with an acute respiratory infection, any breastfeeding, cigarette smoke exposure (anyone smoking inside the house), birth weight (low if <2500 gram; not included in ‘adverse pneumonia outcome’ but important consideration children under two), any wheeze or runny nose, fever on admission (no if temperature <38.5^{0}C), consolidation on CXR using WHO endpoint criteria for consolidation [17], absolute neutrophil count (low if <5x10^9/L), peripheral oxygen saturation (low if SpO_2 <90% in room air), and the presence of WHO danger signs (inability to drink or breastfeed, vomiting everything, lethargy or convulsions, respiratory distress (grunting or nasal flaring), severe malnutrition [11]. Wheeze on auscultation was not reliably recorded in all children. For comparative analyses unrecorded data were regarded as missing values, without the use of imputation.

A Bayesian Model Averaging (BMA) approach was used to search for the most parsimonious predictive model with maximal discriminatory power. Unlike conventional stepwise model-building approaches, which use approximate asymptotic ratio tests to search for a single “best” model, the BMA approach identify models with the highest posterior probabilities [18]. After selecting the optimal model, its validity was assessed using the Classification And Regression Training (CARET) technique from the CARET package in R [19]. This technique performs internal validation of both the diagnostic and predictive performance of the model. We also assessed the screening value of variables selected by the model, by calculating its negative predictive value (NPV) within the study cohort.

Results

In total, 4,206 children were hospitalised with 'pneumonia'; as assessed by the admitting doctor. Figure 1 provides an overview of participant recruitment. We excluded 1,515 children admitted to the private ward, as well as 398 children referred from other hospitals. Of the 3,817 'pneumonia' admissions included in the analysis 2,199 (57.6%) met WHO pneumonia criteria. A CXR was performed in 3,606 (94.5%) children and a CRP collected in 1,076 (28.2%). Among those with a CRP result 8.0% (305/1,076) were classified as 'likely viral pneumonia' and 3.4% (129/1,076) as 'likely bacterial pneumonia', based on specified CRP cut-offs. Those without a CRP result or with values between the specified cut-offs (10-49 mg/L) were considered to have disease of 'uncertain aetiology' (2,399, 62.9%) and excluded from the comparative analysis.

Table 2 presents the CRP results and adverse outcomes documented in children admitted with 'pneumonia'. Among those not meeting WHO pneumonia criteria 984/1,618 (60.8%) had a normal CXR and were classified as 'no pneumonia'. Nearly a third (53/184; 28.5%) of children with 'WHO severe pneumonia' had a CRP <10 mg/L, suggestive of a viral infection. Of the children who met WHO pneumonia criteria, 189/2,199 (8.6%) experienced an adverse outcome (as defined). A small number of children (13/984; 1.3%) in the 'no pneumonia' group were admitted to the ICU; 10 with bacteraemia and a normal CXR, and one each with severe diarrhoea, foreign body inhalation, and severe malnutrition.

Table 3 provides a detailed overview of characteristics associated with 'unlikely' and 'likely' bacterial pneumonia, as well as 'adverse pneumonia outcome'. Boys were over-represented among children with 'likely bacterial pneumonia' and 'adverse pneumonia outcome'. Pneumococcal vaccination uptake was low overall (~5%), but lowest (2.1%) in those with 'adverse pneumonia outcome'. Cigarette smoke exposure was high (>50%) in all pneumonia categories. SpO_2 was only selectively recorded and therefore 'SpO_2 <90% in room air' was combined with other WHO danger signs for prediction model analyses.

The best predictive model for 'unlikely bacterial pneumonia' included three variables 1) 'no fever on admission', 2) 'neutrophil count <$5x10^9$/L' and 3) 'no consolidation on CXR' (Table 4). These predictors independently increased the chance of 'unlikely bacterial pneumonia' by 2.2, 3.1, and 15.0 fold respectively. Figure 2a presents a nomogram for determining the likelihood of 'unlikely bacterial pneumonia'. Its use as a 'diagnostic tool' is not envisioned, since the main purpose of the model was to inform a pragmatic screening approach to rule out 'likely bacterial pneumonia', Table 5 reflects the negative predictive value (NPV) of variables identified by the model to screen the study population for 'likely bacterial pneumonia' (NPV 99.0%).

For 'adverse pneumonia outcome' the selected model included two variables 1) "WHO danger signs" and 2) "consolidation on CXR" (Table 4). Some models that included a 3rd variable had slightly better predictive value (Table S1), but the 2 variable model was considered more pragmatic and likely to perform consistently across the age range. Figure 2b presents a nomogram for determining the likelihood of 'adverse pneumonia outcome'. Table S2 indicates the diagnostic accuracy of selected models for 'unlikely bacterial pneumonia' and 'adverse pneumonia outcome', using the CARET package for internal validation.

Figure 3 presents a pragmatic algorithm that combines study findings, existing WHO guidance and previous findings from Vietnam that used CRP values to guide rational antibiotic use [10]. If this algorithm was in place during the study period then hospital admission and antibiotic use would have been averted in 955 (25.0%) cases who presented with wheeze and/or runny nose and no fever or danger signs. An additional 1,259 (33.0%) cases with no consolidation on CXR and neutrophil count <$5x10^9$/L (or CRP <10 mg/L) was unlikely to benefit from hospitalisation or antibiotic use. Table 6 provides an overview of potential positive and negative impacts associated with algorithm implementation. Some children admitted to the ICU did not meet hospital admission criteria, as specified in the algorithm. Most of these children (19/24; 71.2%) had chest in-drawing in the absence of WHO danger signs, which was attributed to bronchiolitis.

Discussion

This is the first prospective study to comprehensively evaluate all pneumonia admissions at a secondary referral hospital in central Vietnam. It demonstrated unnecessary hospitalisations in a large number of children [14] and supports previous observations that many children with respiratory symptoms in Vietnam receive antibiotics without a strong indication [8, 20, 21]. Clinicians often feel that hospitalisation is the 'safe option', but for children who do not warrant admission this only increases their risk of adverse effects related to medical care. It is also hugely disruptive to families and their livelihoods, particularly in settings where caretakers have to stay in hospital with their children. Developing a rational approach to reduce unnecessary hospitalisation and antibiotic use is a daunting task, given existing patient expectations, clinicians' risk aversion, profits generated from antibiotic prescription and funding models that sometimes encourage hospitalization [7].

We used our large prospectively collected dataset to develop prediction models for 'unlikely bacterial pneumonia' and 'adverse pneumonia outcome' to assist rational antibiotic use and guide hospital admission strategies. The study focused on children who presented to hospital, where CXR and blood tests are readily available. The best performing model for 'unlikely bacterial pneumonia' provided reasonable diagnostic accuracy and excellent NPV for 'likely bacterial pneumonia', providing a good indication of when antibiotics are NOT required. The emphasis here is different to the standard WHO case management approach [11], which focuses mainly on pneumonia death reduction in resource-limited settings with restricted antibiotic access. East Asia presents a unique challenge given that healthcare access is generally good, antibiotic use unrestricted and pneumonia death rates low.

Given excessive antibiotic use and increasing antimicrobial resistance in Asian countries [7, 10], we aimed to identify children unlikely to benefit from antibiotics. Previous prediction studies identified high temperature on admission $\geq 39^{0}$C, neutrophil count $\geq 8x10^{9}$/L (bands $\geq 5\%$) and an abnormal CXR as risk factors for bacterial pneumonia [22, 23]. Consolidation on CXR has shown consistent value between studies [17, 24], although it is not considered specific for bacterial infection [12]. Vietnam is an exemplar of an Asian country in transition to low child mortality [13], with relatively low risk for bacterial pneumonia [25] and an increased need to reduce unnecessary antibiotic use and hospitalisation [14]. Our findings only relate to children who present to hospital emergency departments with ready access to CXR and first-line blood tests. WHO guidelines should be applied to children presenting to community clinics, for which it was primarily developed [11].

Wheeze has been associated with viral infections in both African [26] and Asian settings [27], but although children with 'likely viral pneumonia' wheezed twice as frequently as those with 'likely bacterial pneumonia' it was not selected by the BMA approach. This may have been affected by the fact that the presence or absence of wheeze on auscultation was not documented in about a third of children on admission. Revised WHO guidance recommends that a child with wheeze and no fever, in the absence of any danger sign, should not receive an antibiotic [28]. However, if an initial clinical determination is not possible, a CXR and full blood count (and/or CRP) could provide clinicians with additional confidence to withhold antibiotics in a child with respiratory symptoms.

We also focused on factors predicting 'adverse pneumonia outcome', which identified the presence of 'WHO danger signs' and 'consolidation on CXR' as the strongest predictors. The WHO case management approach utilizes the presence of 'WHO danger signs' to guide hospitalisation, but in hospital-based settings with adequate resources 'consolidation on CXR' provides clinicians with another important line of information. Despite the good NPV of 'WHO danger signs' or 'consolidation on CXR' for 'adverse pneumonia outcome', it is difficult to be too prescriptive given the variety of clinical syndromes with which children present to hospital, including asthma, foreign body aspiration and sepsis. However, our data shows that adoption of a simple pragmatic approach could greatly reduce unnecessary hospital admissions.

The Respiratory Index of Severity in Children (RISC) was developed in South Africa [26], but its translatability to Asian settings is limited by increased rates of hospitalization [14], wheezy pneumonia [14, 27], and preadmission antibiotic use [10, 14], while rates of human immunodeficiency virus (HIV) infection and death is greatly reduced compared to African countries

[1]. Our study identified 'WHO danger signs' or SpO_2<90% in room air as an important predictor of adverse outcome. Although hypoxemia is not included among traditional 'WHO danger signs' [11], the use of pulse oximetry in combination with integrated management of childhood illness (IMCI) has been found to be highly cost effective [29]. Unfortunately pulse oximetry is not universally available and was only recorded in 10% of patients in our study, but we believe it is an important factor that should be grouped with WHO danger signs [14].

Study strengths include the prospective study design and rigorous analytical approach. While conventional stepwise approaches focus mainly on the strengths of association between selected predictors and the outcome to identify a single "best" model, the BMA approach considers all potential models, which substantially improves its predictive performance [30]. In addition, internal model validation was performed using the CARET technique. Study limitations include the fact that children with 'uncertain pneumonia', which represented the largest group, were excluded from the analysis. However, focusing on those with a 'certain' diagnosis facilitated detection of the most reliable predictive signal, which should apply to the whole study cohort. Few children had co-morbid conditions such as HIV co-infection or severe malnutrition, although this is broadly representative of the situation in Asia. We could only assess likely aetiology in the absence of microbiological confirmation, but this is a major challenge in all pneumonia research [4, 12, 13]. We acknowledge that 'likely bacterial pneumonia' (as defined), may have excluded children with 'atypical pneumonia' or tuberculosis, but infections with atypical pathogens are relatively uncommon in children <5 years old [31], while a history of recent tuberculosis exposure or typical CXR findings [32], should direct a tuberculosis diagnosis. Any proposed algorithm will have to be augmented by basic clinical acumen.

Conclusion

Identifying accurate predictors of 'unlikely bacterial pneumonia' and 'adverse pneumonia outcome' in children who present to hospital with respiratory symptoms may reduce unnecessary antibiotic use and hospital admission. Based on our study findings and existing guidance we propose a pragmatic management algorithm to improve rational decision making, which requires validation in a prospective study to confirm its clinical utility and assess potential risks.

Authors' contributions

PTKN, SMG, and BJM conceptualised the study and designed the protocol. PTKN collected the data and drafted the manuscript. PTKN, BJM and TST analysed the data. All authors reviewed and approved the final manuscript.

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Declaration of interests

Authors declare no competing interests.

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Table 1: Overview of case definitions used for pneumonia, including assigned 'likely aetiology' and adverse outcome definitions

Classification	Definition
WHO case definition	
No pneumonia	Hospital admission with respiratory symptoms – but no tachypnea[a] or chest in-drawing
Pneumonia	
- non-severe	Hospital admission with tachypnea[a] or chest in-drawing
- severe	As above plus a danger sign[b]
Assigned 'likely aetiology'	
No pneumonia[c]	'WHO no pneumonia' and a normal chest radiograph
Likely viral pneumonia[c]	'WHO pneumonia' and CRP <10 mg/L
Likely bacterial pneumonia	'WHO pneumonia' and CRP ≥ 50 mg/L
Uncertain	All cases not meeting the definitions above
'Adverse pneumonia outcome' definition	
Death or	Died in hospital
ICU admission	Admitted to ICU at any time during this admission

CRP - C-reactive protein; ICU – intensive care unit; WHO – World Health Organization
[a]Defined as breath rate of ≥50/minute aged 2–11 months, or ≥40/minute aged 12–59 months [11]
[b]Including inability to drink or breastfeed, vomiting everything, lethargy or convulsions, respiratory distress (grunting or nasal flaring), severe malnutrition.
[c]Combined to constitute those identified as 'unlikely bacterial pneumonia'

Table 2: Overview of CRP grading (used to assign likely aetiology) and adverse outcome in different WHO pneumonia categories

CRP grading and adverse outcome	WHO no pneumonia[a]		WHO pneumonia[a]		Total n (%)
	CXR normal n (%)	CXR abnormal n (%)	Not severe n (%)	Severe n (%)	
CRP grading					
CRP <10 mg/L	**123 (12.5)**	59 (9.3)	**252 (12.5)**	**53 (28.8)**	487 (12.7)
CRP ≥ 50 mg/L	**35 (3.6)**	57 (9.0)	**118 (5.9)**	**11 (6.0)**	221 (5.8)
Other[b]	**826 (83.9)**	518 (81.7)	1645 (81.6)[c]	120 (65.2)[c]	3109 (81.5)
Adverse outcome*					
Yes	13 (1.3)	16 (2.5)	**108 (5.4)**	**81 (44.0)**	218 (5.7)
No	971 (98.7)	618 (97.5)	**1907 (94.6)**	**103 (56.0)**	3599 (94.3)
Total	984 (25.8)	634 (16.6)[c]	2015 (52.8)	184 (4.8)	3817

CXR – chest X ray; WHO – World Health Organization; CRP – C-reactive protein
[a]As per definitions provided in Table 1; numbers highlighted indicate patient groups included in the comparative analyses
[b]Other - CRP 10-49 mg/L or unknown
[c]These cases were excluded from the comparative analysis, since the pneumonia diagnosis or assigned aetiology was considered uncertain

Table 3: Characteristics of children admitted with 'unlikely' and 'likely' bacterial pneumonia, and those who experienced an 'adverse pneumonia outcome', in central Vietnam

Characteristic	Pneumonia classification* n (%)			Adverse outcome* n (%)
	Unlikely bacterial		Likely bacterial	
	No pneumonia	Likely viral		
Age 2 – 11 months	359 (36.5)	121 (39.7)	31 (24.0)	119 (63.0)
12 – 23 months	278 (28.3)	123 (40.3)	73 (56.6)	48 (25.4)
24 – 59 months	347 (35.3)	61 (20.0)	25 (19.4)	22 (11.6)
Gender (male)	567 (57.6)	181 (59.3)	83 (64.3)	119 (63.0)
Pre-admission antibiotics	472 (48.0)	155 (50.8)	57 (44.2)	67 (35.4)
Recent TB contact[a]	15 (1.5)	4 (1.3)	5 (3.9)	4 (2.1)
ARI readmission[b]	95 (9.7)	55 (18.0)	22 (17.1)	41 (21.7)
Breastfeeding[c]	913 (92.8)	269 (88.2)	117 (90.7)	160 (84.7)
Pneumococcal vaccination[d]	39 (4.0)	14 (4.6)	8 (6.2)	4 (2.1)
Cigarette smoke exposure[e]	505 (51.3)	151 (49.5)	68 (52.7)	100 (52.9)
Biomass fuel exposure[f]	189 (19.2)	63 (20.7)	23 (17.8)	34 (18.0)
Low birth weight (<2500g)	56 (5.7)	47 (15.4)	7 (5.4)	41 (21.7)
Preterm (<37weeks)	78 (7.9)	44 (14.4)	10 (7.8)	41 (21.7)
Day care	497 (50.5)	113 (37.0)	71 (55.0)	27 (14.3)
Any wheeze[g]	160 (16.3)	100 (32.8)	21 (16.3)	67 (35.4)
Runny nose	232 (23.6)	51 (16.7)	20 (15.5)	21 (11.1)
Fever ($\geq 38.5^0$C)	357 (36.3)	133 (43.6)	80 (62.0)	78 (41.3)
Any WHO danger sign[h]	25 (2.5)	58 (19.0)	14 (10.9)	87 (46.0)
SpO_2 <90%	2/30 (6.7)	28/85 (32.9)	9/27 (33.3)	57/148 (38.5)
Abnormal chest radiograph	0	151 (49.5)	92 (71.3)	130 (68.8)
Consolidation[i]	0	59 (19.3)	61 (47.3)	82 (43.4)
Absolute neutrophil count				
$<5 \times 10^9$/L	447 (45.4)	150 (49.2)	22 (17.1)	75 (39.7)
$\geq 10 \times 10^9$/L	149 (15.1)	38 (12.5)	62 (48.1)	57 (30.2)
Total	**984**	**305**	**129**	**189**

ARI – acute respiratory infection; SpO_2 - peripheral oxygen saturation; WHO – World Health Organization; TB - Tuberculosis

*As defined in Table 1; [a]Tuberculosis contact within the last 12 months; [b]ARI readmission within 2 weeks of discharge; [c]Any breastfeeding; [d]Child received at least one dose; [e]Anyone smoking inside the house; [f]Used solid fuel for cooking; [g]Audible wheeze or wheeze on auscultation; [h]Including inability to drink or breastfeed, vomiting everything, lethargy or convulsions, respiratory distress (grunting or nasal flaring), severe malnutrition; [i]Assessed by the lead investigator using WHO endpoint criteria for consolidation [17].

Table 4: Selected predictive models for 'unlikely bacterial pneumonia' and 'adverse pneumonia outcome' identified by the Bayesian Model Averaging (BMA) approach

Independent predictors	**Adjusted OR** (95% CI)	**p-value**	**AUC**
'Unlikely bacterial pneumonia'			
No fever on admission (<38.5^{0}C)	2.2 (1.4-3.3)	<0.001	0.80
Neutrophils < 5x10^9/L	3.1 (1.9-5.2)	<0.001	
No consolidation on chest radiograph	15.0 (9.6-23.4)	<0.001	
'Adverse pneumonia outcome'			
Consolidation on chest radiograph	4.4 (3.1-6.2)	<0.001	0.79
Any WHO danger sign*	11.6 (8.2-16.5)	<0.001	

OR – odds ratio; CI – confidence interval; AUC - area under the receiver operating characteristic curve
*Including peripheral oxygen saturation <90% in room air, respiratory distress (grunting or nasal flaring), inability to drink or breastfeed, vomiting everything, lethargy or convulsions, severe malnutrition.

Table 5: Screening value, of variables identified by the BMA approach, to rule out 'likely bacterial pneumonia' and 'adverse pneumonia outcome'

Screening value	Likely bacterial pneumonia*	Adverse pneumonia outcome*
	Fever on presentation[a], consolidation on chest radiograph[b] OR neutrophil count $\geq 5x10^9/L$	WHO danger sign[c] OR consolidation on chest radiograph[b]
Sensitivity	96.9%	72.0%
Specificity	30.3%	80.5%
Positive predictive value	12.2%	25.8%
Negative predictive value	99.0%	96.8%
Without considering fever on presentation[a]	**Consolidation on chest radiograph[b] OR neutrophil count $\geq 5x10^9/L$**	
Sensitivity	89.1%	
Specificity	45.0%	
Positive predictive value	14.0%	
Negative predictive value	97.6%	

BMA - Bayesian Model Averaging approach; CI – confidence interval; WHO – World Health Organization
*As defined in Table 1; [a]Temperature on admission $\geq 38{\cdot}5^0$C; [b]Assessed by the lead investigator using WHO endpoint criteria for consolidation [17]; [c]Including inability to drink or breastfeed, vomiting everything, lethargy or convulsions, respiratory distress (grunting or nasal flaring), severe malnutrition and peripheral oxygen saturation <90% in room air.

Table 6: Potential positive and negative impacts if the suggested algorithm[a] was implemented

Impacts resulting from algorithm use (N=3,817)	N (%)
Potential positive impact	
Hospitalisation and antibiotic use avoided	955 (25.0)
Chest radiograph avoided	955 (25.0)
Hospitalisation reconsidered	1,259 (33.0)
Antibiotics use reconsidered	2,191 (57.4)
Potential negative impact	
ICU admissions that might have been sent home	24 (0.7)
Chest indrawing without WHO danger signs	19/24 (71.2)
Nosocomial infection	3/24 (12.5)
Congenital heart disease	2/24 (8.3)
Presumed sepsis	1/24 (4.0)
Foreign body	1/24 (4.0)

ICU – intensive care unit; WHO – World Health Organisation; CXR – chest X Ray
[a]As presented in Figure 3

Figure 1: Flow diagram of participant recruitment

Figure 2: Nomogram for predicting 'unlikely bacterial pneumonia' and 'adverse outcome'

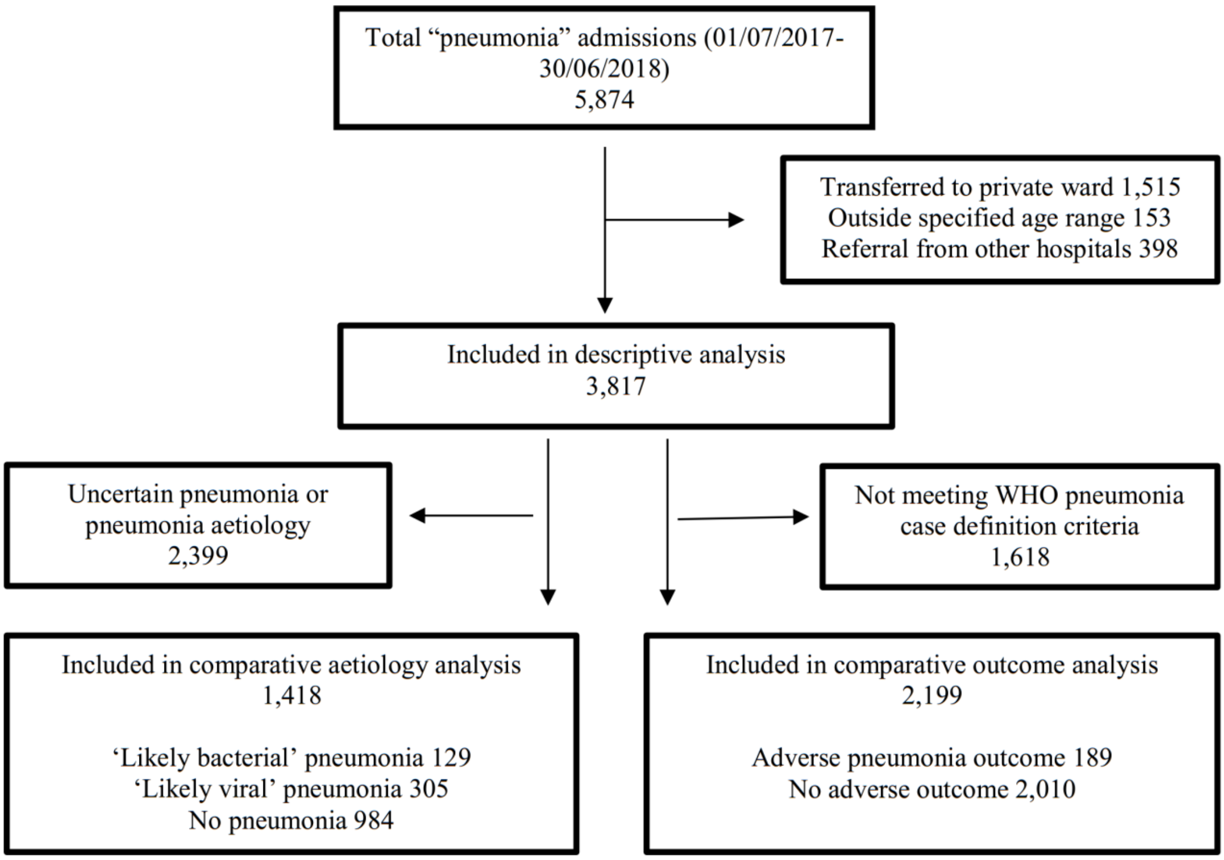
WHO – World Health Organization; SpO_2: peripheral oxygen saturation
* Including inability to drink or breastfeed, vomiting everything, lethargy or convulsions, respiratory distress (grunting or nasal flaring), severe malnutrition and peripheral oxygen saturation <90% in room air (when documented)

Instructions for use: Sum the points awarded to each specified predictor and plot the final sum on the "Total Points" axis; draw a vertical line down to the risk bar below to find the individual's probability of having the particular outcome. However, its use as a diagnostic tool is not envisioned.

Figure 3: Proposed pragmatic algorithm[a] to guide rational antibiotic use and hospitalization, in children who present to hospital with respiratory symptoms

ANC – absolute neutrophil count; CXR – chest radiograph; IV – intravenous; FBC – full blood count; SpO2 - peripheral oxygen saturation; WHO – World Health Organization
[a]Incorporating study findings, existing WHO guidance and previous findings from Vietnam that used CRP values to guide rational antibiotic use [10]
[b]Including inability to drink or breastfeed, vomiting everything, lethargy or convulsions, respiratory distress (grunting or nasal flaring), severe malnutrition
[c]As per WHO recommendation [28]
[d]Admit and consider antibiotics if any deterioration or relevant clinical concern

Figure 1



Total "pneumonia" admissions (01/07/2017-30/06/2018)
5,874
Transferred to private ward 1,515
Outside specified age range 153
Referral from other hospitals 398
Included in descriptive analysis
3,817
Uncertain pneumonia or pneumonia aetiology
2,399
Not meeting WHO pneumonia case definition criteria
1,618
Included in comparative aetiology analysis
1,418
'Likely bacterial' pneumonia 129
'Likely viral' pneumonia 305
No pneumonia 984
Included in comparative outcome analysis
2,199
Adverse pneumonia outcome 189
No adverse outcome 2,010

Figure 2

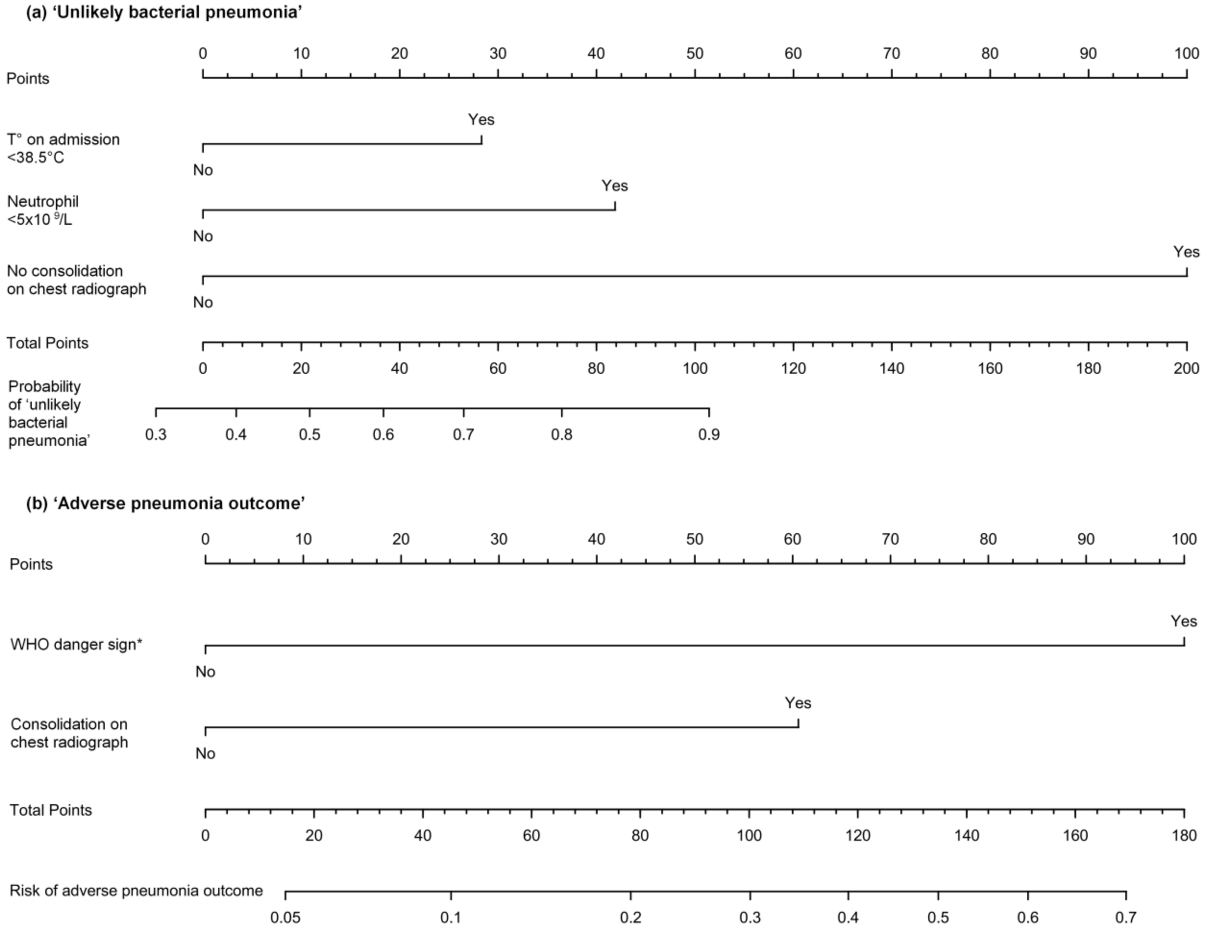
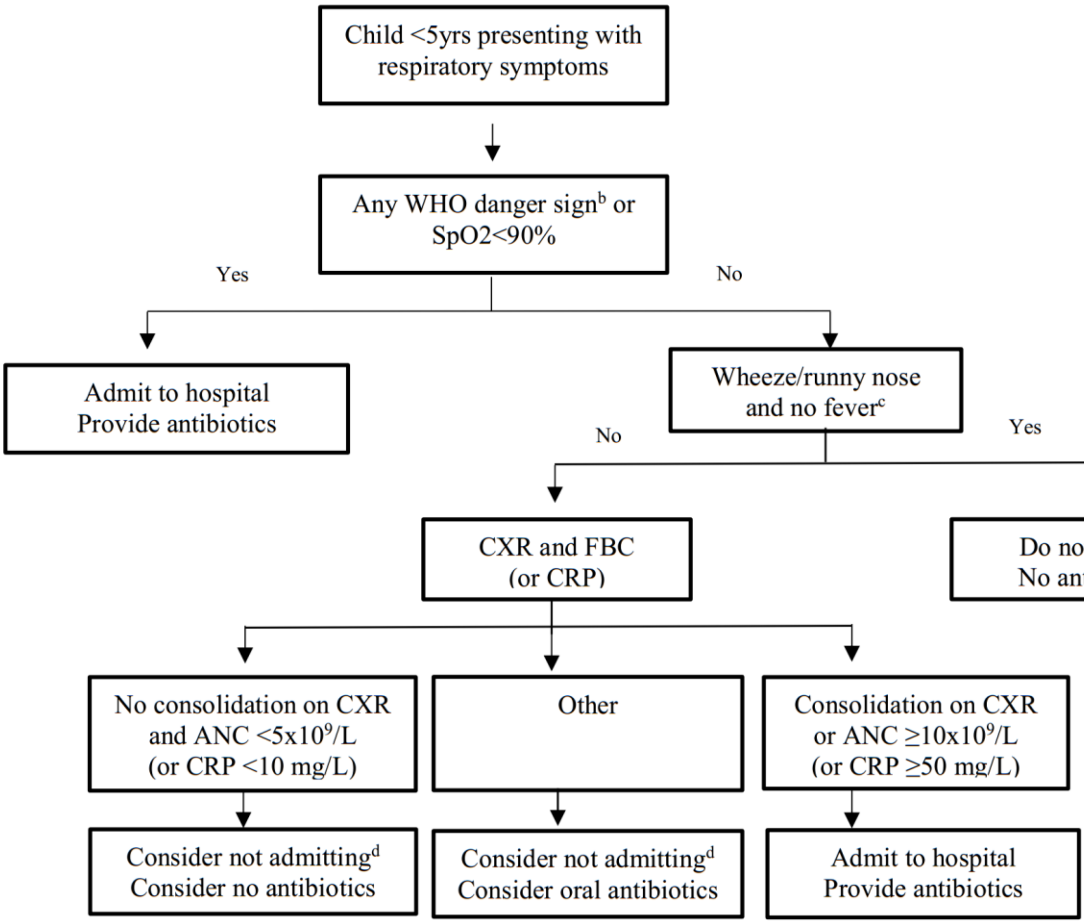

(a) 'Unlikely bacterial pneumonia'
Points
0 10 20 30 40 50 60 70 80 90 100
T° on admission <38.5°C
Yes
No
Neutrophil <5x10 9/L
Yes
No
No consolidation on chest radiograph
Yes
No
Total Points
0 20 40 60 80 100 120 140 160 180 200
Probability of 'unlikely bacterial pneumonia'
0.3 0.4 0.5 0.6 0.7 0.8 0.9
(b) 'Adverse pneumonia outcome'
Points
0 10 20 30 40 50 60 70 80 90 100
WHO danger sign*
Yes
No
Consolidation on chest radiograph
Yes
No
Total Points
0 20 40 60 80 100 120 140 160 180
Risk of adverse pneumonia outcome
0.05 0.1 0.2 0.3 0.4 0.5 0.6 0.7

Figure 3



Child <5yrs presenting with respiratory symptoms
Any WHO danger sign[b] or SpO2<90%
Yes
No
Admit to hospital
Provide antibiotics
Wheeze/runny nose and no fever[c]
No
Yes
CXR and FBC (or CRP)
Do not admit[c]
No antibiotics
No consolidation on CXR and ANC <5x10⁹/L (or CRP <10 mg/L)
Other
Consolidation on CXR or ANC ≥10x10⁹/L (or CRP ≥50 mg/L)
Consider not admitting[d]
Consider no antibiotics
Consider not admitting[d]
Consider oral antibiotics
Admit to hospital
Provide antibiotics