

# Hypoxaemia in young Kenyan children with acute lower respiratory infection

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## Abstract

**Objectives**—To determine the prevalence, clinical correlates, and outcome of hypoxaemia in acutely ill children with respiratory symptoms.

**Design**—Prospective observational study.

**Setting**—Paediatric casualty ward of a referral hospital at 1670 m altitude in Nairobi, Kenya.

**Subjects**—256 Infants and children under 3 years of age with symptoms of respiratory infection.

**Main outcome measures**—Prevalence of hypoxaemia, defined as arterial oxygen saturation  $<90\%$  determined by pulse oximetry, and condition of patient on the fifth day after admission.

**Results**—Over half (151) of the children were hypoxaemic, and short term mortality was 4.3 times greater in these children. In contrast, the relative risk of a fatal outcome in children with radiographic pneumonia was only 1.03 times that of children without radiographic pneumonia. A logistic regression model showed that in 3-11 month old infants a respiratory rate  $\geq 70/\text{min}$ , grunting, and retractions were the best independent clinical signs for the prediction of hypoxaemia. In the older children a respiratory rate of  $\geq 60/\text{min}$  was the single best clinical predictor of hypoxaemia. The presence of hypoxaemia predicted radiographic pneumonia with a sensitivity of 71% and specificity of 55%.

**Conclusions**—Over half the children presenting to this referral hospital with respiratory symptoms were hypoxaemic. A group of specific clinical signs seem useful in predicting hypoxaemia. The clear association of hypoxaemia with mortality suggests that the detection and effective treatment of hypoxaemia are important aspects of the clinical management of acute infections of the lower respiratory tract in children in hospital in developing regions.

## Introduction

Acute infections of the lower respiratory tract are a major cause of preventable death, causing about one third of all deaths in childhood.<sup>1</sup> Systems of treatment based on simple clinical signs have been developed and validated for the management of respiratory infections. Whereas several studies of acute infections of the lower respiratory tract in developing countries have defined the use of clinical signs to predict diagnosis by a doctor or by radiography<sup>2-5</sup> or to predict death,<sup>6</sup> only one study of the prevalence and clinical prediction of hypoxaemia has been reported from developing regions.<sup>7</sup> Oxygen is recommended for use in children admitted to hospital with severe pneumonia but the recently suggested clinical criteria for treatment with oxygen have not been validated in a clinical setting.<sup>8</sup> We are not aware of reports from developing countries of the outcome of hypoxaemia in children with acute lower respiratory tract infection.

We prospectively determined the prevalence and outcome of hypoxaemia in children with respiratory illness presenting to an urban referral hospital in Kenya and sought to correlate clinical signs with its presence. Our hypothesis was that hypoxaemia occurred more often than suspected clinically from the presence of cyanosis and that selected clinical signs,

including respiratory rate, would be useful to predict its presence.

## Patients and methods

This study was carried out from March to December 1989 at the Kenyatta National Hospital, which is the only free public hospital in Nairobi, a city of 1.28 million residents. Infants and children from the age of 7 days to 36 months who presented to the paediatric casualty unit of the hospital with a history of cough and other symptoms of acute infection of the respiratory tract for less than seven days were eligible for inclusion in this study. Exclusion criteria were the presence of moderate or severe dehydration or evidence of cardiac, renal, or metabolic disease, disease of the central nervous system, or severe anaemia. Each weekday morning no more than the first three eligible children presenting to the casualty unit were recruited by the study physician (SW), who explained the nature and purpose of the study to parents and obtained their consent. A history was obtained from the mother or guardian about the presence of rapid breathing, chest retraction, grunting, fever, refusal to breast feed or drink, difficulty in arousal, and blue appearance. The study physician also recorded respiratory rate, pulse, temperature, central cyanosis, chest retractions, grunting, nasal flaring, wheezing, crepitations or rhonchi on auscultation, and the state of consciousness. After the clinical assessment a portable battery powered oximeter (N-10, Nellcor, Hayward, California) was used for oximetry and pulse readings with an appropriately sized sensor on the finger or toe. Three oximetry readings were taken while the child was breathing room air and the average reading was used.

All children entered into the study had a posteroanterior chest radiograph after the above data were recorded. All radiographs were interpreted by a single radiologist (JK), who did not have access to the clinical data. The study protocol was approved by institutional review boards at the Johns Hopkins University and the University of Nairobi.

To determine the range of oxygen saturation in healthy children in Nairobi, which is 1670 m above sea level, oximetry was carried out in 87 normal healthy children aged 7 days to 36 months who were attending child welfare clinics for immunisation. In these children the range of arterial oxygen saturation was 89.3% to 99.3% and the mean was 95.7% (SD 1.6%). Eighty six of the 87 normal children had an arterial oxygen saturation of greater than 90%; one child had a saturation of 89.3%.

**Outcome definitions**—Hypoxaemia was defined as arterial oxygen saturation less than or equal to 90%. (A publication which appeared after the preparation of this manuscript reported the normal range of arterial oxygen saturation by pulse oximetry at 1610 m altitude in Denver. In 150 healthy infants aged  $<3$  months 88% to 89% saturation was the lower limit of normal.<sup>9</sup>) Radiographic pneumonia was defined as the presence of an alveolar or interstitial infiltrate in a chest radiograph.<sup>10</sup> The outcome of the illness in children admitted to hospital was recorded as clinically improved,

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clinically worse, or causing death before the fifth day after entry into the study.

**Statistical analysis**—The findings were analysed in the following age groups: newborn infants (0-2 months), infants (3-11 months), and children (12-36 months). Each clinical finding was assessed by  $\chi^2$  test for association with the outcomes of hypoxaemia and radiographic pneumonia. Sensitivity, specificity, and accuracy were calculated for each finding for each age group.<sup>11</sup> Individual signs and symptoms that seemed useful in the  $\chi^2$  analyses were evaluated for their independent ability to predict hypoxaemia with a multiple logistic regression technique. For each age group we evaluated a series of prediction models in which hypoxaemia was the dependent variable and selected predictor variables were added in a step wise manner with an inclusion rule of  $p \leq 0.05$ .<sup>12 13</sup>

## Results

### FINDINGS IN ILL CHILDREN

The data from 256 children were evaluated; 209 were admitted to the hospital. Pneumonia was the most common clinical diagnosis followed by bronchiolitis; these two syndromes comprised 86% of the diagnoses. Table I shows the outcome in each age group of children. The overall mortality of 10% and the prevalence of radiographic pneumonia of 53% indicate that this was a group of severely ill patients. Although there was a trend for mortality to be lower in the older children, the differences between age groups were not significant ( $\chi^2$  test for trend=3.32,  $p=0.07$ ). A total of 151 (59%) children had hypoxaemia. All the enrolled patients with clinically evident cyanosis were under 12 months of age, but of all the hypoxaemic infants, only 13 out of 117 (11%) were cyanotic.

TABLE I—Outcome in infants and children with acute infection of lower respiratory tract admitted to Kenyatta National Hospital

Age group (months)	No of children	No (%) with radiographic pneumonia	No (%) with hypoxaemia*	No (%) who died†
0-2	45	20 (44)	25 (56)	6 (17)
3-11	144	77 (54)	92 (64)	13 (11)
12-36	67	39 (58)	34 (51)	2 (4)
Total	256	136 (53)	151 (59)	21 (10)

\*Arterial oxygen saturation  $\leq 90\%$ .

†Death within 5 days of admission among 209 children admitted.

TABLE II—Hypoxaemia\* and outcome in young children with respiratory infection

Arterial oxygen saturation	Outcome		
	Died	Survived	Risk
$\leq 90$	19	125	0.13
$\geq 91$	2	63	0.03
	21	188	0.10

\*Positive predictive value for death=0.13, negative predictive value=0.97.

TABLE III—Symptoms and signs associated with hypoxaemia in infants and children

Variable	Age $\leq 2$ months (n=45)			Age 3-11 months (n=144)			Age $\geq 12$ months (n=67)		
	Prevalence†	Sensitivity (%)	Specificity (%)	Prevalence	Sensitivity (%)	Specificity (%)	Prevalence	Sensitivity (%)	Specificity (%)
Retractions	40	96	20	126	97	29***	53	88	30
Grunting	19	48	65	73	64	73***	27	56	76*
Cyanosis	5	20	100*	10	9	96	0	—	—
Respiratory rate (/min):									
$\geq 60$	32	76	35	102	86	56***	30	65	76**
$\geq 70$	18	48	70	56	51	83**	14	32	90*
Unresponsive	27	68	50	75	63	67***	26	56	78**
Crepitations	31	91	50**	102	77	40*	52	91	36*
Refusal to breast feed	25‡	66	47	56§	50	75**	13	40	71
History of:									
Blueness	9	36	100**	7	8	100*	1	3	100*
Difficult respiration	41	92	10	128	95	21**	57	91	21

\* $\chi^2$  test;  $p < 0.05$  for association of sign and hypoxaemia.

\*\* $\chi^2$  test;  $p < 0.01$  for association of sign and hypoxaemia.

\*\*\* $\chi^2$  test;  $p < 0.001$  for association of sign and hypoxaemia.

†No of subjects in age group with sign or symptom.

Twenty one children died within five days of admission; most deaths were within 48 hours of admission. Nineteen of the children who died were hypoxaemic on admission with arterial oxygen saturations ranging from 88% to 40%. Children admitted with hypoxaemia were 4.3 times more likely to die within five days than children without hypoxaemia (95% confidence interval of relative risk 1.03 to 17.8,  $\chi^2=5.1$ ,  $p=0.02$ ). Hypoxaemia on admission thus predicted short term hospital mortality with 90% (68% to 98%) sensitivity and 34% (26% to 41%) specificity (table II). Among children who survived for at least five days arterial oxygen saturation on admission ranged from 41% to 98%. In contrast, the relative risk of death in hospital in children with radiographic pneumonia compared with those without was only 1.03 (0.5 to 2.3,  $\chi^2=0.004$ ,  $p=0.9$ ).

In these infants and children the presence of hypoxaemia predicted radiographic pneumonia with a 71% sensitivity, a 55% specificity, and an overall accuracy of 64% ( $p < 0.0001$ ).

### PREDICTION OF HYPOXAEMIA: UNIVARIATE ANALYSIS

Table III shows the association of individual signs or symptoms with hypoxaemia. In newborn infants a respiratory rate of  $\geq 70$ /min was 48% sensitive and 70% specific in predicting hypoxaemia. Other individual signs that seemed useful were the observation or history of cyanosis and the finding of crepitations on examination. Retractions were sensitive but not specific, and grunting was not significantly associated with hypoxaemia in these newborn infants.

Although many signs were associated with hypoxaemia in infants 3-11 months of age, retractions, grunting, and unresponsiveness seemed to be the most useful signs of hypoxaemia in this age group. Among the children  $\geq 12$  months of age a respiratory rate  $\geq 70$ /min had a specificity of 90%, a sensitivity of only 32%, and an accuracy of 61%, but a rate of  $\geq 60$ /min had an accuracy of 70%.

### PREDICTION OF HYPOXAEMIA: LOGISTIC REGRESSION

With multiple logistic regression a mother's report of "blueness" was the best predictor for hypoxaemia in the newborn infants, with an accuracy of 62%. Inclusion of respiratory rate greater than 60 or 70/min or refusal to breast feed, grunting, chest retractions, or cyanosis on examination did not significantly improve prediction in these infants. Among the infants 3-11 months of age, a multiple logistic regression model including retractions, respiratory rate  $\geq 70$ /min, and grunting was the best predictor, with an accuracy of 70% (table IV). Cyanosis, refusal to breast feed, and the other signs in table III were not independently useful predictors in the regression model in the infants aged 3-11 months. In the children older than 12 months a respiratory rate of  $\geq 60$ /min alone was the

‡Of 41 infants regularly breast fed.

§Of 137 infants regularly breast fed.

||Of 37 children regularly breast fed.

TABLE IV—Prediction of hypoxaemia in infants 3-11 months of age by logistic regression analysis

Variable	Coefficient	Odds ratio (95% confidence interval)
Retractions	2.06	7.9 (1.5 to 20.4)
Grunting	1.03	2.7 (1.2 to 6.7)
Respiratory rate $\geq 70$ /min	0.96	2.6 (1.02 to 6.6)
Constant	-4.14	

best discriminatory sign, with an odds ratio of 5.1 (1.19 to 22.1) and an overall accuracy of 70%. The ability of the model to predict hypoxaemia in this older age group was not significantly improved by the addition of any other symptoms or signs to the model or by the use of a respiratory rate criterion of 70/min.

## Discussion

We found that over half the children presenting to this hospital with respiratory symptoms were hypoxaemic. In addition, we have shown that the physiological measurement of hypoxaemia is significantly related to prognosis and to clinical signs. The presence of hypoxaemia is predictive of short term mortality, indicating that the detection and treatment of hypoxaemia may be a crucial part of clinical management of severely ill children in hospital. Conversely, the absence of hypoxaemia predicts a low risk of death, even in the presence of radiographic pneumonia. Other studies of young children with lower respiratory tract infections and wheezing illnesses in developed<sup>14-19</sup> and developing countries<sup>7</sup> have shown that hypoxaemia was a better predictor of outcome than individual clinical signs. None of the cited studies of children evaluated the prediction of mortality. Several studies in adults in developed countries, however, have shown that hypoxaemia on admission is a predictor of death in hospital.<sup>20-22</sup>

We have shown that central cyanosis is seen in few hypoxaemic children. We were, however, able to identify a group of clinical findings which seem useful in predicting the presence of hypoxaemia in this clinical setting. After we started this study the World Health Organisation published recommendations for hospital management of pneumonia in developing countries, suggesting that with limited availability of oxygen only children with central cyanosis or inability to drink should be given oxygen.<sup>8</sup> When oxygen is readily available the following criteria were suggested for starting oxygen treatment: severe indrawing of the chest; restlessness (if improved by giving oxygen); respiratory rate  $>70$ /min in children 2 months to 7 years; and grunting in infants less than 2 months of age.<sup>8</sup> In severely ill children presenting to a referral hospital at 1670m altitude the logistic regression prediction models we have developed indicate that for newborn infants and those up to 2 months of age history of cyanosis reported by the mother was the best predictor of hypoxaemia; a respiratory rate of  $\geq 70$ /min, retractions, and grunting were the best predictors in infants 3-11 months old; and in children 12 months and older a respiratory rate of  $\geq 60$ /min was the best predictor of hypoxaemia.

Our findings in infants aged 3-11 months in essence confirm and validate the suggested WHO criteria for provision of oxygen when readily available. The use of multiple logistic regression allowed the selection of the most useful clinical signs which are predictive of hypoxaemia. We studied only a few newborn infants up to 2 months old, which made it difficult to assess fully the usefulness of the WHO criteria for detecting hypoxaemia in this age group. Further studies are needed to validate the suggested criteria for newborn infants. In children older than 11 months both the univariate and multivariate analyses suggest that a

respiratory rate of 60/min is preferable to the suggested 70/min as a cut off value for the prediction of hypoxaemia. We have evaluated the prediction models in the patients from whom they were derived, a procedure which maximises their apparent predictive ability. Therefore, to prove their usefulness the suggested criteria for hypoxaemia will have to be prospectively validated in other clinical settings, at sea level and above, and in groups of patients with a range of severity of disease.<sup>23</sup> We recommend that the WHO clinical indicators of hypoxaemia (which we have validated) be used to institute treatment with oxygen in referral hospitals where oxygen is available.

This study and a previous study<sup>7</sup> indicate that hypoxaemia predicts radiographic pneumonia with a sensitivity of 70-71% and a specificity of 55-71%, a degree of accuracy equivalent to that of recommended algorithms and prediction by doctors.<sup>5,8</sup> We have suggested further examination of the role of the oximeter as a diagnostic and screening tool.<sup>7</sup>

What are the implications of our data showing hypoxaemia to be an important predictor of short term mortality of children admitted to hospital with symptoms of acute lower respiratory tract infection in Nairobi? Although this study was not designed to evaluate treatment, a review of hospital records showed that all the children who died received antibiotics, and the hypoxaemic children received this hospital's standard treatment with oxygen, which is by face mask without monitoring of arterial oxygen saturation. The provision of oxygen may have benefited some of the hypoxaemic children. Although effective treatment will probably prevent a proportion of deaths in hypoxaemic children,<sup>24</sup> we are unaware of controlled trials to prove that treatment with oxygen will influence outcome in these severely ill children. Indeed, studies of adults with bacteraemic pneumococcal pneumonia in the United States suggest that the institution of intensive care with intubation, mechanical ventilation, and careful monitoring does not influence mortality.<sup>25</sup> A proportion of hypoxaemic children may be so physiologically compromised late in the course of illness that treatment with oxygen will not prevent death.

These considerations indicate that well designed studies of the clinical effectiveness of appropriate treatment with oxygen in the prevention of death of hypoxaemic infants and children in hospital are now required. Although many children with pneumonia are hypoxaemic, the limited availability of oxygen in developing regions indicates that the clinical studies should be designed to determine which hypoxaemic children will benefit most from treatment.

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## Case-control study of leukaemia and non-Hodgkin's lymphoma among children aged 0-4 years living in West Berkshire and North Hampshire health districts

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### Abstract

**Objective**—To investigate the relation between parental employment in the nuclear industry and childhood leukaemia and non-Hodgkin's lymphoma.

**Design**—Case-control study.

**Setting**—West Berkshire and Basingstoke and North Hampshire District Health Authorities.

**Subjects**—54 children aged 0-4 years who had leukaemia or non-Hodgkin's lymphoma diagnosed during 1972-89, who were born in the study area and were resident there when cancer was diagnosed. Six controls were selected for each case: four from hospital delivery registers and two from livebirth registers maintained by the NHS central register. Controls were matched for sex, date of birth (within six months), and area of residence at birth and time of diagnosis.

**Main outcome measures**—Parents' employment by the nuclear industry and exposure to ionising radiation at work.

**Results**—Five (9%) of the 54 cases and 14 (4%) of the 324 controls had fathers or mothers, or both, who had been employed by the nuclear industry (relative risk 2.2, 95% confidence interval 0.6 to 6.9). Nuclear industry employees who work in areas where exposure to radiation is possible are given film badges to monitor their exposure to external penetrating ionising radiation. Three fathers of cases and two fathers of controls (and no mothers of either) had been monitored in this way before their child was conceived (relative risk 9.0, 95% confidence interval 1.0 to 107.8). No father (of a case or control) had accumulated a recorded dose of more than 5 mSv before his child was conceived, and no father had been monitored at any time in the four years before his child was conceived. A dose-response relation was not evident among fathers who had been monitored.

**Conclusions**—These results suggest that the children of fathers who had been monitored for exposure to external penetrating ionising radiation in the nuclear industry may be at increased risk of developing leukaemia before their fifth birthday. The finding is based on small numbers and could be due to chance. If the relationship is real the mechanisms are far from clear, except that the effect is unlikely to be due to external radiation; the

possibility that it could be due to internal contamination by radioactive substances or some other exposure at work should be pursued. The above average rates of leukaemia in the study area cannot be accounted for by these findings.

### Introduction

We previously found an increased incidence of childhood leukaemia in the West Berkshire and Basingstoke and North Hampshire District Health Authorities during 1972-85.<sup>1</sup> The excess was concentrated in children under 5 years who were living within 10 km of the atomic weapons establishments at Aldermaston and Burghfield. We report here the results of a case-control study set up to investigate whether the excess was related to parents' employment in the nuclear industry.

### Subjects and methods

The study was carried out in the West Berkshire and the Basingstoke and North Hampshire District Health Authorities. Information about children under 5 years old living in the study area who had leukaemia or non-Hodgkin's lymphoma diagnosed between 1972 and 1989 was ascertained from multiple sources. Children with non-Hodgkin's lymphoma were included because of the current understanding, based on immunological studies, that acute lymphoblastic leukaemia and non-Hodgkin's lymphoma represent opposite ends of the same spectrum of disease.<sup>2,3</sup> Most cases were notified by consultants at the Royal Berkshire District Hospital, the Basingstoke District Hospital, and hospitals in the surrounding districts. General practitioners within the study area also provided details of children with cancer. In addition, listings of children with leukaemia or non-Hodgkin's lymphoma were obtained from the childhood cancer research group's national registry of childhood tumours.<sup>4</sup> All diagnoses were histologically confirmed.

We studied only children who were born and had cancer diagnosed in the study area. The mothers of 56 of the 71 children diagnosed during 1972-89 were living in the study area at the time of their child's birth. Two of these 56 children are not included in the analyses; both died in the early 1970s shortly after

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