The prevalence of hypoxaemia among ill children in developing countries: a systematic review

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Hypoxaemia is a common complication of childhood infections, particularly acute lower respiratory tract infections. In pneumonia—a disease that disproportionately impacts developing countries, and accounts for more than two million deaths of children worldwide—hypoxaemia is a recognised risk factor for death, and correlates with disease severity. Hypoxaemia also occurs in severe sepsis, meningitis, common neonatal problems, and other conditions that impair ventilation and gas exchange or increase oxygen demands. Despite this, hypoxaemia has been overlooked in worldwide strategies for pneumonia control and reducing child mortality. Hypoxaemia is also often overlooked in developing countries, mainly due to the low accuracy of clinical predictors and the limited availability of pulse oximetry for more accurate detection and oxygen for treatment. In this Review of published and unpublished studies of acute lower respiratory tract infection, the median prevalence of hypoxaemia in WHO-defined pneumonia requiring hospitalisation (severe and very severe classifications) was 13%, but prevalence varied widely. This corresponds to at least 1·5 to 2·7 million annual cases of hypoxaemic pneumonia presenting to health-care facilities. Many more people do not access health care. With mounting evidence of the impact that improved oxygen systems have on mortality due to acute respiratory infection in limited-resource health-care facilities, there is a need for increased awareness of the burden of hypoxaemia in childhood illness.

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Introduction

The fourth Millennium Development Goal has concentrated efforts on addressing priority areas for improving worldwide child survival, with the aim of reducing national child mortality rates by two-thirds between 1990 and 2015.[1] The 30th anniversary of the Alma Ata conference[2] rightly emphasised that advances in primary health-care interventions are needed if the fourth Millennium Development Goal is to be achieved. As part of the primary-care approach, children with severe illness require access to good quality basic first-referral-level care. Pneumonia is the leading cause of death in children younger than 5 years, being responsible for at least 19% of the annual 9·7 million deaths in this age-group.[3] Advances in the case-management of major causes of child death, such as pneumonia and neonatal conditions, should be a priority in improving child survival.[2,4]

In pneumonia, hypoxaemia is a predictor of severe disease and has been shown to be a risk factor for death.[5,6] There is now evidence that ensuring ample supplies of oxygen and promoting a routine and systematic approach of screening for hypoxaemia using pulse oximetry is associated with improved quality of care and reduced mortality, and that the technology required to do so is sustainable and affordable in district hospitals in developing countries.[5,7–11] Despite such evidence, oxygen remains inaccessible for a substantial proportion of severely ill children admitted to hospitals in developing countries. The inaccessibility of oxygen is particularly true for those admitted to district-level hospitals, where even if some facility for delivering oxygen is available, supplies are often unreliable, equipment is poorly maintained, or there is a lack of staff training or guidelines.[12–14] Moreover, oxygen therapy in developing countries continues to be a low priority on the child-health agenda. Oxygen was not mentioned, for example, in the recent publication by WHO and UNICEF on efforts to control pneumonia.[3]

Studies have explored the possibility of managing children with WHO-defined severe pneumonia and no danger signs at home, thereby directing the limited facility-based health-care resources to children most in need of them.[15] For home management to be safe and ethical, it is essential that only children without hypoxaemia are managed outside health-care facilities. Children with hypoxaemic pneumonia need to be identified (which is difficult using only clinical signs), admitted, and given supplemental oxygen and close monitoring. This necessitates a heightened awareness of the prevalence and risk of hypoxaemia among children presenting to health-care facilities, and robust mechanisms to detect it.

Increased awareness of the important role of oxygen in improving child survival requires a better understanding of the global burden of hypoxaemia in children. In this systematic review we bring together the current knowledge from published and unpublished data on the prevalence of hypoxaemia amongst acutely ill children and neonates in developing countries.

Methods

Search strategy

Systematic literature searches were conducted in December 2006 (by MA), and updated in November 2008 (by RS). The electronic databases used were: Medline (1950 to July 2008), EmBase (1980 to 2008 week 26), and Global Health (1973 to July 2008). The search was conducted using various combinations of the following terms: "anoxia/hypoxaemia/hypoxemia", "pneumonia",

"oximetry/oxymetry", "arterial oxygen saturation", "developing countries", and "children", with limits for studies of children younger than 12 years. More detail on searches run is available from the authors on request. Reference lists from the articles retrieved were used to identify further relevant articles. Citation searches using Web of Science and the find citing articles facility in Ovid Medline also yielded additional papers. Unpublished data sets were sought in a systematic survey of key researchers in the field. We contacted researchers who, through lists of published antibiotic or vaccine trials, were known to have done studies on acute respiratory infection in developing countries where oximetry was recorded. We also contacted researchers and clinicians who had contributed to WHO's acute respiratory infection programme. Given the intended focus on developing countries, and the anticipated differences in aetiology of disease between developed and developing countries, we only included studies conducted in countries in the developing regions, according to the UN Statistics Division.[11]

Selection criteria and definitions

Our initial literature search indicated that few studies measured hypoxaemia prevalence as a primary outcome. Therefore, we anticipated the potential heterogeneity of studies addressing the search question and set broad inclusion and exclusion criteria. Studies were eligible for inclusion in the Review if they included populations of children younger than 12 years, with a specific acute infection (or any illness in neonates apart from cardiac disease) presenting to a health-care facility in a country in a developing region, and for whom saturation of peripheral oxygen (SpO_2) was measured using room-air pulse oximetry at the time of presentation. We included studies that had consecutively or randomly recruited children. Studies where pulse oximetry was used to select a particular illness severity or diagnose cases were excluded. Relevant publications that did not publish all the required data were included if the authors, when contacted, could provide the additional data and satisfy quality criteria. Abstracts of all suitable articles were read, and the full text versions of those appearing to fit the inclusion criteria for the Review were then obtained (figure 1).

The main outcome was hypoxaemia, as defined by pulse oximetry measurements of SpO_2. Many studies in developing countries have used SpO_2 of less than 90% as the threshold for giving oxygen, and this is the WHO recommendation.[16,17] For standardisation, we applied this definition at sea level, and allowed for adjustment with altitude, where authors took into account the lower normal oxygen saturation in children to derive a definition of hypoxaemia lower than SpO_2 of below

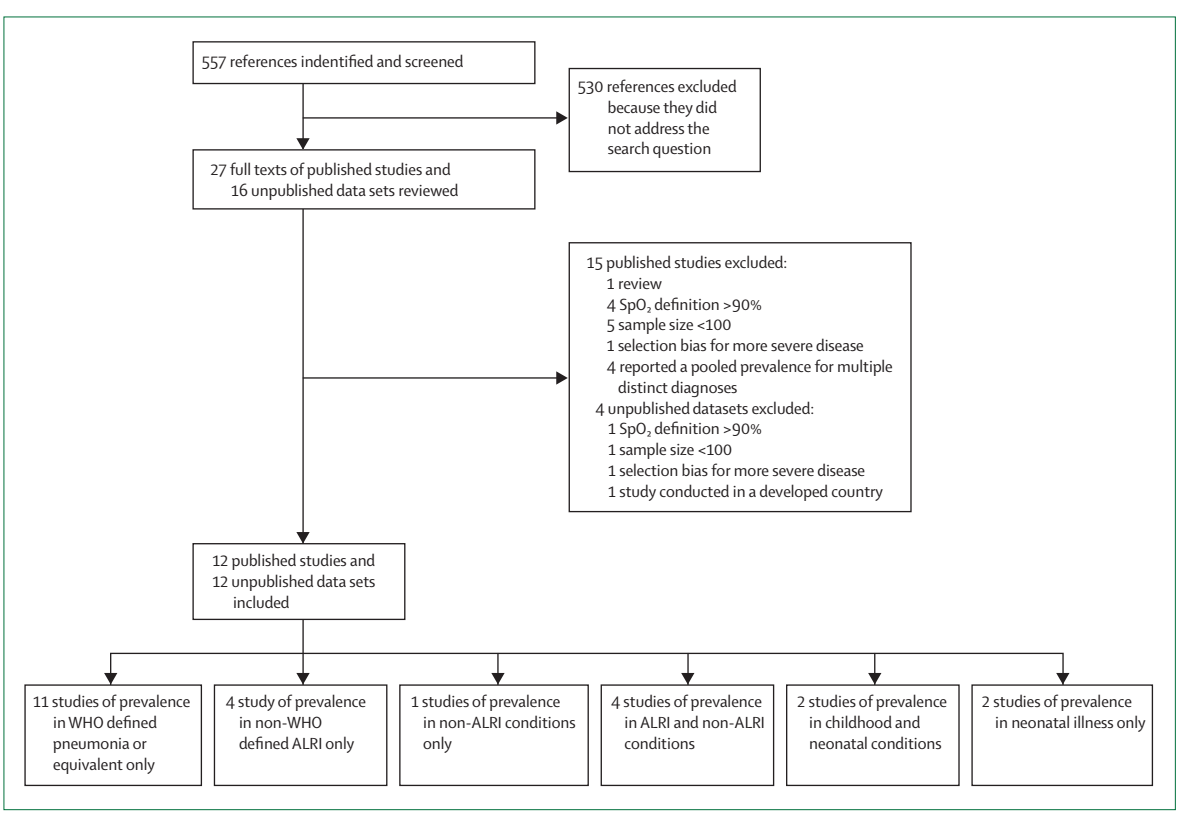

Figure 1: **Summary of study selection process**
ALRI=acute lower respiratory tract infections.

90%. Studies that applied a threshold of hypoxaemia likely to overestimate prevalence (such as a threshold level above SpO_2 of 90% at sea level) were excluded if the authors could not be contacted to provide prevalence data for the standard threshold. We defined secondary level health-care facilities as district or small provincial hospitals.

Data abstraction

Data were entered into an Excel database by two authors (RS and TD). The following fields were included: diagnoses, health-care setting (primary care, secondary level health-care facilities, or tertiary hospitals), age, criteria used to diagnose pneumonia, severity classification of pneumonia (if reported according to WHO criteria), definition of hypoxaemia used, overall and disease-specific sample size, and number of children fulfilling the standardised definition for hypoxaemia.

Quality assessment

We adhered to the meta-analysis of observational studies in epidemiology guidelines.[18] Study quality was assessed by four authors (MA, RS, HC, TD), and included a consideration of study design and case selection, sources of bias, and confounding. With agreement of these four authors, we excluded studies where there was high potential for selection bias, such as where there was selective recruitment of subpopulations of patients with more severe illness, or where oximetry was not measured and recorded in a systematic way within the study. Because of the likelihood that small studies would have overestimated prevalence, we also excluded studies that involved fewer than 100 participants.

Quantitative data analysis

All statistical analyses were done in Stata 10 statistical software.[19] Exact binomial 95% CIs for the prevalence were calculated from summary statistics reported in the original articles. Forest plots were constructed from these data.[19,20]

After subgrouping to standardise for diagnosis, diagnostic and severity criteria for pneumonia, altitude, and geographical locations of studies, we did meta-analyses to obtain point prevalence of hypoxaemia for: pneumonia, as defined by WHO criteria (non-severe, severe, and very severe); acute lower respiratory tract infections (ALRI) according to the geographical region studied (Africa, Asia, and South America); and non-ALRI illness—especially neonatal illnesses. We determined the I^2 value (index of the proportion of total variation across studies that is due to heterogeneity rather than to chance) for each estimate of prevalence as an indication of the between-study heterogeneity, and therefore, the validity of the estimate. Where the point-prevalence by the described analysis was considered potentially misleading, because of inherent and irreconcilable differences between study populations in each subgroup, we present the results as the medians and IQRs of the proportion of hypoxaemic children in the studies within each subgroup. Prevalence is reported as the estimated percentage of children with hypoxaemia within each diagnostic subgroup, geographical region, and by high (1000 m above sea level and higher) and low altitude (lower than 1000 m above sea level).

	Patients with diagnosis (total study sample size)	Number with hypoxaemia (prevalence, %)
Non-severe pneumonia		
Ashraf et al (b)	55 (367)	1 (1·8)
Basnet et al[34]	105 (250)	18 (17·0)
Brent et al[35]	145 (1030)	1 (0·69)
Mwaniki et al	697 (15 297)	14 (2·0)
Nadjm et al	903 (3683)	4 (0·44)
Nokes et al	669 (7564)	9 (1·3)
Singhi et al[36]	225 (2216)	8 (3·6)
Severe pneumonia		
Ashraf et al (a)	189 (251)	21 (11·1)
Ashraf et al (b)	300 (367)	28 (9·3)
Basnet et al[34]	25 (250)	20 (80·0)
Fu et al[37]	843 (843)	80 (9·5)
Mwaniki et al	2267 (15 297)	156 (6·9)
Nadjm et al	259 (3683)	21 (8·1)
Nokes et al	325 (7564)	12 (3·7)
Singhi et al[36]	331 (2216)	86 (26·0)
Very severe pneumonia		
Ashraf et al (a)	62 (251)	12 (19·4)
Ashraf et al (b)	12 (367)	7 (58·3)
Basnet et al	20 (150)	20 (100)
Bose et al†	300 (300)	56 (18·7)
Brent et al†	126 (1030)	8 (6·3)
Brooks et al†	270 (270)	37 (13·7)
Djelantik et al[38]†‡	4306 (4306)	1616 (37·5)
Mwaniki et al	2525 (15 297)	291 (11·5)
Nadjm et al	445 (3683)	38 (8·5)
Nokes et al	15 (7564)	2 (13·3)
Singhi et al[36]	126 (2216)	93 (73·8)
Wandi et al[14]†	578 (1313)	315 (54·5)
All categories		
Lodha et al[39]	109 (109)	28 (25·7)
O'Dempsey et al[40]	1033 (1033)	105 (10·2)
Zaman et al	1012 (1012)	86 (8·5)

References without citations are unpublished: Ashraf H, et al, Clinical Sciences Division, International Centre for Diarrhoeal Diseases Research, Bangladesh; Bose A, et al, Department of Community Health, Christian Medical College, Vellore, India; Brent A, et al, Nuffield Department of Infectious Diseases and Microbiology, John Radcliffe Hospital, Headington, Oxford, UK; Brooks A, et al, Centre for Health and Population Research, International Centre for Diarrhoeal Disease Research, Bangladesh; Bruce N, et al, Division of Public Health, University of Liverpool, Liverpool, UK; Djelantik B, et al, Agence de Médecine Préventive, Paris, France; Mwaniki M, et al, Kenya Medical Research Institute, Center for Geographic Medicine Research (Coast), Kilifi, Kenya; Nadjm B, et al, London School of Hygiene and Tropical Medicine, London, UK; Nokes J, et al, Kenya Medical Research Institute, Centre for Geographic Medicine Research (Coast), Kilifi, Kenya and Department of Biological Sciences, University of Warwick, UK; Zaman, S, et al, Medical Research Council Laboratories, Banjul, The Gambia. †Diagnosis equivalent to WHO severe or very severe pneumonia; analysed with very severe pneumonia to produce a conservative estimate of prevalence. ‡Unpublished data provided by Gessner BD, Agence de Médecine Préventive.

Table 1: **Hypoxaemia in children fulfilling WHO criteria for clinical diagnosis of non-severe, severe, or very severe pneumonia**

Where studies classified children as "severe or very severe pneumonia", or used a definition equivalent to this severity classification, these children were grouped as having very severe pneumonia. This meant that some children labelled as having very severe pneumonia for the purposes of this Review had less severe disease, leading to an underestimation of prevalence in this group. This was done to ensure that prevalence estimates are conservative and not overstated.

Limitations

We made every effort to identify and exclude biased results, especially those that would over-estimate prevalence. We reduced publication bias (ie, bias towards publication of studies that report high prevalence) by systematically seeking unpublished data. The large amount of unpublished data is explained by the fact that, in recent years, many investigators have recorded SpO_2 readings either as a component of composite secondary outcomes or as a baseline characteristic of populations studied. To standardise the populations between studies, we focused on studies employing WHO diagnostic criteria for pneumonia. We could not, however, control for differences in study design, data collection methodology, or, entirely, for case selection.

See Online for webappendix

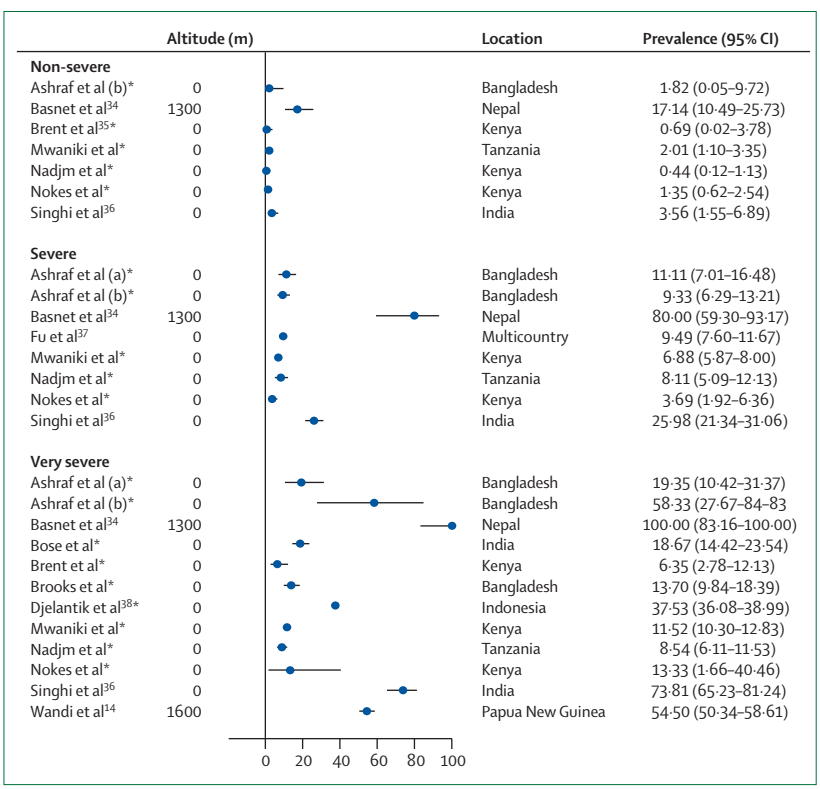

Figure 2: **Hypoxaemia prevalence in WHO non-severe, severe, and very severe pneumonia**
Studies which included children with severe or very severe pneumonia were groups as very severe to avoid over-estimation of prevalence. *Unpublished data. †Fu et al studied nine different sites, seven of which were at sea level. ‡Wandi et al studied five sites, but 90% of children were recruited from high altitude locations.

Heterogeneity was high between studies, and this made formal meta-analysis potentially misleading. The reasons for variations were several. Hypoxaemia prevalence was not the primary question of most of the published and unpublished studies. Also, the methodology of measuring oxygen saturation, the types of oximeters used, the setting in which oximetry was done (community or hospital-based measurements), and the level of training of health-care workers doing the measurements could not be standardised. Although we predefined SpO_2 threshold of hypoxaemia, there remained variation in the threshold used in studies at high altitude. We made every effort to ensure that the quality criteria for published and unpublished data were similar, and although it is possible, we do not believe that publication bias was a major confounder.

Results

Figure 1 shows the number of studies that were included and the reasons for exclusion. The search of the published literature yielded 27 papers comprising 26 cohort analyses and one systematic review, which was excluded. Another 14 studies did not fit all of the selection or quality criteria and were excluded. Four of these used a high definition of hypoxaemia[21–24] and another five studies of hypoxaemia had a sample size of less than 100 children.[25–29] For one study, there was a strong possibility of selection for a more severely ill subgroup of children with pneumonia seen by a consultant paediatrician.[30] In total, four studies reported a pooled prevalence for multiple diagnoses. This included one study that systematically underestimated the prevalence of hypoxaemia by reporting a prevalence for a population that included a control group of children with fever and rhinorrhoea, but not other respiratory symptoms.[31] One study reported a pooled prevalence for all acute respiratory infections, including upper respiratory infections.[6] Two studies of young infants were also excluded: one reported a pooled prevalence for both infants and neonates with any condition,[32] and the other used hypoxaemia to define severe illness but did not report its prevalence.[33]

The search for unpublished data yielded 16 separate data sets, 12 of which contained sufficient data and fulfilled the study criteria. Four data sets were excluded for reasons outlined in figure 1.

Therefore, there were 12 published and 12 unpublished data sets included in this Review. Some studies reported prevalence in more than one condition and in different age groups, such that four of the five studies of prevalence in non-ALRI conditions and two of the four studies of prevalence in neonatal illness also looked at hypoxaemia in pneumonia or ALRI. The webappendix summarises the 21 data sets that reported prevalence in pneumonia and ALRI.

Meta-analysis by subgroups of pneumonia severity revealed a high degree of heterogeneity between studies (I^2=79% for non-severe pneumonia, 95% for severe

pneumonia, and 99% for very severe pneumonia). A similar finding was noted for analysis by geographic region, where both African and Asian studies had a high degree of heterogeneity (I^2=99% and 98%, respectively). There were only three studies from South America, and this limited the validity of the meta-analysis of this region.

To account for the high degree of heterogeneity, we do not report a point prevalence of hypoxaemia prevalence by meta-analysis. We present medians and IQRs (in a forest plot) of the proportion of hypoxaemic children in the studied populations.

Prevalence of hypoxaemia in pneumonia

21 studies reported the prevalence of hypoxaemia in pneumonia (webappendix). Eight studies reported disaggregated prevalence estimates according to the three standard WHO definitions: non-severe, severe, and very severe pneumonia (table 1). Among the remaining 13 studies, three reported a single prevalence for all WHO categories of pneumonia[39,40] (Zaman et al, unpublished data) and five studies used a definition equivalent to the WHO "severe or very severe pneumonia"[14] (Bose et al, Brent A et al, Brooks A et al, Gessner et al, all unpublished data). Another three studies defined pneumonia according to clinical and radiographic findings as assessed by clinicians,[41–43] and one study selected for radiographically confirmed pneumonia.[44] For one study, the definition of pneumonia was not specified.[45]

Prevalence of hypoxaemia in WHO-defined pneumonia

Figure 2 is a graphical representation (forest plot) of the proportion (95% CI) of children with hypoxaemia reported by each study according to WHO definitions of pneumonia severity.

Eight studies reported hypoxaemia prevalence in WHO-severe pneumonia, and seven of these also studied children with very severe pneumonia. Five studies classified children with "severe or very severe pneumonia",[14] (Bose et al, Brent A et al, Brooks et al, Gessner et al, all unpublished data). These children were analysed as having very severe pneumonia. Therefore, the analysis of prevalence within the classification of very severe pneumonia included 12 studies.

The median hypoxaemia prevalence among studies of children with severe pneumonia was 9·4% (IQR 7·5–18·5%). In studies of pneumonia requiring hospitalisation according to the WHO clinical classifications "severe and very severe pneumonia", the median hypoxaemia prevalence is 13·3% (IQR 9·3–37·5%).

Prevalence of hypoxaemia by geographic region

There was evidence that the documented prevalence of hypoxaemia in hospitalised children with pneumonia differs between regions (figure 3). These differences were within comparable pneumonia severity classifications and

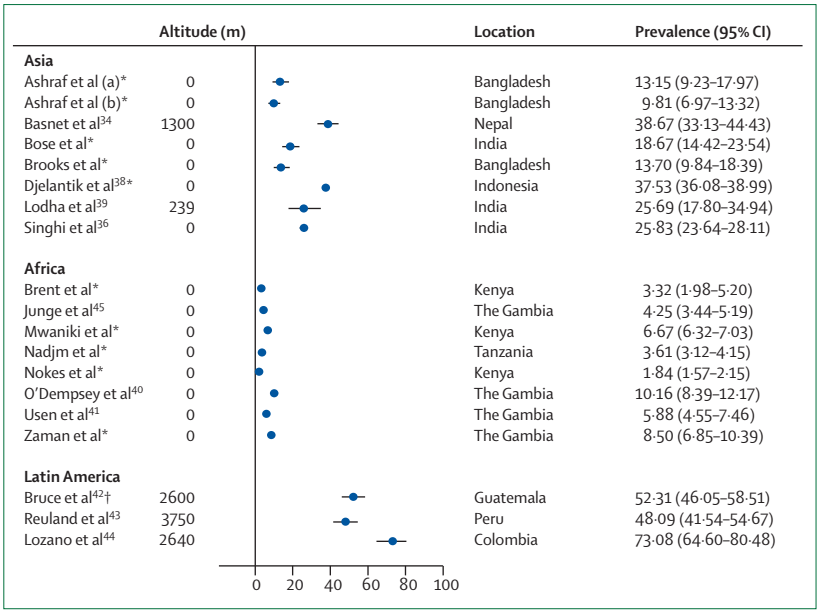

Figure 3: **Hypoxaemia prevalence by geographic region**
*Unpublished data, see table 1 for details. †Unpublished data: Bruce N, et al, Division of Public Health, University of Liverpool, Liverpool, UK.

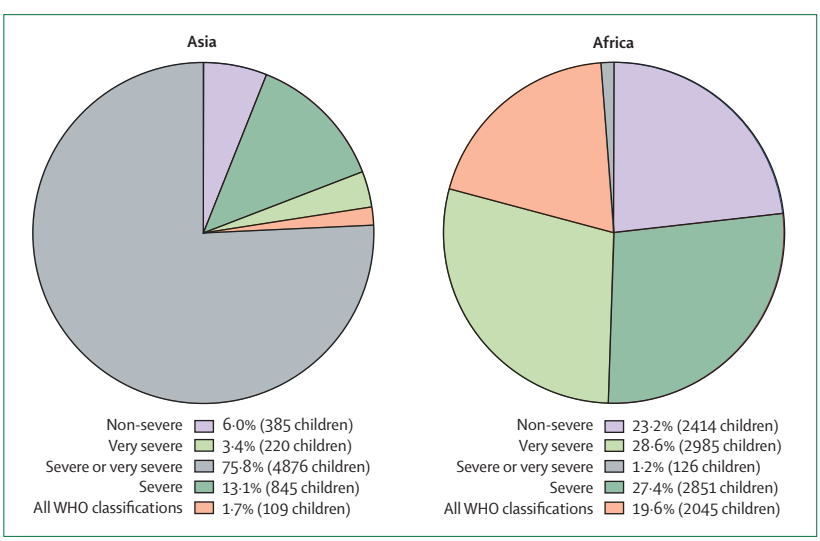

Figure 4: **Severity of ALRI in studies from Asia and Africa**

altitudes. The reported prevalence was consistently lower in Africa (eight studies; range of prevalence 3–10%) than Asia (eight studies; range of prevalence 9–39%). More studies from Asia were conducted in higher level health-care facilities than those from Africa: six of eight studies in tertiary-level facilities in Asia compared with six of eight studies in secondary-level facilities in Africa. WHO-defined disease severity of children included in the studies from each of these regions is represented in figure 4.

In Latin America, three studies, all conducted at high altitude locations, used non-WHO classifications and reported a prevalence ranging from 48%,[43] for all clinical pneumonia, to 73%, for radiographically confirmed

	Patient age	Patients with diagnosis (total sample size)	Number with hypoxaemia (prevalence, %)
Malaria			
Wandi et al[14]	0–unspecified (median age 11 months)	272 (1313)	9 (3·3)
Mwaniki et al	0–5 years	4982 (15 297)	244 (4·9)
Junge et al[45]	0–10 years	1044 (3269)	30 (2·9)
Maitland et al[46]	0–5years	501 (501)	86 (17·1)
Meningitis			
Wandi et al[14]	0–unspecified (median age 11 months)	41 (1313)	6 (14·6)
Junge et al[45]	0–10 years	74 (3269)	2 (2·7)
Nadjm et al	2 months to 13 years	21 (3683)	2 (9·5)
Diarrhoeal diseases			
Wandi et al[14]	0–unspecified (median age 11 months)	127 (1313)	6 (4·7)
Mwaniki et al	0–5 years	2026 (15 297)	49 (2·4)
Junge et al[45]	0–10 years	114 (3269)	0
Nadjm et al	2 months to 13 years	535 (3683)	11 (2·1)
Malnutrition			
Wandi et al[14]	0–unspecified (median age 11 months)	12 (1313)	1 (8·3)
Mwaniki et al	0–5 years	1261 (15 297)	68 (5·4)
Junge et al[45]	0–10 years	271 (3269)	5 (1·8)
Nadjm et al	2 months to 13 years	105 (3683)	4 (3·8)
Anaemia			
Wandi et al[14]	0–unspecified (median age 11 months)	63 (1313)	2 (3·2)
Junge et al[45]	0–10 years	225 (3269)	4 (1·8)
Nadjm et al	2 months to 13 years	927 (3683)	23 (2·5)
Pulmonary tuberculosis			
Wandi et al[14]	0–unspecified (median age 11 months)	20 (1313)	4 (20·0)
Febrile convulsions or epilepsy			
Wandi et al[14]	0–unspecified (median age 11 months)	17 (1313)	2 (11·8)
Nadjm et al	2 months to 13 years	17 (3683)	2 (11·8)
Neonatal illnesses			
Mwaniki et al	Younger than 7 days	1105 (15297)	206 (18·6)
Weber et al[33]*	Younger than 1 month	724 (4552)†	129 (17·8)
Junge et al[45]	Younger than 1 month	259 (3269)	51 (19·7)
English et al[47]	Younger than 30 days	376 (1080)	87 (23·1)

Studies of non-ALRI illness might include children with concurrent ALRI. Hypoxaemia defined as SpO_2 of less than 90%. References without citations are unpublished. *Neonates recruited had signs of infection. †Hypoxaemia definition adjusted for site altitude: less than 90% at sea level locations, and as low as less than 85% for one high altitude location.

Table 2: **Prevalence of hypoxaemia in non-ALRI diagnostic categories**

pneumonia.[44] One included study in Papua New Guinea reported a prevalence of 54·5% for "severe or very severe pneumonia". The majority of these cases were in hospitals at high altitude.[14]

Prevalence of hypoxaemia by altitude

There were five studies of hypoxaemia prevalence in pneumonia based at locations more than 1000 m above sea level (see webappendix).[14,34,42,43,44] The reported prevalence in these studies ranged from 39%, for a study of all WHO severities,[34] to 73%, for a study of radiographically confirmed pneumonia.[44]

Prevalence of hypoxaemia in non-pneumonia conditions and neonatal illness

The prevalence of hypoxaemia in non-pneumonia conditions and neonatal illness is summarised in table 2.

Five published papers were found evaluating non-ALRI illness in children, four of which also included data on ALRI. Prevalence of hypoxaemia ranged from 2·9% to 17·1% for four studies of malaria, 2·7% to 14·6% for three studies of meningitis, and 1·8% to 8·3% for four studies of malnutrition.

Four published papers were found evaluating neonatal illness, two of which also contained data on ALRI. Three studies of hypoxaemia in all neonatal admissions and one study of all neonatal admissions with signs of infection, showed that one in five neonates was hypoxaemic.

Discussion

The global burden of hypoxaemia

This Review highlights the substantial burden of hypoxemia in childhood infections in developing countries, and the differences in data reported between regions and studies. In terms of the magnitude of the problem, in the developing world each year there are an estimated 150 million episodes of pneumonia, 11–20 million of which require hospitalisation.[48,49] If the median prevalence in studies of children with severe or very severe pneumonia is representative of the worldwide burden of hypoxaemia in hospitalised pneumonia, this would correspond to 1·5–2·7 million annual cases (13·3% of 11–20 million). Many more cases of hypoxaemia complicate other common infections of childhood and neonatal conditions. We believe this is a conservative estimate of the global burden of hypoxaemia, and that it is an issue that demands serious attention.

Differences in hypoxaemia prevalence between WHO-severity categories

Hypoxaemia prevalence increases in accordance with current WHO-defined clinical categories of non-severe, severe, and very severe pneumonia. WHO recommends, in its guidelines for children older than 2 months, the use of oxygen in very severe disease, as ascertained by the presence of a number of clinical indicators of hypoxaemia, including cyanosis, inability to drink, severe chest indrawing, respiratory rate greater than 70 breaths per min, grunting, or head nodding.[17] With the exception of chest indrawing, such signs of oxygen deprivation are absent in children with severe pneumonia; however, some studies have reported a prevalence of greater than 20% in children with this classification.[34,36] Therefore, while most children with WHO-severe pneumonia will not need oxygen, the requirement for oxygen therapy

should not be dismissed in this category. Without pulse oximetry, managing such children relies on the accurate identification of clinical signs of hypoxaemia that might be difficult to recognise in many children. These findings support the calls for adopting pulse oximetry for improving the detection of hypoxaemia, for making SpO_2 a regularly measured vital sign, and for incorporating measurement of SpO_2 in algorithms for categorising pneumonia severity.[6,10,44,50]

Differences between geographical regions

Studies of WHO-defined pneumonia from Africa consistently reported lower prevalence of hypoxaemia than similar studies from Asia. These differences existed even at similar altitudes and within comparable classifications of pneumonia severity. Such observations need to be interpreted with caution, as there are differences between studies from both regions. The majority of the studies from Africa were conducted in secondary-level hospitals, as compared to the predominantly tertiary hospital setting of the Asian studies. It is possible, given referral biases, that higher-level facilities represent populations with more severe disease. Figure 4 further explores these differences in disease severity between studied populations from both regions as defined by WHO classifications, but direct comparison between the two regions is difficult. Nearly three-quarters of children studied in Asia were classified according to national guidelines, equating to WHO "severe or very severe pneumonia".

There are likely to be other complex determinants of the prevalence of hypoxaemia not yet extensively explored in published studies. For example, the lower prevalence in studies from Africa will not be representative of the whole of Africa, and may be influenced by such factors as the frequency of *Pneumocystis jirovecii* as a cause of pneumonia in infants.[51] Most of the African studies included in this Review are from east and west Africa, which have low HIV prevalence compared with southern Africa. Clinical overlap too may be important; for example, in Africa, malaria, severe sepsis, and anaemia might present with similar clinical signs as pneumonia, with a lower risk of hypoxaemia. In addition, the microbial aetiology of respiratory disease (especially viral versus bacterial), co-morbidities, host and environmental factors, care-seeking behaviour, availability of effective antibiotics in primary-care facilities, and referral patterns might be important in explaining regional differences in reported hypoxaemia prevalence. In South America, the higher prevalence reported may have been influenced by the more selective definitions of pneumonia used (often using auscultatory or radiographic findings), and the higher altitudes of study locations.

Altitude

Higher altitude is associated with a higher prevalence and severity of hypoxaemia in children with pneumonia than at sea level, despite comparable clinical diagnostic criteria, and adjustment of the definition of hypoxaemia for a lower normal SpO_2 at altitude.[14,44] Two high-altitude studies that used standard WHO pneumonia definitions (or their equivalent) reported prevalence of 39% and 54·5%.[14,34] The high prevalence in the remaining three high-altitude studies from Latin America might have been influenced by the more selective clinical and imaging criteria used in diagnosing pneumonia.[42,43,44]

Non-pneumonia conditions

Hypoxaemia adds to the global burden of morbidity by complicating acute conditions other than pneumonia and by its high prevalence in neonatal illness; this burden has important implications for resource availability and training. It also highlights the need for an integrated, rather than disease-specific, approach to providing oxygen in hospitals in developing countries. However, the prevalence estimates for non-pneumonia conditions are less robust than for pneumonia since there were small numbers of cases within specific conditions in the studies found. Furthermore diagnostic criteria were not always standardised, and children with concurrent lower-respiratory infections might not have been excluded from the cohorts studied. The rates of hypoxaemia seen in common non-pneumonia illnesses may partly reflect the proportion of cases in which coexisting pneumonia remains undiagnosed, owing to the insensitivity of clinical criteria for diagnosing hypoxaemia in these children.[30] However, even a relatively low prevalence of hypoxaemia in a common illness like malaria translates to a significant global burden. Many health workers in developing countries may not be sufficiently aware of the need to screen for hypoxaemia in many non-ALRI illnesses and in sick neonates.

Implications for global and local policy

The high burden of hypoxaemia and the evidence of the survival benefit of oxygen administration to hypoxemic children necessitates investment in the widespread implementation of appropriate systems for its detection and treatment.[8,11] The occurrence of hypoxaemia in children with pneumonia who do not display clinical signs of oxygen deficits (WHO-defined severe pneumonia) and in children with non-pneumonia conditions, highlight the need for more accurate detection of hypoxaemia through the use of pulse oximetry. Recent suggestions that WHO-defined severe pneumonia can be managed at home, coupled with the finding of this Review that a significant proportion of these children were hypoxaemic, suggests that the accurate identification of hypoxaemia in severe pneumonia will be crucial in determining the safety of outpatient treatment.[52] Pulse oximetry would enable accurate identification and might increase the safety and cost effectiveness of this recommendation.[53] This is demonstrated by a recent study from Bangladesh[15] reporting successful day-care case management of severe and very severe pneumonia

Search strategy and selection criteria

These are described in detail in the Methods section.

using pulse oximetry as an important part of the treatment algorithm.

Oxygen concentrators will be the most reliable and most economical source of therapeutic oxygen where there are difficulties transporting oxygen cylinders and where there is a continuous power supply, whereas oxygen cylinders may be necessary in health-care facilities without power.[54] The findings presented in this Review should act as a strong impetus for increasing global awareness of hypoxaemia in childhood illness and in making the relevant resources available.

Conclusions

Hypoxaemia is a very common and treatable complication of childhood respiratory and non-respiratory infections in developing countries. Investment in pulse oximetry for the diagnosis of hypoxaemia will allow more precise classification of disease severity than that currently possible using clinical signs. Other conditions, particularly in the neonatal period, make up an additional substantial burden of hypoxaemia in developing countries. Global awareness of this aspect of the management of sick children, and for the need to increase the availability of pulse oximetry and effective oxygen delivery systems in developing countries is necessary.

Hypoxaemia in Developing Countries Study Group

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Conflict of interest

We declare that we have no conflict of interest.

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