Author/s:
Graham, H;Bakare, AA;Ayede, AI;Oyewole, OB;Gray, A;Peel, D;McPake, B;Neal, E;Qazi, SA;Izadnegahdar, R;Duke, T;Falade, AG

Title:
Hypoxaemia in hospitalised children and neonates: A prospective cohort study in Nigerian secondary-level hospitals

Date:
2019-11-01

Citation:
Graham, H., Bakare, A. A., Ayede, A. I., Oyewole, O. B., Gray, A., Peel, D., McPake, B., Neal, E., Qazi, S. A., Izadnegahdar, R., Duke, T. & Falade, A. G. (2019). Hypoxaemia in hospitalised children and neonates: A prospective cohort study in Nigerian secondary-level hospitals. Eclinicalmedicine, 16, pp.51-63. https://doi.org/10.1016/j.eclinm.2019.10.009.

Persistent Link:
https://hdl.handle.net/11343/247093

EClinicalMedicine 16 (2019) 51–63

Contents lists available at ScienceDirect

EClinicalMedicine

journal homepage: www.elsevier.com/locate/eclinm

Hypoxaemia in hospitalised children and neonates: A prospective cohort study in Nigerian secondary-level hospitals

Hamish Graham[a,b,*], Ayobami A. Bakare[a], Adejumoke I. Ayede[a,c], Oladapo B. Oyewole[a], Amy Gray[b], David Peel[d], Barbara McPake[e], Eleanor Neal[b,f], Shamim A. Qazi[g,1], Rasa Izadnegahdar[h], Trevor Duke[b], Adegoke G. Falade[a,c]

[a] Department of Paediatrics, University College Hospital, Ibadan, Nigeria
[b] Centre for International Child Health, University of Melbourne, MCRI, Royal Children's Hospital, Parkville, Australia
[c] Department of Paediatrics, University of Ibadan, Ibadan, Nigeria
[d] Ashdown Consultants, Hartfield, England
[e] Nossal Institute of Global Health, University of Melbourne, Parkville, Australia
[f] Pneumococcal Research, MCRI, Royal Children's Hospital, Parkville, Australia
[g] Department of Maternal, Newborn, Child and Adolescent Health, World Health Organization, Geneva, Switzerland
[h] Bill and Melinda Gates Foundation, Seattle, USA

ARTICLE INFO

Article history:
Received 20 May 2019
Accepted 15 October 2019
Available online 24 October 2019

Keywords:
Hypoxaemia
Child
Neonate
Africa
Nigeria
Pulse oximetry
Oxygen

ABSTRACT

Background: Hypoxaemia is a common complication of pneumonia and a major risk factor for death, but less is known about hypoxaemia in other common conditions. We evaluated the epidemiology of hypoxaemia and oxygen use in hospitalised neonates and children in Nigeria.

Methods: We conducted a prospective cohort study among neonates and children (<15 years of age) admitted to 12 secondary-level hospitals in southwest Nigeria (November 2015–November 2017) using data extracted from clinical records (documented during routine care). We report summary statistics on hypoxaemia prevalence, oxygen use, and clinical predictors of hypoxaemia. We used generalised linear mixed-models to calculate relative odds of death (hypoxaemia vs not).

Findings: Participating hospitals admitted 23,926 neonates and children during the study period. Pooled hypoxaemia prevalence was 22.2% (95%CI 21.2–23.2) for neonates and 10.2% (9.7–10.8) for children. Hypoxaemia was common among children with acute lower respiratory infection (28.0%), asthma (20.4%), meningitis/encephalitis (17.4%), malnutrition (16.3%), acute febrile encephalopathy (15.4%), sepsis (8.7%) and malaria (8.5%), and neonates with neonatal encephalopathy (33.4%), prematurity (26.6%), and sepsis (21.0%). Hypoxaemia increased the adjusted odds of death 6-fold in neonates and 7-fold in children. Clinical signs predicted hypoxaemia poorly, and their predictive ability varied across ages and conditions. Hypoxaemic children received oxygen for a median of 2–3 days, consuming ~3500 L of oxygen per admission.

Interpretation: Hypoxaemia is common in respiratory and non-respiratory acute childhood illness and increases the risk of death substantially. Given the limitations of clinical signs, pulse oximetry is an essential tool for detecting hypoxaemia, and should be part of the routine assessment of all hospitalised neonates and children.

Research in context

Evidence before this study

Hypoxaemia is a well-recognised complication of pneumonia, increasing the risk of death four-fold and difficult to detect using clinical signs alone. Previous systematic reviews have collated data on the epidemiology of hypoxaemia in children with pneumonia,

* Corresponding author at: Centre for International Child Health, Department of Paediatrics, Level 2 East, 50 Flemington Road, Parkville, VIC 3052, Australia.
E-mail addresses: Hamish.graham@rch.org.au (H. Graham), idayede@yahoo.co.uk (A.I. Ayede), Amy.Gray@rch.org.au (A. Gray), ashdownconsult@btconnect.com (D. Peel), barbara.mcpake@unimelb.edu.au (B. McPake), Eleanor.Neal@mcri.edu.au (E. Neal), Rasa.Izadnegahdar@gatesfoundation.org (R. Izadnegahdar), Trevor.Duke@rch.org.au (T. Duke).
[1] Present address: Independent Consultant Paediatrician, Cointrin, Switzerland.

https://doi.org/10.1016/j.eclinm.2019.10.009

but fewer studies have addressed hypoxaemia in non-pneumonia cohorts or provided comparative data across age or diagnostic categories. With growing policy attention towards the scale up of pulse oximetry and oxygen therapy in low and middle-income countries (LMICs), policy-makers and program managers need data to inform decision-making. Current modelling estimates have addressed hypoxaemia, pulse oximetry and oxygen therapy primarily through the lens of child pneumonia. However, the burden of hypoxaemia, and the potential for reducing mortality through improved pulse oximetry and oxygen access, is much greater when non-pneumonia conditions are considered.

Added value of this study

This multi-centre cohort study was nested in the Nigerian Oxygen Implementation project, a large stepped wedge field trial evaluating pulse oximetry and improved oxygen systems. Our cohort included over 23,000 hospitalised children from birth to adolescence with various conditions, enabling us to describe the epidemiology of hypoxaemia in children and neonates admitted to secondary-level hospitals in low-altitude African towns. We found high hypoxaemia prevalence in pneumonia and other common childhood conditions, and particularly high prevalence in neonates. We found that hypoxaemia increased the risk of death across all age groups and all diagnostic categories, with higher risk in non-respiratory conditions. We found that clinical signs recorded during routine care were particularly poor at predicting hypoxaemia in children and neonates with non-respiratory conditions, having much lower sensitivity for hypoxaemia in non-respiratory conditions than respiratory conditions. The predictive value of the WHO combination of signs for hypoxaemia was reasonably good for child pneumonia, but was much poorer for non-respiratory conditions (particularly for children over the age of 1 year). We found that most hypoxaemic children required oxygen therapy for 2–3 days and calculated the mean annual oxygen requirements for small- and medium-sized hospitals that admit children.

Implications of all the available evidence

Hypoxaemia is common in respiratory and non-respiratory acute childhood illness and increases the risk of death substantially. Given the limitations of clinical signs recorded during routine care, pulse oximetry is an essential tool for detecting hypoxaemia, and should be part of the routine assessment of all hospitalised neonates and children.

1. Introduction

Hypoxaemia refers to low blood oxygen levels, typically defined as haemoglobin oxygen saturations less than 90% as measured by pulse oximetry (peripheral oxygen saturation, SpO_2) or blood gas analysis (arterial oxygen saturation, SaO_2) [1]. In childhood pneumonia, hypoxaemia is a common complication and an important marker of severity. Approximately 13% of children hospitalised with pneumonia in low- or middle-income countries are hypoxaemic [2] and hypoxaemia increases their risk of death approximately four-fold [3].

Multifaceted interventions to improve the detection of hypoxaemia and use of oxygen therapy can reduce inpatient child pneumonia mortality by approximately 35% [4–6]. Modelling estimates suggest that better use of pulse oximetry and oxygen therapy in the 12 highest mortality countries could prevent up to 148,000 child pneumonia deaths annually [7].

While hypoxaemia is less well studied in non-pneumonia cohorts, the available data suggests that hypoxaemia may be common in many non-respiratory conditions [2,8–17], and that addressing oxygen access issues for these populations could deliver substantial mortality reductions [5,6].

Nigeria is a highly-populated, lower middle-income country in sub-Saharan Africa that contributes disproportionately to global child and neonatal mortality (2017: under-five mortality 100, neonatal mortality 33, per 1000 live births) [18]. The biggest childhood killers are pneumonia (18%), malaria (14%), prematurity (12%), perinatal complications (11%), diarrhoeal diseases (10%), and neonatal sepsis (5%) [19]. Recent global estimates show that Nigeria contributed one-third of U/5 malaria deaths and one-sixth of U/5 pneumonia deaths globally [19].

This multi-centre study aimed to describe the prevalence of hypoxaemia in children and neonates admitted to secondary-level hospitals in Nigeria with pneumonia, malaria, and other common childhood and neonatal conditions, using data recorded during routine care. In addition, we sought to determine: (i) the degree to which hypoxaemia predicts mortality; (ii) the duration of oxygen therapy required for hypoxaemic conditions; and (iii) which clinical signs best predict hypoxaemia - for children of different ages and with different conditions. This will inform estimates of the benefit of improved pulse oximetry and oxygen practices for children and neonates in resource-limited settings and assist with oxygen-related program planning.

2. Methods

2.1. Design

This prospective cohort study was nested within a stepped-wedge trial to improve oxygen use in 12 secondary-level hospitals in southwest Nigeria [20]. The first stage of this trial involved a needs-assessment [21] and retrospective clinical review. The second stage involved the introduction of pulse oximetry to participating hospitals, commencing in October/November 2015 [22]. The third stage involved the stepped introduction of comprehensive oxygen systems, with hospitals randomised to receive the intervention between March 2016 and March 2017. This paper reports prospective data from November 2015 to October 2017, using data extracted from clinical records.

2.2. Participants

We conducted this study in 12 small to medium-sized hospitals in southwest Nigeria, selected to be representative of secondary healthcare facilities that admit children [20]. This included a mix of government ($n = 7$) and mission ($n = 5$) hospitals of varying capacity (Table 1, more detail in Appendix 1). All hospitals were low-altitude (elevation 50–500 m above sea level).

We included all children aged under 15 years (including neonates) who were admitted to participating hospitals during the study period (November 2015 to October 2017, inclusive). This included neonates born in the facility as well as neonates (and children) referred in from elsewhere, without prejudice to gestational age, birthweight or diagnosis. Table 1 shows the participating hospital demographics.

2.3. Materials and procedures

We introduced pulse oximetry into routine clinical care for paediatrics (including neonates) using adapted WHO oxygen guidelines [1,23] (Appendix 2). The guidelines required all children (aged under 15 years) to have pulse oximetry performed on admission, and at least twice per day while receiving oxygen. Individual hospitals determined the specific pulse oximetry procedures (e.g. timing, location, personnel) based on local workflow and practices.

Table 1
Baseline characteristics, admissions, and pulse oximetry adoption patterns of 12 secondary-level hospitals in southwest Nigeria. Additional detail in Web Appendix 1.

	H1	H2	H3	H4	H5	H6	H7	H8	H9	H10	H11	H12
Hospital characteristics												
Hospital Type	Mission	Mission	State	State	State	Mission	State	State	State	Mission	Mission	State
Paediatric Beds	70	32	25	36	60	20	48	46	13	63	14	36
child + neonatal	(40+30)	(20+12)	(21+4)	(16+20)	(44+16)	(15+5)	(20+28)	(22+24)	(9 + 4)	(38+25)	(12+2)	(26+10)
Access to Paediatrician	Yes[ii]	No[i]	Yes	Yes	Yes	Yes	Yes	No	No[i]	Yes[ii]	Yes[ii]	No[i]
Doctors in hospital	4	4	2	11	17	5	16	12	7	6	6	7
Nurses in child/newborn wards	18	7	16	33	62	9	26	31	11	18	4	26
Oxygen cylinders	Yes[iv]	Yes[iv]	Yes[iv]	Yes	Yes	Yes[iv]	Yes[iii]	Yes	Yes[iv]	Yes	Yes[iv]	Yes[iv]
Oxygen concentrators	Yes[v]	No	Yes[v]	Yes[v]	No	Yes	Yes[v]	No	No	Yes[v]	Yes[v]	No
Pulse oximeters	0	0	0	0	3[v]	1	0	0	0	0	1[v]	0
Participants (total)	**4133**	**674**	**1655**	**2943**	**2176**	**635**	**4313**	**1790**	**495**	**3327**	**869**	**916**
Neonates <28 days	2228	100	112	1322	406	102	1480	455	9	1170	89	0
Infants 28 days to 1 year	519	176	327	449	600	97	1085	388	117	543	131	187
Children 1–4 years	921	259	775	785	790	288	1669	582	235	990	312	455
Children 5–14 years	449	138	436	378	342	143	76	347	133	624	333	272
Sex:% female	44.8	44.7	46.9	42.2	42.0	41.6	44.6	43.8	45.3	43.7	42.9	40.6
Median age, months (IQR)	0 (0–20)	15 (5–48)	24 (11–60)	5 (0–24)	14 (2–39)	24 (9–55)	8 (0–18)	13 (1–44)	25 (12–60)	11 (0–36)	36 (11–90)	24 (12–60)
Median LOS, days (IQR)	4 (3–7)	3 (2–5)	3 (2–4)	3 (2–6)	8 (7–10)	3 (2–4)	3 (2–5)	7 (4–9)	2 (1–2)	4 (3–5)	2 (1–3)	3 (2–4)
Neonates <28 days	5 (3–9)	4 (2–5)	3 (2–7)	4 (2–6)	11(10–13)	4 (2–6)	4 (2–6)	10 (4–11)	3 (3–4)	5 (3–7)	3 (2–4)	-
Children	3 (2–5)	3 (2–4)	3 (2–5)	3 (2–5)	7 (7–9)	3 (2–4)	3 (2–4)	6 (4–7)	2 (1–2)	4 (3–5)	2 (1–3)	3 (2–4)
Pulse oximetry documented, n (%)	3586 (88.4)	559 (82.9)	1415 (86.8)	2365 (80.4)	1911 (87.8)	610 (96.1)	2406 (57.2)	1292 (74.4)	364 (74.6)	2965 (90.2)	819 (94.3)	585 (64.7)
Hypoxaemia prevalence	16.9	16.6	12.9	16.2	11.3	11.0	20.1	13.2	4.4	11.3	7.5	9.6
Neonates <28 days	20.2	44.3	20.6	25.9	17.5	32.7	30.6	18.6	33.3	16.8	7.9	-
Children	12.5	12.1	12.3	8.9	9.8	6.7	13.7	11.1	4.2	8.0	7.4	9.6
Deaths	411	59	134	160	79	43	207	124	18	141	28	26
Case fatality rate (%)	10.0	8.8	8.1	5.5	3.6	6.8	4.8	7.0	3.6	4.2	3.2	2.8
Neonates <28 days	14.1	23.0	14.3	7.1	5.4	21.6	9.4	11.9	11.1	4.9	1.1	-
Children	5.1	6.3	7.7	4.2	3.2	4.0	2.5	5.3	3.5	3.9	3.5	2.8

Neonate ≤28 days, Child 29 days-15 years. IQR = inter-quartile range, 25th/75th centiles. LOS = length of stay. (i) Family Medicine Consultant; (ii) part-time; (iii) piped system connected to large oxygen cylinder; (iv) not available in paediatric areas; (v) present but not fit for use.

Typically, patients presented to the children's outpatient or emergency area and a nurse would perform pulse oximetry alongside other vital signs prior to admission. In most hospitals, the admitting doctor would also perform pulse oximetry when completing the formal admission procedures.

We conducted hospital-based pulse oximetry training for nurses and doctors working in paediatric areas in October/November 2015 and supplied handheld Lifebox™ pulse oximeters (Acare Technology, Taiwan). Lifebox oximeters were developed for low-resource settings by the World Health Organization (WHO) and the World Federation of Societies for Anaesthesiologists, with rated accuracy of +/−2% [24,25]. We instructed healthcare workers to conduct pulse oximetry using an appropriately-sized probe applied to a well-perfused finger or toe, and to wait until there was a strong and steady waveform before recording the SpO_2 reading. We provided supportive supervision through onsite project nurses in each hospital and regular visits from the project manager and/or nurse supervisor [20,22]. We introduced a comprehensive improved oxygen system to all hospitals at stepped intervals (3 hospitals every 4 months from March 2016 to March 2017), including oxygen concentrators (with reliable power), individually titratable flowmeter assemblies, appropriately-sized nasal prongs, and guidelines for using, cleaning and maintaining equipment (details in protocol [20]).

We collected data from the clinical records, including case notes and nursing observation charts. We did not provide additional training or standardization of healthcare worker diagnostic, treatment or documentation practices. Trained research nurses extracted data from case notes using a standardised data collection form. This included SpO_2 on admission, oxygen use, as well as demographic data, diagnoses, symptoms and signs on admission, and clinical care practices.

2.4. Data analysis

Trained data entry clerks double-entered data from data collection forms using EpiData 3.1 [26], following standard data management procedures. We performed data cleaning and analysis using Stata 15.1 [27]. We defined hypoxaemia as $SpO_2 < 90\%$, irrespective of age or condition. We calculated hypoxaemia prevalence based on the SpO_2 recorded on admission, in order to consistently represent the condition of the patient and to enable temporal correlation with the recorded admission signs. We calculated proportions and 95% confidence intervals for hypoxaemia prevalence and case fatality rates using complete case analysis approach (i.e. dropping missing data from analysis) [28]. We conducted sensitivity testing to evaluate the effect of missing data on the primary hypoxaemia prevalence outcome, by comparing prevalence estimates from periods with high missing data (earlier time periods) to periods with low missing data (later time periods) [28].

We calculated relative odds of death and 95% confidence intervals for patients with and without hypoxaemia, using generalised linear mixed-model (GLMM) analysis to adjust for clustering (at hospital level), time (in 4-month periods), age, sex, comorbid diagnoses, and the presence of the improved oxygen system [29,30]. We calculated median and inter-quartile ranges for oxygen use (duration, starting flow rate) and pre-treatment SpO_2, restricting analysis to the post-intervention period to reflect clinical practice in the presence of adequate oxygen access. We calculated means for oxygen use (duration, starting flow rate) to enable the calculation of total oxygen demand. We calculated total volume of oxygen consumed by multiplying the mean duration of therapy by the starting flow rate (field observation showed that the flow rate was rarely altered after starting oxygen).

We calculated the sensitivity, specificity, positive and negative likelihood ratios, and area under the receiver operator characteristic (ROC) curve (AUC) for various clinical signs in predicting hypoxaemia (both individually and in combination) using the *diagt* program for Stata [31]. We provide tabular comparison of the predictive accuracy of various combinations of signs against the WHO combination: respiratory rate (RR) ≥70 breaths per minute (bpm), severe chest wall indrawing, grunting, inability to feed due to respiratory distress [23].

We report this data for various age groups (neonates <28 days, infants 28–364 days, young children 1–4 years, older children 5–14 years) and diagnoses. We report for the most common presenting clinical syndromes and diagnoses: acute lower respiratory infection (which includes pneumonia and bronchiolitis), acute febrile encephalopathy (which includes cerebral malaria, viral and bacterial encephalopathies), malaria, sepsis, acute watery diarrhoea, small/premature neonate (including premature and low birth weight), and neonatal jaundice. We also report additional conditions we considered of particular interest (e.g. HIV, severe acute malnutrition, asthma). We determined diagnostic case status for most conditions based on recorded admission symptoms, signs, and laboratory testing using standard case definitions (Table 2). If a sign was not recorded, we assumed that it was not present. We used the recorded admission diagnosis for diagnoses with more complex case definitions that required data not readily available from case notes (e.g. sepsis).

We present overall hypoxaemia prevalence findings in a bubble plot, illustrating prevalence (y-axis) and numbers affected (bubble size), across age groups (x-axis) and diagnoses (labelled bubbles). We report hypoxaemia prevalence and case fatality rates based on 'any diagnosis' (i.e. irrespective of whether it was identified as a primary or additional diagnosis, or whether it met criteria for multiple case definitions), with adjustment for comorbidity where relevant. For comparative purposes, we report additional analysis for 'primary diagnosis' and particular combinations of case definitions (e.g. ALRI with or without malaria) in Appendix 3. For reporting purposes we classified hospitals as small (<500 child admissions annually) and medium (500–2500 child admissions annually).

2.5. Role of the funding source

RI represented the funding agency and participated in site selection and methods meetings which informed the study design. The corresponding author, AAB, AIA, OBO, AGF, and TD had full access to all the data in the study. All authors had final responsibility for the decision to submit for publication.

3. Results

Participating hospitals admitted 16,453 children (aged 28 days or more) and 7473 neonates over the 24 month study period (November 2015 – October 2017). 23,846 (99.7%) had a documented clinical outcome and 18,877 (78.9%) had a documented SpO_2 on admission.

3.1. Hypoxaemia prevalence

Hypoxaemia prevalence was 22.2% (95%CI 21.2–23.2) for neonates and 10.2% (9.7–10.8) for children aged ≥28 days (Table 3, Fig. 1). Hypoxaemia prevalence decreased with increasing age. Hypoxaemia prevalence varied between hospitals (median 12.1%, range 4.4–20.1%). Medium-sized hospitals typically admitted a higher proportion of hypoxaemic patients than small hospitals (15% vs 10%) and this was primarily accounted for by a higher proportion of neonates. Sensitivity testing showed that these prevalence estimate results remained robust to the effects of missing data.

Fig. 1 is a bubble plot showing the prevalence of hypoxaemia in various conditions across age groups. Among children, hypoxaemia

Table 2
Diagnostic case definitions.

Diagnosis	Diagnostic Definition and notes
ALRI, acute lower respiratory infection	Case definition (WHO) [23]: Cough or difficult breathing and any of: fast breathing, lower chest wall in-drawing.
Severe ALRI	Case definition (WHO) [23]: ALRI plus any of: central cyanosis, SpO_2 <90%, severe respiratory distress (e.g. grunting, very severe chest wall in-drawing), general danger sign (inability to breastfeed/drink, lethargy or unconscious, convulsions).
AFE, acute febrile encephalopathy	Case definition [65]: Fever and any of: seizures, altered conscious state. This clinical syndrome includes viral and bacterial encephalopathies, cerebral malaria, and non-infective encephalopathies.
Diarrhoea	Case definition (WHO) [23]: >3 loose stools per day, not >14 days duration.
Malaria	Case definition (WHO) [23]: Fever (or history of fever) and positive malaria test (rapid test or microscopy).
Sepsis	Clinical diagnosis [23]: Based on assessment of fever (or history of fever) and a sign of severe illness or haemodynamic instability (e.g. inability to breastfeed/drink, lethargy or unconscious, convulsions, shock) without other cause.
Seizures	Case definition [23]: Seizures (or history of seizures).
Meningitis / Encephalitis	Clinical diagnosis [23]: Based on assessment of stiff neck, pain on neck flexion, bulging fontanelle, photophobia, altered conscious state.
Haemoglobinopathy (typically sickle cell disease)	Clinical diagnosis [23]: Based on history of haemoglobinopathy (e.g. SS disease) and admission signs of crisis (e.g. limb pain, stroke, chest pain).
SAM, severe acute malnutrition.	Case definition [23]: Weight-for-height less than −3 z scores of median (WHO growth standards), MUAC<115 cm, or nutritionally-associated oedema (kwashiorkor). These parameters were not routinely assessed for all children, so likely underestimates the prevalence of SAM.
URTI (upper respiratory tract infection)	Clinical diagnosis: Based on assessment of upper airway obstruction/discharge, without signs of lung involvement.
Asthma	Clinical diagnosis [23]: Based on assessment of fast or difficult breathing, and wheezing, with bronchodilator response.
Trauma, Burns, Poisoning	Clinical diagnoses: Based on assessment of history (trauma, burns, poisoning).
Typhoid fever	Clinical diagnosis [23]: Based on assessment of fever (or history of fever) and gastrointestinal signs (e.g. constipation, vomiting, pain, hepatosplenomegaly), headache, cough, or rash, without other cause.
HIV (human immunodeficiency virus)	Clinical diagnosis [23]: Based on known history of HIV infection, positive HIV test result, or presentation with signs of HIV-related illness (e.g. pneumocystis jirovecii, oesophageal candidiasis) or possible HIV-related illness (e.g. oral thrush, recurrent infections).
Small	Case definition (WHO) [23]: <2500 g birth weight. Low birth weight (LBW) 1500–2499 g; Very Low Birth Weight (VLBW) 1000–1499 g; Extremely Low Birth Weight (ELBW) <1000 g.
Preterm	Case definition (WHO) [23]: <37 weeks gestational age. Gestational age typically estimated from last menstrual period and/or ultrasound scan, but was unknown for the majority of participants.
Neonatal sepsis (suspected)	Clinical diagnosis: Based on assessment of temperature (high or low), altered conscious state, other signs of possible infection (e.g. umbilical discharge), major risk factors for sepsis (e.g. maternal chorioamnionitis).
NE (Neonatal encephalopathy)	Clinical diagnosis [66]: Based on assessment of persisting altered conscious state and seizures or other neurobehavioural symptoms (e.g. abnormal posturing, hypotonia, weak or absent suck or reflexes).
Jaundice	Clinical diagnosis: Based on clinical assessment (e.g. skin colour, feeding) and laboratory confirmation with serum bilirubin.

Wherever possible we determined case status using recorded admission symptoms, signs, and laboratory testing ("case definition"). For diagnoses for which we were unable to determine cases from the documented clinical data we relied on the recorded admission diagnosis ("clinical diagnosis").

was most prevalent in those with acute lower respiratory tract infection (ALRI), affecting 1 in 3 children (36.1%) who met WHO criteria for severe disease based on clinical signs, and 1 in 6 (16.6%) children who had no other signs of severe disease. Hypoxaemia was highly prevalent in children with asthma (20.4%), meningitis/encephalitis (17.4%), malnutrition (16.3%), and acute febrile encephalopathy (AFE) (15.4%).

Hypoxaemia affected 1 in 7 (15.3%) children with complicated malaria and 1 in 20 (4.6%) children with uncomplicated malaria (Table 3, Fig. 1). In absolute numbers there were similar numbers of hypoxaemic children with diagnoses of ALRI ($n = 486$), confirmed malaria ($n = 428$), and acute febrile encephalopathy ($n = 412$). Together these three presentations accounted for almost three-quarters of hypoxaemia cases (948/1304, 72.7%).

Among neonates, hypoxaemia was highly prevalent in all three of the major causes of mortality – prematurity (26.6%), sepsis (21.0%), and neonatal encephalopathy (33.4%) (Table 3, Fig. 1). These presentations accounted for almost all of the neonatal hypoxaemia cases (1218/1363, 89.4%).

Table 3 presents hypoxaemia prevalence data for the most common diagnostic categories. We found minor differences between hypoxaemia prevalence when analysed by "any diagnosis" compared to "primary diagnosis" (see Appendix 3).

3.2. Hypoxaemia as a risk factor for mortality

Table 3 presents data on the relative odds of death comparing hypoxaemic to non-hypoxaemic cohorts for the most common diagnoses. Hypoxaemia was a major predictor for mortality across all age groups and all diagnostic categories. The relative odds of death were higher in older children and those with conditions where hypoxaemia was less common (e.g. malaria versus ALRI). The risk of death was higher with lower admission SpO_2 (Fig. 2).

When adjusted for clustering, age, sex, comorbid diagnoses, and the presence of the improved oxygen system, neonates who were hypoxaemic on admission had 6-fold higher odds of death than those without hypoxaemia (aOR 5.6, 4.5–6.8), and hypoxaemic children had 7-fold higher odds of death than those without hypoxaemia (aOR 7.3, 6.0–9.0) (Table 3).

3.3. Oxygen therapy for hypoxaemia

Table 4 presents oxygen use data for various age and diagnostic categories. Children and neonates with hypoxaemia received oxygen for a median duration of 1.5 days (IQR 0.5–3.5) with little variation across age groups. Children with ALRI tended to require longer time on oxygen (median 2.5, IQR 1.5–3.5), as did preterm neonates (median 2.5, IQR 1.5–4.5). Among children and neonates with hypoxaemia, the median recorded SpO_2 before starting oxygen therapy was 81% (IQR 67–88), with little variation across age groups or presenting conditions. Clinicians appeared to follow the guidelines regarding oxygen flow-rate, with neonates tending to be started on 0.5–1.0 litre per minute (LPM), younger children on 1.0–1.5 LPM and older children on 1.0–2.0 LPM. Based on these data, neonates with hypoxaemia can be expected to receive ~3500 L of oxygen during admission, and children ~5000 L. These rates are

Table 3
Hypoxaemia on admission and corresponding case fatality rates and relative odds of death among children (aged <15 years) admitted to 12 secondary-level hospitals in southwest Nigeria over a 2 year period (Nov 2015–Oct 2017 inclusive).

Cohort / Condition	No. (%)	No. hypoxaemic (%)	Hypoxaemia prevalence (95% CI)	Case fatality rate (95% CI)	Relative odds of death, hypoxaemic vs non-hypoxaemic, OR (95% CI) Crude	Adjusted [1]
Total	**23,926 (100)**	**2667 (100)**	**14.1% (13.6–14.6)**	**6.0% (5.7–6.3)**	**8.4 (7.4–9.6)**	**7.9 (7.0–9.0)**
Neonates <28 days	7473 (31.2)	1363 (51.1)	22.2% (21.2–23.2)	9.9% (9.3–10.6)	6.2 (5.2–7.3)	5.6 (4.5–6.8)
Infants 28 days to 1 year	4619 (19.3)	543 (20.4)	15.6% (14.4–16.9)	5.6% (5.0–6.3)	8.2 (6.1–11.1)	7.7 (5.4–11.1)
Children 1–4 years	8060 (33.7)	537 (20.1)	8.8% (8.1–9.5)	3.8% (3.4–4.3)	8.9 (6.7–11.9)	7.5 (5.5–10.2)
Children 5–14 years	3671 (15.3)	220 (8.2)	7.2% (6.3–8.2)	3.4% (2.8–4.0)	9.5 (6.0–14.8)	7.6 (4.7–12.4)
Female	10,468 (43.7)	1147 (43.0)	13.9% (13.2–14.7)	5.9% (5.5–6.4)	9.1 (7.5–11.0)	8.7 (7.2–10.5)
Male	13,436 (56.1)	1519 (57.0)	14.3% (13.6–15.0)	6.0 (5.6–6.4)	7.9 (6.7–9.4)	7.3 (6.2–8.7)
Government ($n=7$)	14,292 (59.7)	1507 (56.5)	14.6% (13.9–15.3)	5.3% (4.9–5.6)	8.1 (6.8–9.7)	8.0 (6.7–9.6)
Mission ($n=5$)	9646 (40.3)	1160 (43.5)	13.6% (12.9–14.3)	7.1% (6.6–7.6)	9.0 (7.5–10.7)	8.2 (6.5–10.5)
Small [2] ($n=5$)	3590 (15.0)	293 (11.0)	10.0% (8.9–11.1)	4.9% (4.2–5.6)	12.4 (8.5–18.0)	11.4 (7.8–16.5)
Medium [2] ($n=7$)	20,348 (85.0)	2374 (89.0)	14.9% (14.3–15.5)	6.2% (5.9–6.5)	7.9 (6.9–9.1)	12.2 (7.9–18.8)
Child diagnoses [3]						
Total children	**16,453 (100)**	**1304 (100)**	**10.2% (9.7–10.8)**	**4.2% (3.9–4.5)**	**9.2 (7.7–11.0)**	**7.3 (6.0–9.0)**
Malaria	6166 (37.5)	428 (32.8)	8.5% (7.7–9.3)	2.9% (2.5–3.3)	9.4 (6.6–13.3)	6.6 (4.6–9.5)
AFE	3526 (21.4)	412 (31.6)	15.4% (14.1–16.9)	8.6% (7.7–9.6)	7.2 (5.4–9.5)	6.5 (4.8–8.9)
ALRI	2073 (12.6)	486 (37.3)	28.0% (25.9–30.2)	7.2% (6.1–8.4)	6.0 (4.0–8.9)	7.1 (4.6–10.9)
Diarrhoea	2007 (12.2)	86 (6.6)	6.1% (4.9–7.5)	3.8% (3.0–4.7)	19.3 (10.5–35.0)	16.2 (7.8–33.6)
Sepsis	5147 (31.6)	356 (27.3)	8.7% (7.8–9.6)	4.7% (4.1–5.3)	8.6 (6.2–11.8)	5.9 (4.1–8.3)
Seizures	2081 (12.6)	238 (18.3)	14.3% (12.7–16.1)	7.7% (6.6–8.9)	6.8 (4.6–10.0)	6.3 (4.2–9.3)
Meningitis/Encephalitis	521 (3.2)	75 (5.8)	17.4% (13.9–21.3)	14.1% (11.2–17.4)	4.4 (2.3–8.2)	4.5 (2.3–8.6)
Haemoglobinopathy	739 (4.5)	56 (4.3)	9.1% (6.9–11.6)	3.4% (2.2–5.0)	4.8 (1.6–13.1)	2.9 (0.9–9.2)
Malnutrition (SAM)	324 (2.0)	45 (3.5)	18.0% (13.4–23.3)	16.4% (12.5–20.9)	6.5 (3.0–14.2)	14.6 (4.6–46.6)
URTI	680 (4.2)	37 (2.8)	6.8% (4.9–9.3)	1.0% (0–2.1)	9.8 (0.8–87.7)	–
Asthma	109 (0.7)	20 (1.5)	20.4% (12.9–29.7)	0.9% (0.0–5.0)	–	–
Trauma, Burns, Poisoning	351 (2.2)	20 (1.5)	7.1% (4.4–10.8)	2.0% (0.8–4.1)	4.5 (0.1–58.5)	–
Typhoid	371 (2.3)	13 (1.0)	4.1% (2.2–6.8)	3.5% (1.9–5.9)	16.6 (3.0–76.0)	21.6 (1.9–241.3)
HIV	21 (0.1)	2 (0.2)	10.5% (1.3–33.2)	19.0% (5.4–41.9)	–	–
Neonatal diagnoses [4]						
Total neonates	**7473 (100)**	**1363 (100)**	**22.2% (21.2–23.2)**	**9.9% (9.3–10.6)**	**6.2 (5.2–7.3)**	**5.6 (4.5–6.8)**
Small / Preterm	1770 (23.7)	387 (28.4)	25.8% (23.6–28.1)	17.5% (15.7–19.3)	4.3 (3.2–5.7)	4.6 (3.3–6.3)
Small (<2500 g)	1399 (18.7)	311 (22.8)	26.4% (23.9–29.0)	17.6% (15.7–19.7)	4.9 (3.5–6.8)	5.5 (3.8–7.8)
- LBW	1105 (14.8)	228 (16.7)	24.3% (21.5–27.1)	10.8% (9.0–12.7)	7.1 (4.5–11.2)	7.7 (4.8–12.6)
- VLBW	231 (3.1)	58 (4.3)	30.7% (24.2–37.8)	32.0% (26.1–38.5)	2.7 (1.4–5.5)	3.1 (1.4–6.9)
- ELBW	63 (0.8)	25 (1.8)	52.1% (37.2–66.7)	85.7% (74.6–93.3)	0.7 (0.1–6.8)	–
Preterm (<37 wks)	1326 (17.7)	299 (21.9)	26.6% (24.1–29.3)	19.6% (17.5–21.9)	3.5 (2.5–4.7)	3.6 (2.5–5.1)
Neonatal encephalopathy	2850 (40.4)	821 (60.2)	33.4% (31.6–35.3)	13.2% (12.0–14.5)	4.1 (3.2–5.3)	4.2 (3.2–5.6)
Neonatal sepsis	3884 (54.9)	671 (49.2)	21.0% (19.6–22.4)	10.0% (9.0–10.9)	5.9 (4.6–7.6)	5.6 (4.2–7.4)
Jaundice	1692 (24.06)	115 (8.4)	8.8% (7.3–10.5)	4.4% (3.5–5.5)	10.1 (5.8–17.6)	8.0 (4.0–16.2)

(1) Adjusted for clustering, time, age, sex, comorbidity, and presence of improved oxygen system using generalised linear mixed model (GLMM); (2) Hospital size: Small - <500 annual paediatric (U/15) admissions; Medium – 500–2500 annual paediatric (U/15) admissions; (3) Malaria, AFE, ALRI, Diarrhoeal, SAM diagnoses based on case definition, other diagnoses based on recorded admission diagnosis; (4) Small and preterm diagnoses based on recorded birthweight and gestation, other diagnoses based on recorded admission diagnosis. AFE = acute febrile encephalopathy (fever on history or examination PLUS altered conscious state or seizures); ALRI = acute lower respiratory infection (cough or difficult breathing PLUS fast breathing for age or lower chest wall in-drawing); Diarrhoea case definition = >3 loose stools per day, not for >14 days duration; ELBW = extremely low birth weight (<1000 g); Hypoxaemia = SpO_2 < 90%; LBW = low birth weight (1500–2499 g); Small / Preterm = <2500 g birthweight or <37 weeks gestational age; SAM = severe acute malnutrition (ght-for-height less than −3 z scores of median (WHO growth standards), MUAC<115 mm, or nutritionally-associated oedema (kwashiakor)); URTI = upper respiratory tract infection; VLBW = very low birth weight (1000–1499 g).

slightly higher for children with ALRI (~5990 L), AFE (~6480 L) and preterm neonates (~4608 L).

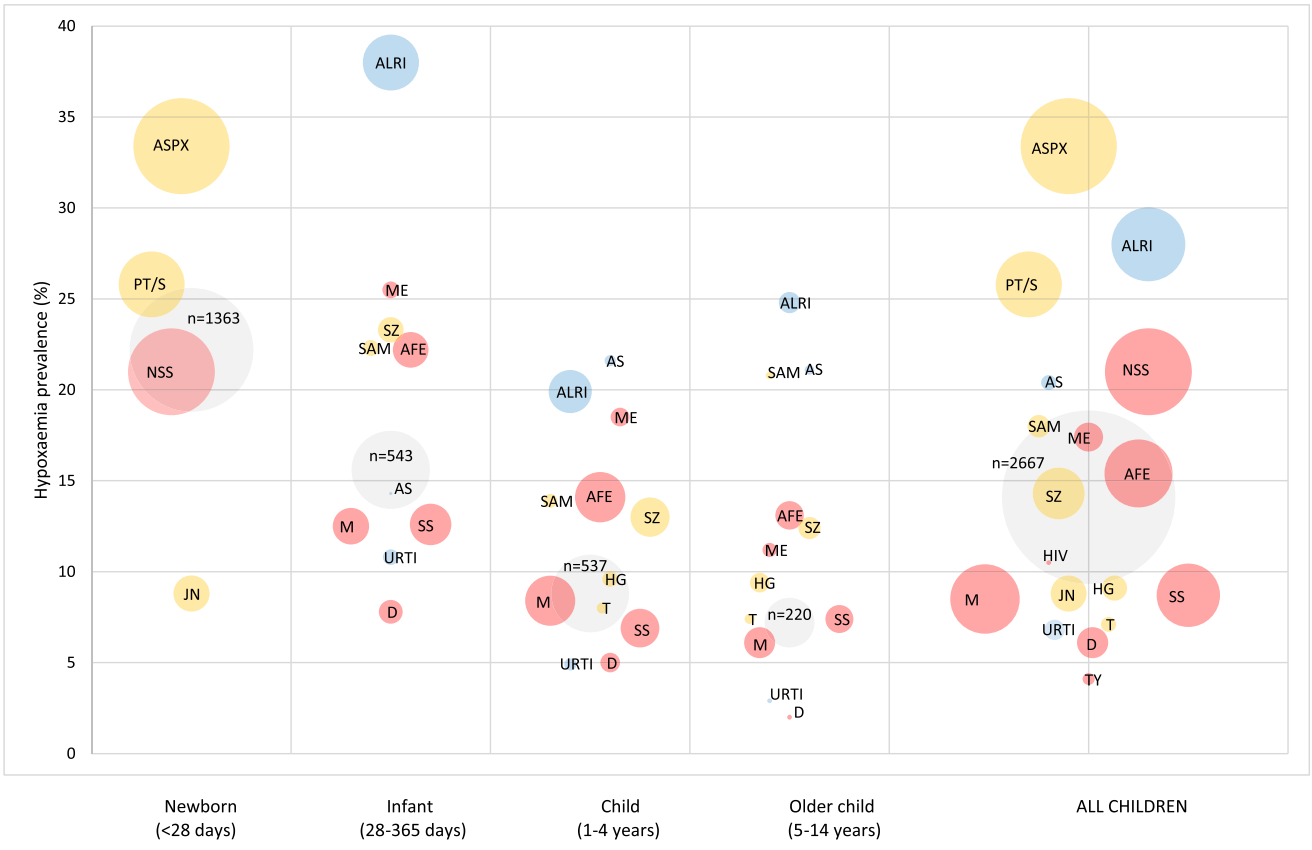
3.4. Clinical signs to predict hypoxaemia

Table 5 shows the predictive value of individual clinical signs for hypoxaemia, recorded during routine care, in sick neonates, infants, younger and older children. In neonates, the most useful sign was tachypnoea with both RR ≥50 and ≥60 bpm cut-offs resulting in sensitivity and specificity between 46% and 69%. Severe respiratory distress and inability to feed had high specificity (93%|84%) but low sensitivity (34%|31%), while the highly specific signs of central cyanosis, decreased conscious state and hypotonia all had very low sensitivity. In infants, severe respiratory distress and tachypnoea (RR ≥50 bpm) both had moderately high sensitivity (40%|61%) and specificity (90%|74%). Tachypnoea (RR ≥40 bpm) remained useful in children aged 1–15 years while respiratory distress was specific but not sensitive (specificity 93–97%, sensitivity 18–27%) in older age groups.

Table 6 shows the predictive value of various combinations of clinical signs. The WHO model (consisting of any of the following: RR ≥70 bpm, central cyanosis, severe chest wall in-drawing, grunting, or inability to feed) would have identified the majority of neonates and children with hypoxaemia (sensitivity 57%) with reasonable specificity (72%). The predictive value could be increased by using age-specific cut-offs for tachypnoea (neonate ≥70 bpm; infant ≥60 bpm; young child ≥50 bpm; older child ≥40 bpm) (Model 2 – sensitivity 65%, specificity 67%). Further modification using conscious state (Model 3) and tachycardia (Heart rate ≥160 beats per min, Model 4) provided marginal improvements in sensitivity at the cost of specificity.

4. Discussion

Our study reports on hypoxaemia and oxygen use in hospitalised children, across multiple sites, multiple clinical conditions, and from birth to mid-adolescence, using data recorded during routine care. Our data fill important evidence gaps, showing that



AFE = acute febrile encephalopathy; ALRI = acute lower respiratory infection; AS = asthma; D = diarrhoea; HG = haemoglobinopathy; HIV = HIV/AIDS; JN = neonatal jaundice; M = malaria; ME = meningitis/encephalitis; NE = neonatal encephalopathy; NSS = neonatal sepsis; PT/S = preterm/small; SAM = severe acute malnutrition; SS = sepsis; SZ = seizures; TY = typhoid; URTI = upper respiratory tract infection. Blue = respiratory condition; Red = other infectious condition; Yellow = non-infectious condition. Malaria, AFE, ALRI, Diarrhoeal, SAM diagnoses based on case definition, small and preterm diagnoses based on recorded birthweight and gestation, other diagnoses based on recorded admission diagnosis.

Fig. 1. Bubble plot showing hypoxaemia prevalence on admission (*y*-axis), of children (<15 years of age) admitted to 12 hospitals in southwest Nigeria (November 2015 to October 2017, inclusive): by condition (labelled bubbles) and age group (*x*-axis). Size (area) of bubbles represent the number of affected participants.
AFE = acute febrile encephalopathy; ALRI = acute lower respiratory infection; AS = asthma; D = diarrhoea; HG = haemoglobinopathy; HIV = HIV/AIDS; JN = neonatal jaundice; M = malaria; ME = meningitis/encephalitis; NE = neonatal encephalopathy; NSS = neonatal sepsis; PT/S = preterm/small; SAM = severe acute malnutrition; SS = sepsis; SZ = seizures; TY = typhoid; URTI = upper respiratory tract infection. Blue = respiratory condition; Red = other infectious condition; Yellow = non-infectious condition. Malaria, AFE, ALRI, Diarrhoeal, SAM diagnoses based on case definition, small and preterm diagnoses based on recorded birthweight and gestation, other diagnoses based on recorded admission diagnosis.

hypoxaemia is highly prevalent in hospitalised children aged 0–15 years with both respiratory and non-respiratory conditions, and is a major independent risk factor for death. Our data on hypoxaemia prevalence and oxygen use is important for national and global efforts to scale up pulse oximetry and oxygen therapy, providing essential data to inform quantification estimates on oxygen requirements and potential clinical impact.

4.1. Hypoxaemia prevalence

4.1.1. Hypoxaemia in pneumonia

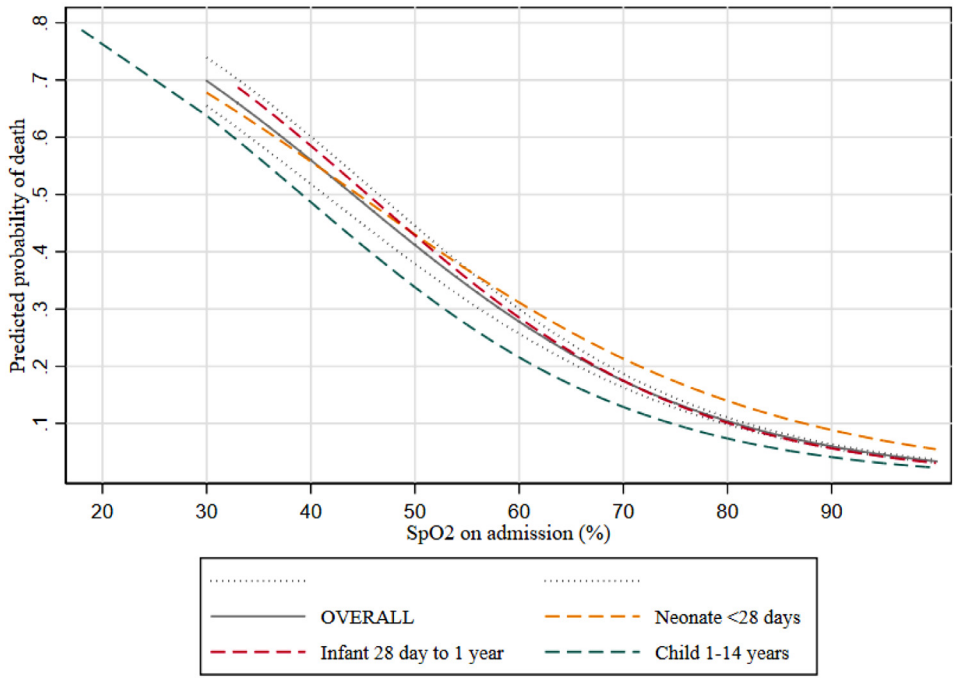
Our hypoxaemia prevalence estimates for children admitted with ALRI were higher than reported by Subhi et al. in a 2009 systematic review [2] (28% in our study, versus median of 13% in the systematic review), especially when compared with the 8 included studies from Africa (all ≤10%). Our study only included low-altitude secondary-level hospitals, whereas most of the studies in the 2009 review reporting higher hypoxaemia prevalence were from tertiary-level facilities and/or higher elevations. Our findings are consistent with more recent studies from large African hospitals (ALRI hypoxaemia prevalence 28–43%) [32–34], including tertiary hospitals in southwest Nigeria (42–49%) [9,35]. We are aware of similar prevalence rates (51%) in a recent survey of 30 hospitals of various sizes in northern Nigeria (personal correspondence, Chizoba Fashanu/CHAI Nigeria, 25 August 2018).

Our findings and these recent studies suggest that hypoxaemia prevalence in children with ALRI may be higher than previously recognised in Africa. This may mean that modelling efforts have underestimated the extent of hypoxaemia and the potential impact of scaling up pulse oximetry and oxygen therapy [7].

4.1.2. Hypoxaemia in other conditions

Our data show higher hypoxaemia prevalence in other conditions than most studies in the 2009 hypoxaemia review and more recent studies (malaria 8.5% versus 2.9–17.1%, meningitis 17.1 vs 2.7–14.6, malnutrition 16.3 vs 1.8–8.3, seizures 14.3 vs 11.8, diarrhoea 6.1 vs 0–4.7) [2,8-15], but similar results to a major tertiary hospital in the same region of Nigeria [8,9]. Our data show hypoxaemia prevalence among neonates is high (22%), with similar overall rates to other studies from Africa (17–41%) [2,9,10,14,15] and particularly high prevalence among preterm neonates (27%) and those with neonatal encephalopathy (33%).

Our study reported hypoxaemia prevalence at the point of admission, classified according to clinical signs and diagnoses (also recorded on admission). It is possible that respiratory illnesses were under-recognised. For example, pneumonia is challenging to diagnose clinically, particularly in settings with high HIV, malnutri-



Predicted values based on simple logistic regression model for each age group (no adjustment for clustering or confounders). Probability of death may have been higher in the absence of oxygen therapy.

Fig. 2. Predicted probability of death according to oxygen saturation, among 23,938 neonates and children in 12 secondary-level hospitals in southwest Nigeria. Predicted values based on simple logistic regression model for each age group (no adjustment for clustering or confounders). Probability of death may have been higher in the absence of oxygen therapy.

tion, and malaria prevalence (conditions which may share or hide the non-specific signs of pneumonia) – even with expert clinical assessment and chest radiography [36–38]. Diagnostic overlap and uncertainty is even more pronounced in the most severely unwell children, many of whom will have multiple pathological processes occurring simultaneously and clinical signs that evolve over time.

Given that we included comorbid diagnoses, the prevalence of hypoxaemia in those with non-respiratory illnesses may have been driven by comorbid respiratory illness (e.g. diarrhoea and pneumonia). Interestingly, our results remained robust when analysed by primary diagnosis (i.e. excluding secondary diagnoses), suggesting that hypoxaemia was real in many children and neonates presenting with a non-respiratory primary illness. This is understandable, as various pathologic processes can lead to hypoxaemia, including:

- hypoventilation (e.g. seizures, acute encephalopathy),
- systemic inflammation causing water retention, capillary leak and lung oedema (e.g. malaria, sepsis, systemic viral infections)
- secretions leading to airway obstruction (e.g. seizures)
- respiratory muscle weakness leading to atelectasis (e.g. malnutrition)
- pulmonary hypertension causing shunting (e.g. neonatal illness)

Irrespective of the underlying cause of hypoxaemia, or whether respiratory illness were under-recognised, high overall prevalence of hypoxaemia strongly supports the routine use of pulse oximetry for all acutely unwell children and neonates on admission to hospital.

4.2. Hypoxaemia as a risk factor for death

Recent meta-analyses have reported that hypoxaemia (SpO_2 < 90%) increased the odds of death five-fold (OR 5.47, 95% CI 3.93–7.63) in children with pneumonia [3] and three-fold in critically ill children in general (OR 3.1; 1.79–5.48) [39] (compared to those without hypoxaemia). Our study found similarly increased odds of death for hypoxaemia in children with ALRI (OR 6.0; 95% CI 4.0–8.9) as well as increased odds of death in other respiratory and non-respiratory conditions, across all age groups. This increased odds of death remained substantial when adjusted for age, co-morbidity and clustering – suggesting that hypoxaemia is a late-stage complication of many conditions that do not primarily involve the lungs.

4.3. Signs of hypoxaemia

Previous studies have explored the utility of various clinical signs to identify hypoxaemia in children with pneumonia [16,32,33,40–49], but few have addressed this question in non-pneumonia cohorts or compared different diagnoses [9,10]. We found no individual or combination of clinical signs that reliably predict hypoxaemia and note significant difference in predictive ability of particular signs between respiratory and non-respiratory conditions (i.e. respiratory signs are more prevalent and sensitive for hypoxaemia in respiratory conditions, and less prevalent but more specific for hypoxaemia in non-respiratory conditions).

We found that the WHO combination of signs for hypoxaemia predicted hypoxaemia in neonates and infants moderately well. However, the WHO combination will miss most cases of hypoxaemia in children aged over 1 year and can be improved by using age-specific tachypnoea cut-offs. This modified WHO combination has moderately high sensitivity and specificity overall (65% sensitivity, 67% specificity) and very high sensitivity for hypoxaemia in ALRI (sensitivity 92%, specificity 25%). However, while it may be appropriate to use such combinations of clinical signs to guide oxygen therapy in hospitals where pulse oximetry is not available, pulse oximetry remains a far superior diagnostic tool.

Table 4
Oxygen duration, starting flow rate, and pre-treatment oxygen saturation (SpO_2) among hypoxaemic children and neonates admitted to participating hospitals.

	Oxygen duration (days)			Starting flow rate (LPM)			Pre-treatment oxygen saturation (%)			Post-treatment oxygen saturation (%)			Mean volume of oxygen required (L)
Overall	**Mean** **2.8**	**Median** **1.5**	**IQR** **0.5–3.5**	**Mean** **1.1**	**Median** **1.0**	**IQR** **0.5–1.0**	**Mean** **74.6**	**Median** **81**	**IQR** **67–88**	**Mean** **94.6**	**Median** **96**	**IQR** **94–98**	**4435**
Age group													
Neonates <28 days	2.9	1.5	0.5–3.5	0.9	1.0	0.5–1.0	74.3	81	66–88	94.5	96	94–97	3758
Infants 28 days to 1 year	3.1	2.5	1.5–3.5	1.2	1.0	1.0–1.5	74.4	80	66.5–88	93.6	96	94–98	5356
Children 1–4 years	2.2	1.5	0.5–2.5	1.3	1.0	1.0–2.0	75.2	82	69–88	94.9	97	96–98	4118
Children 5–14 years	2.4	1.5	0.5–2.5	1.5	1.5	1.0–2.0	76.1	81.5	70.5–87	96.7	98	96–99	5184
Condition													
ALRI	3.2	2.5	1.5–3.5	1.3	1.0	1.0–2.0	74.8	81	68–88	94.3	96	94–98	5990
AFE	3.0	1.5	0.5–2.5	1.5	1.5	1.0–2.0	74.2	80.0	65–88	94.1	98	96–98	6480
Malaria	2.4	1.5	1.0–2.5	1.4	1.0	1.0–2.0	76.7	82	71–88	95.1	97	96–98	4838
Diarrhoeal disease	2.5	1.5	0.5–3.5	1.3	1.0	1.0–2.0	72.5	80	60–85	86.3	97	94–98	4680
Sepsis	2.6	1.5	0.5–3.5	1.2	1.0	1.0–2.0	75.8	82	68–88	93.9	97	95–98	4320
Preterm	4.0	2.5	1.5–4.5	0.8	0.5	0.5–1.0	75.6	82	68–89	95.4	96	94–97	4608
Neonatal sepsis	3.1	1.5	1.5–3.5	1.0	1.0	0.5–1.0	75.7	82.5	68–88	93.8	96	94–98	4464
Neonatal encephalopathy	2.7	1.5	1.5–3.5	0.9	1.0	0.5–1.0	73.8	80	66–88	94.3	96	94–97	3499

Analysis restricted to enhanced oxygen systems period to ensure limited supply did not prevent access. We report medians and interquartile ranges as the data is not normally distributed and report means for calculation total oxygen use (and easy comparison with previous studies). AFE = acute febrile encephalopathy; ALRI = acute lower respiratory infection; IQR = inter-quartile range, 25th75th centiles; LPM = litres per minute. Neonate = <28 days
Mean volume of oxygen required assuming the starting flow rate is maintained throughout admission (i.e. mean oxygen duration x starting flow rate x 60×24).

4.4. Practical implications

Pulse oximetry and oxygen therapy are essential medical practices that are poorly available to hospitalised children globally [5,50–54]. International collaborations recently formed to address oxygen access in key high burden countries (e.g. United for Oxygen Alliance, Every Breath Counts coalition). Ethiopia and Nigeria have led the way in launching national strategies for the scale up of pulse oximetry and oxygen therapy. However, lack of data on which to base oxygen quantification estimates have hampered program planning and advocacy, and individual hospitals have struggled to know how they should respond.

At the hospital management level, our data show that hypoxaemia is common in many conditions – including all the biggest causes of child mortality in Nigeria. Hypoxaemic children typically require 3500–5000 L of oxygen over 2–3 days. Small hospitals (<500 child admissions annually) may admit up to 50 hypoxaemic children per year, requiring oxygen for 2–3 days, and consuming approximately 200,000 L of oxygen annually. Medium-sized hospitals (500–1500 child admissions annually) may admit 100–200 hypoxaemic children/neonates per year using up to 1 million litres of oxygen, and larger hospitals will likely admit new hypoxaemic children/neonates every day and use over 1 million litres of oxygen annually.

At a policy and planning level, our data support calls for the routine use of pulse oximetry in all neonates and children admitted to hospital, irrespective of diagnosis [22,55].We know healthcare workers (including low-level community-based healthcare workers) are able to use pulse oximetry effectively [6,22,52,56–58]. However, introducing pulse oximetry into routine care is challenging and requires a multi-faceted approach (e.g. clinical guidelines, equipment, education, record keeping, finances, and policies) [22]. Making pulse oximetry a “vital sign” (along with heart rate, respiratory rate and temperature) may facilitate faster adoption, but does require more oximeters and more measurement time [22]. Encouragingly, pulse oximeters are becoming more affordable (e.g. the Lifebox Foundation [25]) and, while time is an initial barrier to pulse oximetry uptake, nurses embrace it as a tool that enhances efficiency [22].

For researchers, future studies and modelling efforts regarding the utility of pulse oximetry and oxygen should consider the potential impact for neonates and children with non-pneumonia conditions.

4.5. Limitations

We report data from a large multi-centre study involving secondary level hospitals at low-altitude locations in southwest Nigeria. These data can inform oxygen estimates and program planning, but they will not negate the need for locally-acquired operational data (and we did not investigate other important indications for oxygen in anaesthetic, obstetric or adult patient care).

We relied on pulse oximetry measurements obtained during routine care by hospital healthcare workers using low-cost handheld pulse oximeters. Findings from our supervision visits and a targeted audit of nurses’ pulse oximetry practices showed high adherence to recommended procedures, low measurement failure rates, and consistency in the number and duration of attempts across different hospitals [22]. Lifebox oximeters do not have motion-resistance or low-perfusion technology, but have been validated for use in children and neonates and displayed equivalent accuracy to leading commercial brands in the US [24,59].

We used a single definition of hypoxaemia (SpO_2 < 90%) irrespective of participant age or condition in keeping with WHO recommendations [23]. We recognise that particular clinical situations may warrant more liberal or conservative application of oxy-

Table 5
Hypoxaemia prevalence, sensitivity, specificity, positive likelihood ratio (LR+) and negative likelihood ratio (LR-) for presenting clinical signs among children in 12 secondary-level hospitals in southwest Nigeria (Nov 2015 to Oct 2017 inclusive).

	Neonate <28 days						Infant 28 days-1 year					
Clinical sign [1]	N (%)	AUC	Sensitivity	Specificity	LR+	LR-	N (%)	AUC	Sensitivity	Specificity	LR+	LR-
RR ≥70bpm	915	0.561	25%	88%	1.98	1.75	301	0.602	26%	94%	4.57	0.784
	15.1%		22–27	87–89			8.9%		22–30	93–95		
RR ≥60bpm	2059	0.577	46%	69%	1.5	0.779	700	0.659	47%	84%	3.02	0.624
	33.9%		43–49	68–71			20.6%		43–52	83–86		
RR ≥50bpm	3279	0.557	63%	49%	1.22	0.764	1079	0.672	61%	74%	2.3	0.533
	54.0%		60–66	47–50			31.7%		56–65	72–75		
RR ≥40bpm	5180	0.504	86%	15%	1.01	0.945	2038	0.614	79%	44%	1.4	0.476
	85.4%		84–88	14–16			59.9%		76–83	42–45		
Heart rate >160bpm	781	0.563	23%	90%	2.25	0.861	741	0.579	35%	81%	1.83	0.805
	12.9%		20–25	89–91			21.8%		31–39	79–82		
Severe respiratory distress	510	0.636	34%	93%	5.03	0.709	510	0.651	40%	90%	4.03	0.665
	8.4%		31–37	93–94			15.0%		36–44	89–91		
Central cyanosis	168	0.533	8%	99%	6.15	0.933	24	0.507	2%	100%	3.86	0.986
	2.8%		6 to 9	98–99			0.7%		1 to 3	99–100		
Unable to feed	1202	0.573	31%	84%	1.89	0.826	663	0.508	20%	81%	1.09	0.98
	19.8%		28–33	83–85			19.5%		17–24	80–83		
Seizures	375	0.520	9%	95%	1.77	0.957	249	0.521	11%	94	1.64	0.955
	6.2%		8 to 11	94–95			7.3%		8 to14	93–94		
Decreased consciousness	257	0.541	11%	98%	4.47	0.916	408	0.547	20%	90%	1.92	0.895
	4.2%		9 to 12	97–98			12.0%		16–23	89–91		
Hypotonia	214	0.524	7%	98%	2.96	0.951	na	na	na	na	na	na
	3.5%		6 to 9	97–98								
Shock	na	na	na	na	na	na	12	0.506	1%	100%	7.63	0.989
							0.4%		1 to 3	100–100		
Severe dehydration	na	na	na	na	na	na	194	0.513	8%	95%	1.51	0.972
							5.7%		6 to 10	94–96		

	Young Child 1–4 years						Older Child 5–14 years					
Clinical sign [1]	**N (%)**	**AUC**	**Sensitivity**	**Specificity**	**LR+**	**LR-**	**N (%)**	**AUC**	**Sensitivity**	**Specificity**	**LR+**	**LR-**
RR ≥70bpm	140	0.533	8%	98%	4.79	0.933	20	0.516	4%	100%	8.67	0.967
	2.3%		6 to 11	98–99			0.7%		2 to 7	99–100		
RR ≥60bpm	472	0.589	24%	94%	3.85	0.809	72	0.545	11%	98%	6.1	0.909
	7.8%		21–28	93–94			2.4%		7 to 16	98–99		
RR ≥50bpm	913	0.642	41%	87%	3.24	0.675	161	0.579	20%	96%	4.74	0.835
	15.2%		37–45	86–88			5.3%		15–26	95–97		
RR ≥40bpm	2360	0.657	68%	64%	1.86	0.505	566	0.634	44%	83%	2.59	0.677
	39.2%		64–72	62–65			18.8%		37–51	82–85		
Heart rate >160bpm	740	0.578	27%	89%	2.45	0.824	62	0.531	8%	98%	4.89	0.937
	12.3%		23–30	88–90			2.1%		5 to 12	98–99		
Severe respiratory distress	511	0.602	27%	93%	4.12	0.781	124	0.576	18%	97%	6.14	0.843
	8.5%		23–31	93–94			4.1%		13–24	96–98		
Central cyanosis	32	0.507	2%	100%	4.73	0.985	21	0.518	4%	100%	9.66	0.963
	0.5%		1 to 3	99–100			0.7%		2 to 8	99–100		
Unable to feed	1355	0.476	18%	77%	0.784	1.06	589	0.482	16%	81%	0.814	1.05
	22.5%		15–21	76–79			19.6%		Nov-21	79–82		
Seizures	1056	0.545	26%	84	1.55	0.892	347	0.544	20%	89%	1.82	0.901
	17.5%		22–29	83–85			11.5%		15–25	88–90		
Decreased consciousness	1073	0.595	35%	84%	2.2	0.775	467	0.577	30%	86%	2.08	0.821
	17.8%		31–39	83–85			15.5%		24–36	85–87		
Hypotonia	na	na	na	na	na	na	na	na	na	na	na	na
Shock	20	0.503	1%	100%	3.47	0.993	5	0.509	2%	100%	51.5	0.982
	0.3%		0–2	100–100			0.2%		0–5	100–100		
Severe dehydration	193	0.504	4%	97	1.27	0.991	48	0.516	5%	99%	3.39	0.968
	3.2%		2 to 6	96–97			1.6%		2 to 8	98–99		

1 – assumes that if a sign is not documented, it was not present. AUC = the area under the ROC curve; LR+ positive likelihood ratio (LR+ = sensitivity/(1-specificity)); LR- negative likelihood ratio (LR- = specificity/(1-sensitivity)). A positive LR >10 and a negative LR <0.1 are considered to exert highly significant changes in probability, such as to alter clinical management. na = not applicable. Decreased consciousness = confusion, unconscious, difficult to wake. Severe respiratory distress = any of: severe chest wall in-drawing, grunting, gasping, tracheal tug, head nodding. Signs of shock = cold hands, capillary refill >3 s, fast and weak pulse, low or unmeasurable blood pressure. Signs of severe dehydration = sunken eyes, decreased skin turgor.

gen therapy due to the relative risk of tissue hypoxia (e.g. brain injury, severe anaemia) or the underlying cause and duration of hypoxaemia (e.g. congenital heart disease). We recognise that normal saturations can be lower for neonates immediately after birth and can vary by probe location (pre-ductal versus post-ductal). However, studies in similar settings have reported that more than 95% of SpO_2 readings are ≥90% even in the first hours of life (irrespective of probe location) [60].

We extracted data from routine clinical care documents using an approach similar to others conducting implementation research through clinical research networks [61]. Our use of dedicated research nurses who extracted data immediately after discharge min-

Table 6
Hypoxaemia prevalence, sensitivity, specificity, positive likelihood ratio (LR+) and negative likelihood ratio (LR-) for combinations of clinical signs among children in 12 secondary-level hospitals in southwest Nigeria (Mar 2016-Mar 2017).

Model	Population	N (%)	AUC	Sensitivity	Specificity	LR+	LR–
Model 1 (WHO)	**Overall**	**6017 (32.0)**	**0.646**	**57%**	**72%**	**2.05**	**0.596**
	- Neonate	2292 (37.3)	0.675	65%	71%	2.2	0.503
	- Infant	1220 (35.1)	0.659	62%	70%	2.05	0.546
	- Young child	1785 (29.2)	0.574	43%	72%	1.53	0.795
	- Older child	701 (22.9)	0.553	33%	78%	1.48	0.865
	- ALRI	1011 (58.2)	0.610	74%	48%	1.42	0.541
	- AFE	912 (34.2)	0.579	48%	68%	1.5	0.768
	- Malaria	1502 (29.8)	0.581	45%	72%	1.6	0.774
	- Preterm	644 (42.9)	0.632	63%	64%	1.73	0.587
	- Neonatal encephalopathy	1281 (40.1)	0.672	67%	67%	2.05	0.488
	- Neonatal sepsis	1190 (48.5)	0.615	64%	59%	1.56	0.613
Model 2	**Overall**	**7132 (37.9)**	**0.656**	**65%**	**67%**	**1.93**	**0.532**
	- Neonate	2292 (37.3)	0.675	65%	71%	2.2	0.503
	- Infant	1466 (42.2)	0.677	72%	63%	1.96	0.442
	- Young child	2265 (37.0)	0.628	60%	65%	1.74	0.608
	- Older child	1090 (35.7)	0.614	57%	66%	1.67	0.655
	- ALRI	1388 (80.0)	0.581	92%	25%	1.21	0.343
	- AFE	1191 (44.6)	0.612	64%	59%	1.55	1.42
	- Malaria	1964 (39.0)	0.626	62%	63%	1.69	0.6
	- Preterm	644 (42.9)	0.632	63%	64%	1.73	0.587
	- Neonatal encephalopathy	1281 (40.1)	0.672	67%	67%	2.05	0.488
	- Neonatal sepsis	1190 (48.5)	0.615	64%	59%	1.56	0.613
Model 3	**Overall**	**8162 (43.4)**	**0.655**	**70%**	**61%**	**1.8**	**0.494**
	- Neonate	2326 (37.9)	0.491	66%	70%	2.19	0.491
	- Infant	1650 (47.5)	0.675	77%	58%	1.83	0.397
	- Young child	2824 (46.1)	0.653	74%	57%	1.71	0.458
	- Older child	1341 (43.9)	0.628	68%	58%	1.61	0.557
	- ALRI	1423 (82.0)	0.575	93%	22%	1.19	1.15
	- AFE	2027 (75.9)	0.574	88%	26%	1.2	0.442
	- Malaria	2408 (47.8)	0.637	73%	55%	1.6	0.497
	- Preterm	652 (43.5)	0.635	64%	64%	1.74	0.574
	- Neonatal encephalopathy	1295 (40.5)	0.676	68%	67%	2.06	0.475
	- Neonatal sepsis	1205 (49.1)	0.616	65%	59%	1.56	0.604
Model 4	**Overall**	**9573 (50.9)**	**0.653**	**77%**	**54%**	**1.66**	**0.429**
	- Neonate	2948 (48.0)	0.669	74%	60%	1.84	0.431
	- Infant	2035 (58.5)	0.657	85%	46%	1.59	0.322
	- Young child	3189 (52.1)	0.646	79%	51%	1.59	0.421
	- Older child	1370 (44.8)	0.633	70%	57%	1.62	1.47
	- ALRI	1501 (86.5)	0.560	95%	17%	1.14	0.293
	- AFE	2128 (79.7)	0.568	91%	22%	1.18	0.39
	- Malaria	2756 (54.7)	0.637	80%	48%	1.52	0.422
	- Preterm	816 (54.4)	0.635	74%	53%	1.57	0.487
	- Neonatal encephalopathy	1646 (51.5)	0.651	75%	55%	1.67	0.448
	- Neonatal sepsis	1406 (57.2)	0.620	73%	51%	1.49	0.528

Model 1 (WHO) = Respiratory rate ≥70 breaths per minute (bpm), Central cyanosis, Severe respiratory distress (any of: severe chest wall in-drawing, grunting, gasping, tracheal tug, head nodding), Inability to feed.
Model 2 = Model 1 with age-specific tachypnoea (Neonate ≥70 bpm; Infant ≥60 bpm; Young child ≥50 bpm; Older child ≥40 bpm).
Model 3 = Model 2 plus Decreased conscious state (unconscious/difficult to rouse/confused).
Model 4 = Model 3 plus Heart rate ≥160 beats per minute.
ALRI = acute lower respiratory infection; AFE = acute febrile encephalopathy; AUC = the area under the ROC curve; LR+ positive likelihood ratio (LR+ = sensitivity/(1-specificity)); LR- negative likelihood ratio (LR- = specificity/(1-sensitivity)). A positive LR >10 and a negative LR <0.1 are considered to exert highly significant changes in probability, such as to alter clinical management.

imised the amount of missing data, and our audit of documentation practices prior to starting the study reassured us that documentation practices overall were excellent [21]. Nonetheless, some clinical signs may not have been identified and/or documented correctly, resulting in under-identification of some signs (and possibly over-identification of others). To address anticipated missing data on gestational age (prematurity was only recorded in 32% of neonates) we reported the composite "small/preterm" category (birth weight was recorded in 91%) [62,63].

We recognise the limits of our diagnostic classifications, and the particular challenges in pneumonia [64]. We aimed to increase reliability of diagnosis by (i) using standardised case definitions based on objectively recorded signs, symptoms, and investigations from the time of admission (rather than clinician diagnosis alone) and (ii) considering multiple diagnoses and adjusting for them in analysis (rather than selecting an arbitrary 'primary' diagnosis). For ALRI, we used the widely accepted WHO definition that is regarded as simple, sensitive, and generalizable with the main limitation being inclusion of a heterogenous group of aetiologies (viral, bacterial and other) [64]. Importantly, our prevalence estimates reflect hypoxaemia prevalence in real-life clinical contexts and are reported according to diagnoses and syndromes that front-line healthcare workers can identify. These estimates may be different in a more controlled trial setting. If our results are influenced by under-recognition of respiratory compromise this would further support the importance of using pulse oximetry as an objective tool to identify hypoxaemia in the high-risk population of hospitalised children.

Mortality is influenced by contextual factors related to case-mix and severity of illness (e.g. care-seeking, admission criteria) and quality of care (e.g. time, staffing, adherence to guidelines, equipment). We accounted for some of these variables through adjust-

ment and stratified reporting, but will explore these issues more fully in a separate paper focussing on clinical outcomes.

We believe that our findings are representative of hypoxaemia as it is encountered among children and neonates admitted to small and medium-sized hospitals in Nigeria. While the precise estimates will vary in other regions, we believe our findings will have wide relevance to healthcare workers and managers in other LMICs, particularly in Africa.

5. Conclusions

Hypoxaemia is common in respiratory and non-respiratory acute childhood illness and increases the risk of death substantially. Given the limitations of clinical assessment, pulse oximetry is an essential tool for detecting hypoxaemia, and should be part of the routine assessment of all hospitalised neonates and children. Efforts to scale up pulse oximetry and oxygen therapy should consider the needs of, and potential impact on, neonates and children with non-pneumonia conditions.

Funding

Bill and Melinda Gates Foundation.

Ethics

This study obtained ethics approval from the University of Melbourne (1543797.1) and University of Ibadan/University College Hospital Ethics Committee, Ibadan, Nigeria (UI/EC/16/0413).

Declaration of Competing Interest

HG, AAB, AIA, OBO, DP, EN, TD, and AGF received payment for services on this project from the funder (Bill and Melinda Gates Foundation) and RI is an employee of the funder. HG reports consultancy grants from WHO for unrelated work during the conduct of the study. All other authors declare no competing interests.

CRediT authorship contribution statement

Hamish Graham: Conceptualization, Data curation, Formal analysis, Writing - original draft. **Ayobami A. Bakare:** Data curation, Writing - review & editing. **Adejumoke I. Ayede:** Conceptualization, Data curation. **Oladapo B. Oyewole:** Data curation, Writing - review & editing. **Amy Gray:** Writing - review & editing. **David Peel:** Writing - review & editing. **Barbara McPake:** Writing - review & editing. **Eleanor Neal:** Writing - review & editing. **Shamim A. Qazi:** Writing - review & editing. **Trevor Duke:** Conceptualization, Writing - review & editing. **Adegoke G. Falade:** Conceptualization, Data curation, Writing - review & editing.

Acknowledgements

We thank the participating hospitals and their clinical, technical and managerial staff: Adeoyo Maternity Hospital (Ibadan, Oyo state); Baptist Medical Centre (Saki, Oyo state); Mother and Child Hospital (Akure, Ondo state); Oluyoro Catholic Hospital (Ibadan, Oyo state); Oni Memorial Children's Hospital (Ibadan, Oyo state); Our Lady of Fatima Catholic Hospital (Osogbo, Osun state); Sacred Heart Hospital (Abeokuta, Ogun state); Seventh Day Adventist Hospital (Ife, Osun state); State Hospital Ijaeye (Abeokuta, Ogun state); State Hospital Oyo (Oyo, Oyo state); State Hospital Saki (Saki, Oyo state); State Specialist Hospital (Akure, Ondo state).

We thank all members of the Nigerian Oxygen Implementation team; representatives from the Federal Ministry of Health; representatives from the state Ministry of Health and Hospital Management Boards in Oyo, Ondo, Ogun, and Osun states; support staff at the Centre for International Child Health in Melbourne Australia.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.eclinm.2019.10.009.

References

[1] WHO. Oxygen therapy for children. Geneva: World Health Organization; 2016.
[2] Subhi R, Adamson M, Campbell H, Weber M, Smith K, Duke T. The prevalence of hypoxaemia among ill children in developing countries: a systematic review. Lancet Infect Dis 2009;9:219–27.
[3] Lazzerini M, Sonego M, Pellegrin MC. Hypoxaemia as a mortality risk factor in acute lower respiratory infections in children in low and middle-income countries: systematic review and meta-analysis. PLoS One 2015;10(9):e0136166.
[4] Duke T, Wandi F, Jonathan M, et al. Improved oxygen systems for childhood pneumonia: a multihospital effectiveness study in Papua New Guinea. Lancet 2008;372(9646):1328–33.
[5] Graham H, Tosif S, Gray A, et al. Providing oxygen to children in hospitals: a realist review. Bull World Health Organ 2017;95(4):288–302.
[6] Gray AZ, Morpeth M, Duke T, et al. Improved oxygen systems in district hospitals in Lao PDR: a prospective field trial of the impact on outcomes for childhood pneumonia and equipment sustainability. BMJ Open 2017;1.
[7] Floyd J, Wu L, Hay Burgess D, Izadnegahdar R, Mukanga D, Ghani AC. Evaluating the impact of pulse oximetry on childhood pneumonia mortality in resource-poor settings. Nature 2015;528(7580):S53–SS9.
[8] Adebola O, Babatunde O, Bose O. Hypoxemia predicts death from severe falciparum malaria among children under 5 years of age in Nigeria: the need for pulse oximetry in case management. Afr Health Sci 2014;14(2):397–407.
[9] Orimadegun AE, Ogunbosi BO, Carson SS. Prevalence and predictors of hypoxaemia in respiratory and non-respiratory primary diagnoses among emergently ill children at a tertiary hospital in south western Nigeria. Trans R Soc Trop Med Hyg 2013;107(11):699–705.
[10] Morgan MC, Maina B, Waiyego M, et al. Pulse oximetry values of neonates admitted for care and receiving routine oxygen therapy at a resource-limited hospital in Kenya. J Paediatr Child Health 2018;54(3):260–6.
[11] Wandi F, Peel D, Duke T. Hypoxaemia among children in rural hospitals in Papua New Guinea: epidemiology and resource availability – a study to support a national oxygen programme. Ann Trop Paediatr 2006;26(4):277–84.
[12] Junge S, Palmer A, Greenwood BM, Kim Mulholland E, Weber MW. The spectrum of hypoxaemia in children admitted to hospital in the Gambia, West Africa. Trop Med Int Health 2006;11:367–72.
[13] Maitland K, Levin M, English M, Mithwani S, Peshu N, Marsh K, Newton CR. Severe P. falciparum malaria in Kenyan children: evidence for hypovolaemia. QJM 2003;96(6):427–34.
[14] English M, Ngama M, Musumba C, et al. Causes and outcome of young infant admissions to a Kenyan district hospital. Arch Dis Child 2003;88:438–43.
[15] Weber MW, Carlin JB, Gatchalian S, Lehmann D, Muhe L, Mulholland EK. Predictors of neonatal sepsis in developing countries. Pediatr Infect Dis J 2003;22:711–17.
[16] Duke T, Blaschke AJ, Sialis S, Bonkowsky JL. Hypoxaemia in acute respiratory and non-respiratory illnesses in neonates and children in a developing country. Arch Dis Child 2002;86:108–12.
[17] Chisti MJ, Duke T, Robertson CF, et al. Clinical predictors and outcome of hypoxaemia among under-five diarrhoeal children with or without pneumonia in an urban hospital, Dhaka, Bangladesh. Trop Med Int Health 2012;17(1):106–11.
[18] UN IGCME.. Levels and trends in child mortality: report 2018. New York, US: United Nations Children's Fund (UNICEF); 2018.
[19] WHO and Maternal and Child Epidemiology Estimation Group (MCEE). UNICEF data: monitoring the situation of children and women: cause of death. 2015. http://data.unicef.org (accessed 4 April 2017).
[20] Graham HR, Ayede AI, Bakare AA, et al. Improving oxygen therapy for children and neonates in secondary hospitals in Nigeria: study protocol for a stepped-wedge cluster randomised trial. Trials 2017;18(1):502.
[21] Graham H, Ayede AI, Bakare A, et al. Oxygen for children and newborns in non-tertiary hospitals in South-West Nigeria: a needs-assessment. Afr J Med Med Sci 2016(45).
[22] Graham HR, Bakare AA, Gray A, et al. Adoption of paediatric and neonatal pulse oximetry by 12 hospitals in Nigeria: a mixed-methods realist evaluation. BMJ glob Health 2018;3:e000812.
[23] WHO. Pocket book of hospital care for children: guidelines for the management of common childhood illnesses. 2nd ed. Geneva: World Health Organization; 2013.
[24] Dubowitz G, Breyer K, Lipnick M, et al. Accuracy of the lifebox pulse oximeter during hypoxia in healthy volunteers. Anaesthesia 2013;68:1220–3.
[25] Enright A, Merry A, Walker I, Wilson I. Lifebox: a global patient safety initiative. A&A Case Rep 2016;6(12):366–9.

[26] Christiansen T, Lauritsen J. Comprehensive data management and basic statistical analysis system, Odense, Denmark: EpiData Association; 2010. Odense, Denmark: EpiData Association.
[27] StataCorp. Stata statistical software: release 15. College Station, Texas: StataCorp LP; 2017.
[28] Thabane L, Mbuagbaw L, Zhang S, et al. A tutorial on sensitivity analyses in clinical trials: the what, why, when and how. BMC Med Res Methodol 2013;13:92.
[29] Hemming K, Haines TP, Chilton PJ, Girling AJ, Lilford RJ. The stepped wedge cluster randomised trial: rationale, design, analysis, and reporting. BMJ Case Rep 2015;350 h391-h.
[30] Davey C, Hargreaves J, Thompson JA, et al. Analysis and reporting of stepped wedge randomised controlled trials: synthesis and critical appraisal of published studies, 2010 to 2014. Trials 2015;16:358.
[31] Seed P, Tobias A. DIAGT: Stata module to report summary statistics for diagnostic tests compared to true disease status. Stata Technical Bulletin 2001;59:sbe36.1.
[32] Bassat Q, Lanaspa M, Machevo S, et al. Hypoxaemia in Mozambican children <5 years of age admitted to hospital with clinical severe pneumonia: clinical features and performance of predictor models. Trop Med Int Health 2016;21(9):1147–56.
[33] Wandeler G, Pauchard JY, Zangger E, Diawara H, Gehri M. Which clinical signs predict hypoxaemia in young Senegalese children with acute lower respiratory tract disease? Paediatr Int Child Health 2015;35(1):65–8.
[34] Salah ET, Algasim SH, Mhamoud AS, NEOSA Husian. Prevalence of hypoxemia in under-five children with pneumonia in an emergency pediatrics hospital in Sudan. Indian J Crit Care Med 2015;19:203.
[35] Abdulkadir MB, Ibraheem RM, Gobir AA, Johnson WB. Hypoxaemia as a measure of disease severity in young hospitalised Nigerian children with pneumonia: a cross-sectional study. SAJCH S Afr J Child Health 2015;9(2):53–6.
[36] Izadnegahdar R, Cohen AL, Klugman KP, Qazi SA. Childhood pneumonia in developing countries. Lancet Respir Med 2013;1(7):574–84.
[37] Graham S. Challenges to improving case management of childhood pneumonia at health facilities in resource-limited settings. Bull World Health Organ 2008;86(5):349–55.
[38] English M, Punt J, Mwangi I, McHugh K, Marsh K. Clinical overlap between malaria and severe pneumonia in African children in hospital. Trans R Soc Trop Med Hyg 1996;90:658–62.
[39] Raman S, Prince NJ, Hoskote A, Ray S, Peters MJ. Admission PaO2 and mortality in critically ill children: a cohort study and systematic review. Pediatr Crit Care Med 2016;17(10):e444–ee50.
[40] Ayieko P, English M. In children aged 2–59 months with pneumonia, which clinical signs best predict hypoxaemia. J Trop Pediatr 2006;52:307–10.
[41] Benet T, Picot VS, Awasthi S, et al. Severity of pneumonia in under 5-year-old children from developing countries: a multicenter, prospective, observational study. Am J Trop Med Hyg 2017;97(1):68–76.
[42] Duke T, Mgone J, Frank D. Hypoxaemia in children with severe pneumonia in Papua New Guinea. Int J Tuberc Lung Dis 2001;5:511–19.
[43] Margolis PA, Ferkol TW, Marsocci S, et al. Accuracy of the clinical examination in detecting hypoxemia in infants with respiratory illness. J Pediatr 1994;124(4):552–60.
[44] Mwaniki MK, Nokes DJ, Ignas J, et al. Emergency triage assessment for hypoxaemia in neonates and young children in a Kenyan hospital: an observational study. Bull World Health Organ 2009;87:263–70.
[45] Onyango FE, Steinhoff MC, Wafula EM, Wariua S, Musia J, Kitonyi J. Hypoxaemia in young Kenyan children with acute lower respiratory infection. Br Med J 1993;306:612–15.
[46] Smyth A, Hart HCC. Clinical predictors of hypoxaemia in children with pneumonia. Ann Trop Paediatr 1998;18:31.
[47] Usen S, Webert M. Clinical signs of hypoxaemia in children with acute lower respiratory infection: indicators of oxygen therapy. Int J Tuberc Lung Dis 2001;5(6):505–10.
[48] Weber MW, Usen S, Palmer A, Jaffar S, Mulholland EK. Predictors of hypoxaemia in hospital admissions with acute lower respiratory tract infection in a developing country. Arch Dis Child 1997;76:310–14.
[49] Zhang L, Mendoza-Sassi R, Santos JCH, Lau J. Accuracy of symptoms and signs in predicting hypoxaemia among young children with acute respiratory infection: a meta-analysis. Int J Tuberc Lung Dis 2011;15(3):317–25.
[50] Duke T, Graham SM, Cherian MN, et al. Oxygen is an essential medicine: a call for international action. Int J Tuberc Lung Dis 2010;14:1362–8.
[51] Duke T, Peel D, Graham S, Howie S, Enarson PM, Jacobson R. Oxygen concentrators: a practical guide for clinicians and technicians in developing countries. Ann Trop Paediatr 2010;30:87–101.
[52] Duke T, Subhi R, Peel D, Frey B. Pulse oximetry: technology to reduce child mortality in developing countries. Ann Trop Paediatr 2009;29:165–75.
[53] Ginsburg AS, Van cleve WC, Thompson MIW, English M. Oxygen and pulse oximetry in childhood pneumonia: a survey of healthcare providers in resource-limited settings. J Trop Pediatr 2012;58:389–93.
[54] Ginsburg AS, Izadnegahdar R, Klugman KP. World Pneumonia Day 2016: pulse oximetry and oxygen. Lancet Glob Health 2016:e893–4.
[55] McCollum ED, Bjornstad E, Preidis GA, Hosseinipour MC, Lufesi N. Multicenter study of hypoxemia prevalence and quality of oxygen treatment for hospitalized Malawian children. Trans R Soc Trop Med Hyg 2013;107(5):285–92.
[56] King C, Boyd N, Walker I, et al. Opportunities and barriers in paediatric pulse oximetry for pneumonia in low-resource clinical settings: a qualitative evaluation from Malawi and Bangladesh. BMJ Open 2018;8:e019177.
[57] Matai S, Peel D, Wandi F, Jonathan M, Subhi R, Duke T. Implementing an oxygen programme in hospitals in Papua New Guinea. Ann Trop Paediatr 2008;28:71–8.
[58] McCollum ED, King C, Deula R, et al. Pulse oximetry implementation with rural frontline and community health workers during three years of child pneumonia care in two central Malawi districts: a prospective observational study. Bull World Health Organ 2016;94(12):893–902.
[59] King C, Mvalo T, Sessions K, et al. Performance of a novel re-usable paediatric pulse oximeter probe. Pediatr Pulmonol 2019;54:1052–9.
[60] Morgan MC, Maina B, Waiyego M, et al. Oxygen saturation ranges for healthy newborns within 24 h at 1800m. Arch Dis Child Fetal Neonatal Ed 2017;102(3):266–8.
[61] English M, Ayieko P, Nyamai R, Were F, Githanga D, Irimu G. What do we think we are doing? How might a clinical information network be promoting implementation of recommended paediatric care practices in Kenyan hospitals? Health Res Policy Syst 2017;15(1):4.
[62] Villar J, Giuliani F, Fenton TR, Ohuma EO, Ismail LC, Kennedy SH. INTERGROWTH-21st very preterm size at birth reference charts. Lancet 2016;387(10021):844–5.
[63] Villar J, Ismail LC, Victora CG, et al. International standards for newborn weight, length, and head circumference by gestational age and sex: the Newborn Cross-Sectional Study of the INTERGROWTH-21st Project. Lancet 2014;384(9946):857–68.
[64] Mackenzie G. The definition and classification of pneumonia. Pneumonia 2016;8:14.
[65] Modi A, Atam V, Jain N, Gutch M, Verma R. The etiological diagnosis and outcome in patients of acute febrile encephalopathy: a prospective observational study at tertiary care center. Neurol India 2012;60(2):168–73.
[66] Lee AC, Kozuki N, Blencowe H, et al. Intrapartum-related neonatal encephalopathy incidence and impairment at regional and global levels for 2010 with trends from 1990. Pediatr Res 2013;74(Suppl 1):S50–72.