

Missed opportunities for hospital referral of young children with severe pneumonia identified at primary care using pulse oximetry: an analysis from the AIRE study in West Africa

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ABSTRACT

Background In line with the Integrated Management of Childhood Illness (IMCI) guidelines, healthcare workers (HCWs) should refer all severe pneumonia among children under 5 seen in primary care in resource-limited settings. We investigated the frequency and correlates of missed opportunities for hospital referral (MOHR) of clinical severe pneumonia. Our study was embedded within the Améliorer l'Identification des détresses Respiratoires chez l'Enfant project, which involved the routine implementation of pulse oximetry (PO) within IMCI consultations at primary healthcare centres (PHCs) in West Africa: Burkina Faso, Guinea, Mali and Niger.

Methods All children aged 2–59 months attending IMCI consultations in 16 PHCs and classified as severe cases using IMCI+PO were enrolled into a prospective cohort for 14 days, with parental consent. We estimated the rate of MOHR for IMCI-defined severe pneumonia, which was either not referred, or referred but did not make it to hospital. Correlates of MOHR at day 14 were investigated using logistic mixed regression with random effect for PHCs.

Results From June 2021 to June 2022, among the 1786 children aged 2–59 months classified as severe cases by IMCI+PO, 682 (38.2%) were severe pneumonia. Of these, 35 (5.1%) also had severe anaemia, 47 (6.9%) severe hypoxaemia ($SpO_2 < 90\%$) and 602 (88.3%) severe malaria. HCW made the referral decision for 125 (18.3%) children, refused by three (2.4%) families; 560 (82.1%) were MOHR. Severe anaemia reduced the odds of MOHR (adjusted OR (aOR): 0.02; 95% CI 0.01 to 0.07) whereas having an SpO_2 between 90% and 93% (aOR: 12.16; 95% CI 3.47 to 42.61) or greater than 94% (aOR: 11.81; 95% CI 3.98 to 35.02) or severe malaria (aOR: 2.55; 95% CI 1.04 to 6.26) significantly increased it.

Conclusion MOHR for severe pneumonia was extremely high at PHC level in these settings, mainly explained by HCW's decisions. Strengthening the referral system and training HCW to reinforce their adherence to IMCI

WHAT IS ALREADY KNOWN ON THIS TOPIC

- ⇒ Pneumonia remains the leading cause of mortality in children under 5 in sub-Saharan Africa.
- ⇒ The implementation of standardised guidelines, such as the WHO's Integrated Management of Childhood Illnesses (IMCI) has reduced pneumonia-related mortality but remains insufficient.
- ⇒ Little is known about the referral to hospital of severe pneumonia cases identified in West African primary care settings that are eligible for hospital referral.
- ⇒ Introduction of pulse oximetry at primary care should improve the diagnosis of severe hypoxemia associated with severe pneumonia and requiring urgent referral.

guidelines remains essential to improve the management of severe pneumonia.

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INTRODUCTION

Globally, there are over 1400 cases of pneumonia per 100 000 children, with the greatest incidence occurring in South Asia (2500 cases per 100 000 children) and West and Central Africa (1620 cases per 100 000 children).¹ Pneumonia is a leading cause of death among children aged under five. In 2019, the global incidence of pneumonia in young children was 45 million, resulting in more than 700 000 deaths.² Research has identified several risk factors for pneumonia incidence and severity, including child age, lack of immunisation, malnutrition, chronic

WHAT THIS STUDY ADDS

- ⇒ This study, which was carried out in 16 primary healthcare centres in four West African countries (Burkina Faso, Guinea, Mali and Niger) showed that there was a high rate of severe pneumonia among severe IMCI cases (38%, 682/1786).
- ⇒ There was also a high rate of missed opportunities for hospital referral for these severe pneumonia (82.1%, 560/682). The latter was mainly attributed to a lack of referral decisions made by healthcare workers (HCW).
- ⇒ It should be noted that co-morbidity with severe malaria was also frequent, 88%.
- ⇒ Severe hypoxemia ($\text{SpO}_2 < 90\%$) and severe anaemia were associated with an increased risk of missed opportunities for hospital referral.
- ⇒ Children with severe pneumonia who did not have severe hypoxemia or severe malaria were at increased risk of not being referred to hospital.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

- ⇒ The use of PO led to HCW decisions to refer severe pneumonia cases with severe hypoxemia to hospital, in contrast to those without severe hypoxemia. However, the latter remained inappropriately managed. This issue must be addressed with the necessary nuance when IMCI guidelines are being developed to incorporate routine PO use.
- ⇒ The management of severe pneumonia co-morbidity with severe malaria should be addressed to improve the quality of care provided.
- ⇒ Decision makers should understand the significance of missed opportunities for hospital referral of severe pneumonia, which continues to be the leading killer of children under five. They should be mobilised to improve HCW training and hospital referral systems to improve the healthcare management of severe pneumonia.

underlying diseases, HIV infection or HIV exposure in young infants, young maternal age, low maternal education, low socio-economic status and smoke exposure or indoor air pollution.³

Management strategies that are effective in reducing pneumonia-related morbidity and mortality in children are of the utmost importance.⁴ The WHO has developed Integrated Management of Childhood Illnesses (IMCI) guidelines for primary care. Many low- and middle-income countries (LMICs) use this syndromic approach to guide healthcare workers (HCWs) decision in disease classification and management of children under 5.⁵ More specifically, the IMCI outlines a comprehensive strategy for the management of childhood illnesses, including pneumonia. This strategy involves a swift assessment and categorisation of the illness, a decision on treatment, provision of supportive care and hospital referral for severe cases. In 2012, the WHO revised its pneumonia management guidelines. Children aged 2–59 months presenting with a cough or breathing difficulties with fast breathing or chest indrawing are classified as ‘pneumonia’ and should receive oral amoxicillin with home care advice. Children aged 2–59 months with cough or difficult breathing, and at least one general danger sign (inability to drink, persistent vomiting, convulsions,

lethargy or unconsciousness, stridor in a calm child or severe malnutrition) are classified as ‘severe pneumonia or very severe disease’. In such cases, the recommended management is to administer an initial antibiotic dose and to urgently refer the patient to the hospital for injectable antibiotics and supportive therapy, including oxygen therapy if severe hypoxaemia is diagnosed using pulse oximetry (PO).⁶ When IMCI guidelines are applied with high adherence, there is evidence to suggest that they can improve health outcomes.⁷ However, data regarding adherence to referral guidelines for severe IMCI-related pneumonia are lacking at primary care level.

From 2021 to 2022, the Améliorer l'Identification des détresses Respiratoires chez l'Enfant/Improving Identification of Respiratory Distress in Children operational research project has implemented the routine use of PO in IMCI consultations for children aged under 5 to improve the diagnosis of severe hypoxemia and its management at primary healthcare centres (PHCs) in Burkina Faso, Guinea, Mali and Niger.⁸ Accompanying publications report on the context, process and children's outcomes after implementation of PO use in this project.^{9–12} In this paper, we specifically aimed to describe the missed opportunities for hospital referral (MOHR) frequency, correlates and outcomes at day 14 of severe pneumonia identified by IMCI once PO has been put into effect in the 16 research PHCs of the four countries participating in AIRE.

METHODS

Study sites

This analysis used individual data from the AIRE project conducted by a consortium of three non-governmental organisations: Alliance for International Medical Action, Solthis, Terre des Hommes and the French Institute of Health and Medical Research (Inserm). Briefly, the AIRE project implemented routine PO use into IMCI consultations in 202 PHCs in the four study countries.⁸ At baseline, all HCWs were also trained or recycled in national IMCI protocols integrating PO. From 14 June 2021 to 19 June 2022, a research operational study was conducted in the 16 selected public PHCs (four per country) and eight district referral hospitals in the four countries to evaluate the implementation of PO use into IMCI guidelines.^{11–13} The study sites were included according to the criteria reported in the research protocol and selected to represent the different volumes of activities within each health district.⁸

Study design, inclusion criteria and procedure

All children aged 0–59 months attending IMCI consultations at the 16 research PHCs were eligible for PO use, except those aged 2–59 months who were classified as simple cases using IMCI and who did not have cough or breathing difficulties. During the consultation, the HCW at the PHC first classified children into three groups using the IMCI classification: green for simple cases,

yellow for moderate cases and red for severe cases. They then used PO. Simple and moderate cases identified using clinical IMCI were classified as severe cases if their SpO₂ was below 90%. All children aged 0–59 months classified as severe cases were consecutively enrolled over 12 months in a prospective cohort and followed up until day 14, provided that written parental consent was obtained. Children were not included on nights, weekends or public bank holidays as the research teams were not always on site. For this specific analysis, children aged 2–59 months and classified as having clinical severe pneumonia were enrolled.

Data collection and definitions

Data were collected using an electronic case report form developed with REDCap software by dedicated data collectors at PHC and hospital levels. The following data were collected: sociodemographic and clinical individual data, IMCI classifications and clinician decisions for hospital referral at the PHC level.

The WHO's revised guidelines for the management of pneumonia define severe pneumonia in children aged 2–59 months as being accompanied by a cough or difficulty breathing as well as at least one of the following general danger signs: inability to drink, persistent vomiting, convulsions, lethargy or unconsciousness, stridor in a calm child or severe malnutrition.⁶ The definition of severe pneumonia in children aged 2–59 months used in Burkina Faso, Mali and Niger was the same as the WHO definition. However, the definition used in Guinea was more sensitive, including the presence of other signs such as chest indrawing or wheezing or nose flapping exhalation or groaning (online supplemental table 1). Fast breathing is defined as a respiratory rate of greater than or equal to 50 bpm for children aged 2–11 months inclusive, and greater than or equal to 40 bpm for children aged 12–59 months inclusive.¹⁴ A normal heart rate is defined as heart rate between 100 bpm and 160 bpm in children aged 0–1 year, 90–150 bpm for children aged 1–3 years, and 80–140 bpm for children aged 3–5 years.¹⁵ In this study, severe hypoxaemia was defined as an SpO₂ level of <90%, and moderate hypoxaemia as an SpO₂ level between 90% and 93%.^{16 17} The definitions of severe malaria and severe anaemia were based on the HCW diagnoses at PHC level using the national IMCI guidelines (online supplemental table 1). The seasons were categorised as rainy (June to October in Burkina Faso and Mali, June to September in Niger, and June to September in Guinea) or dry (November to May in Burkina Faso and Mali, October to May in Niger and October to May in Guinea).

Outcomes

The WHO revised pneumonia management guidelines recommended urgent referral to hospital for severe pneumonia diagnosed using IMCI, immediately after an initial antibiotic dose was administered at the PHC.⁶ The existing IMCI guidelines were consistent with this

recommendation in all four AIRE countries. The study outcome was the MOHR for IMCI-defined severe pneumonia diagnosed at PHC. A MOHR occurred if children were either not referred, or referred but did not make it to hospital, regardless of the reasons.

Statistical analysis

The proportions of children with severe pneumonia, their sociodemographic and clinical characteristics, and their vital status on day 14 were described and compared according to their referral status. Quantitative data were summarised using means and SD or using medians and IQRs and compared using Student's t-tests. Categorical data were described as proportions and were compared using Pearson's χ^2 or Fisher's exact tests. All analyses were considered statistically significant with a p value <0.05.

We analysed the factors associated with MOHR, using a logistic mixed-effects regression model with a random effect for the PHC to account for potential clustering effects. We conducted a global analysis including all participants, and a specific analysis for those enrolled in Guinea, where most severe pneumonia cases were recorded. To develop our explicative model, we first selected the potential variables known to impact family health-seeking behaviour (mother's vital status and education level of the household responsible person, carrying on an income-generating activity, travel time from home to the PHC >30 min, consultation delay >2 days since the onset of symptoms and season), and also those that could impact on the HCW decision-making (type of IMCI support, paper or electronic, SpO₂ level and the presence of comorbidities, such as severe malaria, severe anaemia and severe malnutrition). For each analysis, we performed an univariable analysis. Variables associated in univariable analysis with a p value <20% were included in the multivariable analysis. Age and sex were forced into the adjusted models. We report adjusted OR (aOR) with their 95% CI. A two-tailed p value of <0.05 was regarded as statistically significant. R software V.4.0.5 was used.

Patient and public involvement

This study was conducted using individual data collected with the ethical committees' and MOHs authorisation. Patients were not involved in the design, or conduct, or reporting or dissemination plans of our research.

RESULTS

From 14 June 2021 to 20 June 2022, 39 360 children under 5 attended IMCI consultations at the 16 research PHCs. Of these, 7760 (19.7%) simple non-respiratory IMCI cases were excluded as they were not eligible for PO. Of the 31 600 (80.3%) children eligible for the use of PO, 15 670 (49.6%) seeking health services at night, over weekends or bank holidays were not invited to participate in the study. Of the 15 930 (50.4%) remaining children who were invited to participate, 33 (0.2%) families refused, mainly because the child's accompanying person needed the father's consent. The

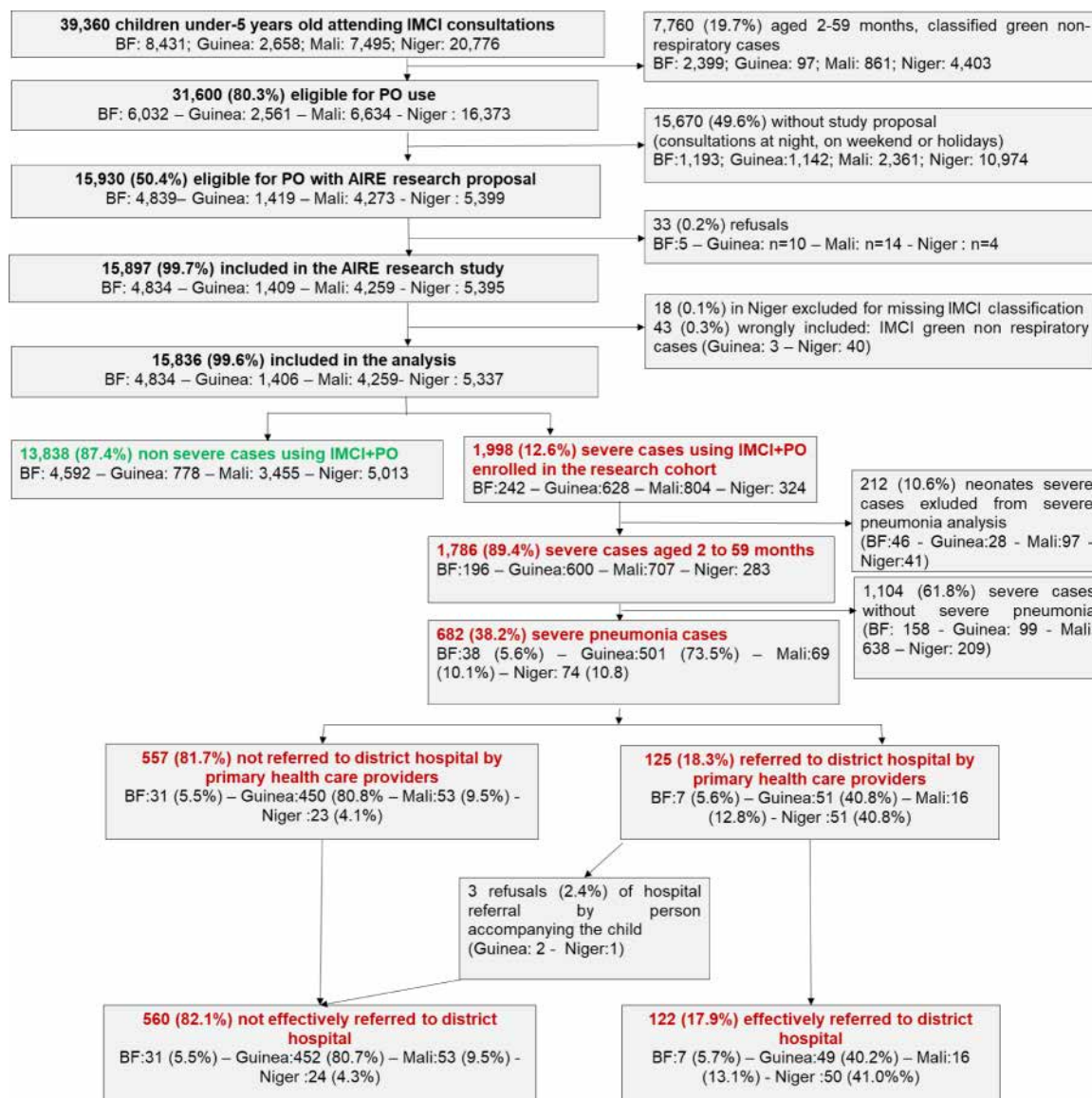


Figure 1 Flowchart of the inclusion process of children 2–59 months of age enrolled in the pneumonia substudy of missed opportunities of hospital referral in the AIRE research study, June 2021–June 2022. AIRE, Améliorer l'Identification des détresses Respiratoires chez l'Enfant; BF, Burkina Faso; IMCI, Integrated Management of Childhood Illness; PO, pulse oximetry.

remaining 15 897 (99.7%) children were included in the research study with parental consent. However, 61 (0.4%) were excluded from the analysis due to missing IMCI classification or uncorrected inclusion. A total of 15 836 children under 5 were included in the study, of whom 1998 were classified as severe cases using IMCI+PO. The 212 (10.6%) neonates aged <2 months were excluded from this analysis (figure 1). Of the 1786 children aged 2–59 months, 682 children were classified as having severe pneumonia using IMCI and were enrolled in this analysis. The proportion of severe pneumonia was 38.2% (682/1786), with significant heterogeneity between countries: 5.6% (38/196) in Burkina Faso, 73.8% (501/600) in Guinea, 12.8% (69/707) in Mali and 26.1% (74/283) in Niger.

Baseline characteristics and missed opportunities of hospital referral

Of the 682 children enrolled with severe pneumonia, median age was 23.2 months (IQR: 12.1–36.4 months); 35 (5.1%) had also a severe anaemia, 47 (6.9%) a severe hypoxaemia ($\text{SpO}_2 < 90\%$) and 602 (88.3%) a severe malaria. Overall, HCW made the referral decision for 125 (18.3%) children, but three families (2.4%) refused it, and 557 (81.7%) were not referred to a district hospital by HCW. Overall, 560 (82.1%) were MOHR: 31 (5.5%) were from Burkina Faso, 452 (80.7%) from Guinea, 53 (9.5%) from Mali and 24 (4.3%) from Niger (figure 1).

Table 1 presents the characteristics of the 682 severe pneumonia cases enrolled according to their referral status. Cases with MOHR were significantly

Table 1 Baseline characteristics of the severe pneumonia cases aged 2–59 months enrolled in the AIRE project according to the missed opportunity of hospital referral after IMCI consultation, June 2021–June 2022, (N=682).

Variables		Missed opportunity of hospital referral after IMCI consultation		P value	Total N=682
		No	Yes		
		N=122	N=560		
Country	Burkina Faso, n (%)	7 (5.7)	31 (5.5)	<0.001	38 (5.6)
	Guinea, n (%)	49 (40.2)	452 (80.7)		501 (73.5)
	Mali, n (%)	16 (13.1)	53 (9.5)		69 (10.1)
	Niger, n (%)	50 (41.0)	24 (4.3)		74 (10.8)
Age groups (months)	(2–23), n (%)	86 (70.5)	285 (50.9)	<0.001	371 (54.0)
	(24–59), n (%)	36 (29.5)	275 (49.1)		311 (46.0)
Sex	Female, n (%)	50 (41.0)	281 (50.2)	0.082	331 (49.0)
Deceased mother	n (%)	1 (0.8)	0 (0.0)	0.402	1 (0.2)
	Missing, n (%)	0 (0.0)	0 (0.0)		0 (0.0)
Education level of household responsible person	Never attended school, n (%)	73 (59.8)	293 (52.3)	0.0321	366 (54.0)
	Missing, n (%)	0 (0.0)	0 (0.0)		0 (0.0)
Child' accompanying person	Mother, n (%)	118 (96.7)	542 (96.8)	0.992	660 (97.0)
	Father, n (%)	1 (0.8)	4 (0.7)		5 (0.7)
	Others, n (%)	3 (2.5)	14 (2.5)		17 (2.5)
	Missing, n (%)	0 (0.0)	0 (0.0)		0 (0.0)
Ability to read or write of the person accompanying the child	No, n (%)	89 (73.0)	358 (63.9)	0.073	447 (65.5)
	Missing, n (%)	0 (0.0)	0 (0.0)		0 (0.0)
Income-generating activity of person accompanying the child	No, n (%)	90 (73.8)	313 (55.9)	<0.001	403 (59.1)
	Missing, n (%)	0 (0.0)	0 (0.0)		0 (0.0)
Electronic IMCI support	Yes, n (%)	15 (12.3)	74 (13.2)	0.900	89 (13.0)
	Missing, n (%)	0 (0.0)	0 (0.0)		0 (0.0)
Travel time home—PHC	> 30 min, n (%)	51 (41.8)	156 (27.9)	0.003	207 (30.4)
	Missing, n (%)	0 (0.0)	0 (0.0)		0 (0.0)
Consultation delay since the onset of symptoms (days)	> 2 days, n (%)	84 (68.9)	340 (60.7)	0.239	424 (62.2)
	Missing, n (%)	10 (8.2)	16 (2.9)		26 (3.8)
Documented temperature	(T>38°C), n (%)	23 (18.9)	92 (16.4)	0.189	115 (16.9)
	Missing, n (%)	68 (55.7)	275 (49.1)		343 (50.3)
Heart rate for age	Bradycardia, n (%)	8 (6.6)	7 (1.3)	<0.001	15 (2.2%)
	Normal, n (%)	52 (42.6%)	348 (62.1)		400 (58.6)
	Tachycardia, n (%)	47 (38.5)	199 (35.5)		246 (36.1)
	Missing, n (%)	15 (12.3)	6 (1.1)		21 (3.1)
Respiratory rate for age	Slow breathing, n (%)	1 (0.8)	0 (0.0)	<0.001	1 (0.1)
	Normal breathing, n (%)	41 (33.6)	351 (62.7)		392 (57.5)
	Fast breathing, n (%)	49 (40.2)	139 (24.8)		188 (27.6)
	Missing, n (%)	31 (25.4)	70 (12.5)		101 (14.8)
Chest indrawing	No, n (%)	99 (81.1)	534 (95.4)	<0.001	633 (92.8)
	Yes, n (%)	23 (18.9)	26 (4.6)		49 (7.2)
	Missing, n (%)	0 (0.0%)	0 (0.0%)		0 (0.0%)

Continued

Table 1 Continued

Variables		Missed opportunity of hospital referral after IMCI consultation		P value	Total N=682
		No	Yes		
		N=122	N=560		
SpO ₂ level	Severe hypoxemia SpO ₂ <90%, n (%)	39 (32.0)	8 (1.4)	<0.001	47 (6.9)
	Moderate hypoxemia SpO ₂ (90–93%), n (%)	13 (10.7)	54 (9.6)		67 (9.8)
	No hypoxemia SpO ₂ ≥94%, n (%)	69 (56.6)	496 (88.6)		565 (82.8)
	Missing, n (%)	1 (0.8)	2 (0.4)		3 (0.4)
Severe malaria	Yes, n (%)	77 (63.1)	525 (93.8)	<0.001	602 (88.3)
Severe anaemia*	Yes, n (%)	27 (22.1)	8 (1.4)	<0.001	35 (5.1)
Severe malnutrition*	Yes, n (%)	15 (12.3)	22 (3.9)	<0.001	37 (5.4)
Season	Rainy season	50 (40.9)	230 (41.0)	0.98	280 (41.1)
	Dry season	72 (59.1)	330 (59.0)		402 (58.9)

* See definitions in the Methods section.
AIRE, Améliorer l'Identification des détresses Respiratoires chez l'Enfant; IMCI, Integrated Management of Childhood Illness; PHC, primary healthcare centre.

older than those referred ($p<0.001$). MOHR rates of severe pneumonia differed according to the education level of the household responsible person, income-generating activity of the person accompanying the child, travel time from home to PHC, clinical symptoms, hypoxaemia, severe malaria, severe anaemia and severe malnutrition. The proportion of heads of household who never attended school (59.8%, 73/122) was significantly higher for children referred compared with those not referred (52.3%, 293/560). The proportion of the child accompanying person who did not have an income-generating activity (73.8%, 90/122) was significantly higher for children referred compared with those not referred (55.9%, 313/560). Compared with children not referred (72.1%, 404/560), those referred had a significantly shorter travel time from home to PHC (58.2%, 71/122). The proportions of children with tachycardia (38.5%, 47/122), fast breathing (40.2%, 49/122) and chest indrawing (18.9%, 23/122) were significantly higher among those referred compared with those not referred. The proportions of children with hypoxemia (32.0%, 39/122), severe anaemia (22.1%, 27/122) and who were severely malnourished (15.3%, 15/122) were significantly higher among those referred compared with those not referred. However, the proportion of severe malaria (63.1%, 77/122) was significantly lower among those referred compared with those not referred (93.8%, 525/560).

Factors associated with MOHR of severe pneumonia

Table 2 presents a multivariable logistic mixed-effects regression model of factors associated with MOHR for all cases of severe pneumonia. Adjusted for age and sex, the income-generating activity of the person accompanying the child, travel time from home

to PHC and type of IMCI used, SpO₂ level, severe malaria and severe anaemia were independently associated with MOHR. The odds of MOHR were significantly higher for children with moderate hypoxaemia (SpO₂ between 90% and 93%, aOR: 11.91, 95% CI 3.39 to 41.89), and those with no hypoxaemia (SpO₂ greater than 94%, aOR: 11.7; 95% CI 3.94 to 34.72) compared with children with severe hypoxaemia (SpO₂<90%). The odds of MOHR were significantly lower for children with severe anaemia (aOR: 0.03; 95% CI 0.01 to 0.07) than for those without. However, the odds of MOHR were significantly higher for children with severe malaria (aOR: 2.58; 95% CI 1.05 to 6.33) than for those without. There was no seasonality effect.

We also carried out a sensitivity analysis of the model restricted to severe pneumonia in Guinea, accounting for 80.7% of all cases, and where the proportion of severe hypoxemia was significantly lower than in other countries (1.2%, 6/501 vs 22.7%, 41/181, $p<0.001$). In Guinea, adjusted for age, sex, travel time from home to PHC, level of SpO₂ and severe malnutrition, severe anaemia and the season during which the child was enrolled were independently associated with MOHR. The odds of MOHR were significantly lower for children with severe anaemia (aOR: 0.02; 95% CI 0.01 to 0.07) compared with those without severe anaemia. But, the odds of MOHR were significantly higher for children enrolled during the dry season (aOR: 2.15; 95% CI 1.01 to 4.57) (table 3).

Day 14 mortality outcomes

By day 14, 2.2% (15/682) of severe pneumonia cases had died, 7.4% (9/122) of those who were referred compared with 1.1% (6/560) of those with MOHR. The proportion of deaths was significantly higher

Table 2 Factors associated with the missed opportunities for hospital referral of severe pneumonia cases in children aged 2–59 months in all countries, logistic mixed regression model (N=682).

Variables		Missed opportunities for hospital referral		Univariate	Adjusted analysis
		Yes	No	OR (95% CI, p value)	aOR (95% CI, p value)
Age (months)	(2–23)	285 (50.9)	86 (70.5)	Reference	
	(24 - 59)	275 (49.1)	36 (29.5)	1.66 (1.02–2.68, p=0.04)	1.52 (0.83–2.77, p=0.171)
Sex	Female	281 (50.2)	50 (41.0)	Reference	
	Male	279 (49.8)	72 (59.0)	0.69 (0.44–1.08, p=0.104)	0.78 (0.45–1.34, p=0.362)
Ability to read or write of the person accompanying the child	No	358 (63.9)	89 (73.0)	Reference	
	Yes	202 (36.1)	33 (27.0)	1.54 (0.85–2.78, p=0.157)	1.26 (0.61–2.61, p=0.540)
Income-generating activity of person accompanying the child	No	313 (55.9)	90 (73.8)	Reference	
	Yes	247 (44.1)	32 (26.2)	1.22 (0.72–2.06, p=0.465)	
Travel time home—PHC	>30mn	156 (27.9)	51 (41.8)	Reference	
	≤30mn	404 (72.1)	71 (58.2)	2.56 (1.49–4.41, p=0.001)	1.55 (0.81–2.96, p=0.186)
Type of IMCI support	Papier-based	486 (86.8)	107 (87.7)	Reference	
	Electronic-based	74 (13.2)	15 (12.3)	4.82 (0.87–26.86, p=0.072)	2.09 (0.45–9.64, p=0.345)
Consultation delay since the onset of symptoms (days)	>2 days	324 (59.6)	74 (66.1)	Reference	
	≤2 days	220 (40.4)	38 (33.9)	1.67 (1.01–2.75, p=0.044)	1.22 (0.68–2.19, p=0.503)
SpO ₂ level	<90%	8 (1.4)	39 (32.2)	Reference	
	(90,93%)	54 (9.7)	13 (10.7)	19.27 (5.94–62.49, p<0.001)	11.91 (3.39–41.89, p<0.001)
	≥94%	496 (88.9)	69 (57.0)	22.82 (8.41–61.91, p<0.001)	11.7 (3.94–34.72, p<0.001)
Severe malaria	No	35 (6.2)	45 (36.9)	reference	
	Yes	525 (93.8)	77 (63.1)	2.39 (1.12–5.1, p=0.024)	2.58 (1.05–6.33, p=0.039)
Severe anaemia	No	552 (98.6)	95 (77.9)	reference	
	Yes	8 (1.4)	27 (22.1)	0.02 (0.01–0.06, p<0.001)	0.03 (0.01–0.07, p<0.001)
Severe acute malnutrition	No	517 (95.9)	103 (87.3)	reference	
	Yes	22 (4.1)	15 (12.7)	1.14 (0.44–2.93, p=0.783)	
Season	Rainy	230 (41.0)	50 (40.9)	reference	
	Dry	330 (59.0)	72 (59.1)	1.48 (0.92–2.38, p=0.109)	1.14 (0.63–2.04, p=0.67)

aOR, adjusted OR; IMCI, Integrated Management of Childhood Illness; PHC, primary healthcare centre.

among those referred compared with those not ($p<0.001$). Of the 15 children who died, those with severe hypoxaemia, 33.3% (2/6) were less likely to be MOHR than 44.4% (4/9) of those without severe hypoxaemia. However, 40.0% (6/15) of those who died were MOHR. Of the three children whose accompanying persons have refused the HCW's referral decision offered and returned to home, one child died and two were lost to follow-up.

DISCUSSION

We sought to describe the frequency, reasons and outcomes of MOHR of severe pneumonia after implementing operational routine PO use into IMCI guidelines at PHC in the four AIRE countries.

In these West African settings, we found that the proportion of severe pneumonia among severe cases aged 2–59 months presenting to IMCI was high,

reaching 38% overall. Our study highlights the high rate of MOHR for severe pneumonia, reaching 82%, which is mostly explained by the HCW's decisions, rather than the family refusals. This occurred mainly because HCW did not adhere to the IMCI severe pneumonia referral guidelines, which recommend systematic referral. Previous studies in children under 5 have similarly reported low adherence to the IMCI referral guidelines, regardless of the referral appropriateness.^{18–21} Reasons for this non-adherence to paediatric IMCI guidelines commonly reported in the literature include the lack of training, lack of diagnostic tools, inadequate assessment, treatment and monitoring, local clinical culture, infrastructure limitations, supply chain challenges, the political context, family poverty, differences in patient-practitioner goals, disease trajectory, patient comorbidities, clarity and applicability of recommendations.^{22–24 24–29} Similarly, a

Table 3 Factors associated with missed opportunities for hospital referral of severe pneumonia cases in Guinea, logistic mixed regression model (N=501).

Variables		Missed opportunities for hospital referral		Univariate	Adjusted analysis
		Yes	No	OR (95% CI, p value)	aOR (95% CI, p value)
Age (months)	(2–23)	217 (48.0)	32 (65.3)	Reference	Reference
	(24–59)	235 (52.0)	17 (34.7)	1.96 (1.05–3.65, p=0.034)	1.7 (0.78–3.68, p=0.181)
Sex	Female	223 (49.3)	25 (51.0)	Reference	Reference
	Male	229 (50.7)	24 (49.0)	1.03 (0.57–1.86, p=0.929)	0.94 (0.45–1.98, p=0.879)
Ability to read or write of the person accompanying the child	No	265 (58.6)	28 (57.1)	Reference	
	Yes	187 (41.4)	21 (42.9)	1.53 (0.73–3.17, p=0.258)	
Income-generating activity of person accompanying the child	No	225 (49.8)	28 (57.1)	Reference	
	Yes	227 (50.2)	21 (42.9)	1.28 (0.7–2.36, p=0.422)	
Travel time home—PHC	>30mn	125 (27.7)	21 (42.9)	Reference	Reference
	≤30mn	327 (72.3)	28 (57.1)	2.18 (1.17–4.07, p=0.014)	1.38 (0.61–3.11, p=0.441)
Consultation delay since the onset of symptoms (days)	>2	281 (63.6)	33 (67.3)	Reference	
	≤2	161 (36.4)	16 (32.7)	1.33 (0.7–2.55, p=0.384)	
SpO ₂ level	<90%	2 (0.4)	4 (8.3)	Reference	Reference
	(90, 93%)	38 (8.4)	6 (12.5)	17.17 (2.29–128.54, p=0.006)	3.31 (0.22–50.95, p=0.39)
	≥94%	410 (91.1)	38 (79.2)	26.33 (4.24–163.68, p<0.001)	4.66 (0.37–58.78, p=0.235)
Severe malaria	No	7 (1.5)	2 (4.1)	Reference	
	Yes	445 (98.5)	47 (95.9)	2.49 (0.5–12.53, p=0.268)	
Severe anaemia	No	445 (98.5)	31 (63.3)	Reference	Reference
	Yes	7 (1.5)	18 (36.7)	0.02 (0.01–0.05, p<0.001)	0.03 (0.01–0.09, p<0.001)
Severe acute malnutrition	No	429 (99.5)	44 (97.8)	Reference	Reference
	Yes	2 (0.5)	1 (2.2)	0.14 (0.01–1.74, p=0.128)	0.43 (0.01–16.9, p=0.656)
Season	Rainy	181 (40.0)	32 (65.3)	Reference	
	Dry	271 (60.0)	17 (34.7)	2.98 (1.59–5.56, p=0.001)	2.15 (1.01–4.57, p=0.047)

PHC, primary healthcare centre.

few previous studies have also reported high frequencies of MOHR for severe cases related to clinicians' decisions in primary care settings: for instance, it was estimated at 40% in rural Burkina Faso in 2012.¹⁹ In Ethiopia, it was 93% for the 1123 sick children aged 2–59 months, and 50% for those requiring urgent referral in 2018–2019.²¹

In our study, the high rate of MOHR could be explained by several factors. First, the lack of appropriation of the IMCI guidelines was related to the lack for IMCI training of HCW in the PHC. Indeed, HCW at the AIRE PHC reported that the IMCI trainings or refreshing training sessions were not regular enough regarding the frequent staff turnover.¹¹ Despite the implementation of standardised guidelines, such as the IMCI guidelines or protocols for managing specific pathologies, children are not properly managed.³⁰ Second, the motivation of HCWs to follow the IMCI guidelines must be considered.

Motivation is a key factor in determining adherence to health guidelines.³¹ To improve the HCW motivation, supervision and follow-up are important to reinforce adherence to guidelines over time. Third, HCWs may have a good level of knowledge, but not apply it because they find it useless due to a lack of support from the health system to further refer and manage severe cases. In a context of high poverty, they do not want to expose households to the high costs of care at district hospital level, as documented in the AIRE study.⁹ These health expenses can be financially devastating for households. In these countries, the referral system may be ineffective due to a lack of ambulances, geographical barriers involving long distances, and security issues, particularly in Burkina Faso, Mali and Niger, as reported elsewhere.¹¹ Our data highlighted that when an HCW decided to refer a child, the vast majority of people accompanying the child agreed to it, with only three families refusing

hospital referral and returning home. Although we did not collect information on the reasons for these refusals, we assume that they were related to poverty, similar to the reasons given by HCWs. Similarly, a study from rural Uganda reported a lack of money, transport problems and responsibilities at home as the main reasons given by parents who refused hospital referral.^{32 33}

Second, our study also provides important findings regarding the HCW decision process when analysing the factors associated with MOHR. HCWs were more likely to refer severe pneumonia cases complicated by severe anaemia or severe hypoxaemia that was diagnosed using PO. In the analysis restricted to cases in Guinea, severe anaemia reduced the odds of not being referred, whereas being sick during the dry season increased them. Thus, except in Guinea, children with $\text{SpO}_2 < 90\%$ and severe anaemia were undoubtedly perceived by HCW as being the sickest and were consistently referred for hospital-level care, which was appropriate. These markers of high severity were also confirmed by the significantly higher mortality at D-14 in the referred group compared with the non-referred group. This result is consistent with other studies,^{34 35} and with our previously reported findings,¹² which reported that PO increased the self-confidence of HCWs in their diagnoses and decision-making regarding the management of the child. This explains why PO was so widely accepted in these decentralised PHCs. However, our data also showed that severe pneumonia with moderate or no hypoxaemia was associated with a higher risk of MOHR. This raises the question of whether HCWs could have been falsely reassured by an SpO_2 measurement $\geq 90\%$. We did not analyse other clinical features of severe illness that are associated with severe hypoxaemia (eg, cyanosis, severe respiratory distress), which may have prompted referral rather than the SpO_2 level, but note from the previous literature that PO detects additional children with hypoxaemia that would have been missed with clinical signs alone, improves confidence and self-efficacy of HCWs.¹⁷ In our study, all the severe pneumonia cases were only clinically diagnosed using IMCI alone, and there is no additional severe cases identified thanks to PO. In comparison to children with severe hypoxaemia, those with moderate or no hypoxaemia were less likely to be referred. We cannot discern from our data whether this reflects increased likelihood of referral for those with severe hypoxaemia, or inversely, whether it reflects false reassurance of HCW. But given that the overall proportion of children referred in this study (18%) was significantly higher than that documented in the baseline assessment survey before implementation of PO (1.5% per PHC),¹¹ we argue that it is unlikely that absence of severe hypoxaemia contributed to MOHR. Therefore, we interpret our findings as an additional benefit of the role of PO at

primary level to improve the detection of the unwell child needing referral. The integration of the PO in IMCI criteria for referral could help HCW in their referral decision. Further analyses from the AIRE project will detail the added value of the use of PO at PHC level. However, our findings raise the important point of carefully planning the integration of PO in IMCI referral guidelines, emphasising that while the presence of severe hypoxaemia should prompt referral, its absence in a child meeting IMCI criteria for severe disease should not delay it. Historically, SpO_2 thresholds $< 90\%$ have been proposed based on when oxygen should be administered, rather than when referral should occur. Recent data suggest that even children with moderate hypoxemia (SpO_2 between 90 and 93%) should be referred, as reported elsewhere from the same project.¹⁰

We also report that MOHR were significantly higher when severe pneumonia was associated with severe malaria, which is worrying. This finding could be explained by HCW's self-perception of their ability to manage severe malaria at the PHC level. Furthermore, national malaria treatment guidelines differ in their approach to referral decisions in cases of severe malaria. In Burkina Faso, severe malaria should be referred in cases of comorbidity with severe anaemia, renal failure or coma, but not in cases of severe pneumonia.¹³ Further guidelines and practices are needed to highlight and mitigate this gap in the management of severe comorbidities involving both pneumonia and malaria.

Finally, our findings also highlight the significant heterogeneity observed in the proportion of severe pneumonia across the four countries, with Guinea bearing the greatest burden, as reported elsewhere. As all HCWs had received the same level of training in terms of pulse oximeter use integrated to IMCI, we attributed this result to differences in national IMCI protocols adapted from the WHO protocol. Guinea's definition of severe pneumonia is more sensitive. In Guinea, chest indrawing, wheezing, nose flapping exhalation or groaning (online supplemental table 1) are signs of severity for the diagnosis of pneumonia, whereas in Mali, Burkina Faso and Niger, these signs classify children as moderate cases. One interpretation would be that Guinea's classification included many more children with mild or moderate disease, that the criteria for diagnosing pneumonia were less stringent, and that HCWs from Guinea paid less attention to SpO_2 findings in their decision-making (hence SpO_2 was not a strong predictor of MOHR). Additionally, Burkina Faso and Niger provide free care policy for all children under 5 years of age.^{36 37} In these countries, it can be assumed that this policy has facilitated an earlier access to care for sick children, resulting in the lowest prevalence of severe pneumonia in these countries.^{38 39} Some sick children also go directly to the hospital, without going to the

PHC first.⁴⁰ Mali and Guinea are countries that apply a policy of partial free healthcare for children under 5,^{41–43} targeting four conditions: malaria, malnutrition, HIV and tuberculosis. In Guinea, this policy may have contributed to an increase in severe cases, including severe pneumonia, by delaying access to primary care.⁹ Geographical factors (relief, rivers), the absence of roads and long travel distances to reach PHC, are additional barriers to access to health facilities in Guinea.¹¹ Additionally, enrolment during the dry season lowered the referral rate at hospital level in Guinea. During this season, infectious diseases such as malaria are less prevalent, which could potentially lower the number of severe pneumonia cases complicated by malaria and anaemia. With fewer complicated severe pneumonia cases, HCWs may feel less urgency to refer children at hospital level.

Our study has some limitations. The IMCI classification was done on the onsite by HCWs; this can lead to information bias. IMCI guidelines are symptom-based guidelines, which are operator dependent, and can lead to inaccurate diagnostic outcomes in the absence of aetiological diagnostic tools. In addition, the adaptation of the WHO standard guidelines in each country presents slightly differences, particularly in Guinea, and more specifically for the IMCI respiratory disease block. These differences in IMCI guideline application are key factors to be considered when comparing the results between the different countries. The referral decision could also have been affected by how the local health system works, the capacities of HCW and by distance between PHC and hospital. We did not include these variables in our analysis because of their low variability between sites. Indeed, the baseline site assessment showed that HCWs at PHCs were all nurses/midwives, and at least one person had received IMCI training at each PHC.¹¹ The AIRE research project was also set up in some selected PHCs not representative of the national level. Our research teams were not present onsite at night, on weekends or during public holidays, due to logistical and also security reasons, particularly in Mali and Burkina Faso. This selection bias may have conducted to underestimate the prevalence of severe pneumonia, assuming the fact that night and weekend attendance could concentrate the most severely ill. Therefore, our study population is probably not representative of all severe pneumonia cases in these West African countries.

Nevertheless, the strengths of our study are standardisation of data collection in these countries, a good data quality with very few missing data overall and the possibility to compare results between countries. We thus, provide original data on the rates of MOHR of severe pneumonia and their associated factors in these West African settings. We also showed that the use of PO has increased HCW confidence in their decision-making for child management and

referral when they diagnosed severe hypoxaemia. Finally, our data are useful for assessing the quality-of-care management of severe pneumonia at the PHC level in these West African settings, and for guiding revision of national policies.

CONCLUSION

The MOHRs for all severe pneumonia in children under 5 were high in these West African primary care settings and were mainly related to the HCW's decision. These MOHRs were less frequent when severe anaemia or severe hypoxaemia diagnosed using routine PO were identified. The full policy implications of integrating routine PO use within IMCI will be further detailed elsewhere. In addition, we demonstrated that severe pneumonia cases without severe hypoxemia or who had severe malaria were less frequently referred, which needs to be further addressed in IMCI guidelines incorporating routine PO use. Our findings raise the question of whether the role of primary care facilities, and the IMCI referral criteria ought to be re-examined. In the meantime, strengthening the referral system, HCW training and supervising HCWs to reinforce their adherence to IMCI guidelines over time is essential to ensure the appropriate referral of all cases of severe pneumonia to improve their survival and the quality of care.

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