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Characterisation of children hospitalised with pneumonia in central Vietnam: A prospective study

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Abstract:	Background Pneumonia is the most common reason for paediatric hospital admission in Vietnam. The potential value of using the World Health Organization (WHO) case management approach in Vietnam has not been documented. Methods We performed a prospective descriptive study of all children (2-59 months) admitted with 'pneumonia' (per clinician assessment) to the Da Nang Hospital for Women and Children to characterise their disease profile and assess risk factors for an adverse outcome. The disease profile was classified using WHO pneumonia criteria, with tachypnea or chest indrawing as defining clinical signs. Adverse outcome was defined as death, intensive care unit admission, tertiary care transfer or hospital stay >10 days. Results Of 4,206 admissions, 1758 (41.8%) were classified as 'no pneumonia' using WHO criteria and only 252 (6.0%) met revised criteria for 'severe pneumonia'. The inpatient death rate was low (0.4% of admissions) with most deaths (11/16; 68.8%) occurring in the 'severe pneumonia' group. An adverse outcome was recorded in 18.7% of all admissions; 60.7% of the 'severe pneumonia' group. Children were hospitalised for a median of 7 days at an average cost of 253 USD per admission. Risk factors for adverse outcome included WHO classified 'severe pneumonia', age <1 year, low birth weight, readmission with an acute respiratory tract

	infection and recent tuberculosis exposure, while breastfeeding, day care attendance and preadmission antibiotic use were associated with reduced risk. Conclusion Few hospital admissions met WHO criteria for 'severe pneumonia', suggesting potential unnecessary hospitalisation and use of intravenous antibiotics. Accurate characterisation of the underlying diagnosis requires careful consideration.

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Dear Editor,

We are pleased to submit our original manuscript entitled: "Characterisation of children hospitalised with pneumonia in central Vietnam: A prospective study" for publication in the *European Respiratory Journal*. Pneumonia is the most common reason for paediatric hospital admission in Vietnam. Revised World Health Organization (WHO) criteria recently adjusted the definition of "severe pneumonia" to reduce unnecessary hospitalization, but its impact on case management practices in Vietnam has not been documented. We performed a prospective descriptive study of all children (2-59 months) admitted with 'pneumonia' to the Da Nang Hospital for Women and Children in central Vietnam, to characterise their disease profile and assess risk factors for adverse outcome. We found that few hospital admissions met WHO criteria for 'severe pneumonia', suggesting unnecessary hospitalisation for intravenous antibiotics in a large number of children. Although adoption of the WHO case management will reduce unnecessary admissions, careful interpretation of signs and symptoms is required to ensure optimal management.

We believe that this manuscript will be of interest to your international readership given that the findings reflect existing practice in large parts of Asia, which is different to reports from sub-Saharan Africa.

This manuscript is not under consideration for publication elsewhere and we have no conflicts of interest to declare.

Thank you for kindly considering our manuscript for publication.

Yours sincerely,
Nguyen Thi Kim Phuong

Characterisation of children hospitalised with pneumonia in central Vietnam: A prospective study

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TAKE HOME MESSAGE

Many child 'pneumonia' admissions in central Vietnam do not meet WHO case management criteria for hospitalization or intravenous antibiotics. Accurate etiological diagnosis remains challenging and astute clinical judgement should guide optimal management.

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ABSTRACT

Background

Pneumonia is the most common reason for paediatric hospital admission in Vietnam. The potential value of using the World Health Organization (WHO) case management approach in Vietnam has not been documented.

Methods

We performed a prospective descriptive study of all children (2-59 months) admitted with 'pneumonia' (per clinician assessment) to the Da Nang Hospital for Women and Children to characterise their disease profile and assess risk factors for an adverse outcome. The disease profile was classified using WHO pneumonia criteria, with tachypnea or chest indrawing as defining clinical signs. Adverse outcome was defined as death, intensive care unit admission, tertiary care transfer or hospital stay >10 days.

Results

Of 4,206 admissions, 1758 (41.8%) were classified as 'no pneumonia' using WHO criteria and only 252 (6.0%) met revised criteria for 'severe pneumonia'. The inpatient death rate was low (0.4% of admissions) with most deaths (11/16; 68.8%) occurring in the 'severe pneumonia' group. An adverse outcome was recorded in 18.7% of all admissions; 60.7% of the 'severe pneumonia' group. Children were hospitalised for a median of 7 days at an average cost of 253 USD per admission. Risk factors for adverse outcome included WHO classified 'severe pneumonia', age <1 year, low birth weight, readmission with an acute respiratory tract infection and recent tuberculosis exposure, while breastfeeding, day care attendance and preadmission antibiotic use were associated with reduced risk.

Conclusion

Few hospital admissions met WHO criteria for 'severe pneumonia', suggesting potential unnecessary hospitalisation and use of intravenous antibiotics. Accurate characterisation of the underlying diagnosis requires careful consideration.

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INTRODUCTION

Globally, pneumonia is the main cause of disease and death among young children, outside the neonatal period [1]. In 2016, child pneumonia accounted for an estimated 650,000 deaths, with the vast majority occurring in developing countries; 57,000 in Southeast and East Asia [2]. The World Health Organization (WHO) developed a clinical case management approach for use in resource-limited settings, aiming to reduce pneumonia-related deaths and improve access to life saving antibiotics for children with bacterial pneumonia, while at same time limiting unnecessary antibiotic use and reducing hospitalisations in those who can be safely managed as outpatients [3].

Although the WHO case management approach provides a simple strategy to reduce pneumonia related mortality, it has important limitations. It may encourage unnecessary antibiotic use in children with viral infections [4] and lead to the misdiagnosis of asthma, if a careful history of recurrent wheeze or night time coughing is not solicited [5], [6]. Despite these limitations, the WHO case management approach has had a positive impact [7], with studies crediting it with a 70% reduction in under-5 pneumonia-related mortality in some settings [8]. Although benefits are well documented in sub-Saharan Africa and South Asia [8], its clinical utility in East Asian settings, where many children present with 'wheezy pneumonia' suggesting reactive airways disease, [9, 10] is not well described. Accurate diagnosis and disease severity assessment is important to limit unnecessary use of intravenous antibiotics and hospital admission. Careful characterisation of patients at risk of an adverse outcome is also important to prioritize these patients for more intensive management.

In Vietnam, pneumonia is the leading cause of paediatric hospital admission and places a huge burden on the health care system [11, 12]. A retrospective study suggested that many 'pneumonia' admissions may not be clinically justified (12), but case management practices in general are poorly documented. Detailed description of children admitted to hospital with 'pneumonia' would provide a better understanding of the clinical utility of the WHO case management approach in Vietnam. Assessment of 'pneumonia' case management practices and risk factors for adverse outcomes would be informative to guide improved clinical care

and public policy regarding resource allocation and vaccination schedules. The primary aim of this study was to describe the clinical characteristics and outcomes of children admitted with 'pneumonia' compared to revised WHO case definition criteria. A secondary aim was to assess social factors associated with an adverse outcome.

MATERIAL AND METHODS

We conducted a prospective descriptive study of children hospitalized with 'pneumonia' over a 1-year study period (1 July 2017 to 30 June 2018). Written approval for the study was obtained from the Ethics Committee of Da Nang Hospital for Women and Children (13 January 2017).

Study setting

The Da Nang Hospital for Women and Children is a secondary referral hospital in central Vietnam. The hospital has 900 beds with 570 beds reserved for children <15 years old. Pediatric bed occupancy in 2017 was more than 150%. Annual reports suggested that around 4,000 children with acute respiratory infections are admitted to the Respiratory Department and intensive care unit (ICU) every year. Children either present directly from home (through outpatient or emergency services) or are referred from district hospitals in Da Nang city or surrounding provincial hospitals in Quang Nam and Quang Ngai. Children with severe disease who do not improve on admission, including treatment in the local ICU, are referred to tertiary training hospitals in Ha Noi (The National Hospital of Pediatrics) or Ho Chi Minh City (Children' Hospitals number I and II). In 2016, the year preceding the study, acute respiratory infection accounted for nearly a third of pediatric hospital admissions to the Da Nang Hospital for Women and Children; 97% were less than 5 years old.

Study population and procedures

We recruited children aged 2-59 months admitted with a primary or secondary diagnosis of 'pneumonia' as assessed by the admitting clinician. These children were routinely admitted to the Respiratory Department, or directly to the ICU. Independent researchers, not involved in

clinical patient care, performed daily ward rounds in the Respiratory Department and the ICU to recruit new patients and record relevant clinical information.

Clinical information included respiratory signs and symptoms documented on admission, date of symptom onset, number of days from onset to admission, antibiotic use before admission, recent admission with an acute respiratory infection (during the past 2 weeks), recent tuberculosis contact (during the past 12 months), gestational age, birth weight and pneumococcal vaccination. Social risk factors such as breastfeeding, indoor biomass fuel or cigarette smoke exposure, child care attendance, or having an ill sibling at home were also documented. Details of all variables collected are summarised in Table S1. Other clinical, laboratory and radiological information, as well as pneumonia outcome data, were updated intermittently during the period of hospital stay and finalised on discharge. A number of patients in a stable clinical condition were admitted to a private fee-paying ward; these patients were excluded from the study. Chest X-rays (CXR) were routinely performed in children admitted to hospital and assessed for consolidation by the lead investigator, using WHO working group definitions [13]. Hyperinflation was not documented.

Pneumonia classification

Children were classified based on revised WHO criteria using tachypnea, defined as ≥50 breaths/minute if aged 2 – 11 months, or ≥40 breaths/minute if aged 12 – 59 months [14], and/or chest in-drawing as defining clinical symptoms. Severe pneumonia was identified in the presence of any danger sign, including peripheral oxygen saturation (SpO_2) <90% in room air, severe respiratory distress (grunting, nasal flaring), inability to drink or breastfeed, vomiting everything, lethargy or convulsions [15]. Table 1 provides an overview of the pneumonia classification and adverse outcome definition used.

Statistical analysis

Categorical data were tabulated and presented as numbers and percentages and their associations with WHO pneumonia criteria determined using Chi-squared or Fisher's exact tests, as appropriate. 'Wheeze heard with a stethoscope' was not recorded in the first 1,038

cases, where after this was reliably recorded. For comparative analyses we considered unrecorded data as missing values and did not use any imputation. In Vietnam, children with respiratory symptoms often receive antibiotics before hospital presentation; we dichotomized the variables 'time since symptom onset' and 'duration of pre-admission antibiotics' using a clinically relevant threshold of 3 days.

Continuous data were summarized as mean (standard deviation) or median (interquartile range) and their associations with WHO classified pneumonia examined using the analysis of variance (ANOVA) or Kruskal Wallis tests for normally and non-normally distributed variables, respectively. We used uni- and multivariate analyses to assess the social factors associated with adverse outcome (as defined) including age, gender, low birth weight, WHO pneumonia classification, readmission with an acute respiratory infection, pre-admission antibiotic use, recent tuberculosis contact, breastfeeding, pneumococcal vaccination, cigarette or biomass smoke exposure and day care attendance; without considering pre-specified confounders. Post-hoc analysis was done for breastfeeding stratified by age. Data analysis was carried out using SPSS (version 24.0; SPSS, Inc., Chicago, IL). A p-value of less than 0.05 was considered statistically significant. The strength of association was determined by estimating the odds ratio (OR) and the 95% confidence interval (CI).

RESULTS

Figure 1 provides a flow diagram of patient enrolment. Of the 4,206 children hospitalized with 'pneumonia' (as assessed by the admitting clinician), 41.8% failed to meet WHO pneumonia criteria by not having tachypnea or chest indrawing on presentation. Table 2 provides an overview of patient demographics and pre-admission care in all children, classified according to revised WHO pneumonia criteria. Children <2 years accounted for 71.5% of the 'pneumonia' admissions, with infants (<1 year of age) accounting for most (139/252; 55.2%) of the 'WHO severe pneumonia' cases. Boys were more commonly admitted than girls (58.8% boys; p<0.01) in all age categories, with the largest gender discrepancy observed among infants (62.5% boys; p<0.01).

Table 3 summarises the clinical signs and symptoms observed. Ten cases with low oxygen saturation on admission did not meet WHO pneumonia criteria, these included children with sepsis (4), congenital heart disease (2), restrictive lung disease (2), near drowning (1) and primary pulmonary hypertension (1). The 4 children transferred to a tertiary hospital with 'WHO no pneumonia' included 2 children with restrictive lung disease, 1 with hemangioma causing airway obstruction and 1 with near drowning. Interestingly, 38.2% of 'WHO severe pneumonia' cases wheezed on auscultation and this was more common in cases with 'WHO pneumonia' and 'severe pneumonia' compared to 'no pneumonia' (446/2,448; 18.2% versus 104/1,758; 5.9%; p <0.001). Children with wheeze and no fever accounted for 24.2% (61/252) of 'WHO severe pneumonia' cases; 15.6% (342/2,196) of the 'pneumonia' and 8.3% (146/1,758) of the 'no pneumonia' group. Few children were tested for human immunodeficiency virus (HIV) infection; of those tested 2/79 (2.5%) were HIV infected. A CXR was performed in 3971 (94.4%) children, with the majority (52.6%) reported as normal and consolidation noted in 36.0%.

Table 4 summarises the outcomes of children according to revised WHO pneumonia classification criteria. An adverse outcome was documented in 18.7% children. Most (60.7%) adverse outcomes and the vast majority of deaths (7/9; 77.8%) occurred in children with 'severe pneumonia'. The single child in the 'no pneumonia' category who died had cyanotic heart disease. The 4 deaths in children with 'non-severe pneumonia' were attributed to sepsis (3) and acute pericarditis (1). Among children with 'WHO no pneumonia' who were admitted for more than 14 days, 58.7% (54/92) were either referred from a district hospital with a clinical diagnosis of pneumonia and slow treatment response, or experienced a worsening of symptoms after hospital admission. Other children in this group had persistent wheezing or stridor (10), chronic diarrhoea (10), or an unrelated surgical problem (28). Those who required assisted ventilation in the 'WHO no pneumonia' group included children with clinical deterioration after admission (8), sepsis (1), hemangioma with airway obstruction (1), congenital heart disease (2), near drowning (2) and acute pericarditis (1).

Table 5 reflects uni- and multivariate analyses of factors associated with an adverse outcome. Children admitted with 'severe pneumonia' experienced the greatest risk (OR 7.4; 95% CI 5.5-10.0). 'WHO severe pneumonia', young age (<1 year), male gender, low birth weight (<2,500 gram), recent tuberculosis contact, readmission with an acute respiratory infection and using biomass fuel for cooking were significantly associated with an adverse outcome. Protective factors included breastfeeding, especially in infants aged 2-11 months (OR 0.8, 95% CI 0.7-0.9 on univariate analysis), older age, day care attendance and preadmission antibiotic use.

DISCUSSION

To our knowledge, this is the first study to provide a detailed characterisation of children admitted to hospital with 'pneumonia' in Vietnam. In our study, nearly half of the children admitted to hospital did not meet WHO pneumonia classification criteria and few met criteria for 'severe pneumonia' that generally justifies hospital admission and the use of intravenous antibiotics. Previous pneumonia studies did not interrogate compliance with WHO classification criteria [16, 17] and potential over-diagnosis has been noted in a retrospective study from Vietnam [12] and in other Asian countries [6, 9, 10, 18]. Unnecessary use of intravenous antibiotics may be a particular problem in settings where hospitalisation is incentivized. However, over-diagnosis has also been observed with decentralised models of care, if inadequate training is provided to frontline health care workers [19]. Our study findings are different to observations in sub-Saharan Africa where inadequate health care access remains a major challenge and pneumonia-related mortality is high [20]. A multi-hospital retrospective cohort study from Kenya found that only 4% (669/16,162) of 'pneumonia' admissions did not meet WHO classification criteria [21].

Without careful interpretation of signs and symptoms, the use of WHO criteria may lead to a misclassification of common respiratory diseases such as bronchiolitis and asthma. A technical update to the WHO pneumonia guidelines recommends careful reconsideration in children with fast breathing who have wheezing without fever [22], which typically signifies reactive airway disease without bacterial infection. We found wheeze without fever in more

than 20% of children diagnosed with 'WHO severe pneumonia'. These children do not require antibiotics and misdiagnosis of asthma may delay optimal management [23]. Unfortunately poor feeding was not recorded in a standardized fashion and it could not be used to assess disease severity. The feeding of sick children often receives inadequate attention. Some children classified as 'WHO no pneumonia' experienced an adverse outcome that was often attributed to 'pneumonia'. Most of these cases were transferred from district hospitals or deteriorated after hospital admission and our WHO classification was based on symptoms and signs documented on admission, which suggests that assessment at an inappropriate time point explain these discrepancies. Although the numbers were relatively small, it illustrates potential pitfalls if the case management approach only considers symptoms and signs documented at presentation and is not applied with adequate clinical judgement.

Unnecessary antibiotic use in children with viral infections is a potential problem [9, 19], but a clear distinction between viral and bacterial pneumonia is highly problematic and even advanced diagnostic tests have major caveats [24]. Recent findings from the Pneumonia Etiology Research for Child Health (PERCH) project, performed in seven low and middle-income countries, found that respiratory syncytial virus (RSV) accounted for >30% of CXR confirmed pneumonia cases in children <5 years old, while <10% of cases were caused by *Streptococcus pneumoniae* [25]. Findings were consistent among the seven participating countries (Mali, the Gambia, Zambia, South Africa, Kenya, Bangladesh, Thailand) [26-28]. A community-based study in Vietnam demonstrated that a point-of-care CRP test can safely reduce unnecessary antibiotic use in children with an acute respiratory infection [29], but we were unable to demonstrate significant differences in CRP or absolute neutrophil count values between different WHO pneumonia categories.

Low birth weight, preterm birth, cigarette smoke exposure, indoor air pollution and poor vaccination uptake are well recognized risk factors for child pneumonia [30, 31], but their correlation with adverse pneumonia outcomes in central Vietnam has not been assessed. The observation that breastfeeding is protective in infancy is well documented [32]. We noted a trend suggesting protection from pneumococcal conjugate vaccine (PCV), but this did not

reach statistical significance as very few children were vaccinated. Despite good evidence from other settings [32, 33], PCV is not provided as part of the extended program of immunization (EPI) in Vietnam. The fact that day care attendance was inversely correlated with an adverse outcome suggests that self-limited viral infections may be more common in this group, or that these children have better access to early appropriate care. We found a significant association between biomass fuel use for home cooking and an adverse pneumonia outcome, which support the existing literature [30] although the same was not observed for cigarette smoke exposure. The reliability of the information provided could not be verified, but the fact that cigarette smoke exposure was reported in more than 50% of households is consistent with the high smoking prevalence among Vietnamese men [30].

The death rate among children admitted to hospital with pneumonia was low compared to other settings [19, 34, 35], but similar to mortality rates recorded in Vietnam [12, 17]. Infants were overrepresented among children with an adverse outcome, but this is a consistent finding even in settings with high PCV-13 vaccination coverage [36]. As in other studies adverse outcomes were more frequent in boys than girls [11, 17], which is potentially explained by delayed immunological maturity in boys [37]. Previous studies in Vietnam reported a 'standard' hospital stay of one week following a pneumonia diagnosis [12, 38], which is consistent with our findings. However, a 3-5 day course of oral antibiotics has been shown to be adequate for non-severe pneumonia and hospitalisation for intravenous antibiotics may not be necessary [39]. In our study, the average cost of a pneumonia admission was 253.1 USD, which is much higher than previous studies in Vietnam that ranged from 31 USD in 2006 to 158 USD in 2016 [12, 17, 38]. Caregivers in Vietnam frequently access antibiotics without formal medical assessment [40] and this is also common in other Asian countries; >40% of children admitted with acute respiratory tract infections in Mongolia [41] and >50% in The Philippines [42]. This is different from sub-Saharan Africa, where access to pre-admission antibiotics is more restricted [20].

Our study was limited by the fact that we only enrolled patients in one secondary hospital in central Vietnam. However, we believe it provides a comprehensive overview of child

pneumonia cases admitted to hospital in central Vietnam and complements a previous retrospective study that included primary, secondary and tertiary hospitals [12]. This retrospective study showed no significant difference in terms of the disease spectrum or outcome of acute respiratory infection in the various hospitals [12]. The absence of information on the children who were not admitted to hospital limits our ability to comment on the safety of the WHO case management approach. However, the admission threshold was generally very low and health care access in Da Nang is good, so it is expected that children would have represented if they deteriorated at home. We were also limited by the extent of the microbiological work-up possible in the study setting and only report the results of standard blood tests performed on admission.

Conclusion

Children who did not meet 'WHO severe pneumonia' criteria often received intravenous antibiotics and a large number of pneumonia admissions seemed unwarranted. Although adoption of the WHO case management will reduce unnecessary admissions, careful interpretation of signs and symptoms is required to ensure optimal management.

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Figure 1. Flow diagram of patient enrolment

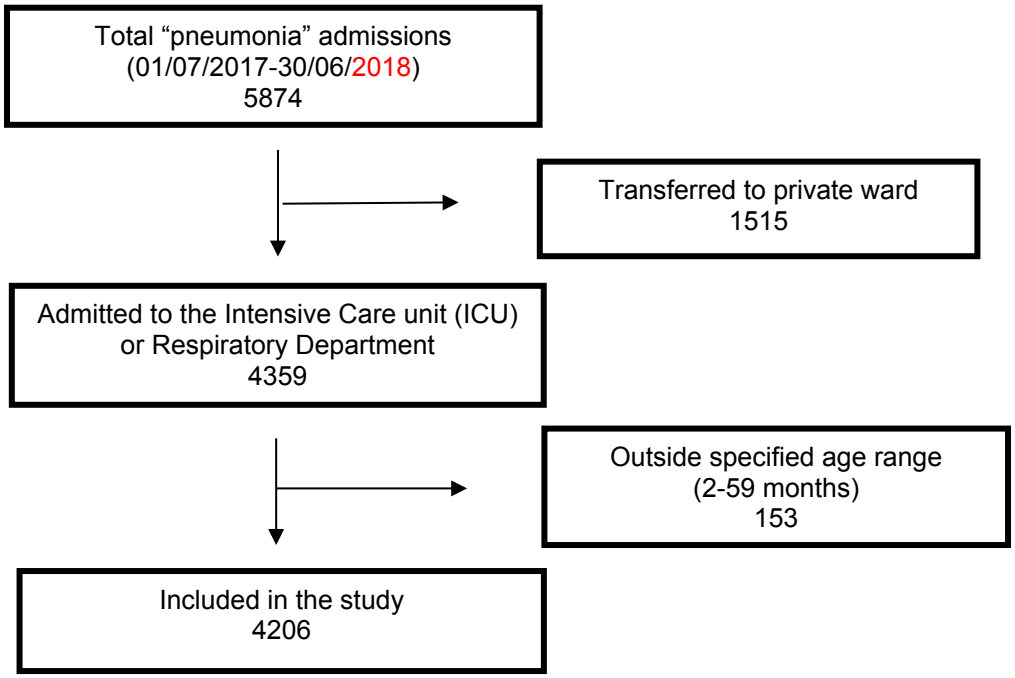

Table 1. Overview of pneumonia classification and adverse outcome definition used

WHO pneumonia classification	**Symptoms and signs**
No pneumonia	No tachypnea* OR chest in-drawing
Pneumonia	Tachypnea* OR chest in-drawing
Severe pneumonia	Tachypnea* OR chest in-drawing PLUS any danger sign – including peripheral oxygen saturation <90% in room air, severe respiratory distress (grunting or nasal flaring), inability to drink or breastfeed, vomiting everything, lethargy or convulsions
Adverse outcome definition**	**Description**
Death	Died in hospital
ICU admission	Admitted to ICU at any time during this admission
Tertiary care transfer	Transferred to tertiary care hospital
Prolonged admission	Hospital stay of >10 days

WHO – World Health Organization; ICU – intensive care unit
*Breath rate of ≥50/minute aged 2–11 months; ≥40/minute aged 12 –59 months [14]
**Composite outcome including death and/or ICU admission and/or tertiary transfer and/or prolonged admission

Table 2. Demographics and pre-admission care of children admitted to hospital with pneumonia* in central Vietnam, according to WHO pneumonia classification criteria

Demographics and pre-admission care	WHO pneumonia classification			Total N = 4206
	No pneumonia n (%)	Pneumonia n (%)	Severe pneumonia n (%)	
Total	N = 1758 (41.8)	N = 2196 (52.2)	N = 252 (6.0)	
Demographics				
Age in months; median (IQR)	18 (10-28)	16 (10-24)	10 (5.5-17)	16 (9-25)
2 – 11 months	589 (33.5)	673 (30.6)	139 (55.2)	1401 (33.3)
12 – 23 months	559 (31.8)	968 (44.1)	79 (31.3)	1606 (38.2)
24 – 59 months	610 (34.7)	555 (25.3)	34 (13.5)	1199 (28.5)
Gender (male)	1031 (58.6)	1301 (59.2)	142 (56.3)	2474 (58.8)
Pre-admission care				
Private clinic	533 (30.3)	657 (29.9)	55 (22.8)	1245 (29.6)
Public clinic	331 (18.6)	374 (17.0)	34 (13.5)	739 (17.6)
Pharmacy	202 (11.5)	301 (13.7)	22 (8.7)	525 (12.5)
Traditional healer	14 (0.8)	19 (0.9)	1 (0.4)	34 (0.8)
Local hospital	75 (4.3)	85 (3.9)	26 (10.3)	186 (4.4)
None	603 (34.3)	760 (34.6)	114 (45.2)	1477 (35.1)
Referral from other hospital	140 (8.0)	181 (8.2)	68 (27.0)	389 (9.2)
Symptom duration; median (IQR)	3 (2-6)	3 (2-5)	3 (1-5)	3 (2-5)
Symptom duration <3 days	603 (34.3)	807 (36.7)	114 (45.2)	1524 (36.2)
Pre-admission antibiotics	894 (50.9)	1097 (50.0)	101 (40.1)	2092 (49.7)
Days of use; median (IQR)	3 (2-5)	3 (2-5)	3 (2-5)	3 (2-5)
Antibiotics duration >3 days	386 (43.2)	387 (35.3)	39 (38.2)	812 (38.3)

WHO – World Health Organization; IQR – interquartile range
*Pneumonia as assessed by the admitting clinician

Table 3. Clinical signs and symptoms of children admitted to hospital with pneumonia* in central Vietnam, according to WHO pneumonia classification criteria

Clinical features	WHO pneumonia classification			Total N = 4206
	No pneumonia n (%)	Pneumonia n (%)	Severe pneumonia n (%)	
Total	N = 1758	N = 2196	N = 252	
Symptoms**				
Cough	1607 (91.4)	2040 (92.9)	204 (81.0)	3851 (91.6)
Fever	1334 (75.9)	1725 (78.6)	163 (64.7)	3222 (76.6)
Runny nose	421 (23.9)	508 (23.1)	37 (14.7)	966 (23.0)
Poor feeding#	31 (1.8)	40 (1.9)	7 (2.8)	78 (1.9)
Convulsions	24 (1.3)	0 (0)	17 (6.8)	41 (1.0)
Signs***				
Tachypnea	0 (0)	2137 (97.3)	228 (90.5)	2365 (56.2)
Chest in-drawing	0 (0)	517 (23.5)	201 (79.8)	718 (17.1)
Fever (≥38.5°C)	648 (36.9)	988 (45.0)	96 (38.1)	1732 (41.2)
SpO2<90%##	10/67 (14.9)	0/323 (0)	131/188 (69.7)	141/578 (24.4)
Grunting	1 (0.1)	0 (0)	105 (41.7)	106 (2.5)
Nasal flaring	1 (0.1)	0 (0)	83 (32.9)	84 (2.0)
Audible wheezing	104 (5.9)	387 (17.6)	59 (23.4)	550 (13.1)
Wheeze on auscultation##	209/1301 (16.1)	535/1660 (32.2)	79/207 (38.2)	823/3168 (26.0)
Stridor	5 (0.3)	22 (1.0)	4 (1.6)	31 (0.7)
Lethargy	7 (0.4)	0 (0)	28 (11.1)	35 (0.8)
Investigations				
Abnormal CXR[a]	693/1638 (42.3)	1032/2087 (49.4)	157/246 (63.8)	1882/3971 (47.4)
Consolidation[b]	254/693 (36.7)	352/1032 (34.1)	72/157 (45.9)	678/1882 (36.0)
FBC				
≥10 neutrophils x 10^9/l	330/1721 (19.2)	422/2132 (19.8)	67/249 (26.9)	819/4102 (20.0)
Hemoglobin <100 g/l	285/1721 (16.6)	443/2133 (20.8)	72/249 (28.9)	800/4103 (19.5)
CRP				
Median (IQR)	18 (6-48)	21 (6-36)	16 (6-32)	18 (6-36)
<10 mg/l	211/465 (45.4)	290/642 (45.2)	71/146 (48.6)	572/1253 (45.7)
10-49 mg/l	151/465 (32.5)	220/642 (34.3)	49/146 (33.6)	420/1253 (33.5)
≥50 mg/l	103/465 (22.2)	132/642 (20.6)	26/146 (17.8)	261/1253 (20.8)

WHO – World Health Organization; SpO2 – peripheral oxygen saturation; CXR- Chest X Ray; IQR – interquartile range; FBC – full blood count; CRP – C-reactive protein
*Pneumonia as assessed by the admitting clinician **Reported by care giver; ***Assessed on admission; #Not reliably captured; ##In children in whom this feature was reliably recorded;
[a]CXR as assessed by the lead investigator using WHO endpoint criteria for consolidation [13];
[b]Using those with an abnormal CXR used as denominator

Table 4. Outcome of children admitted to hospital with pneumonia* in central Vietnam, according to WHO pneumonia classification criteria

Adverse outcome	WHO pneumonia classification			Total N=4206
	No pneumonia n (%)	Pneumonia n (%)	Severe pneumonia n (%)	
Total	N=1758	N=2196	N=252	
Overall adverse outcome**	236 (13.4)	399 (18.2)	153 (60.7)	788 (18.7)
Died	1 (0.1)	4 (0.2)	11 (4.4)	16 (0.4)
ICU admission Median number of days (IQR)	57 (3.2) 5 (3-9)	145 (6.6) 4 (2-7)	136 (54.6) 5.5 (3-12)	338 (8.0) 4 (3-10)
Tertiary care transfer	4 (0.2)	11 (0.5)	10 (4.0)	25 (0.6)
Hospital stay >10 days **Hospital stay >14 days** Median number of days (IQR)	213 (12.1) 92 (5.2) 6 (5-8)	319 (14.5) 124 (5.6) 7 (5-9)	97 (38.5) 63 (25.0) 9 (8-15)	629 (15.0) 279 (6.6) 7 (5-9)
Oxygen supplementation Median number of days (IQR)	67 (3.8) 2 (1-5)	224 (10.2) 2 (1-4)	174 (69.0) 3 (1-6)	465 (11.1) 2 (1-5)
Assisted ventilation Median number of days (IQR)	15 (0.9) 6 (3-14)	26 (1.2) 6 (3-11)	42 (16.7) 5 (3-18)	83 (2.0) 6 (3-14)
Mean hospital cost (in USD)	112.5	121.5	515.7	253.1

WHO – World Health Organization; IQR – interquartile quarter; ICU – intensive care unit;
*Pneumonia as assessed by the admitting clinician; **As defined in Table 1

Table 5. Uni- and multivariate analyses of social factors associated with adverse outcome* in children admitted to hospital with pneumonia**

Factors	Adverse outcome		Univariate OR (95%CI)	Multivariate OR (95%CI)
	n/N	%		
WHO pneumonia classification				
No pneumonia	236/1758	13.4	1	1
Pneumonia	399/2196	18.2	1.4 (1.2-1.7)	1.4 (1.2-1.7)
Severe pneumonia	153/252	60.7	10.0 (7.5-13.3)	7.4 (5.5-10.0)
Age				
2 – 11 months	388/1401	27.7	1	1
12 – 23 months	263/1606	16.4	0.6 (0.4-0.6)	0.7 (0.6-0.8)
24 – 59 months	137/1199	11.4	0.3 (0.3-0.4)	0.6 (0.5-0.7)
Gender				
Female	287/1732	16.6	1	1
Male	501/2474	20.3	1.3 (1.1-1.5)	1.3 (1.1-1.5)
Breastfeeding [a]				
No breastfeeding	84/319	26.3	1	1
Breastfeeding	704/3887	18.1	0.6 (0.5-0.8)	0.8 (0.6-1.0)
Pneumococcal vaccination [b]				
No	700/4037	17.3	1	1
Yes	23/169	13.6	0.7 (0.4-1.1)	0.9 (0.6-1.5)
Cigarette smoke exposure [c]				
No	370/1994	18.6	1	1
Yes	418/2212	18.9	1.0 (0.9-1.2)	1.0 (0.8-1.1)
Cooking with biomass fuel [d]				
No	633/3418	18.5	1	1
Yes	191/788	24.2	1.4 (1.2-1.7)	1.2 (1.0-1.5)
Low birth weight (<2500gram)				
No	679/3879	17.5	1	1
Yes	109/327	33.3	2.4 (1.9-3.0)	1.8 (1.3-2.5)
Day care attendance				
No	546/2097	26.0	1	1
Yes	242/2109	11.5	0.4 (0.3-0.4)	0.6 (0.5-0.7)
ARI readmission [e]				
No	638/3700	17.2	1	1
Yes	150/506	29.6	2.0 (1.7-2.5)	1.5 (1.2-1.9)
Antibiotic use before admission				
No	1763/3418	51.6	1	1
Yes	329/788	41.8	0.7 (0.6-0.8)	0.8 (0.7-0.9)
Recent TB contact [f]				
No	761/4117	18.7	1	1
Yes	27/89	30.3	1.9 (1.2-3.0)	2.0 (1.2-3.3)

WHO – World Health Organization; OR – Odds Ratio; CI – Confidence Interval; ARI – acute respiratory infection; TB - tuberculosis

* As defined in Table 1; *Pneumonia as assessed by the admitting clinician

[a]Any breastfeeding; [b]Child received at least one dose; [c]Anyone smoking inside the house; [d]Cooking with wood or charcoal; [e]Readmission to hospital within 2 weeks of discharge; [f]TB contact within the last 12 months

Characterisation of children hospitalised with pneumonia in central Vietnam: A prospective study

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TAKE HOME MESSAGE

Many child 'pneumonia' admissions in central Vietnam do not meet WHO case management criteria for hospitalization or intravenous antibiotics. Accurate etiological diagnosis remains challenging and astute clinical judgement should guide optimal management.

Character count (with spaces): 255

ABSTRACT

Background

Pneumonia is the most common reason for paediatric hospital admission in Vietnam. The potential value of using the World Health Organization (WHO) case management approach in Vietnam has not been documented.

Methods

We performed a prospective descriptive study of all children (2-59 months) admitted with 'pneumonia' (per clinician assessment) to the Da Nang Hospital for Women and Children to characterise their disease profile and assess risk factors for an adverse outcome. The disease profile was classified using WHO pneumonia criteria, with tachypnea or chest indrawing as defining clinical signs. Adverse outcome was defined as death, intensive care unit admission, tertiary care transfer or hospital stay >10 days.

Results

Of 4,206 admissions, 1758 (41.8%) were classified as 'no pneumonia' using WHO criteria and only 252 (6.0%) met revised criteria for 'severe pneumonia'. The inpatient death rate was low (0.4% of admissions) with most deaths (11/16; 68.8%) occurring in the 'severe pneumonia' group. An adverse outcome was recorded in 18.7% of all admissions; 60.7% of the 'severe pneumonia' group. Children were hospitalised for a median of 7 days at an average cost of 253 USD per admission. Risk factors for adverse outcome included WHO classified 'severe pneumonia', age <1 year, low birth weight, readmission with an acute respiratory tract infection and recent tuberculosis exposure, while breastfeeding, day care attendance and preadmission antibiotic use were associated with reduced risk.

Conclusion

Few hospital admissions met WHO criteria for 'severe pneumonia', suggesting potential unnecessary hospitalisation and use of intravenous antibiotics. Accurate characterisation of the underlying diagnosis requires careful consideration.

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INTRODUCTION

Globally, pneumonia is the main cause of disease and death among young children, outside the neonatal period [1]. In 2016, child pneumonia accounted for an estimated 650,000 deaths, with the vast majority occurring in developing countries; 57,000 in Southeast and East Asia [2]. The World Health Organization (WHO) developed a clinical case management approach for use in resource-limited settings, aiming to reduce pneumonia-related deaths and improve access to life saving antibiotics for children with bacterial pneumonia, while at same time limiting unnecessary antibiotic use and reducing hospitalisations in those who can be safely managed as outpatients [3].

Although the WHO case management approach provides a simple strategy to reduce pneumonia related mortality, it has important limitations. It may encourage unnecessary antibiotic use in children with viral infections [4] and lead to the misdiagnosis of asthma, if a careful history of recurrent wheeze or night time coughing is not solicited [5], [6]. Despite these limitations, the WHO case management approach has had a positive impact [7], with studies crediting it with a 70% reduction in under-5 pneumonia-related mortality in some settings [8]. Although benefits are well documented in sub-Saharan Africa and South Asia [8], its clinical utility in East Asian settings, where many children present with ‘wheezy pneumonia’ suggesting reactive airways disease, [9, 10] is not well described. Accurate diagnosis and disease severity assessment is important to limit unnecessary use of intravenous antibiotics and hospital admission. Careful characterisation of patients at risk of an adverse outcome is also important to prioritize these patients for more intensive management.

In Vietnam, pneumonia is the leading cause of paediatric hospital admission and places a huge burden on the health care system [11, 12]. A retrospective study suggested that many ‘pneumonia’ admissions may not be clinically justified (12), but case management practices in general are poorly documented. Detailed description of children admitted to hospital with ‘pneumonia’ would provide a better understanding of the clinical utility of the WHO case management approach in Vietnam. Assessment of ‘pneumonia’ case management practices and risk factors for adverse outcomes would be informative to guide improved clinical care

and public policy regarding resource allocation and vaccination schedules. The primary aim of this study was to describe the clinical characteristics and outcomes of children admitted with 'pneumonia' compared to revised WHO case definition criteria. A secondary aim was to assess social factors associated with an adverse outcome.

MATERIAL AND METHODS

We conducted a prospective descriptive study of children hospitalized with 'pneumonia' over a 1-year study period (1 July 2017 to 30 June 2018). Written approval for the study was obtained from the Ethics Committee of Da Nang Hospital for Women and Children (13 January 2017).

Study setting

The Da Nang Hospital for Women and Children is a secondary referral hospital in central Vietnam. The hospital has 900 beds with 570 beds reserved for children <15 years old. Pediatric bed occupancy in 2017 was more than 150%. Annual reports suggested that around 4,000 children with acute respiratory infections are admitted to the Respiratory Department and intensive care unit (ICU) every year. Children either present directly from home (through outpatient or emergency services) or are referred from district hospitals in Da Nang city or surrounding provincial hospitals in Quang Nam and Quang Ngai. Children with severe disease who do not improve on admission, including treatment in the local ICU, are referred to tertiary training hospitals in Ha Noi (The National Hospital of Pediatrics) or Ho Chi Minh City (Children' Hospitals number I and II). In 2016, the year preceding the study, acute respiratory infection accounted for nearly a third of pediatric hospital admissions to the Da Nang Hospital for Women and Children; 97% were less than 5 years old.

Study population and procedures

We recruited children aged 2-59 months admitted with a primary or secondary diagnosis of 'pneumonia' as assessed by the admitting clinician. These children were routinely admitted to the Respiratory Department, or directly to the ICU. Independent researchers, not involved in

clinical patient care, performed daily ward rounds in the Respiratory Department and the ICU to recruit new patients and record relevant clinical information.

Clinical information included respiratory signs and symptoms documented on admission, date of symptom onset, number of days from onset to admission, antibiotic use before admission, recent admission with an acute respiratory infection (during the past 2 weeks), recent tuberculosis contact (during the past 12 months), gestational age, birth weight and pneumococcal vaccination. Social risk factors such as breastfeeding, indoor biomass fuel or cigarette smoke exposure, child care attendance, or having an ill sibling at home were also documented. Details of all variables collected are summarised in Table S1. Other clinical, laboratory and radiological information, as well as pneumonia outcome data, were updated intermittently during the period of hospital stay and finalised on discharge. A number of patients in a stable clinical condition were admitted to a private fee-paying ward; these patients were excluded from the study. Chest X-rays (CXR) were routinely performed in children admitted to hospital and assessed for consolidation by the lead investigator, using WHO working group definitions [13]. Hyperinflation was not documented.

Pneumonia classification

Children were classified based on revised WHO criteria using tachypnea, defined as ≥50 breaths/minute if aged 2 – 11 months, or ≥40 breaths/minute if aged 12 – 59 months [14], and/or chest in-drawing as defining clinical symptoms. Severe pneumonia was identified in the presence of any danger sign, including peripheral oxygen saturation (SpO_2) <90% in room air, severe respiratory distress (grunting, nasal flaring), inability to drink or breastfeed, vomiting everything, lethargy or convulsions [15]. Table 1 provides an overview of the pneumonia classification and adverse outcome definition used.

Statistical analysis

Categorical data were tabulated and presented as numbers and percentages and their associations with WHO pneumonia criteria determined using Chi-squared or Fisher's exact tests, as appropriate. 'Wheeze heard with a stethoscope' was not recorded in the first 1,038

cases, where after this was reliably recorded. For comparative analyses we considered unrecorded data as missing values and did not use any imputation. In Vietnam, children with respiratory symptoms often receive antibiotics before hospital presentation; we dichotomized the variables 'time since symptom onset' and 'duration of pre-admission antibiotics' using a clinically relevant threshold of 3 days.

Continuous data were summarized as mean (standard deviation) or median (interquartile range) and their associations with WHO classified pneumonia examined using the analysis of variance (ANOVA) or Kruskal Wallis tests for normally and non-normally distributed variables, respectively. We used uni- and multivariate analyses to assess the social factors associated with adverse outcome (as defined) including age, gender, low birth weight, WHO pneumonia classification, readmission with an acute respiratory infection, pre-admission antibiotic use, recent tuberculosis contact, breastfeeding, pneumococcal vaccination, cigarette or biomass smoke exposure and day care attendance; without considering pre-specified confounders. Post-hoc analysis was done for breastfeeding stratified by age. Data analysis was carried out using SPSS (version 24.0; SPSS, Inc., Chicago, IL). A p-value of less than 0.05 was considered statistically significant. The strength of association was determined by estimating the odds ratio (OR) and the 95% confidence interval (CI).

RESULTS

Figure 1 provides a flow diagram of patient enrolment. Of the 4,206 children hospitalized with 'pneumonia' (as assessed by the admitting clinician), 41.8% failed to meet WHO pneumonia criteria by not having tachypnea or chest indrawing on presentation. Table 2 provides an overview of patient demographics and pre-admission care in all children, classified according to revised WHO pneumonia criteria. Children <2 years accounted for 71.5% of the 'pneumonia' admissions, with infants (<1 year of age) accounting for most (139/252; 55.2%) of the 'WHO severe pneumonia' cases. Boys were more commonly admitted than girls (58.8% boys; p<0.01) in all age categories, with the largest gender discrepancy observed among infants (62.5% boys; p<0.01).

Table 3 summarises the clinical signs and symptoms observed. Ten cases with low oxygen saturation on admission did not meet WHO pneumonia criteria, these included children with sepsis (4), congenital heart disease (2), restrictive lung disease (2), near drowning (1) and primary pulmonary hypertension (1). The 4 children transferred to a tertiary hospital with 'WHO no pneumonia' included 2 children with restrictive lung disease, 1 with hemangioma causing airway obstruction and 1 with near drowning. Interestingly, 38.2% of 'WHO severe pneumonia' cases wheezed on auscultation and this was more common in cases with 'WHO pneumonia' and 'severe pneumonia' compared to 'no pneumonia' (446/2,448; 18.2% versus 104/1,758; 5.9%; p <0.001). Children with wheeze and no fever accounted for 24.2% (61/252) of 'WHO severe pneumonia' cases; 15.6% (342/2,196) of the 'pneumonia' and 8.3% (146/1,758) of the 'no pneumonia' group. Few children were tested for human immunodeficiency virus (HIV) infection; of those tested 2/79 (2.5%) were HIV infected. A CXR was performed in 3971 (94.4%) children, with the majority (52.6%) reported as normal and consolidation noted in 36.0%.

Table 4 summarises the outcomes of children according to revised WHO pneumonia classification criteria. An adverse outcome was documented in 18.7% children. Most (60.7%) adverse outcomes and the vast majority of deaths (7/9; 77.8%) occurred in children with 'severe pneumonia'. The single child in the 'no pneumonia' category who died had cyanotic heart disease. The 4 deaths in children with 'non-severe pneumonia' were attributed to sepsis (3) and acute pericarditis (1). Among children with 'WHO no pneumonia' who were admitted for more than 14 days, 58.7% (54/92) were either referred from a district hospital with a clinical diagnosis of pneumonia and slow treatment response, or experienced a worsening of symptoms after hospital admission. Other children in this group had persistent wheezing or stridor (10), chronic diarrhoea (10), or an unrelated surgical problem (28). Those who required assisted ventilation in the 'WHO no pneumonia' group included children with clinical deterioration after admission (8), sepsis (1), hemangioma with airway obstruction (1), congenital heart disease (2), near drowning (2) and acute pericarditis (1).

Table 5 reflects uni- and multivariate analyses of factors associated with an adverse outcome. Children admitted with 'severe pneumonia' experienced the greatest risk (OR 7.4; 95% CI 5.5-10.0). 'WHO severe pneumonia', young age (<1 year), male gender, low birth weight (<2,500 gram), recent tuberculosis contact, readmission with an acute respiratory infection and using biomass fuel for cooking were significantly associated with an adverse outcome. Protective factors included breastfeeding, especially in infants aged 2-11 months (OR 0.8, 95% CI 0.7-0.9 on univariate analysis), older age, day care attendance and preadmission antibiotic use.

DISCUSSION

To our knowledge, this is the first study to provide a detailed characterisation of children admitted to hospital with 'pneumonia' in Vietnam. In our study, nearly half of the children admitted to hospital did not meet WHO pneumonia classification criteria and few met criteria for 'severe pneumonia' that generally justifies hospital admission and the use of intravenous antibiotics. Previous pneumonia studies did not interrogate compliance with WHO classification criteria [16, 17] and potential over-diagnosis has been noted in a retrospective study from Vietnam [12] and in other Asian countries [6, 9, 10, 18]. Unnecessary use of intravenous antibiotics may be a particular problem in settings where hospitalisation is incentivized. However, over-diagnosis has also been observed with decentralised models of care, if inadequate training is provided to frontline health care workers [19]. Our study findings are different to observations in sub-Saharan Africa where inadequate health care access remains a major challenge and pneumonia-related mortality is high [20]. A multi-hospital retrospective cohort study from Kenya found that only 4% (669/16,162) of 'pneumonia' admissions did not meet WHO classification criteria [21].

Without careful interpretation of signs and symptoms, the use of WHO criteria may lead to a misclassification of common respiratory diseases such as bronchiolitis and asthma. A technical update to the WHO pneumonia guidelines recommends careful reconsideration in children with fast breathing who have wheezing without fever [22], which typically signifies reactive airway disease without bacterial infection. We found wheeze without fever in more

than 20% of children diagnosed with 'WHO severe pneumonia'. These children do not require antibiotics and misdiagnosis of asthma may delay optimal management [23]. Unfortunately poor feeding was not recorded in a standardized fashion and it could not be used to assess disease severity. The feeding of sick children often receives inadequate attention. Some children classified as 'WHO no pneumonia' experienced an adverse outcome that was often attributed to 'pneumonia'. Most of these cases were transferred from district hospitals or deteriorated after hospital admission and our WHO classification was based on symptoms and signs documented on admission, which suggests that assessment at an inappropriate time point explain these discrepancies. Although the numbers were relatively small, it illustrates potential pitfalls if the case management approach only considers symptoms and signs documented at presentation and is not applied with adequate clinical judgement.

Unnecessary antibiotic use in children with viral infections is a potential problem [9, 19], but a clear distinction between viral and bacterial pneumonia is highly problematic and even advanced diagnostic tests have major caveats [24]. Recent findings from the Pneumonia Etiology Research for Child Health (PERCH) project, performed in seven low and middle-income countries, found that respiratory syncytial virus (RSV) accounted for >30% of CXR confirmed pneumonia cases in children <5 years old, while <10% of cases were caused by *Streptococcus pneumoniae* [25]. Findings were consistent among the seven participating countries (Mali, the Gambia, Zambia, South Africa, Kenya, Bangladesh, Thailand) [26-28]. A community-based study in Vietnam demonstrated that a point-of-care CRP test can safely reduce unnecessary antibiotic use in children with an acute respiratory infection [29], but we were unable to demonstrate significant differences in CRP or absolute neutrophil count values between different WHO pneumonia categories.

Low birth weight, preterm birth, cigarette smoke exposure, indoor air pollution and poor vaccination uptake are well recognized risk factors for child pneumonia [30, 31], but their correlation with adverse pneumonia outcomes in central Vietnam has not been assessed. The observation that breastfeeding is protective in infancy is well documented [32]. We noted a trend suggesting protection from pneumococcal conjugate vaccine (PCV), but this did not

reach statistical significance as very few children were vaccinated. Despite good evidence from other settings [32, 33], PCV is not provided as part of the extended program of immunization (EPI) in Vietnam. The fact that day care attendance was inversely correlated with an adverse outcome suggests that self-limited viral infections may be more common in this group, or that these children have better access to early appropriate care. We found a significant association between biomass fuel use for home cooking and an adverse pneumonia outcome, which support the existing literature [30] although the same was not observed for cigarette smoke exposure. The reliability of the information provided could not be verified, but the fact that cigarette smoke exposure was reported in more than 50% of households is consistent with the high smoking prevalence among Vietnamese men [30].

The death rate among children admitted to hospital with pneumonia was low compared to other settings [19, 34, 35], but similar to mortality rates recorded in Vietnam [12, 17]. Infants were overrepresented among children with an adverse outcome, but this is a consistent finding even in settings with high PCV-13 vaccination coverage [36]. As in other studies adverse outcomes were more frequent in boys than girls [11, 17], which is potentially explained by delayed immunological maturity in boys [37]. Previous studies in Vietnam reported a ‘standard’ hospital stay of one week following a pneumonia diagnosis [12, 38], which is consistent with our findings. However, a 3-5 day course of oral antibiotics has been shown to be adequate for non-severe pneumonia and hospitalisation for intravenous antibiotics may not be necessary [39]. In our study, the average cost of a pneumonia admission was 253.1 USD, which is much higher than previous studies in Vietnam that ranged from 31 USD in 2006 to 158 USD in 2016 [12, 17, 38]. Caregivers in Vietnam frequently access antibiotics without formal medical assessment [40] and this is also common in other Asian countries; >40% of children admitted with acute respiratory tract infections in Mongolia [41] and >50% in The Philippines [42]. This is different from sub-Saharan Africa, where access to pre-admission antibiotics is more restricted [20].

Our study was limited by the fact that we only enrolled patients in one secondary hospital in central Vietnam. However, we believe it provides a comprehensive overview of child

pneumonia cases admitted to hospital in central Vietnam and complements a previous retrospective study that included primary, secondary and tertiary hospitals [12]. This retrospective study showed no significant difference in terms of the disease spectrum or outcome of acute respiratory infection in the various hospitals [12]. The absence of information on the children who were not admitted to hospital limits our ability to comment on the safety of the WHO case management approach. However, the admission threshold was generally very low and health care access in Da Nang is good, so it is expected that children would have represented if they deteriorated at home. We were also limited by the extent of the microbiological work-up possible in the study setting and only report the results of standard blood tests performed on admission.

Conclusion

Children who did not meet 'WHO severe pneumonia' criteria often received intravenous antibiotics and a large number of pneumonia admissions seemed unwarranted. Although adoption of the WHO case management will reduce unnecessary admissions, careful interpretation of signs and symptoms is required to ensure optimal management.

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Figure 1. Flow diagram of patient enrolment

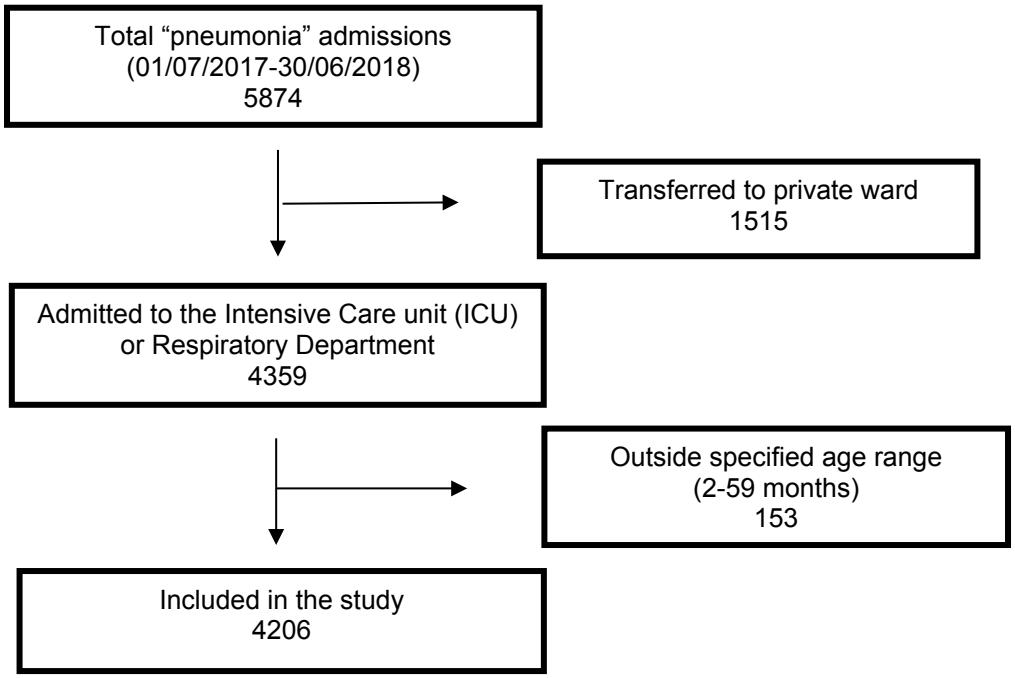

Table 1. Overview of pneumonia classification and adverse outcome definition used

WHO pneumonia classification	**Symptoms and signs**
No pneumonia	No tachypnea* OR chest in-drawing
Pneumonia	Tachypnea* OR chest in-drawing
Severe pneumonia	Tachypnea* OR chest in-drawing PLUS any danger sign – including peripheral oxygen saturation <90% in room air, severe respiratory distress (grunting or nasal flaring), inability to drink or breastfeed, vomiting everything, lethargy or convulsions
Adverse outcome definition**	**Description**
Death	Died in hospital
ICU admission	Admitted to ICU at any time during this admission
Tertiary care transfer	Transferred to tertiary care hospital
Prolonged admission	Hospital stay of >10 days

WHO – World Health Organization; ICU – intensive care unit
*Breath rate of ≥50/minute aged 2–11 months; ≥40/minute aged 12 –59 months [14]
**Composite outcome including death and/or ICU admission and/or tertiary transfer and/or prolonged admission

Table 2. Demographics and pre-admission care of children admitted to hospital with pneumonia* in central Vietnam, according to WHO pneumonia classification criteria

Demographics and pre-admission care	WHO pneumonia classification			Total N = 4206
	No pneumonia n (%)	**Pneumonia** n (%)	**Severe pneumonia** n (%)	
Total	N = 1758 (41.8)	N = 2196 (52.2)	N = 252 (6.0)	
Demographics				
Age in months; median (IQR)	18 (10-28)	16 (10-24)	10 (5.5-17)	16 (9-25)
2 – 11 months	589 (33.5)	673 (30.6)	139 (55.2)	1401 (33.3)
12 – 23 months	559 (31.8)	968 (44.1)	79 (31.3)	1606 (38.2)
24 – 59 months	610 (34.7)	555 (25.3)	34 (13.5)	1199 (28.5)
Gender (male)	1031 (58.6)	1301 (59.2)	142 (56.3)	2474 (58.8)
Pre-admission care				
Private clinic	533 (30.3)	657 (29.9)	55 (22.8)	1245 (29.6)
Public clinic	331 (18.6)	374 (17.0)	34 (13.5)	739 (17.6)
Pharmacy	202 (11.5)	301 (13.7)	22 (8.7)	525 (12.5)
Traditional healer	14 (0.8)	19 (0.9)	1 (0.4)	34 (0.8)
Local hospital	75 (4.3)	85 (3.9)	26 (10.3)	186 (4.4)
None	603 (34.3)	760 (34.6)	114 (45.2)	1477 (35.1)
Referral from other hospital	140 (8.0)	181 (8.2)	68 (27.0)	389 (9.2)
Symptom duration; median (IQR)	3 (2-6)	3 (2-5)	3 (1-5)	3 (2-5)
Symptom duration <3 days	603 (34.3)	807 (36.7)	114 (45.2)	1524 (36.2)
Pre-admission antibiotics	894 (50.9)	1097 (50.0)	101 (40.1)	2092 (49.7)
Days of use; median (IQR)	3 (2-5)	3 (2-5)	3 (2-5)	3 (2-5)
Antibiotics duration >3 days	386 (43.2)	387 (35.3)	39 (38.2)	812 (38.3)

WHO – World Health Organization; IQR – interquartile range
*Pneumonia as assessed by the admitting clinician

Table 3. Clinical signs and symptoms of children admitted to hospital with pneumonia* in central Vietnam, according to WHO pneumonia classification criteria

Clinical features	WHO pneumonia classification			Total N = 4206
	No pneumonia n (%)	Pneumonia n (%)	Severe pneumonia n (%)	
Total	N = 1758	N = 2196	N = 252	
Symptoms**				
Cough	1607 (91.4)	2040 (92.9)	204 (81.0)	3851 (91.6)
Fever	1334 (75.9)	1725 (78.6)	163 (64.7)	3222 (76.6)
Runny nose	421 (23.9)	508 (23.1)	37 (14.7)	966 (23.0)
Poor feeding[#]	31 (1.8)	40 (1.9)	7 (2.8)	78 (1.9)
Convulsions	24 (1.3)	0 (0)	17 (6.8)	41 (1.0)
Signs***				
Tachypnea	0 (0)	2137 (97.3)	228 (90.5)	2365 (56.2)
Chest in-drawing	0 (0)	517 (23.5)	201 (79.8)	718 (17.1)
Fever (≥38.5^{o}C)	648 (36.9)	988 (45.0)	96 (38.1)	1732 (41.2)
SpO2<90%[##]	10/67 (14.9)	0/323 (0)	131/188 (69.7)	141/578 (24.4)
Grunting	1 (0.1)	0 (0)	105 (41.7)	106 (2.5)
Nasal flaring	1 (0.1)	0 (0)	83 (32.9)	84 (2.0)
Audible wheezing	104 (5.9)	387 (17.6)	59 (23.4)	550 (13.1)
Wheeze on auscultation[##]	209/1301 (16.1)	535/1660 (32.2)	79/207 (38.2)	823/3168 (26.0)
Stridor	5 (0.3)	22 (1.0)	4 (1.6)	31 (0.7)
Lethargy	7 (0.4)	0 (0)	28 (11.1)	35 (0.8)
Investigations				
Abnormal CXR[a]	693/1638 (42.3)	1032/2087 (49.4)	157/246 (63.8)	1882/3971 (47.4)
Consolidation[b]	254/693 (36.7)	352/1032 (34.1)	72/157 (45.9)	678/1882 (36.0)
FBC				
≥10 neutrophils x 10^{9}/l	330/1721 (19.2)	422/2132 (19.8)	67/249 (26.9)	819/4102 (20.0)
Hemoglobin <100 g/l	285/1721 (16.6)	443/2133 (20.8)	72/249 (28.9)	800/4103 (19.5)
CRP				
Median (IQR)	18 (6-48)	21 (6-36)	16 (6-32)	18 (6-36)
<10 mg/l	211/465 (45.4)	290/642 (45.2)	71/146 (48.6)	572/1253 (45.7)
10-49 mg/l	151/465 (32.5)	220/642 (34.3)	49/146 (33.6)	420/1253 (33.5)
≥50 mg/l	103/465 (22.2)	132/642 (20.6)	26/146 (17.8)	261/1253 (20.8)

WHO – World Health Organization; SpO2 – peripheral oxygen saturation; CXR- Chest X Ray; IQR – interquartile range; FBC – full blood count; CRP – C-reactive protein
*Pneumonia as assessed by the admitting clinician **Reported by care giver; ***Assessed on admission; [#]Not reliably captured; [##]In children in whom this feature was reliably recorded;
[a]CXR as assessed by the lead investigator using WHO endpoint criteria for consolidation [13];
[b]Using those with an abnormal CXR used as denominator

Table 4. Outcome of children admitted to hospital with pneumonia* in central Vietnam, according to WHO pneumonia classification criteria

Adverse outcome	WHO pneumonia classification			Total N=4206
	No pneumonia n (%)	Pneumonia n (%)	Severe pneumonia n (%)	
Total	N=1758	N=2196	N=252	
Overall adverse outcome**	236 (13.4)	399 (18.2)	153 (60.7)	788 (18.7)
Died	1 (0.1)	4 (0.2)	11 (4.4)	16 (0.4)
ICU admission Median number of days (IQR)	57 (3.2) 5 (3-9)	145 (6.6) 4 (2-7)	136 (54.6) 5.5 (3-12)	338 (8.0) 4 (3-10)
Tertiary care transfer	4 (0.2)	11 (0.5)	10 (4.0)	25 (0.6)
Hospital stay >10 days **Hospital stay >14 days** Median number of days (IQR)	213 (12.1) 92 (5.2) 6 (5-8)	319 (14.5) 124 (5.6) 7 (5-9)	97 (38.5) 63 (25.0) 9 (8-15)	629 (15.0) 279 (6.6) 7 (5-9)
Oxygen supplementation Median number of days (IQR)	67 (3.8) 2 (1-5)	224 (10.2) 2 (1-4)	174 (69.0) 3 (1-6)	465 (11.1) 2 (1-5)
Assisted ventilation Median number of days (IQR)	15 (0.9) 6 (3-14)	26 (1.2) 6 (3-11)	42 (16.7) 5 (3-18)	83 (2.0) 6 (3-14)
Mean hospital cost (in USD)	112.5	121.5	515.7	253.1

WHO – World Health Organization; IQR – interquartile quarter; ICU – intensive care unit;
*Pneumonia as assessed by the admitting clinician; **As defined in Table 1

Table 5. Uni- and multivariate analyses of social factors associated with adverse outcome* in children admitted to hospital with pneumonia**

Factors	Adverse outcome		Univariate OR (95%CI)	Multivariate OR (95%CI)
	n/N	%		
WHO pneumonia classification				
No pneumonia	236/1758	13.4	1	1
Pneumonia	399/2196	18.2	1.4 (1.2-1.7)	1.4 (1.2-1.7)
Severe pneumonia	153/252	60.7	10.0 (7.5-13.3)	7.4 (5.5-10.0)
Age				
2 – 11 months	388/1401	27.7	1	1
12 – 23 months	263/1606	16.4	0.6 (0.4-0.6)	0.7 (0.6-0.8)
24 – 59 months	137/1199	11.4	0.3 (0.3-0.4)	0.6 (0.5-0.7)
Gender				
Female	287/1732	16.6	1	1
Male	501/2474	20.3	1.3 (1.1-1.5)	1.3 (1.1-1.5)
Breastfeeding [a]				
No breastfeeding	84/319	26.3	1	1
Breastfeeding	704/3887	18.1	0.6 (0.5-0.8)	0.8 (0.6-1.0)
Pneumococcal vaccination [b]				
No	700/4037	17.3	1	1
Yes	23/169	13.6	0.7 (0.4-1.1)	0.9 (0.6-1.5)
Cigarette smoke exposure [c]				
No	370/1994	18.6	1	1
Yes	418/2212	18.9	1.0 (0.9-1.2)	1.0 (0.8-1.1)
Cooking with biomass fuel [d]				
No	633/3418	18.5	1	1
Yes	191/788	24.2	1.4 (1.2-1.7)	1.2 (1.0-1.5)
Low birth weight (<2500gram)				
No	679/3879	17.5	1	1
Yes	109/327	33.3	2.4 (1.9-3.0)	1.8 (1.3-2.5)
Day care attendance				
No	546/2097	26.0	1	1
Yes	242/2109	11.5	0.4 (0.3-0.4)	0.6 (0.5-0.7)
ARI readmission [e]				
No	638/3700	17.2	1	1
Yes	150/506	29.6	2.0 (1.7-2.5)	1.5 (1.2-1.9)
Antibiotic use before admission				
No	1763/3418	51.6	1	1
Yes	329/788	41.8	0.7 (0.6-0.8)	0.8 (0.7-0.9)
Recent TB contact [f]				
No	761/4117	18.7	1	1
Yes	27/89	30.3	1.9 (1.2-3.0)	2.0 (1.2-3.3)

WHO – World Health Organization; OR – Odds Ratio; CI – Confidence Interval; ARI – acute respiratory infection; TB - tuberculosis

* As defined in Table 1; *Pneumonia as assessed by the admitting clinician

[a]Any breastfeeding; [b]Child received at least one dose; [c]Anyone smoking inside the house; [d]Cooking with wood or charcoal; [e]Readmission to hospital within 2 weeks of discharge; [f]TB contact within the last 12 months

Table S1: Available and missing data for each variable collected in children admitted to hospital with pneumonia*

Variable	Available data	Not done or missing data
Gender	4206	0
Age	4206	0
Preadmission care	4206	0
Referral from other hospital	4206	0
Diagnosis at referral	4206	0
Symptom duration	4116	90
Pre-admission antibiotic use	4116	90
Type of antibiotic use	4116	90
Symptoms		
Cough	4026	0
Fever	4206	0
Runny nose	4206	0
Poor feeding (classification inconsistent)	4206	0
Convulsions	4206	0
Signs		
Breath rate	4206	0
Temperature	4206	0
Weight	4206	0
Chest indrawing	4206	0
Peripheral oxygen saturation level	578	2
Grunting	4206	0
Nasal flaring	4206	0
Audible wheezing	4206	0
Wheeze on auscultation	3168	1038
Stridor	4206	0
Lethargy	4206	0
Investigation		
Chest radiograph done	4106	100
Full blood count (FBC) done*	4102	104
C-Reactive protein (CRP) done*	4098	108
CRP level (in children with a positive CRP)	1253	0
Outcome	4206	0
Hospital cost	4206	0
Breastfeeding		
Any breastfeeding	4206	0
Months of exclusive breastfeeding	3887	0
Duration of breastfeeding	3887	0
Pneumococcal vaccination	4094	0
Cigarette smoke exposure	4206	0
Biomass fuel cooking	4206	0
Daycare attendance	4206	0
Number of children in class (for children in daycare)	2109	952
Classmate sick (for children in daycare)	2109	952
Sibling ill (for children who had a sibling)	2189	3
Acute respiratory infections		
Over last 12 months	4206	0
Readmission last 12 months	4206	0
Readmission last 2 weeks	4206	0
Tuberculosis contact	4026	0

*All patients had either a CRP and/or FBC recorded

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Y/N
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Y
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Y
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Y
Objectives	3	State specific objectives, including any prespecified hypotheses	Y
Methods			
Study design	4	Present key elements of study design early in the paper	Y
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Y
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	Y
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Y
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*Y*
Bias	9	Describe any efforts to address potential sources of bias	Y
Study size	10	Explain how the study size was arrived at	Y
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	NA
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Y
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	Y
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	NA
		(*e*) Describe any sensitivity analyses	NA

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Y
		(b) Give reasons for non-participation at each stage	Y
		(c) Consider use of a flow diagram	Y
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Y
		(b) Indicate number of participants with missing data for each variable of interest	Y
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	NA
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	*Y*
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Y
		(*b*) Report category boundaries when continuous variables were categorized	Y
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Y
Discussion			
Key results	18	Summarise key results with reference to study objectives	Y
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Y
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Y
Generalisability	21	Discuss the generalisability (external validity) of the study results	Y
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Y

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Dear Editor

Manuscript ID: ERJ-02256-2018
Title: Characterisation of children hospitalised with pneumonia in central Vietnam: A prospective study

Thank you for the constructive feedback received. We hope that the revised version will meet with your expectations.

Section Editor 1
1) There are a number of important issues to address, in particular relating to more attention to alternative diagnoses. Please note that a revised manuscript that does not satisfy the concerns can still be rejected.
Reply: We addressed all issues raised by the reviewers, including those related to alternative diagnoses. Please see point-by-point response below.

Reviewer 1
This prospective study by Nguyen et al. aims to describe the characteristics of children hospitalised for pneumonia, to assess the WHO case management criteria among these children and to investigate risk factors for adverse outcomes. For this, they collected data prospectively of all children 2-59 months old admitted with the diagnosis of pneumonia to a secondary hospital in Vietnam, between July 2017 and June 2018. They included 4206 children, of which 1758 (42%) did not fulfill the WHO criteria for 'pneumonia', 2196 (52%) were classified as 'pneumonia' and 252 (6%) as 'severe pneumonia', according to these criteria. They described the demographics, pre-admission care and clinical signs and symptoms stratified into these 3 categories. In the multivariable logistic regression model, the authors found that male sex, age 2-11 months, low birth weight, no breastfeeding, no day care attendance, classification as severe pneumonia (WHO), and readmission within 2 weeks of a previous acute respiratory infection, were risk factors for an adverse outcome (death, ICU admission, tertiary care transfer or hospital stay >10 days). The study is relevant and important as respiratory infections are the leading cause of childhood hospitalisation in this and other similar settings. A better understanding of these events could improve health care organisation and reduce unnecessary hospitalisations and antibiotic prescription. However, there are certain aspects that should be more clearly defined.

Major comments
General
1) The study is centred around the overdiagnosis of pneumonia and the misclassification of its severity with a high proportion of children hospitalised with a non-severe pneumonia. However, there is not a lot of discussion around the underdiagnosis of other respiratory diseases that may be responsible for an important part of these hospitalisations, such as bronchiolitis and asthma. Even among the WHO 'severe pneumonia' category, 38% of the children presented with wheeze at auscultation. Maybe this is an important limitation of the WHO criteria, and should be further investigated in this setting. If there are different aetiologies behind the respiratory infections of the children included in the study, it would be good to identify the specific risk factors for adverse outcomes among those with bacterial pneumonia, excluding children with asthma and bronchiolitis.
Reply: The reviewer touches on an important and difficult issue. Pneumonia remains an ill-defined term (see Reviewer 4) and the WHO pneumonia case definition relies on clinical criteria that are considered to be generally indicative of acute parenchymal disease. Establishing an accurate aetiological diagnosis remains problematic, even with the best available tests, and was not the focus of our study. We expanded the relevant discussion. A technical update of WHO recommendations for the management of pneumonia recommended no antibiotic treatment in children with fast breathing if they have wheezing without fever (*WHO. Recommendation for management of common childhood conditions: evidence for technical update of pocket book recommendations: newborn conditions, dysentery, pneumonia, oxygen use and delivery, common causes of fever, severe acute malnutrition and supportive care, 2012*). We did a sub-analysis of these children (wheeze without fever, which is considered indicative of reactive airway disease rather than bacterial pneumonia) and found that they accounted for 8.3% (146/1758) of the 'no pneumonia', 15.6% (342/2196) of the pneumonia and 24.2% (61/252) of the severe pneumonia group.

This was added to the results section. We plan to assess predictors of 'likely bacterial pneumonia' in a separate analysis, but optimal criteria are still under discussion.

Abstract

2) I find the methods of the abstract a little bit short. Maybe the results section could be shorten to include more details in the methods, such as the definition of adverse outcomes.

***Reply:** We included a short definition of WHO 'pneumonia' criteria and adverse outcome in the methods section of the abstract. The full manuscript contains a detailed overview of the pneumonia classification and outcome definitions used (Table 1).

Introduction

3) The authors mention the 'limitations' of the WHO case management approach in the second paragraph, but do not describe what these limitations are. This is relevant for the study as these limitations could explain part of their findings.

***Reply:** We placed greater emphasis on the limitations of the WHO case management approach in the introduction and expanded the relevant discussion.

4) Similarly, the authors mention in the second paragraph that many children in East Asia present with 'wheezy pneumonia'. I suggest the authors to describe what they mean by this term. Is it really pneumonia or a viral respiratory infection with wheeze?

***Reply:** We indicated that "wheezy pneumonia" suggests a viral infection (viral pneumonia or bronchiolitis) or asthma rather than bacterial pneumonia. The WHO clinical case definition used does not differentiate the underlying aetiology.

Methods

5) It would be very informative to report all the data that was collected, which is described as 'relevant clinical information' (paragraph 3). This could be included in a supplementary table.

***Reply:** We included all relevant clinical information and added a supplementary table as requested. Details of all variables collected are summarised in Table S1.

6) The definition used for some factors has not been described, e.g. cigarette smoke exposure (mother or father, inside or outside the house?), pneumococcal vaccination (how many doses were considered as 'Yes'), breastfeeding (is this any breastfeeding?), etc.

***Reply:** We described the definition of each variable in the footnotes of the relevant table (Table 5).

7) The authors should better explain what this statement means: 'audible wheeze was only reliably captured after the first 1000 cases' (statistical analysis, first paragraph).

***Reply:** We clarified this sentence by stating that: " 'Wheeze heard with a stethoscope' was not recorded in the first 1,038 cases, where after this was reliably captured."

8) In the second paragraph of the statistical analysis, there is a description of the variables included in the multivariable model, however, there is no explanation of how the model was developed (eg. forward or backward selection, p value used for inclusion, etc.). I would also suggest the authors to clarify if all the pre-specified confounders that may play a role in the occurrence of adverse outcomes have been included in the model. The use of Direct Acyclic Graphs (DAG) may be useful for this purpose.

***Reply:** We expanded the methods section to better explain the approach adopted. We focused on social risk factors associated with adverse outcome and hope to develop a formal risk prediction model in a subsequent paper.

Results

9) There is a slight repetition between the information in the tables and in the text, so maybe the text could be reduced to some extent.

***Reply:** The text has been reduced to limit duplication.

10) In the last paragraph of the results, 'tuberculosis contact' is included as one of the risk factors for adverse outcomes, however, this factor has not been mentioned previously and does not appear in the

tables. This may be just a typo, but it makes the reader unsure about how many other factors were studied as possible risk factors and have not been mentioned because the association with the outcome was not 'statistically significant'. (See point in 1, Methods).
***Reply:** We included all measured variables in the supplementary table and added 'tuberculosis contact' as a factor in Table 5.

11) It would be of interest to see the specific findings of the CXR in each WHO category (Table 3).
***Reply:** We inserted CXR findings related to consolidation. Hyperinflation was not recorded.

12) The authors should discuss why 10/67 of the 'no pneumonia group' had SpO2<90% with no tachypnoea. Was this because of sepsis with altered peripheral perfusion?
***Reply:** We provided a detailed overview of this group in the results section: "Ten cases with SpO2<90% did not meet WHO pneumonia criteria, these included sepsis (4), congenital heart disease (2), restrictive lung disease (2); accidental drowning (1), primary pulmonary hypertension (1)."

13) The last sentence of the results introduces an additional analysis of the protective effect of breastfeeding stratified by age. This analysis was not previously described in the methods. It should be identified as a post-hoc analysis, if it is.
***Reply:** This was added to the methods section: "…Post-hoc analysis was done for breastfeeding stratified by age."

Discussion
14) I suggest the authors to start the discussion with a paragraph stating their main findings.
***Reply:** We included our main finding in the first paragraph: "To our knowledge, this is the first study to provide a detailed characterisation of children admitted to hospital with 'pneumonia' in Vietnam. In our study, nearly half of the children admitted to hospital did not meet formal WHO pneumonia criteria and few met criteria for 'severe pneumonia' that generally justifies hospital admission and the use of intravenous antibiotics."

15) As I pointed out in the general comment, it would be interesting to include some discussion around the under-diagnosis of severe viral respiratory infections (e.g. bronchiolitis) or chronic respiratory diseases (e.g. asthma). The management of these diseases is very different from that of pneumonia, and an incorrect diagnosis and treatment may lead to severe adverse outcomes. What is the expected incidence of bronchiolitis and prevalence of asthma in this setting?
***Reply:** We agree that accurate etiological diagnosis remains problematic and that liberal use of the 'pneumonia' label may lead to an under-appreciation of viral respiratory infections (e.g. bronchiolitis) or chronic respiratory diseases (e.g. asthma). We expanded our discussion to emphasise this.

16) The authors describe the role of exposure to tobacco smoke, but not to biomass fuel exposure, which has been associated with an increased risk of pneumonia in children. Was this information collected? Is this relevant in this setting?
***Reply:** Yes, we collected data related to biomass fuel exposure, but didn't find any relevant association in this setting (see revised Table 5)

17) The final sentence of the conclusion states that: 'Routine use of the revised WHO pneumonia criteria to guide clinical management should be more widely implemented in Asia.' Given the findings from this study, I do not agree completely with this statement. If they had used the WHO criteria, they would have avoided 3954/4206 (94%) of pneumonia hospitalisations. However, they would have missed 5/16 deaths and 635/788 (81%) adverse outcomes, which could have resulted in a greater number of deaths.
***Reply:** We agree that routine use of the WHO case management approach would have missed some kids who died or had an adverse outcome. Among the children who died, only 1 with congenital heart disease was in the 'no pneumonia' category. He should have been admitted for a cardiac indication. The 4 deaths in children with 'non-severe pneumonia' occurred in children with sepsis (3) and acute pericarditis (1). The children who would have been missed by a standard case management approach are now better described in the results section and the conclusion have been adjusted accordingly.

Minor comments

Abstract

18) The authors use the term 'case-fatality rate' in the results, but then report and absolute number and a proportion.

****Reply:*** We acknowledge that "case-fatality rate" is a problematic term, since it is not strictly a "rate", but generally reflects the "proportion of deaths within a designated population". It is widely used within the scientific literature to indicate the outcome of diseases with a limited time course, such as pneumonia.

19) The last sentence of the conclusion is a repetition of the results.

****Reply:*** We revised the conclusion to emphasize our key findings without repeating previously mentioned results.

Introduction

20) In the third paragraph, line 43, there appears the number 12 in brackets. I am not sure if this is supposed to be a reference or not. If it is indeed a reference, it should be number 10.

****Reply:*** Thank you for pointing out this oversight. We renumbered the references.

Methods

21) In the third paragraph (study population), the authors describe also the study procedures, so I suggest including this in the subheading too.

****Reply:*** Sub-heading adjusted to read: "Study population and procedures"

22) Last sentence of third paragraph, the authors say that in the X-ray 'hyperinflation was not documented'. It is unclear for me if it was not reported by the caring physician or if the investigators did not consider this as an 'abnormal CXR'.

****Reply:*** Hyperinflation was not reported. As a result, we were unable to comment on hyperinflation as a potential marker of small airway obstruction (bronchiolitis or asthma) – this has been clarified.

Results

23) It is a bit misleading when the authors refer to children admitted with 'pneumonia' (line 34, page 7) meaning the whole cohort, as it could be interpreted as those classified as 'pneumonia' according to the WHO classification.

****Reply:*** We agree that it is important to distinguish between those children admitted with 'pneumonia; (as assessed by the admitting clinician) and those classified by formal WHO criteria. We clarified this in the text.

24) First sentence of page 8, it says that two 'no pneumonia cases were transferred to a tertiary hospital, while in the table it says there were four.

** Thank you for pointing out this discrepancy, which has been corrected. All 4 cases are now described.

25) There is a similar problem in line 36, where it reads that two cases without 'severe pneumonia' died, while in the table there is one death from the 'no pneumonia group' and other 4 from the 'pneumonia group'.

****Reply:*** All deaths are now clarified in the text

Tables and Figures

26) Figure 1: There is a typo in the dates of inclusion. It should say: 01/07/2017-30/06/2018

****Reply:*** Thank you - corrected

27) Table 2: What other test was used apart from Kruskal Wallis?

****Reply:*** We also used the Chi-squared test where applicable. As requested reviewer 2, we deleted all p values in the descriptive tables, but still indicate relevant p-values in the text.

28) Table 3: Check the footnote, there are several symbols missing (***, ###)

***Reply:** Checked and corrected. Thank you.

29) Table 4: Next to each factor, the measure should be described, e.g. N (%) or median (IQR). Also the specific test used to estimate the p value for each of the factors.
***Reply:** Inserted

Reviewer 2
This is a simple research design, but a well-executed and written paper, which describes the application of the WHO criteria for pneumonia in a setting in which there is little existing data available. The authors provide a thorough description of the cases in this setting and draw appropriate conclusions in particular the case for over treatment. It is useful data which highlights an important area of care which needs addressing in this region. For this reason I would support its publication after consideration of the comments below.

1) My main comments relate to the statistical analysis used in what is essentially a descriptive paper and whether in some instances it is potentially overused. For example Table 2 expresses a p-value against each row which essentially tells us a difference between categories of WHO classified pneumonia but not what these differences are.
***Reply:** We deleted all p-values in the descriptive tables and only retained them where relevant in the text.

2) There is some commentary in the text which points towards differences that the authors think are important, but otherwise there is no interpretation of this. For example high proportions of SpO2<90, grunting, lethargy and nasal flaring in the severe classification are expected given this is how the severe pneumonia is defined. On the other hand poor feeding shows little difference (and is also an important marker of severity), but this is attributed to poor data capture. This is likely true but this also highlights that attention to feeding in sick children is often weak in such settings.
***Reply:** We inserted a short discussion to emphasize that attention to feeding is often neglected.

3) As a final example the CRP data in this table is described as both medians and numerical ranges - all of which points to no difference between categories of severity. In a paper pointing to over treatment and the cost of care it may be valuable to highlight relative lack of utility of CRP in severity determination.
***Reply:** We included a brief discussion of the limited utility of CRP and neutrophil count to distinguish between WHO pneumonia categories. A more detailed assessment of its potential value in etiology determination is planned.

Reviewer 3
This a large, well-conducted prospective cohort of children hospitalised with pneumonia in Vietnam. It provides a useful, real-life evaluation of the WHO clinical case management approach for paediatric pneumonia. It suggests a tendency of clinicians to unnecessarily hospitalise children with a very low risk of adverse outcome. Overall, I think that this manuscript would form a useful contribution to the Journal and would recommend its acceptance after addressing the following comments:

1) Could the authors please clarify the relationship between the clinical and research teams? Whilst devised as a descriptive study, there is a possibility that the conduct of the study increased general awareness of WHO case management guidelines and influenced admission practice. Is there any evidence that admission practice changed during the study period?
***Reply:** None of the researchers were involved in any clinical work and no study feedback has been provided to clinicians (although we plan to do this). There was no training provided on WHO case management and no change in pneumonia admissions observed during the course of the study. We clarified this in the text.

2) Are the authors able to provide any data on the group of children who were reviewed and immediately discharged from hospital? If not, could they discuss this further as a limitation. To suggest that WHO clinical case management is safe and effective in this setting, it would be necessary to demonstrate

satisfactory outcomes in those children managed at home, particularly those who had 'no pneumonia' by WHO criteria and in whom antibiotics were accordingly with-held.
***Reply:** We described this as a study limitation, since we only collected information on children admitted to the Respiratory Department or ICU. However, the admission threshold was very low and health care access is generally good in Da Nang. It is unlikely that any of the children discharged home would have come to harm, but we acknowledge that this was not documented. Our main aim was to characterise the clinical profile and outcome of children admitted to hospital with 'pneumonia' and we recognize that we are unable to comment with certainty on the safety of the WHO case management approach.

3) Are the authors able to provide details of the treatment administered? In the discussion, they make an assumption that inpatient stays were prolonged for continued administration of intravenous antibiotics. Presumably there are other factors that could have contributed to prolonging hospital stays.
***Reply:** Children admitted with pneumonia routinely received 'a course' of intravenous antibiotics. We are planning to write up a separate manuscript focusing on pneumonia treatment, describing the duration, route and type of antibiotic used in hospital and pre/post admission, since we were unable to cover this in detail in the current manuscript. We agree that several factors contributed to prolonged hospital stay, including disease complications, hospital acquired infections and co-morbid conditions. Most children with uncomplicated disease were routinely admitted for 5-7 days of IV antibiotics, which explains why we selected 'admission for >10 days' as an adverse outcome.

4) Approximately one quarter of total pneumonia admissions (i.e. 1515 patients) were admitted to the private ward and excluded from the study. I think that this amounts to more than a 'small number of patients' as described in the text (page 8, line 6) and if systematically different to the recruited population (e.g. in terms of illness severity) could potentially introduce bias.
***Reply:** We agree that this is not a small number and deleted the word "small". Children with severe disease or in an unstable condition are not allowed into the private ward. Patients on the private ward who deteriorate are immediately transferred to either the Respiratory Department or ICU and therefore we are confident that all 'pneumonia cases' admitted to the private ward would have been in a stable condition and that our main study findings should apply to this group as well.

5) Could the authors provide further details on the interpretation of the chest radiographs? What proportion of the children with abnormal chest radiographs had primary endpoint consolidation as previously defined by the WHO working group (Cherian et al. Bull WHO 2005; 83:353-359)?
***Reply:** We added this information to Table 3. Consolidation was more common among children with 'WHO severe pneumonia', but it did not accurately differentiate 'pneumonia' from 'no pneumonia' using clinical WHO criteria.

6) The authors advocate routine use of revised WHO pneumonia criteria to guide clinical management in Asia. Could they be more specific in their recommendations, particularly for the group defined as 'no pneumonia.' Within this group, 42% had abnormal chest radiograph and 19% and 22% had significantly elevated white cell count and CRP. In Asian settings where these tests are routinely available, would the authors suggest, withholding antibiotics in these patients or not performing the tests? Is further research required to support a treatment recommendation in this patient group in this setting?
***Reply:** We believe routine use of revised WHO pneumonia criteria will help to reduce unnecessary hospital admissions. We tried to be more specific (and more reserved) in our recommendation and hope to explore the clinical features associated with 'likely bacterial pneumonia' in greater detail in a subsequent paper.

7) Please could the authors provide more details on the methods used in the multivariable logistic regression analysis. Were the variables included in the multivariable model specified a priori or only included if significant in univariable analyses?
***Reply:** We included all variables listed in both the uni- and multivariate models for full transparency. We expanded the methods section and adjusted Table 5 to make this apparent.

8) There is a typographical error on Page 13, line 53: It should read, "extent of the microbiological work-up…"

***Reply:** Thank you - corrected.

Reviewer: 4

Nguyen and colleagues present a prospective observational study of an impressive number of children hospitalised for suspected pneumonia in a large Vietnamese children's hospital. They report that 42% of cases did not meet WHO criteria for pneumonia, and that antibiotics overuse was a common observation. They conclude that many hospital admissions for IV antibiotics were unnecessary. The study is well documented and the manuscript is written in a concise manner. Strengths and weaknesses are discussed.

1) Pneumonia is an ill-defined term, being inconsistently used strictly for lung parenchymal infectious disease to anything that could or could not be a pneumonia, like pneumonias according to the WHO definition, which encompass numerous differential diagnoses like e.g. sepsis (tachypnoea) are laryngotracheitis (retractions). It is clear (and acknowledged by the authors) that many of these children did not have (bacterial) pneumonia but would have better been labeled bronchiolitis, wheezy bronchitis or even just lower respiratory tract infections (LRTIs). Tachypnea with chest in-drawing and inability to drink in a febrile 2 month-old baby is much more likely to represent bronchiolitis than severe pneumonia (as per WHO). I recognize that the authors are aware of this and that a lot of educational work lies ahead to reduce unnecessary use of antibiotics by primary care health professionals in Vietnam.

***Reply:** Thank you for this comment. We agree that pneumonia remains an ill-defined term and that a lot of educational work, as well as research, should be done to improve the case management of children with respiratory tract infections.

Thank you once again for all the valuable comments received. We trust that we addressed all issues raised and that the revised manuscript is sufficiently improved to meet your expectations.

Yours sincerely
Phuong Nguyen