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Care management and determinants of day 14 mortality in severely ill children aged under 5 years subsequent to hypoxaemia diagnosed using routine pulse oximetry in primary care: evidence from the AIRE project

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ABSTRACT

Background The Amélioration de l'Identification des détresses Respiratoires de l'Enfant (AIRE) project introduced the routine use of pulse oximetry (PO) into Integrated Management of Childhood Illness (IMCI) consultations within primary health centres (PHCs) in Burkina Faso, Guinea, Mali and Niger. We analysed how severe cases were managed and 14-day mortality by hypoxaemia severity.

Methods All children aged under 5 years attending IMCI consultations integrating PO use at 16 research PHCs and classified as severe cases (severe IMCI cases or severe hypoxemia: SpO_2 <90%) were eligible for referral and enrolled in a 14-day prospective cohort with parental consent. Referral decisions, admissions, access to oxygen therapy and Kaplan-Meier probability of death were compared by hypoxaemia severity. An adjusted mixed-effects Cox regression model with a random effect for PHC estimated adjusted ORs (aORs) and 95% CIs of mortality by day 14.

Results From July 2021 to July 2022, 1998 severe cases were enrolled, including 10.6% aged <2 months; 7.1% had severe hypoxaemia, and 10.5% had moderate hypoxaemia (90%≤oxygen saturation≤93%). By day 14, 625 (31.3%) were referred, 463 (23.2%) hospitalised, and 95 children (4.8%) had died. Referral decisions, hospitalisations and oxygen therapy rates were significantly higher for severe hypoxaemic cases (83.8%, 82.3% and 34.5%, respectively) than for moderate hypoxaemic cases (32.7%, 26.5% and 7.1%, respectively) and cases without hypoxaemia (26.3%, 17.5% and 1.4%, respectively). Similarly, day 14 mortality rates were 26.1%, 7.5% and 2.3%, respectively. The aORs for mortality were severe hypoxaemia (9.34, 95% CI 5.08 to 17.16), moderate hypoxaemia (2.32, 95% CI 1.16 to 4.64), age <2 months (3.68, 95% CI 1.67 to 8.13), severe malaria (2.02, 95% CI 1.03 to 3.97) and living in Niger (4.06, 95% CI 1.41 to 11.67).

Conclusion Regardless of severity, hypoxaemia was common among outpatients screened using PO and meeting criteria for severity. Its presence was associated with mortality risk. Incorporating PO within IMCI prompted care management of severely hypoxaemic cases, but hospital referrals and access to oxygen remain sub-optimal and are crucial levers for reducing under-five mortality.

Study registration number PACTR202206525204526 registered retrospectively on 15 June 2022.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ At the primary care level, hypoxaemia in sick children is more frequently detected than expected, irrespective of underlying cause, and associated with an unacceptably high mortality.

⇒ Because pulse oximetry (PO) screening is not routinely implemented at the primary care level in low- and middle-income countries, hypoxaemia is often underdiagnosed, resulting in inappropriate and delayed care management (hospital referral for oxygen therapy) and high residual mortality.

⇒ Some studies have explored the pathways and patterns of care for severe cases identified at the primary care level using PO routinely integrated within Integrated Management of Childhood Illness (IMCI) guidelines. However, none have been conducted in West Africa.

INTRODUCTION

Since the 1990s, mortality among children aged under 5 years has progressively and steadily declined. The global under-five

WHAT THIS STUDY ADDS

⇒ Hypoxaemia, diagnosed using routine PO, is common, reaching 17.6% of children aged under 5 years with serious respiratory and non-respiratory illnesses in primary care settings in Burkina Faso, Guinea, Mali and Niger.

⇒ Despite hospitalisation and access to oxygen remaining unsatisfactory, all examined care management indicators (referral decisions, actual hospitalisations and oxygen therapy) gradually increased in line with hypoxaemia severity.

⇒ The majority of deaths occurred during hospital transfers or admissions, with a gradual increase in the mortality rate on day 14 as hypoxaemia severity increased.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Implementing the systematic use of PO within IMCI consultations could improve the decision-making of healthcare workers in managing severe cases.

⇒ It is crucial to strengthen the hospital referral system in West Africa to ensure that all severe cases identified in primary care are managed correctly and that those with severe hypoxaemia have access to hospital-level oxygen.

⇒ There is a need to update the IMCI guidelines to introduce the routine use of PO in primary care to improve the diagnosis and care management of children based on risk stratification according to the severity of hypoxaemia.

mortality rate fell from 93 per 1000 live births in 1990 to 38 in 2019.[1] Despite this progress, globally, 5 million children aged under 5 years still died in 2021, with sub-Saharan Africa reporting the highest mortality rates.[2] Africa faces challenges in diagnosing severe illness in children, particularly pneumonia (24%), diarrhoea (15%)[3] and malaria (9%), with malnutrition being involved in as many as half of the deaths in children aged 1–59 months.[4 5] Severe hypoxaemia, defined as low peripheral arterial oxyhaemoglobin saturation (SpO_2) <90% at sea level, is a life-threatening complication of different conditions that requires urgent life-saving oxygen therapy.[6] It is a common sign of severe illness in children with acute respiratory and non-respiratory illnesses, and it substantially increases their risk of death sixfold to sevenfold.[7–9]

Despite several strategies put in place, such as programmes to combat targeted diseases, for example, malaria[10–12] or malnutrition,[13 14] challenges in such settings in accurately diagnosing illness in children still remain. This is particularly true at the primary healthcare centre (PHC) level, the first entry point to the healthcare system for sick children in much of Africa. There, healthcare workers (HCWs) have low diagnostic capacity. In 1996, the WHO developed its Integrated Management of Childhood Illness (IMCI) guidelines, an algorithm-based syndromic approach intended for the triage and management of sick children aged under 5 years within primary care throughout low- and middle-income countries (LMICs).[15–17] This approach aims to distinguish children eligible for outpatient treatment from those with severe illness requiring hospital referral for adequate management. Since the 2000s, the use of malaria rapid diagnostic tests (mRDT) has been introduced into IMCI guidelines,[18] which has improved the diagnosis and treatment of malaria among children seen at the outpatient level.[19]

However, poor clinical identification of severe hypoxaemia at the PHC level still contributes to a high level of residual child mortality in West Africa.[20] Pulse oximetry (PO) is a simple, low-cost and reliable tool for diagnosing hypoxaemia.[6] Therefore, using PO within PHCs for the early detection of severe hypoxaemia in respiratory and non-respiratory cases, with emergency referral for oxygen therapy at the hospital level, could contribute to reducing child mortality. In 2014, the WHO IMCI guidelines recommended the use of PO for managing pneumonia in LMICs.[17] Unfortunately, this is generally not being implemented. PO was introduced for the first time within PHCs in Africa for care management of rural Malawian children with pneumonia.[21 22] By 2020, only a few reports of PO introduction at the PHC level in Africa had been reported.[7 21 23] These studies have demonstrated that compared with IMCI alone, combining IMCI and PO use at the PHC level was associated with an increase in the severe pneumonia cases and in referral rates of severe hypoxaemia. However, there have been no studies reported from West Africa.

The Amélioration de l'Identification des détresses Respiratoires de l'Enfant/Improving Identification of Respiratory Distress in Children (AIRE) project was implemented in 2021–2022 by a consortium (ALIMA, Solthis, Terre des Hommes and INSERM, the French Institute of Health and Medical Research). It aimed to improve the detection of severe hypoxaemia and subsequent management in children aged under 5 years by introducing the routine use of PO within IMCI consultations at the PHC level in four West African countries.[24] The initial AIRE study design was a quasi-experimental design intended to evaluate the impact of PO use before and after its implementation. However, the study was disrupted by the 2020 COVID-19 pandemic. Consequently, a new study design was developed for an operational AIRE research component aimed at investigating the consequences of PO deployment on the diagnosis of children with severe illness at the PHC level, their subsequent care management and mortality by day 14. A cross-sectional study from the project reports on the prevalence of severe cases using IMCI+PO and its correlates at the PHC level.[25] According to standard care guidelines, all severe cases should be hospitalised, and those with severe hypoxaemia should receive immediate oxygen therapy.

The main objective reported in this paper is to characterise the relationship between SpO_2 levels diagnosed using routine PO within PHC and subsequent care management (referral decisions, hospitalisation and access to oxygen therapy) for the nested cohort of severe cases identified. Secondarily, we analysed the determinants of day 14 mortality outcomes.

METHODS

Study sites

The AIRE project took place in Burkina Faso, Guinea, Mali and Niger, covering two health districts per country, with eight district hospitals and 202 interventional PHCs, providing training on the use of the PO and refresher training on IMCI prior to the project launch.[24] PHCs were upgraded to conduct IMCI consultations (basic equipment and medicines), and oxygen extractors were provided at the hospital level, but hospital referral was not supported for sustainability reasons.[24] The operational research component was conducted in 16 research PHCs (four per country). All were managed by nurses with similar training and had beds available for daily monitoring of severe cases.

Study design

All the children aged under 5 years attending IMCI consultations at the 16 research PHCs and classified as severe cases using IMCI and PO (severe IMCI cases or with severe hypoxaemia defined as SpO_2 <90%) were enrolled in a 14-day prospective cohort with parental consent.

Study population and inclusion process

From 14 June 2021 to 20 June 2022, all the neonates (0–59 days) and older children (2–59 months) attending IMCI consultations at the 16 research PHCs were screened by PHC-based HCWs using the national IMCI guidelines to manage them into three groups based on their disease severity: green for simple cases (eligible to be sent home), yellow for moderate cases (observed and treated at PHCs then at home) and red for severe cases requiring urgent hospital transfer. All were eligible for PO use, except children aged 2–59 months classified as simple cases and without cough or breathing difficulties. During the consultation, HCWs classified them using the IMCI classification, then used PO. Children initially classified as green or yellow IMCI cases but with SpO_2 <90% were additional severe cases joining the red group. After the IMCI consultation, all children eligible for PO use were enrolled with parental written informed consent in a cross-sectional study reported elsewhere.[25] Severe cases, as defined above, were followed up over 14 days. Children were not included on nights, weekends and public holidays because research teams were not on site.

Clinical procedures and definitions

Procedures for the IMCI consultations and for carrying out the mRDT were not modified by the AIRE project. PO (Acare Technology, Taiwan; AH-M1 S0002033) was used after IMCI classification to measure SpO_2 and heart rate. Standard operating procedures recommend waiting for the wave stability of the PO tool, indicating the ideal timing for reliable reading and repeating pathological measurements. Severe hypoxaemia was defined as SpO_2 <90%, moderate hypoxaemia as SpO_2 between 90% and 93%, and hypoxaemia as SpO_2 ≤93%. A normal heart rate was defined as a heart rate between 100 and 160 beats per minute for children aged 0–1 years, 90–150 beats per minute for children aged 1–3 years and 80–140 beats per minute for those aged 3–5 years.[26] There were no guidelines for linking SpO_2 to heart rate. Respiratory rate was measured according to IMCI guidelines. Fast breathing was defined as a respiratory rate ≥60 breaths per minute for neonates aged 0–59 days, ≥50 breaths per minute for children aged 2–11 months and ≥40 breaths per minute for those aged 12–59 months.[17] We defined children as 'respiratory cases' when the HCW identified at least one respiratory symptom such as coughing, rapid breathing and stridor. All other vital parameters, body temperature, weight and height, were measured in the triage room or at the beginning of IMCI consultations. This was made using a digital thermometer, child scale and stadiometer. Axillary temperature was used, corrected by adding 0.5°C to the reading temperature. Fever was defined as a temperature ≥38°C.[26] Severe IMCI case definitions used by each country based on national IMCI protocols were broadly similar, except for severe pneumonia in children aged 2–59 months. Severe pneumonia was defined by at least one general danger sign (inability to eat or drink, vomiting of anything eaten, convulsions, lethargy or unconsciousness) or stridor in a calm child, or chest indrawing or wheezing or nose flapping exhalation or groaning in Guinea, whereas in other countries (Burkina Faso, Mali and Niger), it was only defined by at least one general danger sign or stridor in a calm child.

Data collection

A separate research team, made up of nurses, was dedicated to research data collection at the PHC and hospital levels. They extracted data from paper consultation registers where IMCI was paper based (Guinea, Niger and two PHCs in Mali) and from electronic IMCI databases elsewhere. At the hospital, data were extracted from the children's medical records, and health outcome data were collected at day 14 via home visits or telephone calls.

Individual data collection has been carried out via an electronic case report form (REDCap software). These included sociodemographic data, clinical data about IMCI consultation (SpO_2 level, main IMCI symptom-based diagnosis blocks, treatments and decision of care management), place of case management (PHC, hospital or none of those), delay of referral, International Classification of Diseases 10th revision (ICD-10) for the main diagnosis retained at hospital, patterns of care (oxygen therapy) and vital status outcome at day 14.

Data analysis

We described the inclusion process of children aged under 5 years and characteristics for all severe cases enrolled, stratified by countries (age, sex, number of people in household, education level of household manager, income-generating activity of child accompanying person and distance from home to PHC). Then,

we described their clinical characteristics according to age groups.

For all severe cases diagnosed at PHCs, we compared referral decisions, hospitalisation, oxygen therapy and day-14 mortality rates (with 95% CIs), categorised by hypoxaemia severity (severe, moderate and none) to better characterise their relationship. Quantitative variables were described using means and SD. Categorical data were described with proportions with their 95% CI and were compared using Pearson χ^2 or Fisher's exact tests.

We estimated the day-14 Kaplan-Meier probability of death by hypoxaemia severity. We analysed determinants of death, using an adjusted mixed-effects Cox regression model with a random effect for PHC. An explanatory model was computed with hypoxaemia severity as the main explanatory variable, alongside other variables known to be associated with child mortality and all those clinically relevant, initially explored in a univariate analysis: low income-generating activity, living more than 30 min' travel from a PHC, the child's age category, delay of consultation, an abnormal heart rate and country. Frequent IMCI diagnoses (pneumonia, malaria and acute malnutrition) were included to assess their individual effects. All variables were included in the full adjusted model, regardless of univariate p values. A two-tailed p value of <0.05 was considered statistically significant. R software V.4.0.5 was used for analyses.

Patient and public involvement

Patient representatives (caregivers) were not involved in the analysis plan or result interpretation. Patient representatives did not contribute to the writing or editing of this manuscript.

RESULTS

From 14 June 2021 to 20 June 2022, 39,360 children aged under 5 years attended IMCI consultations in the 16 research PHCs (figure 1); 7,760 (19.7%) were not eligible for PO use according to the criteria. Among the 31,600 (80.3%) children aged under 5 years eligible for PO use, 15,670 (49.6%) seeking services at night or over the weekends were not offered enrolment into the study. Among the 15,930 remaining who were offered the study, 33 (0.2%) families refused, and 15,897 (99.7%) were included in the study with parental consent, of whom 61 (0.4%) were excluded for missing IMCI classification or wrong inclusion. Overall, 15 836 (99.6%) were analysed, of whom 13,838 (87.4%) were classified as non-severe cases and 1,998 (12.6%) as severe cases using IMCI+PO. All the latest were followed up until day 14, except 27 (1.4%, 9 in Mali and 18 in Niger), who were lost to follow-up.

Baseline characteristics of severe cases by country and age groups

Sociodemographic characteristics of the 1,998 severe cases at PHCs (table 1) were similar to those of the 15 836 children included in the study. Overall, 10.6% were aged under 2 months, ranging from 4.5% in Guinea to 19% in Burkina Faso. Female children represented 48% of the sample. The median number of people living in the same child household was 5. The mothers were dead in 0.6% of cases. Children were accompanied by their father or

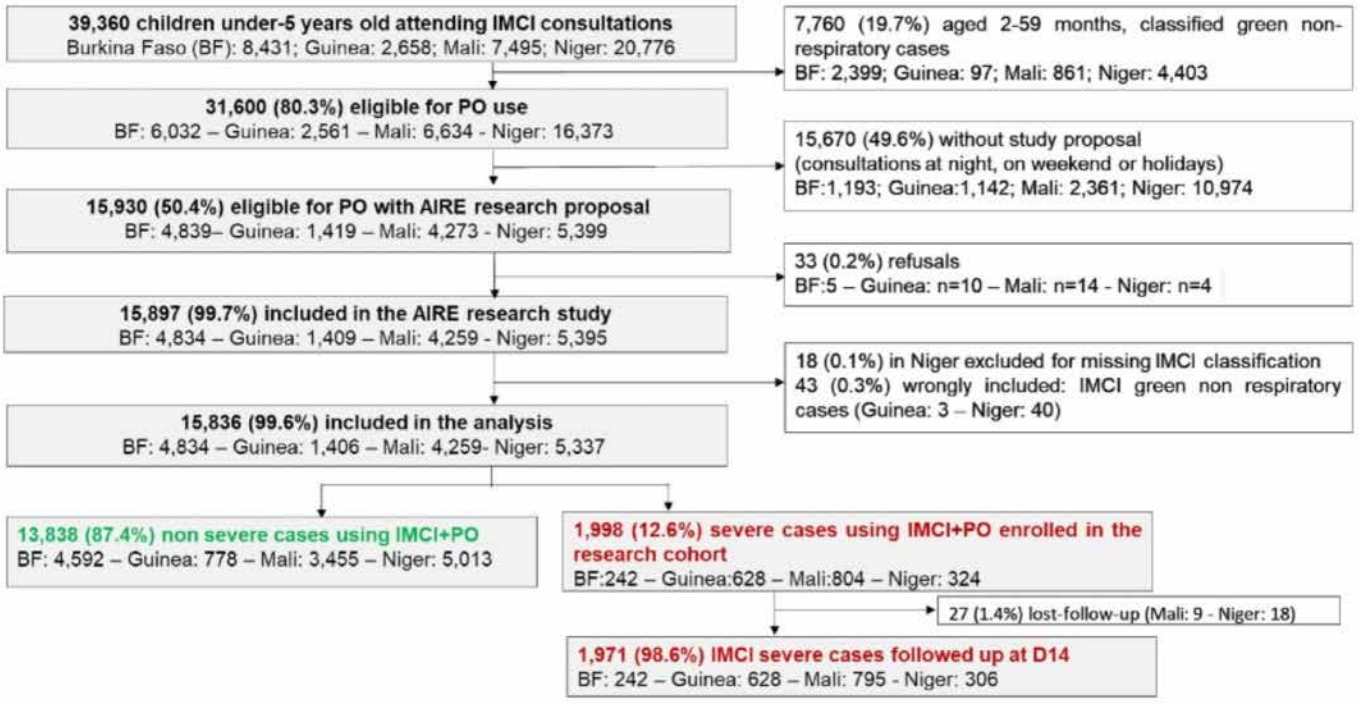

Figure 1 Flowchart of the inclusion process in the AIRE research project. June 2021–June 2022. AIRE, Amélioration de l'Identification des détresses Respiratoires de l'Enfant; IMCI, Integrated Management of Childhood Illness; PO, pulse oximetry.

Table 1 Sociodemographic and access-to-care characteristics of the IMCI severe cases included at PHC level in the AIRE research sites, 2021 June–2022 June (N=1998)

Variables		Burkina Faso N=242	Guinea N=628	Mali N=804	Niger N=324	Total N=1,998	P value
Age groups in months	<2 months, n (%)	46 (19)	28 (4.5)	97 (12.1)	41 (12.7)	212 (10.6)	<0001
	(2–23 months), n (%)	71 (29.3)	301 (47.9)	279 (34.7)	195 (60.2)	846 (42.3)	
	(24–59 months), n (%)	125 (51.7)	299 (47.6)	428 (53.2)	88 (27.2)	940 (47.1)	
Sex	Female, n (%)	105 (43.4)	311 (49.5)	389 (48.4)	155 (47.8)	960 (48)	0.441
Number of people living in household	Median (Q1; Q3)	5 (4; 8)	5 (4; 6)	9 (3; 16)	6 (4; 8)	5 (4; 9)	<0.001*
Deceased mother	Yes n (%)	2 (0.8)	1 (0.2)	4 (0.5)	5 (1.5)	12 (0.6)	0.06
	No, n (%)	240 (99.2)	627 (99.8)	800 (99.5)	319 (98.5)	1,986 (99)	
Education level of the household responsible	Never attended school, n (%)	205 (84.7)	303 (48.2)	488 (60.7)	219 (67.6)	1,215 (60.8)	<0.001
	Primary school, n (%)	22 (9.1)	135 (21.5)	239 (29.7)	54 (16.7)	450 (22.5)	
	Secondary school, n (%)	15 (6.2)	153 (24.4)	73 (9.1)	46 (14.2)	287 (14.4)	
	University level, n (%)	0 (0)	37 (5.9)	4 (0.5)	5 (1.5)	46 (2.3)	
Accompanying person of the child to the IMCI consultation	Mother, n (%)	234 (96.7)	602 (95.9)	791 (98.4)	310 (95.7)	1,937 (96.9)	<0.001
	Father, n (%)	0 (0)	4 (0.6)	1 (0.1)	7 (2.2)	12 (0.6)	
	Others, n (%)	8 (3.3)	22 (3.5)	12 (1.5)	7 (2.2)	49 (2.5)	
Income-generating activity of the accompanying	Yes, n (%)	40 (16.5)	318 (50.6)	168 (20.9)	36 (11.1)	562 (28.1)	<0.001
	No, n (%)	202 (83.5)	310 (49.4)	636 (79.1)	288 (88.9)	1,436 (71.9)	
Family situation of the accompanying person	Currently married/coupled, n (%)	240 (99.2)	609 (97)	792 (98.5)	321 (99.1)	1,962 (98.2)	0.178
	Divorced, widowed, single, no answer, n (%)	2 (0.8)	19 (3)	12 (1.5)	3 (0.9)	36 (1.8)	
Consultation delay since the onset of symptoms (days)	Median (Q1; Q3)	2 (1; 2.25)	3 (2; 4)	2 (1; 3)	3 (2; 5)	2 (2; 4)	<0.001*
	≤2 n (%)	156 (64.5)	239 (38.1)	463 (57.6)	139 (42.9)	997 (49.9)	<0.001
	>2 n (%)	52 (21.5)	387 (61.6)	320 (39.8)	171 (52.8)	930 (46.5)	
	Missing, n (%)	34 (14.1)	2 (0.3)	21 (2.6)	14 (4.3)	71 (3.6)	
Travel delay home—PHC	Less than or equal to 30 min, n (%)	216 (89.3)	442 (70.4)	572 (71.1)	218 (67.3)	1,448 (72.5)	<0.001
	More than 30 min, n (%)	26 (10.7)	186 (29.6)	232 (28.9)	106 (32.7)	550 (27.5)	
Means to get to the PHC	Foot/cart/bike, n (%)	152 (62.8)	182 (29)	106 (13.1)	192 (59.2)	632 (31.6)	<0.001
	Car/motorcycle/bus: public or private transport, n (%)	92 (38.0)	403 (64.1)	706 (87.8)	133 (41.1)	1,334 (66.8)	

*Kruskal-Wallis Test.
AIRE, Amélioration de l'Identification des détresses Respiratoires de l'Enfant; IMCI, Integrated Management of Childhood Illness; PHC, primary healthcare centre.

mother in 97.5%. For 60.8%, the head of the household had received no school education (ranging from 48.2% in Guinea to 84.7% in Burkina Faso); 71.9% of child's accompanying persons had no income-generating activity; 72.5% of cases lived within a 30-min travel distance of the PHC attended. The median delay from the onset of the first symptoms to the IMCI consultation ranged between 2 days (Burkina Faso and Mali) and 3 days elsewhere.

Of the 1,998 severe cases at PHCs, 1% had no SpO_2 measurement. Hypoxaemia (SpO_2 ≤93%) was common, affecting 17.6% of cases. Severe hypoxaemia was diagnosed in 142 children (7.1%), impacting both respiratory (9.9%; 107/1,075) and non-respiratory (3.7%; 33/897) cases. Moderate hypoxaemia was present in 211 cases (10.5%). Of the severe hypoxaemic children, 27 (19%) were diagnosed using only PO, while the remaining also had IMCI severity. Among the 212 neonates (10.6% of the sample), 34.9% had hypoxaemia (15.1% severe and 19.8% moderate), while among the 1,786 children aged 2–59 months, hypoxaemia was estimated at 15.7% (6.2% severe and 9.5% moderate) (online supplemental table).

Of the 212 neonates, 7.1% had reported pharmaceutical medication before the IMCI consultation. Main reasons for consulting reported by child accompanying persons were fever (68%), cough or breathing difficulties

(42.5%), vomiting (9.4%) and diarrhoea (2.8%). Fever was clinically measured in 38.7%, 24% had tachycardia, and 42.9% had respiratory signs. Their most common IMCI diagnosis was 'very serious illness or severe bacterial infection' (78.8%) (online supplemental table).

Of the 1,786 children aged 2–59 months, 17.5% had reported pharmaceutical medication before the IMCI consultation. Main reasons for consultation reported by accompanying persons were fever (91.4%), cough or breathing difficulties (50.1%), vomiting (35.6%) and diarrhoea (20.5%); 57.7% had a clinically measured fever, 39.8% had tachycardia, and 55.1% had respiratory signs. Several diagnoses could co-exist for the same child. The most common IMCI diagnoses were 'very severe febrile illness or severe malaria' (78.4%), followed by 'severe pneumonia or very serious illness' (38.2%).

Primary outcome: care management

After the IMCI consultation, 31.3% (625/1,998) of severe cases were referred, regardless of their SpO_2 level, and 23.2% (463/1,998) were admitted. Referral rates for severe cases differed significantly between countries (p<0.001): in Burkina Faso, 73.1% were managed at the PHC, while 26.9% were transferred to the hospital. The respective proportions were 88.9% and 10.6% in Guinea, 84.8% and 14.2% in Mali, and 25.3% and 67.0% in Niger. Thus, except in Niger, most severe cases were managed at the PHC level (75.0%), while a small proportion (1.8%) refused care and returned home without receiving any treatment (online supplemental figure 1).

All care indicators, including proportions of referrals made by HCWs, hospitalisations and oxygen therapy, showed a gradual improvement in the management of severe hypoxaemia compared with moderate hypoxaemia and absent hypoxaemia. Of the 142 children with severe hypoxaemia, 83.8% were referred to hospital, 82.3% were admitted, and 34.5% received oxygen therapy. These figures were significantly higher than those observed for the 211 cases of moderate hypoxaemia (32.7%, 26.5% and 7.1%, respectively) and for the 1,624 cases without hypoxaemia (26.3%, 17.3% and

Table 2 Care management of severe cases identified at PHC level in AIRE research sites, and day-14 mortality according to hypoxaemia severity measured at PHC, globally and by age groups, June 2021–June 2022 (n=1,998)

	Referred to hospital		Admitted to hospital		Oxygen therapy		Mortality at day 14	
	#	%	#	% (95% CI)	#	%	#	% (95% CI)
Global, n=1998 (100%)								
Severe hypoxaemia: 142 (7.1%)	119	83.8 (76.7–89.4)	117	82.3 (75.1 to 88.3)	49	34.5 (26.7–42.9)	37	26 (19.1 to 34.1)
Moderate hypoxaemia: 211 (10.6%)	69	32.7 (26.4–39.5)	56	26.5 (20.7 to 33)	15	7.1 (4–11.5)	16	7.5 (4.4 12)
No hypoxaemia: 1624 (81.3%)	426	26.3 (24.1–28.4)	281	17.3 (15.5 to 19.2)	23	1.4 (0.9–2.1)	38	2.3 (1.7 3.2)
Children without SpO_2 measurement: 21 (1)	11	52.4 (29.8–74.3)	9	42.9 (21.8 to 66)	1	4.8 (0.1–23.8)	4	19 (5.4 to 41.9)
Neonates, n=212 (10.6%)								
Severe hypoxaemia: 32 (15.1%)	27	84.4 (67.2–94.7)	27	84.4 (67.2 to 94.7)	15	46.9 (29.1–65.3)	15	46.8 (29.1 to 65.3)
Moderate hypoxaemia: 42 (19.8%)	18	42.9 (27.7–59)	16	38.1 (23.6 to 54.4)	5	11.9 (4–25.6)	6	14.3 (5.4 to 28.5)
No hypoxaemia: 131 (61.8%)	50	38.2 (29.8–47.1)	30	22.9 (16.0 to 31.1)	6	4.6 (1.7–9.7)	8	6.1 (2.7 to 11.7)
Neonates without SpO_2 measurement: 7 (3.3)	5	71.4 (29–96.3)	5	71.4 (29 to 96.3)	0	0.0 (0–41)	3	42.9 (9.9 to 81.6)
Children (2–59), n=1786 (89.4%)								
Severe hypoxaemi: :110 (6.2%)	92	83.6 (75.4–90)	90	81.8 (73.3 to 88.5)	34	30.9 (22.4–40.4)	22	20.0 (13 to 28.7)
Moderate hypoxaemia: 169 (9.5%)	51	30.2 (23.4–37.7)	40	23.7 (17.5 to 30.8)	10	5.9 (2.9–10.6)	10	5.9 (2.9 to 10.6)
No hypoxaemia: 1493 (83.5%)	376	25.2 (23–27.5)	251	16.8 (14.9 to 18.8)	17	1.1 (0.7–1.8)	30	2 (1.4 to 2.9)
Children without SpO_2 measurement: 14 (0.8)	6	42.9 (17.7–71.1)	4	28.6 (8.4 to 58.1)	1	7.1 (0.2–33.9)	1	7.1 (0.2 to 33.9)

AIRE, Amélioration de l'Identification des détresses Respiratoires de l'Enfant; PHC, Primary Healthcare Centre; SpO_2, oxygen saturation.

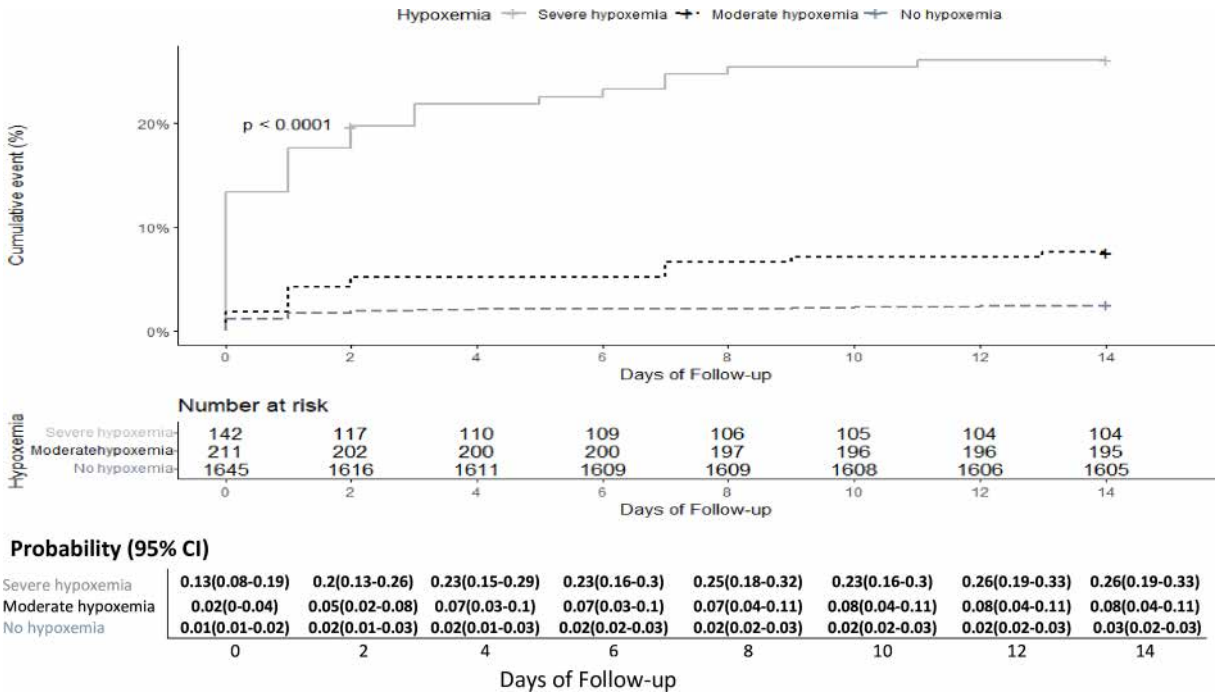

Figure 2 Kaplan Meier probability of death of severe cases according to the severity of hypoxaemia (Log-Rank test); AIRE research project, June 2021–June 2022 (n=1,998). AIRE, Amélioration de l'Identification des détresses Respiratoires de l'Enfant.

1.4%, respectively) (table 2). Subgroup analyses by age group revealed comparable trends.

Secondary outcome: day-14 mortality

Of the 1,998 severe cases, 1,971 (98.6%) were followed up until day 14. Of these, 95 died (16 in Burkina Faso, 6 in Guinea, 42 in Mali and 31 in Niger), yielding an estimated overall mortality rate of 4.8% (95% CI 3.9% to 5.8%), with significant heterogeneity between countries: 6.6% (95% CI 3.8% to 10.5%) in Burkina Faso, 1% (95% CI 0.4% to 2.1%) in Guinea, 5.2% (95% CI 3.8% to 7%) in Mali and 9.6% (95% CI 6.6% to 13.3%) in Niger. Overall, 34% of deaths occurred among neonates, with varying distributions between countries: 62.5% (10/16) in Burkina Faso, 33.3% (2/6) in Guinea, 31% (13/42) in Mali and 22.6% (7/31) in Niger.

The day-14 mortality rate was highest for severe hypoxaemic cases, reaching 46.8% for neonates and 20% for children aged 2–59 months (table 2). Overall, hypoxaemia was strongly associated with the Kaplan-Meier probability of dying by day 14, with an increasing gradient according to severity (Log-Rank test; p<0.0001): 26% (95% CI 19% to 33%), 8% (95% CI 4% to 11%) and 3% (95% CI 2% to 3%) for severe hypoxaemia, moderate hypoxaemia and no hypoxaemia, respectively (figure 2). Death occurred within a median of 1 day for severe hypoxaemic cases. The same trends were observed when stratifying by age group.

The Kaplan-Meier probability of dying by day 14 according to the place of case management also varied significantly (Log-Rank test; p<0.0001). It was significantly higher among severe cases who returned home without care after the IMCI consultation (22%; 95% CI 7% to 35%) and among those who were referred to hospital (15%; 95% CI 11% to 18%), compared with those treated at PHC (1.3%; 95% CI 0.8% to 2%) (online supplemental figures 2 and 3). The probability of death was 17% on the day of the initial consultation for those who returned home. Except in Guinea, where 83.3% of deaths occurred at the PHC level, in other AIRE countries, most deaths occurred during hospital transfer or upon arrival at the hospital, with proportions ranging from 64.3% in Mali to 90.3% in Niger. The median delay between the IMCI consultation and death for children referred to the hospital ranged from 2.2 days in Niger to 9.5 days in Guinea. For those managed at the PHC level, this ranged from 0.7 days in Guinea to 10.7 days in Burkina Faso.

Using the ICD-10 codes provided by HCWs, the main cause of death among children who died at the PHC level was malaria (52.6%). Among those who died in hospital, malaria was the primary diagnosis (33.8%), followed by acute respiratory infections (16.2%). In Burkina Faso and Guinea, respiratory cases accounted for 31.2% and 33.3% of deaths, respectively, whereas this figure was estimated at 57.1% in Mali and 61.2% in Niger.

The mixed-effects Cox regression model identified the following factors as being independently associated with an increased risk of day-14 mortality for severe cases diagnosed at the PHC level (table 3): moderate hypoxaemia (aHR 2.32, 95% CI 1.16 to 4.64), severe hypoxaemia (aHR 9.34, 95% CI 5.08 to 17.16), young age under 2 months (aHR 3.68, 95% CI 1.67 to 8.13), severe malaria (aHR 2.02, 95% CI 1.03 to 3.97) and the country 'Niger' (aHR 4.06, 95% CI 1.41 to 11.67).

Table 3 Explanatory factors of day-14 mortality among the IMCI severe cases identified at PHC level using a mixed-effect Cox regression adjusted model with a random effect on PHC (n=91 deaths/1,785 observations without missing data); AIRE research project, Burkina Faso, Guinea, Mali and Niger, June 2021–June 2022

				Univariate	Full adjusted
Label	Levels	Alive	Died	HR (95% CI, P value)	Adjusted HR (95% CI)
Age (months)	(24–59)	915 (48.1)	25 (26.3)	1	1
	<2	180 (9.5)	32 (33.7)	5.15 (3 to 8.85, <0.001)	3.68 (1.67 to 8.13)
	(2–23)	808 (42.5)	38 (40.0)	1.68 (1 to 2.82, 0.048)	1.45 (0.81 to 2.61)
Sex	Female	915 (48.1)	45 (47.4)	1	1
	Male	988 (51.9)	50 (52.6)	1.00 (0.67 to 1.5, 0.99)	1.03 (0.64 to 1.64)
Ability to read or write of the accompanying	Yes	459 (24.1)	20 (21.1)	1	1
	No	1,444 (75.9)	75 (78.9)	0.92 (0.55 to 1.55, 0.76)	0.75 (0.42 to 1.32)
Income-generating activity of the accompanying	Yes	545 (28.6)	17 (17.9)	1	1
	No	1,358 (71.4)	78 (82.1)	0.68 (0.39 to 1.18, 0.17)	1.15 (0.64 to 2.06)
Consultation delay since the onset of symptoms (days)	Mean (SD)	4.68 (27.2)	2.98 (3.4)	0.97 (0.92 to 1.03, 0.35)	0.97 (0.91 to 1.04)
Travel delay home to PHC	≤30 mn	1,387 (72.9)	61 (64.2)	1	1
	>30 mn	516 (27.1)	34 (35.8)	1.71 (1.04 to 2.82, 0.034)	1.18 (0.72 to 1.93)
Hypoxaemia level	No hypoxaemia SpO_2 >94%	1,586 (84.1)	38 (41.8)	1	1
	Moderate hypoxaemia (90.93%)	195 (10.3)	16 (17.6)	3.32 (1.84 to 5.98, <0.001)	2.32 (1.16 to 4.64)
	Severe hypoxemia <90%	105 (5.6)	37 (40.7)	10.98 (6.83 to 17.65, <0.001)	9.34 (5.08 to 17.16)
Heart rate according to age	Normal	1,387 (78.5)	62 (75.6)	1	1
	Bradycardia	52 (2.9)	12 (14.6)	5.72 (3.03 to 10.81, <0.001)	1.79 (0.88 to 3.65)
	Tachycardia	329 (18.6)	8 (9.8)	0.87 (0.53 to 1.43, 0.58)	0.91 (0.54 to 1.54)
Severe pneumonia	No	1,236 (65)	80 (84.2)	1	1
	Yes	667 (35)	15 (15.8)	0.56 (0.3 to 1.04, 0.067)	0.66 (0.34 to 1.31)
Severe malaria	No	1,119 (58.8)	58 (61.1)	1	1
	Yes	784 (41.2)	37 (38.9)	0.60 (0.37 to 0.97, 0.036)	2.02 (1.03 to 3.97)
Severe acute malnutrition	No	1,726 (90.7)	81 (85.3)	1	1
	Yes	177 (9.3)	14 (14.7)	1.15 (0.63 to 2.1, 0.66)	1.16 (0.53 to 2.58)
Country	Guinea	622 (32.7)	6 (6.3)	1	1
	Burkina Faso	226 (11.9)	16 (16.8)	6.91 (2.7 to 17.67, <0.001)	2.40 (0.73 to 7.87)
	Mali	762 (40.0)	42 (44.2)	5.60 (2.38 to 13.17, <0.001)	1.82 (0.62 to 5.3)
	Niger	293 (15.4)	31 (32.6)	10.54 (4.39 to 25.27, <0.001)	4.06 (1.41 to 11.67)

AIRE, Amélioration de l'Identification des détresses Respiratoires de l'Enfant; CI, Confidence Interval; HR, Hazard Ratio; IMCI, Integrated Management of Childhood Illness; PHC, primary healthcare centre; SpO_2, oxygen saturation.

DISCUSSION

This cohort provides short-term follow-up data on the care management and mortality outcomes by SpO_2 level in severely ill children aged under 5 years, diagnosed with IMCI integrated with routine use of

PO in West African PHCs. Some specific findings are as follows.

First, hypoxaemia was common among severely ill children in primary care, affecting 17.6% of cases (7.1% severe and 10.5% moderate) and impacting both respiratory and non-respiratory cases. Similarly, high rates of severe hypoxaemia were reported among severe cases in Papua New Guinea at hospital admission, reaching 73% and 32% of those with and without acute lower respiratory illness, respectively.[27] Severe hypoxaemia was also significantly higher among the youngest children compared with older ones, which is consistent with findings reported among hospitalised children in Nigeria: 22.2% for neonates versus 10.2% for older children,[8] and in a study conducted in Malawi among 27,586 children aged under 5 years with clinical pneumonia (11.4% for children aged 0–5 months, 8.4% for children aged 6–23 months and 4.7% for children aged 24–59 months).[28]

Second, despite WHO IMCI recommendations to urgently refer severe cases, we observed an overall very low hospital referral rate (31.3%), including for hypoxaemic children, except in Niger, where the referral rate was 67%. All the PHCs were similar in terms of HCW qualifications and had day-hospitalisation facilities.[29] Several factors may explain the higher hospital referral rates in Niger than in other countries: the proximity of PHCs to the district hospital in the Niamey IV health district and to the paediatric hospital in Dosso. In addition, most districts in Niger implement a strategy to collect 'extra cents' (100 CFA francs) per consultation to finance fuel for referral ambulances.[30 31] In Guinea, referral to the hospital was complicated by long distances between PHCs and the district hospital, difficult road conditions and a lack of adequate transport.[29] This low overall compliance with hospital referrals is consistent with reports from other contexts. In Ethiopia, 37% of young infants and 50% of children aged 2–59 months were referred for treatment.[32] In Papua New Guinea, 60% of those referred were hospitalised[33]; in Uganda, 44% (12/27) of severe hypoxaemic cases were referred.[7] In Malawi, none of the severe cases were referred.[21] More recently, in Nigeria, of the 52 severe hypoxaemic children identified using PO at PHCs, 21% were referred and 12% were admitted.[23] Several contextual factors could explain these low referral rates. The main reason is poverty, as most families cannot afford the referral fees. Hospital referral is indeed expensive[34] and also entails the cessation of income-generating activities, loss of resources and disruption to the family unit, often leaving other children at home. Graham *et al* reported similar findings in Uganda, where 16% (8/51) of families were unable to pay.[7] When faced with their child's poor clinical presentation, parents may doubt the severity of the disease and refuse the HCW's referral decision, considering it unnecessary[7 35] or on the basis of their previous experience.[36] In addition, in AIRE countries specifically, some national disease management programmes for conditions such as malaria or malnutrition recommend treating severe cases at the PHC level (unpublished national health protocols). Religious leaders such as marabouts or traditional healers might be a factor hindering access to care, as reported in a study from Mozambique; this study found that children who were taken to a traditional healer had significantly longer delays in seeking care.[37] A study in rural Mali found that traditional healers were a barrier to seeking care for 8% of children aged under 5 years.[38] Finally, HCWs sometimes did not refer severe cases due to non-functional ambulances,[39] the road insecurity, or geographical barriers.[7 37 40–42]

Third, access to oxygen therapy remained insufficient, as recently reported by the Lancet Global Health Commission on Oxygen.[43] In our study, only 34.5% of severe hypoxaemia cases identified at the PHC level received oxygen, with mortality in this group exceeding 26%—likely indicating late referral. In Malawi, 22.5% of severely hypoxaemic children identified at the PHC level received oxygen[44]; it was 12% in Uganda.[7] These low rates of oxygen therapy among children who need it reveal the difficulties in accessing oxygen. This may be due to a lack of supply,[45] the unavailability of oxygen or even supply difficulties at the hospital level, but also due to the lack of affordability for patients. In 2021, in Nigeria, only 59% of the health facilities had a functional oxygen supply on the day of inspection, and oxygen services were expensive in hospitals and private facilities.[46] Finally, this lack of access may be related to a lack of knowledge regarding the use of oxygen among HCWs, who may have received inadequate training,[47] and to a lack of ambulances or efficient hospital referral systems. Our results highlighted the major issue of access to oxygen in most African countries, a problem that was exacerbated by the COVID-19 pandemic.[48 49] Several initiatives are being set up in conjunction with the Africa Centres for Diseases Control and Prevention and other stakeholders to make oxygen available sustainably, including at peripheral levels.[43 50 51] Graham *et al* have shown that large-scale improvements in hospital oxygen services could have the potential to improve clinical outcomes.[52] Interestingly, we did not anticipate observing severe cases without hypoxaemia receiving oxygen therapy, yet this occurred in 1.4% of cases. This may be due to a lack of knowledge among HCWs regarding the indications for oxygen therapy, or it may be because all cases were severely ill and at risk of developing secondary hypoxaemia due to a deterioration in their clinical status.

Fourth, our study found that the risk of day-14 mortality was high and strongly predicted by the severity of hypoxaemia for all children with SpO_2

≤93%. These deaths occurred early, and the cases ultimately referred to the hospital were very serious, suggesting late referral to the hospital. Day-14 mortality was also significantly higher for those referred to the hospital and for those who returned home without care, compared with those managed at the PHC level. Although the hospital referral rate in Niger was high, we noted that living in Niger was a risk factor for child mortality at day 14 compared with children living in other countries. This could be due to the quality of hospital-level care (training of HCWs and lack of equipment). Further research is needed to confirm this in order to address it more effectively. Several barriers to accessing care could explain the high day-14 mortality observed, including delayed consultations,[40 53–55] delayed hospital transfers, difficult transfer conditions[39] and inadequate treatment during transfer, as many deaths occur during transfer to the hospital. According to our baseline assessment data from the AIRE project,[29] only 16.3% of all PHCs had a functional ambulance in 2020, and only two of these had oxygen on board. Both severe and moderate hypoxaemia were independent predictors of death among severely ill children in our study, which is consistent with previous studies involving hospitalised children. In 2019, hypoxemic newborns and children had a sixfold and sevenfold greater risk of death, respectively, compared with non-hypoxaemic children in Nigerian hospitals.[8] A systematic review conducted in 2023 demonstrated that severe hypoxaemia presented a 3.4-fold greater risk of death in hospitalised children with pneumonia and chest indrawing.[56] A 2016 study of Mozambican children aged under 5 years admitted to hospital with severe pneumonia showed that hypoxaemia <90% was associated with a 3.2-fold greater risk of death.[57] This finding was also consistent with a 2023 systematic review of risk factors for death in cases with pneumonia.[58]

Fifth, our study highlighted that integrating the routine use of PO within IMCI guidelines at the PHC level and allowing for the diagnosis of hypoxaemia has the potential to improve case management for the most severely hypoxic patients, who are at the greatest risk of death. According to the baseline site assessment conducted before the introduction of PO, annual referral rates of severe cases, regardless of SpO_2 level, were much lower in the 2019 registries, although probably underestimated. These rates were 1% in Burkina Faso, 1.6% in Guinea, 2.2% in Mali and 4.4% in Niger, compared with an overall referral rate of 31.3% decided by HCWs after the implementation of PO.[29] Referral decisions, admissions and oxygen therapy rates were all significantly higher for severely hypoxaemic children than for those with moderate or no hypoxaemia. Their significantly higher day-14 mortality rate justified retrospectively the decisions of HCW to trigger their management. Despite the lack of a comparison group of children managed without PO, the observed gradient in the relationship between hypoxaemia severity and improved care management suggests the usefulness of PO use within IMCI. Similarly, McCollum *et al* reported in 2016 that Malawian outpatients with severe hypoxaemia were significantly more than twice as likely to be referred as those with SpO_2 ≥90%, 84.3% (385/457) versus 41.5% (871/2,099).[21] In an Ethiopian cluster-randomised trial, diagnosing hypoxaemia using PO increased the referral rate for severe cases.[59] We assume that PO improves the HCWs' decision-making in case management by providing them with self-confidence and assurance in their diagnosis, as reported in our study[58] and elsewhere.[6061–63]

Numerous barriers that families encounter when transferring their child to a hospital (security issues, poor road conditions, long distances between PHCs and hospitals and poverty), combined with the unavailability of oxygen at the PHC level, increase the risk of death for ill children with hypoxaemia. In light of this, our results strongly suggest considering a SpO_2 level higher than 90% at the PHC level for indicating hospital referrals to provide earlier access to oxygen for hypoxaemic children before they reach the threshold of 90%, indicating urgent oxygen therapy,[21 64] as recently reported by Graham *et al* in 2024.[65] However, this could also overwhelm the health system with referrals, thereby increasing the workload of HCWs in hospitals and healthcare costs for families.[21 66] This issue must therefore be evaluated in further comparative research.

Our study has some limitations. The main limitation is the lack of a comparison group of children managed without PO, so we cannot deduce a causal effect of PO in prompting care management.[24] A quasi-experimental before-and-after study was chosen to compare the processes and outcomes before and after the implementation of PO integration into IMCI. Unfortunately, the onset of the global pandemic made this approach obsolete. This was a missed opportunity to provide robust research evidence from a comparative study design to strengthen the WHO and IMCI guidelines towards mandatory recommendations for pulse oximetry use. The definition of severe cases, as defined by IMCI guidelines, varies slightly from country to country, particularly with regard to cases of pneumonia in Guinea. This could lead to an overestimation of severe cases in Guinea that needs to be considered when comparing data between countries. Additionally, the absence of an aetiological diagnosis other than mRDT results leads to an imprecise or inaccurate clinical diagnosis, based solely on the HCW's expertise and knowledge. This issue was partially addressed during the initial training and supervision sessions organised jointly with the project and Ministries of Health staff, with the aim of improving IMCI practice using PO. Furthermore, the

selection process for the AIRE intervention health districts and research PHCs[24] made them unrepresentative of all PHCs at a national level. As enrolment mainly took place during working days and not at night, on public holidays or at weekends when cases may be more severely ill, this may have biased the representativeness of severe cases. To address this issue, we have reorganised the work of the research teams, increased staff and set up a special inclusion procedure at sites with high attendance during these periods. While these factors make statistical inference difficult, our results still inform health authorities by providing scientific evidence to guide them in making the best decisions for the population's health.

Our study also has strengths; the data collected as part of this large sample size, including neonates, is valuable and rare, especially the care pathway data. Very few studies have examined the same topic in a West African context. The high quality of the almost complete data and the low rate of patients lost to follow-up (around 1.4%) are strengths of the AIRE study, especially since the follow-up was carried out at the community level.

CONCLUSION

Hypoxaemia was common in severe cases, but many of these, including those with severe hypoxaemia, remained inadequately managed at the PHC level, where oxygen was unavailable. Nevertheless, using PO improved children's case management, particularly the referral decision for those with severe hypoxaemia. However, there were difficulties accessing the hospital and obtaining oxygen at the hospital level. Day 14 mortality was high, especially for children managed at the hospital level, indicating delayed treatment. Both severe and moderate hypoxaemia were independent predictors of day 14 mortality in severely ill children aged under 5 years, supporting the need to consider higher SpO_2 levels when deciding on hospital referral.[65] Further work will specifically address the added value of the routine use of PO to improve the diagnosis and subsequent management of severe hypoxaemia compared with cases without severe hypoxaemia. To improve the survival of severe cases identified at the PHC level, including those with severe hypoxaemia, West African governments should support earlier and more effective hospital transfers, provide access to oxygen and consider the associated costs.

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Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Consent obtained from parent(s)/guardian(s).

Ethics approval The AIRE research protocol, the information notice (translated in vernacular languages), the written consent form and any other relevant document have been submitted to each national ethics committee, to the Inserm Institutional Evaluation Ethics Committee (IEEC) and to the WHO Ethics Review Committee (WHO-ERC). All the aforementioned ethical committees reviewed and approved the protocol and other key documents (Comité d'Ethique pour la Recherche en Santé (CERS), Burkina Faso n°2020–4-070; Comité National d'Ethique pour la Recherche en Santé (CNERS), Guinea n°169/CNERS/21; Comité National d'Éthique pour la Santé et les Sciences de la vie (CNESS), Mali n°127/MSDS-CNESS; Comité National d'Ethique pour la Recherche en Santé (CNERS), Niger n°67/2020/CNERS; Inserm IEEC n°20–720; WHO-ERC n° ERC.0003364). This study has been retrospectively registered by the Pan African Clinical Trials Registry on 15 June 2022 under the following trial registration number: PACTR202206525204526.

Provenance and peer review Commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. Data may be obtained from a third party and are not publicly available. The datasets generated and analysed during the current study are not publicly available. Access to processed de-identified participant data will be made available to any third party after the publication of the main AIRE results stated in the Pan African Clinical Trial Registry Study statement (PACTR202206525204526, registered on 06/15/2022), upon a motivated request (concept sheet), and after the written consent of the AIRE research coordinator (Valeriane Leroy, valeriane.leroy@inserm.fr, Inserm U1295 Toulouse, France, orcid.org/0000-0003-3542-8616) obtained after the approval of the AIRE publication committee, if still active.

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