Early View

Review

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

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

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Take Home Message:

Current SpO2 thresholds of 90-94% for children with respiratory distress may be too high, as lower SpO2 thresholds have equivalent safety outcomes and better effectiveness. An SpO2 threshold of 88% is potentially safe, but further research is required.
Abstract

Background In children with respiratory distress, supplemental oxygen is indicated at oxygen saturation thresholds of 90-94%. However, these thresholds are poorly studied. We conducted a systematic review to summarize the existing evidence for SpO2 thresholds in children with respiratory distress.

Methods Electronic databases and registries were searched for original articles published from January 1st 2010 to February 1st 2022 comparing two or more SpO2 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 RoB-2 or ROBINS-I tools. Results were narratively synthesised.

Results We retrieved 3322 results; 7 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 SpO2 thresholds had equivalent mortality, neurocognitive outcomes and readmissions or re-attendance to healthcare as higher thresholds. Lower SpO2 thresholds showed a significant decrease in admission rates by up to 40% and shortened hospitalisation duration by 10 to 18 hours.

Conclusions The current SpO2 thresholds of 90-94% in children with respiratory distress may be too high, which could lead to unnecessary hospitalizations and prolonged hospitalisation duration. SpO2 thresholds to levels 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 hospitalizations of children, with a variety of underlying causes such as bronchiolitis, asthma or lower respiratory tract infection (LRTI) [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 hypoxemia 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 (SpO2) thresholds. These are meant as either a threshold or a target, recommending keeping SpO2 levels 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 due to longstanding practice, rather than being substantiated by evidence. In a 2014 Cochrane review on the indications for oxygen therapy in children with LRTIs, no studies on safe and effective SpO2 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 SpO2 levels of 94-99% was associated with increased mortality [7]. In mechanically ventilated children, exposure to oxygen supplementation targeting SpO2 levels of
95% or higher in the first 24 hours 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 SpO2 thresholds may lead to prolonged hospitalization, 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 as symptoms overlap, especially in younger patients. Even though the pathophysiology of each disease may be different, the resulting hypoxemia leading to tissue hypoxia is the same and it is therefore possible a single SpO2 threshold could be applied for this group.

Therefore, the purpose of this systematic review is to summarize the existing evidence regarding safe and effective SpO2 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 January 1st 2010 (since the Cochrane systematic review had revealed no available literature [6]) and January 7th 2022 was conducted in MEDLINE, EMBASE, and the Cochrane database, using the key terms described in the Supplemental
File. Additionally, the ClinicalTrials.gov register, ISRCTN registry, and the WHO 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 health care) and effectiveness (symptom duration, symptom severity, hospital admission and length of hospitalization). 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 SpO2 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, utilizing the appropriate tools as outlined in the Cochrane Handbook for Systematic Reviews [12]. The RoB-2 tool was used for randomized trials and the ROBINS-I for non-randomized 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 summarized, emphasizing safety and effectiveness.

**Results**

The search strategy yielded 3322 results, including 125 duplicates. After screening and selection, 7 studies were included: 5 RCTs and 2 observational studies (see Figure 1) [15-21]. Three studies were performed in paediatric wards [15,17,21], three in emergency departments [16,19,20] and one in a paediatric intensive care unit [18]. SpO2 thresholds varied from 80% to 94% or ‘liberal’ 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 summarized in a narrative manner.

**Safety**

Two studies compared mortality [18,21]. Maitland 2021, which compared an 80% threshold with a 92% threshold in Kenyan and Ugandan children under the age of 12 with pneumonia, found a lower mortality rate at 48 hours in the 80% group (1.4% respectively 2.5%, statistical significance not reported) and similar mortality at 28 days (3.9% respectively 4.1%%) [21]. Peters 2018, a pilot randomized controlled trial in paediatric intensive cares in the United Kingdom, found no difference
in mortality among critically ill children in need of mechanical ventilation who were assigned either to 88%-92% or >94% SpO2 oxygen saturation target (7.4% vs 7.5% respectively) [18]. However, it should be noted that this study was not powered for mortality.

Neurocognitive sequelae were only investigated in the previously mentioned Maitland 2021 study using the Kilifi Developmental Milestones Assessment which covers three broad domains of child functioning: motor, language and personal–social development, at 28 and 90 days post-randomization [21]. Neurocognitive sequelae were present in 2.3% in the group that received no supplemental oxygen if SpO2 was above 80% (16/689) and 2.9% (20/696) 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 SpO2 < 92% plus respiratory distress at 48 hours, was only reported by Maitland 2021. The rate of failure was higher in the group that received no supplemental oxygen if SpO2 was between 80-92% (4.6% vs 2.6%, significance not reported) [21]. No other studies reported on treatment failure.

Readmissions and re-attendance at healthcare facilities were evaluated in Cunningham 2015, a high-quality double-blind randomized controlled trial in children up to 12 months with bronchiolitis in the United Kingdom [17]. Patients were randomly assigned to either a 90% or 94% SpO2 threshold. There were no significant differences in the rates of readmissions and re-attendance within 7 days following discharge between the two groups (5/307 vs 8/308 in the 90% and 94% groups, respectively). The readmissions rate at 28 days was higher in the 94% group (26/308, 8.4%) than in the 90% group, but not statistically significant (3.7%, 12/307).
Effectiveness

In Cunningham 2015, 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 one day earlier compared to the 94% group (HR 1.19; 95%CI 1.01 to 1.41; p = 0.043) [17]. Furthermore, patients in the 90% group were more likely to return to normal feeding sooner (HR 1.22; 95%CI 1.04 to 1.44; p = 0.015). Four studies have investigated the impact of SpO2 thresholds on the length of hospital stay in different patient populations [17,18,20,21]. In Cunningham 2015 the median difference in length of stay was 10 hours (40.9 hours vs 50.9 hours in the 90% and 94% groups, respectively) [17]. This shorter length of stay probably contributed to the 91.5% likelihood that a 90% SpO2 threshold would be cost-effective in comparison to the 94% threshold in patients with bronchiolitis. Cunningham 2012, an observational study in children with bronchiolitis found that these children reached a stable SpO2 of greater than 90% 22 hours sooner than reaching a stable SpO2 of greater than 94%[15]. Van Hasselt 2020, a subsequent observational study in bronchiolitis patients 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, compared to patients in the centres using the 92% threshold, (median of 41 hours vs 59 hours) [20]. Maitland 2021 found that pneumonia patients up to 12 years in the 80% arm had a 0.62 day shorter length of stay (95%CI 0.53 - 1.59) than patients in the 92% arm [21]. In Peters 2018, the pilot-RCT on mechanically ventilated patients in paediatric intensive care units in the UK, the length of stay was not significantly different in the group with a SpO2 target of 88-92%, compared to a SpO2 target of 94% or higher (median difference 1 day; 95%CI -0.8 to 2.9; p = 0.29) [18]. Again, the study was underpowered for this outcome.

Admission rates were reported by Schuh 2014, a Canadian double-blind randomized controlled trial in children up to 12 months with bronchiolitis and an SpO2 above 88%, which investigated the effect
of emergency department SpO2 levels on admission rates [16]. Randomizing patients to either a normal SpO2 monitor or one that gave altered values of 3 percentage points higher, they found that significantly less patients with falsely higher values were admitted to the paediatric ward (25% vs 41%; p = 0.005). No more unscheduled visits were observed in either group (14.3% in the altered monitor group vs 21.3% in the normal monitor group; p = 0.18).

Patel 2019, an open-label randomized controlled trial in 2 to 18 year olds with asthma exacerbations in the USA, compared a conservative and liberal oxygenation strategy [19]. In the conservative strategy, children received supplemental oxygen during nebulization only if SpO2 was below 92%, and SpO2 ≥ 95% was avoided, while in the liberal group children received 100% oxygen at 4L/min with each nebulization, irrespective of SpO2 levels. The results showed significantly lower asthma scores after 60 minutes of treatment in the conservative group compared to the liberal group, though exact data was not reported.

Risk of bias

The risk of bias for the five randomized controlled trials evaluated using the Cochrane RoB-2 tool ranged from low to high, and differed within studies for specific outcomes (see Table 1 and Supplemental File). Van Hasselt 2020, observationally comparing centres with 90% and 92% thresholds, was assessed using the Cochrane ROBINS-1 tool. The risk of bias was considered to be serious, as the comparison was not adjusted for confounding factors. Cunningham 2012 was an observational single-centre cohort study and, as such, was not eligible for risk of bias assessment. Peters 2018, in mechanically ventilated children, used deferred informed consent, so 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 [18].
Discussion

In this systematic review, we included seven studies that evaluated the safety and effectiveness of various SpO2 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 is that the commonly used SpO2 thresholds of 90-94% may be lowered, as this could result in a reduction in the length of hospital stay and improved health outcomes without compromising safety. The optimal lower threshold for SpO2 is not known. In this review, all safety outcomes were equivalent and some effectiveness outcomes were better for SpO2 thresholds between 88% and 92% when compared to higher thresholds between 92% and 94% or ‘liberal oxygen therapy’.

Safety of lower SpO2 thresholds

The safety of lower SpO2 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 SpO2 thresholds were mortality, neurocognitive sequelae, treatment failure and unscheduled health-care visits or readmissions. Only one outcome in this systematic review favoured the higher threshold. Treatment failure in Maitland 2021 was higher in the permissive hypoxemia group with a threshold of 80% than in the 92% threshold group receiving low flow [21]. However, the way treatment failure was defined as having an SpO2 <92% at 48 hours confounded this outcome. Mortality rates were the primary outcome in Maitland 2021 and favoured the permissive hypoxemia group. In other studies reporting on the safety of oxygen saturation thresholds, the lower threshold varied from 88%-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 on mortality, neurological sequelae and readmission and re-attendance to health care [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 2021.

In Maitland 2021 there were no differences in neurocognitive outcomes between the group that received no supplemental oxygen if SpO2 was above 80% and the group that did, and no neurocognitive sequelae persisted at the 90-day follow-up [21]. 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 hypoxemia, nor was it validated for children older than 24 months. There was a risk of bias for this outcome as patients and assessors were not blinded for treatment allocation. Also there was some loss to follow-up, although equally divided between groups.

The literature on the neurocognitive effects of short (hours to days) periods of hypoxemia in respiratory illnesses is limited and no good data is available on previously healthy children. In children with sleep-disordered breathing or congenital heart defects, neurocognitive sequelae have been reported for SpO2 levels lower than 94% [23]. However, these children are chronically exposed to these low SpO2 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 which caused very low SpO2 for prolonged time. In the case of sleep-disordered breathing, it is difficult to determine the extent to which neurocognitive sequelae are related to intermittent hypoxemia or to
interrupted sleep [24]. Additionally, iron deficiency and anaemia have been previously 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 hypoxemia (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 which include standardized and validated measures of neurocognitive function, to contribute to better evidence on the safety of SpO2 thresholds.

**Effectiveness of lower SpO2 thresholds**

The goal of lowering SpO2 thresholds is to prevent potential adverse effects and complications of excessive oxygen therapy. In this systematic review, reported outcomes on the effectiveness of lower SpO2 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 80-92% were found to be equally effective or even more effective than the higher thresholds varying from 92% to 94% or ‘liberal’, as 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 4%-point SpO2 threshold reduction could lead to a reduction in length of stay of between 10 and 18 hours [17,20,21]. A 3%-point difference could reduce admissions by approximately 40%, based on a single study, Schuh 2014, in children with bronchiolitis [16]. These effects have repercussions for the patient, the parents/caregivers and the health care 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 SpO2 thresholds could help to reduce the burden of paediatric respiratory illnesses on the health care 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 SpO2 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 has been shown to negatively affect the cardiovascular and nervous systems [29,30]. In children admitted to PICUs hyperoxia has been shown to be 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 SpO2 threshold*

The ideal SpO2 threshold strikes a balance between safety and effectiveness. It should be high enough to be safe, thus preventing hypoxic damage, and low enough to minimize unwanted effects of oxygen supplementation like unnecessary admissions, prolongation of hospital stay or hyperoxic damage. Based on this systematic review, for short-term outcomes, SpO2 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 have been published and peer reviewed, no high quality RCT evidence supports this. And still, the issue of neurocognitive sequelae persists even though there are
currently no signals of harm. Taking both safety and effectiveness into account, an SpO2 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 SpO2 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. Reversely, a leftward shift is caused by hypothermia or alkalosis which impairs oxygen unloading. Lower than current SpO2 targets are situated at the more steep part of the oxygen dissociation curve. Therefore, a clinician employing a lower SpO2 target should also be aware of the fact that small changes in disease, with small changes in partial pressure of oxygen, could result in larger changes in SpO2 than in patients with higher SpO2 levels. Lastly, it should be noted that to arrive at an ideal SpO2 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 utilization of a structured search strategy and the application of standardized methods for study selection and assessment of the risk of bias, in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. However, the review also has some limitations. First, there are some issues with generalizability. 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, as children with severe comorbidities were excluded, which makes the conclusions of this systematic review not generalizable to all children with respiratory distress. The findings are more generalizable to other populations where cardiac output and haemoglobin content and function are expected to be within normal range, for whom
SpO2 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 SpO2 values at presentation. As stated by the authors, a much higher prevalence of anaemia and severe malnutrition might make these children more vulnerable to hypoxemia [32-34]. They found higher risk of mortality in patients with SpO2 values <90% and between 90-93% when compared to levels >93%. Even though it is unsure if 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 hypoxemia due to the darker skin pigmentation.

Recently, more attention has been given to potential racial differences in oxygen saturation measurements, as people with darker pigmnetations have been shown to be more likely to have inaccurate SpO2 readings which are often higher than PaO2 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 this systematic review results from Maitland 2021, a study with children from Kenya and Uganda with likely darker pigmentation, were similar to the other Western studies, likely with predominantly light pigmentation populations. This might indicate the difference in accuracy does not lead to a need for differences in SpO2 thresholds, but it does require further investigation.

A final issue with generalizability is the heterogeneity in pathologies investigated in these studies. The difference in pathophysiology might require different SpO2 thresholds. Falling SpO2 in asthma is considered to represent bronchoconstriction and ventilation perfusion mismatch, rather than 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 hypoxemia is different, the level of hypoxemia that is harmful, thus leads to tissue hypoxia, is the same across patients which have otherwise healthy compensatory mechanisms. However, there is another aspect to consider when choosing an
appropriate SpO2 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 dyspnoea is thought to be mainly driven by hypoxemia, as ventilation is often sufficient for exhaling carbon dioxide except in the most severe cases. As such, in patients with acute asthma, supplemental oxygen might provide a relief of dyspnoea, potentially reducing the risk of muscle fatigue and further deterioration. If this is true, a higher SpO2 threshold in patients with acute asthma might be more appropriate. Patel 2019, the only study in this review in children with an asthma attack, showed a reduction in asthma score when given less oxygen, but always with an SpO2 above 92%, in an emergency department setting [19]. The theory that the breathing frequency of children with an asthma attack is steered by the hypoxic drive, is not directly reflected in this study. As saturation, breathing frequency and dyspnea are both components of the Qureshi asthma score, further data on the separate components of the asthma score in the studied patients is required to test this hypothesis. The studies in this systematic review provide insufficient data on the safety and effectiveness of lower SpO2 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, as it cannot be ruled out that studies showing negative effects of lower SpO2 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 SpO2 thresholds for children with respiratory distress.

**Conclusion**
The evidence for safe and effective SpO2 thresholds for children with respiratory distress is limited and poorly generalizable for different diseases and ages. Studies have shown that current SpO2 thresholds of 90-94% may be too high, leading to increased hospitalizations 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%, as it may come with serious reductions in risk of hospitalization, 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 is very limited.

**Support statement**

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<th>Result per outcome (intervention vs control)</th>
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<tr>
<td>Cunningham 2012</td>
<td>Scotland, paediatric ward</td>
<td>Observational cohort</td>
<td>&lt;18 months with bronchiolitis</td>
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<td>Usual care (68)</td>
<td>Time to stable SpO2 above 90% and 94%</td>
<td>22 hours difference</td>
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<td>Schuh 2014</td>
<td>Canada, tertiary care emergency department</td>
<td>double-blind RCT</td>
<td>&lt;12 months with bronchiolitis</td>
<td>Altered SpO2 monitor by +3% (105)</td>
<td>Normal SpO2 monitor (108)</td>
<td>- Admission rates</td>
<td>- 25% vs 41%; p = 0.005</td>
<td>LOW</td>
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<td>- Unscheduled visits</td>
<td>14.3% vs 21.3%; p = 0.18</td>
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<td>Cunningham 2015</td>
<td>UK, multicentre, paediatric wards</td>
<td>double-blind RCT</td>
<td>&lt;12 months with bronchiolitis</td>
<td>90% threshold (307)</td>
<td>94% threshold (308)</td>
<td>- Length of disease</td>
<td>1.0 days shorter; 95% CI 1 to 2</td>
<td>LOW</td>
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<td>2.7 days shorter; 95% CI 0.3 to 7; HR 1.22 (1.04 to 1.44); p = 0.015</td>
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<td>- Return to normal health</td>
<td>1.0 days shorter; 95% CI 0 to 3; HR 1.19 (1.01 to 1.41); p = 0.043</td>
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<td>- Length of stay</td>
<td>40.9 hours vs 50.9 hours; HR 1.28 (1.09 to 1.50); p = 0.003</td>
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<td>- Readmissions/re-attendance</td>
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<td>- Cost-effectiveness</td>
<td>£290; 95% CI £657 to £78</td>
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<td>Peters 2018</td>
<td>UK, multicentre, paediatric intensive care units</td>
<td>pilot-RCT, open-label</td>
<td>&lt;16 years with critical illness</td>
<td>88-92% oxygenation target (53)</td>
<td>&gt;94% oxygenation target (54)</td>
<td>- Mortality</td>
<td>7.4% vs 7.5%; RR 0.98; 95% CI 0.26 to 3.72</td>
<td>SOME</td>
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<td>- Length of stay</td>
<td>1.0 day shorter; 95% CI 0.8 to 2.9; p = 0.29</td>
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<tr>
<td>Patel 2019</td>
<td>USA, emergency department</td>
<td>open-label RCT</td>
<td>&lt;2-18 years with asthma exacerbation</td>
<td>Titrated oxygen, only if SpO2 &lt;92%, during nebulization (47)</td>
<td>High concentration oxygen, 100% 4L/min, during nebulization (49)</td>
<td>- % of patients with PtCO2 rise of &gt;4 mmHg at 60 minutes</td>
<td>10.6% vs 40.8%; p = 0.001</td>
<td>SOMEx4.5; p = 0.0001</td>
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<td>- Asthma score at 60 minutes</td>
<td>only reported in figure, 3.5 vs4.5; p = 0.0001</td>
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<td>Van Hasselt 2020</td>
<td>UK, multicentre, emergency departments</td>
<td>Observational cohort</td>
<td>6 weeks - 12 months with bronchiolitis</td>
<td>Centres with 90%-threshold (162)</td>
<td>Centres with 92% threshold (158)</td>
<td>- SpO2 as reason for admission</td>
<td>-27% vs 37%; p&gt;0.05</td>
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<td>- Length of stay</td>
<td>- 41 hours vs 59 hours; p = 0.0074</td>
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<td>Maitland 2021**</td>
<td>Uganda and Kenya, multicentre, paediatric wards</td>
<td>open-label RCT</td>
<td>&lt;12 years with pneumonia and hypoxemia (80-92%)</td>
<td>80% threshold (727)</td>
<td>92% threshold (729)</td>
<td>- Mortality at 48 hours</td>
<td>- 1.4% vs 2.5%; p = not reported</td>
<td>LOW</td>
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<td>- 3.9% vs 4.1%; p = not reported</td>
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<td>- Treatment failure</td>
<td>- 4.6% vs 2.3%; p = not reported</td>
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<td>- Length of stay</td>
<td>- 0.62 day shorter; 95% CI 0.53 to 1.59</td>
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<td>- Neurocognitive sequelae at 28 days</td>
<td>- 2.3% vs 2.9%; p = not reported</td>
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<td>- Cost-effectiveness</td>
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</table>


* Risk of Bias assessed as low, some or high by ROB2 tool, or as low, moderate, serious or critical by ROBINS-I tool.
** The trial was stopped early when a local doctor started multiple court cases to stop the trial due to safety concerns. However, monitoring and ethics committees saw no safety issues in the trial and all court cases were won. Nonetheless, inclusions slowed to a halt which made the trial unfeasible. The results of all included patients up to that point were analysed.
References


Supplemental File

Searches

Medline

Period: January 1st 2010 to January 7th 2022

Results: 1635


(((("oxygen saturation"[MeSH Terms] OR ("oxygen"[Title/Abstract] AND "saturation"[Title/Abstract]) OR "oxygen saturation"[Title/Abstract] OR ("peripheral"[Title/Abstract] AND "oxygen"[Title/Abstract] AND "saturation"[Title/Abstract]) OR ("target"[Title/Abstract] OR "targetability"[Title/Abstract] OR "targetable"[Title/Abstract] OR "targeted"[Title/Abstract] OR "targeting"[Title/Abstract] OR "targetings"[Title/Abstract] OR "targets"[Title/Abstract] OR "targeted"[Title/Abstract] OR "targeted"[Title/Abstract])) OR ("oxygen saturation"[MeSH Terms] OR ("oxygen"[Title/Abstract] AND "saturation"[Title/Abstract]) OR "oxygen saturation"[Title/Abstract] OR ("blood"[Title/Abstract] OR "oxygen"[Title/Abstract] AND "levels"[Title/Abstract]) OR ("blood oxygen levels"[Title/Abstract]))) NOT ("preterm"[Title] OR "neonatal"[Title] OR "neonate"[Title] OR "neonates"[Title] OR "premature"[Title] OR "newborn"[Title]) AND 2010/01/01:2022/01/07[Date - Publication]) NOT ("Animals"[MeSH Terms] NOT "Humans"[MeSH Terms])

The colours represent individual search records, written in full due to alterations to the fields components.
**Embase**

Period: January 1st 2010 to January 7th 2022

Results: 1448

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**Cochrane**

Period: January 1st 2010 to January 7th 2022

Results: 301

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with Cochrane Library publication date from Jan 2010 to present,
in Cochrane Reviews, Trials 301
### Risk of bias

In the table below the risk of bias per domain as assessed with the Cochrane RoB-2 tool for all randomized controlled trials included in the systematic review.

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**Supplemental Table: risk of bias per domain for each RCT in the systematic review.**