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The Care of Preterm and Term Newborns with Respiratory Conditions: A Systematic Synthesis of Evidence from Low- and Middle-Income Countries

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Title: The Care of Preterm and Term Newborns with Respiratory Conditions: A Systematic Synthesis of Evidence from Low- and Middle-Income Countries
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Abstract

Introduction: Neonatal respiratory conditions are leading causes of mortality and morbidity during the neonatal period. This review evaluated 11 management interventions for respiratory distress syndrome (RDS), apnoea of prematurity (AOP), meconium aspiration syndrome (MAS), transient

tachypnea of the newborn (TTN), as well as bronchopulmonary dysplasia (BPD) as a potential complication from respiratory care in low- and middle-income countries (LMICs).

Methods: Two different methodological approaches were completed: (1) updating outdated reviews and pooling all LMIC studies and (2) re-analysis of LMIC studies from up-to-date reviews. Review updates were conducted between October 2022 and February 2023 and followed systematic methodology. A total of 50 studies were included across four review updates and seven review re-analyses.

Results: Findings indicate that bubble CPAP (RR 0.74, 95% CI 0.58 to 0.96) and prophylactic CPAP (RR 0.39, 95% CI 0.26 to 0.57) for RDS reduced the risk of treatment failure compared to other ventilation types or supportive care, respectively. Postnatal corticosteroids reduced BPD assessed as oxygen requirement at 36 weeks' postmenstrual age (RR 0.56, 95% CI 0.41 to 0.77). All other outcomes were found to be non-significant across remaining interventions.

Conclusions: Our findings indicate that prophylactic and bubble CPAP may provide some benefit by reducing treatment failure compared to other pressure sources. The safety and efficacy of other management interventions for RDS, AOP, BPD, MAS, and TTN remains uncertain given limited evaluations in LMICs. Future research should conduct adequately powered trials in underrepresented LMIC regions, investigate long-term outcomes, and evaluate cost-effectiveness.

Introduction

The under-five mortality in 2021 was approximately five million, of which 2.7 million represented deaths in children aged 1 to 59 months and the remaining 2.3 million during the neonatal period—their first month of life. Evidence has shown that this burden disproportionally impacts low- and middle-income countries (LMICs) since 80% of under-five mortality is found in Sub-Saharan Africa and Southern Asia. However, these estimates may even underrepresent the full extent of child mortality given only 36 countries had high-quality data available while most countries had records which were outdated by at least five years [1].

Neonatal respiratory distress (NRD) serves as an umbrella term which encompasses multiple disorders that contribute to the predominant causes of morbidity and mortality among neonates: preterm birth complications (16.6%), intrapartum-related events (11.0%), and lower respiratory infections (3.8%) [2]. Moreover, NRD represents the most neonatal intensive care unit (NICU) admissions during the neonatal period [3]. Regardless of the disorder, NRD can be characterized by one or more of the following symptoms and indicates a sustained difficulty in breathing: an abnormal respiratory rate (tachypnea), apnoea (an absence of breathing greater than 20 seconds), laboured respirations (grunting, nasal flaring, or chest retractions) and generalized cyanosis (the appearance of blue skin due to decreased oxygen tension) [3-5]. A few of the most common manifestations of NRD will be explored in this paper which are namely respiratory distress syndrome (RDS), apnoea of prematurity (AOP), meconium aspiration syndrome (MAS), and transient tachypnea of the newborn (TTN) [4]. An additional evaluation of bronchopulmonary dysplasia (BPD) management will be investigated given it is a potential complication of respiratory care interventions. Definitions and characteristics of these conditions are provided in Table 1 [3, 4, 6-14].

Providing universal coverage of quality maternal and newborn care could save an estimated three million children and their mothers every year [15]. However, management of neonatal disorders remain difficult in LMICs and can vary from common practice in high-income countries (HICs). Successful implementation of recommended and life-saving therapies can be inhibited by poor health infrastructure, the lack of skilled health workers, higher costs associated with neonatal intensive care coupled with reduced availability and access to resources [16, 17]. Given these inequities, there is a need to appraise current evaluations conducted in these low-resource settings and identify key evidence gaps.

Respiratory Distress Syndrome

Signs of RDS often manifest within the first 24 hours post-delivery and are more common among preterm infants, with apparent severity inversely related to gestational age [7, 14]. The World Health Organization (WHO) strongly recommends continuous positive airway pressure (CPAP) to treat preterm infants with RDS, while surfactant therapy is conditionally recommended based on the capacity of facility settings to administer treatment alongside adequate newborn nursing care and monitoring [18]. Given the proven efficacy of these interventions, most trials in recent literature have been comparative due to ethical considerations around withholding CPAP or surfactant treatment from control groups [19-21]. However, there remains no guidance regarding the most effective type of CPAP device or animal-derived surfactant derivation, which has led to the rise in low-cost and less complex varieties that raises questions regarding comparative efficacy between derivations (e.g. bovine- vs. porcine-derived extracts) and pressure generators (e.g. bubble devices, flow drivers, and conventional ventilators) [7, 22].

Apnoea for Prematurity

AOP is generally attributed to physiological immaturity and found among preterm infants [9]. Pharmacological interventions such as methylxanthines, particularly caffeine, have commonly been used to prevent or treat apnoea in addition to preventing the need for re-intubation after mechanical ventilation [9, 17]. At present, the WHO strongly recommends only caffeine, as opposed to all methylxanthines, for the treatment of apnoea and for the extubation of preterm infants while conditionally recommending use for the prevention of apnoea based on shared decision-making with parents [18]. However, caffeine availability is often difficult to procure and has resulted in the use of other strategies, such as nasal CPAP [9].

Bronchopulmonary Dysplasia

Identifying associations with BPD is central to NRD management given invasive treatments, such as mechanical ventilation, serve as major risk factors to consequential pulmonary injury, oxidative stress, inflammation, and fibrosis. BPD is a type of multifactorial chronic lung disease that often follows RDS and results in varying levels of oxygen dependency for at least 28 days and may persist past 36 weeks' postmenstrual age [10, 23]. In LMICs, recommended treatments for BPD are largely intended for facility settings and preventing prolonged ventilation and further inflammation. These include non-invasive ventilation, oxygen therapy, caffeine, vitamin A supplementation, postnatal corticosteroids, sometimes in combination with surfactant therapy [8, 13, 24]. While substantial evidence has shown mixed benefits and harms associated with systemic corticosteroids, such as early administration leading to reduced BPD yet increased risk of neurological harm, more evidence is needed to assess the efficacy of intrapulmonary administration (inhaled/intratracheal) for routine clinical practice [25].

Meconium Aspiration Syndrome

The risk of MAS is heightened among late preterm and term infants with fully developed digestive systems that may undergo fetal distress, such as hypoxic-ischemic events or infections [3, 4, 10]. While current resuscitation guidelines discourage any type of tracheal suction use among infants born through MSAF, suctioning for non-vigorous infants remains controversial and is still occurring in practice [26, 27]. Other MAS management techniques include supplementary oxygen, CPAP and mechanical ventilation for respiratory support; antibiotic use for potentially acquired bacterial infections; and surfactant therapy to address surfactant inactivation due to meconium [28, 29].

Transient Tachypnea of the Newborn

Tachypnea can occur at any gestational age, but especially among newborns born through caesarean section given rapid fluid reabsorption requires fully developed lungs and is triggered by hormonal changes during natural labour [6]. Although usually benign and self-limiting, TTN can persist and require further medical treatment. Evidence has shown that TTN is a leading etiology of NRD and neonatal respiratory failure, especially in low-resource settings [16, 30]. Various treatments have previously been explored in LMICs, including postnatal corticosteroids, diuretic therapy, fluid restriction, and respiratory support (e.g., supplemental oxygen and CPAP) [6, 31]. Salbutamol (or albuterol), a β-agonist that promotes lung fluid clearance, is considered a pharmacological method of interest in low-resource settings where other supportive therapies may be lacking, but its safety and effectiveness remain unclear [32].

Objective

To our knowledge, no recent review has been conducted to compile the available evidence regarding these conditions (RDS, AOP, BPD, MAS, and TTN) and the effectiveness of such interventions mentioned above within LMIC contexts. The purpose of this paper is to examine 11 management interventions for RDS, AOP, BPD, MAS, and TTN, which is part of an extensive synthesis to update the evidence compiled for the Every Newborn Action Plan and Lancet Series originally published in 2014.

Methods

Given the scope of this paper and existing systematic reviews of relevance, the present study combines different methodological approaches: (1) updates conducted to existing systematic reviews considered outdated and (2) re-analysis of identified systematic reviews considered high-quality and up to date. Figure 1 [32-42] provides a comprehensive list of research questions of all from all reviews updated or re-analyzed using these methodologies. Figure 2 provides an overview of topics included in this review and whether an update was required or whether the existing review was considered up to date with LMIC data available for analysis. Given the various CPAP approaches included in this paper, it is important to note that the Any CPAP approach represents the comparison of any type of CPAP with oxygen therapy delivered by headbox or low-flow nasal cannula, which differs from the other CPAP approaches whose comparison groups used supportive care and/or other ventilation and CPAP devices. A summary of the methods is provided below but a detailed description of methodology, including the selection of outdated and up-to-date reviews, screening, extraction, quality assessment, the definition of significant p-values, and further analyses for this review are referenced here [43]. This paper is intended to explore secondary prevention and management interventions, while other interventions associated with the continuum of neonatal care are considered in detail in separate papers of this supplement, including the efficacy of antenatal corticosteroids [44].

Updates to Existing Systematic Reviews

To update systematic reviews, the search strategy from the existing review was replicated using the original search syntax where possible or key terms were developed by our team based on the review's eligibility criteria. See Suppl. Table 1 for a detailed description of the eligibility criteria used to capture studies for each intervention reviewed. We searched the same databases that were reported in reviews for updated evidence syntheses, such that at least two or a combination of the following databases were searched: MEDLINE via Ovid, Cochrane Central Register of Controlled Trials (CENTRAL) in The Cochrane Library, Embase via Ovid, and CINAHL. No language limits were applied, and date limits were based on the last search date of the original systematic review to present. All updated searches were conducted between October 2022 and February 2023. MEDLINE search strategies for updated intervention topics can be found in Suppl. Text 1.6-1.9 while detailed strategies are included in the original reviews [33, 37, 39, 41].

Data from only LMIC studies in the original review were extracted and combined with data from newly found LMIC studies. Extraction and quality assessments were conducted in duplicate. If no new studies were identified for the intervention topic, only LMIC data from the original review was used to produce pooled effect estimates specific to the LMIC context.

Re-analysis of Existing Systematic Reviews

Reviews were considered up to date if they were conducted after 2020, apart from the review on bolus surfactant for MAS which was deemed relevant and up to date by our technical advisory

group (TAG) of experts in newborn care. The authors from up-to-date reviews used at least two or a combination of the following electronic databases: MEDLINE via Ovid, Cochrane CENTRAL Register of Controlled Trials, Embase via Ovid, CINAHL, Epistemonikos, Maternity & Infant Care Database (MIDIRS), and PubMed. No language or date limits were applied. Detailed search strategies and search dates can be found in the up-to-date reviews [32, 34-36, 38, 40, 42].

For up-to-date reviews, we only extracted studies conducted in LMICs. The term LMIC includes low-income, lower-middle income, and upper-middle income economies, as defined by the World Bank [45]. Effect measures for outcomes of interest were then pooled using data from the LMIC studies.

Data Synthesis & Statistical Analysis
All meta-analyses were conducted using the Review Manager 5.4 software [46]. All primary and secondary outcomes pre-defined by the original review authors were re-analyzed if LMIC studies were available. Given the diverse scope of topics we report, primary outcomes from the original reviews were considered key outcomes of interest for each intervention. Given these respiratory conditions contribute to a substantial proportion of neonatal deaths worldwide, identifying the effectiveness of these interventions for reducing mortality is crucial to our objective. Therefore, if mortality was not considered a primary outcome by the original review authors, we still considered this a key outcome of interest.

Subgroup analyses for updated evidence syntheses were also performed where possible and in accordance with the subgroups defined by the original review authors. For both update and re-analysis topics, we ran additional subgroup analyses by level of care where possible (i.e., community, primary, secondary, or tertiary facility settings) to inform our understanding of neonatal respiratory prevention and management at different levels of care. All key outcomes that were considered for each intervention are outlined in Suppl. Table 1. Forest plots of all key outcomes are provided in Suppl. Fig. 2.1-2.10. The remaining secondary outcomes can be found in Suppl. Table 3.1-3.10. Excluded studies are listed in Suppl. Table 4.1-4.4.

Results

Study Inclusion
A total of 15,711 studies were screened for all topics, which comprised of 13,479 studies previously screened by authors of the up-to-date systematic reviews while the remaining 2,232 studies were screened by our team during the process of updating reviews. These totals exclude the animal-derived surfactant for MAS topic whose authors did not specify how many studies were screened. An overview of respective screening processes per intervention (PRISMA) can be found in Suppl. Fig. 1.1-1.11.

In total, 50 studies related to respiratory care management among preterm and/or term neonates in LMICs were included in this review: 29 studies were related to RDS (representing 13 for bubble CPAP, two for prophylactic CPAP, one for any CPAP vs. oxygen therapy, 13 for animal-derived surfactant), two studies were related to AOP, five were related to BPD, eight were related to MAS (representing one for bolus surfactant, three for antibiotics, four for endotracheal suctioning), and six were related to TTN.

Summary of Study Characteristics

Of the 50 included studies, all were randomized-controlled trials (RCTs) except for two quasi-randomized studies included in the animal-derived surfactant for RDS and methylxanthines for AOP topics. For the interventions associated with RDS, AOP, and BPD all included newborns were preterm (<37 weeks' gestation). For the MAS and TTN interventions, preterm and term (≥34 weeks' gestation) newborns were included. The following nine LMICs were represented in the included studies: Albania, Armenia, Brazil, China, India, Iran, Mexico, Tanzania, Turkey. All studies were conducted in tertiary facility settings, except for one study [47] included in Comparison 7 of the surfactant for RDS intervention, which was a multi-centre trial that was conducted in mixed hospital settings (primary, secondary, and tertiary). The publication dates of included studies ranged from 1995 to 2022. A summary of included studies can be found in Table 2, while a detailed description of study characteristics for all included studies by topic reviewed can be found in Suppl. Table 2.1-2.4. All key outcomes are reported below while additional outcomes per intervention can be found in Suppl. Table 3.1-3.10.

Methodological Quality of Included Studies
A total of 48 RCTs were included across all topics, of which 26 (54.2%) were rated as having high risk of bias (RoB), five (10.4%) as having some concerns, 10 (20.8%) were rated as low RoB, and seven (14.6%) were rated as unclear RoB. Only two (4.0%) quasi-randomized studies were included under the animal-derived surfactant for RDS and methylxanthines for AOP interventions respectively, of which both were rated as having a high RoB [48, 49].

Respiratory Distress Syndrome

Continuous Positive Airway Pressure (CPAP)
Prophylactic CPAP vs. Supportive Care
No effect on death at any time for newborns with a birth weight ≥1000 grams when prophylactic CPAP was compared with supportive care via oxygen supplementation (RR 3.03, 95% CI 0.32 to 28.64; 1 study; 197 infants) (Table 4) [50]. In contrast, a significant 61% reduction in treatment failure was found (RR 0.39, 95% CI 0.26 to 0.57; 1 study; 197 infants). Treatment failure was defined as recurrent apnoea, hypoxia, hypercarbia (such as $PaCO_2$ > 60 mmHg), increasing oxygen requirement, or the need for mechanical ventilation. No significant effect was found for either the incidence of BPD assessed at 28 days (RR 1.37, 95% CI 0.78 to 2.40; 1 study; 197 infants) or the incidence of BPD assessed at 36 weeks (RR 1.11, 95% CI 0.49 to 2.50; 1 study; 197 infants).

Prophylactic CPAP vs. Very Early CPAP
When prophylactic CPAP was compared with very early CPAP, death at any time similarly showed no effect (RR 0.75, 95% CI 0.29 to 1.94; 1 study; 72 infants) where all neonates were ≥28 weeks' gestation. Similar to the previous comparison, no significant effect was found for the incidence of BPD assessed at 28 days (RR 0.50, 95% CI 0.05 to 5.27; 1 study; 72 infants) [51]. No other data was available for treatment failure and BPD assessed at 36 weeks.

Early vs. Delayed CPAP
No LMIC-specific studies were found or re-analyzed (Table 4).

Any CPAP vs. Oxygen Therapy
No significant reduction in mortality when Pumani bubble CPAP was compared to oxygen therapy (RR 0.61, 95% CI 0.31 to 1.23; 1 study; 48 infants) (Table 4). Treatment failure also showed no

significant reduction in the intervention group receiving CPAP (RR 0.46, 95% CI 0.21 to 1.02) (Table 3) [52].

Bubble CPAP

A total of 13 trials compared bubble CPAP to other pressure sources [53-65]. Table 4 indicates that no significant effect on mortality before discharge was identified (RR 0.85, 95% CI 0.57 to 1.25; 8 studies; 1013 infants) irrespective of the comparison group [53, 55-58, 60, 61, 63]. In contrast, treatment failure was found to be significantly reduced by 26% (RR 0.74, 95% CI 0.58 to 0.96, 11 studies; 1054 infants) regardless of the comparison group, although some heterogeneity between studies was identified (I^2 = 28%) [53-58, 60, 62-65]. The incidence of BPD assessed at 36 weeks' postmenstrual age via oxygen requirement did not show a significant impact (RR 0.84, 95% CI 0.52 to 1.35; 5 studies; 427 infants) when specifically compared to other ventilator CPAP devices [54, 55, 60, 61, 64].

Animal-Derived Surfactant for RDS

Seven animal-derived surfactant comparisons are provided in Table 4 from 13 trials [47, 49, 66-76]. No animal-derived surfactant derivation was found to be significantly more effective than another at reducing mortality prior to discharge after analyzing six of the seven comparisons. Comparison 1 found no difference between bovine-derived bovactant and bovine-derived beractant (RR 1.00, 95% CI 0.22 to 4.49; 1 study; 50 infants) [75]. Six trials compared beractant with porcine-derived poractant alfa and presented identical estimates at any initial dosage for Comparison 3 and at >100 mg/kg of porcine minced lung for Comparison 4 (RR 1.22, 95% CI 0.86 to 1.73; 6 studies; 555 infants) [49, 67, 69, 72, 74, 76]. Comparison 5 found no significant effect when beractant was compared with porcine-derived Surfacen (RR 1.10, 95% CI 0.60 to 1.99; 1 study; 44 infants) [73]. Comparison 6 reported on goat lung surfactant extract (GLSE) and found no significant difference in mortality reduction when compared with beractant (RR 1.33, 95% CI 0.77 to 2.29; 1 study; 98 infants) [68]. Similarly, Comparison 7 reported no significance after comparing porcine-derived Butantan with a control group that received either beractant or poractant alfa assessed within 72 hours after the 1st surfactant (RR 1.01, 95% CI 0.59 to 1.73) and assessed on the 28th day (RR 1.20, 95% CI 0.89 to 1.61; 1 study; 308 infants) [47].

Out of all comparisons, only Comparison 7 showed a significant increase in oxygen requirement at 28 days of age when Butantan was used in contrast with a beractant or poractant alfa control (RR 1.26, 95% CI 1.01 to 1.58; 1 study; 294 infants) [47]. Similarly, oxygen requirement assessed at 36 weeks' postmenstrual age showed no significant effect between surfactants used in Comparisons 1, 3 and 4. Comparison 1 reported identical risk between bovactant and beractant (RR 1.00, 95% CI 0.07 to 15.12; 1 study; 50 infants) [75]. The same three trials included in comparisons 3 and 4 showed a slight reduction in oxygen requirement at 36 weeks' postmenstrual age in the beractant group compared to the poractant alfa group, although this was not significant and presented substantial heterogeneity between included studies (I^2 = 51%) [49, 67, 69].

Comparison 3 was the only group that provided a composite outcome of death or oxygen requirement at 36 weeks' postmenstrual age, which presented a significant increase when poractant alfa was used in comparison to beractant (RR 1.95, 95% CI 1.11 to 3.42; 1 study; 126 infants) [67].

Apnoea of Prematurity

Methylxanthines

Two trials assessed methylxanthines (one administered aminophylline and one administered caffeine) compared with a normal saline placebo for the prevention of apnoea [48, 77]. No LMIC studies aiming to administer methylxanthines for the treatment of apnoea or prevention of re-intubation were available. Pooled analyses of preterm infants found no impact on death at discharge (RR 3.00, 95% CI 0.49 to 18.21; 2 studies; 104 infants) for the prevention of apnoea (Table 5). No significant subgroup differences were found between aminophylline or caffeine administration (p=1.00).

Bronchopulmonary Dysplasia

Postnatal Corticosteroids

This review also explored the intrapulmonary administration (inhaled/intratracheal) of postnatal corticosteroids to preterm infants with RDS for the prevention of BPD as a potential complication of some of the treatments discussed above, particularly CPAP. Budesonide was the corticosteroid used in all studies, with one trial specifically comparing its aerosol form to surfactant only [78]. The remaining four trials compared a combination of budesonide, administered via intratracheal instillation, and surfactant as a vehicle with a surfactant-only control group [79-82]. The use of budesonide had no significant reduction on mortality (RR 0.67, 95% CI 0.32 to 1.41; 2 studies; 198 infants) (Table 7). There was a significant 34% reduction in BPD assessed as oxygen requirement at 36 weeks' of postmenstrual age (RR 0.56, 95% CI 0.41 to 0.77; 2 studies; 250 infants), which was identical to the effect on the composite outcome of BPD or death assessed at 36 weeks of postnatal age given the same trials were included [79, 81].

Meconium Aspiration Syndrome

Endotracheal Suctioning for MAS

Endotracheal suctioning was associated with no significant reduction in all-cause neonatal mortality (RR 1.24, 95% CI 0.76 to 2.02; 4 studies; 575 infants) when compared to oro-nasopharyngeal suctioning (Table 6) [83-86]. The effect on the incidence of MAS had no significant effect (RR 1.00, 95% CI 0.80 to 1.25; 4 studies; 575 infants), although this outcome presented moderate heterogeneity (I^2 = 49%). Endotracheal suctioning did not seem to significantly impact the incidence of any hypoxic-ischaemic encephalopathy (HIE) (RR 1.05, 95% CI 0.68 to 1.63; 1 study; 152 infants) or moderate to severe HIE (RR 0.68, 95% CI 0.43 to 1.09; 1 study; 175 infants), although these estimates were analyzed from only one LMIC-specific trial [85, 86]. No significant effect on culture-positive sepsis was reported (RD 0.01, 95% CI -0.03 to 0.05; 3 studies; 406 infants) [83, 84, 86].

Antibiotics for MAS

Various antibiotic types were compared with a control group that received no antibiotics in three trials [87-89]. Table 6 indicates that the use of antibiotics in symptomatic neonates, specifically ampicillin and gentamicin, had no significant effect on mortality before discharge (RD 0.01, 95% CI -0.03 to 0.05; 2 studies; 186 infants) [87, 89], nor the incidence of confirmed sepsis in the first 28 days (RD 0.01, 95% CI -0.04 to 0.06; 2 studies; 186 infants). Similarly, the use of piperacillin-tazobactam and amikacin in asymptomatic neonates had no significant effects on mortality before discharge (RD 1.07, 95% CI 0.22 to 5.18; 1 study; 250 infants) and confirmed sepsis in the first 28 days (RD -0.01, 95% CI -0.07 to 0.04; 1 study; 250 infants) [88].

Bolus Surfactant for MAS

Table 6 indicates that bolus surfactant therapy for MAS had no significant effect on mortality before discharge in only one LMIC-specific trial (RR 0.32, 95% CI 0.04 to 2.93; 1 study; 61 infants) [90].

Transient Tachypnea of the Newborn

Salbutamol

All six included studies administered nebulized doses of salbutamol between 0.10mg/kg to 0.15 mg/kg within the first three days of life. No mortality outcomes were identified in any of the six trials included for this intervention [91-96]. The duration of oxygen therapy (hours) was found to be significantly lower in the intervention groups receiving salbutamol (MD -18.91, 95% CI -23.46 to -14.35; 3 studies; 298 infants) (Table 3) [92-94]. The need for CPAP had no significant effect (RR 0.73, 95% CI 0.38 to 1.39; 1 study; 46 infants) [95]. Similarly, salbutamol suggested no benefit to reducing the need for mechanical ventilation (RR 0.60, 95% CI 0.13 to 2.86; 3 studies; 154 infants) [93, 95, 96].

Discussion

This review compiled the existing evidence and assessed the efficacy of several interventions aimed to manage critical respiratory conditions found among newborns in LMICs. Our synthesis found 48 RCTs and two quasi-randomized studies that represented 10 unique interventions related to RDS (bubble CPAP, prophylactic CPAP, any CPAP vs. oxygen therapy, animal-derived surfactant), AOP (methylxanthines), BPD (postnatal corticosteroids), MAS (antibiotics, endotracheal suctioning and bolus surfactant), and TTN (salbutamol).

Our findings indicate that prophylactic and bubble CPAP reduced the risk of treatment failure compared to other ventilation types or supportive care, respectively. Traditional bovine- (beractant) and porcine-derived (poractant alfa) surfactants showed greater effectiveness at reducing oxygen requirement at 28 days of age when compared to a new porcine-derived (Butantan) surfactant. However, beractant was found to be more effective at reducing the composite outcome of death and oxygen requirement at 36 weeks' postmenstrual age when compared with poractant alfa alone. While small-scale LMIC trials from LMICs indicate potential benefit for postnatal corticosteroids for the prevention of BPD and nebulized salbutamol for TTN, safety and efficacy remain uncertain due to adverse effects identified in other settings. Other than these results, the remaining key mortality and morbidity outcomes were found to be non-significant across all included interventions.

Respiratory Distress Syndrome

Among the CPAP interventions, our review found that bubble CPAP was more effective at reducing the risk of treatment failure compared to other ventilation devices. These results were comparable to our findings for prophylactic CPAP which was found to be more effective at reducing treatment failure than supportive care alone. Despite this, the efficacy of all three CPAP interventions were deemed uncertain due to low certainty of the evidence even when HIC and LMIC data was aggregated by original review authors. Furthermore, single-study estimates were only available for prophylactic CPAP and any CPAP, indicating a key evidence gap in LMIC contexts [35, 42].

While CPAP is considered the gold standard and most effective therapy to reduce mortality and morbidity associated with RDS in neonates [18], the WHO has also provided a conditional recommendation for bubble CPAP based on shared decision-making with parents. However, CPAP

devices, including the bubble CPAP system, remain particularly challenging to procure in low-resource settings due to rising device costs. Further, successful CPAP implementation goes beyond device acquisition and is dependent on adequate infrastructure with sustainable supply chains, reliable electricity and oxygen sources, quality training and access to bioengineering for maintenance and repair [7, 22]. This has led to the proliferation of low-cost, locally improvised devices which may operate without electricity and include easily constructable O2 blenders, but have often been developed without clear safety standards and are therefore not recommended for use by the WHO [17, 97-100]. While the limited evidence identified in this review may show some benefit in bubble and prophylactic CPAP use, further investigation is required to compare the efficacy, optimal application timing, and cost-effectiveness of low-cost alternatives when implemented in LMIC settings given overcoming infrastructural and logistical barriers is crucial to providing quality care [101].

Moreover, no LMIC-specific studies were identified for the early versus delayed CPAP intervention for RDS, indicating another key evidence gap. Results from the up-to-date review indicate that the clinical benefit of early CPAP compared to delayed CPAP remains ambiguous based on HIC-only studies that had no significant effect on mortality at any time ($p>0.05$) or BPD at 36 weeks ($p=0.80$), which lacks generalizability to LMICs [36]. This lack of data may be due to the evolution of research and clinical practice into the 21st century, whereby CPAP use has become common practice and the primary recommendation for treating respiratory distress as soon as the diagnosis is made [18]. Recent studies have also shifted focus to prophylactic methods to prevent RDS, although more invasive, such as steroids and surfactant therapy [18, 25].

Which animal-derived surfactants is most effective for RDS treatment remains uncertain given four out of six comparisons derived estimates from single-studies and significant effects were only found in two outcomes: (1) Comparison 3, which found an increase in death and oxygen requirement at 36 weeks ($p=0.02$) after poractant alfa use and (2) Comparison 7, which found an increase in oxygen requirement at 28 days of age ($p=0.04$) after Butantan use. Surfactant therapy is considered the definitive pharmacological treatment for RDS since the early 21st century and the WHO recommends therapy to begin within the first two hours of birth after surfactant deficiency has been established in neonates [102, 103]. Although the type of animal-derived surfactant remains unspecified and leaves some ambiguity surrounding which derivation may be most effective. While initial surfactant trials included synthetic preparations, the first commercially available surfactants were bovine-derived (i.e., Surfactant-TA) and natural surfactants have since shown greater efficacy at decreasing RDS-related mortality and morbidity, such as the incidence of pneumothorax and need for ventilation [104, 105]. For this reason, only animal-derived surfactants were investigated in this review. A new generation of synthetic surfactants is an area of ongoing investigation that has shown promise in animal models, although few human trials have been evaluated [106-108].

Despite this, surfactant use remains variable in LMIC settings mostly due to lack of availability and high costs. A study surveying 49 African countries found that surfactant was only available in 33% and 39% of well-equipped public and private hospitals, respectively, while the cost of one vial borne by families could surpass USD$500 [109]. Similar to CPAP devices for RDS, these constraints have triggered a proliferation of locally manufactured surfactant extracts [110]. For instance, Comparison 7 compared a new porcine-derived surfactant, Butantan, with the most popular bovine- and porcine-derived surfactants used based on existing evidence (i.e., beractant and poractant alfa). Although found to be less effective at reducing oxygen requirement, Butantan

serves as a low-cost alternative that is only marketed and available in Brazil [47]. A review conducted by Tridente and colleagues [110] found that poractant alfa shows better respiratory outcomes than bovine alternatives. However, no studies have compared other porcine-derived substances with one another, partly because poractant alfa is the only internationally marketed porcine-derived surfactant. The outcomes from Rebello et al. [47] may indicate a need for future adequately powered trials to conduct these porcine comparisons or comparisons with other internationally marketed options that may provide both clinical and financial benefit for other LMIC settings.

Apnoea of Prematurity

While the LMIC evidence indicates no significant effects for death at discharge when aminophylline or caffeine were administered for the prevention of apnoea, the original authors of the review have highlighted significant benefits identified in HIC contexts. One large, international multi-centre trial has particularly shown a significant decrease in death and major neurodevelopmental disability after caffeine administration [38, 111]. The WHO has used this data from HIC contexts in their most recent recommendations to promote the administration of caffeine for AOP [18]. However, caffeine availability for neonatal administration in LMIC contexts remains variable due to high costs and insufficient stock while overall care of this vulnerable population remains starkly different from high-resource settings which serve as the basis of these recommendations [112, 113]. This indicates a greater need for research in LMICs, especially trials that are sufficiently powered, administered in non-tertiary facilities, and focused on cost-effectiveness, dosage, timing of initiation and/or the duration of administration.

Bronchopulmonary Dysplasia

Our review update of postnatal corticosteroids found significant reductions in the composite outcome for death or oxygen requirement at 36 weeks of postnatal age (p=0.0003). In the original review [33], a significant reduction in death or BPD in eight trials from HICs only was reported, whereby intratracheal instillation of corticosteroids was found to be more beneficial than inhaled corticosteroids. Intratracheal administration of corticosteroids using surfactant as a vehicle has also shown promise at significantly reducing BPD in preterm infants, although more evidence is needed [114]. The inclusion of underpowered LMIC studies cannot conclude the same benefit before more well-designed trials are conducted, especially given recent literature has indicated long-term outcomes of preterm infants administered budesonide resulted in significantly higher mortality rates [115]. This aligns with guidelines from HIC settings, such as the European Respiratory Society which reports certainty of evidence is too low to warrant a strong recommendation for routine use [8]. While this review only looked at budesonide, data from HICs indicate that there may be benefit in evaluating other corticosteroids (e.g., beclomethasone and fluticasone), their route of administration, and long-term neurodevelopmental effects [33, 115, 116]. Alternatively, WHO-recommended interventions mentioned in this review have also been shown to reduce BPD and mortality, primarily non-invasive ventilation (i.e., CPAP), surfactant, and caffeine [24].

Meconium Aspiration Syndrome

The effectiveness of endotracheal suctioning, antibiotics, and bolus surfactant administration in neonates at risk or with established MAS were found to be inconclusive after no outcomes indicated significant improvements in preventing mortality and associated morbidities. Evidence also remains limited and outdated given no new studies were identified in our update for endotracheal suctioning and antibiotics, and only a single-study estimate was produced for bolus

surfactant. The effectiveness of endotracheal suctioning at preventing MAS also shows heterogeneity (I^2=49%) among non-vigorous infants born through meconium-stained amniotic fluid (MSAF), which lends to the low certainty of evidence. These results align with current WHO and International Liaison Committee on Resuscitation guidelines which do not recommend the use of endotracheal suctioning for vigorous and non-vigorous neonates born through MSAF [117-119].

While evidence from HICs indicate that antibiotics and bolus surfactant use show no significant effects across all key outcomes [34, 37], current guidelines in HICs, specifically the American Academy of Pediatrics and the Canadian Pediatric Society, conditionally recommend the use of bolus and lung lavage surfactant therapy at the clinician's discretion given some evidence indicating improved oxygenation among MAS patients despite showing no differences in mortality [120, 121]. Current prophylactic measures remain multi-faceted and focused on enhancing overall prepartum and postpartum monitoring to avoid fetal distress [122, 123]. Alternative treatments that have historically shown benefit include a range of respiratory support measures (i.e., oxygen therapy, ventilation devices), inhaled nitric oxide, inotropic therapy, steroids and extracorporeal membrane oxygenation depending on the severity of MAS [123, 124].

Transient Tachypnea of the Newborn

Although the administration of nebulized salbutamol has shown a significant decrease in the duration of oxygen therapy among neonates with transient tachypnea, the considerable heterogeneity between studies (I^2=78%) makes it difficult to conclude the effectiveness of this intervention. Similarly, the original review authors could not conclude the safety or efficacy of salbutamol in treating TTN after aggregating both HIC and LMIC data [32], especially in light of adverse effects (i.e., tachycardia, tremors, hypokalaemia) associated with salbutamol in other studies [31]. Given TTN was found to be the most prevalent etiology of NRD [16], future research would also benefit from investigating dosage, timing of administration, route of administration and administration in combination with other pharmacological treatments.

Future Directions

More high-quality trials with adequate power are needed to evaluate the efficacy of interventions in LMIC settings that were not represented in this review. This is evident in the dearth of evidence found in six out of 11 interventions which used single-study estimates from one LMIC setting to assess efficacy: prophylactic CPAP (Brazil), any CPAP vs. oxygen therapy (Tanzania), methylxanthines (Iran), antibiotics for MAS (India), endotracheal suctioning for MAS (India), and bolus surfactant (China). Key areas that lacked data were South America, Africa, and Southeast Asia.

Strong WHO recommendations for immediate kangaroo mother care (iKMC) for preterm and low-birthweight infants may also influence future management of NRD in LMICs [18]. Recent evidence has shown that iKMC in tandem with CPAP or intermittent positive pressure ventilation can reduce overall duration of treatment, need for supplemental oxygen, and frequency of apneas [125]. Although combining similar recommended interventions may provide opportunities to improve future neonatal respiratory care, resolving barriers to implementation, must first be addressed to support these innovative approaches. Filling knowledge gaps ultimately requires overcoming resource and quality care gaps in low-resource settings. Financial, infrastructural, and logistical challenges massively impact decision-making for neonatal care, as seen with the proliferation of low-cost alternatives and the growing interest in pharmacological approaches given the high costs associated with oxygen administration and monitoring equipment for neonatal intensive care [16].

Evidence supporting the benefits of these interventions for long-term developmental outcomes is greatly lacking in the existing evidence but should be evaluated where possible. For instance, no neurodevelopmental outcomes were considered primary outcomes in the original reviews used for updates and re-analysis. Longitudinal trials remain difficult to conduct but are very much needed to truly conclude the effectiveness and applicability of these interventions in clinical practice. Investigating and accounting for gender differences in future trials should remain a priority, especially for conditions such as RDS where mortality and morbidity is more likely among male neonates than females [126]. Future studies should also consider conducting cost-benefit analyses and assessing the feasibility of implementing these interventions at various levels of care given most included studies were conducted in tertiary facilities. This should include cost comparisons between interventions since, for instance, use of surfactant therapy may be limited in LMIC contexts as opposed to CPAP interventions which are widely used and are more accessible in settings lacking intensive care capacity [7, 35]. Nonetheless, the current LMIC evidence compiled in this review can act as a template to inform future research.

Limitations

While this may be the first review to synthesize the available LMIC literature on secondary prevention and management interventions for major respiratory conditions among neonates, there are some limitations to this approach that should be considered. In every review we updated or re-analyzed, the diagnostic criteria for each respiratory condition were left to the discretion of individual study authors. While this allowed us to adequately compile all available LMIC evidence for these interventions, this may undermine the generalizability of our results given considerable heterogeneity was found in defining RDS, AOP, BPD, MAS, and TTN. This review was explicitly interested in the LMIC context, but the lack of evidence lends to low certainty given data for some interventions were only retrieved from a singular LMIC or a select few LMICs in specific regions. For instance, although four trials were identified for the use of endotracheal suctioning to prevent MAS in preterm infants, all included studies were conducted in India and had high RoB.

Moreover, successful implementation of these interventions would require availability and accessibility to adequate infrastructure and resources, which is often limited to referral facilities. While all the studies included in this review were conducted entirely or in-part in a tertiary facility setting, there are opportunities for implementation at secondary levels, such as district headquarter hospitals. At present, however, intervention efficacy in other settings remains lacking. The dearth of evidence also prevented us from evaluating publication bias via funnel plot asymmetry in any of the outcomes for interventions discussed in this paper. Limitations of the review methodology can be found elsewhere [43].

Conclusions

To our knowledge, this is the first review to synthesize LMIC evidence of respiratory care practices for RDS, AOP, BPD, MAS, and TTN. Our findings identified key evidence gaps, which should be prioritized for future research. This includes conducting adequately powered trials which consider various levels of care in LMIC regions that are currently underrepresented in the literature; investigating long-term outcomes to further validate efficacy; and evaluating cost-effectiveness for implementation given the current challenges faced by LMICs in accessing several of these interventions. Current data from LMICs indicate that prophylactic and bubble CPAP may provide some benefit for reducing treatment failure. Despite small-scale LMIC evidence indicating postnatal corticosteroids may reduce death or BPD and treating TTN with salbutamol may reduce

the duration of oxygen therapy, their safety and efficacy remain unclear due to potential harms found in other settings. Further, the efficacy of other recommended interventions for RDS, AOP, MAS in LMICs remains uncertain given low quality and limited evidence.

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Statement of Ethics
A Statement of Ethics is not applicable because this study is based exclusively on published literature.

Conflicts of Interest
The authors have no conflict of interest to declare.

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Author Contributions
Z.A.B. secured funding and provided senior supervision for all aspects of this study. L.H. and Z.A.B. conceptualized and designed the study. G.D., O.M.and R.L.H. carried out the search and study selection for all topics requiring an updated synthesis. G.D., O.M. and R.L.H completed data collection and critical appraisal for all topics. G.D. led data analysis, the interpretation of evidence and the writing of this paper with substantial contributions from O.M., R.L.H, L.H., T.V. and Z.A.B. All authors approved the final manuscript for submission.

Data Availability Statement
All data generated or analyzed during this study are included in this article and its supplementary material files. Further enquiries can be directed to the corresponding author.

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Figure Legends

Fig. 1. Research questions per intervention of interest

Fig. 2. Flow diagram of topics of interest and associated interventions for respiratory conditions amongst newborns in low- and middle-income countries

Research Questions

Respiratory Distress Syndrome

1. Does bubble CPAP versus other pressure sources (mechanical ventilators or Infant Flow Driver) reduce treatment failure and associated morbidity and mortality in newborn preterm infants with or at risk of respiratory distress? [40]
2. Can breathing support using CPAP, given within the first hour of life, prevent death and illness in premature babies? [42]
3. Would applying CPAP early (at birth or very soon after birth) result in increased benefit and less harm than if it were applied later for preterm infants in respiratory distress? [36]
4. Would using CPAP compared with oxygen alone, delivered by headbox or low-flow nasal cannula, safely reduce death or the use of mechanical ventilation in preterm infants with breathing difficulties? [35]
5. Does the use of one animal-derived surfactant preparation compared with an alternative animal-derived surfactant preparation lead to improved outcome in infants at risk for or having respiratory distress syndrome? [41]

Apnoea of Prematurity

1. Does administration of methylxanthines during the peri-extubation period prevent apneic episodes and lead to improved survival and long-term development of preterm newborns at risk for or having apnea of prematurity? [38]

Bronchopulmonary Dysplasia

Does the pulmonary application of postnatal corticosteroids compared to standard treatments or placebo lead to improved health and safety outcomes of preterm infants with RDS in LMICs? [33]

Meconium Aspiration Syndrome

1. Does endotracheal intubation and suctioning of the airways at birth lead to better outcomes than oropharyngeal suctioning, oro-nasopharyngeal suctioning or routine resuscitation among non-vigorous preterm and term infants born through MSAF in LMICs? [39]
2. What is the efficacy and safety of antibiotics for prevention of infection, morbidity, and mortality, compared to no antibiotics or placebo, among infants born through MSAF in LMICs? [37]
3. Does the administration of surfactant improve lung function and lead to better clinical outcomes in infants born at or near term who have inhaled meconium in or around the time of birth? [34]

Transient Tachypnea of the Newborn

1. Does salbutamol within the first three days of life reduce the duration of oxygen therapy and the need for respiratory support in newborns with transient tachypnea? [32]

1.

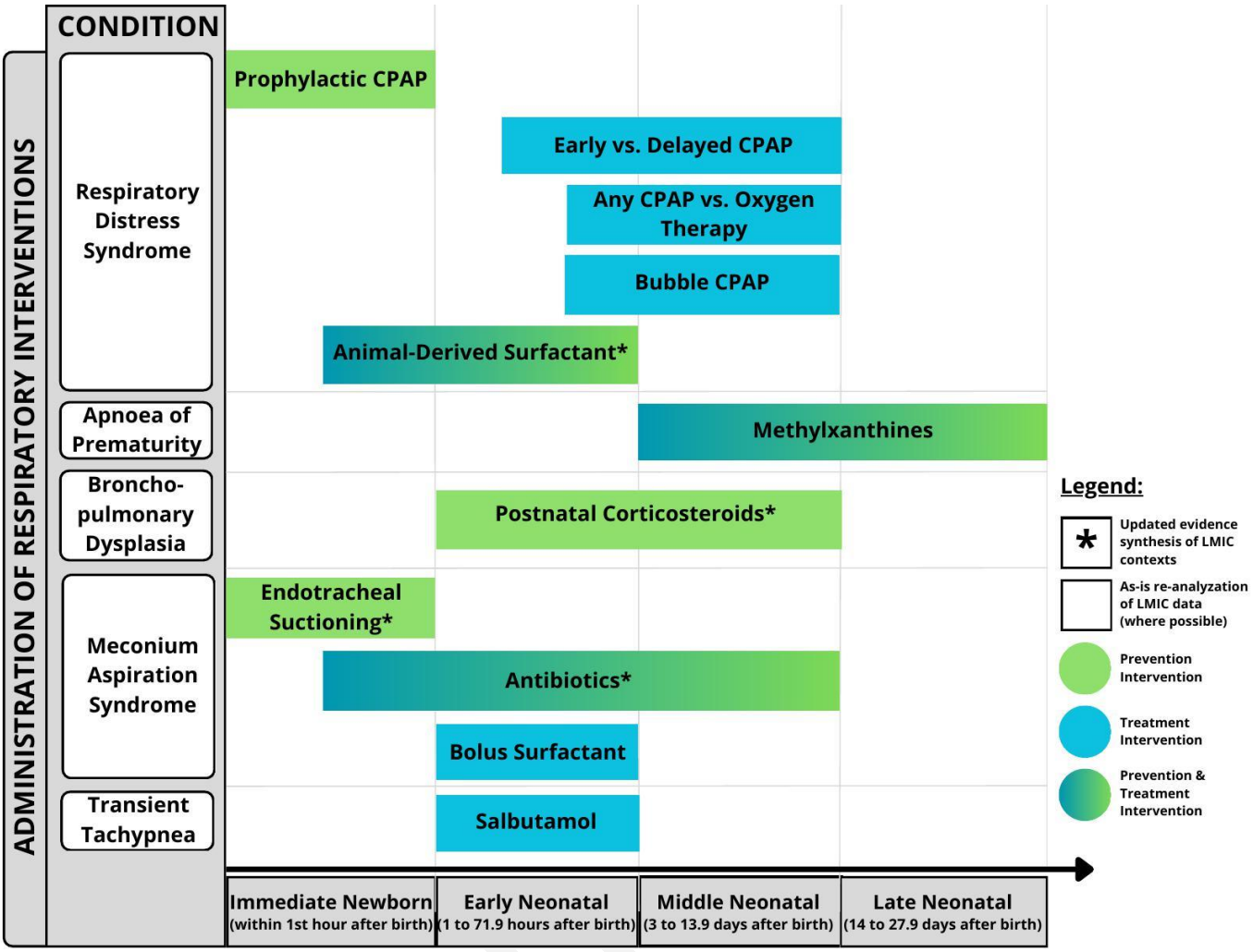

Table 1. Summary of definitions and characteristics of neonatal respiratory conditions

Condition	Term or Preterm Status	Definition & Etiology	Clinical Characteristics	Radiographic Characteristics	Risk Factors
Respiratory Distress Syndrome (RDS) [7, 10, 12, 14]	Preterm	Respiratory distress caused by surfactant deficiency or deficiency from immature lung development and/or airway collapse.	Tachypnea, grunting, retractions, and cyanosis.	Poorly inflated lungs and ground-glass appearance with air bronchograms.	Prematurity, male sex, white race, and/or maternal diabetes.
Apnoea of Prematurity (AOP) [9, 12]	Preterm	A self-limiting disorder with pauses in breathing caused by immature development of the lungs and brain (central), lung obstruction (obstructive), or both (mixed). May also be considered a symptom of other conditions, such as low blood sugar or infection.	Cessation of breathing for more than 20 seconds, bradycardia, cyanosis, and/or pallor.	Radiograph not necessary.	Prematurity and genetic susceptibility.
Bronchopulmonary Dysplasia (BPD) [8, 10, 12, 13]	Preterm	Also known as a type of chronic lung disease resulting in oxygen dependency for at least 28 days and may persist by 36 weeks postmenstrual age caused by immature, damaged lungs previously exposed to invasive treatment(s).	Apnoea, tachypnea, grunting, retractions and/or wheezing.	Pulmonary fibrosis, hyperinflated lungs with larger alveoli and smaller surface area and reticular markings.	Prematurity, mechanical ventilation, chorioamnionitis, postnatal sepsis, oxygen toxicity, fluid overload and/or patent ductus arteriosus.
Meconium Aspiration Syndrome (MAS) [3, 4, 10, 12]	Late preterm to post-term	Lung obstruction, inflammation, irritation, infection and/or surfactant deactivation caused by inhaled meconium.	Tachypnea, grunting, retractions, and/or cyanosis.	Hyperinflated lungs with patchy densities.	Meconium-stained amniotic fluid, post-term birth, small for gestation age, fetal distress, placental issues, and/or umbilical cord problems.
Transient Tachypnea of the Newborn (TTN) [4, 6, 10, 11, 12]	Any	A self-limiting disorder with persistent alveolar fluid caused by delayed or inadequate reabsorption and/or pulmonary maladaptation.	Tachypnea, hypoxemia, acidosis, and cyanosis.	Lung hyper-expansion, perihilar markings with fissure fluid, or pleural effusions.	Caesarean delivery, maternal asthma, male sex, macrosomia, and/or maternal diabetes.

Table 2. Summary of study characteristics per respiratory condition

Topics	Study Design	Population	Comparisons	Setting	Publication Date Range
Respiratory Distress Syndrome					
Prophylactic CPAP	2 RCTs	269 neonates <37 weeks GA	1 Prophylactic CPAP vs. supportive care or mechanical ventilation 1 Prophylactic CPAP vs. very early CPAP	Brazil and Iran All tertiary facilities	2013-2014
Early vs. Delayed CPAP	No studies from LMICs found	NA	0 Early CPAP vs. delayed CPAP (at approximately FiO_2 0.6 or more)	NA	NA
Any CPAP vs. Oxygen Therapy	1 RCT	48 neonates <37 weeks GA	1 Pumani bubble CPAP vs. humidified oxygen	Tanzania All tertiary facilities	2020
Bubble CPAP	13 RCTs	1261 neonates <37 weeks GA	13 Underwater Bubble CPAP vs. other ventilators or Infant Flow Driver CPAP devices	Albania, Armenia, Brazil, India, and Iran All tertiary facilities	2010-2017
Animal-Derived Surfactant	12 RCTs 1 Quasi-RT	1451 neonates <37 weeks GA	3 bovine lung lavage vs. modified bovine lung 2 bovine lung lavage vs. porcine minced lung 9 modified bovine lung vs. porcine minced lung (any initial dosage) 7 modified bovine lung vs. porcine minced lung (initial dosage of >100 mg/kg) 1 modified bovine lung vs. porcine lung lavage 1 goat lung surfactant extract vs. modified bovine lung 1 porcine minced lung vs. modified bovine lung or porcine minced lung	Brazil, India, Iran, Mexico, and Turkey 12 tertiary facilities 1 mixed facility	2004-2022
Apnoea of Prematurity					
Methylxanthines	1 RCT 1 Quasi-RT	52 neonates <37 weeks GA	1 Aminophylline or caffeine vs. normal saline placebo	Iran All tertiary facilities	2016
Bronchopulmonary Dysplasia					
Postnatal Corticosteroids	5 RCTs	534 neonates <37 weeks GA	1 budesonide vs. surfactant 4 budesonide and surfactant vs. surfactant only	China and Iran All tertiary facilities	2016-2022
Meconium Aspiration Syndrome					
Endotracheal Suctioning	4 RCTs	571 neonates ≥34 weeks GA	2 Endotracheal suctioning vs. oropharyngeal suctioning 2 Endotracheal suctioning vs. oro-nasopharyngeal suctioning	India All tertiary facilities	2015-2019
Antibiotics	3 RCTs	336 neonates ≥34 weeks GA	1 Ampicillin and amikacin vs. no antibiotics 1 Piperacillin-tazobactam and amikacin vs. no antibiotics 1 Gentamicin vs. no antibiotics	India All tertiary facilities	1995-2015
Bolus Surfactant	1 RCT	61 neonates	1 Porcine minced lung (poractant alfa) vs. unspecified non-surfactant control therapy	China All tertiary facilities	2005

		Unspecified age range			
Transient Tachypnea of the Newborn					
Salbutamol	6 RCTs	458 neonates ≥34 weeks GA	6 Nebulized salbutamol (0.15 mg/kg) vs. nebulized normal saline placebo	Iran, Mexico, and Turkey All tertiary facilities	2011-2019

Note: RCT=randomized controlled trial; GA=gestational age; CPAP=continuous positive airway pressure; NA =not applicable; Quasi-RT=quasi-randomized trial

Table 4. Pooled effect estimates associated with respiratory distress syndrome

Outcome	Group	# of studies (# of participants)	Effect Estimate (95% CI)	Heterogeneity (I^2)	Test for subgroup differences
Prophylactic CPAP – Comparison 1: Versus supportive care (oxygen supplementation)					
Death at any time	Total	1 (197)	RR 3.03 (0.32, 28.64)	-	-
BPD (oxygen requirement) at 28 days	Total	1 (197)	RR 1.37 (0.78, 2.40)	-	-
BPD (oxygen requirement) at 36 weeks postmenstrual age	Total	1 (197)	RR 1.11 (0.49, 2.50)	-	-
Treatment failure	Total	1 (197)	**RR 0.39 (0.26, 0.57)**	-	-
Prophylactic CPAP – Comparison 2: Versus very early CPAP					
Death at any time	Total	1 (72)	RR 0.75 (0.29, 1.94)	-	-
BPD (oxygen requirement) at 28 days	Total	1 (72)	RR 0.50 (0.05, 5.27)	-	-
Early vs. Delayed CPAP					
None.					
Any CPAP vs. Oxygen Therapy					
Mortality	Total	1 (48)	RR 0.61 (0.31, 1.23)	-	-
Treatment failure due to death or use of additional ventilatory assistance	Total	1 (48)	RR 0.46 (0.21, 1.02)	-	-
Treatment failure due to additional ventilation required at tertiary hospital without NICU	Total	1 (48)	RR 0.46 (0.21, 1.02)	-	-
Bubble CPAP vs. Other Devices					
All-cause mortality before discharge	Total	8 (1013)	RR 0.85 (0.57, 1.25)	0%	P=0.68
	Bubble vs. ventilator CPAP	6 (688)	RR 0.81 (0.52, 1.27)	0%	-
	Bubble vs. Infant Driver CPAP	2 (325)	RR 0.98 (0.44, 2.20)	0%	-
BPD (oxygen requirement) at 36 weeks postmenstrual age	Total	5 (427)	RR 0.84 (0.52, 1.35)	0%	-
Treatment failure*	Total	11 (1054)	**RR 0.74 (0.58, 0.96)**	28%	P=0.05
	Bubble vs. ventilator CPAP	9 (729)	**RR 0.64 (0.47, 0.86)**	16%	-
	Bubble vs. Infant Driver CPAP	2 (325)	**RR 1.15 (0.58, 0.96)**	4%	-
Animal-Derived Surfactant – Comparison 1: Bovine lung lavage vs. modified bovine minced lung					
Neonatal mortality	Total	1 (50)	RR 1.00 (0.22, 4.49)	-	-
Oxygen requirement at 28 days of age	Total	1 (103)	RR 0.45 (0.04, 4.85)	-	-
Oxygen requirement at 36 weeks' post menstrual age	Total	1 (50)	RR 1.00 (0.07, 15.12)	-	-
Animal-Derived Surfactant – Comparison 2: Bovine lung lavage vs. porcine minced lung					
Oxygen requirement at 28 days of age	Total	1 (116)	RR 1.15 (0.07, 17.92)	-	-
Animal-Derived Surfactant – Comparison 3: Modified bovine minced lung vs. porcine minced lung					
Mortality prior to discharge	Total	6 (555)	RR 1.22 (0.86, 1.73)	17%	-
Oxygen requirement at 28 days of age	Total	1 (111)	RR 2.53 (0.24, 27.10)	-	-
Oxygen requirement at 36 weeks' post menstrual age	Total	3 (368)	RR 0.90 (0.71, 1.13)	51%	-
Death or oxygen requirement at 36 weeks' post menstrual age	Total	1 (126)	**RR 1.95 (1.11, 3.42)**	-	-
Animal-Derived Surfactant – Comparison 4: Modified bovine minced lung vs. porcine minced lung, > 100 mg/kg					
Mortality prior to discharge	Total	6 (555)	RR 1.22 (0.86, 1.73)	17%	-
Oxygen requirement at 28 days of age	Total	1 (111)	RR 2.53 (0.24, 27.10	-	-
Oxygen requirement at 36 weeks' post menstrual age	Total	3 (368)	RR 0.90 (0.71, 1.13)	51%	-
Animal-Derived Surfactant – Comparison 5: Modified bovine minced lung vs. porcine lung lavage					
Mortality prior to discharge	Total	1 (44)	RR 1.10 (0.60, 1.99)	-	-
Animal-Derived Surfactant – Comparison 6: Goat lung surfactant extract (GLSE) vs. modified bovine minced lung					
Mortality prior to discharge	Total	1 (98)	RR 1.33 (0.77, 2.29)	-	-
Animal-Derived Surfactant – Comparison 7: Porcine minced lung (Butantan) vs. (modified bovine minced lung (beractant/Survanta®) OR porcine minced lung (poractant alfa))					
Overall mortality within 72 hours	Total	1 (324)	RR 1.01 (0.59, 1.73)	-	-
Overall mortality at 28th day of life	Total	1 (308)	RR 1.20 (0.89, 1.61)	-	-
Oxygen requirement at 28 days of age	Total	1 (294)	**RR 1.26 (1.01, 1.58)**	-	-

*Note: treatment failure was defined as recurrent apnoea, hypoxia, hypercarbia (such as PaCO2 > 60 mmHg), increasing oxygen requirement, or the need for mechanical ventilation.

Table 5. Pooled effect estimates associated with apnoea of prematurity

Outcome	Group	# of studies (# of participants)	Effect Estimate (95% CI)	Heterogeneity (I^2)	Test for subgroup differences
Methylxanthines - Comparison 2: For Prevention of Apnoea Only					
Death at discharge	Total	2 (104)	RR 3.00 (0.49, 18.21)	0%	P=1.00
	Aminophylline	1 (52)	RR 3.00 (0.33, 26.99)	-	-
	Caffeine	1 (52)	RR 3.00 (0.13, 70.42)	-	-

Table 7. Pooled effect estimates associated with bronchopulmonary dysplasia

Outcome	Group	# of studies (# of participants)	Effect Estimate (95% CI)	Heterogeneity (I^2)	Test for subgroup differences
Postnatal Corticosteroids (inhaled or intratracheal) vs. Control					
Mortality	Total	2 (198)	RR 0.67 (0.32, 1.41)	0%	P=1.00
	28 days from birth	1 (70)	RR 0.67 (0.21, 2.16)	-	-
	Assessed any time	1 (128)	RR 0.67 (0.25, 1.76)	-	-
BPD (oxygen requirement at 36 weeks of postmenstrual age)	Total	2 (250)	**RR 0.56 (0.41, 0.77)**	0%	-
Death or BPD (oxygen requirement at 36 weeks of postmenstrual age)	Total	2 (250)	**RR 0.56 (0.41, 0.77)**	0%	-

Table 6. Pooled effect estimates associated with meconium aspiration syndrome

Outcome	Group	# of studies (# of participants)	Effect Estimate (95% CI)	Heterogeneity (I^2)	Test for subgroup differences
Endotracheal Suctioning vs. Oro-(naso)pharyngeal Suctioning					
All-cause neonatal mortality	Total	4 (575)	RR 1.24 (0.76, 2.02)	12%	-
Incidence of meconium aspiration syndrome	Total	4 (575)	RR 1.00 (0.80, 1.25)	49%	-
Hypoxic ischemic encephalopathy (HIE)	Total	2 (327)	RR 0.86 (0.62, 1.18)	41%	P=0.19
	Any severity	1 (152)	RR 1.05 (0.68 to 1.63)	-	-
	Moderate to severe	1 (175)	RR 0.68 (0.43 to 1.09)	-	-
Culture positive sepsis	Total	3 (406)	RD 0.01 (-0.04, 0.06)	0%	-
Antibiotics – Comparison 1: Among Symptomatic Infants					
Mortality (before discharge)	Total	2 (186)	RD 0.01 (-0.03, 0.05)	0%	-
Incidence of confirmed sepsis in the first 28 days	Total	2 (186)	RD 0.01 (-0.04, 0.06)	0%	-
Antibiotics – Comparison 2: Among Asymptomatic Infants					
Mortality (before discharge)	Total	1 (250)	RR 1.07 (0.22, 5.18)	-	-
Incidence of meconium aspiration syndrome	Total	1 (250)	RR 1.17 (0.67, 2.04)	-	-
Incidence of confirmed sepsis in the first 28 days	Total	1 (250)	RD -0.01 (-0.07, 0.04)	-	-
Bolus Surfactant vs. Control					
Mortality	Total	1 (61)	RR 0.32 (0.04, 2.93)	-	-

Table 3. Pooled effect estimates associated with transient tachypnea of the newborn

Outcome	Group	# of studies (# of participants)	Effect Estimate (95% CI)	Heterogeneity (I^2)	Test for subgroup differences
Salbutamol vs. Control					
Duration of oxygen therapy (hours)	Total	3 (298)	**MD -18.91 (-23.46, -14.35)**	78%	-
Need for continuous positive airway pressure	Total	1 (46)	RR 0.73 (0.38, 1.39)	-	-
Need for mechanical ventilation	Total	3 (154)	RR 0.60 (0.13, 2.86)	0%	-