

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

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Abstract

Hypoxaemia is a common complication of childhood infections, particularly acute lower respiratory tract infections (ALRI). In pneumonia – a disease that disproportionately impacts developing countries and accounts for more than two million deaths in children worldwide - hypoxaemia is a recognized risk factor for death and correlates with disease severity. Hypoxaemia also occurs in septicaemia, meningitis, common neonatal problems and other conditions that impair ventilation and gas exchange, or increase oxygen demands. Despite this, hypoxaemia has been overlooked in global strategies for pneumonia control and for reducing child mortality. Hypoxaemia is also often overlooked in practice in developing countries, mainly due to the low accuracy of its clinical predictors, and the limited availability of pulse oximetry for its more accurate detection, and oxygen for its 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 In this review of published and unpublished studies of acute lower respiratory tract infection the median prevalence of hypoxaemia in WHO-defined pneumonia requiring hospitalization (severe or very severe classification) 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 facilities. Countless more do not access health care. With mounting evidence of the impact that improved oxygen systems have mortality due to acute respiratory infection in limited-resource health facilities, there is a need for increased global awareness of the burden of hypoxaemia in childhood illness.

Introduction

The fourth Millennium Development Goal (MDG 4) has concentrated efforts at addressing priority areas for improving global child survival with the aim of reducing national child mortality rates by two-thirds between 1990 and 2015.¹ Making advances in primary health care interventions has been rightly emphasized recently for achieving MDG 4, with the 30th anniversary of the Alma Ata conference.² 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 under 5 years of age, being responsible for at least 19% of the annual 9.7 million deaths in this age category.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 significant proportion of severely ill children admitted to hospitals in developing countries. This 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 global child health agenda. Oxygen was not mentioned, for example, in the recent publication by the World Health Organization and UNICEF on efforts to control pneumonia.³

Recent 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 healthcare 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 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 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 newborns 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 less than 12 years old (more detail on searches run are 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 were known to have done studies on acute respiratory infection in developing countries where oximetry was recorded, through lists of antibiotic or vaccine trials that had been published, and researchers and clinicians who had contributed to the World Health Organization’s acute respiratory infection (ARI) program. 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 United Nations Statistics Division.¹¹

Selection criteria and definitions

Our initial literature search indicated that few studies set-out to measure hypoxaemia prevalence as a primary outcome. Therefore, we anticipated the potential heterogeneity of studies addressing the search question, and set broad inclusions and exclusion criteria. Studies were eligible for inclusion in the review if they included populations of children less than 12 years of age, with a specific acute infection (or any illness in neonates apart from cardiac disease) presenting to a healthcare facility in a country in a developing region, and for whom SpO₂ was measured using pulse oximetry on room air at the time of presentation (Textbox 1). 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 which 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 SpO₂. Many studies in developing countries have used SpO₂ of <90% as the threshold for giving oxygen, and this is the WHO recommendation.^{16,17} For standardization, 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 SpO₂ < 90%. Studies that applied a threshold of hypoxaemia likely to overestimate prevalence (such as a threshold level *above* SpO₂ 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 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, healthcare setting (primary care, secondary level health 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 standardized definition for hypoxaemia.

Quality assessment

We adhered to the ‘Meta-analysis of Observational Studies in Epidemiology’ (MOOSE) guidelines (ref).¹⁸ Study quality was assessed by 4 authors (MA, RS, HC, TD), and included a consideration of study design and case-selection, sources of bias and confounding. With agreement of 4 authors, we excluded studies where there was high potential for selection bias, such as where there was selective recruitment of sub-populations 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 less than 100 participants.

Quantitative data analysis

All statistical analyses were done in Stata 10 statistical software.¹⁹ Exact binomial 95% confidence intervals for the prevalence were calculated from summary statistics reported in the original articles. Forest plots were constructed.^{19;20}

After sub-grouping to standardize for diagnosis, diagnostic and severity criteria for pneumonia, altitude and geographical locations of studies, we performed meta-analyses to obtain point prevalence of hypoxaemia for: pneumonia, as defined by WHO criteria (non-severe, severe and very severe); 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 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 median and inter-quartile ranges 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 ($\geq 1000\text{m}$ above sea level) and low altitude ($< 1000\text{m}$ above sea level).

Where studies classified children with ‘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 labeled 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 unduly overstated.

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 1 systematic review. 14 studies did not fit all of the selection or quality criteria and were excluded. Four of these used a high definition of hypoxaemia²¹⁻²⁴ and another 5 studies of hypoxaemia had a sample size less than 100 children.²⁵⁻²⁹ For one study, there was a strong possibility of selection for a more severely ill sub-group of children with pneumonia seen by a consultant paediatrician.³⁰ Another study systematically underestimated the prevalence of hypoxaemia by reporting a prevalence for a population which included well children.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 condition³², 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 4 of the 5 studies of prevalence in non-ALRI conditions and 2 of the 4 studies of prevalence in neonatal illness also studied hypoxaemia in pneumonia or ALRI. Web table 1 summarizes the 21 data sets which 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 3 studies from South America, and this limited the validity of a meta-analysis.

Due to these considerations, we do not report a point prevalence of hypoxaemia prevalence by meta-analysis. We present medians and inter-quartile ranges (on 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 (Webtable 1). 8 studies reported disaggregated prevalence estimates according to the three standard WHO definitions of non-severe, severe and very severe pneumonia (Table 2). Among the remaining 13 studies, 3 reported a single prevalence for all WHO categories of pneumonia^{34,35} (Zaman, S, Medical Research Council Laboratories, Banjul, The Gambia, unpublished data) and 5 studies used a definition equivalent to the WHO severe or very severe pneumonia¹⁴ (Bose, A, Christian Medical College, Vellore, India, unpublished data; Brent, A, Nuffield Department of Infectious Diseases and Microbiology, Oxford, UK, unpublished data; Brooks, A, International Centre for Diarrhoeal Disease Research, Dhaka, Bangladesh; Gessner, B, Agence de Médecine Préventive, Paris, France, unpublished data). Another 3 studies defined pneumonia according to clinical and radiographic findings as assessed by clinicians³⁶⁻³⁸ and one study selected for radiographically confirmed pneumonia.³⁹ For one study, the definition of pneumonia was not specified.⁴⁰

Prevalence of hypoxaemia in WHO defined pneumonia

Figure 2 is a graphical representation (forest plot) of the proportion (95% confidence interval) 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 7 of these also studied children with very severe pneumonia. Five studies classified children with ‘severe *or* very severe pneumonia’,¹⁴ (Bose, A, Christian Medical College, Vellore, India, unpublished data; Brent, A, Nuffield Department of Infectious Diseases and Microbiology, Oxford, UK, unpublished data; Brooks, A, International Centre for Diarrhoeal Disease Research, Dhaka, Bangladesh; Gessner, B, Agence de Médecine Préventive, Paris, France, 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% (interquartile range 7.5% – 18.5%). In studies of pneumonia requiring hospitalization using the WHO clinical classification (severe and very severe pneumonia), the median hypoxaemia prevalence is 13.3% (9.3% – 37.5%).

Prevalence of hypoxaemia by geographic region

There was evidence that the documented prevalence of hypoxaemia in hospitalized children with pneumonia differs between regions (Figure 3). These differences were within comparable pneumonia severity classifications and altitudes. The reported prevalence was consistently lower in Africa (8 studies; range 3-10%) than Asia (8 studies; range 9-39%). More studies from Asia were conducted in higher level health facilities than those from Africa: 6 of 8 studies in tertiary level facilities in Asia compared to 6 of 8 studies in secondary level facilities in Africa. The WHO-defined disease severity of children included in the studies from each of these regions is represented in Figure 4.

In South America, 3 studies, all conducted at high altitude locations, used non-WHO classification and reported a prevalence ranging from 48%³⁷ for all clinical pneumonia and 73% for radiographically confirmed pneumonia³⁹. 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 5 studies of hypoxaemia prevalence in pneumonia based at high altitude locations (>1000 metres above sea level) (see Web-table).^{14;36;37;39;41} The reported prevalence in these studies ranged from 39% for a study of all WHO severities⁴¹ to 73% for a study of radiographically confirmed pneumonia.³⁹

Prevalence of hypoxaemia in non-pneumonia conditions and neonatal illness

The prevalence of hypoxaemia in non-pneumonia conditions and neonatal illness is summarized in Table 3.

Five published papers were found evaluating non-ALRI illness in children, 4 of which also included data on ALRI. Prevalence of hypoxaemia ranged from 2.9-17.1% for 4 studies of malaria, 2.7-14.6% for 3 studies of meningitis, and 1.8-8.3% for 4 studies of malnutrition.

Four published papers were found evaluating neonatal illness, 2 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 to 20 million of which require hospitalization.^{42;43} If the median of the prevalence in studies of children with severe or very severe pneumonia is taken to approximate the global burden of hypoxaemia in hospitalized pneumonia, this corresponds to 1.5 to 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 guidelines for children more than 2 months old recommend 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 per minute, 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.^{41;44} 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, which may be either difficult to recognize in many children. These findings support the calls for adopting pulse oximetry for improving the detection of hypoxaemia, for making SpO₂ a regularly measured vital sign, and for incorporating measurement of SpO₂ in algorithms for categorizing pneumonia severity.^{6;10;39;45}

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 studies from Africa were conducted in secondary-level hospitals, as compared to the predominantly tertiary hospital setting of 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 the literature. For example, the relatively 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 jiroveci* as a cause of pneumonia in infants.⁴⁶ Most of the African studies included in this review are from East and West Africa, which have comparatively low HIV prevalence compared with Southern Africa. Clinical overlap too may be important. For example in Africa, malaria, septicaemia and anaemia may 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 may 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 SpO₂ at altitude.^{14;39} Two high altitude studies which used standard WHO pneumonia definitions (or their equivalent) reported prevalence of 39% and 54.5%.^{14;41} The high prevalence in the remaining 3 high altitude studies from South America may have been influenced by the more selective clinical and imaging criteria used in diagnosing pneumonia.^{36;37;39}

Non-pneumonia conditions

That hypoxaemia complicates acute conditions other than pneumonia, and has a high prevalence in neonatal illness adds to the global burden, and 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, there were relatively small numbers within specific conditions in the studies found. Furthermore diagnostic criteria were not always standardized, and children with concurrent lower respiratory infections may 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.

Study methodology and limitations

We made every effort to identify and exclude biased results, especially those that would over-estimate prevalence. Where studies included children with either severe *or* very severe pneumonia, we adopted the conservative approach of reassigning the entire population to the very severe pneumonia category. We reduced publication bias (i.e. 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 SpO₂ readings either as a component of composite secondary outcomes or as a baseline characteristic of populations studied. To standardize 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.

Heterogeneity was high between studies, and this made a formal meta-statistic potentially misleading. The reasons for variations were several. Hypoxaemia prevalence in itself was not the primary question of most published and unpublished studies. Also, the methodology of measuring oxygen saturation, the types of oximeters used, the setting in which oximetry was performed (community or hospital-based measurements) as well as the level of training of health workers conducting the measurements could not be standardized. Although we pre-defined SpO₂ 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 don't believe that publication bias was a major confounder.

Implications for global and local policy

The high burden of hypoxaemia, and the evidence for 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 from this review that a significant proportion of these children were hypoxaemic in some studies suggests that the accurate identification of hypoxaemia in severe pneumonia will be crucial in determining the safety of outpatient treatment.⁴⁷ Pulse oximetry would enable this and might increase the safety and cost effectiveness of this recommendation.⁴⁸ This is demonstrated by a recent study from Bangladesh reporting successful day-care case management of severe and very severe pneumonia using pulse oximetry as a crucial part of the treatment algorithm.¹⁵

Oxygen concentrators will be the most reliable and most economical source where there are difficulties transporting oxygen cylinders and where there is a continuous power supply, whereas oxygen cylinders may be necessary in health facilities without power.⁴⁹ The findings presented in this review should act as a strong impetus for increasing global awareness of hypoxaemia in childhood illness and making such 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 its diagnosis 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.

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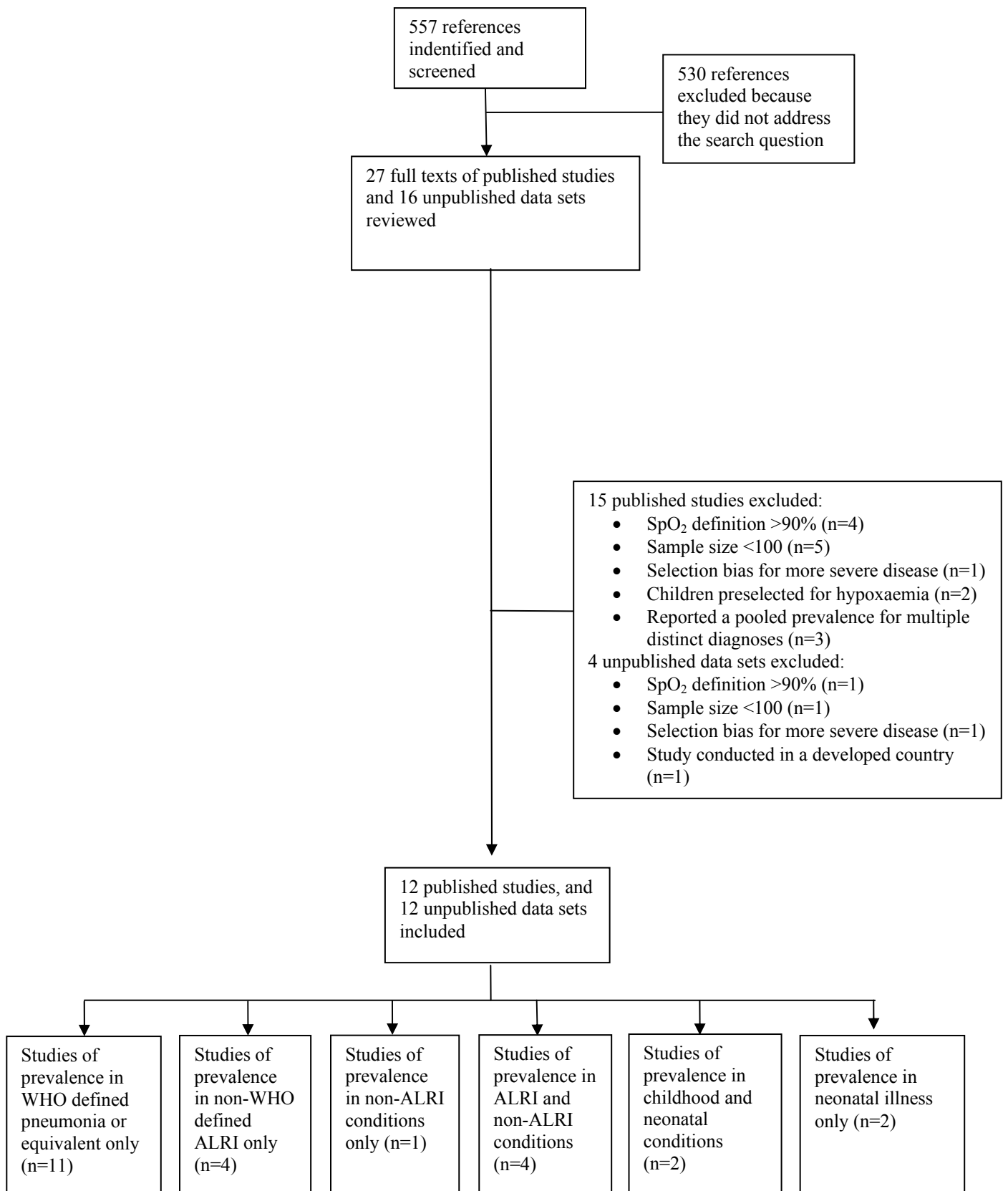
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Conflict of interest statement

All authors declare there are no competing interests and therefore have nothing to declare.

Figure 1. Selection process



Webtable 1. Characteristics of pneumonia and ALRI studies included in this review

Reference	Altitude (m) above sea level	Setting	Age	Hypoxaemia def ^a (SpO ₂)	Diagnosis	Number hypoxaemic / number with diagnosis	Prevalence (%)
Basnet et al ⁴¹ Nepal	1300	Tertiary hospital	2 months – 5 yrs	< 90%	WHO-defined pneumonia (all categories of severity) ^c	58 / 150	38.7 (30.8-47.0)
Fu et al ⁵⁰ Multi-country	All sites at 0 m except Bogota and Mexico City	Tertiary hospitals in 9 facilities in 8 countries	3 months – 5 years	< 88% (high altitude sites) < 90% (sea level sites)	WHO defined severe pneumonia	80 / 843	9.490 (7.695-11.658)
Junge et al ⁴⁰ The Gambia	0	Tertiary hospital	1 month - 10 yrs	< 90%	ALRI (definition not reported)	51 / 436	11.7 (8.3-14.2)
Lodha et al ³⁴ India	239	Tertiary hospital	0 - 5 years	< 90%	WHO-defined pneumonia	28 / 109	25.7 (17.8-34.9)
Lozano et al ³⁹ Colombia	2640	Tertiary hospital	7 days – 3 years	< 88%	Radiographically confirmed pneumonia	95 / 130	73.0 (64.6-80.5)
O’Dempsey et al ³⁵ The Gambia	< 200	Primary care facility	0 - 5 years	≤ 90%	WHO-defined pneumonia	105 / 1033	10.2 (8.4-12.7)
Reuland et al ³⁷ Peru	3750	Tertiary hospital	2 months – 5 years	< 82% (2 – 11 months) < 85% (> 12 months)	Clinical diagnosis of non-pneumonia ALRI and bronchopneumonia	113 / 235	48.1 (41.5-54.7)
Singhi et al ⁴⁴ India	0	Tertiary hospital	2 months – 5 years	≤ 90%	WHO-defined pneumonia (all severities) and bronchiolitis	203 / 828	24.5 (21.6-27.6)
Usen et al ³⁸ The Gambia	0	Tertiary hospital	2 – 33 months	< 90%	Pneumonia or any other form of ALRI	63 / 1072	5.9 (4.5-7.5)
Wandi et al ¹⁴ Papua New Guinea	Data obtained from 5 different sites, 2 at sea level and 3 at 1600 m. 90% of children from high altitude (1600m)	Secondary hospitals	0 – unspecified age (median 11 months)	< 90%	PNG standard definition, equivalence to WHO severe <i>or</i> very severe pneumonia	315 / 578	54.5 (50.3-58.6)
Ashraf et al ¹⁵ (a)* Bangladesh	0	Primary care facility	2 months – 5 years	< 90%	WHO-defined severe or very severe pneumonia	33 / 251	13.1 (9.2-18.0)
Ashraf et al (b)* Bangladesh	0	Primary care facility and tertiary hospital	2 months – 5 years	< 90%	WHO defined pneumonia (all severities) and bronchiolitis	36 / 367	9.8 (7.0-13.3)
Bose et al ^{51*} India	0	Tertiary hospital	2 months – 2 years	< 90%	Crepitations on auscultation AND respiratory rate > 50 breaths/min AND any danger sign (lethargy, inability to feed, chest indrawing, central cyanosis). Equivalent to WHO severe <i>or</i> very severe pneumonia	56 / 300	18.7 (14.4-23.5)
Brent et al ^{14;52*}	0	Secondary hospital	0 - 5 years	< 90%	WHO defined pneumonia.	9 / 271	3.3 (1.5-6.2)

Kenya					Non-severe and severe <i>or</i> very severe		
Brooks et al ^{53*} Bangladesh	0	Tertiary hospital	2 months – 2 years	< 90%	Cough, crepitations on auscultation, respiratory rate > 50 breaths/min AND any danger sign (lethargy, inability to feed, chest indrawing, central cyanosis). Equivalent to WHO severe <i>or</i> very severe pneumonia	37 / 270	13.7 (10.1-18.3)
Bruce et al ^{36*} Guatemala	2600	Community case finding of children with respiratory illness, or children presenting to health centre or hospital with respiratory illness	0 – 18 months	< 87%	Clinical diagnosis of pneumonia	136 / 260	52.3 (46.0-58.5)
Gessner et al [†] Indonesia ⁵⁴	0	Secondary hospital	0 – 2 years	< 90%	WHO defined severe or very severe pneumonia	1616 / 4306	37.5 (36.1-40.0)
Mwaniki et al [*] Kenya	0	Secondary hospital	0 – 5 years	< 90%	WHO defined pneumonia (all categories of severity)	461 / 5489	8.4 (7.7-9.2)
Nokes et al ^{55,56*} Kenya	0	Primary care facility and secondary hospital	0 – 30 months	< 90%	WHO defined pneumonia (all categories of severity)	135 / 7564	1.8 (1.5-2.1)
Nadjm et al, [*] Tanzania	150	Secondary hospital	2 months – 13 years	< 90%	WHO defined pneumonia (all categories of severity)	63 / 1607	3.9 (3.0-5.0)
Zaman et al ^{57*} The Gambia	0	Primary care facility and secondary hospital	2 – 29 months	< 90%	WHO-defined pneumonia / suspected invasive pneumococcal disease [*]	86 / 1012	8.5 (6.9-10.4)

Note: Citations are provided where unpublished pulse oximetry data was collected as part of a published study.

WHO defined syndromes are mutually exclusive: severe pneumonia excludes children with very severe etc...

OP/ED – Paediatric outpatients and/or emergency department

PNG – Papua New Guinea

* Unpublished data

Table 2. Hypoxaemia in children fulfilling WHO criteria for clinical diagnosis of non-severe, severe or very severe pneumonia

Diagnostic category	Reference	No with diagnosis (Total study sample size)	Number hypoxaemic (Prevalence (%))
Non-severe pneumonia	Ashraf et al (b)	55 (367)	1 (1.8)
	Basnet et al ⁴¹	105 (250)	18 (17.0)
	Brent et al ⁵²	145 (1030)	1 (0.69)
	Nadjm et al	903 (3683)	4 (0.44)
	Singhi et al ⁴⁴	225 (2216)	8 (3.6)
	Mwaniki et al	697 (15297)	14 (2.0)
	Nokes et al	669 (7564)	9 (1.3)
Severe pneumonia	Ashraf et al (a)	189 (251)	21 (11.1)
	Ashraf et al (b)	300 (367)	28 (9.3)
	Basnet et al ⁴¹	25 (250)	20 (80.0)
	Fu et al ⁵⁰	843 (843)	80 (9.5)
	Mwaniki et al	2267 (15297)	156 (6.9)
	Nokes et al	325 (7564)	12 (3.7)
	Nadjm et al	259 (3683)	21 (8.1)
	Singhi et al ⁴⁴	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)
	Nokes et al	15 (7564)	2 (13.3)
	Mwaniki et al	2525 (15297)	291 (11.5)
	Nadjm et al	445 (3683)	38 (8.5)
	Singhi et al ⁴⁴	126 (2216)	93 (73.8)
	Bose et al [*]	300 (300)	56 (18.7)
	Brooks et al [*]	270 (270)	37 (13.7)
	Brent et al [*]	126 (1030)	8 (6.3)
	Gessner et al ^{*54}	4306 (4306)	1616 (37.5)
	Wandi et al ^{14*}	578 (1313)	315 (54.5)
All categories	O'Dempsey et al ³⁵	1033 (1033)	105 (10.2)
	Lodha et al ³⁴	109 (109)	28 (25.7)
	Zaman et al	1012 (1012)	86 (8.5)

* Diagnosis equivalent to WHO severe *or* very severe pneumonia. Analyzed with very severe pneumonia to produce a conservative estimate of prevalence.

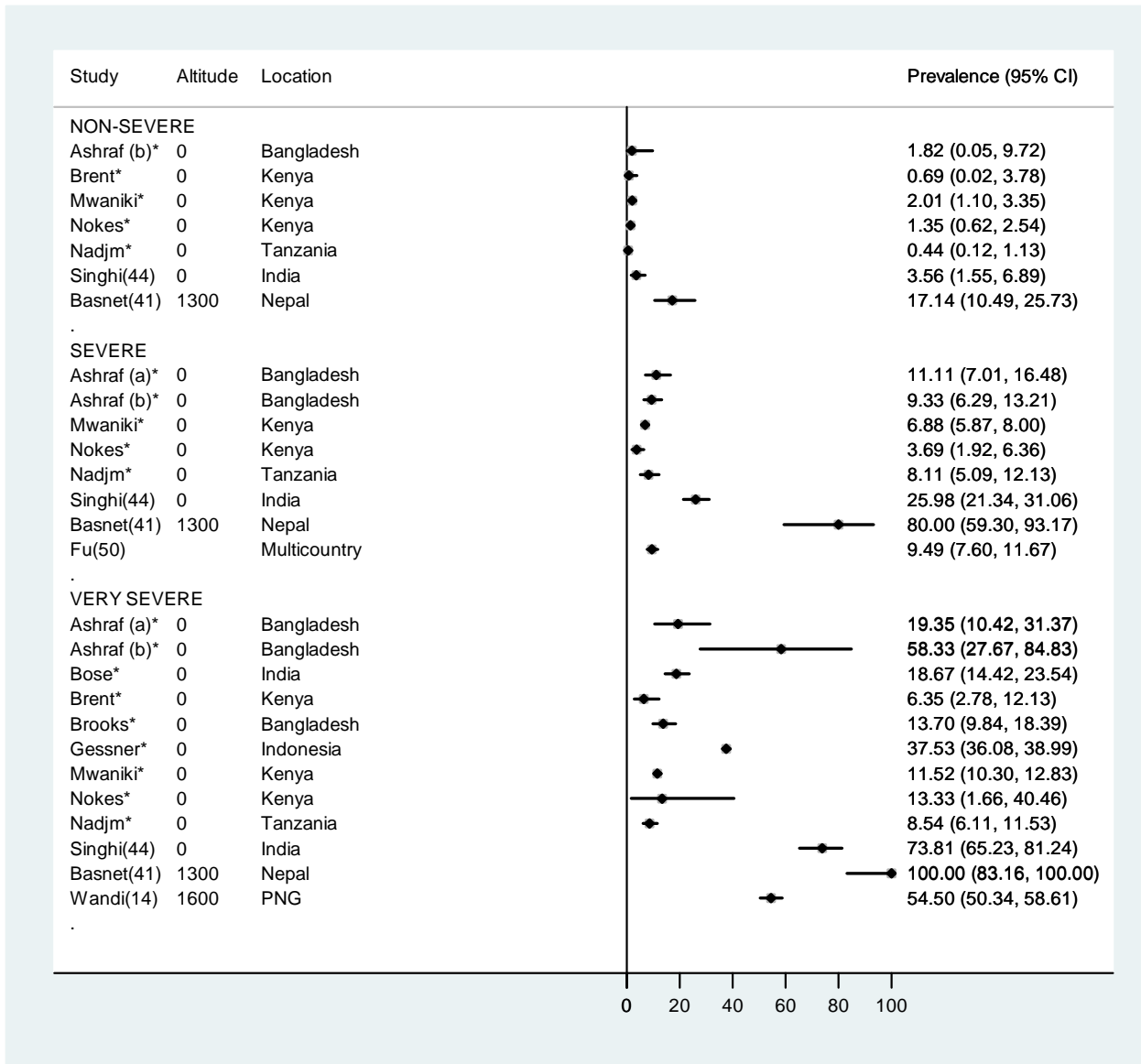
Table 3. Prevalence of hypoxaemia in non-ALRI diagnostic categories

Diagnosis	Reference	Age	No with diagnosis (Total sample size)	Hypoxaemia def ⁿ (SpO ₂)	Number hypoxaemic (Prevalence (%))
Malaria	Junge et al ⁴⁰	0 - 10 years	1044 (3269)	< 90%	30 (2.9)
	Maitland et al ⁵⁸	0 - 5 years	501 (501)	< 90%	86 (17.1)
	Mwaniki et al	0 – 5 years	4982 (15297)	< 90%	244 (4.9)
	Wandi et al ¹⁴	0 – unspecified (median age 11 months)	272 (1313)	< 90%	9 (3.3)
Meningitis	Junge et al ⁴⁰	0 - 10 years	74 (3269)	< 90%	2 (2.7)
	Nadjm et al	2 months – 13 years	21 (3683)	<90%	2 (9.5)
	Wandi et al ¹⁴	0 – unspecified (median age 11 months)	41 (1313)	< 90%	6 (14.6)
Diarrhoeal diseases	Junge et al ⁴⁰	0 - 10 years	114 (3269)	< 90%	0
	Mwaniki et al	0 – 5 years	2026 (15297)	< 90%	49 (2.4)
	Nadjm et al	2 months – 13 years	535 (3683)	< 90%	11 (2.1)
	Wandi et al ¹⁴	0 – unspecified (median age 11 months)	127 (1313)	< 90%	6 (4.7)
Malnutrition	Junge et al ⁴⁰	0 - 10 years	271 (3269)	< 90%	5 (1.8)
	Mwaniki et al	0 – 5 years	1261 (15297)	< 90%	68 (5.4)
	Nadjm et al	2 months – 13 years	105 (3683)	< 90%	4 (3.8)
	Wandi et al ¹⁴	0 – unspecified (median age 11 months)	12 (1313)	< 90%	1 (8.3)
Anaemia	Junge et al ⁴⁰	0 - 10 years	225 (3269)	< 90%	4 (1.8)
	Nadjm et al	2 months – 13 years	927 (3683)	< 90%	23 (2.5)
	Wandi et al ¹⁴	0 – unspecified (median age 11 months)	63 (1313)	< 90%	2 (3.2)
Pulmonary TB	Wandi et al ¹⁴	0 – unspecified (median age 11 months)	20 (1313)	< 90%	4 (20.0)
Febrile convulsions/epilepsy	Nadjm et al	2 months – 13 years	17 (3683)	< 90%	2 (11.8)
	Wandi et al ¹⁴	0 – unspecified (median age 11 months)	17 (1313)	< 90%	2 (11.8)
Neonatal illnesses	English et al ⁵⁹	<30 days	376 (1080)	< 90%	87 (23.1)
	Junge et al ⁴⁰	< 1 month	259 (3269)	< 90%	51 (19.7)
	Mwaniki et al.	< 7 days	1105 (15297)	< 90%	206 (18.6)
	Weber et al. ^{33*}	< 1 month	724 (4552)	Adjusted for site altitude: <90% in sea level locations and as low as <85% for one high altitude location	129 (17.8)

Note: Studies of non-ALRI illness may include children with concurrent ALRI

* Neonates recruited had signs of infection

Figure 2. Hypoxaemia prevalence in WHO non-severe, severe and very severe pneumonia.

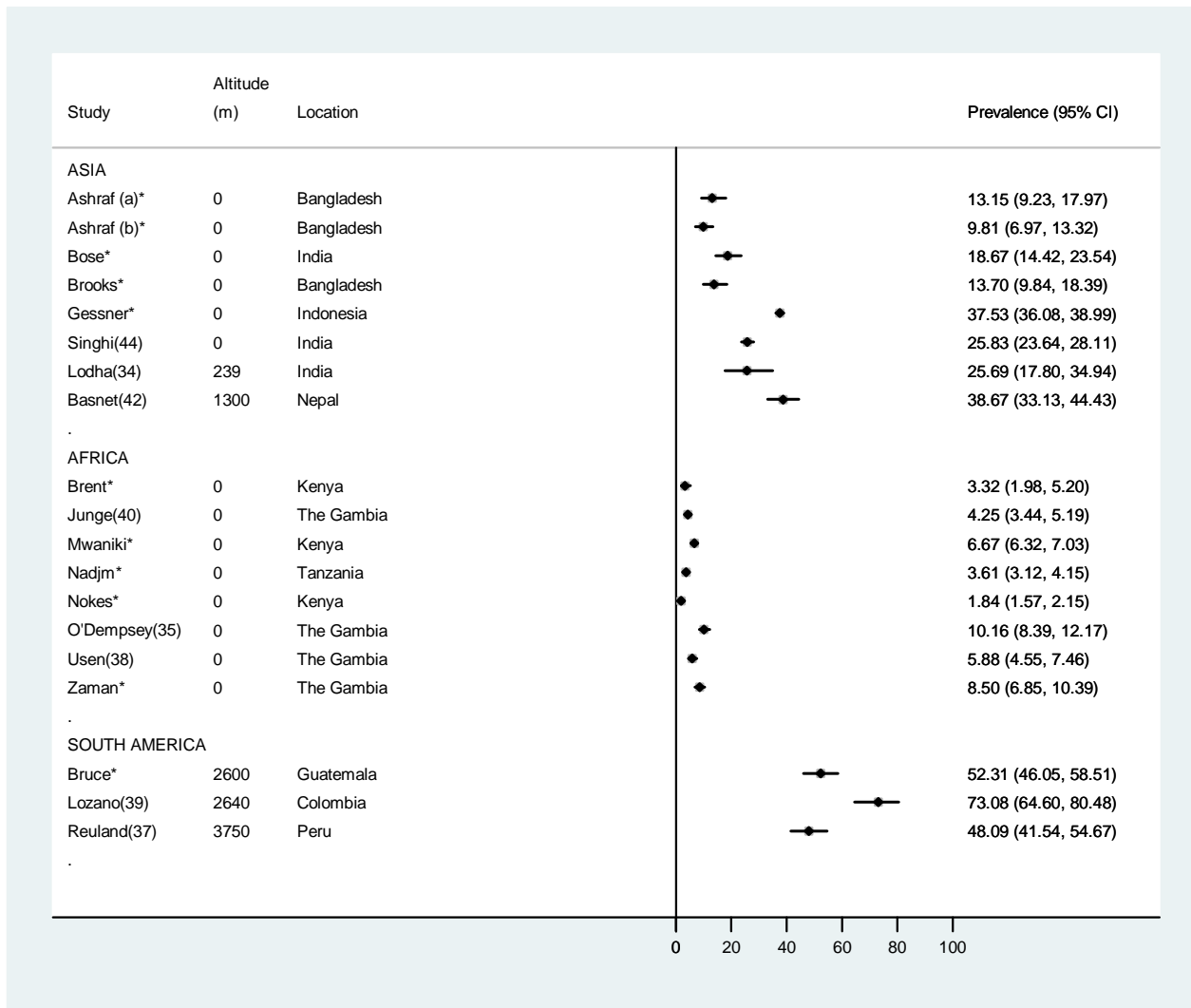


* Unpublished data: **Ashraf H et al**, Clinical Sciences Division, International Centre for Diarrhoeal Diseases Research, Bangladesh; **Brent A et al**, Nuffield Department of Infectious Diseases and Microbiology, John Radcliffe Hospital, Headington, Oxford, UK; **Mwaniki M et al**, Kenya Medical Research Institute, Center for Geographic Medicine Research - Coast, Kilifi, Kenya; **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; **Nadjm B et al**, London School of Hygiene and Tropical Medicine, London, UK; **Bose A et al**, Department of Community Health, Christian Medical College, Vellore, India; **Brooks A et al**, Centre for Health and Population Research, International Centre for Diarrhoeal Disease Research, Bangladesh; **Gessner B et al**, Agence de Médecine Préventive, Paris, France

Note:

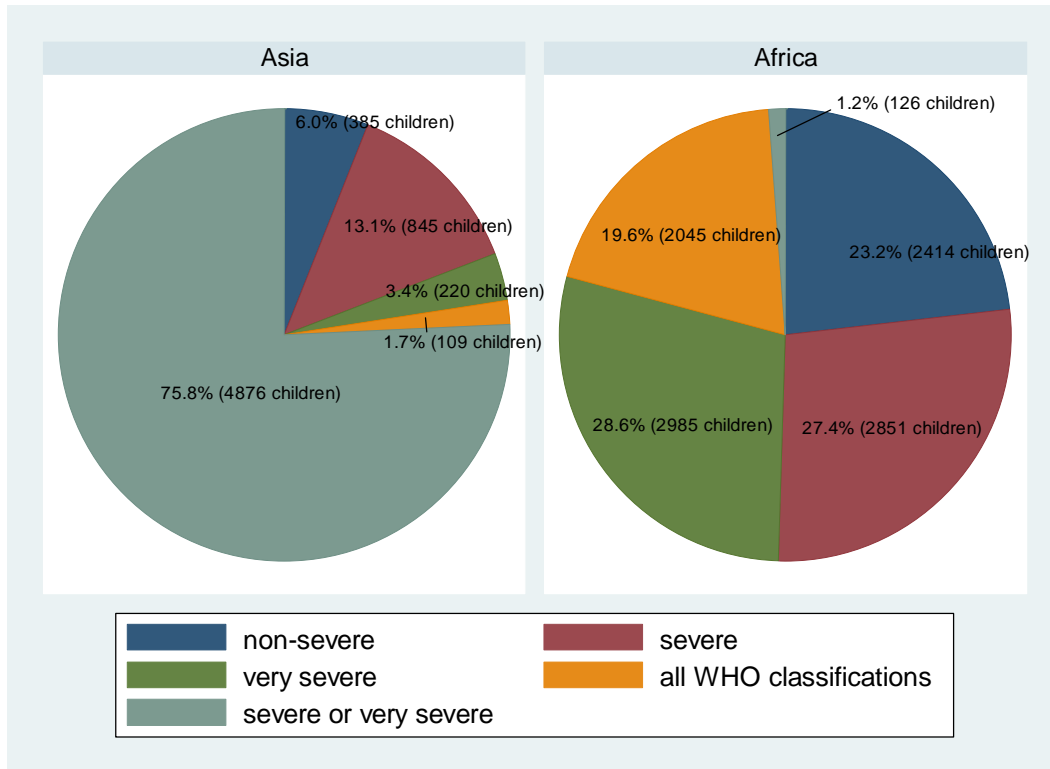
- Studies which included children with severe or very severe pneumonia were groups as “very severe” to avoid over-estimation of prevalence
- Wandt et al studied 5 sites, but 90% of children were recruited from high altitude locations.
- Fu et al studied 9 different sites, 7 of which were at sea level.

Figure 3. Hypoxaemia prevalence by geographic region



* Unpublished data: **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; **Brooks A et al**, Centre for Health and Population Research, International Centre for Diarrhoeal Disease Research, Bangladesh; **Gessner B et al**, Agence de Médecine Préventive, Paris, France; **Brent A et al**, Nuffield Department of Infectious Diseases and Microbiology, John Radcliffe Hospital, Headington, Oxford, UK; **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; **Bruce N et al**, Division of Public Health, University of Liverpool, Liverpool, England.

Figure 4. Severity of ALRI in studies from Asia and Africa (actual number and percentage of total within each severity classification)



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