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Louman, Sam; van Stralen, Karlijn J; Pijnenburg, Mariëlle W H; Koppelman, Gerard H; Boehmer, Annemie L M

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Oxygen saturation targets for children with respiratory distress: a systematic review

Sam Louman [1], Karlijn J. van Stralen[1], Mariëlle W.H. Pijnenburg[2], Gerard H. Koppelman [3] and Annemie L.M. Boehmer[4]

[1]Spaarne Gasthuis Academy, Spaarne Gasthuis Hospital, Hoofddorp, The Netherlands. [2]Department of Paediatrics/Division of Paediatric Respiratory Medicine and Allergology, Erasmus University Medical Centre, Sophia Children's Hospital, Rotterdam, The Netherlands. [3]University of Groningen, University Medical Center Groningen, Groningen Research Institute for Asthma and COPD, Groningen, The Netherlands. [4]Department of Paediatrics, Spaarne Gasthuis Hospital, Hoofddorp, The Netherlands.

Corresponding author: Sam Louman (slouman@spaarnegasthuis.nl)

Shareable abstract (@ERSpublications)
Current S_{pO_2} thresholds of 90–94% for children with respiratory distress may be too high, as lower S_{pO_2} thresholds have equivalent safety outcomes and better effectiveness. An S_{pO_2} threshold of 88% is potentially safe, but further research is required. https://bit.ly/3YAE6q8

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Abstract

Background In children with respiratory distress, supplemental oxygen is indicated at peripheral oxygen saturation (S_{pO_2}) thresholds of 90–94%. However, these thresholds are poorly studied. We conducted a systematic review to summarise the existing evidence for S_{pO_2} thresholds in children with respiratory distress.

Methods Electronic databases and registries were searched for original articles published from 1 January 2010 to 7 January 2022 comparing two or more S_{pO_2} thresholds in children with respiratory distress. Primary outcomes were safety, including mortality, neurocognitive outcomes and readmissions, and effectiveness, including admission rate and length of hospital stay. Methodological appraisal was performed using the Cochrane Risk of Bias 2 (RoB-2) or Risk of Bias in Non-Randomized Studies – of Interventions (ROBINS-I) tools. Results were narratively synthesised.

Results We retrieved 3384 results; seven studies were included. Lower thresholds ranged from 80% to 92% and were compared with higher thresholds ranging from 92% to 94%. Studies were highly heterogeneous in setting, design, population and outcomes. Risk of bias varied from low to high. Lower S_{pO_2} thresholds had equivalent mortality, neurocognitive outcomes and readmissions or re-attendance to healthcare to higher thresholds. Lower S_{pO_2} thresholds showed a significant decrease in admission rates by up to 40% and shortened hospitalisation duration by 10–18 h.

Conclusions The current S_{pO_2} thresholds of 90–94% in children with respiratory distress may be too high, which could lead to unnecessary hospitalisations and prolonged hospitalisation duration. S_{pO_2} thresholds as low as 88% are potentially safe in children with respiratory distress and may reduce hospitalisation rates and length of stay. However, high-quality evidence is needed to support this.

Introduction

Acute respiratory distress is a common reason for hospitalisation of children, with a variety of underlying causes such as bronchiolitis, asthma or lower respiratory tract infection [1]. One of the primary interventions for treating acute respiratory distress is the administration of supplemental oxygen. The safe and effective use of oxygen therapy in children is crucial because both hypoxaemia and hyperoxia can have serious consequences for children.

Hypoxic damage occurs when tissue oxygenation demands are not met by the delivery of oxygen to those tissues. Hypoxia may lead to organ failure, neurological damage and death. The delivery of oxygen is dependent on three major factors: cardiac output, haemoglobin content and function, and oxygen

saturation. In children who are previously healthy, thus not expected to have impaired cardiac output, be anaemic or have haemoglobinopathies, the need for supplemental oxygen is largely determined by the oxygen saturation. It is for this reason that in most paediatric guidelines for bronchiolitis, asthma and lower airway infection, the need for oxygen supplementation is dependent on peripheral oxygen saturation (S_{pO_2}) thresholds. These are meant as either a threshold or a target, with S_{pO_2} levels to be kept at or above the recommended value at all times, which currently varies between 90% and 94% [2–5]. However, thresholds in these guidelines are largely based on expert opinion and have been maintained owing to longstanding practice, rather than being substantiated by evidence. In a 2014 Cochrane review on the indications for oxygen therapy in children with lower respiratory tract infections, no studies on safe and effective S_{pO_2} thresholds in children with respiratory distress were found [6].

Hyperoxia, when lungs and tissues are exposed to a surplus of oxygen, increases the risk of lung damage and other complications, such as multiple organ dysfunction and mortality. In acutely ill adults, oxygen therapy targeting S_{pO_2} levels of 94–99% was associated with increased mortality [7]. In mechanically ventilated children, exposure to oxygen supplementation targeting S_{pO_2} levels of 95% or higher in the first 24 h after admission to the paediatric intensive care unit (PICU) was associated with more severe subsequent multiple organ dysfunction and mortality [8]. Furthermore, the use of unnecessarily high S_{pO_2} thresholds may lead to prolonged hospitalisation, which can have significant negative consequences such as increased stress and anxiety in both the child and their family, as well as for healthcare systems and society as a whole [9]. This issue is particularly relevant in the context of paediatrics, where annual viral epidemics lead to overcrowding in hospital wards and increased patient transfers. The disease entities most prevalent in these children are acute respiratory infections and asthma, which are sometimes hard to distinguish from one another because symptoms overlap, especially in younger patients. Even though the pathophysiology of each disease may be different, the resulting hypoxaemia leading to tissue hypoxia is the same and so it is possible that a single S_{pO_2} threshold could be applied for this group.

Therefore, the purpose of this systematic review is to summarise the existing evidence regarding safe and effective S_{pO_2} thresholds in children with acute respiratory disease.

Methods

This systematic review was conducted and reported in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) reporting guideline [10]. The study protocol was registered in the PROSPERO International Prospective Register of Reviews database before the initiation of the study (ID CRD42022300135).

Searches

A comprehensive search strategy for articles published between 1 January 2010 (since the Cochrane systematic review had revealed no available literature [6]) and 7 January 2022 was conducted in Cochrane MEDLINE, Embase and the Cochrane database, using the key terms described in the supplementary material. Additionally, the ClinicalTrials.gov register, ISRCTN registry and the World Health Organization International Clinical Trials Registry Platform Search Portal were searched to identify any unpublished or ongoing studies. Hand searches of the reference lists of included articles were conducted to identify additional articles for inclusion.

Study selection

All citations retrieved in the search were uploaded into Rayyan and duplicate records were removed after manual verification [11]. Potential duplicates were screened and either retained or removed. We included studies comparing two or more oxygen saturation thresholds or targets in children 1 month to 18 years of age with bronchiolitis, viral wheeze, acute asthma or lower respiratory tract infection. Studies in neonates were excluded. Primary outcomes were safety (mortality, neurological sequelae, organ dysfunction or damage, and readmissions or re-attendance to healthcare) and effectiveness (symptom duration, symptom severity, hospital admission and length of hospitalisation). No exclusion criteria for outcomes were pre-established. Only original articles were included in the analysis; case reports, teaching documents, editorials, guidelines, study protocols and animal studies were excluded. There were no restrictions on study setting, country or language.

Retrieved citations were independently screened by three authors (S.L., K.S. and A.B.) based on title and abstract, thus ensuring that all records were screened at least twice. Any discrepancies were resolved through additional discussion. Full-text articles for potentially eligible studies were retrieved and independently screened for eligibility by two authors (S.L. and A.B.).

Data extraction and risk of bias assessment

All outcomes that were related to either the safety or effectiveness of the studied S_{pO_2} thresholds were extracted by a single reviewer (S.L.) using a structured data form. The extracted data were subsequently checked for correctness by a second reviewer (K.S.).

Two researchers (S.L. and K.S.) independently assessed the risk of bias for each extracted outcome, using the appropriate tools as outlined in the Cochrane Handbook for Systematic Reviews [12]. The Risk of Bias 2 (RoB-2) tool was used for randomised trials and the Risk of Bias in Non-Randomized Studies – of Interventions (ROBINS-I) for non-randomised studies [13, 14]. Any discrepancies were resolved through discussion or by involving a third evaluator (A.B.). Each domain for risk of bias was classified as low, intermediate or high.

Synthesis of results

In case of adequate similarity in outcomes and limited heterogeneity, meta-analysis was considered. Otherwise, individual outcomes were reported and narratively summarised, emphasising safety and effectiveness.

Results

The search strategy yielded 3384 results, including 125 duplicates. After screening and selection, seven studies were included: five randomised controlled trials (RCTs) and two observational studies (figure 1)

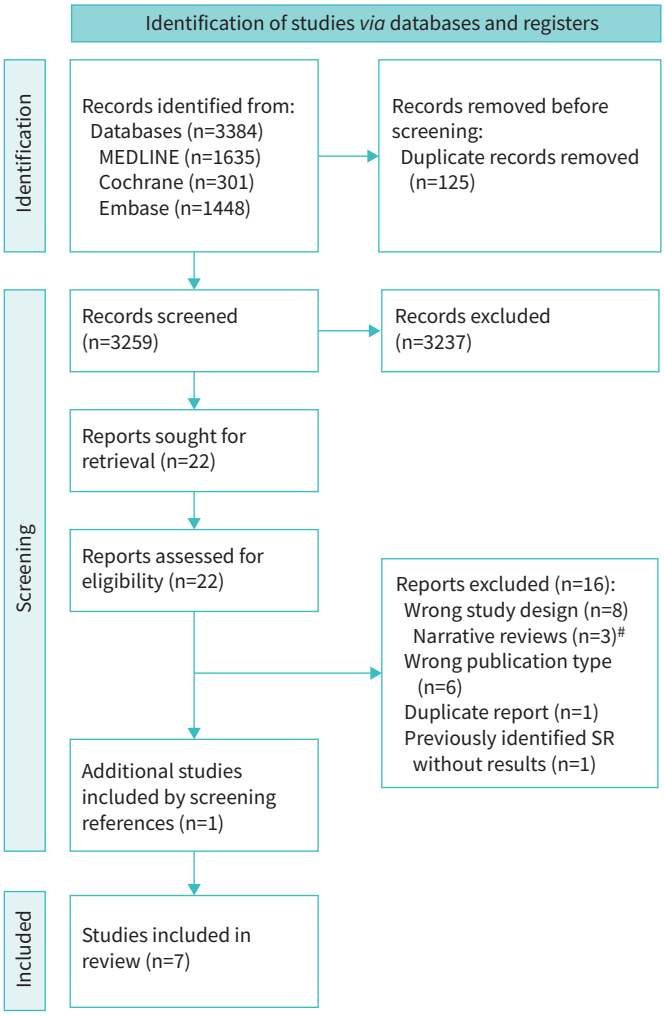

FIGURE 1 Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) flow diagram. SR: systematic review. #: narrative reviews were included in the screening of references to detect potentially missed relevant studies in our search.

[15–21]. Three studies were performed in paediatric wards [15, 17, 21], three in emergency departments [16, 19, 20] and one in a PICU [18]. S_{pO_2} thresholds varied from 80% to 94% or "liberal oxygen therapy" and populations varied across studies. Study characteristics are detailed in table 1. The heterogeneity in study settings, populations, interventions and outcomes did not enable a formal meta-analysis; therefore, the findings are summarised in a narrative manner.

Safety

Two studies compared mortality [18, 21]. Maitland *et al*. [21] compared an 80% threshold with a 92% threshold in Kenyan and Ugandan children under the age of 12 years with pneumonia, and found a lower mortality rate at 48 h in the 80% group (1.4% *versus* 2.5%, statistical significance not reported) and similar mortality at 28 days (3.9% *versus* 4.1%). Peters *et al*. [18] performed a pilot RCT in PICUs in the UK and found no difference in mortality among critically ill children in need of mechanical ventilation who were assigned either to an 88–92% or >94% S_{pO_2} oxygen saturation target (7.4% *versus* 7.5%). However, it should be noted that this study was not powered for mortality.

Neurocognitive sequelae were only investigated by Maitland *et al*. [21], who used the Kilifi Developmental Milestones Assessment. This covers three broad domains of child functioning (motor, language and personal–social development), and was used at 28 and 90 days post-randomisation. Neurocognitive sequelae were present in 2.3% (16 out of 689) in the group that received no supplemental oxygen if S_{pO_2} was >80% and in 2.9% (20 out of 696) in the group that did. Moreover, all sequelae had disappeared at 90 days follow-up. No other studies reported on neurocognitive sequelae.

Treatment failure, defined as having a persisting S_{pO_2} <92% plus respiratory distress at 48 h, was only reported by Maitland *et al*. [21]. The rate of failure was higher in the group that received no supplemental oxygen if S_{pO_2} was between 80% and 92% (4.6% *versus* 2.6%, significance not reported). No other studies reported on treatment failure.

Readmissions and re-attendance at healthcare facilities were evaluated by Cunningham *et al*. [17] in a high-quality double-blind RCT in children up to 12 months old with bronchiolitis in the UK. Patients were randomly assigned to either a 90% or 94% S_{pO_2} threshold. There were no significant differences in the rates of readmissions and re-attendance within 7 days following discharge between the two groups (five out of 307 *versus* eight out of 308 in the 90% and 94% groups, respectively). The readmissions rate at 28 days was higher in the 94% group (26 out of 308, 8.4%) than in the 90% group (12 out of 307, 3.7%), but this was not statistically significant.

Effectiveness

In the study by Cunningham *et al*. [17], symptom duration assessed as the duration of cough was equivalent between groups but parents indicated that children in the 90% group returned to normal health 1 day earlier than those in the 94% group (HR 1.19, 95% CI 1.01–1.41, p=0.043). Furthermore, patients in the 90% group were more likely to return to normal feeding sooner (HR 1.22, 95% CI 1.04–1.44, p=0.015).

Four studies have investigated the impact of S_{pO_2} thresholds on the length of hospital stay in different patient populations [17, 18, 20, 21]. In Cunningham *et al*. [17], the median difference in length of stay was 10 h (40.9 h *versus* 50.9 h in the 90% and 94% groups, respectively). This shorter length of stay probably contributed to the 91.5% likelihood that a 90% S_{pO_2} threshold would be cost-effective in comparison to the 94% threshold in patients with bronchiolitis. Cunningham and McMurray [15] also performed an observational study in children with bronchiolitis and found that these children reached a stable S_{pO_2} of >90% 22 h sooner than reaching a stable S_{pO_2} of >94%. In a subsequent observational study in bronchiolitis patients, Van Hasselt *et al*. [20] compared the length of stay between centres with a 90% threshold and a 92% threshold and found that patients in the 90% threshold centres were discharged significantly earlier than patients in the centres using the 92% threshold, (median of 41 h *versus* 59 h). Maitland *et al*. [21] found that pneumonia patients up to 12 years old in the 80% arm had a 0.62 day shorter length of stay (95% CI 0.53–1.59 days) than patients in the 92% arm. Peters *et al*. [18], in their pilot RCT on mechanically ventilated patients in PICUs in the UK, found that the length of stay was not significantly different in the group with a S_{pO_2} target of 88–92% than in the group with a S_{pO_2} target of ⩾94% (median difference 1 day, 95% CI −0.8–2.9, p=0.29). Again, the study was underpowered for this outcome.

Admission rates were reported by Schuh *et al*. [16] in a Canadian double-blind RCT in children up to 12 months with bronchiolitis and an S_{pO_2} >88%, which investigated the effect of emergency department S_{pO_2} levels on admission rates. Randomising patients to either a normal S_{pO_2} monitor or one that gave

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TABLE 1 Summary of the literature

Study	Setting	Study design	Population	Intervention	Control	Outcome(s)	Result per outcome (intervention *vs* control)	Risk of bias per outcome[#]
Cunningham and McMurray, 2012 [15]	Scotland, paediatric ward	Observational cohort	<18 months with bronchiolitis	NA	Usual care (n=68)	Time to stable S_{pO_2} above 90% and 94%	22 h difference	NA
Schuh *et al.*, 2014 [16]	Canada, tertiary care ED	Double-blind RCT	<12 months with bronchiolitis and S_{pO_2} ⩾88%	Altered S_{pO_2} monitor by +3% (n=105)	Normal S_{pO_2} monitor (n=108)	Admission rates Unscheduled visits	25% *vs* 41%; p=0.005 14.3% *vs* 21.3%; p=0.18	Low Low
Cunningham *et al.*, 2015 [17]	UK, multicentre, paediatric wards	Double-blind RCT	<12 months with bronchiolitis	90% threshold (n=307)	94% threshold (n=308)	Length of disease	1.0 day shorter, 95% CI −1–2 days	Low
						Return to feeding	2.7 days shorter, 95% CI −0.3–7 days; HR 1.22 (95% CI 1.04–1.44); p=0.015	Low
						Return to normal health	1.0 day shorter, 95% CI 0–3 days; HR 1.19 (95% CI 1.01–1.41); p=0.043	Low
						Length of stay	40.9 h *vs* 50.9 h; HR 1.28 (95% CI 1.09–1.50); p=0.003	Low
						Readmissions/ re-attendance	12/307 *vs* 26/308 (reported as nonsignificant, no p-value)	Low
						Cost-effectiveness	£290, 95% CI −£657–£78	Low
Peters *et al.*, 2018 [18]	UK, multicentre, PICUs	Pilot RCT, open-label	<16 years with critical illness	88–92% oxygenation target (n=53)	>94% oxygenation target (n=54)	Mortality	7.4% *vs* 7.5%; relative risk 0.98; 95% CI 0.26–3.72	Some
						Length of stay	1.0 day shorter; 95% CI −0.8–2.9 days; p=0.29	Some
Patel *et al.*, 2019 [19]	USA, EDs	Open-label RCT	2–18 years with asthma exacerbation	Titrated oxygen, only if S_{pO_2} <92%, during nebulisation (n=47)	High concentration oxygen, 100% 4 L·min^{-1}, during nebulisation (n=49)	% of patients with P_{tcCO_2} rise of >4 mmHg at 60 min	10.6% *vs* 40.8%; p=0.001	Some
						Asthma score at 60 min	Only reported in figure, 3.5 *vs* 4.5; p=0.0001	High

Continued

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TABLE 1 Continued

Study	Setting	Study design	Population	Intervention	Control	Outcome(s)	Result per outcome (intervention *vs* control)	Risk of bias per outcome[#]
Van Hasselt *et al.*, 2020 [20]	UK, multicentre, EDs	Observational cohort	6 weeks–12 months with bronchiolitis	Centres with 90% threshold (n=162)	Centres with 92% threshold (n=158)	S_{pO_2} as reason for admission	27% *vs* 37%; p=0.05	Serious
						Length of stay	41 h *vs* 59 h; p=0.0074	Serious
Maitland *et al.*, 2021[¶] [21]	Uganda and Kenya, multicentre, paediatric wards	Open-label RCT	<12 years with pneumonia and hypoxaemia (80–92%)	80% threshold (n=727)	92% threshold (n=729)	Mortality at 48 h	1.4% *vs* 2.5%; p=not reported	Low
						Mortality at 28 days	3.9% *vs* 4.1%; p=not reported	Low
						Treatment failure	4.6% *vs* 2.3%; p=not reported	Low
						Length of stay	0.62 days shorter; 95% CI 0.53–1.59 days	High
						Neurocognitive sequelae at 28 days	2.3% *vs* 2.9%; p=not reported	Some

NA: not applicable; S_{pO_2}: peripheral oxygen saturation; ED: emergency department; RCT: randomised controlled trial; HR: hazard ratio; PICU: paediatric intensive care unit; P_{tcCO_2}: transcutaneous carbon dioxide. [#]: risk of bias assessed as low, some or high by the Risk of Bias 2 tool, or as low, moderate, serious or critical by the Risk Of Bias In Non-Randomized Studies – of Interventions tool; [¶]: the trial was stopped early when a local doctor started multiple court cases to stop the trial owing to safety concerns; although monitoring and ethics committees saw no safety issues in the trial and all court cases were won, inclusions slowed to a halt, which made the trial unfeasible (results of all included patients up to that point were analysed).

altered values of 3 percentage points higher, they found that significantly fewer patients with falsely higher values were admitted to the paediatric ward (25% *versus* 41%, p=0.005). No additional unscheduled visits were observed in either group (14.3% in the altered monitor group *versus* 21.3% in the normal monitor group, p=0.18).

PATEL *et al.* [19] used an open-label RCT in 2–18-year-olds with asthma exacerbations in the USA to compare a conservative and liberal oxygenation strategy. In the conservative strategy, children received supplemental oxygen during nebulisation only if S_{pO_2} was <92%, and a S_{pO_2} ⩾95% was avoided, while in the liberal group children received 100% oxygen at 4 L·min^{-1} with each nebulisation, irrespective of S_{pO_2} levels. The results showed significantly lower asthma scores after 60 min of treatment in the conservative group than in the liberal group, though exact data were not reported.

Risk of bias

The risk of bias for the five RCTs evaluated using the Cochrane RoB-2 tool ranged from low to high, and differed within studies for specific outcomes (table 1 and supplementary material). The study by VAN HASSELT *et al.* [20], who observationally compared centres with 90% and 92% thresholds, was found to have a serious risk of bias using the Cochrane ROBINS-I tool, because the comparison was not adjusted for confounding factors. The study by CUNNINGHAM and MCMURRAY [15], as an observational single-centre cohort study, was not eligible for risk of bias assessment. PETERS *et al.* [18], who studied mechanically ventilated children, used deferred informed consent, *i.e.* patients were assigned to either the intervention or the control group before giving informed consent. This results in a potentially high risk of bias; however, the rate of drop-outs was low and equal between the two groups.

Discussion

In this systematic review, we included seven studies that evaluated the safety and effectiveness of various S_{pO_2} thresholds ranging from 80% to 94% in children with acute respiratory distress. The studies were conducted in various settings and involved different populations and outcomes, hampering a formal meta-analysis. The majority of the studies were on bronchiolitis, lower airway infection or pneumonia. Only one study was done in patients with asthma.

The key finding of this systematic review was that it may be possible to lower the commonly used S_{pO_2} thresholds of 90–94%, because this could result in a reduction in the length of hospital stay and improved health outcomes without compromising safety. The optimal lower threshold for S_{pO_2} is not known. In this review, all safety outcomes were equivalent and some effectiveness outcomes were better for S_{pO_2} thresholds between 88% and 92% when compared to higher thresholds between 92% and 94% (liberal oxygen therapy).

Safety of lower S_{pO_2} thresholds

The safety of lower S_{pO_2} thresholds is evaluated by their ability to prevent or alleviate hypoxic damage, resulting from impaired tissue oxygenation. In this systematic review, the chosen safety outcomes of lower S_{pO_2} thresholds were mortality, neurocognitive sequelae, treatment failure and unscheduled healthcare visits or readmissions. Only one outcome in this systematic review favoured the higher threshold. MAITLAND *et al.* [21] found that treatment failure was higher in the permissive hypoxaemia group with a threshold of 80% than in the 92% threshold group receiving low flow. However, the way treatment failure was defined as having an S_{pO_2} <92% at 48 h confounded this outcome. Mortality rates were the primary outcome in the MAITLAND *et al.* [21] study and favoured the permissive hypoxaemia group. In other studies reporting on the safety of oxygen saturation thresholds, the lower threshold varied from 88% to 92% and was compared with higher thresholds ranging from 92% to 94%, with the results indicating that lower thresholds were as safe as the higher thresholds for mortality, neurological sequelae and readmission and re-attendance to healthcare [16–18, 20]. However, the evidence on neurocognitive sequelae is too sparse for safety conclusions.

Neurocognitive sequelae

It is important to note that in all studies, short-term parameters of safety such as mortality and unscheduled visits or readmissions were better represented than long-term issues such as neurocognitive sequelae, which were only investigated by MAITLAND *et al.* [21].

In their study, MAITLAND *et al.* [21] found no differences in neurocognitive outcomes between the group that received no supplemental oxygen if S_{pO_2} was >80% and the group that did, and no neurocognitive sequelae persisted at the 90-day follow-up. The tool used to assess neurocognitive sequelae was the Kilifi Developmental Milestone Assessment, which has been shown to have good clinimetric properties [22]. However, it is unclear if this tool is valid for identifying small changes in neurocognition due to short

intermittent hypoxaemia, nor was it validated for children older than 24 months. There was a risk of bias for this outcome because patients and assessors were not blinded for treatment allocation. There was also some loss to follow-up, although equally divided between groups.

The literature on the neurocognitive effects of short (hours to days) periods of hypoxaemia in respiratory illnesses is limited and no good data are available in previously healthy children. In children with sleep-disordered breathing or congenital heart defects, neurocognitive sequelae have been reported for S_{pO_2} levels <94% [23]. However, these children are chronically exposed to these low S_{pO_2} values, and, in the case of congenital heart defects, it is likely that these children have impaired cardiac compensation mechanisms and may have had complications that caused very low S_{pO_2} for a prolonged time. In the case of sleep-disordered breathing, it is difficult to determine the extent to which neurocognitive sequelae are related to intermittent hypoxaemia or to interrupted sleep [24]. Additionally, iron deficiency and anaemia have previously been linked to sleep-disordered breathing in children, which may further impair oxygen delivery [25, 26].

Long-term neurocognitive effects of periods (hours to days) of mild hypoxaemia (88–94%) are not well studied. Studying these effects poses significant challenges due to the potentially small differences in groups and many confounders. Moreover, neurocognitive effects may be subtle and therefore difficult to detect. Further studies are required that include standardised and validated measures of neurocognitive function to contribute to better evidence on the safety of S_{pO_2} thresholds.

Effectiveness of lower S_{pO_2} thresholds

The goal of lowering S_{pO_2} thresholds is to prevent potential adverse effects and complications of excessive oxygen therapy. In this systematic review, reported outcomes on the effectiveness of lower S_{pO_2} thresholds were duration of symptoms, the severity of symptoms, return to normal feeding, admission rates and the length of hospital stay. In all studies, lower thresholds varying from 80% to 92% were found to be equally effective or even more effective than the higher thresholds varying from 92% to 94% (liberal oxygen therapy), because a reduction in length of hospital stay, lower admission rates and faster return to normal health status and normal feeding were found for the lower thresholds compared to the higher thresholds.

Based on the results of three studies in this systematic review, a S_{pO_2} threshold reduction of 4 percentage points could lead to a reduction in length of stay of between 10 h and 18 h [17, 20, 21]. A 3 percentage point difference could reduce admissions by ∼40%, based on a single study in children with bronchiolitis [16]. These effects have repercussions for the patient, the parents/caregivers and the healthcare system. Patients potentially recover better in a home setting, as is shown by the faster return to normal health in patients with bronchiolitis who were treated with a 90% threshold compared to 94% [17]. Additionally, reductions in length of stay and admission rates are especially important in the paediatric setting. Annual viral epidemics, such as respiratory syncytial virus, may cause excessive pressure on paediatric ward capacity, resulting in patient transfers to other hospitals. In this regard, lower S_{pO_2} thresholds could help to reduce the burden of paediatric respiratory illnesses on the healthcare system. This is also shown by a very high likelihood that a 90% threshold in bronchiolitis patients is cost-effective, compared to a 94% threshold [17].

It is also possible that unnecessarily high S_{pO_2} thresholds cause direct damage. As the gaseous exchange organ, the lungs are first at risk when exposed to high concentrations of oxygen. Damage to the capillary endothelium and alveolar cells has been shown at prolonged exposures to high concentrations of oxygen [27]. Hyperoxia may also lead to the release of free oxygen radicals and oxidative stress [28]. The excess of pro-oxidants can damage cell structure and function by interacting with lipids, DNA and proteins. In addition, hyperoxia can negatively affect the cardiovascular and nervous systems [29, 30]. In children admitted to PICUs, hyperoxia is associated with increased risk of death [31]. Whether children with more mild respiratory illness admitted to general paediatric wards are also at risk of these effects is not well studied.

The ideal S_{pO_2} threshold

The ideal S_{pO_2} threshold strikes a balance between safety and effectiveness. It should be high enough to be safe, thus preventing hypoxic damage, and low enough to minimise unwanted effects of oxygen supplementation, *e.g.* unnecessary admissions, prolongation of hospital stay or hyperoxic damage. Based on this systematic review, for short-term outcomes, S_{pO_2} thresholds as low as 88% are potentially safe in children with respiratory distress who are otherwise healthy. However, until the results of the Oxy-PICU trial (ISRCTN92103439) have been published and peer reviewed, no high-quality RCT evidence supports this. The issue of neurocognitive sequelae persists, even though there are currently no signals of harm. Taking both safety and effectiveness into account, an S_{pO_2} threshold of 88% deserves further investigation as an optimal threshold for otherwise healthy children with respiratory distress. When applying an ideal

threshold to an admitted patient, one should always consider the scope of oxygen demand and delivery to the tissues, and how a patient's clinical status affects the oxygen dissociation curve. For example, severely anaemic patients with high S_{pO_2} values might still not meet tissue oxygen demands. Furthermore, patients with fever or acidosis experience a rightward shift of the oxygen dissociation curve, thus favouring the unloading of oxygen to the tissues. By contrast, a leftward shift is caused by hypothermia or alkalosis, which impairs oxygen unloading. Lower than current S_{pO_2} targets are situated at the steeper part of the oxygen dissociation curve. Therefore, a clinician employing a lower S_{pO_2} target should also be aware that small changes in disease, with small changes in partial pressure of oxygen, could result in larger changes in S_{pO_2} than in patients with higher S_{pO_2} levels. Last, it should be noted that to arrive at an ideal S_{pO_2} threshold, engaging with patients and parents is instrumental in determining the risk–benefit balance.

Strengths and limitations

This systematic review has several strengths, such as the use of a structured search strategy and the application of standardised methods for study selection and assessment of the risk of bias, in accordance with the PRISMA guidelines. However, the review also has some limitations. First, there are some issues with generalisability. There was a wide variety in populations and settings (age, disease, ethnicity, emergency department, paediatric ward or PICU) and outcomes. The populations in these studies consisted mostly of children who were relatively healthy, because children with severe comorbidities were excluded, which makes the conclusions of this systematic review not generalisable to all children with respiratory distress. The findings are more generalisable to other populations in which cardiac output and haemoglobin content and function are expected to be within the normal range, for which S_{pO_2} thresholds will generally apply. The impact of these factors is illustrated by a recent study in Bangladesh, investigating the mortality risk in outpatient children with pneumonia and different S_{pO_2} values at presentation [32–34]. As stated by the authors, a much higher prevalence of anaemia and severe malnutrition might make these children more vulnerable to hypoxaemia. They found higher risk of mortality in patients with S_{pO_2} values <90% and between 90% and 93% when compared to levels >93%. Even though it is not known whether hospitalisation and supplemental oxygen would have prevented death in these patients, relative health status might explain differences in risks between the Bangladesh population and relatively healthy Western populations. Additionally, there might have been more occult hypoxaemia due to darker skin pigmentation.

Recently, more attention has been given to potential racial differences in oxygen saturation measurements, because people with more pigmentation are more likely to have inaccurate S_{pO_2} readings, which are often higher than arterial oxygen tension readings [35–37]. The studies in this systematic review did not report on skin pigmentation or any potential differences in effect based on skin pigmentation subgroups. However, in the systematic review by MAITLAND *et al.* [21], which comprised children from Kenya and Uganda with likely darker pigmentation, results were similar to the other Western studies, which likely had predominantly light pigmentation populations. This might indicate the difference in accuracy does not lead to a need for differences in S_{pO_2} thresholds, but it does require further investigation.

A final issue with generalisability is the heterogeneity in pathologies investigated in these studies. The difference in pathophysiology might require different S_{pO_2} thresholds. Falling S_{pO_2} in asthma is considered to represent bronchoconstriction and ventilation perfusion mismatch, rather than reduced alveolar gas exchange as is more often the case in lower respiratory tract infections. In both cases, bronchial wall oedema and sputum plugging are present, which might result in some similarities and overlap. Even when the mechanism leading to hypoxaemia is different, the level of hypoxaemia that is harmful (*i.e.* leading to tissue hypoxia) is the same across patients who have otherwise healthy compensatory mechanisms. However, there is another aspect to consider when choosing an appropriate S_{pO_2} threshold, and that is symptom relief. While in patients with lower respiratory tract infection or bronchiolitis, dyspnoea is mainly driven by hypercapnia for which supplemental oxygen provides no relief, in patients with acute asthma the dyspnoea is thought to be mainly driven by hypoxaemia, because ventilation is often sufficient for exhaling carbon dioxide except in the most severe cases. As such, in patients with acute asthma, supplemental oxygen might relieve dyspnoea, potentially reducing the risk of muscle fatigue and further deterioration. If this is true, a higher S_{pO_2} threshold in patients with acute asthma might be more appropriate. The only study in this review in children with an asthma attack [19] showed a reduction in asthma score when given less oxygen, but always with an S_{pO_2} >92%, in an emergency department setting. The theory that the breathing frequency of children with an asthma attack is steered by hypoxic drive is not directly reflected in this study. Because saturation, breathing frequency and dyspnoea are components of the Qureshi asthma score, further data on the separate components of the asthma score in the studied patients are required to test this hypothesis. The studies in this systematic review provide insufficient data on the safety and effectiveness of lower S_{pO_2} thresholds in children with acute asthma, or whether a different threshold is required.

A last limitation of this systematic review is the possibility of publication bias, because it cannot be ruled out that studies showing negative effects of lower S_{pO_2} targets are less likely to be published than those showing beneficial effects. Standard ways of investigating publication bias such as funnel plots or Egger's linear regression tests were not possible due to the large variation in populations and outcomes. However, our search in clinical trial registries did not reveal any unpublished works. Together with the high or serious risk of bias of some outcomes, this systematic review cannot establish safe and effective S_{pO_2} thresholds for children with respiratory distress.

Conclusion

The evidence for safe and effective S_{pO_2} thresholds for children with respiratory distress is limited and poorly generalisable for different diseases and ages. Studies have shown that current S_{pO_2} thresholds of 90–94% may be too high, leading to increased hospitalisation and prolonged length of stay. Further research is needed to determine the ideal lower safe and effective threshold, which could potentially be a threshold of 88%, because it may come with serious reductions in risk of hospitalisation, reductions in length of stay and may potentially improve health outcomes. Additionally, further research is needed to investigate the potential neurocognitive effects on which current data are very limited.

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References

1 Weiss AJ, Liang L, Martin K. Overview of Hospital Stays Among Children and Adolescents, 2019. HCUP Statistical Brief #299. Rockville, Agency for Healthcare Research and Quality, 2022.
2 Scottish Intercollegiate Guidelines Network, British Thoracic Society. SIGN 158: British Guideline on the Management of Asthma. Edinburgh, Healthcare Improvement Scotland, 2019.
3 Dutch Paediatric Society. Guideline: Bronchiolitis. Date last updated: 11 April 2012. Date last accessed: September 2023. www.nvk.nl/themas/kwaliteit/richtlijnen/richtlijn?componentid=6356993
4 Dutch Paediatric Society. Guideline: Asthma in children. Date last updated: 29 September 2021. Date last accessed: September 2023. www.nvk.nl/themas/kwaliteit/richtlijnen/richtlijn?componentid=151814144
5 Dutch Paediatric Society. Guideline: Lower respiratory infections. Date last updated: 14 October 2015. Date last accessed: September 2023. www.nvk.nl/themas/kwaliteit/richtlijnen/richtlijn?componentid=7864320
6 Rojas-Reyes MX, Granados Rugeles C, Charry-Anzola LP. Oxygen therapy for lower respiratory tract infections in children between 3 months and 15 years of age. *Cochrane Database Syst Rev* 2014; 12: CD005975.
7 Chu DK, Kim LH, Young PJ, *et al.* Mortality and morbidity in acutely ill adults treated with liberal versus conservative oxygen therapy (IOTA): a systematic review and meta-analysis. *Lancet* 2018; 391: 1693–1705.
8 Balcarcel DR, Coates BM, Chong G, *et al.* Excessive oxygen supplementation in the first day of mechanical ventilation is associated with multiple organ dysfunction and death in critically Ill children. *Pediatr Crit Care Med* 2022; 23: 89–98.
9 Unger S, Cunningham S. Effect of oxygen supplementation on length of stay for infants hospitalized with acute viral bronchiolitis. *Pediatrics* 2008; 121: 470–475.
10 Page MJ, McKenzie JE, Bossuyt PM, *et al.* The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021; 372: n71.
11 Ouzzani M, Hammady H, Fedorowicz Z, *et al.* Rayyan – a web and mobile app for systematic reviews. *Syst Rev* 2016; 5: 210.
12 Higgins JPT, Thomas J, Chandler J, *et al.* Cochrane Handbook for Systematic Reviews of Interventions version 6.3 (updated February 2022). London, Cochrane, 2022.
13 Sterne JAC, Savović J, Page MJ, *et al.* RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 2019; 366: l4898.
14 Sterne JA, Hernán MA, Reeves BC, *et al.* ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ* 2016; 355: i4919.

15 Cunningham S, McMurray A. Observational study of two oxygen saturation targets for discharge in bronchiolitis. *Arch Dis Child* 2012; 97: 361–363.
16 Schuh S, Freedman S, Coates A, *et al.* Effect of oximetry on hospitalization in bronchiolitis: a randomized clinical trial. *JAMA* 2014; 312: 712–718.
17 Cunningham S, Rodriguez A, Boyd KA, *et al.* Bronchiolitis of Infancy Discharge Study (BIDS): a multicentre, parallel-group, double-blind, randomised controlled, equivalence trial with economic evaluation. *Health Technol Assess* 2015; 19.
18 Peters MJ, Jones GAL, Wiley D, *et al.* Conservative versus liberal oxygenation targets in critically ill children: the randomised multiple-centre pilot Oxy-PICU trial. *Intensive Care Med* 2018; 44: 1240–1248.
19 Patel B, Khine H, Shah A, *et al.* Randomized clinical trial of high concentration versus titrated oxygen use in pediatric asthma. *Pediatr Pulmonol* 2019; 54: 970–976.
20 van Hasselt TJ, Singham B, Bassett E, *et al.* Oxygen saturation thresholds in bronchiolitis: examining admissions. *Arch Dis Child* 2020; 105: 1197–1199.
21 Maitland K, Kiguli S, Olupot-Olupot P, *et al.* Randomised controlled trial of oxygen therapy and high-flow nasal therapy in African children with pneumonia. *Intensive Care Med* 2021; 47: 566–576.
22 Abubakar A, Holding P, Van de Vijver F, *et al.* Developmental monitoring using caregiver reports in a resource-limited setting: the case of Kilifi, Kenya. *Acta Paediatr* 2010; 99: 291–297.
23 Bass JL, Corwin M, Gozal D, *et al.* The effect of chronic or intermittent hypoxia on cognition in childhood: a review of the evidence. *Pediatrics* 2004; 114: 805–816.
24 Brockmann PE, Gozal D. Neurocognitive consequences in children with sleep disordered breathing: who is at risk? *Children (Basel)* 2022; 9: 1278.
25 Kerstein R, Stimpson P, Caulfield H, *et al.* Iron deficiency and sleep disordered breathing in children - cause or effect? *Int J Pediatr Otorhinolaryngol* 2009; 73: 275–280.
26 Reynolds Z, Hibbert N, Stevenson P, *et al.* The effect of iron deficiency on quality of life outcomes after surgery for obstructive sleep apnoea. *J Paediatr Child Health* 2022; 58: 1816–1823.
27 Thomson L, Paton J. Oxygen toxicity. *Paediatr Respir Rev* 2014; 15: 120–123.
28 Saugstad OD. Bronchopulmonary dysplasia – oxidative stress and antioxidants. *Semin Neonatol* 2003; 8: 39–49.
29 Fisher AB. Oxygen therapy. Side effects and toxicity. *Am Rev Respir Dis* 1980; 122: 61–69.
30 Wijesinghe M, Perrin K, Ranchord A, *et al.* Routine use of oxygen in the treatment of myocardial infarction: systematic review. *Heart* 2009; 95: 198–202.
31 Numa A, Aneja H, Awad J, *et al.* Admission hyperoxia is a risk factor for mortality in pediatric intensive care. *Pediatr Crit Care Med* 2018; 19: 699–704.
32 McCollum ED, Ahmed S, Roy AD, *et al.* Risk and accuracy of outpatient-identified hypoxaemia for death among suspected child pneumonia cases in rural Bangladesh: a multifacility prospective cohort study. *Lancet Respir Med* 2023; 11: 769–781.
33 Stevens GA, Paciorek CJ, Flores-Urrutia MC, *et al.* National, regional, and global estimates of anaemia by severity in women and children for 2000–19: a pooled analysis of population-representative data. *Lancet Glob Health* 2022; 10: e627–e639.
34 Das SK, Chisti MJ, Malek MA, *et al.* Changing childhood malnutrition in Bangladesh: trends over the last two decades in urban–rural differentials (1993–2012). *Public Health Nutr* 2015; 18: 1718–1727.
35 Sjoding MW, Dickson RP, Iwashyna TJ, *et al.* Racial bias in pulse oximetry measurement. *N Engl J Med* 2020; 383: 2477–2478.
36 Gray KD, Subramaniam HL, Huang ES. Effects of racial bias in pulse oximetry on children and how to address algorithmic bias in clinical medicine. *JAMA Pediatr* 2023; 177: 459–460.
37 Ruppel H, Makeneni S, Faerber JA, *et al.* Evaluating the accuracy of pulse oximetry in children according to race. *JAMA Pediatr* 2023; 177: 540–543.