Hypoxaemia in Mozambican children < 5 years of age admitted to hospital with clinical severe pneumonia: clinical features and performance of predictor models

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Background

Pneumonia remains the major cause of childhood deaths globally. It accounts for 18% of the under five mortality, and an estimated 14·9 million (95% CI: 12·4–18·1 million) hospital admissions among young children worldwide.[1,2] Hypoxaemia is the most severe complication of pneumonia in children, and is strongly associated with increased mortality.[3-6] The gold standard to diagnose hypoxaemia is arterial blood gas analysis, but non-invasive point-of-care pulse oximetry provides an accurate measure at non-extreme levels of oxygen saturation presenting obvious advantages in everyday practice.[7] However, pulse oximetry is not widely available in developing countries because of its cost, and hypoxaemia diagnosis relies on clinical signs and symptoms.[8]

A recent Cochrane review on 14 observational studies concluded that there is no single clinical sign or symptom that accurately identifies hypoxaemia in children with lower respiratory tract infection.[9] Different authors have attempted to determine combinations of signs and symptoms to improve the accuracy of hypoxaemia clinical diagnosis. The WHO criteria for hypoxaemia (i.e. inability to feed or drink or cyanosis or respiratory rate >70 breaths/min or severe chest indrawing) are a sensitive combination of clinical signs, although its moderate specificity could be problematic in limited-resource settings due to the risk of wasting oxygen treating non-hypoxaemic children.[10,11] There is no consensus on whether to prioritize sensitivity or specificity of the variables used to build combined models.[4,11-17]

The present study aimed to describe hypoxaemia in children admitted with severe clinical pneumonia to a District Hospital in Southern Mozambique, to study clinical signs and symptoms alone and in combination to diagnose hypoxaemia, and to identify microorganisms associated with hypoxaemia. Mathematical modelling is proposed as a convenient way to compare different diagnostic models.

Methods

Study setting and population

This prospective study was conducted from September 2006 to September 2007 at Manhiça District Hospital (MDH), the referral health facility for a rural area in Southern Mozambique. The *Centro de Investigação em Saúde de Manhiça* (CISM) runs a Demographic Surveillance System (DSS) since 1996, linked with a morbidity surveillance system at Manhiça District Hospital and peripheral health centers.[18] Such surveillance covered, at the time of the study, an area of approximately 500 km^2 and 80,000 persons. By then, severe pneumonia accounted for 16% of hospitalizations among children less than two years of age, and had an associated case-fatality rate (CFR) of 11%.[19] The average altitude of the Manhiça district is 50 meters above sea level.

Procedures for recruited children and sample collection

This study was part of a larger project designed to characterize children less than five years of age admitted with respiratory distress.[20] Children fulfilling inclusion criteria and whose parents had signed an informed consent form underwent study procedures. Children with a known congenital heart or pulmonary malformation, a known history of asthma, and those who were household contacts of know tuberculosis cases or suspected to have pulmonary tuberculosis were excluded. Antero-posterior chest radiographs were obtained within the first 48 hours of hospitalization. Pulse oximetry (Nellcor, Boulder, CO) was used to determine oxygen saturation, and nasopharyngeal aspirates were collected using NPAK® Kits (MPRO, Farmington Hills, MI). Venous blood was obtained at admission for malaria diagnosis, blood culture, full blood cell count, and biochemical determinations.

X-ray interpretation

Chest X-rays, performed with a Siemens machine, were interpreted blindly by two independent readers following a WHO-designed X-ray interpretation protocol.[21] Episodes with consolidation and/or pleural effusion were defined as radiologically confirmed pneumonia ("endpoint pneumonia"). Other radiological endpoints included interstitial infiltrates or normal radiographs. A third reader interpreted images with discordant results from the two primary readers.

Laboratory methods

Packed cell volume was measured with haematocrit reader (Hawksley and Sons Ltd., Lancing, United Kingdom). Thick and thin blood films for malaria diagnosis were processed and examined according to standard methods.[18] Blood lactate levels were determined using Lactate Pro® (FaCT Canada, Quesnel, British Columbia, Canada) at the bedside. Haematology analyser (Kx21; Sysmex, Denver, CO), and biochemistry analyser (Vitros DT60; Ortho Clinical Diagnostics, Raritan, NJ) were used. Blood cultures were processed and bacterial isolates identified as previously described. [22-24] The presence of different respiratory viruses (influenza virus A and B, respiratory syncytial virus A and B, parainfluenza virus 1, 2, 3 and 4, adenovirus, human rhinovirus, human metapneumovirus, and enterovirus) in nasopharyngeal aspirates (NPA) was determined using four different polymerase chain reactions.[20] *Pneumocystis jirovecii* infections were investigated in NPA samples using molecular methods.[25] Three specific genes were targeted: 1) mtLSU rRNA locus; 2) mtSSU rRNA locus; and 3) DHPS locus. [26,27]

HIV-specific procedures

Recruited study children were referred for HIV counselling and testing, which required an additional parental consent.[28] HIV-1 serodiagnosis was performed using a sequential testing

algorithm with two rapid HIV-1 antibody tests (Determine®; Abbott Laboratories, Abbott Park, IL and Unigold®; Trinity Biotech, Plc., Bray, Ireland). HIV infection was confirmed in seropositive children <18 months and older children with discordant tests using HIV-1 DNA Amplicor Test (version 1.5; Roche Molecular Systems, Inc., Branchburg, NJ). HIV diagnosed children were followed-up according to national guidelines.

Definitions

Severe pneumonia was defined as cough and/or difficult breathing, plus increased respiratory rate according to age group and chest indrawing. An increased respiratory rate was defined according to age following standard WHO definitions.[29] Hypoxaemia was defined as having oxygen saturation from pulse oximetry < 90%, and severe hypoxaemia as having oxygen saturation < 80%. Nutritional status was based on weight-for-age Z scores, which were calculated using the least mean square method and the 2000 CDC Growth Reference (Centers for Disease Control and Prevention, Atlanta, GA). *Pneumocystis jirovecii* pneumonia (PCP) was defined as having at least two *Pneumocystis jirovecii* genes amplified by PCR in a child with symptoms of pneumonia. This was decided to increase the specificity of the definition. Coagulase-negative staphylococci, *Bacillus* species, or *Micrococcus* species were considered contaminants if isolated in the blood culture.

Signs and symptoms were individually assessed by the medical staff responsible for the child admission (single observer), and recorded in study specific questionnaires as binary variables (present/absent). A paediatrician involved in the study trained the medical staff in recognition of respiratory signs and symptoms following standardized definitions. Difficult breathing and intake refusal were reported by parents or guardians as a common practice consistent with IMCI guidelines.

Case fatality rates represent in-hospital mortality and do not include patients who absconded or were transferred. The rainy season was defined as November–April, and the dry season as May–October.

Case management and treatment

Severe pneumonia was managed according to national guidelines, consistent with the IMCI WHO guidelines.[29] Children requiring specialized care were transferred to Maputo Central Hospital. Oxygen was available through oxygen concentrators or oxygen cylinders throughout the study in Manhiça. By the time children were recruited, *Haemophilus influenzae* b or pneumococcal vaccines were not available in Mozambique.

Data management and statistical analysis

All study questionnaires were double-entered in FoxPro version 5.0 (Microsoft Corp., Redmond, WA). Statistical analyses were done with Stata 13 (Stata Corp., College Station, TX).

Categorical variables were compared using a chi-square test or Fisher's exact test. Normal distribution was assessed visually. For non-normally distributed variables, medians and interquartile ranges are presented, and Wilcoxon rank-sum test was used to assess differences. Univariate and multivariate logistic regression analyses were performed to assess associations between explanatory variables and presenting hypoxaemia. Positive and negative likelihood ratios were calculated for all the variables suitable for use as clinical predictors of hypoxaemia. For the multivariate analysis, automated backward stepwise estimations were calculated. All variables associated with hypoxaemia at a significance level of $p\text{-value} < 0{\cdot}10$ in the univariate analysis were included in the model. Odds ratios (OR) and 95% confidence intervals (CI) are presented. Combinations of significant and independent variables with high positive likelihood ratios were used to build models for hypoxaemia prediction. Diagnostic values were calculated for these predictor models and for the WHO-recommended model

(Intake refusal or cyanosis or respiratory rate ≥ 70 bpm or chest indrawing), and receiver-operating curves (ROC) and the area under the ROC curve (AUC) were obtained as well.

We built and tested models described in the literature to predict hypoxaemia in the dataset of the present study. Moreover, we tested combinations of the independent predictors from the multivariate analysis, and non-independent predictors significantly associated with hypoxaemia in the univariate analysis with a high positive likelihood ratio. In order to compare their performances in a convenient, straightforward way, a deterministic model was set to calculate the number of hypoxaemic children not receiving oxygen due to 1) remaining undetected (low sensitive models) and 2) shortage of oxygen supplies (highly sensitive/low specific models in a limited-resource setting) according to different scenarios of oxygen availability.

Ethical approvals

The study was approved by the Mozambican National Bioethics Committee, the Institutional Review Board of the Hospital Clinic (Barcelona, Spain), and the World Health Organization review board.

Role of the funding source

The sponsors of the study did not play any role in the study design, analysis, or manuscript writing.

Results

General overview

During the study period (20th September 2006-20th September 2007), 2,943 children were admitted to MDH, from which 926 (31·5%) had severe pneumonia according to the IMCI definition. A total of 825 of these patients (28% of all admissions; 89% of all children with study criteria) provided consent and were included in the analysis. The median age was 10·5 months (IQR 4.2 – 21), 440 (53·3%) were infants (<12 months old), and 328 (39·8%) were female. Among admitted children with available results blood culture was positive in 14·4% (104/723) of cases, viral detection in NPA was positive in 48·8% (390/800), malaria slide in 13% (106/816), and *Pneumocystis jirovecii* in 6·9% (57/825) of the NPA. Co-infections were common. HIV infection was present in 25·7% (133/517) of the patients tested.

Characteristics of patients according to hypoxaemia status on admission

A total of 230 (27·9%) children had hypoxaemia detected by pulse oximetry on admission (Table 1); 81 (9·8%) of them being severely hypoxaemic. Median duration of hypoxaemia among study children was 24 hours (IQR 6-96 hours), and 41% (78/190) of initially hypoxaemic children presented sustained hypoxaemias of over 48 hours of duration. Hypoxaemic children were younger than non-hypoxaemic children (median age 6·8 months vs. 12·1 months, p<0·001), and were admitted longer (median duration of admission among survivors 4·9 days vs. 4·3 days, p=0·001) (Table 1). Of those children without hypoxaemia upon admission, 10% (60/595) developed hypoxaemia throughout their admissions.

Regarding complementary exams (Table 1), hypoxaemic children more frequently had abnormal chest radiographs (i.e. infiltrates, consolidation or pleural effusion) than non-hypoxaemic children, more frequently had acidosis on admission, higher venous lactate

levels, and were less frequently anaemic than non-hypoxaemic children. There were no significant differences between the two groups in terms of gender or nutritional status.

The in-hospital case fatality rate was significantly higher in hypoxaemic children (unadjusted OR for death 3·22, 95%CI 1·98 – 5·21, p<0·001).

Signs and symptoms associated with hypoxaemia

Univariate analysis

Mothers reported difficult breathing before admission very frequently in both groups, but significantly more in the hypoxaemic group (Table 2). A history of fever, cough, anorexia or refusal to feed, diarrhoea or seizures was reported with a similar frequency by mothers in both groups. Hypoxaemic children presented more frequently cyanosis, thoracoabdominal breathing, respiratory rate ≥ 70 breaths per minute (bpm), deep breathing, grunting, chest indrawing, prostration and deep coma than non-hypoxaemic children. Digital clubbing, a sign associated with chronic respiratory or cardiac condition, was significantly more frequent among hypoxaemic children, although rare. Age-specific tachypnea or pathological auscultation (hypophonesis, wheezing or crackles) were not associated with hypoxaemia.

Validity of single clinical signs to diagnose hypoxaemia

The most sensitive clinical signs (sensitivity around 90% or more) to diagnose hypoxaemia were, in descending order, difficult breathing, chest indrawing, fever, age-specific tachypnea and cough (Supplementary table 1); although specificity for these variables was low (below 17%). The most specific signs (specificity >90%) were digital clubbing, cyanosis, deep coma, hypophonesis, seizures, thoracoabdominal breathing, and deep breathing; but their sensitivity was very low in all cases (below 17·8%).

Independent clinical predictors of hypoxaemia

In the multivariate analysis (Table 3), cyanosis (adjusted OR 2·76; 95%CI 1·13-6·73), difficult breathing (aOR 2·69; 95%CI 1·06-6·81), thoracoabdominal breathing (aOR 1·76; 95%CI 1·08-2·87), respiratory rate ≥70 bpm (aOR 1·92; 95%CI 1·34-2·77), crackles (aOR 1·60; 95%CI 1·12-2·31), and prostration (aOR 1·64; 95%CI 1·02-2·64) were independently associated with having hypoxaemia on admission. Nasal flaring and chest indrawing were not independently associated with hypoxaemia.

Predictor models for hypoxaemia

The WHO-like model (model 1), which included intake refusal or cyanosis or respiratory rate ≥ 70 bpm or chest indrawing, had a very high sensitivity (97%) but very low specificity (12·8%). The model with the greater AUC was model 3 (Figure 1), combining cyanosis or thoracoabdominal breathing or respiratory rate ≥ 70 bpm.

Deterministic model to evaluate predictor models by oxygen availability

Applying the deterministic model to the population of the present study in different scenarios of oxygen availability showed that the best model in case of very low availability (total oxygen stock <60% of total requirements) was model 2 (Figure 2). In the case of a stock that would cover 100% of total oxygen requirements, i.e., just enough for all hypoxaemic children if hypoxaemia diagnosis was perfect, model 3 would perform better. However, due to errors in prediction, 56% (129/230) of hypoxaemic children would not receive oxygen.

Association between hypoxaemia and microbiologic results

Regarding microbiologic results, infection by *Pneumocystis jirovecii*, *Staphylococcus aureus* or human metapneumovirus were significantly associated with hypoxaemia, occurring in 51%, 71% and 46% of children with these infections, respectively (Table 5). The association

between HIV infection and hypoxaemia was partially confounded by PCP diagnosis, and the adjusted Odds Ratio was 1·51 (95%CI 0·97 – 2·36, p=0.07). Malaria parasitemia was associated with lower risk of hypoxaemia in children with the syndrome of clinical pneumonia.

Regarding duration of hypoxaemia by aetiology, the longest median period until recovery was 72 hours corresponding to PCP (IQR 30 – 168 hours), and the shortest was 6 hours in parainfluenza virus infected children (IQR 6 – 24 hours) and in human metapneumovirus infected children (IQR 6 – 48 hours; Figure 3). In children with invasive bacterial disease, the median duration of hypoxaemia was 48 hours (IQR 6 – 96 hours). Regarding chest x-ray results, duration of hypoxaemia was significantly longer in children with infiltrates (median 24 hours, IQR 6 – 72) and consolidation (median 24 hours, IQR 6 – 96) compared to children with normal chest x-ray (median 6 hours, IQR 1 – 24; p-value from Kruskal-Wallis test < 0·001).

Discussion

In our series, the prevalence of hypoxaemia among admitted children with clinical severe pneumonia was 27·9%, and a significant proportion of the children presented sustained hypoxaemia episodes, which, in the absence of oxygen, would likely have resulted in death. Hypoxaemia was very strongly associated with risk of death in our series (unadjusted OR 3·22, p<0·001), which is consistent with other reports from developing countries.[3-5,16] Almost one out of five hypoxaemic children admitted to our hospital died. One limitation of this analysis is that HIV results were not available for over one-third of the patients, and HIV infection was not included in the multivariable analysis. However, HIV infection was not a strong confounder of the association between hypoxaemia on admission and death when assessed in the subsample of children with available HIV results. The high mortality among hypoxaemic children despite the high oxygen availability at MDH, better than in most health

facilities in Sub-Saharan Africa outside of a research context, warrants further studies on oxygen delivery.

The median prevalence of hypoxaemia in children from developing countries admitted with WHO-defined pneumonia has been estimated at 13%, but is highly variable across studies.[6] Studies with greater reported hypoxaemia were closely examined to extract data about hypoxaemia definition, pneumonia definition, inclusion criteria and setting altitude.[5,12,14,30-32] Hypoxaemia definition –either <90% or <2SD of normal values, corresponding to 85-90% - and pneumonia definition – based on WHO-defined pneumonia – were mostly consistent across studies. Altitude of settings was consistently higher (255 to 3750 meters) than the average Manhiça district altitude (50 meters) and may account for the lower prevalence. Interestingly, 10% (60/595) of the non-hypoxaemic children on admission developed hypoxaemia during admission. This was not associated with *Pneumocystis jirovecii* infection, and may be evidence of prompt assistance seeking among mothers from Manhiça district who consulted after a median time of 1 day of fever (IQR 1 – 3 days) and 2 days of cough (IQR 1 – 3 days). This information was not available in the examined studies.

Several clinical signs were independently associated with hypoxaemia, with most of them having been previously identified such as cyanosis, difficult breathing, and respiratory rate ≥70 bpm. Thoracoabdominal breathing, one of the signs with best combination of positive and negative likelihood ratio in our series, has not been commonly assessed in previous studies. Other studies have similar merits identifying signs likely to predict hypoxaemia that had not been previously reported such as head nodding, restlessness, or thoroughly assessing different respiratory rate cut-offs, or the validity of combined predictor models in different age-groups.[16,30,33] However, none of the identified signs or symptoms, or combination of predictors have proved to be accurate enough to diagnose hypoxaemia, and even the

performance of validated predictor models may be importantly driven by clinician's subjectivity.[34]

Comparing accuracy and validity of different predictor models is challenging and to base the decision on the test characteristics (such as sensitivity, specificity, likelihood ratios or AUC) may be misleading. A deterministic model is proposed in this analysis as a straightforward way to compare predictor models in different scenarios of oxygen availability. The best model, defined as one that leaves fewer hypoxaemic children without oxygen supplements, changes according to availability of oxygen. Noteworthy, the proportion of hypoxaemic children not receiving oxygen was unacceptably high when the decision to treat was based on clinical grounds, even in situations of abundant oxygen supply.

Studies assessing pulse oximetry combined with oxygen bottles or oxygen concentrators support the cost-effectiveness of pulse oximetry in limited-resource settings, with median estimates ranging from US$2.97 to $52.92 per disability-adjusted life year averted.[8,35-37] Considering the inaccuracy of clinical predictors to diagnose hypoxaemia and the unsuccessful attempts to improve clinical models, cost-effectiveness studies and research on new more affordable technologies for oxygen delivery seem to be the way forward.

Conclusions

Hypoxaemia is a frequent condition in Mozambican children with clinical severe pneumonia, and its presence is a marker of severity, supporting the need of improving oxygen availability in health facilities. Although many variables were independently associated with hypoxaemia, no clinical sign or symptom alone or in combination was an accurate predictor. Mathematical modelling could be useful to compare predictor models for hypoxaemia diagnosis in limited-resource settings. The use of pulse oximeters should be encouraged, as the use of oxygen cannot be adequately prioritized otherwise.

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Declaration of interests

The authors declare no conflict of interest.

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Tables

Table 1. Characteristics of children and complementary test results, by hypoxemia (O_2 saturation < 90%) status on admission, univariate analysis

Characteristics and test results	Hypoxemic children; n (%) (n=230)	Non-Hypoxemic children; n (%) (n=595)	*p**
Female sex	100 (43·5)	228 (38·3)	0·18
Age. Median (IQR)	6·8 (2·8 – 16·2)	12·1 (5·1 – 22·2)	<0·001#
Age-group			
Infants	145 (63)	295 (49·6)	
1-5 years	85 (37)	300 (50·4)	0·001
Admission during rainy season	134 (58·3)	357 (60)	0·65
Nutritional status (n_{hypox}=227 / n_{normal}=589)			
WAZ > - 1 SD	79 (34·8)	192 (32·6)	
WAZ -1 to – 3 SD	86 (37·9)	249 (42·3)	
WAZ < - 3 SD	62 (27·3)	148 (25·1)	0·52
Axillary temperature	37·5 (36·8-38·5)	37·8 (36·8-38·8)	0·17#
Complementary exams			
Chest X-ray features (n_{hypox}=217 / n_{normal}=579)			
Normal	75 (34·6)	335 (57·9)	
Infiltrates	25 (11·5)	42 (7·3)	
Consolidation / pleural effusion	117 (53·9)	202 (34·9)	<0·001
Anemia (<33%)	108 (47·0)	344 (57·8)	0·01
Acidosis (n_{hypox}=225 / n_{normal}=567)	31 (13·8)	42 (7·4)	0·01
Venous lactate (mEq/L) Median (IQR)	2·2 (1·7 – 3·4)	2·1 (1·7 – 3)	0·04#
Outcome			
Duration of admission, days Median (IQR) (n_{hypox}=190 / n_{normal}=556)	4·9 (3·1-7·7)	4·3 (2·9 – 6·6)	0·001#
Duration of hypoxemia, hours Median (IQR)	24 (6 – 96)	NA	NA
In-hospital CFR (n_{hypox}=202 / n_{normal}=547)	40 (19·8)	39 (7·1)	< 0·001

* p-value from Chi^2 test, unless indicated otherwise

p-value from Wilcoxon rank-sum test

IQR = interquartile range. WAZ = weight-for- age Z-score. CFR = Case Fatality Rate.

Table 2. Clinical features of hypoxemic and non-hypoxemic children (univariate analysis), and validity of the variables to detect hypoxemia (O2 saturation < 90%)

Variables	Hypoxemic children; n(%) (n_{hypox}=230)	Non-Hypoxemic children; n(%) (n_{normal}=595)	*p**	Positive likelihood ratio	Negative likelihood ratio
Clinical history and complaints					
Difficult breathing	223 (97)	502 (84·4)	<0·001	1·1	0·2
Intake refusal	48 (20·9)	124 (20·8)	0·99	1·0	1·0
Cough	205 (89·1)	546 (91·2)	0·24	1·0	1·3
Fever	207 (90)	539 (90·6)	0·80	1·0	1·1
Diarrhoea	48 (20·9)	144 (24·2)	0·31	0·9	1·0
Seizures	12 (5·2)	42 (7·1)	0·34	0·7	1·0
Clinical signs on admission					
Cyanosis	18 (7·8)	9 (1·5)	<0·001	5·2	0·9
Digital clubbing	6 (2·6)	3 (0·5)	0·02#	5·2	1·0
Thoracoabdominal breathing	41 (17·8)	47 (7·9)	<0·001	2·3	0·9
Deep coma	12 (5·2)	14 (2·35)	0·04	2·2	1·0
Respiratory rate ≥70 bpm	88 (38·3)	116 (19·5)	< 0·001	2·0	0·8
Grunting	61 (26·5)	82 (13·8)	<0·001	1·9	0·9
Prostration	68 (29·6)	112 (18·8)	0·001	1·6	0·9
Hypophonesis	15 (6·5)	23 (3·9)	0·10	1·7	1·0
Deep breathing	31 (13·5)	52 (8·7)	0·04	1·5	0·9
Nasal flaring	146 (63·5)	286 (48·1)	<0·001	1·3	0·7
Chest indrawing	221 (96·1)	494 (83)	<0·001	1·2	0·2
Crackles	163 (70·9)	394 (66·2)	0·20	1·1	0·9
Wheezing	54 (23·5)	122 (20·5)	0·35	1·1	1·0
Tachypnea (age-specific)	206 (89·6)	527 (88·6)	0·68	1·0	0·9
Pallor	30 (13)	74 (12·4)	0·81	1·0	1·0
Hyperpyrexia (≥ 39ºC)	41 (17·8)	136 (22·9)	0·11	0·8	1·1
Rhinorrhoea	25 (10·9)	92 (15·5)	0·09	0·7	1·0

* p-value from Chi2 test, unless indicated otherwise

p-value from Fisher's Exact test

Table 3. Independent predictors of hypoxemia, multivariate analysis (adjusted by age-group and variables associated with hypoxemia at a significance level p<0.10 in the univariate analysis)

		95% CI		
Potential predictors of hypoxemia	**Adjusted OR**	**Lower**	**Upper**	***p***
Cyanosis	2·76	1·13	6·73	0·03
Difficult breathing	2·69	1·06	6·81	0·04
Thoracoabdominal breathing	1·76	1·08	2·87	0·02
Grunting	1·53	0·98	2·39	0·06
Respiratory rate ≥70 bpm	1·92	1·34	2·77	<0·001
Crackles	1·60	1·12	2·31	0·01
Prostration	1·64	1·02	2·64	0·04
Deep coma	2·06	0·79	5·35	0·13

Table 4. Validity of different combination models to detect hypoxemia in children from the present study

Combination of variables	Sn	Sp	PPV	NPV	Positive likelihood ratio	Negative likelihood ratio	AUC
Model 1: Intake refusal or cyanosis or respiratory rate ≥ 70 bpm or chest indrawing	97·0	12·8	30·1	91·6	1·1	0·2	0·55
Model 2: Cyanosis or thoracoabdominal breathing or deep coma (BCS ≤ 2)	27·4	89·4	50·0	76·1	2·6	0·8	0·58
Model 3: Cyanosis or thoracoabdominal breathing or respiratory rate ≥ 70 bpm	51·3	74·5	43·7	79·8	2·0	0·7	0·63

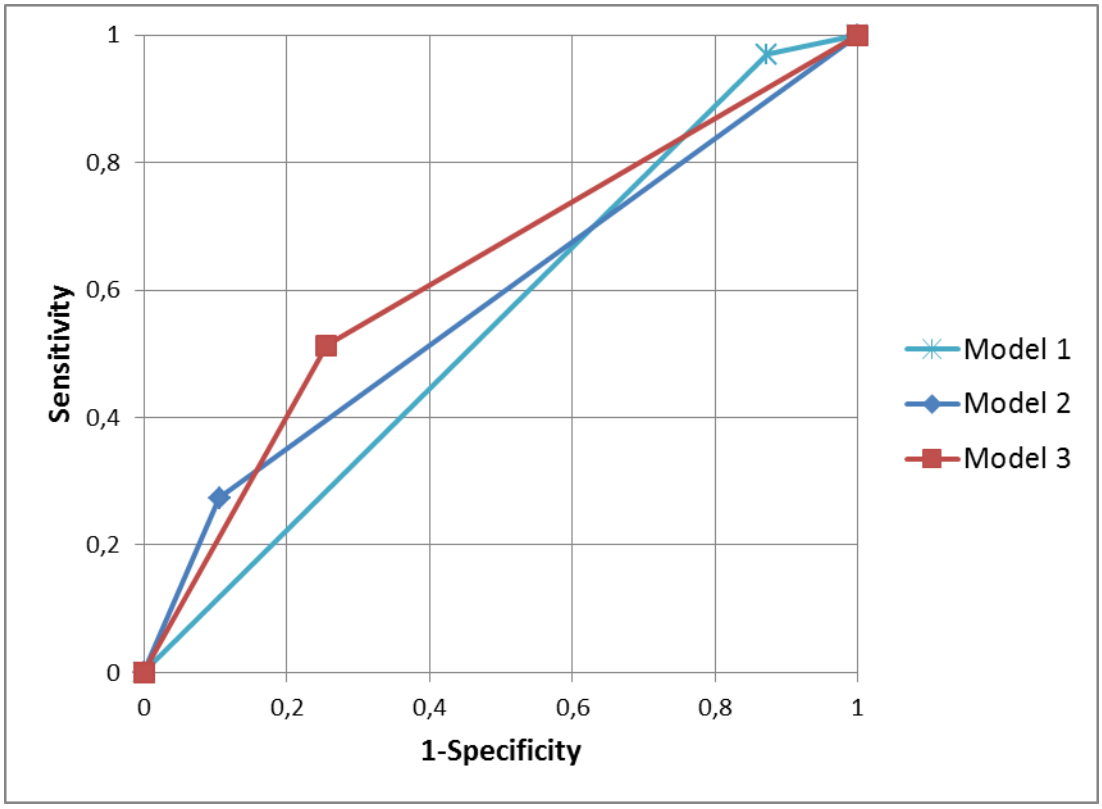
Sn = Sensitivity. Sp = Specificity. PPV = Positive predictive value. NPV = Negative predictive value. AUC = area under the ROC curve. BCS = Blantyre coma scale

Table 5. Prevalence of hypoxaemia and Odds Ratio (OR) for hypoxaemia, by microbiology result, univariate analysis

Microbiology result	Prevalence of hypoxaemia	OR for hypoxaemia	95% CI	*p value*
Positive malaria slide	18% (19/106)	0·53	0·31 – 0·90	0·02
Positive blood culture	27% (28/104)	0·96	0·60 – 1·53	0·86
Streptococcus pneumoniae	18% (8/45)	0·56	0·26 – 1·23	0·15
Haemophilus influenzae **b**	20% (5/25)	0·65	0·24 – 1·76	0·39
Enteric Gram negative bacilli	40% (4/10)	1·73	0·48 – 6·23	0·39
Staphylococcus aureus	71% (5/7)	6·50	1·24 – 34·14	0·01
Non-typhi *Salmonella*	20% (1/5)	0·65	0·07 – 5·87	0·70
Other (non contaminants)	42% (5/12)	1·86	0·58 – 5·94	0·29
Resp. virus detected in NPA	29% (113/390)	1·09	0·80 – 1·48	0·60
Human rhinovirus	29% (55/193)	1·02	0·72 – 1·47	0·90
Adenovirus	23% (23/102)	0·71	0·44 – 1·17	0·18
Respiratory syncytial virus	33% (16/49)	1·26	0·68 – 2·33	0·47
Human metapneumovirus	46% (18/39)	2·29	1·19 – 4·41	0·01
Influenza virus A-B	26% (10/39)	0·88	0·42 – 1·82	0·72
Parainfluenza virus 1-4	16% (5/31)	0·48	0·18 – 1·27	0·13
Enterovirus	29% (5/17)	1·07	0·37 – 3·06	0·91
Viral detection				
Single	30% (95/314)	1		
Double/Triple	24% (18/76)	0·71	0·39 – 1·29	0·26
Positive HIV status	31% (46/133)	1·71	1·11 – 2·63	0·01
Pneumocystis jirovecii	51% (29/57)	2·92	1·69 – 5·06	<0·001

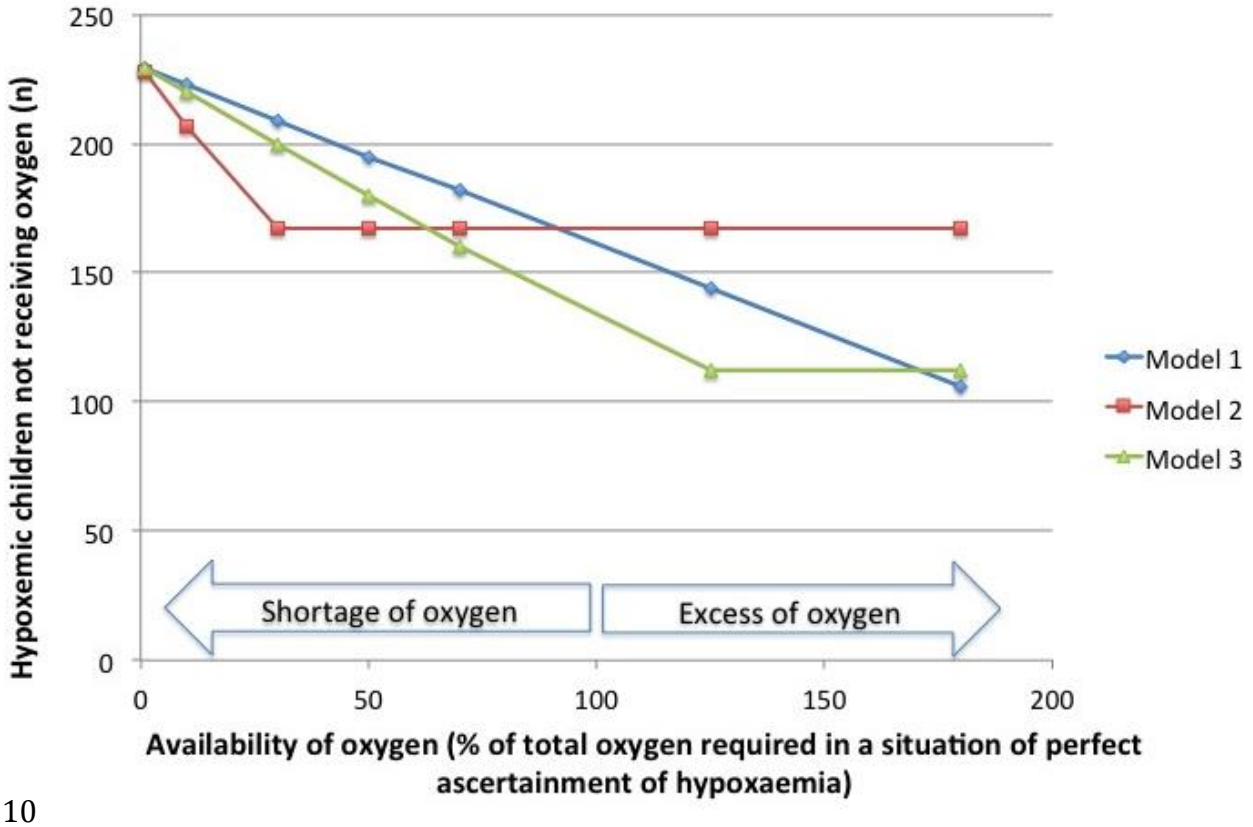
Figures

Figure 1. Accuracy of models to diagnose hypoxaemia



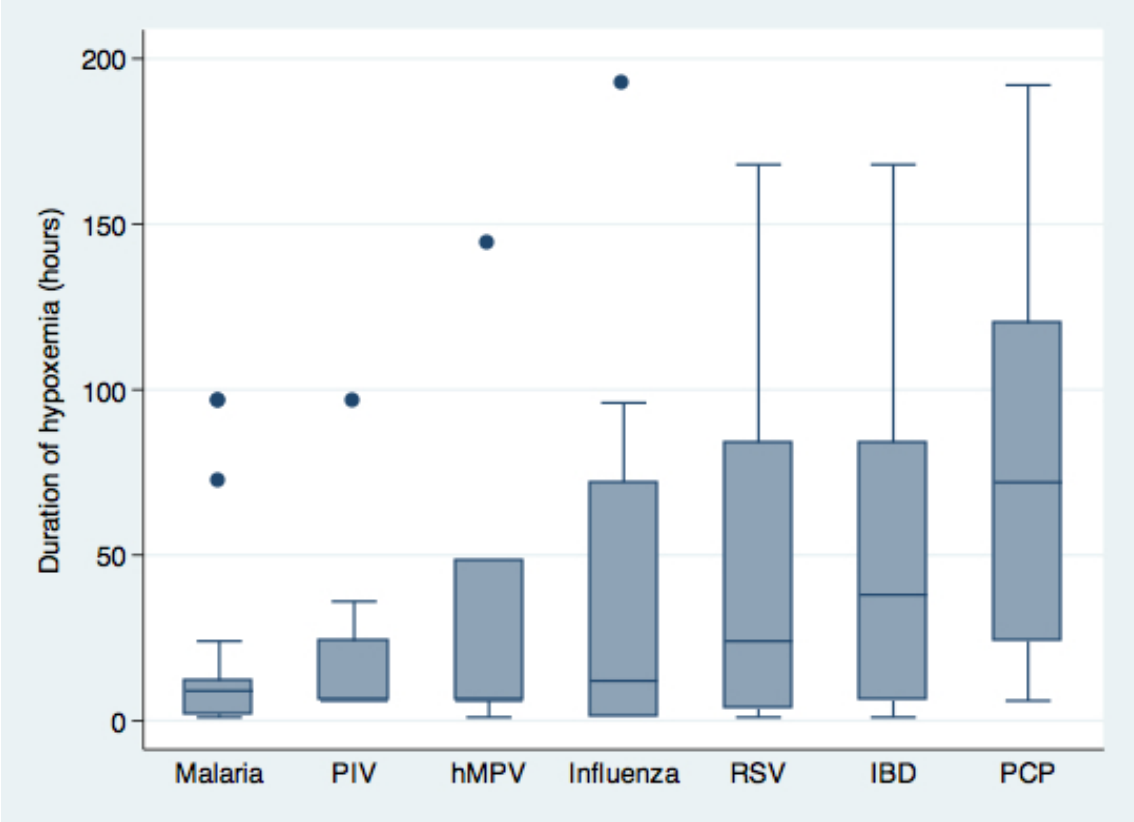
Receiver operating characteristic (ROC) curves for models predicting hypoxaemia in the present study. Model 1: Intake refusal or cyanosis or respiratory rate ≥ 70 bpm or chest indrawing (AUC_1 = 0·55). Model 2: Cyanosis or thoracoabdominal breathing or deep coma (BCS ≤ 2) (AUC_2= 0·58). Model 3: Cyanosis or thoracoabdominal breathing or respiratory rate ≥ 70 bpm (AUC_3 = 0·63).

Figure 2. Performance of models to diagnose hypoxaemia, by oxygen availability



Total number of hypoxaemic children not receiving oxygen in different scenarios of oxygen availability, by predictor model. This is a deterministic model taking into account undetected hypoxaemic children (greater in model 2, with high specificity) and hypoxaemic children admitted after all the available oxygen has been used (greater in model 1, with high sensitivity), applied to the population of the present study (N=825, and n=230 hypoxaemic children).

Figure 3. Duration of hypoxaemia (hours), by aetiology



Only surviving children with single infection have been considered (n=167). PIV = parainfluenza virus. hMPV = human metapneumovirus. RSV = respiratory syncytial virus. IBD = invasive bacterial disease. PCP = *Pneumocystis jirovecii* pneumonia. *P value* from Kruskal-Wallis rank test <0·001.