

The Epidemiology of Hypoxemic Pneumonia among Young Infants in Malawi

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Abstract. We describe hypoxemic pneumonia prevalence in outpatient and inpatient settings, in-hospital mortality, and clinical guideline performance for identifying hypoxemia in young infants in Malawi. In this retrospective analysis of a prospective cohort study, we investigate infants younger than 2 months participating in pneumonia surveillance at seven hospitals and 18 outpatient health centers in Malawi between 2011 and 2014. Logistic regression, multiple imputations with chained equations, and pattern mixture modeling were used to determine the association between peripheral oxyhemoglobin saturation (SpO₂) levels and hospital mortality. We describe referral recommendations based on clinical characteristics and SpO₂ distributions. Among 1,879 analyzed cases, SpO₂ < 90% was more prevalent among outpatient health center cases than that among hospitalized cases (22.6% versus 13.5%, 95% CI: 17.6–28.4% and 12.0–15.3%, respectively). A larger proportion of hospitalized infants had signs of respiratory distress than infants at health centers (67.7% versus 56.6%, *P* < 0.001) and the signs were higher in male versus female infants (56.7% versus 40.6%, *P* < 0.001). An SpO₂ of 90–92% and < 90% was associated with similarly increased odds of in-hospital mortality (adjusted odds ratio [aOR]: 4.3 and 4.4, 95% CI: 1.7–11.1 and 1.8–10.5, respectively). Unrecorded, or unobtainable, SpO₂ was highly associated with mortality (*n* = 127, aOR: 18.1; 95% CI: 7.6–42.8). Four of 22 (18%) infants at health centers who did not meet clinical referral criteria had an SpO₂ ≤ 92%. Clinicians should consider hospital referral in young infants with SpO₂ ≤ 92%. Infants with unobtainable SpO₂ readings should be considered a high-risk group, and hospital referral of these cases may be appropriate.

INTRODUCTION

In 2015, lower respiratory tract infections were the leading cause of death in children younger than 5 years.¹ Despite an overall reduction in pneumonia-related mortality, infants younger than 2 months continue to have high case-fatality rates.¹ The 2014 WHO Integrated Management of Childhood Illness (IMCI) guidelines used in outpatient health facilities in low- and middle-income countries (LMICs) state that in children aged 2–59 months, a peripheral capillary oxyhemoglobin saturation (SpO₂) < 90% warrants hospital referral.² The IMCI guidelines provide no referral guidance when pulse oximetry is used in infants younger than 2 months. Studies suggest that moderate hypoxemia (SpO₂ 90–92%) independently confers an increased risk of mortality in children aged 2–59 months.^{3,4} Most frontline facilities in LMICs do not have pulse oximeters, devices considered the standard for noninvasively measuring SpO₂,^{5,6} and physical examination findings alone do not reliably detect hypoxemia.^{7–11} Previously, we reported that 68.7% of Malawian children aged 2–59 months with hypoxemia were misidentified as appropriate for outpatient care when screened using the 2014 WHO IMCI guidelines without pulse oximetry.¹²

We describe the epidemiology of hypoxemia in Malawian infants younger than 2 months with pneumonia using data collected prospectively during a pneumococcal conjugate vaccine effectiveness study.¹³ We determined 1) hypoxemia prevalence and 2) the association between inpatient mortality

and different thresholds of hypoxemia, and 3) if clinical guidelines alone, without pulse oximetry, identified hypoxemic young infants requiring hospital referral.

MATERIALS AND METHODS

Setting. Malawi is a landlocked country in sub-Saharan Africa with 17.6 million people, 51.5% of whom live on less than \$1.25 per day.^{14,15} Community health workers, nurses, and nonphysician clinicians deliver health center services. More than 90% of hospital-based care is provided at government-operated district hospitals free of charge, and church-operated rural hospitals charge small fees and have limited inpatient capacity.¹⁶ Our study sites included 18 health centers, four rural hospitals, two district hospitals, and one regional tertiary referral hospital in Mchinji and Lilongwe districts at an altitude of 1,000–1,200 meters above sea level.

Data collection. This is a retrospective secondary analysis of a prospective cohort study evaluating pneumococcal vaccine effectiveness. Full details of training methodology and quality assessment are published elsewhere.^{12,13} Using procedures that had been in place and embedded within routine clinical care since 2001, we conducted active pneumonia surveillance. Government healthcare providers were trained to use pulse oximeters using a standardized protocol and collected data during routine care of children aged 0–59 months with cough and/or difficulty breathing from October 2011 to June 2014. At district and referral hospitals, lay health workers, called vital sign assistants, were trained to ensure that vital signs, including SpO₂, were recorded for each patient.¹⁷

Pulse oximeters outfitted with adult clip probes (Acare Technology, Xinzhuang, Taiwan, China), validated in Malawian infants younger than 2 months, were supplied by the Lifebox Foundation (London, England).¹⁸ Providers applied

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the probe to the great toe of children weighing < 10 kg or aged 2 years or younger. Hospital staff completed case report forms on all patients.¹⁹ All participating healthcare providers were retrained at the study's midpoint (early 2013) by a pediatric pulmonologist and Malawi Ministry of Health (MoH) staff. Monthly supervisory visits by study staff consisted of direct observation of patient care, including pulse oximetry use, and review of case classification, management, and data record quality. Supervisory visits emphasized case identification and remediation of poorly performing sites. Weekly death audits at district and rural hospitals were performed to ensure case report forms agreed with facility death registers. Using this same dataset, we previously published a description of the epidemiology of hypoxemia and the performance of the 2014 WHO IMCI guidelines in identifying hypoxemia among Malawian children aged 2–59 months.¹²

Definitions. Table 1 describes hospital referral criteria for pneumonia according to the 2000 Malawi MoH and 2014 WHO IMCI guidelines

Inclusion and exclusion criteria. In the original vaccine effectiveness study, all children aged 0–59 months with cough and/or shortness of breath met the study inclusion criteria.¹³ In this study, only infants younger than 2 months were included. Those who received supplemental oxygen at the time pulse oximetry was measured were excluded. Cases with documented clinical findings of pneumonia (Table 1) were included in the primary analysis except when we evaluated if clinical guidelines identify all hypoxemic infants at outpatient health centers as hospital referral eligible.

Analysis. Hypoxemia prevalence. We compared the clinical characteristics and prevalence of hypoxemia at different thresholds among eligible infants at hospitals and outpatient health centers. Data were described using Student's *t*-test for normally distributed data, Mann–Whitney U for nonparametric data, and chi-squared and Fisher's exact tests for proportions.

Association between in-hospital mortality and hypoxemia. Deaths were recorded only in the hospital dataset. If outcome data were missing, we assumed the child did not die in the hospital as we conducted weekly intensive death audits. We used multivariable logistic regression to measure the association between inpatient mortality and SpO₂ at different thresholds. We defined the following as potential confounders a priori as they are parameters included in the WHO IMCI guidelines and based on our clinical experience: gender, degree of malnutrition defined by WHO weight-for-age z-score, lower chest wall indrawing (retractions), audible wheezing, severe respiratory distress (grunting, head nodding, or nasal flaring), tachypnea (respiratory rate \geq 60, 70, or 80 breaths per minute), tachycardia (heart rate \geq 160, 180, or 190 beats per minute), bradycardia (heart rate < 110 or 100 beats

per minute), fever (temperature \geq 37.5°C, as per the WHO guidelines), hypothermia (temperature < 35.5°C), and general WHO danger signs (central cyanosis, stridor, inability to drink, lethargy, or convulsions).²⁰ We chose tachypnea, tachycardia, and bradycardia cutoffs based on population normative values and international guidelines, including the Pediatric Advanced Life Support and the WHO.²⁰ All potential confounders were investigated in bivariate analysis, and those with a *P*-value < 0.2 were included in the final model. In the primary analysis (Model 1), missing values for confounders were imputed, using multiple (10) imputations with chained equations (MICEs), and unrecorded SpO₂ was included as a nominal group.²¹

We observed staff unsuccessfully attempt to obtain pulse oximetry measurements, with SpO₂ left unrecorded in these cases, suggesting these data may be missing not at random (MNAR). To test our assumption, we conducted three sensitivity analyses. In Model 2, we created a composite binary pattern mixture variable to identify cases that had a high degree of missing confounders.²² First, we compared missing confounders by survival outcomes. Peripheral oxyhemoglobin saturation was excluded from consideration, as our goal was to determine if pulse oximetry readings were MNAR. Tachycardia and bradycardia were excluded, given that SpO₂ and heart rates were both measured using pulse oximetry. Confounders were included in the composite binary pattern mixture variable if they were missing in more than 25% of the deceased or surviving cases. Cases were identified as having high instance of missing confounders if they were missing one of the identified confounders. We treated unrecorded SpO₂ as a nominal group and used MICE to account for missing confounders but included a binary pattern mixture variable in the multivariable logistic regression model. In Model 3, unrecorded SpO₂ and missing confounders were imputed using MICE. Model 4 was the same as Model 3 but included the pattern mixture variable.

Referral guidelines and pulse oximetry. We evaluated the added value of using pulse oximetry among young infants at outpatient health centers in two ways. First, we determined the proportion of cases classified as appropriate for outpatient management based on Malawi MoH clinical guidelines alone (Table 1). Second, we retrospectively applied the 2014 WHO IMCI guidelines to compare the number of infants meeting the referral criteria, assuming perfect application of these guidelines, with and without the availability of pulse oximetry.

Stata software version 14.2. (StataCorp. 2015. College Station, TX) was used to perform all analyses.

Ethical approval. The National Health Sciences Research Committee of Malawi (protocol: 941) and the Ethics Committee of University College London (protocol: 2006/002) provided ethical approval. Given that the study collected routine clinical data, the ethical boards did not require informed consent.

TABLE 1

Hospital referral criteria for infants aged 0–2 months with pneumonia

2000 Malawi Ministry of Health	2014 WHO Integrated Management of Childhood Illness
Fast breathing* or chest wall indrawing or danger signs†	Fast breathing* or chest wall indrawing or poor feeding or convulsions or temperature \geq 37.5°C or < 35.5°C or decreased movement

* Fast breathing defined as a respiratory rate > 60 breaths per minute.

† Danger signs include central cyanosis, severe respiratory distress (grunting, head nodding, and nasal flaring), stridor in a calm child, a general WHO danger sign (inability to drink and/or breastfeed, lethargy or unconscious, or convulsions), and apnea.

RESULTS

A total of 2,071 encounters were evaluated for study inclusion. Documented clinical findings warranting either referral or hospitalization as per the Malawi MoH guidelines were noted in 235 (90.0%) encounters at health centers and 1,694 (93.6%) encounters at hospitals. Of the hospitalized patients, 76 (4.5%) were excluded, leaving 1,618 hospitalized cases in the analysis (Figure 1).

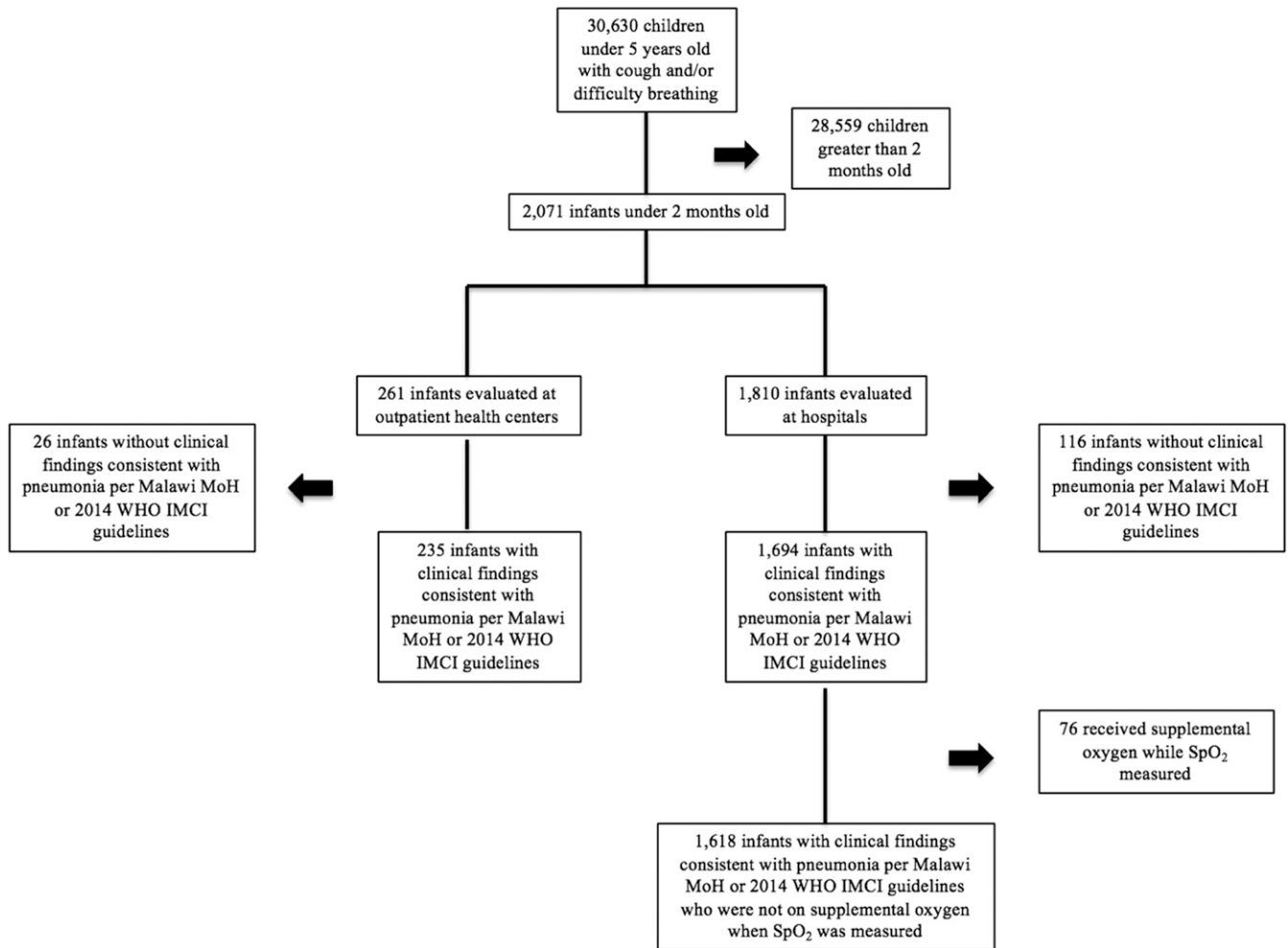


FIGURE 1. Cases included in analysis.

Hypoxemia prevalence A larger proportion of cases at outpatient health centers, compared with hospitals, had an $\text{SpO}_2 < 90\%$ or had an unrecorded SpO_2 . Hospitalized infants, compared with those evaluated at health centers, had a higher prevalence of chest wall indrawing and severe respiratory distress. A larger proportion of hospitalized infants were male versus female (56.7% versus 40.6%, $P < 0.001$) (Table 2).

At outpatient health centers, infants with an unrecorded SpO_2 had a lower mean weight (3.9 versus 4.6 kg, $P = 0.03$) and a higher prevalence of WHO danger signs (44.8% versus 24.3%, $P = 0.02$) compared with those with a recorded SpO_2 (Table 3). A larger proportion of hospitalized infants with an unrecorded SpO_2 measurement, compared with hospitalized infants with a recorded SpO_2 , had WHO danger signs (33.1% versus 22.5%, $P < 0.001$), and a lower proportion had fever (26.0% versus 32.7%, $P = 0.02$). Otherwise, clinical characteristics of patients with recorded versus unrecorded SpO_2 measurements were not statistically different. Notably, a large proportion of cases with unrecorded SpO_2 measurements were missing other covariates (Table 3).

Association between in-hospital mortality and hypoxemia The overall hospital case fatality rate was 3.6% ($n = 59$). Generally, death cases had a higher prevalence of missing data (Supplemental Material 1). Table 4 describes the

bivariate analysis for confounder selection and the adjusted odds (aOR) for mortality using logistic regression with MICE and pattern mixture modeling. In Model 1, infants with an SpO_2 90–92% or an $\text{SpO}_2 < 90\%$ had a similarly increased aOR for in-hospital mortality at 4.3 (95% CI: 1.7–11.1) and 4.4 (95% CI: 1.8–10.5), respectively. Children with an unrecorded SpO_2 had the highest case fatality rate at 18.9% (95% CI: 13.0–26.7%) and an aOR for in-hospital mortality of 18.1 (95% CI: 7.6, 42.8). Model 2, using a binary pattern mixture composite variable for missing danger signs or malnutrition, produced similar results to Model 1, noting the wide CIs for each. Models 3 and 4, imputing unrecorded SpO_2 using MICE, produced aOR for mortality associated with an SpO_2 90–92% and an $\text{SpO}_2 < 90\%$ similar to those of Models 1 and 2. There was a modest increase in the associated odds for mortality attributed to the pattern mixture variable in Model 4, compared with Model 2, at 3.7 versus 2.4 (aOR 95% CI: 1.2, 4.7 and 1.9, 7.2, respectively).

Referral guidelines and pulse oximetry At outpatient health centers, a similar proportion of infants were eligible for hospital referral based on the Malawi MoH ($n = 235/261$) and 2014 WHO IMCI ($n = 237/261$) guidelines when retrospectively assuming pulse oximetry was unavailable (90.0% versus 90.8%, $P = 0.88$). Four cases had too much missing data to

TABLE 2

Observed clinical characteristics of infants admitted to hospitals or evaluated at health centers diagnosed with pneumonia based on the 2000 Malawi Ministry of Health guidelines

Patient and clinical characteristics	Hospitals, N = 1,618	Health centers, N = 235	P-value
SpO ₂ , median value, % (IQR)	96 (92–98)	94 (89–97)	< 0.001
SpO ₂ > 92%, n (%), 95% CI	1,088 (67.2, 64.9–69.5)	123 (52.3, 45.9–58.7)	< 0.001
SpO ₂ 90–92%, n (%), 95% CI	184 (11.4, 9.9–13.0)	30 (12.8, 9.1–17.7)	
SpO ₂ < 90%, n (%), 95% CI	219 (13.5, 12.0–15.3)	53 (22.6, 17.6–28.4)	
Unrecorded SpO ₂ , n (%), 95% CI	127 (7.9, 6.6–9.3)	29 (12.3, 8.7–17.2)	
Respiratory rate, median (IQR)	64 (59–69)	63 (61–67)	0.50
Missing, n (%)	110 (6.8)	16 (6.8)	
Weight (kg), mean (SD)	4.4 (1.6)	4.5 (1.5)	0.23
Missing, n (%)	69 (4.3)	12 (5.1)	
Male, n (%), 95% CI	918 (56.7, 54.3–59.1)	113 (48.1, 41.7–54.5)	0.07
Female, n (%), 95% CI	657 (40.6, 38.2–43.0)	105 (44.7, 38.4–51.1)	
Missing, n (%)	43 (2.7)	17 (7.2)	
WAZ > -2, n (%), 95% CI	1,256 (77.6, 75.5–79.6)	175 (74.5, 68.5–79.6)	0.37
-3 < WAZ ≤ -2, n (%), 95% CI	172 (10.6, 9.2–12.2)	26 (11.1, 7.6–15.8)	
WAZ ≤ -3, n (%), 95% CI	85 (5.3, 4.3–6.5)	7 (3.0, 1.4–6.1)	
Missing, n (%)	105 (6.5)	27 (11.5)	
Chest wall indrawing, n (%), 95% CI	1,471 (90.9, 89.4–92.2)	165 (70.2, 64.0–75.7)	< 0.001
Missing, n (%)	67 (4.1)	7 (3.0)	
WHO danger signs,* n (%), 95% CI	377 (23.3, 21.3–25.4)	63 (26.8, 21.5–32.9)	0.64
Missing, n (%)	196 (12.1)	10 (4.3)	
Severe respiratory distress,† n (%), 95% CI	1,096 (67.7, 65.4–70.0)	133 (56.6, 50.2–62.8)	< 0.001
Missing, n (%)	147 (9.1)	8 (3.4)	

IQR = interquartile range; SpO₂ = peripheral capillary oxyhemoglobin saturation; WAZ = WHO weight-for-age z-score.

* Danger signs include central cyanosis, stridor in a calm child, apnea, or a general danger sign (inability to drink and/or breastfeed, lethargy or unconscious, or convulsions).

† Severe respiratory distress: grunting, head nodding, or nasal flaring.

determine if they met the Malawi MoH referral guidelines and were excluded from the rest of the analyses. The Malawi MoH clinical guidelines, without pulse oximetry, classified 22/257 (8.6%) infants as appropriate for outpatient management. One (5%) of these 22 infants had an SpO₂ < 90%, three (14%) had

an SpO₂ of 90–92%, and pulse oximetry was unrecorded for three (14%) (Figure 2). Application of the Malawi MoH guidelines without pulse oximetry misclassified 2% (1/54) with an SpO₂ < 90% and 5% (4/87) of infants with an SpO₂ ≤ 92% as appropriate for outpatient management (Supplemental

TABLE 3

Clinical characteristics of infants with pneumonia categorized by successful pulse oximetry measurement and clinical setting

Variable	Hospitals (n = 1,618)			Health centers (n = 235)		
	Successful, n (%)	Unsuccessful, n (%)	P	Successful, n (%)	Unsuccessful, n (%)	P
Peripheral capillary oxyhemoglobin saturation measurement	1,491 (92.2)	127 (7.8)	–	206 (87.7)	29 (12.3)	–
Male	855 (57.3, 54.8–59.8)	63 (49.6, 41.0–58.3)	0.31	103 (50.0, 43.2–56.8)	10 (34.5, 19.4–53.5)	0.07
Female	603 (40.4, 38.0–43.0)	54 (42.5, 34.2–51.3)		87 (42.2, 35.6–49.1)	18 (62.1, 43.2–77.9)	
Missing	33 (2.2)	10 (7.9)		16 (7.8)	1 (3.5)	
Weight in kg, mean (SD)	4.4 (1.7)	4.3 (1.3)	0.80	4.6 (1.5)	3.9 (0.9)	0.03
Missing	33 (2.2)	36 (28.4)		6 (2.9)	6 (20.7)	
Respiratory rate, median (interquartile range)	64 (59–68)	65 (59–71)	0.61	63 (60–67)	64 (62–67)	0.65
Missing	39 (2.6)	71 (55.9)		8 (3.9)	8 (27.6)	
Heart rate ≥ 190	89 (6.0, 4.9–7.3)	0	0.16	2 (1.0, 0.2–3.8)	0	0.66
Heart rate < 110	67 (4.5, 3.6–5.7)	2 (1.6, 0.4–6.1)		96 (46.6, 39.8–53.5)	1 (3.5, 0.5–21.6)	
Missing	24 (1.6)	113 (89.0)		1 (0.5)	25 (86.2)	
Fever	488 (32.7, 30.4–35.2)	33 (26.0, 19.1–34.3)	0.02	84 (40.8, 34.2–47.7)	9 (31.3, 16.8–50.2)	0.29
Hypothermia	29 (2.0, 1.4–2.8)	4 (3.2, 1.2–8.1)		5 (2.4, 1.0–5.7)	2 (6.9, 1.7–24.4)	
Missing	26 (1.7)	50 (39.4)		12 (5.8)	6 (20.7)	
WHO danger signs*	335 (22.5, 20.4–24.7)	42 (33.1, 25.4–41.7)	< 0.001	50 (24.3, 18.9–30.6)	13 (44.8, 27.8–63.2)	0.02
Missing	163 (10.9)	33 (26.0)		9 (4.4)	1 (3.5)	
Severe respiratory distress†	1,015 (68.1, 65.7–70.4)	81 (63.8, 55.0–71.7)	0.68	113 (54.9, 48.0–61.6)	20 (69.0, 49.8–83.2)	0.23
Missing	117 (7.8)	20 (15.8)		8 (3.9)	0	
Chest wall indrawing	1,349 (90.5, 88.9–91.9)	122 (96.1, 90.9–98.4)	0.40	142 (68.9, 62.2–74.9)	23 (79.3, 60.5–90.6)	0.37
Missing	66 (4.4)	1 (0.8)		7 (3.4)	0	
2014 integrated management of childhood illness referral eligible‡	1,486 (99.7)	127 (100.0)	1.00	203 (98.5)	28 (96.6)	0.77
Missing	5 (0.3)	0		3 (1.5)	1 (3.5)	

* WHO danger signs: central cyanosis, stridor in a calm child, a general danger sign (inability to drink and/or breastfeed, lethargy or unconscious, and convulsions), apnea.

† Severe respiratory distress: grunting, head nodding, and nasal flaring.

‡ WHO Integrated Management of Childhood Illness guidelines.

TABLE 4
Predictors of in-hospital mortality of young infants aged 0–2 months with pneumonia defined as per the 2000 Malawi Ministry of Health guidelines

Variable	Bivariate		P	Model 1†† (n = 1,618), aOR (95% CI)	Model 2‡ (n = 1,618), aOR (95% CI)	Model 3§ (n = 1,618), aOR (95% CI)	Model 4 (n = 1,618), aOR (95% CI)
	Died, n (%) (3.6)	Survived, n (%) (1,559 (96.4))					
SpO ₂ 93–100%	10 (0.9)	1,078 (99.1)	< 0.001	1.0	1.0	1.0	1.0
SpO ₂ 90–92%	10 (5.4)	174 (94.6)		6.2 (2.5–15.1)	3.3 (1.7–7.8)	3.3 (1.4–7.7)	3.3 (1.4–7.7)
SpO ₂ < 90%	15 (6.8)	204 (93.2)		7.9 (3.5–17.9)	4.4 (1.8–10.7)	4.5 (2.0–10.2)	4.5 (2.0–10.2)
Unrecorded SpO ₂	24 (18.9)	103 (81.1)		25.1 (11.7–54.0)	12.9 (4.8–34.5)	1.0	1.0
Male	27 (2.9)	891 (97.1)	0.16	1.0	1.0	1.0	1.0
Female	28 (4.3)	629 (95.7)		1.5 (0.9–2.5)	–	–	–
Missing	4 (9.3)	39 (90.7)		1.3 (0.7–2.3)	1.3 (0.7–2.3)	1.2 (0.6–2.3)	1.2 (0.6–2.3)
WAZ > -2	24 (1.9)	1,232 (98.1)	< 0.001	1.0	1.0	1.0	1.0
-3 < WAZ ≤ -2	8 (4.7)	164 (95.3)		2.5 (1.1–5.7)	2.2 (1.0–5.2)	2.5 (1.1–5.6)	2.3 (1.0–5.6)
WAZ ≤ -3	12 (14.1)	73 (85.9)		8.4 (4.1–17.5)	6.3 (2.6–15.4)	6.4 (2.5–16.0)	6.5 (2.3–18.6)
Missing	15 (14.3)	90 (85.7)		0.8 (0.4–1.7)	–	–	–
Respiratory rate < 60	26 (2.3)	1,092 (97.7)	0.59	1.0	–	–	–
Respiratory rate ≥ 60	22 (20.0)	88 (80.0)		0.8 (0.4–1.7)	–	–	–
Missing	28 (2.4)	1,152 (97.6)		1.0	–	–	–
Respiratory rate < 70	9 (2.7)	319 (97.3)	0.70	1.0	–	–	–
Respiratory rate ≥ 70	22 (20.0)	88 (80.0)		1.2 (0.5–2.5)	–	–	–
Missing	32 (2.3)	1,352 (97.7)		1.0	–	–	–
Respiratory rate < 80	5 (4.0)	119 (96.0)	0.24	1.0	–	–	–
Respiratory rate ≥ 80	22 (20.0)	88 (80.0)		1.8 (0.7–4.6)	–	–	–
Missing	27 (2.0)	1,297 (98.0)		1.0	1.0	1.0	1.0
Heart rate > 110 and < 190	5 (5.6)	84 (94.4)	0.06, < 0.001	32.5 (9.9–6.4)	3.0 (0.9–10.0)	3.5 (1.2–10.9)	3.4 (1.2–9.3)
Heart rate ≥ 190	7 (10.1)	62 (89.9)		5.0 (2.1–11.9)	4.2 (1.7–10.6)	3.5 (1.2–10.5)	4.5 (1.6–12.8)
Heart rate < 110	21 (15.3)	116 (84.7)		1.0	–	–	–
Missing	20 (2.0)	968 (98.0)		1.0	1.0	1.0	1.0
Normal temperature	19 (3.6)	502 (96.4)	0.06, < 0.001	1.8 (1.0–3.5)	1.6 (0.9–3.1)	1.7 (0.8–3.3)	1.7 (0.8–3.7)
Fever	8 (24.2)	25 (75.8)		15.5 (6.2–38.5)	6.1 (1.8–20.8)	6.8 (2.3–20.4)	6.1 (1.9–19.2)
Hypothermia	12 (15.8)	64 (84.2)		–	–	–	–
Missing	15 (1.4)	1,030 (98.6)		1.0	1.0	1.0	1.0
No danger signs	26 (6.9)	351 (93.1)	< 0.001	5.1 (2.7–9.7)	2.7 (1.3–5.5)	2.8 (1.4–5.7)	2.4 (1.2–4.9)
WHO danger signs	3 (8.3)	33 (91.7)		3.4 (1.0–11.6)	–	–	–
Cyanosis	2 (3.5)	55 (96.5)	0.07	1.3 (0.3–5.7)	–	–	–
Stridor	7 (5.9)	111 (94.1)	0.46	2.5 (1.1–5.9)	–	–	–
Apnea	17 (8.6)	180 (91.4)	0.03	5.2 (2.7–10.0)	–	–	–
Inability to drink	8 (23.5)	26 (76.5)	< 0.001	13.2 (5.5–31.5)	–	–	–
Convulsions	4 (5.6)	67 (94.4)	< 0.001	2.2 (0.7–6.2)	–	–	–
Lethargy	18 (9.2)	178 (90.8)	0.14	–	–	–	–
Missing	4 (1.1)	371 (98.9)		1.0	1.0	1.0	1.0
No severe respiratory distress	42 (3.8)	1,054 (96.2)	< 0.001	3.0 (1.2–7.7)	3.7 (1.2–11.7)	2.3 (0.7–7.3)	2.4 (0.8–7.4)
Severe respiratory distress	24 (5.1)	446 (94.9)	0.001	2.8 (1.5–5.2)	2.9 (0.9–9.4)	–	–
Grunting	33 (3.6)	872 (96.4)	0.12	1.7 (0.9–3.3)	–	–	–
Nasal flaring	13 (3.1)	412 (96.9)	0.67	1.2 (0.6–2.3)	–	–	–
Head nodding	55 (3.7)	1,416 (96.3)		–	–	–	–
Chest wall indrawing	1 (1.5)	66 (98.5)	0.59	1.0 (0.3–3.3)	–	–	–
Missing	8 (3.0)	260 (97.0)	0.81	1.1 (0.5–2.4)	–	–	–
Wheezing	21 (8.5)	226 (91.5)		–	–	–	–
Missing	32 (2.4)	1,327 (97.6)		1.0	1.0	1.0	1.0
Low amount of missing data*	27 (10.4)	32 (89.6)		2.4 (1.2–4.7)	2.4 (1.2–4.7)	–	3.7 (1.9–7.2)
High amount of missing data							

aOR = adjusted odds ratio; SpO₂ = peripheral capillary oxygen saturation; WAZ = weight-for-age z-score. Statistically significant findings are in bold.
 * Pattern mixture variable, binary variable in which either the degree of malnutrition or the presence of danger signs was not recorded.
 † Logistic regression, unrecorded pulse oximetry reading treated as a nominal category.
 ‡ Logistic regression, unrecorded pulse oximetry reading treated as a nominal category, analysis includes a binary missing data variable (bottom of the table).
 § Logistic regression, unrecorded pulse oximetry reading treated as missing data and imputed using MICE.
 || Logistic regression, unrecorded pulse oximetry reading treated as missing data and imputed using MICE, analysis includes a binary missing data variable (bottom of the table).

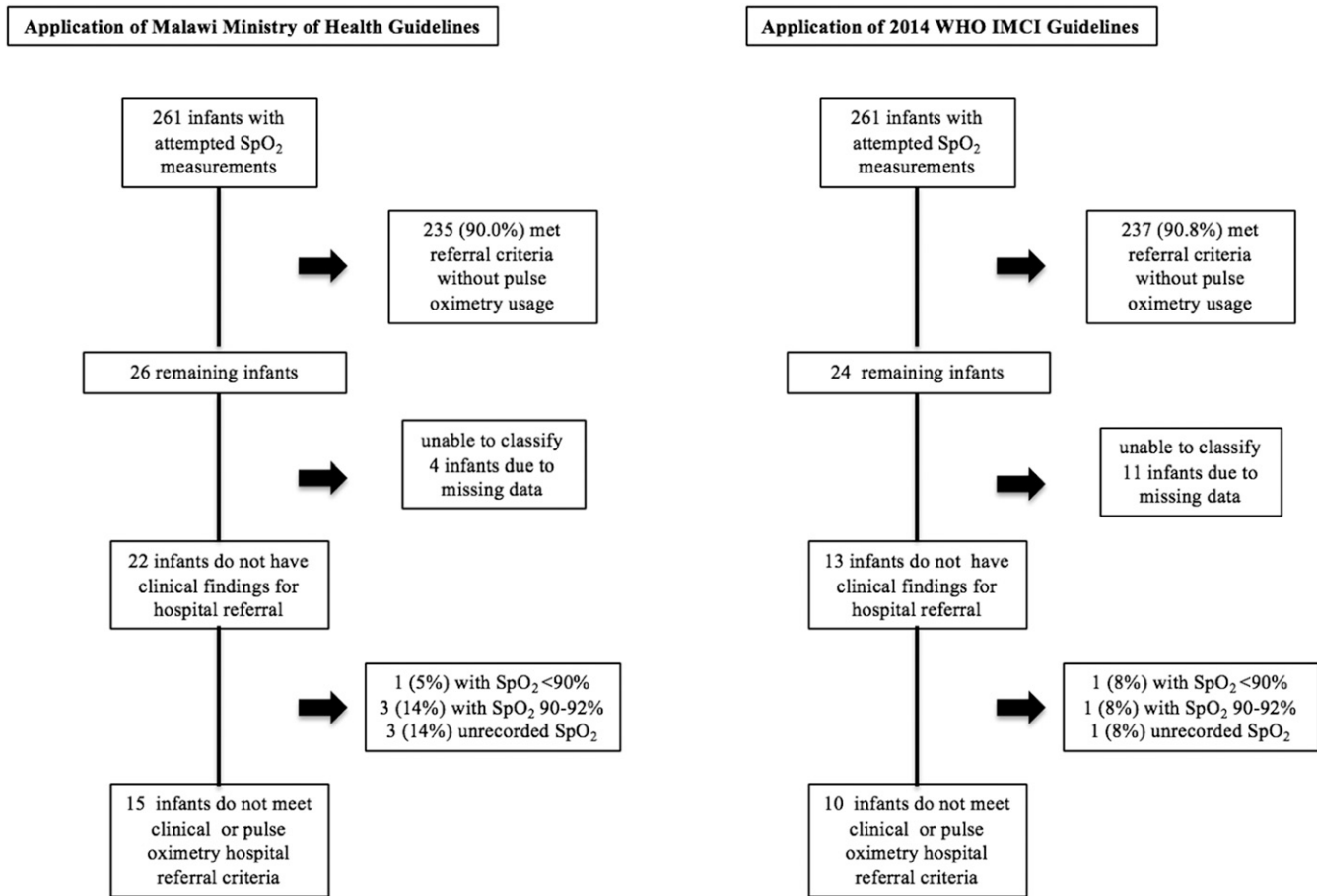


FIGURE 2. Performance of the Malawi Ministry of Health and 2014 WHO Integrated Management of Childhood Illness guidelines at identifying hypoxemic infants with cough and/or shortness of breath.

Material 2). Comparatively, the 2014 WHO IMCI guidelines misclassified 2% (1/54) with an SpO₂ < 90% and 1/87 (1%) of infants with an SpO₂ ≤ 92% (Supplemental Material 3). Of the 13 infants who did not meet hospital referral clinical criteria, one (8%) had an SpO₂ < 90% and one (8%) had an SpO₂ ≤ 92%.

DISCUSSION

We analyzed 1,879 cases of Malawian infants younger than 2 months presenting to outpatient health centers and hospitals with WHO-defined pneumonia and found that infants with an SpO₂ of 90–92% had a near-equal aORs for inpatient mortality compared with those with an SpO₂ < 90%. This is not surprising as SpO₂ in some cases may overestimate arterial blood oxygen saturation (SaO₂).²³ An SpO₂ of 89–92% on average correlates with an SaO₂ of 90% and partial pressure of oxygen of 60 mmHg in an otherwise healthy child.²⁴ The 2013 WHO Pocket Book of Hospital Care, used in hospital settings, recommends starting supplemental oxygen in young infants with an SpO₂ < 90% or those with central cyanosis or severe respiratory distress.²⁵ We found a high (24.9–35.4%) prevalence of clinically meaningful hypoxemia (SpO₂ ≤ 92%) similar to other studies that defined hypoxemia as an SpO₂ < 90%.^{26–28} Among the small proportion of infants with upper respiratory tract infection symptoms who did not meet the 2014 WHO IMCI hospital referral criteria, 15% were still

hypoxemic (SpO₂ ≤ 92%) and, therefore, at high risk of mortality. The WHO IMCI guidelines, used by health workers at outpatient health centers, do not provide any referral guidance when SpO₂ is measured in infants younger than 2 months but state that older children aged 2–59 months with an SpO₂ < 90%, independent of other examination findings, should be referred to hospitals.² Without more specific guidance from the WHO on the application of SpO₂ measurements among young infants, clinicians may or may not apply these recommendations to infants younger than 2 months. Our findings generate uncertainty around the generalizability of the current WHO guidelines that lack pulse oximetry recommendations for young infants in Malawi and potentially other LMICs.

Notably, we found a markedly elevated aOR of mortality associated with an unrecorded SpO₂ which was robust to multiple modeling approaches. These infants comprised 8% of hospitalized cases and accounted for 41% of all deaths. Both health center outpatients and hospital inpatients had a higher prevalence of WHO danger signs among infants with an unrecorded SpO₂. One explanation for the associated increased mortality, based on direct observations, is that SpO₂ was not documented after attempted but failed measurements. A high proportion of these cases were likely infants with circulatory compromise due to shock and poor peripheral perfusion that rendered obtaining pulse oximetry readings difficult. Indicators of poor perfusion such as capillary refill

time, cool extremities, or history of reduced frequency of urination, which are included in the WHO's Emergency Triage and Treatment guidelines,²⁹ are not included in the WHO IMCI guidelines. A study conducted in the United States found that the capillary refill time and cool extremities had moderate to poor inter-rater reliability.³⁰ We recommend further exploration on the feasibility and reliability of healthcare providers collecting these signs, especially in the context of the inability to obtain SpO₂ measurement.

Like many LMICs, pulse oximetry and supplemental oxygen availability and uptake are poor in Malawi, especially in outpatient health centers.^{5,6,31} This situation is particularly disturbing, as the prevalence of hypoxemia, regardless of the threshold used, was higher among outpatients. A retrospective analysis of the Malawi Child Lung Health Program from 2001 to 2012 found that among infants younger than 2 months, referral from a health center was an independent mortality risk factor.¹⁶ This finding may reflect discrepancies among care-seeking behaviors of communities living near hospitals, challenges in the referral pathway, or lack of oxygen and antibiotic availability at health centers. Some of these children may have died en route to the hospital or families may not go to the hospital despite referral. The use of pulse oximetry in outpatient settings has the potential to strengthen multiple aspects of young infant primary care, including improving the identification of true high-risk cases, strengthening referral recommendations by healthcare providers currently relying solely on nonspecific clinical signs such as respiratory rate, increase the uptake of referral recommendations by families, and ultimately improve clinical care through refinement of hospital transfer processes and supplemental oxygen prescribing practices. Further research will be needed to more fully evaluate pulse oximetry effects on the primary care health system, especially as it pertains to young infants.

A large proportion of infants evaluated at health centers met the hospital referral criteria, even without pulse oximetry usage because of the high prevalence of tachypnea. Young infants are at high risk of rapid decompensation from serious bacterial infections including pneumonia. Given the relative high prevalence of serious bacterial infections in this age-group, the WHO guidelines set a very low threshold for hospital referral for expert evaluation or, if indicated, inpatient admission. The Malawi MoH clinical guidelines misclassified 5% of infants with cough and/or shortness of breath with an SpO₂ ≤ 92% as appropriate for outpatient management. Implementation of the 2014 WHO IMCI guidelines would reduce this proportion by half. If healthcare workers were to adhere to the IMCI guidelines, very few infants with an SpO₂ ≤ 92% would be discharged home. This finding is in contrast with our previous finding among Malawian children aged 2–59 months that 68.7% with an SpO₂ < 90% were misclassified by the clinical guidelines as appropriate for outpatient care.¹² Our dataset does not explicitly indicate how healthcare workers may have been influenced by either a “normal” or “abnormal” SpO₂, and it remains unclear whether busy healthcare workers may over-rely on SpO₂ reading, compared with the clinical criteria, when making referral decisions. Further research on whether “normal” SpO₂ measurements among children otherwise clinically eligible for referral may detrimentally affect referral decision-making.

Limitations. Understanding practices and outcomes in routine clinical care is essential to informing guideline and

program development. Although a primary strength of our study is that these data reflect real-life clinical practices in Malawi, programmatic data have some limitations, most notably missing data. Death cases had a high degree of missing data on other variables, limiting the certainty of our conclusions. It is possible that the need to stabilize these critically ill patients precluded hospital staff's recording of clinical data at the time of admission. We found evidence that many of these measurements were MNAR, as inclusion of the pattern mixture variable in the logistic regression model still resulted in an unrecorded SpO₂ associated with an increased aOR for in-hospital mortality. We did not conduct home-based follow-up to assess if families followed referral recommendations, and infants were later taken to higher level health facilities or returned for re-evaluation, developed more severe disease, or died. Hemoglobin and malaria testing were not routinely documented as part of the pneumonia surveillance program. Both would be useful in assessing illness etiology and the former to determine inherently low oxygen-carrying capacity. Finally, our conclusions regarding the proportion of hypoxemic infants with upper respiratory infection symptoms missed by clinical guidelines alone are limited by the small sample size and should be interpreted within this context.

CONCLUSION

This observational study reflects real-world pneumonia care practices for young infants at outpatient health centers and hospitals by healthcare providers in a nonclinical trial setting in Malawi. Our findings pose several important questions for further research and on areas of focus for guideline revisions with regard to use of pulse oximetry and its feasibility of implementation and operationalization. Given that this was an observational study, with missing data, caution should be taken in the interpretation of these results. Nonetheless, our findings remain compelling, particularly when considering the strong association of an SpO₂ of 90–92% and < 90% with hospital mortality, along with the high prevalence of hypoxemia in outpatient settings. Importantly, our findings, if replicated elsewhere, provide evidence supporting revision of the WHO guidelines to recommend hospital referral of young infants at outpatient centers with an SpO₂ ≤ 92%, or for whom a pulse oximetry reading is unobtainable.

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