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Repeat assessment of examination signs among children in Malawi with fast-breathing pneumonia

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ABSTRACT

Background: As part of a randomised controlled trial of treatment with placebo *versus* 3 days of amoxicillin for nonsevere fast-breathing pneumonia among Malawian children aged 2–59 months, a subset of children was hospitalised for observation. We sought to characterise the progression of fast-breathing pneumonia among children undergoing repeat assessments to better understand which children do and do not deteriorate.

Methods: Vital signs and physical examination findings, including respiratory rate, arterial oxygen saturation measured by pulse oximetry (S_{pO_2}), chest indrawing and temperature were assessed every 3 h for the duration of hospitalisation. Children were assessed for treatment failure during study visits on days 1, 2, 3 and 4.

Results: Hospital monitoring data from 436 children were included. While no children had S_{pO_2} 90–93% at baseline, 7.4% (16 of 215) of children receiving amoxicillin and 9.5% (21 of 221) receiving placebo developed S_{pO_2} 90–93% during monitoring. Similarly, no children had chest indrawing at enrolment, but 6.6% (14 of 215) in the amoxicillin group and 7.2% (16 of 221) in the placebo group went on to develop chest indrawing during hospitalisation.

Conclusion: Repeat monitoring of children with fast-breathing pneumonia identified vital and physical examination signs not present at baseline, including S_{pO_2} 90–93% and chest indrawing. This information may support providers and policymakers in developing guidance for care of children with nonsevere pneumonia.

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This study characterised the progression of fast-breathing pneumonia among children in Malawi. Repeat monitoring of children identified vital and physical exam signs not present at baseline, including oxygen saturation of 90–93% and chest indrawing. http://bit.ly/2vUlckS

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Introduction

Nearly one million children worldwide die of pneumonia each year [1]. Despite its prevalence, pneumonia remains difficult to diagnose, particularly in low-resource settings (LRS), where diagnostic imaging is often unavailable [2]. A challenge in identifying pneumonia in the absence of diagnostics lies in differentiating those children with pneumonia and more severe illness from those with upper respiratory infections or other less severe conditions [3]. In LRS, pneumonia typically is diagnosed using the World Health Organization (WHO) Integrated Management of Childhood Illnesses (IMCI) requirements, which identify and treat pneumonia based on clinical signs and symptoms such as fast breathing and chest indrawing in children under 5 years with cough and/or difficulty breathing [4]. Previous research suggests that the diagnosis of pneumonia based on these subjective signs and symptoms is challenging, can be nonspecific, and may be less reliable than imaging methods [2, 5].

Given this low specificity, it is challenging to differentiate which children will deteriorate and which will improve. Several studies have sought to develop risk-score models to identify clinical signs that predict progression [2, 3, 6, 7]. These studies have identified factors, including very fast breathing and low arterial oxygen saturation measured by pulse oximetry (S_{pO_2}). However, most of this work uses measurements from a single time point, or daily measurements. Using inpatient monitoring data collected every 3 h as part of a randomised controlled trial of treatment with placebo *versus* 3 days of amoxicillin for fast-breathing pneumonia, we sought to analyse the progression of vital signs and physical examination findings among children aged 2–59 months diagnosed with fast-breathing pneumonia. Characterising the progression of pneumonia among children undergoing frequent serial assessments could make strides in better understanding which children deteriorate and which children do not, and the potential value of repeated evaluations. With this analysis, we seek to build on this body of work with longitudinal data collected every 3 h among children in Malawi diagnosed with fast-breathing pneumonia.

Methods

Participants and study design

Data for this analysis were obtained during a prospective, double-blind, randomised controlled two-arm, noninferiority trial that aimed to determine whether treatment with placebo in children uninfected with HIV, 2–59 months of age with nonsevere fast-breathing pneumonia was as effective as 3 days of treatment with amoxicillin [8, 9]. Children aged 2–59 months presenting to the outpatient departments of Kamuzu Central Hospital and Bwaila District Hospital in Lilongwe, Malawi with cough <14 days or difficulty breathing and fast breathing for age were enrolled in the study. A full list of inclusion and exclusion criteria is included in table 1. Children enrolled in the study were randomised to receive 3 days of either placebo (intervention) or amoxicillin (control) [10]. Study visits took place at days 1 (enrolment), 2, 3, 4 and 14.

Procedures

Informed consent was obtained from caregivers of children prior to screening and again prior to enrolment. Study staff described the study purpose, procedures, risks and benefits. Caregivers were encouraged to ask questions and a comprehension checklist was administered prior to obtaining consent to ensure that caregivers fully comprehended the nature of the study.

Once enrolled, children were observed in the hospital for 2–8 h prior to being assessed for discharge. Children without fever or very fast breathing were discharged after 2 h, whereas those with fever and/or very fast breathing remained under observation. Children aged <6 months, those with moderate malnutrition (11.5–13.5 cm mid-upper arm circumference), and those with fever and a negative malaria test were hospitalised overnight and assessed for discharge on day 2 [11]. Observations were conducted by study nurses with immediate referral to a study clinician if further evaluation was needed. Children could remain under hospital observation until the morning of day 3. Those whose condition necessitated hospitalisation past the morning of day 3 were considered to have prolonged hospitalisation and met criteria to be classified as treatment failure (TF). Additional TF criteria are described in table 2.

In addition to study assessments, vital signs (respiratory rate (RR), S_{pO_2}, and temperature), other respiratory signs (wheeze or stridor when calm), signs of severe respiratory distress (head nodding, nasal flaring, grunting, chest indrawing), and WHO IMCI general danger signs (lethargy or unconsciousness, convulsions, vomiting everything, and inability to drink or breastfeed) were assessed by study nurses every 3 h.

Children were assessed for TF by a study clinician during the observation period following enrolment. During observation, if a child developed a WHO IMCI general danger sign or sign of severe respiratory distress, hypoxaemia (S_{pO_2} <90%), or RR 10 breaths higher than RR at enrolment, the child was hospitalised and considered a TF. Children were also assessed for TF during the study visits on days 1, 2, 3 and 4. TF was defined as any of the following on or before day 4: WHO IMCI general danger sign, severe

TABLE 1 Eligibility criteria

Inclusion criteria	2–59 months of age
	Cough <14 days or difficulty breathing
	Fast breathing for age (⩾50 breaths·min^{-1} among children 2–11 months; ⩾40 breaths·min^{-1} among children ⩾12 months)
Exclusion criteria	Severe respiratory distress (head nodding, nasal flaring, grunting, and/or chest indrawing)
	Hypoxaemia (S_{pO_2}<90%)
	Resolution of fast breathing after bronchodilator challenge, if wheezing at screening examination
	WHO IMCI general danger signs (lethargy or unconsciousness, convulsions, vomiting everything, inability to drink or breastfeed)
	Stridor when calm
	HIV-1 seropositivity or HIV-1 exposure (children <24 months of age with a HIV-infected mother)
	Severe acute malnutrition (weight for height/length < −3 SD, mid-upper arm circumference <11.5 cm, or peripheral oedema)
	Possible tuberculosis (coughing ⩾14 days)
	Anaemia with haemoglobin <8.0 g·dL^{-1}
	Severe malaria (positive malaria rapid diagnostic test with any WHO IMCI general danger sign, stiff neck, abnormal bleeding, clinical jaundice, or haemoglobinuria)
	Known allergy to penicillin or amoxicillin
	Receipt of an antibiotic treatment in the 48 h prior to the study
	Hospitalised within 14 days prior to the study
	Living outside the study area
	Any medical or psychosocial condition or circumstance that, in the opinion of the investigators, would interfere with the conduct of the study or for which study participation might jeopardise the child's health
	Any nonpneumonia acute medical illness which requires antibiotic treatment per local standard of care
	Participation in a clinical study of another investigational product within 12 weeks prior to randomisation or planning to begin participation during this study
	Prior participation in the study during a previous pneumonia diagnosis

S_{pO_2}: arterial oxygen saturation measured by pulse oximetry; WHO: World Health Organization; IMCI: Integrated Management of Childhood Illnesses.

respiratory distress, hypoxaemia, missing ⩾2 study drug doses due to vomiting, change in antibiotics prescribed by a study clinician, hospitalisation due to pneumonia (if not initially admitted), prolonged hospitalisation or re-admission due to pneumonia, and death (table 2). Children determined to have TF were hospitalised and received second-line therapy based on standard of care at Kamuzu Central Hospital.

TABLE 2 Treatment failure criteria and hospital discharge criteria

Treatment failure criteria	Any time on or before day 4:
	Severe respiratory distress
	Hypoxaemia
	WHO IMCI general danger signs
	Missing >2 study drug doses due to vomiting
	Change in antibiotics prescribed by a study clinician
	Hospitalisation due to pneumonia (if not initially admitted)
	Prolonged hospitalisation or re-admission due to pneumonia (if initially admitted)
	Death
	On day 4 only:
	Axillary temperature ⩾38°C in the absence of a diagnosed co-infection with fever symptoms (*e.g.* malaria)
Hospital discharge criteria	None of the criteria for treatment failure are present:
	WHO IMCI danger signs
	Severe respiratory distress, hypoxaemia, chest indrawing
	Vomiting within 30 min of two or more doses of study product
	Change in antibiotics prescribed by a study clinician (*e.g.* switch to a second-line antibiotic or prescription for onset of a co-infection)
	Death

WHO: World Health Organization; IMCI: Integrated Management of Childhood Illnesses.

Statistical analysis

Measurements collected every 3 h during the hospital monitoring assessments described above were used for analysis. Data from the observation period and the hospitalisation immediately following enrolment (for those children admitted) were included. For children classified as having TF, hospital monitoring data from checks that occurred after a TF designation were excluded from the analysis.

Descriptive statistics were calculated regarding vital signs, signs of severe respiratory distress, and WHO IMCI general danger signs during the duration of this observation/hospitalisation. Progression of these signs over the first 24 h following enrolment was also described. In addition to the standard definition of hypoxaemia of S_{pO_2} <90%, an S_{pO_2} range of 90–93% was also assessed [2, 12–16].

Mean values at baseline were compared using two-sided t-tests assuming unequal variances. Differences in categorical variables were assessed using a chi-squared test, except for in analyses where the expected number in any cell was less than five, in which case Fisher's exact tests were used. The ability of S_{pO_2}, fever and fast breathing (measured during the first 24 h) to predict TF was calculated using receiver operating characteristic curves. All analyses were stratified by whether children were in the amoxicillin or placebo group, and further divided by whether children did or did not experience TF. No adjustments were made for multiple comparisons. Analyses were performed using Stata (Stata Corporation, College Station, TX, USA).

Ethical approvals

This study was conducted in accordance with the International Conference on Harmonisation, Good Clinical Practice and the Declaration of Helsinki 2008, and was approved by the Western Institutional Review Board in the state of Washington, USA; the College of Medicine Research and Ethics Committee, Blantyre, Malawi; and the Malawi Pharmacy, Medicines and Poisons Board. The study was registered at ClinicalTrials.gov under identifier NCT02760420.

Results

Enrolment in this study took place from June 2016 to June 2017. Overall, 1126 children were enrolled and 436 (38.7%) were hospitalised for observation. The duration of monitoring ranged from 2 h to 7 days (median=23.8 h; IQR=22.6–25.9). TF was documented for 48 children (11.0% of hospitalised children), comprising 16 children in the amoxicillin group and 32 children in the placebo group.

Baseline characteristics

In the amoxicillin group, most baseline characteristics were similar between children with and without TF, (table 3). However, while the sample was approximately equally split between males and females, 13 male children (80%) went on to have TF compared to 3 female children (20%) (p=0.017). Occurrence of fever also differed between the TF and non-TF groups, where 111 children (55.5%) in the TF group had fever at enrolment compared with 4 (26.7%) in the non-TF group (p=0.03). In the placebo group, there were no significant differences at baseline between the TF and non-TF groups.

The mean age at enrolment was 15.4 months among children in the amoxicillin group, and 15.8 months among children in the placebo group. All children had fast breathing at screening, as this was an inclusion criterion. Median S_{pO_2} was 98% in both the amoxicillin and placebo groups, and was similar among those children who did and did not go on to experience TF. No child was hypoxaemic at baseline, as hypoxaemia was an exclusion criterion.

Hospital monitoring

S_{pO_2} 90–93%, fast breathing, very fast breathing, chest indrawing and fever were documented in both the amoxicillin and placebo groups, as described below and in table 4. Vomiting everything was documented in one child, who was in the amoxicillin group; the remaining general and respiratory danger signs were not documented in any children. Temporal trends for S_{pO_2} 90–93%, fast breathing, chest indrawing and fever over the first 24 h of hospitalisation are shown in figure 1.

S_{pO_2} measurements ranged from 90 to 100%. Sixteen children in the amoxicillin group (7.4%) and 21 children in the placebo group (9.5%) had S_{pO_2} 90–93%. In both the amoxicillin and placebo groups, a larger proportion of children with TF had S_{pO_2} 90–93% (7.0% *versus* 12.5%, p=0.338 in the amoxicillin group and 9.0% *versus* 12.5%, p=0.518 in the placebo group), but these differences were not statistically significant.

Fast breathing was identified in 214 children in the amoxicillin group (99.5%) and 222 children in the placebo group (100%). Approximately half (48.4%) of the children monitored had fast breathing documented one to two times during monitoring, whereas the other half (51.6%) had fast breathing

TABLE 3 Characteristics of enrolled children undergoing hospital monitoring

Characteristic	Amoxicillin				Placebo			
	Overall (n=215)	No treatment failure (n=199)	Treatment failure (n=16)	p-value	Overall (n=221)	No treatment failure (n=189)	Treatment failure (n=32)	p-value
Age months	15.4±14.8	15.2±14.7	17.4±16.4	0.57	15.8±13.6	15.4±13.7	18.3±12.8	0.25
2–11	120 (55.8%)	111 (55.8%)	9 (56.3%)	1.00	114 (51.6%)	103 (54.5%)	11 (34.4%)	0.11
12–35	67 (31.2%)	62 (31.1%)	5 (31.3%)		80 (36.2%)	64 (33.9%)	16 (50.0%)	
36–59	28 (13.0%)	26 (13.1%)	2 (12.4%)		27 (12.2%)	22 (11.6%)	5 (15.6%)	
Female	108 (50.2%)	105 (52.5%)	3 (20.0%)	0.017	123 (55.7%)	104 (55.0%)	19 (59.4%)	0.65
MUAC cm	14.8±1.2	15.0±2.2	14.8±1.2	0.54	14.6±1.2	14.6±1.2	14.6±1.0	0.77
<11.5	0	0	0	0.14	0	0	0	1.00
11.5–13.5	30 (14.0%)	30 (15.1%)	0		45 (30.4%)	39 (20.6%)	6 (18.8%)	
>13.5	185 (86.0%)	169 (84.9%)	16 (100%)		176 (79.6%)	150 (79.4%)	26 (81.2%)	
Respiratory rate[#] breaths·min^{-1}								
Age 2–11 months[¶]	57.3±6.0	57.1±6.0	59.3±5.8	0.30	56.8±5.7	56.9±5.9	55.9±3.6	0.58
<50	0	0	0	0.21	0	0	0	0.64
50–59	77 (64.2%)	73 (65.8%)	4 (44.4%)		79 (69.3%)	70 (68.0%)	9 (81.8%)	
60–69	38 (31.7%)	34 (30.6%)	4 (44.4%)		32 (28.1%)	30 (29.1%)	2 (18.2%)	
⩾70	5 (4.2%)	4 (3.6%)	1 (1.1%)		3 (2.6%)	3 (2.9%)	0	
Age 12–59 months	48.9 (7.1)	49.1 (7.0)	46.3 (8.4)	0.32	48.5 (7.1%)	48.2 (7.0%)	49.7 (7.4)	0.37
<40	0	0	0	0.10	0	0	0	0.52
40–49	55 (57.9%)	49 (55.7%)	6 (85.7%)		64 (59.8%)	53 (61.6%)	11 (52.4%)	
50–59	32 (33.7%)	32 (36.4%)	0		37 (34.6%)	29 (33.7%)	8 (38.1%)	
⩾60	8 (8.4%)	7 (7.9%)	1 (14.3%)		6 (5.6%)	4 (4.7%)	2 (9.5%)	
Oxygen saturation[¶]	98 (97–99)	98.5 (97–99)	98 (97–99)	0.21	98 (97–99)	98 (97–99)	98 (97–99)	0.89
<90%	0	0	0		0	0	0	
90–93%	0	0	0		0	0	0	
⩾94%	215 (100%)	199 (100%)	16 (100%)		221 (100%)	189 (100%)	32 (100%)	
Axillary temperature[#] °C	37.9±1.0	38.0±1.0	37.7±0.9	0.27	37.8±1.0	37.8±1.0	37.8±0.9	0.91
<38	100 (46.5%)	89 (44.5%)	11 (73.3%)	0.03	112 (50.7%)	92 (48.7%)	20 (62.5%)	0.15
⩾38	115 (53.5%)	111 (55.5%)	4 (26.7%)		109 (49.3%)	97 (51.3%)	12 (37.5%)	
Heart rate[#] beats·min^{-1}	151.3±14.3	151.1±14.1	153.9±17.0	0.45	150.2±13.7	150.5±14.1	148.7±11.2	0.51

Data are mean±SD, n (%) or median (interquartile range), unless otherwise stated. MUAC: mid-upper arm circumference. [#]: higher value between screening and enrolment visits; [¶]: lower value between screening and enrolment visits.

documented three or more times. This followed a similar pattern between those children who went on to experience TF and those who did not.

Fourteen children in the amoxicillin group (6.6%) and 16 in the placebo group (7.2%) had chest indrawing identified; 10 had chest indrawing recorded at one time point, whereas 20 had chest indrawing recorded at multiple time points. The proportion of children with chest indrawing at a single time point *versus* multiple time points was similar in the amoxicillin and placebo groups. The proportion of children with chest indrawing in both groups increased over the first 24 h of monitoring (figure 1).

Fever was documented in 122 children in the amoxicillin group (56.7%) and 117 children in the placebo group (52.7%). In the amoxicillin group, a larger proportion of children without TF had fever documented compared to those children with TF (58.8% *versus* 33.3%, p=0.032). This pattern was not noted in the placebo group, where 52.9% of children with TF and 53.1% of children without TF had fever (p=0.98).

In both the amoxicillin and placebo groups, approximately 50% of those children without TF had fever at the initiation of hospital monitoring (figure 1). This dropped steadily through approximately hour 20. Among children with TF, 25–40% had fever at the initiation of hospital monitoring. In the TF groups, the proportions did not follow a consistent pattern through the remainder of monitoring; this may be due to the small number of children with TF.

S_{pO_2} 90–93%, fast breathing and fever all had very low sensitivity and high specificity to identify children who would experience TF when measured during the first 24 h from initiation of monitoring. Sensitivity tended to be higher in the placebo group, which may have been due to the higher number of children with

TABLE 4 Clinical signs identified at any time during hospital monitoring

Characteristic	Amoxicillin (n=215)				Placebo (n=221)			
	Overall (n=215)	No treatment failure (n=199)	Treatment failure (n=16)	p-value	Overall (n=221)	No treatment failure (n=189)	Treatment failure (n=32)	p-value
Oxygen saturation 90–93%	16 (7.4%)	14 (7.0%)	2 (12.5%)	0.338	21 (9.5%)	17 (9.0%)	4 (12.5%)	0.518
Fast breathing	214 (99.5%)	198 (99.5%)	16 (100%)	0.776	221 (100%)	189 (100%)	32 (100%)	
Chest indrawing[#]	14 (6.6%)				16 (7.2%)			
Fever	122 (56.7%)	117 (58.8%)	6 (33.3%)	0.032	117 (52.9%)	100 (52.9%)	17 (53.1%)	0.98

A description of hospital monitoring checks among children prior to any treatment failure. Data collected during hospital monitoring assessments after children were classified as having treatment failure are excluded. This includes all hospital monitoring data from children classified as having treatment failure within 2 h following enrolment (n=7). Sample sizes in this table have been adjusted to remove these children. [#]: chest indrawing was a treatment failure criterion.

TF in that group. For S_{pO_2} 90–93%, sensitivity was 10.0% and specificity was 95.4% in the amoxicillin group, *versus* 18.8% sensitivity and 87.7% specificity in the placebo group. Fast breathing had a sensitivity of 5.6% and specificity of 95.9% in the amoxicillin group, compared with 14.7% sensitivity and 89.1% specificity in the placebo group. For fever, sensitivity was 1.6% and specificity was 94.7% in the amoxicillin group; sensitivity was 15.9% and specificity was 88.2% in the placebo group.

Discussion

The value of repeat monitoring of vital signs among hospitalised children has been previously described [17, 18]. A multicountry trial found that models including both baseline data and vital sign information obtained after 12 or 24 h of patient monitoring more accurately predicted which children experienced TF when compared with models that included baseline data alone [17]. The value of repeat monitoring extends beyond pneumonia; continuous monitoring, including pulse oximetry, has also demonstrated potential for optimising outcomes among ill neonates [18].

Previous studies have characterised vital sign progression among children with pneumonia. A study enrolling children in the United States found a median time to clinical stability of 38.6 h for RR, 39.5 h for

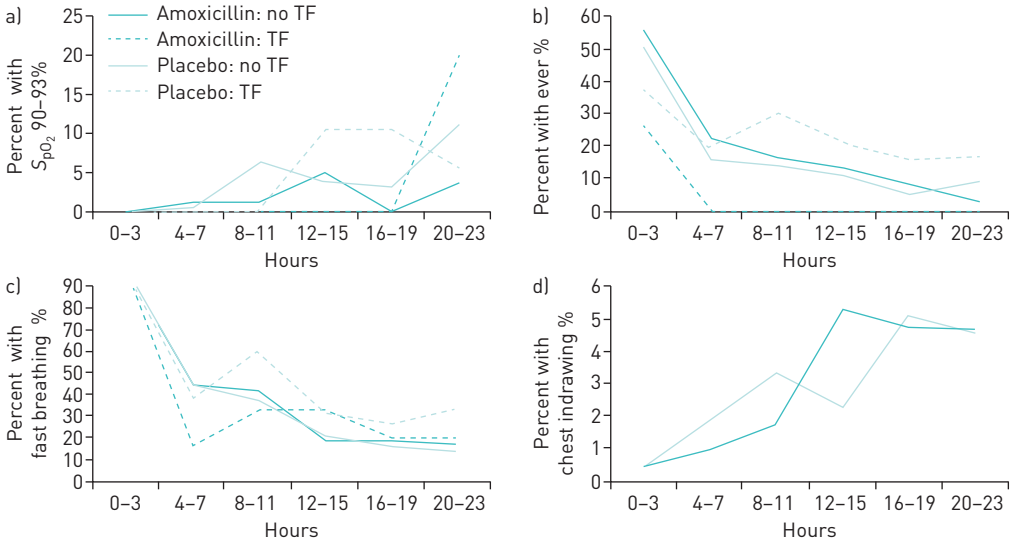

FIGURE 1 Proportion of children experiencing clinical signs during the first 24 h of hospital monitoring. a) Oxygen saturation measured by pulse oximetry (S_{pO_2}) 90–93%; b) fever; c) fast breathing; d) chest indrawing. Denominators (total children monitored during the designated time window) were as follows. Hours 0–3: amoxicillin, no treatment failure (TF): n=200; amoxicillin, TF: n=15; placebo, no TF: n=189; placebo, TF: n=32. Hours 4–7: amoxicillin, no TF: n=190; amoxicillin, TF: n=12; placebo, no TF: n=186; placebo, TF: n=31. Hours 8–11: amoxicillin, no TF: n=165; amoxicillin, TF: n=6; placebo, no TF: n=159; placebo, TF: n=20. Hours 12–15: amoxicillin, no TF: n=164; amoxicillin, TF: n=6; placebo, no TF: n=158; placebo, TF: n=19. Hours 16–19: amoxicillin, no TF: n=163; amoxicillin, TF: n=5; placebo, no TF: n=158; placebo, TF: n=19. Hours 20–23: amoxicillin, no TF: n=165; amoxicillin, TF: n=5; placebo, no TF: n=156; placebo, TF: n=18.

S_{pO_2}, and 14.5 h for temperature among children <2 years [19]. Additionally, a study in Taiwan assessed risk factors for pneumonia progression among hospitalised children and found persistent fever that did not respond to therapy within 72 h to be a risk factor for progression [20].

In our study, the monitoring of vital and physical exam signs every 3 h among hospitalised enrolled children allowed for an in-depth characterisation of illness progression that would not have been possible using vital sign data collected through study visits alone. The value of this periodic monitoring is demonstrated by the S_{pO_2} findings. While no children had S_{pO_2} 90–93% documented during screening/enrolment, 7.4% of children in the amoxicillin group and 9.5% of children in the placebo group went on to have S_{pO_2} 90–93% measured during the monitoring period. Identifying these dips in S_{pO_2} can be critically important, as described by previous literature. A study describing hypoxemia among children with acute lower respiratory infections found that for children with S_{pO_2} below 95%, the OR of death was 3.56 [21]. Similarly, while no children had chest indrawing at enrolment, approximately 7% of children developed chest indrawing during monitoring, showing that a proportion of children diagnosed with fast-breathing pneumonia may subsequently develop chest-indrawing pneumonia, or that chest indrawing may be missed in the initial assessment. These proportions were similar in the amoxicillin and placebo groups.

Conversely, the proportion of children with fever was higher at enrolment than at 24 h, most likely due to the administration of paracetamol, a fever-reducing medication, during hospitalisation. The amoxicillin group had a larger proportion of children with fever in the non-TF group (55.5% *versus* 26.7%, p=0.03), which may also be due to the administration of paracetamol: 75.9% of children without TF and 93.8% of children with TF were administered paracetamol. Another explanation for this may be the protocol-specified hospitalisation of all children with fever but with a negative malaria test. If these children were otherwise not as ill as the other hospitalised children, this may have introduced bias into the relationship between fever and TF. This difference in fever between the TF and non-TF groups was not noted in the placebo group, although the administration of paracetamol was similarly differential.

While fast breathing was present among all children at enrolment, it was transient during monitoring. Repeat measurements of RR are important to improve the reliability and validity of this measure [22–24]. However, fast breathing is known to be a nonspecific assessment tool for pneumonia, as children may exhibit fast breathing for a variety of reasons, including malaria, asthma, and metabolic acidosis, as well as nonpathological reasons [2, 25, 26].

The progression of vital signs and physical examination findings over the first 24 h of hospital monitoring followed a similar pattern among children receiving amoxicillin and those receiving placebo. However, more children receiving placebo went on to experience TF, and the parent study identified a day 4 TF rate of 4% among children receiving amoxicillin and 7% among children receiving placebo (adjusted relative risk, 1.78) [6]. This analysis, therefore, may indicate that the first 24 h of treatment are not sufficient to determine the child's response. Alternatively, considering the overall low TF rate and the 3% absolute difference in the TF rate between children in the amoxicillin and placebo groups of the parent study, this may also indicate that a substantial proportion of children in this analysis did not have bacterial pneumonia. The difference in the relationships between fever and TF as well as sex and TF between the amoxicillin and placebo groups may suggest that a different infectious process is occurring in children with TF between the two groups. Indeed, sex differences in paediatric infectious diseases may vary across pathogens [27].

There are several limitations to this analysis. Statistical analyses were not adjusted for multiple comparisons and observed statistically significant results may be spurious. The association of vital and physical exam signs experienced during hospital monitoring with subsequent TF is complicated by the design of the parent study (*i.e.* the association of chest indrawing and TF could not be assessed because chest indrawing itself was a TF criterion). Aside from the treatment group assignments, these children were receiving standard supportive care in a hospital setting, so their vital and physical exam signs may have been affected by the administration of fever-reducing medication, which impacted the ability of this analysis to assess the progression of fever. Children with severe disease or comorbidities such as HIV were excluded, which may limit the generalizability of these findings. Finally, in order to be admitted for monitoring, children had to meet certain criteria (aged <6 months, moderate malnutrition, or fever with a negative malaria rapid diagnostic test), which may have introduced artefacts into the analysis.

Conclusions

This secondary analysis describes the progression of pneumonia over the first 24 h of hospitalisation among children aged 2–59 months enrolled in a fast-breathing pneumonia treatment study, some receiving antibiotic treatment and some receiving placebo. Children in the amoxicillin and placebo treatment groups experienced similar trends across RR, S_{pO_2}, chest indrawing and fever. Overall, regular monitoring of vital

and physical exam signs among children with fast-breathing pneumonia led to the identification of clinical signs that were not apparent at baseline. This information may support providers and policymakers in developing guidance for care of children with nonsevere pneumonia, particularly with regard to establishing appropriate guidelines for determining when to admit or discharge children presenting with nonsevere pneumonia at the outpatient level.

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