

LONDON
SCHOOL of
HYGIENE
& TROPICAL
MEDICINE



LSHTM Research Online

Bassat, Quique; Lanaspá, Miguel; Machevo, Sónia; O'Callaghan-Gordo, Cristina; Madrid, Lola; Nhampossa, Tacilta; Acácio, Sozinho; Roca, Anna; Alonso, Pedro L; (2016) Hypoxaemia in Mozambican children <5 years of age admitted to hospital with clinical severe pneumonia: clinical features and performance of predictor models. *Tropical medicine & international health*, 21 (9). pp. 1147-1156. ISSN 1360-2276 DOI: <https://doi.org/10.1111/tmi.12738>

Downloaded from: <http://researchonline.lshtm.ac.uk/id/eprint/4655917/>

DOI: <https://doi.org/10.1111/tmi.12738>

Usage Guidelines:

Please refer to usage guidelines at <https://researchonline.lshtm.ac.uk/policies.html> or alternatively contact researchonline@lshtm.ac.uk.

Available under license: <http://creativecommons.org/licenses/by-nc-nd/2.5/>

<https://researchonline.lshtm.ac.uk>

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

3
4 Quique Bassat, MD, PhD^{1,2}; Miguel Lanaspá, MD, PhD^{1,2}; Sónia Machevo, MD, MPH²;
5 Cristina O’Callaghan-Gordo, PhD^{1,2,3}; Lola Madrid, MD, MSc^{1,2}; Tacilta Nhampossa, MD,
6 PhD^{2,5}; Sozinho Acácio MD^{2,5}; Anna Roca, PhD^{2,4}; Pedro L. Alonso, MD, PhD^{1,2}

7
8 **Affiliations and addresses**

9 1. ISGlobal, Barcelona Ctr. Int. Health Res. (CRESIB), Hospital Clínic - Universitat de
10 Barcelona, Barcelona, Spain

11 *Address: Rosselló, 132, 5^o 2^a (08036), Barcelona. Spain.*

12 2. Centro de Investigação em Saúde de Manhiça (CISM), Maputo, Mozambique

13 *Address: Bairro Cambeve, Rua 12, Distrito da Manhiça, CP 1929, Maputo. Mozambique.*

14 3. Centre for Research in Environmental Epidemiology (CREAL), Barcelona, Spain

15 *Address: Doctor Aiguader, 88 (08003), Barcelona. Spain*

16 4. Medical Research Council Unit, Banjul, The Gambia.

17 *Address: Atlantic Boulevard, Fajara. P. O. Box 273, Banjul. The Gambia*

18 5. National Institute of Health (INS), Ministry of Health, Mozambique

19 *Address: Avenida Eduardo Mondlane, N^o 1008, Maputo. Mozambique*

20

21

22

23

24

25

26 **Contact information:**

27 Miguel Lanaspa, corresponding author

28 miguel.lanaspa@isglobal.org

29 Address: Instituto de Salud Global de Barcelona. Rosselló, 132, 5º 2ª (08036). Barcelona.
30 Spain.

31 Tel. +34 93 227 1806

32 Fax: +34 932 279 853

33

34 **Background**

35 Pneumonia remains the major cause of childhood deaths globally. It accounts for 18% of the
36 under five mortality, and an estimated 14.9 million (95% CI: 12.4–18.1 million) hospital
37 admissions among young children worldwide.^{1,2} Hypoxaemia is the most severe complication
38 of pneumonia in children, and is strongly associated with increased mortality.³⁻⁶ The gold
39 standard to diagnose hypoxaemia is arterial blood gas analysis, but non-invasive point-of-care
40 pulse oximetry provides an accurate measure at non-extreme levels of oxygen saturation
41 presenting obvious advantages in everyday practice.⁷ However, pulse oximetry is not widely
42 available in developing countries because of its cost, and hypoxaemia diagnosis relies on
43 clinical signs and symptoms.⁸

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

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

58 **Methods**

59 **Study setting and population**

60 This prospective study was conducted from September 2006 to September 2007 at Manhiça
61 District Hospital (MDH), the referral health facility for a rural area in Southern Mozambique.
62 The *Centro de Investigação em Saúde de Manhiça* (CISM) runs a Demographic Surveillance
63 System (DSS) since 1996, linked with a morbidity surveillance system at Manhiça District
64 Hospital and peripheral health centers.¹⁸ Such surveillance covered, at the time of the study,
65 an area of approximately 500 km² and 80,000 persons. By then, severe pneumonia accounted
66 for 16% of hospitalizations among children less than two years of age, and had an associated
67 case-fatality rate (CFR) of 11%.¹⁹ The average altitude of the Manhiça district is 50 meters
68 above sea level.

69 **Procedures for recruited children and sample collection**

70 This study was part of a larger project designed to characterize children less than five years of
71 age admitted with respiratory distress.²⁰ Children fulfilling inclusion criteria and whose
72 parents had signed an informed consent form underwent study procedures. Children with a
73 known congenital heart or pulmonary malformation, a known history of asthma, and those
74 who were household contacts of known tuberculosis cases or suspected to have pulmonary
75 tuberculosis were excluded. Antero-posterior chest radiographs were obtained within the first
76 48 hours of hospitalization. Pulse oximetry (Nellcor, Boulder, CO) was used to determine
77 oxygen saturation, and nasopharyngeal aspirates were collected using NPAK® Kits (MPRO,
78 Farmington Hills, MI). Venous blood was obtained at admission for malaria diagnosis, blood
79 culture, full blood cell count, and biochemical determinations.

80 **X-ray interpretation**

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

87 **Laboratory methods**

88 Packed cell volume was measured with haematocrit reader (Hawksley and Sons Ltd.,
89 Lancing, United Kingdom). Thick and thin blood films for malaria diagnosis were processed
90 and examined according to standard methods.¹⁸ Blood lactate levels were determined using
91 Lactate Pro® (FaCT Canada, Quesnel, British Columbia, Canada) at the bedside.
92 Haematology analyser (Kx21; Sysmex, Denver, CO), and biochemistry analyser (Vitros
93 DT60; Ortho Clinical Diagnostics, Raritan, NJ) were used. Blood cultures were processed and
94 bacterial isolates identified as previously described.²²⁻²⁴ The presence of different respiratory
95 viruses (influenza virus A and B, respiratory syncytial virus A and B, parainfluenza virus 1, 2,
96 3 and 4, adenovirus, human rhinovirus, human metapneumovirus, and enterovirus) in
97 nasopharyngeal aspirates (NPA) was determined using four different polymerase chain
98 reactions.²⁰ *Pneumocystis jirovecii* infections were investigated in NPA samples using
99 molecular methods.²⁵ Three specific genes were targeted: 1) mtLSU rRNA locus; 2) mtSSU
100 rRNA locus; and 3) DHPS locus.^{26,27}

101 **HIV-specific procedures**

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

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

109 **Definitions**

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

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

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

130 **Case management and treatment**

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

136 **Data management and statistical analysis**

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

140 Categorical variables were compared using a chi-square test or Fisher's exact test. Normal
141 distribution was assessed visually. For non-normally distributed variables, medians and
142 interquartile ranges are presented, and Wilcoxon rank-sum test was used to assess differences.
143 Univariate and multivariate logistic regression analyses were performed to assess associations
144 between explanatory variables and presenting hypoxaemia. Positive and negative likelihood
145 ratios were calculated for all the variables suitable for use as clinical predictors of
146 hypoxaemia. For the multivariate analysis, automated backward stepwise estimations were
147 calculated. All variables associated with hypoxaemia at a significance level of $p\text{-value} < 0.10$
148 in the univariate analysis were included in the model. Odds ratios (OR) and 95% confidence
149 intervals (CI) are presented. Combinations of significant and independent variables with high
150 positive likelihood ratios were used to build models for hypoxaemia prediction. Diagnostic
151 values were calculated for these predictor models and for the WHO-recommended model

152 (Intake refusal or cyanosis or respiratory rate ≥ 70 bpm or chest indrawing), and receiver-
153 operating curves (ROC) and the area under the ROC curve (AUC) were obtained as well.
154 We built and tested models described in the literature to predict hypoxaemia in the dataset of
155 the present study. Moreover, we tested combinations of the independent predictors from the
156 multivariate analysis, and non-independent predictors significantly associated with
157 hypoxaemia in the univariate analysis with a high positive likelihood ratio. In order to
158 compare their performances in a convenient, straightforward way, a deterministic model was
159 set to calculate the number of hypoxaemic children not receiving oxygen due to 1) remaining
160 undetected (low sensitive models) and 2) shortage of oxygen supplies (highly sensitive/low
161 specific models in a limited-resource setting) according to different scenarios of oxygen
162 availability.

163

164 **Ethical approvals**

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

168

169 **Role of the funding source**

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

172

173

174 **Results**

175 **General overview**

176 During the study period (20th September 2006-20th September 2007), 2,943 children were
177 admitted to MDH, from which 926 (31.5%) had severe pneumonia according to the IMCI
178 definition. A total of 825 of these patients (28% of all admissions; 89% of all children with
179 study criteria) provided consent and were included in the analysis. The median age was 10.5
180 months (IQR 4.2 – 21), 440 (53.3%) were infants (<12 months old), and 328 (39.8%) were
181 female. Among admitted children with available results blood culture was positive in 14.4%
182 (104/723) of cases, viral detection in NPA was positive in 48.8% (390/800), malaria slide in
183 13% (106/816), and *Pneumocystis jirovecii* in 6.9% (57/825) of the NPA. Co-infections were
184 common. HIV infection was present in 25.7% (133/517) of the patients tested.

185 **Characteristics of patients according to hypoxaemia status on admission**

186 A total of 230 (27.9%) children had hypoxaemia detected by pulse oximetry on admission
187 (Table 1); 81 (9.8%) of them being severely hypoxaemic. Median duration of hypoxaemia
188 among study children was 24 hours (IQR 6-96 hours), and 41% (78/190) of initially
189 hypoxaemic children presented sustained hypoxaemias of over 48 hours of duration.
190 Hypoxaemic children were younger than non-hypoxaemic children (median age 6.8 months
191 vs. 12.1 months, $p<0.001$), and were admitted longer (median duration of admission among
192 survivors 4.9 days vs. 4.3 days, $p=0.001$) (Table 1). Of those children without hypoxaemia
193 upon admission, 10% (60/595) developed hypoxaemia throughout their admissions.
194 Regarding complementary exams (Table 1), hypoxaemic children more frequently had
195 abnormal chest radiographs (i.e. infiltrates, consolidation or pleural effusion) than non-
196 hypoxaemic children, more frequently had acidosis on admission, higher venous lactate

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

199 The in-hospital case fatality rate was significantly higher in hypoxaemic children (unadjusted
200 OR for death 3.22, 95%CI 1.98 – 5.21, $p < 0.001$).

201 **Signs and symptoms associated with hypoxaemia**

202 *Univariate analysis*

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

212 *Validity of single clinical signs to diagnose hypoxaemia*

213 The most sensitive clinical signs (sensitivity around 90% or more) to diagnose hypoxaemia
214 were, in descending order, difficult breathing, chest indrawing, fever, age-specific tachypnea
215 and cough (Supplementary table 1); although specificity for these variables was low (below
216 17%). The most specific signs (specificity $>90\%$) were digital clubbing, cyanosis, deep coma,
217 hypophonesis, seizures, thoracoabdominal breathing, and deep breathing; but their sensitivity
218 was very low in all cases (below 17.8%).

219 *Independent clinical predictors of hypoxaemia*

220 In the multivariate analysis (Table 3), cyanosis (adjusted OR 2.76; 95%CI 1.13-6.73),
221 difficult breathing (aOR 2.69; 95%CI 1.06-6.81), thoracoabdominal breathing (aOR 1.76;
222 95%CI 1.08-2.87), respiratory rate ≥ 70 bpm (aOR 1.92; 95%CI 1.34-2.77), crackles (aOR
223 1.60; 95%CI 1.12-2.31), and prostration (aOR 1.64; 95%CI 1.02-2.64) were independently
224 associated with having hypoxaemia on admission. Nasal flaring and chest indrawing were not
225 independently associated with hypoxaemia.

226 *Predictor models for hypoxaemia*

227 The WHO-like model (model 1), which included intake refusal or cyanosis or respiratory rate
228 ≥ 70 bpm or chest indrawing, had a very high sensitivity (97%) but very low specificity
229 (12.8%). The model with the greater AUC was model 3 (Figure 1), combining cyanosis or
230 thoracoabdominal breathing or respiratory rate ≥ 70 bpm.

231 *Deterministic model to evaluate predictor models by oxygen availability*

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

238

239 **Association between hypoxaemia and microbiologic results**

240 Regarding microbiologic results, infection by *Pneumocystis jirovecii*, *Staphylococcus aureus*
241 or human metapneumovirus were significantly associated with hypoxaemia, occurring in
242 51%, 71% and 46% of children with these infections, respectively (Table 5). The association

243 between HIV infection and hypoxaemia was partially confounded by PCP diagnosis, and the
244 adjusted Odds Ratio was 1.51 (95%CI 0.97 – 2.36, p=0.07). Malaria parasitemia was
245 associated with lower risk of hypoxaemia in children with the syndrome of clinical
246 pneumonia.

247 Regarding duration of hypoxaemia by aetiology, the longest median period until recovery was
248 72 hours corresponding to PCP (IQR 30 – 168 hours), and the shortest was 6 hours in
249 parainfluenza virus infected children (IQR 6 – 24 hours) and in human metapneumovirus
250 infected children (IQR 6 – 48 hours; Figure 3). In children with invasive bacterial disease, the
251 median duration of hypoxaemia was 48 hours (IQR 6 – 96 hours). Regarding chest x-ray
252 results, duration of hypoxaemia was significantly longer in children with infiltrates (median
253 24 hours, IQR 6 – 72) and consolidation (median 24 hours, IQR 6 – 96) compared to children
254 with normal chest x-ray (median 6 hours, IQR 1 – 24; p-value from Kruskal-Wallis test <
255 0.001).

256 **Discussion**

257 In our series, the prevalence of hypoxaemia among admitted children with clinical severe
258 pneumonia was 27.9%, and a significant proportion of the children presented sustained
259 hypoxaemia episodes, which, in the absence of oxygen, would likely have resulted in death.
260 Hypoxaemia was very strongly associated with risk of death in our series (unadjusted OR
261 3.22, p<0.001), which is consistent with other reports from developing countries.^{3-5,16} Almost
262 one out of five hypoxaemic children admitted to our hospital died. One limitation of this
263 analysis is that HIV results were not available for over one-third of the patients, and HIV
264 infection was not included in the multivariable analysis. However, HIV infection was not a
265 strong confounder of the association between hypoxaemia on admission and death when
266 assessed in the subsample of children with available HIV results. The high mortality among
267 hypoxaemic children despite the high oxygen availability at MDH, better than in most health

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

270 The median prevalence of hypoxaemia in children from developing countries admitted with
271 WHO-defined pneumonia has been estimated at 13%, but is highly variable across studies.⁶
272 Studies with greater reported hypoxaemia were closely examined to extract data about
273 hypoxaemia definition, pneumonia definition, inclusion criteria and setting altitude.^{5,12,14,30-32}
274 Hypoxaemia definition –either <90% or <2SD of normal values, corresponding to 85-90% -
275 and pneumonia definition – based on WHO-defined pneumonia – were mostly consistent
276 across studies. Altitude of settings was consistently higher (255 to 3750 meters) than the
277 average Manhica district altitude (50 meters) and may account for the lower prevalence.
278 Interestingly, 10% (60/595) of the non-hypoxaemic children on admission developed
279 hypoxaemia during admission. This was not associated with *Pneumocystis jirovecii* infection,
280 and may be evidence of prompt assistance seeking among mothers from Manhica district who
281 consulted after a median time of 1 day of fever (IQR 1 – 3 days) and 2 days of cough (IQR 1
282 – 3 days). This information was not available in the examined studies.

283 Several clinical signs were independently associated with hypoxaemia, with most of them
284 having been previously identified such as cyanosis, difficult breathing, and respiratory rate
285 ≥ 70 bpm. Thoracoabdominal breathing, one of the signs with best combination of positive
286 and negative likelihood ratio in our series, has not been commonly assessed in previous
287 studies. Other studies have similar merits identifying signs likely to predict hypoxaemia that
288 had not been previously reported such as head nodding, restlessness, or thoroughly assessing
289 different respiratory rate cut-offs, or the validity of combined predictor models in different
290 age-groups.^{16,30,33} However, none of the identified signs or symptoms, or combination of
291 predictors have proved to be accurate enough to diagnose hypoxaemia, and even the

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

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

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

308 **Conclusions**

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

316

317

318 **Funding**

319 This work was supported by the World Health Organization (WHO-C6-181-489).

320 Quique Bassat has a fellowship from the program Miguel Servet of the ISCIII (Plan Nacional
321 de I+D+I 2008-2011, grant number: CP11/00269). Lola Madrid has a fellowship from the
322 program Río Hortega of the ISCIII (CM13/00260).

323 **Declaration of interests**

324 The authors declare no conflict of interest.

325 **Acknowledgements**

326 We are indebted to the children and mothers participating in the study. The work of the
327 clinical officers, medical “estagiarios”, HIV counsellors, data managers, laboratory workers
328 and laboratory coordinator was important for the successful collection of data.

329

330 **Reference list**

- 331 1. Nair H, Simoes EA, Rudan I, et al. Global and regional burden of hospital
332 admissions for severe acute lower respiratory infections in young children in 2010: a
333 systematic analysis. *Lancet* 2013; **381**(9875): 1380-90.
- 334 2. Liu L, Johnson HL, Cousens S, et al. Global, regional, and national causes of child
335 mortality: an updated systematic analysis for 2010 with time trends since 2000. *Lancet*
336 2012; **379**(9832): 2151-61.
- 337 3. Ayieko P, English M. Case management of childhood pneumonia in developing
338 countries. *Pediatr Infect Dis J* 2007; **26**(5): 432-40.
- 339 4. Chisti MJ, Duke T, Robertson CF, et al. Clinical predictors and outcome of
340 hypoxaemia among under-five diarrhoeal children with or without pneumonia in an
341 urban hospital, Dhaka, Bangladesh. *Trop Med Int Health* 2012; **17**(1): 106-11. doi:
342 10.1111/j.365-3156.2011.02890.x. Epub 2011 Sep 23.
- 343 5. Onyango FE, Steinhoff MC, Wafula EM, Wariua S, Musia J, Kitonyi J. Hypoxaemia in
344 young Kenyan children with acute lower respiratory infection. *BMJ* 1993; **306**(6878):
345 612-5.
- 346 6. Subhi R, Adamson M, Campbell H, Weber M, Smith K, Duke T. The prevalence of
347 hypoxaemia among ill children in developing countries: a systematic review. *Lancet*
348 *Infect Dis* 2009; **9**(4): 219-27. doi: 10.1016/S1473-3099(09)70071-4.
- 349 7. Ross PA, Newth CJ, Khemani RG. Accuracy of pulse oximetry in children.
350 *Pediatrics* 2014; **133**(1): 22-9.
- 351 8. Floyd J, Wu L, Hay Burgess D, Izadnegahdar R, Mukanga D, Ghani AC. Evaluating
352 the impact of pulse oximetry on childhood pneumonia mortality in resource-poor
353 settings. *Nature* 2015; **528**(7580): S53-9.
- 354 9. Rojas-Reyes MX, Granados Rugeles C, Charry-Anzola LP. Oxygen therapy for
355 lower respiratory tract infections in children between 3 months and 15 years of age.
356 *Cochrane Database Syst Rev* 2014; **12**:CD005975.(doi):
357 10.1002/14651858.CD005975.pub3.
- 358 10. World Health Organisation programme for the control of acute respiratory
359 infections. Acute respiratory infections in children: case management in small hospitals
360 in developing countries. Geneva: WHO/ARI; 1990.
- 361 11. Usen S, Weber M, Mulholland K, et al. Clinical predictors of hypoxaemia in
362 Gambian children with acute lower respiratory tract infection: prospective cohort study.
363 *BMJ* 1999; **318**(7176): 86-91.
- 364 12. Basnet S, Adhikari RK, Gurung CK. Hypoxemia in children with pneumonia and its
365 clinical predictors. *Indian J Pediatr* 2006; **73**(9): 777-81.
- 366 13. Chisti MJ, Salam MA, Ashraf H, et al. Predictors and outcome of hypoxemia in
367 severely malnourished children under five with pneumonia: a case control design. *PloS*
368 *one* 2013; **8**(1): e51376. doi: 10.1371/journal.pone.0051376. Epub 2013 Jan 8.
- 369 14. Duke T, Blaschke AJ, Sialis S, Bonkowsky JL. Hypoxaemia in acute respiratory and
370 non-respiratory illnesses in neonates and children in a developing country. *Arch Dis*
371 *Child* 2002; **86**(2): 108-12.
- 372 15. Lodha R, Bhadauria PS, Kuttikat AV, et al. Can clinical symptoms or signs
373 accurately predict hypoxemia in children with acute lower respiratory tract infections?
374 *Indian Pediatr* 2004; **41**(2): 129-35.
- 375 16. Mwaniki MK, Nokes DJ, Ignas J, et al. Emergency triage assessment for
376 hypoxaemia in neonates and young children in a Kenyan hospital: an observational
377 study. *Bull World Health Organ* 2009; **87**(4): 263-70.

- 378 17. Rao YK, Midha T, Kumar P, Tripathi VN, Rai OP. Clinical predictors of hypoxemia
379 in Indian children with acute respiratory tract infection presenting to pediatric
380 emergency department. *World J Pediatr* 2012; **8**(3): 247-51. doi: 10.1007/s12519-012-
381 0365-1. Epub 2012 Aug 12.
- 382 18. Guinovart C, Bassat Q, Sigauque B, et al. Malaria in rural Mozambique. Part I:
383 children attending the outpatient clinic. *Malaria journal* 2008; **7**: 36.
- 384 19. Sigauque B, Roca A, Bassat Q, et al. Severe pneumonia in Mozambican young
385 children: clinical and radiological characteristics and risk factors. *Journal of tropical*
386 *pediatrics* 2009; **55**(6): 379-87.
- 387 20. O'Callaghan-Gordo C, Bassat Q, Morais L, et al. Etiology and epidemiology of viral
388 pneumonia among hospitalized children in rural Mozambique: a malaria endemic area
389 with high prevalence of human immunodeficiency virus. *The Pediatric infectious disease*
390 *journal* 2011; **30**(1): 39-44.
- 391 21. Cherian T, Mulholland EK, Carlin JB, et al. Standardized interpretation of
392 paediatric chest radiographs for the diagnosis of pneumonia in epidemiological studies.
393 *Bulletin of the World Health Organization* 2005; **83**(5): 353-9.
- 394 22. Sigauque B, Roca A, Mandomando I, et al. Community-acquired bacteremia
395 among children admitted to a rural hospital in Mozambique. *The Pediatric infectious*
396 *disease journal* 2009; **28**(2): 108-13.
- 397 23. Roca A, Sigauque B, Quinto L, et al. Invasive pneumococcal disease in children <5
398 years of age in rural Mozambique. *Tropical medicine & international health : TM & IH*
399 2006; **11**(9): 1422-31.
- 400 24. Valles X, Flannery B, Roca A, et al. Serotype distribution and antibiotic
401 susceptibility of invasive and nasopharyngeal isolates of *Streptococcus pneumoniae*
402 among children in rural Mozambique. *Tropical medicine & international health : TM & IH*
403 2006; **11**(3): 358-66.
- 404 25. Lanaspá M, O'Callaghan-Gordo C, Machevo S, et al. High prevalence of
405 *Pneumocystis jirovecii* pneumonia among Mozambican children <5 years of age
406 admitted to hospital with clinical severe pneumonia. *Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious*
407 *Diseases* 2015; **21**(11): 1018 e9- e15.
- 409 26. de Armas Y, Friaza V, Capo V, et al. Low genetic diversity of *Pneumocystis*
410 *jirovecii* among Cuban population based on two-locus mitochondrial typing. *Medical*
411 *mycology* 2012; **50**(4): 417-20.
- 412 27. Friaza V, Morilla R, Respaldiza N, de la Horra C, Calderon EJ. *Pneumocystis*
413 *jirovecii* dihydropteroate synthase gene mutations among colonized individuals and
414 *Pneumocystis pneumonia* patients from Spain. *Postgraduate medicine* 2010; **122**(6): 24-
415 8.
- 416 28. Roca A, Sigauque B, Quinto L, et al. Estimating the vaccine-preventable burden of
417 hospitalized pneumonia among young Mozambican children. *Vaccine* 2010; **28**(30):
418 4851-7.
- 419 29. World Health Organization. Pocket Book for Hospital Care of Children: Guidelines
420 of the Management of Common Illness with Limited Resources.; 2005.
- 421 30. Ibraheem RM, Johnson WB, Abdulkarim AA. Hypoxaemia in hospitalised under-
422 five Nigerian children with pneumonia. *West Afr J Med* 2014; **33**(1): 37-43.
- 423 31. Orimadegun AE, Ogunbosi BO, Carson SS. Prevalence and predictors of
424 hypoxaemia in respiratory and non-respiratory primary diagnoses among emergently ill
425 children at a tertiary hospital in south western Nigeria. *Trans R Soc Trop Med Hyg* 2013;
426 **107**(11): 699-705. doi: 10.1093/trstmh/trt082. Epub 2013 Sep 23.

- 427 32. Reuland DS, Steinhoff MC, Gilman RH, et al. Prevalence and prediction of
428 hypoxemia in children with respiratory infections in the Peruvian Andes. *J Pediatr* 1991;
429 **119**(6): 900-6.
- 430 33. Weber MW, Usen S, Palmer A, Jaffar S, Mulholland EK. Predictors of hypoxaemia
431 in hospital admissions with acute lower respiratory tract infection in a developing
432 country. *Arch Dis Child* 1997; **76**(4): 310-4.
- 433 34. McCollum ED, Bjornstad E, Preidis GA, Hosseinipour MC, Lufesi N. Multicenter
434 study of hypoxemia prevalence and quality of oxygen treatment for hospitalized
435 Malawian children. *Trans R Soc Trop Med Hyg* 2013; **107**(5): 285-92. doi:
436 10.1093/trstmh/trt017.
- 437 35. Duke T, Peel D, Wandu F, Subhi R, Sa'avu M, Matai S. Oxygen supplies for hospitals
438 in Papua New Guinea: a comparison of the feasibility and cost-effectiveness of methods
439 for different settings. *Papua and New Guinea medical journal* 2010; **53**(3-4): 126-38.
- 440 36. Duke T, Wandu F, Jonathan M, et al. Improved oxygen systems for childhood
441 pneumonia: a multihospital effectiveness study in Papua New Guinea. *Lancet* 2008;
442 **372**(9646): 1328-33. doi: 10.016/S0140-6736(08)61164-2. Epub 2008 Aug 15.
- 443 37. Graham SM, English M, Hazir T, Enarson P, Duke T. Challenges to improving case
444 management of childhood pneumonia at health facilities in resource-limited settings.
445 *Bull World Health Organ* 2008; **86**(5): 349-55.
- 446

447

448 **Tables**

449

450 **Table 1. Characteristics of children and complementary test results, by hypoxemia (O₂ saturation < 90%)**
451 **status on admission, univariate analysis**

452

453

| 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 |

454

455 * p-value from Chi² test, unless indicated otherwise

456 # p-value from Wilcoxon rank-sum test

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

458

459

460

461

462 **Table 2. Clinical features of hypoxemic and non-hypoxemic children (univariate analysis), and validity of**
 463 **the variables to detect hypoxemia (O₂ saturation < 90%)**
 464
 465

| Variables | Hypoxemic children; n(%) (n _{hypox} =230) | Non-Hypoxemic children; n(%) (n _{normal} =595) | <i>p</i> * | 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 (≥ 39°C) | 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 |

466
 467 * p-value from Chi2 test, unless indicated otherwise
 468 # p-value from Fisher's Exact test
 469

470
471
472
473
474

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)

| Potential predictors of hypoxemia | Adjusted OR | 95% CI | | <i>p</i> |
|-----------------------------------|-------------|--------|-------|-----------|
| | | Lower | Upper | |
| 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 |

475
476
477

478 **Table 4. Validity of different combination models to detect hypoxemia in children from the present study**
 479
 480

| Combination of variables | Sn | Sp | PPV | NPV | Positive likelihood ratio | Negative likelihood ratio | AUC |
|--|------|------|------|------|---------------------------|---------------------------|------|
| Model 1: Intake refusal or cyanosis or respiratory rate \geq 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 \leq 2) | 27.4 | 89.4 | 50.0 | 76.1 | 2.6 | 0.8 | 0.58 |
| Model 3: Cyanosis or thoracoabdominal breathing or respiratory rate \geq 70 bpm | 51.3 | 74.5 | 43.7 | 79.8 | 2.0 | 0.7 | 0.63 |

481
 482 Sn = Sensitivity. Sp = Specificity. PPV = Positive predictive value. NPV = Negative predictive value. AUC =
 483 area under the ROC curve. BCS = Blantyre coma scale
 484
 485

486
487
488
489
490
491

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 |
| <i>Streptococcus pneumoniae</i> | 18% (8/45) | 0.56 | 0.26 – 1.23 | 0.15 |
| <i>Haemophilus influenzae b</i> | 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 |
| <i>Staphylococcus aureus</i> | 71% (5/7) | 6.50 | 1.24 – 34.14 | 0.01 |
| <i>Non-typhi Salmonella</i> | 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 |
| <i>Pneumocystis jirovecii</i> | 51% (29/57) | 2.92 | 1.69 – 5.06 | <0.001 |

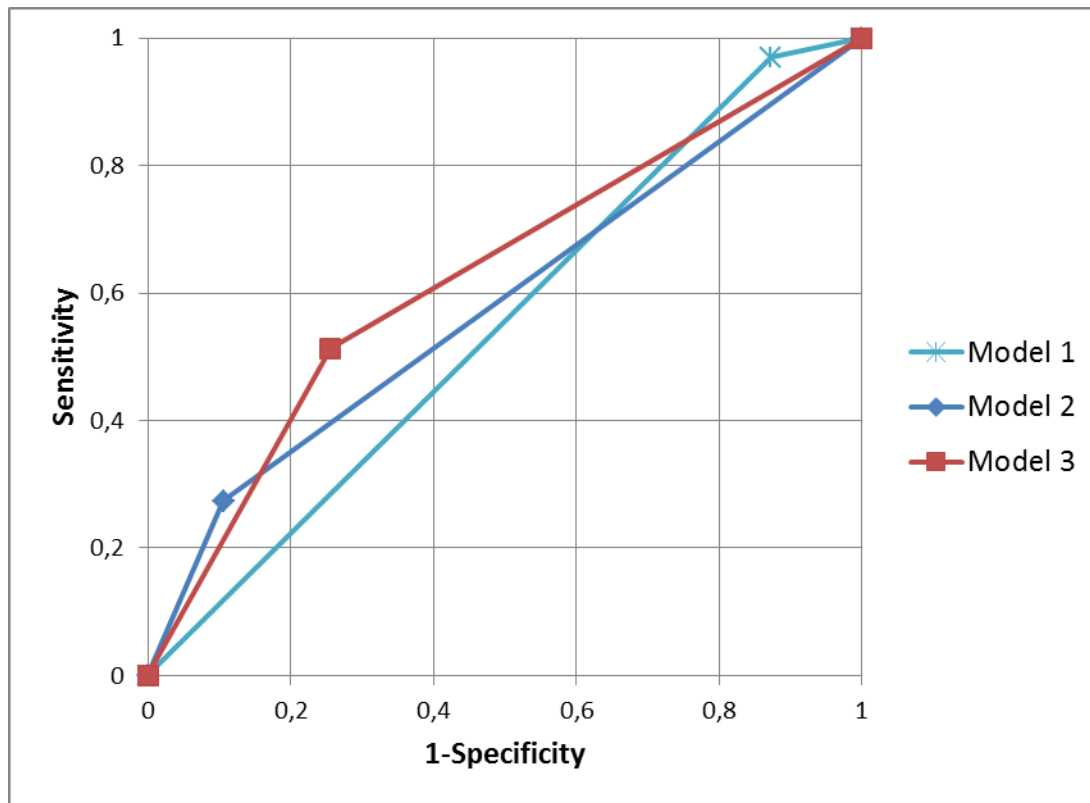
492
493
494
495

496 **Figures**

497

498 **Figure 1. Accuracy of models to diagnose hypoxaemia**

499



500

501

502 Receiver operating characteristic (ROC) curves for models predicting hypoxaemia in the present study. Model 1:

503 Intake refusal or cyanosis or respiratory rate ≥ 70 bpm or chest indrawing ($AUC_1 = 0.55$). Model 2: Cyanosis or

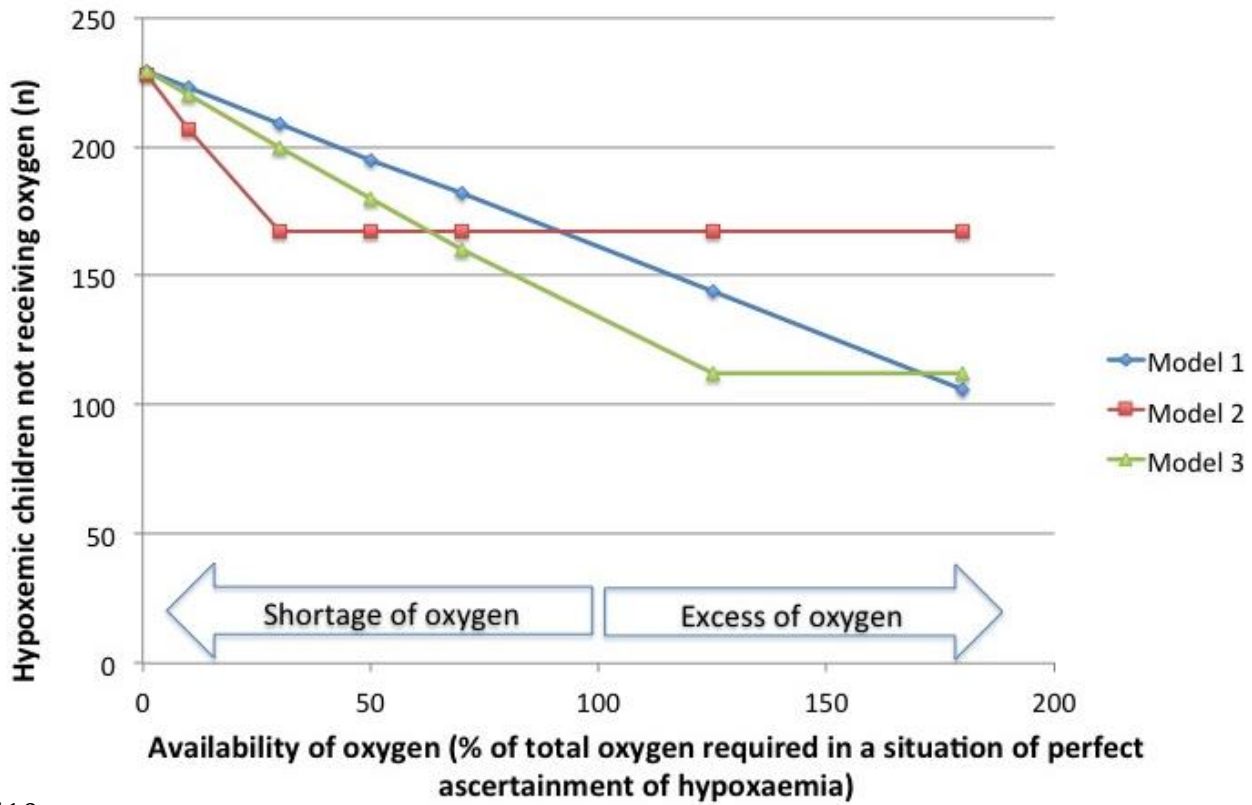
504 thoracoabdominal breathing or deep coma ($BCS \leq 2$) ($AUC_2 = 0.58$). Model 3: Cyanosis or thoracoabdominal

505 breathing or respiratory rate ≥ 70 bpm ($AUC_3 = 0.63$).

506

507
508
509

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

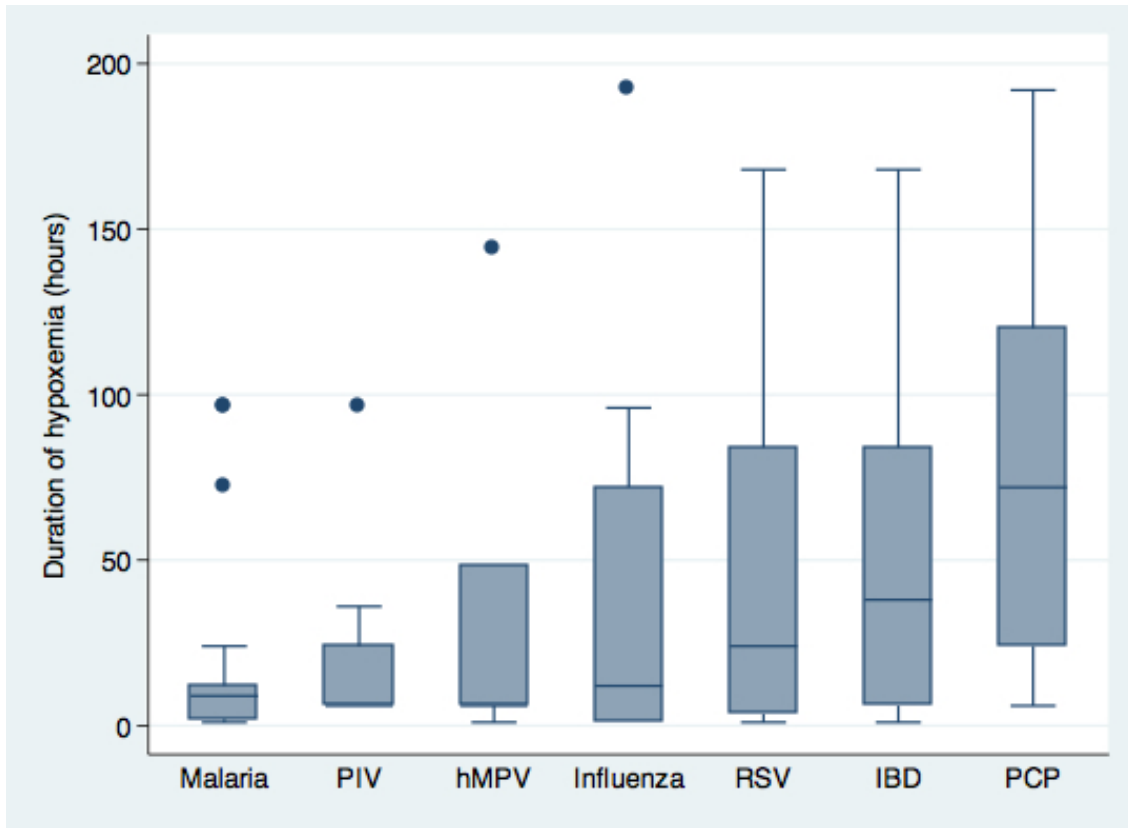


510
511
512
513
514
515
516
517
518

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).

519
520
521

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



522
523
524
525
526
527

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.