Ventilation devices for neonatal resuscitation at birth: a systematic review and meta-analysis

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Abstract

Initial management of inadequate adaptation to extrauterine life relies on non-invasive respiratory support. Two types of devices are available: fixed pressure devices (FPD; T-pieces or ventilators) and hand driven pressure devices (HDPD; self- or flow-inflating bags). This systematic review and meta-analysis aims to compare clinical outcomes after neonatal resuscitation according to device type.

Methods

Four databases were searched from inception to 2022, January. Search strategies included Mesh/Emtree terms as well as free language without any restriction. Randomized, quasi-randomized studies and prospective cohorts comparing the use of the two types of devices in neonatal resuscitation were included.

Results

Nine studies recruiting 3621 newborns were included: 5 RCTs, 2 RCTs with interventions bundles and 2 prospective cohorts. Meta-analysis of the 5 RCTs demonstrated significant reductions in bronchopulmonary dysplasia (RR0,68[0,48-0,96]-NNT 31) and other respiratory outcomes: intubation in the delivery room (RR0,72[0,58-0,88]-NNT 13,4), mechanical ventilation requirements (RR0,81[0,67-0,96]-NNT 17) and duration (MD-1,54 days[-3,03- -0,05]), need for surfactant (RR0,79[0,64-0,96]-NNT 7,3).

The overall analysis found a lower mortality in the FPD group (OR0,57[0,47-0,69]-NNT 12,7) and confirmed decreases in intubation, surfactant requirement and mechanical ventilation rates (OR 0,56[0,40-0,79]- NNT7,5; OR 0,67[0,55-0,82]-NNT10,7 and OR0,58[0,42-0,80]- NNT 7,4 respectively). The risk of cystic periventricular leukomalacia (cPVL) decreased significantly with FPD (OR0.59[0.41–0.85]−NNT 27). Pneumothorax rates were similar (OR0.82[0.44–1.52]).

Conclusion and relevance

Resuscitation at birth with FPD improves respiratory transition and decreases BPD with a very low to moderate certainty of evidence. There is suggestion of decreases in mortality and cPVL. Further studies are still needed to confirm those results.

Introduction

Establishing adequate ventilation is one of the most important steps in perinatal transition.[1,2] Around 6% of infants require positive pressure ventilation (PPV) at birth.[3,4] The number of infants at risk of respiratory transition delay increases at lower gestational ages, and reaches 100% for extremely preterm infants.[3] Effective ventilation is considered the cornerstone of neonatal resuscitation.[5–7]

Different devices are used to provide PPV at birth. Hand driven pressure devices (HDPD) include self-inflating bags (SIB) and flow-inflating bags. The manual squeezes of the operator lead to variable insufflation pressures. Adding an expiratory valve on SIB to provide some positive end expiratory pressure (PEEP) remains mostly inadequate.[8] As the valve between the SIB and the facemask is unidirectional, it impedes spontaneous breathing. Alternatively, T-piece resuscitators (TPR) and conventional ventilators provide fixed insufflatory and end-expiratory pressures (fixed pressure devices- FPD). Variations in pressure occur only with adjustments of device settings and gas flow, and with mask leak.

Differences between SIB and TPR have been extensively studied in manikins.[9,10] Pressures provided by TPR were less variable and more often within the target range, with a decreased variability of tidal volumes. However, SIB increased awareness of changes in lung compliance during the dynamic resuscitation process and allowed for faster pressure adjustments. TPR is considered as more technically difficult to prepare and use. Increments in gas flow or inadvertent rotation of the control valve during resuscitation could increase pressures,[9] leading to barotrauma.

TPR usage increased with time.[11] Two retrospective studies compared TPR and SIB with mixed results.[12,13] One reported decreased delivery room (DR) intubation rates.[12] The other found higher mortality or oxygen requirement at 36 wGA in the TPR group, with however a high risk of bias given lower gestational ages and birth weight in this group.[13] A quality improvement process for DR management of VLBW included implementation of TPR, and allowed a reduction in broncho-pulmonary dysplasia (BPD).[14] In contrast, two other retrospective studies considering term infants reported increased pneumothoraxes following the introduction of TPR and face mask CPAP at birth.[15,16] Currently, ILCOR (International Liaison Committee on Resuscitation) suggests using TPR where possible in order to provide PEEP, with a very-low certainty of evidence, due to paucity of data, serious risk of bias, imprecision and indirectness.[7,17]

The aim of this meta-analysis is to assess clinically relevant benefits from ventilation at birth with either FDP or HDPD.

Methods

1. Research protocol

This systematic review and meta-analysis was conducted in accordance with the Cochrane Handbook for Systematic Reviews of Interventions and reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement for meta-analysis in health care interventions.[18]

The protocol was registered after search but in advance of data extraction with the Prospective Register of Systematic Reviews (registered July 11, 2020; CRD42020191685).

2. Criteria of Eligibility

Studies comparing fixed-pressure devices and hand-driven pressure devices for neonatal resuscitation at birth were considered eligible. Subgroup analyses were planned for term and preterm infants.

RCTs, quasi-RCTs and prospective cohorts were eligible, without language restriction.

Retrospective studies, manikin or animal models, and case reports were excluded.

3. Search strategy

Medline via Ovid, Embase, Scopus and Cochrane Library of Trials were searched between inception and May 20, 2020 without language restriction, filter or limit, with an update on January 20, 2022 (eFig1). The search included Mesh/Emtree terms and free language. Search strategies are available in online supplementary material. Google Scholar was searched for grey literature. References from publications eligible for full-text review and systematic reviews allowed for an additional "snowball search".

4. Study selection

Rayyan QCRI web app was used for a 2 steps study selection. After exclusion of duplicates, two independent reviewers screened titles and abstracts for potentially relevant studies.

Full texts were then independently assessed for eligibility. Conflicts at any step of the selection process were resolved through discussion with a third reviewer.

5. Outcomes

Patient-oriented outcomes were determined in advance.

Mortality, hypoxic-ischemic encephalopathy (HIE) in patients born at term and BPD (defined as oxygen requirement at 36 weeks' postmenstrual age) in preterm infants were selected as main outcomes.

Secondary outcomes focused on markers of resuscitation efficiency and safety (DR intubation; advanced resuscitation (drug or chest compressions); air leaks; Apgar scores at 5 minutes; heart rate > 100 bpm at 2 minutes of life).

Secondary outcomes describing respiratory evolution included surfactant needs, mechanical ventilation (MV) requirements and duration as well as oxygen therapy occurrence and duration. Finally, morbidities commonly associated with very preterm birth (patent ductus arteriosus (PDA), severe intraventricular haemorrhage (IVH), cystic periventricular leukomalacia (cPVL), retinopathy of prematurity (ROP) and necrotizing enterocolitis (NEC)) were investigated.

6. Data extraction and analysis

Data were independently extracted on a prespecified form by two reviewers and discussed with a third when discordant.

Authors were contacted to provide additional data for missing information.

Review Manager software (RevMan 5.4; The Nordic Cochrane Centre, Copenhagen, Denmark) were used for data analyses.

For the meta-analysis of the RCT, Risk Ratios (RR) and 95% confidence intervals (CI) are reported using the Mantel-Haenszel method for dichotomous data with a fixed-effect model. Given the heterogeneity of study designs and devices, the analysis of all studies evaluated Odds Ratio (OR) with a random-effect model, as it allows for generalization inference.[19]

For continuous outcomes, mean differences (MD) and 95% CI were computed. When data were communicated in median and interquartile range, mean and standard deviation were mathematically estimated.[20,21]
Numbers needed to treat (NNT) were computed for statistically significant results.[22]
Heterogeneity was assessed with I^2 statistic.

7. Bias, quality and GRADE assessment

Two independent authors evaluated the risk of bias (RoB) and assessed quality in individual studies using the Revised Cochrane Risk-of-Bias for randomized trials (RoB2) or the Newcastle Ottawa Scales (NOS) for cohort studies. For RCT, the following domains were assessed: randomization process, deviation from intended intervention, missing outcome data, measurement of outcome and selection of reported results. For cohort studies, quality of selection, comparability and outcomes were evaluated.
The GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) method[23] was used to assess the strength of evidence across studies for outcome with significant difference. The importance of each outcome was assigned consistently with the ILCOR rating.[24]

Results

1. Literature search and study selection

The search strategy allowed identification of 8783 records. After accounting for 3552 duplicates, 5231 records were screened by title and abstract, leading to selection of 61 articles. Among these, 9 studies met the inclusion criteria (PRISMA flowchart, Figure 1).

2. Study Characteristics

Studies' characteristics are summarized in table 1.

Three randomized controlled trials[25–27] and two quasi-RCTs were eligible [28,29].

Two additional RCTs[30,31] evaluating bundle of interventions in preterm patients only were included. In both, bag and mask ventilation was compared to the use of TPR for sustained inflation and ventilation. In the TPR group, the interface was a nasopharyngeal tube[31] or a facemask[30].

Two prospective observational studies were included.[32,33] One evaluated prespecified cohorts before and after the implementation of TPR.[32] In a large multicentric prospective study in preterm infants[33], the decision to use TPR or SIB was at discretion of resuscitation teams.

Eight studies compared TPR versus SIB[26–33] and one mask ventilation with a neonatal ventilator versus anaesthetic rebreathing circuits.[25]

One qRCT and one prospective observational study were multicentric.[28,33]

3. Patient characteristics

In total, 3621 newborns (1271 in the 5 (q)RCT) were included. Studies recruitments ranged from 24 to 1962 infants. Five studies focused on preterm infants.[25,26,30,31,33] The 4 others included newborns of all gestational ages[27–29,32], with a preterm subgroup analysis in 2.[28,29]

In all RCTs and quasi-RCTs, groups were matched in term of gestational ages, birth weight and antenatal steroid exposure.[25–31] In Guinsburg et al., infants in the HDPD group had a significant two days decrease in gestational age and increased antenatal steroids exposure.[33]

Ng et al. didn't reported mean gestational age.[32]

4. RoB and Grade Assessment

The RoB of the RCTs and quasi-RCTs were evaluated as "some concern"[25,26,31] or high[27,28,30], given high risks of bias in the randomization process or deviations from the intended intervention.

Quality of the cohort studies were assessed as mild, as differences between groups decreased their comparability.[32,33] Assessments are summarized in online additional data (eFig2).

Certainty of evidence was graded as low or moderate for all outcomes in RCTs analysis and as very low for outcomes of overall analysis. (eFig3).

5. Outcomes analysis

Meta-analysis' results are detailed below, and summarized in figures 2 and 3. All forest plots are available in online supplemental material (eFig4).

RCTs and qRCTs analysis[25–29]

Mortality was similar between groups (RR 0,68[0,38-1,20]).[25–29]

HIE was reported in populations of all gestational ages, without significant difference between interventions.[27,28]

Statistically less BPD occurred following FPD resuscitation (RR 0,68[0,48-0,96]-NNT 31).[25–29]

DR intubation was significantly reduced with FPD (RR 0,72[0,58-0,88]- NNT 13,4).[26–29] The need for advanced resuscitation(RR 0,50[0,23-1,11]),[26–28] five minutes Apgar score (MD 0,11[-0,19-0,41])[26–29], occurrences of heart rate >100 bpm at 2 minutes of life (RR 1,04[1,00-1,07])[27,28] and air leaks (RR 0,98[0,50-1,95])[25–29] were similar between groups.

Surfactant needs were lower in the FPD group (RR 0,79[0,64-0,96]- NNT 7,3).[26,28,29] Following FPD resuscitation, significant reductions in MV requirements (RR 0,81[0,67-0,96]- NNT 17) [26,28,29] and duration (MD -1,54 days[-3,03- -0,05]) were observed with FPD.[28,29] The duration of non-invasive ventilation was comparable between groups (MD -0,15 days[-1,46- +1,15]).[28,29] A shorter duration of oxygenotherapy was also reported in FPD group in Szyld et al. (MD -9,00 days[-13,02- -4,98]).[28]

Subgroup analysis focused on preterm infants gave results in the same direction without reaching the level of significance. Preterm infants resuscitated with FPD experienced a trend to decreased DR intubation (RR 0,84[0,69-1,03])[26,28,29] and MV requirements (RR 0,89[0,76-1,03)[26,28,29].

Similar incidence of preterm birth morbidities were reported by Thakur et al.[29]

Overall analysis, including RCTs with bundle interventions and cohort studies

The pooled estimate demonstrates a significant reduction in mortality with FPD compared with HDPD (OR 0,57[0,47-0,69]-NNT 12,7) without heterogenetity.[25–33]
A trend toward reduction of BPD with FPD was found (OR 0,70[0,48-1,02]) with moderate heterogeneity ($I^2 = 38\%$).[25–31]

Improvement of resuscitation efficiency markers with FPD compared to HDPD was confirmed in the overall analysis. DR intubation rates significantly decreased with FPD (OR 0,56[0,40-0,79]- NNT 7,5).[26–31,33] Apgar scores at 5 minutes were higher in the FPD group (MD 0,57[0,20-0,94]).[26–31,33] Air leaks were similar between groups (OR 0,82[0,44-1,52]).[26–31,33]

Early respiratory outcomes were also improved following resuscitation with FPD in the global analysis, with lower needs for surfactant (OR 0,67[0,55-0,82]- NNT 10,7)[26,28,29,33], a significant reduction in MV requirements (OR 0,58[0,42-0,80]- NNT 7,4)[26,28–33] and duration (MD -1,79 days[-2,91- -0,66]). Duration of oxygenotherapy was not significantly different between groups (MD -5,09 days[-12,63-+2,46]).[28,33]

The global analysis focused on preterm infants found statistically significant benefits with FPD: decreases in mortality (OR 0,57[0,46-0,69]- NNT 8,7)[25,26,29,31,33], DR intubation (OR 0,51[0,31-0,82]- NNT6,4)[26,28–31,33] and MV requirements (OR 0,60[0,46-0,78]- NNT 9,3)[26,28–31,33].

Among common morbidities of preterm birth, incidences of PDA requiring treatment[29–31,33], IVH[29–31,33], ROP[29,31] and NEC[30,31,33] were similar between groups. According to data from 3 publications[29,31,33], resuscitation with FPD was associated with a significant reduction in cPVL (OR 0,59[0,41-0,85]- NNT 26,6), without heterogeneity (I^2 = 0%).

Discussion

This systematic review and meta-analysis of 9 studies, including 3621 infants, demonstrated improved outcomes following support of neonatal transition with “fixed pressure devices” (mostly T-piece resuscitators) compared to “hand-driven pressure devices” (as self-inflating bags). Meta-analysis of 5 RCT demonstrated that FPD resuscitation is associated with significant reductions in BPD, intubation rate in DR, MV requirements and duration, and need for surfactant without increase in pneumothoraxes. Most of these benefits remained when the analysis was extended to RCTs with bundle intervention and cohort studies, with the added benefit of significant reductions in mortality and cPVL (figure 4). Those favourable outcomes were also demonstrated in preterm infants.

Differences between the devices potentially explain the benefits associated with FPD resuscitation. The main difference and most likely explanation is the provision of a constant PEEP with FPD. In animal studies, PEEP allows for a faster clearance of lung fluids and improves lung aeration. In contrast, airway collapse and fluid refilling at the end of expiration have been described without PEEP.[34] In addition to its impact on ventilation, lung aeration is a key determinant of pulmonary vascular transition.[1] In very preterm infants, early initiation of CPAP after birth compared with intubation reduces the combined risk of death or BPD.[35,36] Improvements in respiratory transition leading to lower DR intubation rates, and MV requirements and duration, may explain the reduction of BPD. Both mechanical ventilation and iatrogenic hypocapnia are recognized risk factors for cPVL.[37]

More consistent inflation pressures provided by FPD decrease the risk of very high tidal volumes.[9] Animal studies showed that a few large manual breaths early in resuscitation can initiate an inflammatory process and ultimately lead to BPD and brain injury.[38,39] Ventilation with high tidal volumes during resuscitation also exacerbated cerebral hemodynamic instability, brain inflammation and injury.[39,40] This could potentially be an additional factor explaining reductions in cPVL and BPD.

Patterns of insufflation pressure waveforms also differ between the types of devices, as illustrated by Tracy et al. in mannikins.[41] With T-piece resuscitators, pressure increase progressively while with self-inflating bags, the pressure rise has a sharp, needle-like aspect. The latter could lead to increased pharyngeal and pulmonary receptors stimulation triggering apnoeic reflexes.[42]

To generate pressure, HDPD require one hand to squeeze the bag, while one finger can occlude a TPR and no hand movement is required for ventilators. Trigeminocardiac reflexes differences resulting from different handling seems unlikely, as pressures applied to the face were similar in mannikin studies.[43] The risk of leaks increased with FPD.[9] An observational study reported comparable rates of airway obstruction with TPR and SIB.[44]

Recently, in parallel with this work, another systematic review and meta-analysis was carried out on behalf of the ILCOR.[17] Benefits from TPR reported in that study were restricted to shorter duration of PPV in DR and decreased risk of BPD, without impact on mortality or intubation in DR.

Among the differences between the two meta-analyses, our broad search strategy identified 5231 unique entries, compared to 908, and led to the inclusion of 4 additional studies.[25,30–32] The RCT of Menakaya et al.[25] compared a neonatal ventilator with an anaesthetic bag, both with facemasks, and fitted our search definition. Neonatal ventilators rely on a bias flow through a T-Piece for generation of fixed inflation pressures. Ng et al. conducted a small prospective cohort study before and after implementation of TPR in a NICU in Malaysia.[32] We retained the RCTs of Te-Pas et al.[31] and El-Chimi et al.[30] where TPR allowed for intervention bundles: sustained inflation (SI) versus standard inflations[30,31] and mask versus nasopharyngeal tube[31]. Recent meta-analyses found no difference between SI and conventional ventilation for neonatal resuscitation[45–47]. The largest study so far on SI was stopped following an increase in mortality in the SI group.[48] Facial mask or nasal tube used as ventilation interfaces led to similar intubation rates. However, airway obstruction and leaks were increased in the nasal tube group.[49] Hence, the impact of those interventions in the analysis would have been either neutral or unfavourable towards the FPD group, and therefore cannot explain the benefits found with FPD.

This systematic review and meta-analysis was conducted with several methodological strengths. We searched 4 databases with indexing terms as well as grey literature. There were no inclusion limits in terms of language.

Some limitations remain. The high number of outcomes could statistically lead to false positive results. They however are interrelated, reflect resuscitation effectiveness, respiratory evolution, and preterm infants' morbidities, are consistent with recent recommendations[24], and results are biologically plausible. Different study designs and heterogeneity of reported results complicated the realization of the meta-analysis. The potential impact of including studies with multiple interventions has been discussed above. Inclusion of prospective cohorts complement the findings of RCTs and provides evidence based on real-world data. To account for those, a more conservative random-effect analysis was computed in the overall analysis.[19] While the protocol did not plan to include long-term outcomes such as cerebral palsy, blindness and neurodevelopmental impairment, no study reported on those.

Use of PEEP-valve or not was not distinguished in our meta-analysis. Szyld et al. performed a subgroup analysis of self-inflating bag with or without a PEEP valve and found results comparable to those from the whole cohort.[28]

Conclusion

This review and meta-analysis compared the use of fixed pressure devices (such as T-piece resuscitators) and hand driven pressure devices (such as self-inflating bags). Resuscitation at birth with FPD appears to improve respiratory transition and may contribute to resuscitation strategies aiming to protect lung and brain.

We found significant reductions in BPD, DR intubation, mechanical ventilation and need for surfactant without increased morbidity, including pneumothorax. Expending the analysis with bundled intervention RCT and prospective cohorts additionally suggests decreases in mortality and cPVL. However, the certainty of evidence according to GRADE is very low to moderate and further studies are needed to confirm those results and to complete data about comorbidities of prematurity and HIE. Where possible, FPD should prevail to support neonatal transition.

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Statement of Ethics

The research was conducted ethically in accordance with the Declaration of Helsinki ethical principles. The paper is exempt from ethical committee approval. All data were collected and synthesised from previous clinical trials for which informed consent had already been obtained by the trial investigators.

The protocol was registered with the Prospective Register of Systematic Reviews (registered July 11,2020;CRD42020191685).

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

ST and NH: search strategy, data selection and analysis. ST manuscript draft and editions. VR: data interpretation, manuscript editions. All authors reviewed and approved the manuscript.

Data Availability Statement

All data generated or analysed are included in this article and its supplementary material. Enquiries can be directed to the corresponding author.

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Figure and table legends

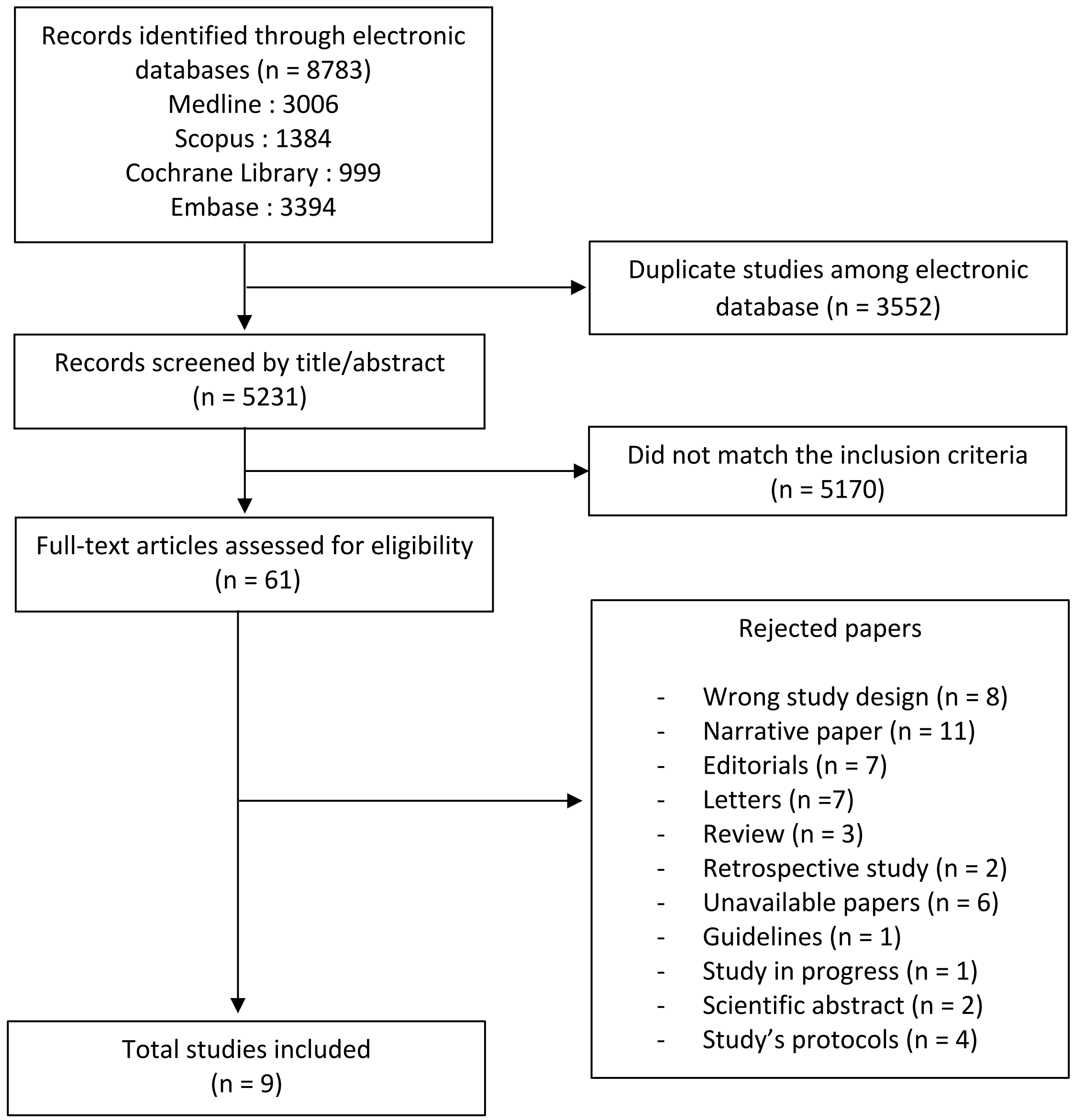
Figure 1. Flow chart of study inclusion.

Figure 2. Forest plots of main outcomes.

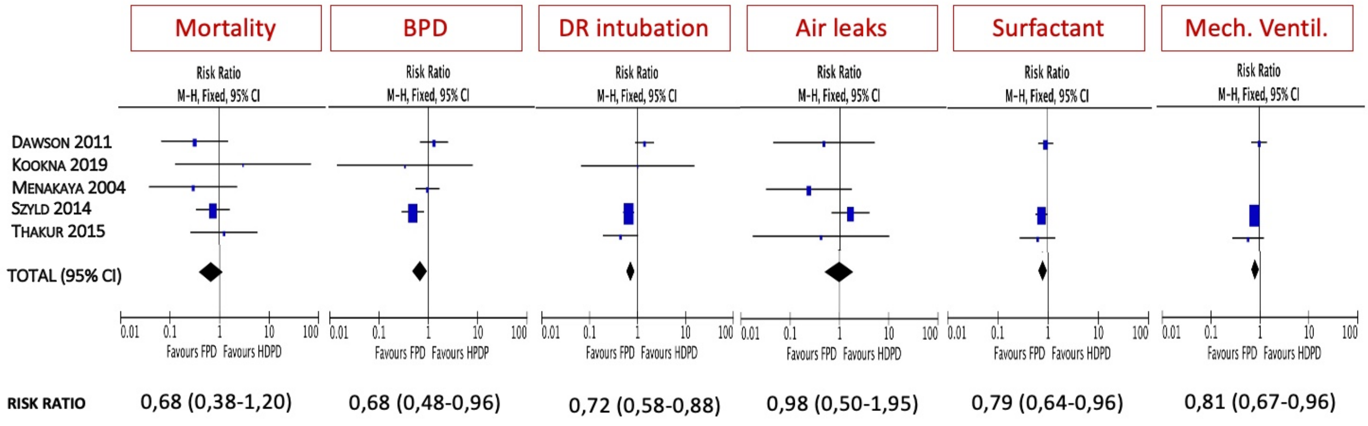
Figure 3. Summary of the outcomes of RCTs and qRCTs analysis (summary of the overall analysis are available in online additional data).

Figure 4. Potential pathways explaining the benefits of TPR use.

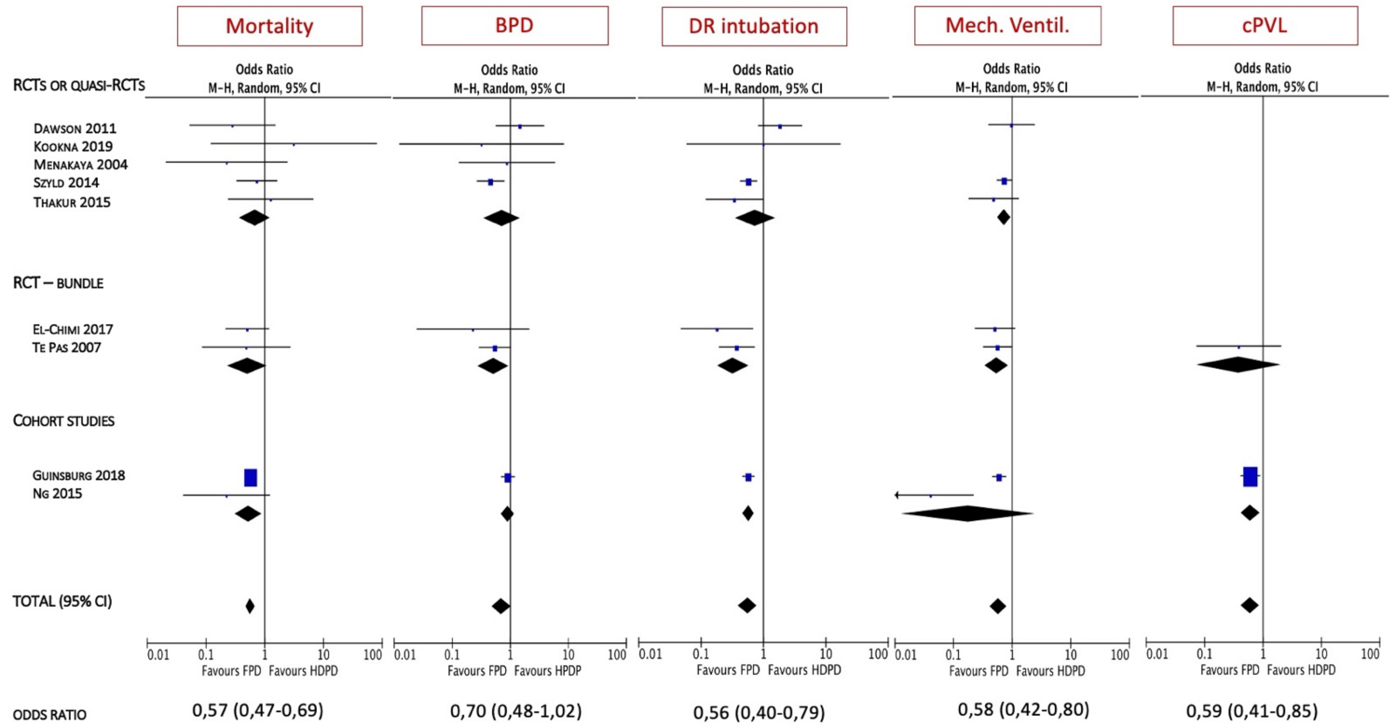
Table 1. Features of included studies.


Records identified through electronic databases (n = 8783)
Medline : 3006
Scopus : 1384
Cochrane Library : 999
Embase : 3394
Duplicate studies among electronic database (n = 3552)
Records screened by title/abstract (n = 5231)
Did not match the inclusion criteria (n = 5170)
Full-text articles assessed for eligibility (n = 61)
Rejected papers
- Wrong study design (n = 8)
- Narrative paper (n = 11)
- Editorials (n = 7)
- Letters (n =7)
- Review (n = 3)
- Retrospective study (n = 2)
- Unavailable papers (n = 6)
- Guidelines (n = 1)
- Study in progress (n = 1)
- Scientific abstract (n = 2)
- Study's protocols (n = 4)
Total studies included (n = 9)

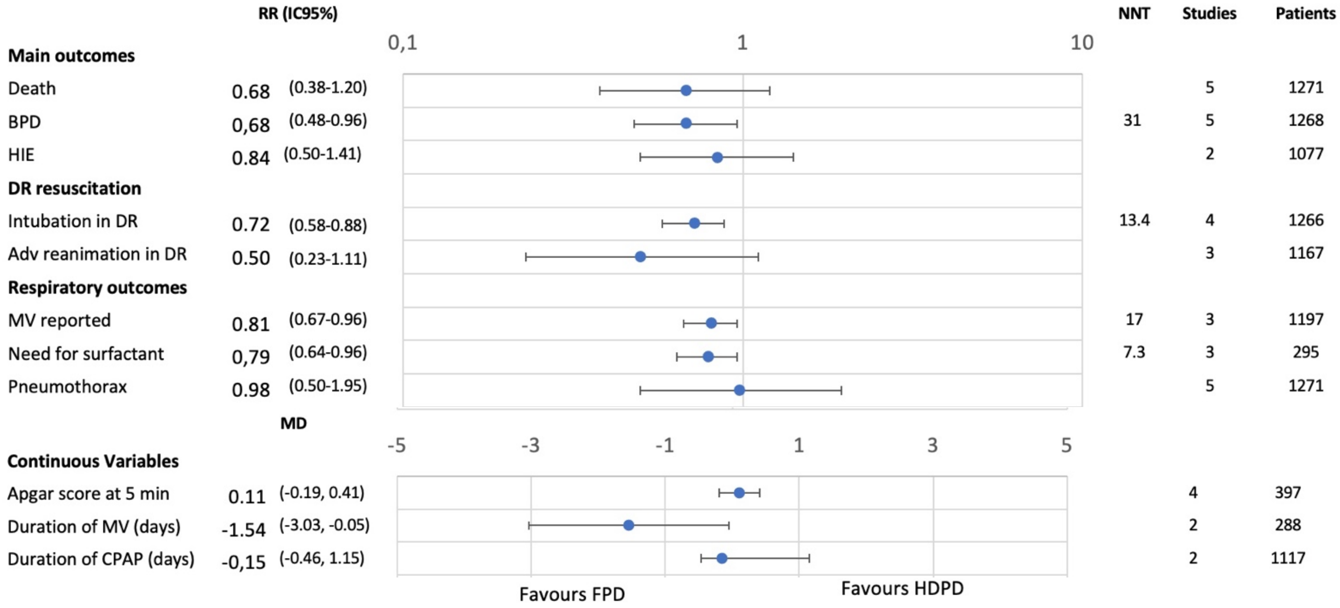
RCTs and qRCTs analysis



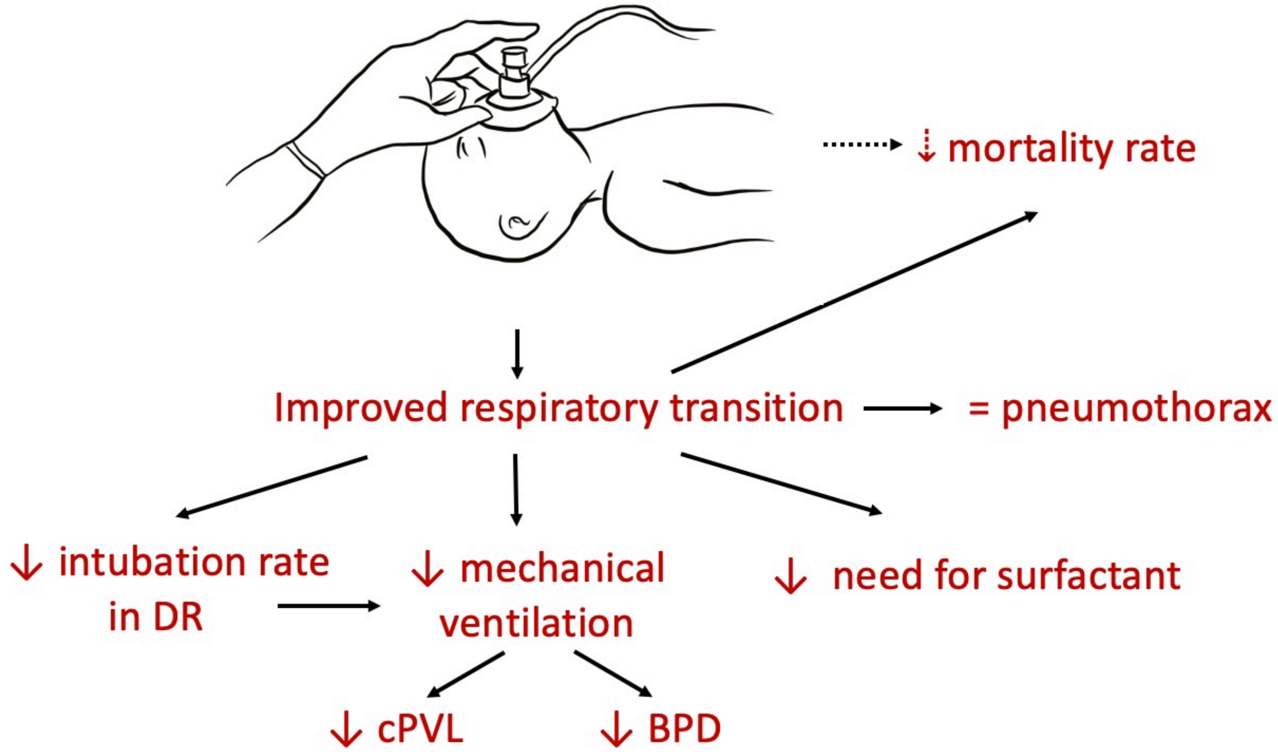
Overall analysis, including RCTs with bundle interventions and cohort studies



BPD: bronchopulmonary dysplasia; DR: delivery room; Mech. Ventil.: mechanical ventilation; cPVL: cystic periventricular leukomalacia



RR: risk ratio – IC: interval confidence – BPD: bronchopulmonary dysplasia – HIE: hypoxic-ischemic encephalopathy – DR: delivery room – Adv: advanced – MV: mechanical ventilation – CPAP: continuous positive air pressure


⇣ mortality rate
Improved respiratory transition
= pneumothorax
↓ intubation rate in DR
↓ mechanical ventilation
↓ need for surfactant
↓ cPVL
↓ BPD

	Study	N	Study population (Intervention/Control)	Intervention vs control	Inclusion criteria	Outcomes
RCT	**Menakaya 2004** [24] Monocentric	24	- n: 11/13 - mean (range) BW (g): 805 (510-1164) / 758 (408-1052) - median (range) GA (weeks): 26 (24-27) / 26 (24-27) - male sex (%): 55/54 - antenatal steroids (%): 100/100	**Infant ventilator (Dräger Babylog)** versus **Standard anesthetic rebreathing bag (500 ml)** Randomization before birth	- GA 24-27 wGA - singletons Exclusion criteria: - congenital thoracic abnormalities	- respiratory mechanics (PEEP – PiP – eVt) - age at intubation - PCO_2 and FIO_2 on admission - mortality - oxygen at 36 weeks and/or death - airleaks
	Dawson 2011 [25] Monocentric	80	- n: 41/39 - mean ± SD GA (weeks): 27 ± 1/ 27 ± 1 (p=0,71) - mean ± SD BW (g): 873 ± 236/889 ± 206 (p=0,52) - male sex (%): 54/59 (p=0,63)	**TPR** (Néopuff©) Versus SIB - PEEP-valve (240 ml) Randomization before birth	- GA < 29 wGA - receiving PPV in DR in the first 5 minutes after birth Exclusion criteria: - uncertainty about gestational age - congenital abnormality	- oxygen saturation at 1, 2 and 5 minutes - heart rate at 1 and 5 minutes - oxygen delivery - rate of CPAP, intubation, chest compressions and surfactant administration in DR - in NICU: intubation rate, BPD, mortality, surfactant administration, combined death/IVH - respiratory variables
	Kookna 2019 [26] Monocentric	50	- n: 25/25 - mean ± SD GA (weeks): 38,88 ± 1,56/ 38,28 ± 1,95 (p=0,23) - male sex (%): 68/48 (p=0,25)	**TPR** (Néopuff©) Versus **SIB** Randomization **before birth**	- GA ≥ 28 wGA requiring PPV (apnea, gasping, HR < 100/min, desaturation despite CPAP) Exclusion criteria: - gross congenital malformation, diaphragmatic hernia or heart disease	- HR, SpO2 and RR at different time in DR - in DR: intubation and chest compression rate - Apgar at 1, 5 and 10 min - duration of PPV in DR - meconium inhalation syndrome, respiratory distress, HIE, BPD - pneumothorax - sequelae, death
Quasi-RCT	**Szyld 2014** [27] Multicentric	1027	- n: 511/516 - mean ± SD GA (weeks): 36 ± 4,1/ 36 ± 4,4 (p=0,539) - mean ± SD BW (g): 2720 ± 1025 / 2686 ± 1069 (p=0,619) - male sex (%): 59/58 (p=0,616) - antenatal steroids (%): 27/30 (p=0,405)	**TPR** (Néopuff©) Versus **SIB +/- PEEP-valve** (300 ml) Randomization in a 2-period cross-over trial	- GA ≥ 26 wGA requiring PPV at birth Exclusion criteria: - immediate endotracheal intubation - major congenital malformation - multiple birth	- proportion of infants with HR ≥ 100/min at 2 minutes - elapsed time to HR ≥ 100/min, time to spontaneous breathing, SpO2 at 2 min - intubation rate after failure of PPV - chest compression and/or drugs rate - airleaks - duration of oxygen administration, mechanical and non-invasive ventilation - HIE, BPD, mortality
	Thakur 2015 [28] Monocentric	90	- n: 40/50 - mean ± SD GA (weeks): 34,3 ± 3,7/ 35,1 ± 3,6 (p=0,27) - mean ±SD BW (g): 2065 ± 814 / 2264 ± 872 (p=0,26) - male sex (%): 50/64 (p=0,20) - antenatal steroids (%): 68,4/72,2 (p=0,80)	**TPR** (Néopuff©) Versus **SIB - PEEP-valve** Randomization before birth	- GA ≥ 26 wGA requiring PPV at birth Exclusion criteria: - chorioamnionitis, meconium amniotic fluid - major congenital anomalies	- duration of PPV in DR - intubation rate in DR - respiratory distress - need for MV within 48h and its duration - need for surfactant - mortality

RCT with bundle interventions	**Te-Pas 2013** [30] Monocentric	207	- n: 104/103 - mean ± SD GA (weeks): 29,4 ± 1,9/ 29,5 ± 1,9 - mean ± SD BW (g): 1311 ± 403 / 1290 ± 392 - male sex (%): 54/55 - antenatal steroids (%): 82/81	**TPR** (Néopuff©) + **nasopharyngeal tube** with **sustained inflation** (10 sec) Versus **SIB** + face **mask** Randomization before birth	- inborn infants GA < 33 wGA Exclusion criteria: - major congenital anomalies	- intubation rate within 72 hours - intubation rate in DR - need for MV, surfactant administration - death, BPD, IVH, cPVL, ROP, PDA, NEC
	El-Chimi 2017 [29] Monocentric	112	- n: 57/55 - mean ± SD GA (weeks): 31,5 ± 1,7/ 31,3 ± 1,7 (p=0,55) - mean ±SD BW (g): 1561 ± 326 / 1510 ± 319 (p=0,4) - male sex (%): 54/47 (p=0,452) - antenatal steroids (%): 39/34,5 (p=0,323)	**TPR** (Néopuff©) with **sustained inflation** (15 sec) Versus **SIB** Randomization before birth	- preterm requiring PPV at birth	- Success: no need for any further ventilatory support, need for exclusive nCPAP, or need for intubation beyond the first 72 hours after delivery - occurrence of air leaks, BPD, IVH, PDA, NEC
Prospective studies	**Ng 2015** [31] Monocentric	50	- n: 25/25 - mean BW (g): 1560/1460	**TPR** (Néopuff©) with **sustained inflation** (15 sec) Versus **SIB** Pre/Post-implementation	- neonates requiring PPV at birth Exclusion criteria: - major congenital anomalies	- intubation rate - need for MV and NIV and duration - mortality - length stay at hospital
	Guinsburg 2018 [32] Multicentric	1962	- n: 1456/506 - mean ±SD GA (weeks): 28,2 ± 2,5/ 27,8 ± 2,7 (p=0,005) - mean ±SD BW (g): 969 ± 277 / 941 ± 279 (p=0,968) - male sex (%): 51/51 (p=0,945) - antenatal steroids (%): 77/69 (p=0,001)	**TPR** (Néopuff© or Babypuff©) Versus **SIB – PEEP-valve** At discretion of resuscitation team	- infants $23^{0/7}$-$33^{6/7}$ wGA and BW 400-1499 g requiring PPV at birth Exclusion criteria: - major congenital anomalies - transfer until 27 days of life	- survival to hospital discharge without BPD, IVH grades III–IV and cPVL - Apgar score at 5 minutes - endotracheal or CPAP in DR - airleaks - need for surfactant - need for MV and duration - PDA, BPD, sepsis, IVH, cPVL, ROP, NEC, death

TPR: T-piece resuscitation – SIB: self-inflating bag – w GA: weeks of gestational age – PEEP: Positive end-expiratory pressure – PiP: Positive insufflatory pressure – eVt: tidal volume – PPV: positive pressure ventilation – DR: delivery room – HR: heart rate – RR: respiratory rate – MV: mechanical ventilation – NIV: non-invasive ventilation – HIE: hypoxic-ischemic encephalopathy – BPD: bronchopulmonary dysplasia – IVH: intraventricular hemorrhage – NEC: necrotizing enterocolitis – ROP: retinopathy of prematurity – PDA: patent ductus arteriosus – cPVL: cystic periventricular leukomalacia

Additional data

eFig 1. Search strategies

eFig 2. Risk of Bias and quality assessment

eFig 3. GRADE assessment

eFig 4. Forest plots

eFig 1

Database: **Ovid MEDLINE(R)** and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions(R) <1946 to January 19, 2022>
Search Strategy:
----
1 (t piece or t-piece or neopuff or neo tee or babypuff or neotee or tom thumb).ti,ab,kf. (675)
2 (((self or flow) adj3 bag*) or mask*).ti,ab,kf. (90664)
3 manual ventilation.ti,ab,kf. (442)
4 (positive adj3 (pressure or ventilation)).ti,ab,kf. (30797)
5 exp Infant/ or (infan* or Neonat* or Newborn* or Prematur* or Preterm or (low adj3 weight*)).ti,ab,kf. (1677278)
6 Delivery Rooms/ or (delivery room* or birth or resuscitation).ti,ab,kf. (387460)
7 exp Positive-Pressure Respiration/ae, is, mt, mo [Adverse Effects, Instrumentation, Methods, Mortality] (10680)
8 Ventilators, Mechanical/ (9422)
9 1 or 2 or 3 or 4 or 7 or 8 (131755)
10 5 and 6 and 9 (3006)

Scopus (1,384 document results)

(TITLE-ABS-KEY (manual AND ventilation) OR TITLE-ABS-KEY (t AND piece OR neopuff OR neo AND tee OR babypuff OR neotee OR tom AND thumb) OR TITLE-ABS-KEY ((self OR flow) W/3 bag*) OR TITLE-ABS-KEY (positive W/3 (pressure OR ventilation)) AND TITLE-ABS-KEY (infan* OR neonat* OR newborn* OR prematur* OR preterm OR (low W/3 weigh t*)) AND TITLE-ABS-KEY (delivery AND room* OR birth OR resuscitation))

Embase

....

No. Query Results	Results
#9. #1 AND #7 AND #8	3,394
#8. #2 OR #3 OR #4 OR #5 OR #6	203,473
#7. 'delivery room' OR birth	516,157
#6. 'positive pressure ventilation'	12,839
#5. 'manual emergency ventilator'	754
#4. (self OR flow) AND inflating AND bag	324
#3. 'ventilator'	68,006
#2. t AND piece OR 't piece' OR neopuff OR (neo AND tee) OR babypuff OR neotee OR (tom AND thumb)	7,356
#1. 'infant'/exp OR 'infant' OR 'newborn'/exp OR 'newborn' OR 'prematurity'/exp OR 'prematurity'	1,447,060

....

eFig 2.

	Menakaya 2004 [24]	Dawson 2011 [25]	Kookna 2019 [26]	Szyld 2014 [27]	Thakur 2015 [28]	Te Pas 2007 [30]	El-Chimi 2016 [29]
Randomisation process	+	+	+	-	-	+	-
Deviations from the intended intervention	?	?	?	?	?	?	?
Missing outcome data	+	+	+	+	+	+	+
Measurement of the outcome	+	+	-	+	+	+	+
Selection of the reported result	+	+	+	+	+	+	+
OVERALL	!	!	-	-	-	!	-

		Ng 2015 [31]	Guinsburg 2018 [32]
A			
	Representativeness of the exposed cohort	+	+
	Selection of the non-exposed cohort	+	+
	Ascertainment of exposure	+	+
	Demonstration that outcome of interest was not present at start of study	+	+
B			
	Comparability of cohorts on the gestational age	NC	-
	Comparability of cohorts for any additional factor	+	-
C			
	Assessment of outcome	+	+
	Was follow-up long enough for outcomes to occur (mortality, HIE, BPD)	+	+
	Adequacy of follow up of cohorts	+	+
TOTAL		!	!

eFig 3. - **Question:** Fixed Pressure Devices compared to Hand Driven Pressure Devices for neonatal resuscitation at birth

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Fixed Pressure Devices	Hand Driven Pressure Devices	Relative (95% CI)	Absolute (95% CI)		
Mortality in all studies												
9	observational studies and RCTs	serious	not serious	not serious	not serious	none	490/2270 (21.6%)	282/1332 (21.2%)	**OR 0.57** (0.47 to 0.69)	**79 fewer per 1 000** (from 100 fewer to 55 fewer)	⨁◯◯◯ Very low	CRITICAL
BPD in RCTs or quasi-RCTs												
5	randomised trials	serious	not serious	not serious	serious (a)	none	43/627 (6.9%)	64/641 (10.0%)	**RR 0.68** (0.48 to 0.96)	**32 fewer per 1 000** (from 52 fewer to 4 fewer)	⨁⨁◯◯ Low	IMPORTANT
Intubation in delivery room in RCTs or quasi-RCTs												
4	randomised trials	serious	not serious	not serious	not serious	none	119/625 (19.0%)	171/641 (26.7%)	**RR 0.72** (0.58 to 0.88)	**75 fewer per 1 000** (from 112 fewer to 32 fewer)	⨁⨁⨁◯ Moderate	IMPORTANT
Mechanical ventilation reported in RCTs or quasi-RCTs												
3	randomised trials	serious	not serious	not serious	not serious	none	149/592 (25.2%)	188/605 (31.1%)	**RR 0.81** (0.67 to 0.96)	**59 fewer per 1 000** (from 103 fewer to 12 fewer)	⨁⨁⨁◯ Moderate	IMPORTANT
Airleaks in RCTs or quasi-RCTs												
5	randomised trials	serious	not serious	not serious	not serious	none	15/628 (2.4%)	16/643 (2.5%)	**RR 0.98** (0.50 to 1.95)	**0 fewer per 1 000** (from 12 fewer to 24 more)	⨁⨁⨁◯ Moderate	IMPORTANT
Need for surfactant in RCTs or quasi-RCTs												
3	randomised trials	serious	not serious	not serious	serious (a)	none	70/137 (51.1%)	103/158 (65.2%)	**RR 0.78** (0.64 to 0.96)	**143 fewer per 1 000** (from 235 fewer to 26 fewer)	⨁⨁◯◯ Low	NOT IMPORTANT(b)
cPVL in all studies												
3	observational studies	serious	not serious	not serious	not serious	none	97/1353 (7.2%)	51/526 (9.7%)	**OR 0.59** (0.41 to 0.85)	**37 fewer per 1 000** (from 55 fewer to 13 fewer)	⨁◯◯◯ Very low	CRITICAL

(a) **Number of patients below the optimal information size.**
(b) Important in low resources settings

CI: confidence interval; **OR:** odds ratio; **RR:** risk ratio; RCT: randomized controlled trials, BPD bronchopulmonary dysplasia; cPVL: cystic periventricular leukomalacia.

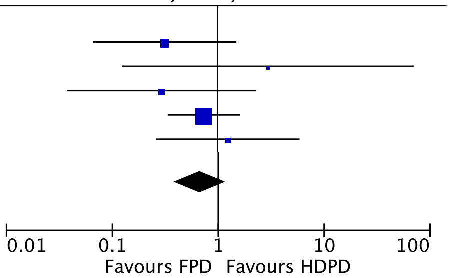
eFig 4 : forest plots

RCTs and qRCTs analysis

Mortality[24–28]

Study or Subgroup	FPD Events	FPD Total	HDPD Events	HDPD Total	Weight	Risk Ratio M-H, Fixed, 95% CI
3.1.1 RCT						
Dawson 2011	2	41	6	39	22.0%	0.32 [0.07, 1.48]
Kookna 2019	1	25	0	25	1.8%	3.00 [0.13, 70.30]
Menakaya 2014	1	11	4	13	13.1%	0.30 [0.04, 2.27]
Szyld 2014	11	511	15	516	53.5%	0.74 [0.34, 1.60]
Thakur 2015	3	40	3	50	9.6%	1.25 [0.27, 5.86]
Total (95% CI)		**628**		**643**	**100.0%**	**0.68 [0.38, 1.20]**
Total events	18		28			

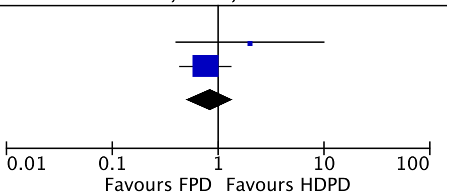
Heterogeneity: $Chi^2 = 3.08$, df = 4 (P = 0.54); $I^2 = 0\%$
Test for overall effect: Z = 1.34 (P = 0.18)
Test for subgroup differences: Not applicable



HIE[26,27]

Study or Subgroup	FPD Events	FPD Total	HDPD Events	HDPD Total	Weight	Risk Ratio M-H, Fixed, 95% CI
3.8.1 RCTs						
Kookna 2019	4	25	2	25	6.7%	2.00 [0.40, 9.95]
Szyld 2014	21	511	28	516	93.3%	0.76 [0.44, 1.32]
Total (95% CI)		**536**		**541**	**100.0%**	**0.84 [0.50, 1.41]**
Total events	25		30			

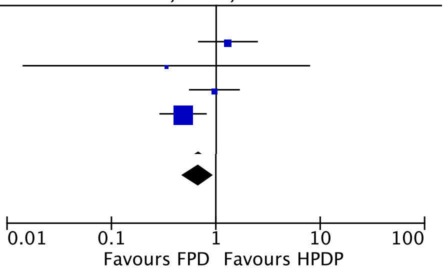
Heterogeneity: $Chi^2 = 1.26$, df = 1 (P = 0.26); $I^2 = 21\%$
Test for overall effect: Z = 0.66 (P = 0.51)
Test for subgroup differences: Not applicable



BPD[24–28]

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
2.1.1 RCT						
Dawson 2011	15	41	11	39	17.6%	1.30 [0.68, 2.47]
Kookna 2019	0	25	1	25	2.3%	0.33 [0.01, 7.81]
Menakaya 2014	7	10	8	11	11.9%	0.96 [0.56, 1.66]
Szyld 2014	21	511	44	516	68.2%	0.48 [0.29, 0.80]
Thakur 2015	0	40	0	50		Not estimable
Total (95% CI)		**627**		**641**	**100.0%**	**0.68 [0.48, 0.96]**
Total events	43		64			

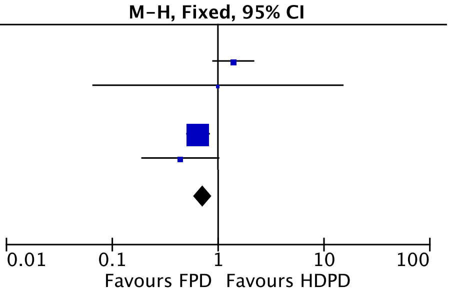
Heterogeneity: $Chi^2 = 7.45$, df = 3 (P = 0.06); $I^2 = 60\%$
Test for overall effect: Z = 2.22 (P = 0.03)
Test for subgroup differences: Not applicable



Intubation in DR[25–28]

Study or Subgroup	FPD Events	FPD Total	HDPD Events	HDPD Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.1.1 RCT						
Dawson 2011	26	49	19	50	11.2%	1.40 [0.90, 2.17]
Kookna 2019	1	25	1	25	0.6%	1.00 [0.07, 15.12]
Menakaya 2014	0	0	0	0		Not estimable
Szyld 2014	86	511	134	516	79.2%	0.65 [0.51, 0.83]
Thakur 2015	6	40	17	50	9.0%	0.44 [0.19, 1.01]
Total (95% CI)		**625**		**641**	**100.0%**	**0.72 [0.58, 0.88]**
Total events	119		171			

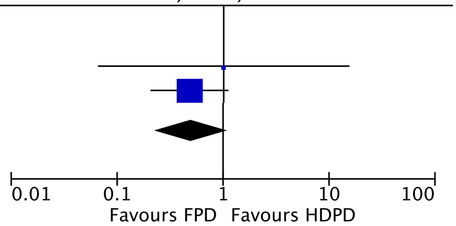
Heterogeneity: $Chi^2 = 10.82$, df = 3 (P = 0.01); $I^2 = 72\%$
Test for overall effect: Z = 3.21 (P = 0.001)
Test for subgroup differences: Not applicable



Need for advanced resuscitation [25–27]

Study or Subgroup	FPD Events	FPD Total	HDPD Events	HDPD Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.6.1 RCT						
Dawson 2011	0	40	0	50		Not estimable
Kookna 2019	1	25	1	25	5.6%	1.00 [0.07, 15.12]
Szyld 2014	8	511	17	516	94.4%	0.48 [0.21, 1.09]
Total (95% CI)		**576**		**591**	**100.0%**	**0.50 [0.23, 1.11]**
Total events	9		18			

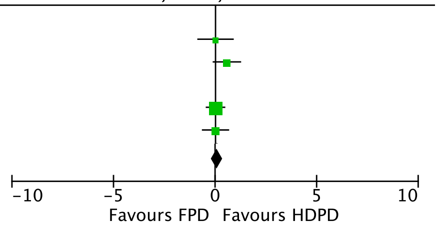
Heterogeneity: Chi² = 0.26, df = 1 (P = 0.61); I² = 0%
Test for overall effect: Z = 1.70 (P = 0.09)
Test for subgroup differences: Not applicable



Five minutes Apgar score [25–28]

Study or Subgroup	FPD Mean	FPD SD	FPD Total	HDPD Mean	HDPD SD	HDPD Total	Weight	Mean Difference IV, Fixed, 95% CI
3.7.1 RCT								
Dawson 2011	7	1.54	41	7	2.3	39	12.1%	0.00 [−0.86, 0.86]
Kookna 2019	8.64	1.2	25	8.08	1.2	25	20.4%	0.56 [−0.11, 1.23]
Menakaya 2014	0	0	0	0	0	0		Not estimable
Szyld 2014	8	1.5	76	8	1.5	101	45.2%	0.00 [−0.45, 0.45]
Thakur 2015	8	1.53	40	8	1.53	50	22.3%	0.00 [−0.64, 0.64]
Total (95% CI)			**182**			**215**	**100.0%**	**0.11 [−0.19, 0.41]**

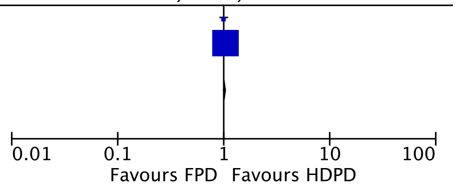
Heterogeneity: Chi² = 2.17, df = 3 (P = 0.54); I² = 0%
Test for overall effect: Z = 0.74 (P = 0.46)
Test for subgroup differences: Not applicable



Occurrences of heart rate >100 bpm at 2 minutes of life [26,27]

Study or Subgroup	FPD Events	FPD Total	HDPD Events	HDPD Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Kookna 2019	25	25	25	25	5.2%	1.00 [0.93, 1.08]
Szyld 2014	479	511	466	516	94.8%	1.04 [1.00, 1.08]
Total (95% CI)		**536**		**541**	**100.0%**	**1.04 [1.00, 1.07]**
Total events	504		491			

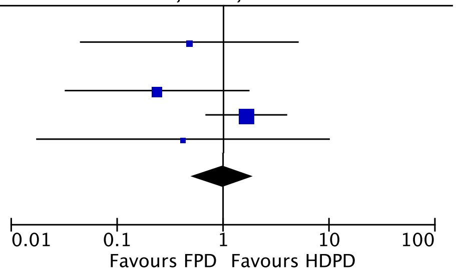
Heterogeneity: Chi² = 0.84, df = 1 (P = 0.36); I² = 0%
Test for overall effect: Z = 2.01 (P = 0.04)



Air leaks [24–28]

Study or Subgroup	FPD Events	FPD Total	HDPD Events	HDPD Total	Weight	Risk Ratio M-H, Fixed, 95% CI
3.2.1 RCT						
Dawson 2011	1	41	2	39	12.9%	0.48 [0.04, 5.04]
Kookna 2019	0	25	0	25		Not estimable
Menakaya 2014	1	11	5	13	28.8%	0.24 [0.03, 1.73]
Szyld 2014	13	511	8	516	50.0%	1.64 [0.69, 3.93]
Thakur 2015	0	40	1	50	8.4%	0.41 [0.02, 9.91]
Total (95% CI)		**628**		**643**	**100.0%**	**0.98 [0.50, 1.95]**
Total events	15		16			

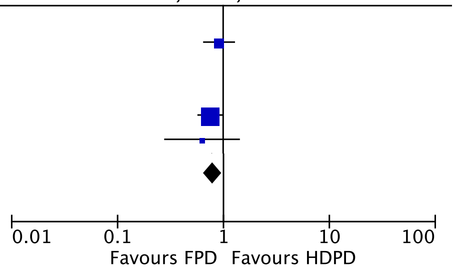
Heterogeneity: Chi² = 3.94, df = 3 (P = 0.27); I² = 24%
Test for overall effect: Z = 0.05 (P = 0.96)
Test for subgroup differences: Not applicable



Surfactant needs [25,27,28]

Study or Subgroup	FPD Events	FPD Total	HDPD Events	HDPD Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.2.1 RCT						
Dawson 2011	25	41	26	39	28.1%	0.91 [0.66, 1.27]
Kookna 2019	0	0	0	0		Not estimable
Menakaya 2014	0	0	0	0		Not estimable
Szyld 2014	39	77	68	101	62.1%	0.75 [0.58, 0.97]
Thakur 2015	6	19	9	18	9.8%	0.63 [0.28, 1.42]
Total (95% CI)		**137**		**158**	**100.0%**	**0.79 [0.64, 0.96]**
Total events	70		103			

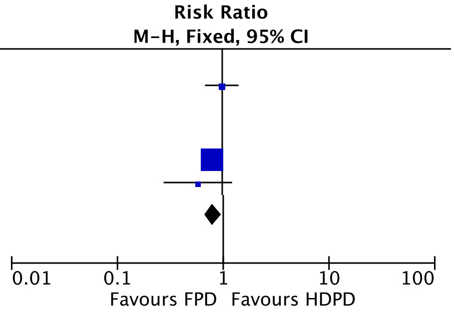
Heterogeneity: Chi² = 1.20, df = 2 (P = 0.55); I² = 0%
Test for overall effect: Z = 2.36 (P = 0.02)
Test for subgroup differences: Not applicable



Mechanical ventilation requirements[25,27,28]

Study or Subgroup	FPD Events	FPD Total	HDPD Events	HDPD Total	Weight	Risk Ratio M-H, Fixed, 95% CI
3.9.1 RCT						
Dawson 2011	25	41	24	39	13.2%	0.99 [0.70, 1.40]
Kookna 2019	0	0	0	0		Not estimable
Menakaya 2014	0	0	0	0		Not estimable
Szyld 2014	116	511	147	516	78.6%	0.80 [0.65, 0.98]
Thakur 2015	8	40	17	50	8.1%	0.59 [0.28, 1.22]
Total (95% CI)		**592**		**605**	**100.0%**	**0.81 [0.67, 0.96]**
Total events	149		188			

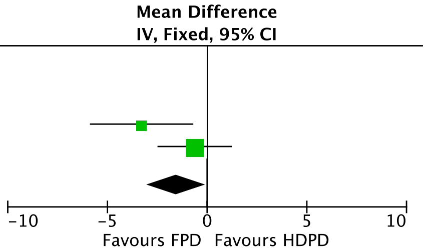
Heterogeneity: $Chi^2 = 2.08$, df = 2 (P = 0.35); $I^2 = 4\%$
Test for overall effect: Z = 2.36 (P = 0.02)
Test for subgroup differences: Not applicable



Mechanical ventilation duration[27,28]

Study or Subgroup	FPD Mean	FPD SD	FPD Total	HDPD Mean	HDPD SD	HDPD Total	Weight	Mean Difference IV, Fixed, 95% CI
1.3.1 RCT								
Dawson 2011	0	0	0	0	0	0		Not estimable
Menakaya 2014	0	0	0	0	0	0		Not estimable
Szyld 2014	5	7.6	116	8.3	13.3	147	33.9%	-3.30 [-5.86, -0.74]
Thakur 2015	1.53	1.6	8	2.17	3.06	17	66.1%	-0.64 [-2.47, 1.19]
Total (95% CI)			**124**			**164**	**100.0%**	**-1.54 [-3.03, -0.05]**

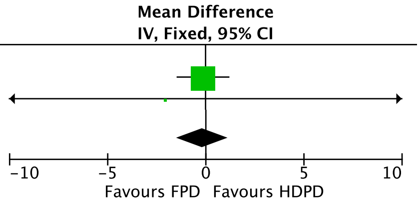
Heterogeneity: $Chi^2 = 2.75$, df = 1 (P = 0.10); $I^2 = 64\%$
Test for overall effect: Z = 2.03 (P = 0.04)
Test for subgroup differences: Not applicable



Non-invasive ventilation duration[27,28]

Study or Subgroup	FPD Mean	FPD SD	FPD Total	HDPD Mean	HDPD SD	HDPD Total	Weight	Mean Difference IV, Fixed, 95% CI
1.4.1 RCTs								
Szyld 2014	7.83	11.3	511	7.96	10.1	516	98.9%	-0.13 [-1.44, 1.18]
Thakur 2015	27.1	30.76	40	29.15	28.6	50	1.1%	-2.05 [-14.45, 10.35]
Total (95% CI)			**551**			**566**	**100.0%**	**-0.15 [-1.46, 1.15]**

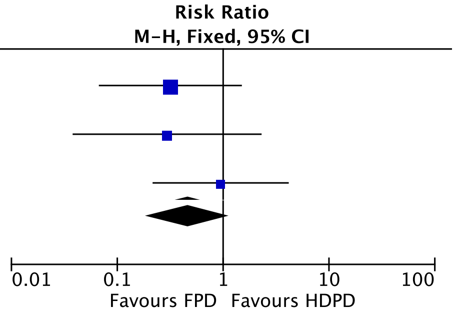
Heterogeneity: $Chi^2 = 0.09$, df = 1 (P = 0.76); $I^2 = 0\%$
Test for overall effect: Z = 0.23 (P = 0.82)
Test for subgroup differences: Not applicable



Mortality in preterm infants[24,25,28]

Study or Subgroup	FPD Events	FPD Total	HDPD Events	HDPD Total	Weight	Risk Ratio M-H, Fixed, 95% CI
3.10.1 RCTs						
Dawson 2011	2	41	6	39	47.7%	0.32 [0.07, 1.48]
Kookna 2019	0	0	0	0		Not estimable
Menakaya 2014	1	11	4	13	28.4%	0.30 [0.04, 2.27]
Szyld 2014	0	0	0	0		Not estimable
Thakur 2015	3	19	3	18	23.9%	0.95 [0.22, 4.10]
Total (95% CI)		**71**		**70**	**100.0%**	**0.46 [0.18, 1.15]**
Total events	6		13			

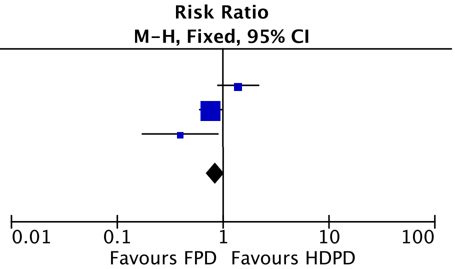
Heterogeneity: $Chi^2 = 1.34$, df = 2 (P = 0.51); $I^2 = 0\%$
Test for overall effect: Z = 1.66 (P = 0.10)
Test for subgroup differences: Not applicable



DR intubation in preterm infants[25,27,28]

Study or Subgroup	FPD Events	FPD Total	HDPD Events	HDPD Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.9.1 RCTs						
Dawson 2011	26	49	19	50	19.3%	1.40 [0.90, 2.17]
Szyld 2014	45	85	76	110	68.0%	0.77 [0.61, 0.97]
Thakur 2015	5	19	12	18	12.7%	0.39 [0.17, 0.90]
Total (95% CI)		**153**		**178**	**100.0%**	**0.84 [0.69, 1.03]**
Total events	76		107			

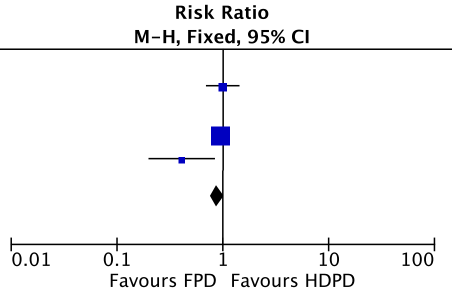
Heterogeneity: $Chi^2 = 8.93$, df = 2 (P = 0.01); $I^2 = 78\%$
Test for overall effect: Z = 1.68 (P = 0.09)
Test for subgroup differences: Not applicable



MV requirements in preterm infants(RR 0,89[0,76-1,03)[25,27,28].

Study or Subgroup	FPD Events	FPD Total	HDPD Events	HDPD Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.7.1 RCT						
Dawson 2011	25	41	24	39	21.8%	0.99 [0.70, 1.40]
Menakaya 2014	0	0	0	0		Not estimable
Szyld 2014	62	85	85	110	65.5%	0.94 [0.80, 1.11]
Thakur 2015	6	19	14	18	12.7%	0.41 [0.20, 0.82]
Total (95% CI)		**145**		**167**	**100.0%**	**0.89 [0.76, 1.03]**
Total events	93		123			

Heterogeneity: $Chi^2 = 5.66$, df = 2 (P = 0.06); $I^2 = 65\%$
Test for overall effect: Z = 1.59 (P = 0.11)
Test for subgroup differences: Not applicable

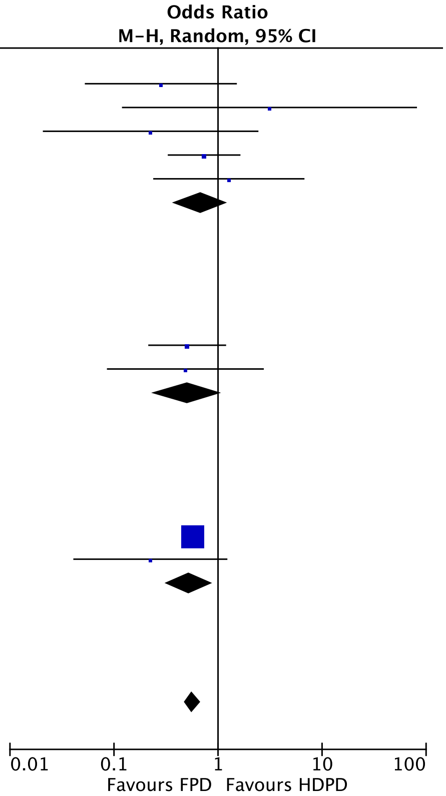


Overall analysis, including RCTs with bundle interventions and cohort studies

Mortality[24–32]

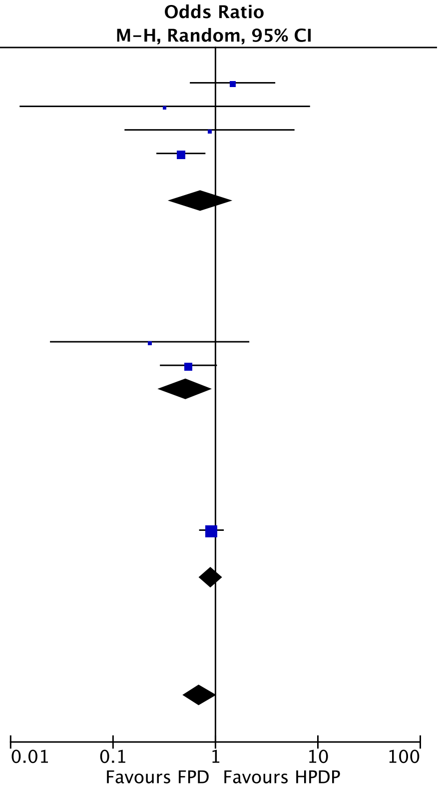
Study or Subgroup	FPD Events	FPD Total	HDPD Events	HDPD Total	Weight	Odds Ratio M-H, Random, 95% CI
3.1.1 RCT						
Dawson 2011	2	41	6	39	1.3%	0.28 [0.05, 1.49]
Kookna 2019	1	25	0	25	0.3%	3.12 [0.12, 80.39]
Menakaya 2014	1	11	4	13	0.6%	0.23 [0.02, 2.40]
Szyld 2014	11	511	15	516	5.8%	0.73 [0.33, 1.62]
Thakur 2015	3	40	3	50	1.3%	1.27 [0.24, 6.66]
Subtotal (95% CI)		**628**		**643**	**9.3%**	**0.68 [0.36, 1.25]**
Total events	18		28			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 3.34$, df = 4 (P = 0.50); $I^2 = 0\%$						
Test for overall effect: Z = 1.24 (P = 0.21)						
3.1.2 RCT with bundle interventions						
El-Chimi 2017	12	57	19	55	5.0%	0.51 [0.22, 1.18]
Te Pas 2007	2	104	4	103	1.2%	0.49 [0.09, 2.71]
Subtotal (95% CI)		**161**		**158**	**6.2%**	**0.50 [0.23, 1.07]**
Total events	14		23			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.00$, df = 1 (P = 0.97); $I^2 = 0\%$						
Test for overall effect: Z = 1.78 (P = 0.07)						
3.1.3 cohort studies						
Guinsburg 2018	456	1456	224	506	83.2%	0.57 [0.47, 0.71]
Ng 2015	2	25	7	25	1.3%	0.22 [0.04, 1.21]
Subtotal (95% CI)		**1481**		**531**	**84.4%**	**0.53 [0.31, 0.89]**
Total events	458		231			
Heterogeneity: $Tau^2 = 0.07$; $Chi^2 = 1.18$, df = 1 (P = 0.28); $I^2 = 15\%$						
Test for overall effect: Z = 2.38 (P = 0.02)						
Total (95% CI)		**2270**		**1332**	**100.0%**	**0.57 [0.47, 0.69]**
Total events	490		282			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 4.92$, df = 8 (P = 0.77); $I^2 = 0\%$
Test for overall effect: Z = 5.80 (P < 0.00001)
Test for subgroup differences: $Chi^2 = 0.48$, df = 2 (P = 0.79), $I^2 = 0\%$



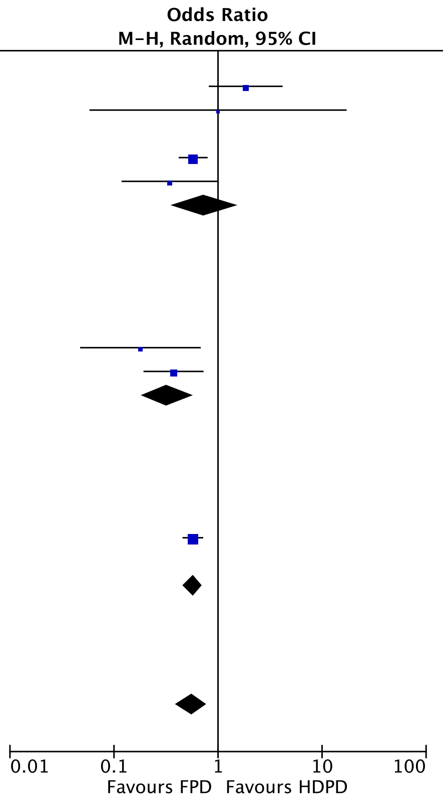
Bronchopulmonary dysplasia[24–30]

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
2.1.1 RCT						
Dawson 2011	15	41	11	39	11.7%	1.47 [0.57, 3.77]
Kookna 2019	0	25	1	25	1.3%	0.32 [0.01, 8.25]
Menakaya 2014	7	10	8	11	3.6%	0.88 [0.13, 5.82]
Szyld 2014	21	511	44	516	23.5%	0.46 [0.27, 0.78]
Thakur 2015	0	40	0	50		Not estimable
Subtotal (95% CI)		**627**		**641**	**40.1%**	**0.71 [0.34, 1.47]**
Total events	43		64			
Heterogeneity: $Tau^2 = 0.19$; $Chi^2 = 4.69$, df = 3 (P = 0.20); $I^2 = 36\%$						
Test for overall effect: Z = 0.92 (P = 0.36)						
2.1.2 RCT with bundle interventions						
El-Chimi 2017	1	57	4	55	2.7%	0.23 [0.02, 2.10]
Te Pas 2007	22	104	34	103	20.0%	0.54 [0.29, 1.02]
Subtotal (95% CI)		**161**		**158**	**22.7%**	**0.51 [0.28, 0.93]**
Total events	23		38			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.55$, df = 1 (P = 0.46); $I^2 = 0\%$						
Test for overall effect: Z = 2.19 (P = 0.03)						
2.1.3 cohort studies						
Guinsburg 2018	254	1456	95	506	37.2%	0.91 [0.70, 1.19]
Ng 2015	0	0	0	0		Not estimable
Subtotal (95% CI)		**1456**		**506**	**37.2%**	**0.91 [0.70, 1.19]**
Total events	254		95			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.67 (P = 0.50)						
Total (95% CI)		**2244**		**1305**	**100.0%**	**0.70 [0.48, 1.02]**
Total events	320		197			
Heterogeneity: $Tau^2 = 0.08$; $Chi^2 = 9.66$, df = 6 (P = 0.14); $I^2 = 38\%$						
Test for overall effect: Z = 1.85 (P = 0.06)						
Test for subgroup differences: $Chi^2 = 3.20$, df = 2 (P = 0.20), $I^2 = 37.4\%$						



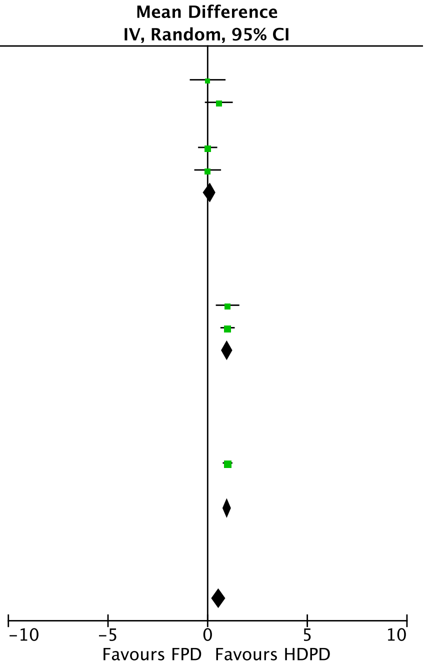
DR intubation rates[25–30,32]

Study or Subgroup	FPD Events	FPD Total	HDPD Events	HDPD Total	Weight	Odds Ratio M-H, Random, 95% CI
1.1.1 RCT						
Dawson 2011	26	49	19	50	12.0%	1.84 [0.83, 4.11]
Kookna 2019	1	25	1	25	1.4%	1.00 [0.06, 16.93]
Menakaya 2014	0	0	0	0		Not estimable
Szyld 2014	86	511	134	516	26.9%	0.58 [0.43, 0.78]
Thakur 2015	6	40	17	50	8.3%	0.34 [0.12, 0.98]
Subtotal (95% CI)		**625**		**641**	**48.7%**	**0.74 [0.35, 1.56]**
Total events	119		171			
Heterogeneity: $Tau^2 = 0.33$; $Chi^2 = 8.63$, df = 3 (P = 0.03); $I^2 = 65\%$						
Test for overall effect: Z = 0.79 (P = 0.43)						
1.1.2 RCT with bundle intervention						
El-Chimi 2017	3	57	13	55	5.7%	0.18 [0.05, 0.67]
Te Pas 2007	18	104	37	103	15.5%	0.37 [0.20, 0.71]
Subtotal (95% CI)		**161**		**158**	**21.2%**	**0.32 [0.18, 0.58]**
Total events	21		50			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.96$, df = 1 (P = 0.33); $I^2 = 0\%$						
Test for overall effect: Z = 3.80 (P = 0.0001)						
1.1.3 cohort studies						
Guinsburg 2018	786	1456	340	506	30.1%	0.57 [0.46, 0.71]
Ng 2015	0	0	0	0		Not estimable
Subtotal (95% CI)		**1456**		**506**	**30.1%**	**0.57 [0.46, 0.71]**
Total events	786		340			
Heterogeneity: Not applicable						
Test for overall effect: Z = 5.15 ($P < 0.00001$)						
Total (95% CI)		**2242**		**1305**	**100.0%**	**0.56 [0.40, 0.79]**
Total events	926		561			
Heterogeneity: $Tau^2 = 0.09$; $Chi^2 = 13.92$, df = 6 (P = 0.03); $I^2 = 57\%$						
Test for overall effect: Z = 3.30 (P = 0.0010)						
Test for subgroup differences: $Chi^2 = 3.94$, df = 2 (P = 0.14), $I^2 = 49.2\%$						



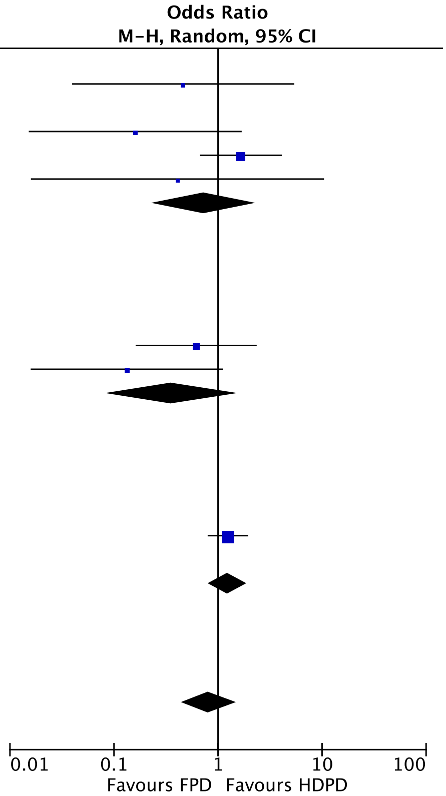
Apgar scores at 5 minutes[25–30,32]

Study or Subgroup	FPD Mean	FPD SD	FPD Total	HDPD Mean	HDPD SD	HDPD Total	Weight	Mean Difference IV, Random, 95% CI
3.7.1 RCT								
Dawson 2011	7	1.54	41	7	2.3	39	9.5%	0.00 [−0.86, 0.86]
Kookna 2019	8.64	1.2	25	8.08	1.2	25	12.1%	0.56 [−0.11, 1.23]
Menakaya 2014	0	0	0	0	0	0		Not estimable
Szyld 2014	8	1.5	76	8	1.5	101	15.5%	0.00 [−0.45, 0.45]
Thakur 2015	8	1.53	40	8	1.53	50	12.6%	0.00 [−0.64, 0.64]
Subtotal (95% CI)			**182**			**215**	**49.8%**	**0.11 [−0.19, 0.41]**
Heterogeneity: Tau² = 0.00; Chi² = 2.17, df = 3 (P = 0.54); I² = 0%								
Test for overall effect: Z = 0.74 (P = 0.46)								
3.7.2 RCT with bundle interventions								
El-Chimi 2017	8	1.5	57	7	1.5	55	13.8%	1.00 [0.44, 1.56]
Te Pas 2007	9	0.75	104	8	1.5	103	17.5%	1.00 [0.68, 1.32]
Subtotal (95% CI)			**161**			**158**	**31.3%**	**1.00 [0.72, 1.28]**
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 1.00); I² = 0%								
Test for overall effect: Z = 7.01 (P < 0.00001)								
3.7.3 cohort studies								
Guinsburg 2018	8	1.48	1456	7	2.23	506	19.0%	1.00 [0.79, 1.21]
Ng 2015	0	0	0	0	0	0		Not estimable
Subtotal (95% CI)			**1456**			**506**	**19.0%**	**1.00 [0.79, 1.21]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 9.39 (P < 0.00001)								
Total (95% CI)			**1799**			**879**	**100.0%**	**0.57 [0.20, 0.94]**
Heterogeneity: Tau² = 0.17; Chi² = 27.70, df = 6 (P = 0.0001); I² = 78%								
Test for overall effect: Z = 3.05 (P = 0.002)								
Test for subgroup differences: Chi² = 25.53, df = 2 (P < 0.00001), I² = 92.2%								



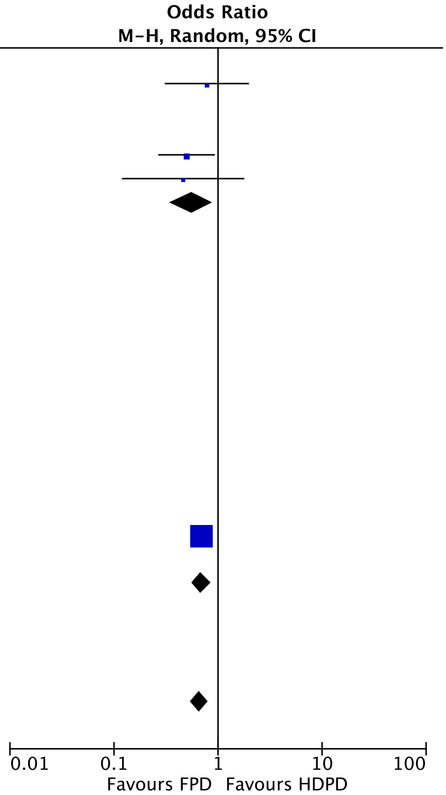
Air leaks[25–30,32]

Study or Subgroup	FPD Events	FPD Total	HDPD Events	HDPD Total	Weight	Odds Ratio M-H, Random, 95% CI
3.2.1 RCT						
Dawson 2011	1	41	2	39	5.7%	0.46 [0.04, 5.32]
Kookna 2019	0	25	0	25		Not estimable
Menakaya 2014	1	11	5	13	6.1%	0.16 [0.02, 1.66]
Szyld 2014	13	511	8	516	24.0%	1.66 [0.68, 4.03]
Thakur 2015	0	40	1	50	3.4%	0.41 [0.02, 10.27]
Subtotal (95% CI)		**628**		**643**	**39.2%**	**0.73 [0.23, 2.35]**
Total events	15		16			
Heterogeneity: Tau² = 0.46; Chi² = 4.29, df = 3 (P = 0.23); I² = 30%						
Test for overall effect: Z = 0.52 (P = 0.60)						
3.2.2 RCT with bundle interventions						
El-Chimi 2017	4	57	6	55	15.0%	0.62 [0.16, 2.32]
Te Pas 2007	1	104	7	103	7.3%	0.13 [0.02, 1.10]
Subtotal (95% CI)		**161**		**158**	**22.3%**	**0.36 [0.08, 1.55]**
Total events	5		13			
Heterogeneity: Tau² = 0.41; Chi² = 1.51, df = 1 (P = 0.22); I² = 34%						
Test for overall effect: Z = 1.38 (P = 0.17)						
3.2.3 cohort studies						
Guinsburg 2018	99	1456	28	506	38.5%	1.25 [0.81, 1.92]
Ng 2015	0	0	0	0		Not estimable
Subtotal (95% CI)		**1456**		**506**	**38.5%**	**1.25 [0.81, 1.92]**
Total events	99		28			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.00 (P = 0.32)						
Total (95% CI)		**2245**		**1307**	**100.0%**	**0.82 [0.44, 1.52]**
Total events	119		57			
Heterogeneity: Tau² = 0.21; Chi² = 9.22, df = 6 (P = 0.16); I² = 35%						
Test for overall effect: Z = 0.63 (P = 0.53)						
Test for subgroup differences: Chi² = 3.03, df = 2 (P = 0.22), I² = 33.9%						



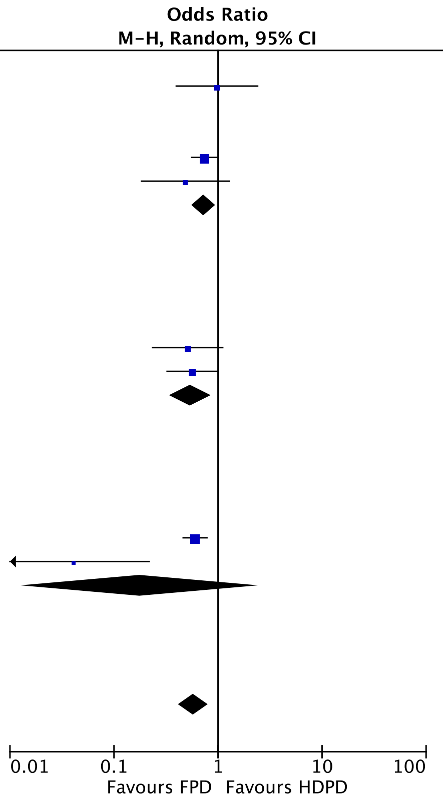
Need for surfactant[25,27,28,32]

Study or Subgroup	FPD Events	FPD Total	HDPD Events	HDPD Total	Weight	Odds Ratio M-H, Random, 95% CI
1.2.1 RCT						
Dawson 2011	25	41	26	39	5.0%	0.78 [0.31, 1.95]
Kookna 2019	0	0	0	0		Not estimable
Menakaya 2014	0	0	0	0		Not estimable
Szyld 2014	39	77	68	101	11.3%	0.50 [0.27, 0.92]
Thakur 2015	6	19	9	18	2.4%	0.46 [0.12, 1.76]
Subtotal (95% CI)		**137**		**158**	**18.7%**	**0.56 [0.35, 0.90]**
Total events	70		103			
Heterogeneity: Tau² = 0.00; Chi² = 0.73, df = 2 (P = 0.69); I² = 0%						
Test for overall effect: Z = 2.42 (P = 0.02)						
1.2.2 RCT with bundle interventions						
El-Chimi 2017	0	57	0	55		Not estimable
Te Pas 2007	0	0	0	0		Not estimable
Subtotal (95% CI)		**57**		**55**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
1.2.3 cohort studies						
Guinsburg 2018	976	1456	377	506	81.3%	0.70 [0.55, 0.87]
Ng 2015	0	0	0	0		Not estimable
Subtotal (95% CI)		**1456**		**506**	**81.3%**	**0.70 [0.55, 0.87]**
Total events	976		377			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.12 (P = 0.002)						
Total (95% CI)		**1650**		**719**	**100.0%**	**0.67 [0.54, 0.82]**
Total events	1046		480			
Heterogeneity: Tau² = 0.00; Chi² = 1.42, df = 3 (P = 0.70); I² = 0%						
Test for overall effect: Z = 3.86 (P = 0.0001)						
Test for subgroup differences: Chi² = 0.69, df = 1 (P = 0.41), I² = 0%						



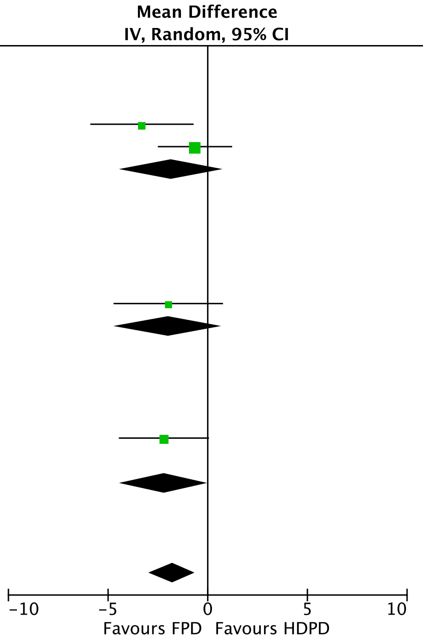
Mechanical ventilation requirements[25,27–32]

Study or Subgroup	FPD Events	FPD Total	HDPD Events	HDPD Total	Weight	Odds Ratio M-H, Random, 95% CI
3.9.1 RCT						
Dawson 2011	25	41	24	39	9.0%	0.98 [0.40, 2.40]
Kookna 2019	0	0	0	0		Not estimable
Menakaya 2014	0	0	0	0		Not estimable
Szyld 2014	116	511	147	516	25.9%	0.74 [0.56, 0.98]
Thakur 2015	8	40	17	50	8.0%	0.49 [0.18, 1.28]
Subtotal (95% CI)		**592**		**605**	**42.9%**	**0.73 [0.57, 0.95]**
Total events	149		188			
Heterogeneity: Tau² = 0.00; Chi² = 1.09, df = 2 (P = 0.58); I² = 0%						
Test for overall effect: Z = 2.36 (P = 0.02)						
3.9.2 RCT with bundle interventions						
El-Chimi 2017	17	57	25	55	11.0%	0.51 [0.23, 1.11]
Te Pas 2007	38	104	52	103	16.3%	0.56 [0.32, 0.98]
Subtotal (95% CI)		**161**		**158**	**27.3%**	**0.55 [0.35, 0.86]**
Total events	55		77			
Heterogeneity: Tau² = 0.00; Chi² = 0.04, df = 1 (P = 0.83); I² = 0%						
Test for overall effect: Z = 2.63 (P = 0.009)						
3.9.3 cohort studies						
Guinsburg 2018	1094	1456	422	506	26.6%	0.60 [0.46, 0.78]
Ng 2015	2	25	17	25	3.2%	0.04 [0.01, 0.22]
Subtotal (95% CI)		**1481**		**531**	**29.8%**	**0.18 [0.01, 2.47]**
Total events	1096		439			
Heterogeneity: Tau² = 3.25; Chi² = 9.73, df = 1 (P = 0.002); I² = 90%						
Test for overall effect: Z = 1.28 (P = 0.20)						
Total (95% CI)		**2234**		**1294**	**100.0%**	**0.58 [0.42, 0.80]**
Total events	1300		704			
Heterogeneity: Tau² = 0.08; Chi² = 13.25, df = 6 (P = 0.04); I² = 55%						
Test for overall effect: Z = 3.37 (P = 0.0007)						
Test for subgroup differences: Chi² = 2.22, df = 2 (P = 0.33), I² = 9.7%						



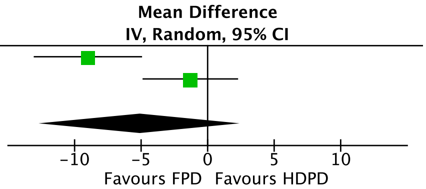
Mechanical ventilation duration

Study or Subgroup	FPD Mean	FPD SD	FPD Total	HDPD Mean	HDPD SD	HDPD Total	Weight	Mean Difference IV, Random, 95% CI
1.3.1 RCT								
Dawson 2011	0	0	0	0	0	0		Not estimable
Menakaya 2014	0	0	0	0	0	0		Not estimable
Szyld 2014	5	7.6	116	8.3	13.3	147	19.4%	-3.30 [-5.86, -0.74]
Thakur 2015	1.53	1.6	8	2.17	3.06	17	37.8%	-0.64 [-2.47, 1.19]
Subtotal (95% CI)			**124**			**164**	**57.2%**	**-1.81 [-4.40, 0.77]**
Heterogeneity: Tau² = 2.25; Chi² = 2.75, df = 1 (P = 0.10); I² = 64%								
Test for overall effect: Z = 1.37 (P = 0.17)								
1.3.2 RCT with bundle interventions								
El-Chimi 2017	0	0	0	0	0	0		Not estimable
Te Pas 2007	4.02	5.62	38	6	7.5	52	17.2%	-1.98 [-4.69, 0.73]
Subtotal (95% CI)			**38**			**52**	**17.2%**	**-1.98 [-4.69, 0.73]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.43 (P = 0.15)								
1.3.3 cohort studies								
Guinsburg 2018	11.6	19.6	1094	13.8	19.9	422	25.6%	-2.20 [-4.43, 0.03]
Ng 2015	0	0	0	0	0	0		Not estimable
Subtotal (95% CI)			**1094**			**422**	**25.6%**	**-2.20 [-4.43, 0.03]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.94 (P = 0.05)								
Total (95% CI)			**1256**			**638**	**100.0%**	**-1.79 [-2.91, -0.66]**
Heterogeneity: Tau² = 0.00; Chi² = 3.01, df = 3 (P = 0.39); I² = 0%								
Test for overall effect: Z = 3.11 (P = 0.002)								
Test for subgroup differences: Chi² = 0.05, df = 2 (P = 0.98), I² = 0%								



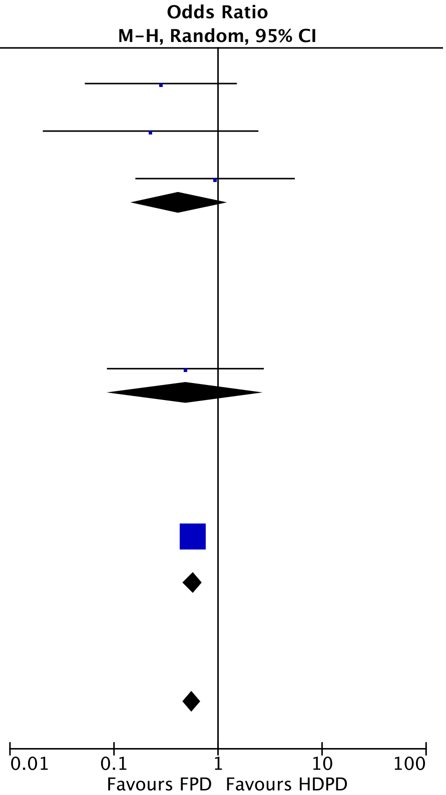
Duration of oxygenotherapy [27,32]

Study or Subgroup	FPD Mean	FPD SD	FPD Total	HDPD Mean	HDPD SD	HDPD Total	Weight	Mean Difference IV, Random, 95% CI
Szyld 2014	13.8	17	208	22.8	25	222	49.2%	-9.00 [-13.02, -4.98]
Guinsburg 2018	26.4	34.4	1413	27.7	34.1	480	50.8%	-1.30 [-4.84, 2.24]
Total (95% CI)			**1621**			**702**	**100.0%**	**-5.09 [-12.63, 2.46]**
Heterogeneity: Tau² = 25.91; Chi² = 7.94, df = 1 (P = 0.005); I² = 87%								
Test for overall effect: Z = 1.32 (P = 0.19)								



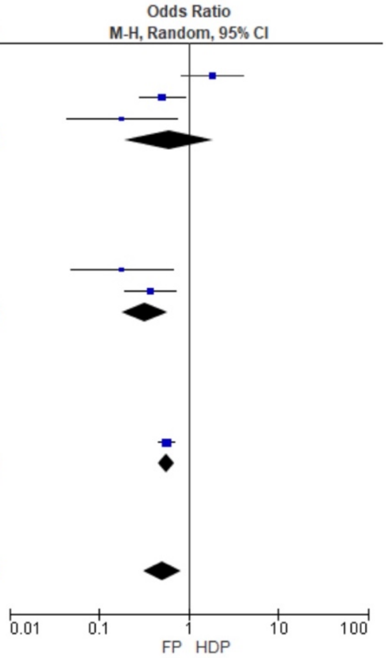
Mortality in preterm infants [24,25,28,30,32]

Study or Subgroup	FPD Events	FPD Total	HDPD Events	HDPD Total	Weight	Odds Ratio M-H, Random, 95% CI
3.10.1 RCTs						
Dawson 2011	2	41	6	39	1.5%	0.28 [0.05, 1.49]
Kookna 2019	0	0	0	0		Not estimable
Menakaya 2014	1	11	4	13	0.7%	0.23 [0.02, 2.40]
Szyld 2014	0	0	0	0		Not estimable
Thakur 2015	3	19	3	18	1.3%	0.94 [0.16, 5.39]
Subtotal (95% CI)		**71**		**70**	**3.5%**	**0.42 [0.14, 1.24]**
Total events	6		13			
Heterogeneity: Tau² = 0.00; Chi² = 1.30, df = 2 (P = 0.52); I² = 0%						
Test for overall effect: Z = 1.56 (P = 0.12)						
3.10.2 RCT with bundle						
El-Chimi 2017	0	0	0	0		Not estimable
Te Pas 2007	2	104	4	103	1.4%	0.49 [0.09, 2.71]
Subtotal (95% CI)		**104**		**103**	**1.4%**	**0.49 [0.09, 2.71]**
Total events	2		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.82 (P = 0.41)						
3.10.3 cohort studies						
Guinsburg 2018	456	1456	224	506	95.1%	0.57 [0.47, 0.71]
Ng 2015	0	0	0	0		Not estimable
Subtotal (95% CI)		**1456**		**506**	**95.1%**	**0.57 [0.47, 0.71]**
Total events	456		224			
Heterogeneity: Not applicable						
Test for overall effect: Z = 5.24 (P < 0.00001)						
Total (95% CI)		**1631**		**679**	**100.0%**	**0.57 [0.46, 0.69]**
Total events	464		241			
Heterogeneity: Tau² = 0.00; Chi² = 1.62, df = 4 (P = 0.80); I² = 0%						
Test for overall effect: Z = 5.50 (P < 0.00001)						
Test for subgroup differences: Chi² = 0.33, df = 2 (P = 0.85), I² = 0%						



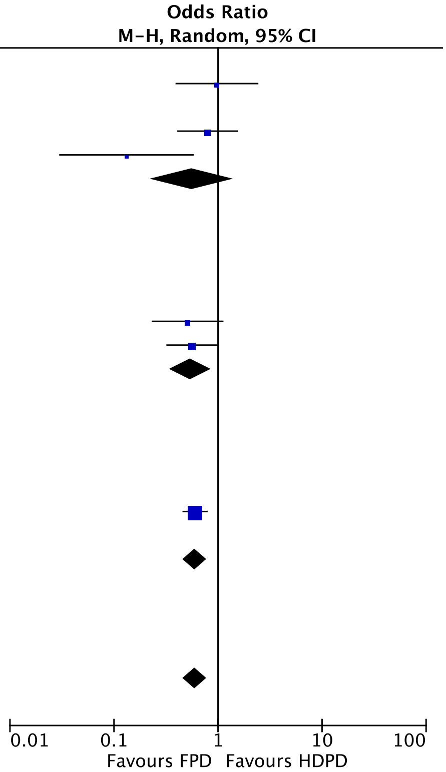
DR intubation in preterm infants[25,27–30,32]

Study or Subgroup	Fixed pressure Events	Fixed pressure Total	Hand driven pressure Events	Hand driven pressure Total	Weight	Odds Ratio M-H, Random, 95% CI
3.4.1 RCT						
Dawson, 2011	26	49	19	50	16.1%	1.84 [0.83, 4.11]
Szyld, 2014	45	85	76	110	20.2%	0.50 [0.28, 0.91]
Thakur, 2015	5	19	12	18	8.2%	0.18 [0.04, 0.74]
Subtotal (95% CI)		**153**		**178**	**44.5%**	**0.61 [0.19, 1.93]**
Total events	76		107			
Heterogeneity: Tau² = 0.80; Chi² = 10.41, df = 2 (P = 0.006); I² = 81%						
Test for overall effect: Z = 0.84 (P = 0.40)						
3.4.2 RCT - bundle interventions						
EL-Chimi, 2017	3	57	13	55	9.1%	0.18 [0.05, 0.67]
Te Pas, 2007	18	104	37	103	19.0%	0.37 [0.20, 0.71]
Subtotal (95% CI)		**161**		**158**	**28.1%**	**0.32 [0.18, 0.58]**
Total events	21		50			
Heterogeneity: Tau² = 0.00; Chi² = 0.96, df = 1 (P = 0.33); I² = 0%						
Test for overall effect: Z = 3.80 (P = 0.0001)						
3.4.3 Cohort						
Guinsburg, 2018	782	1456	340	506	27.4%	0.57 [0.46, 0.70]
Subtotal (95% CI)		**1456**		**506**	**27.4%**	**0.57 [0.46, 0.70]**
Total events	782		340			
Heterogeneity: Not applicable						
Test for overall effect: Z = 5.25 (P < 0.00001)						
Total (95% CI)		**1770**		**842**	**100.0%**	**0.51 [0.31, 0.82]**
Total events	879		497			
Heterogeneity: Tau² = 0.21; Chi² = 15.51, df = 5 (P = 0.008); I² = 68%						
Test for overall effect: Z = 2.78 (P = 0.005)						
Test for subgroup differences: Chi² = 3.19, df = 2 (P = 0.20), I² = 37.3%						



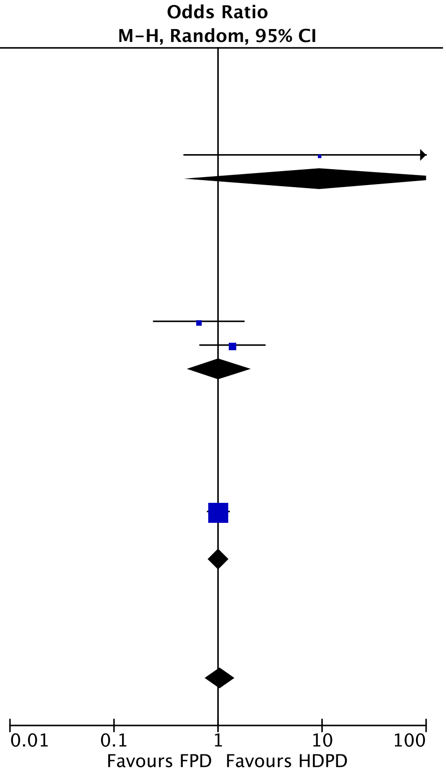
MV requirements in preterm infants[25,27–30,32].

Study or Subgroup	FPD Events	FPD Total	HDPD Events	HDPD Total	Weight	Odds Ratio M-H, Random, 95% CI
1.7.1 RCT						
Dawson 2011	25	41	24	39	7.9%	0.98 [0.40, 2.40]
Menakaya 2014	0	0	0	0		Not estimable
Szyld 2014	62	85	85	110	13.8%	0.79 [0.41, 1.52]
Thakur 2015	6	19	14	18	3.1%	0.13 [0.03, 0.58]
Subtotal (95% CI)		**145**		**167**	**24.8%**	**0.57 [0.23, 1.43]**
Total events	93		123			
Heterogeneity: Tau² = 0.42; Chi² = 5.60, df = 2 (P = 0.06); I² = 64%						
Test for overall effect: Z = 1.20 (P = 0.23)						
1.7.2 RCT with bundle intervention						
El-Chimi 2017	17	57	25	55	10.3%	0.51 [0.23, 1.11]
Te Pas 2007	38	104	52	103	18.0%	0.56 [0.32, 0.98]
Subtotal (95% CI)		**161**		**158**	**28.3%**	**0.55 [0.35, 0.86]**
Total events	55		77			
Heterogeneity: Tau² = 0.00; Chi² = 0.04, df = 1 (P = 0.83); I² = 0%						
Test for overall effect: Z = 2.63 (P = 0.009)						
1.7.3 cohort studies						
Guinsburg 2018	1094	1456	422	506	46.9%	0.60 [0.46, 0.78]
Ng 2015	0	0	0	0		Not estimable
Subtotal (95% CI)		**1456**		**506**	**46.9%**	**0.60 [0.46, 0.78]**
Total events	1094		422			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.79 (P = 0.0001)						
Total (95% CI)		**1762**		**831**	**100.0%**	**0.60 [0.46, 0.78]**
Total events	1242		622			
Heterogeneity: Tau² = 0.02; Chi² = 6.10, df = 5 (P = 0.30); I² = 18%						
Test for overall effect: Z = 3.75 (P = 0.0002)						
Test for subgroup differences: Chi² = 0.14, df = 2 (P = 0.93), I² = 0%						



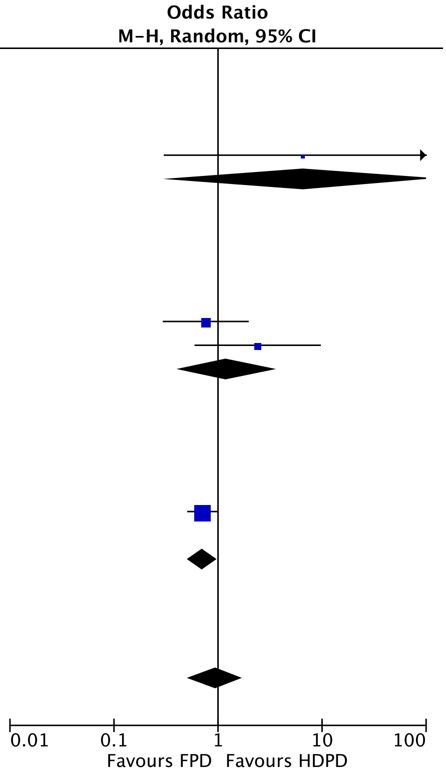
PDA requiring treatment[28–30,32]

Study or Subgroup	FPD Events	FPD Total	HDPD Events	HDPD Total	Weight	Odds Ratio M–H, Random, 95% CI
3.3.1 RCT						
Dawson 2011	0	0	0	0		Not estimable
Menakaya 2014	0	0	0	0		Not estimable
Szyld 2014	0	0	0	0		Not estimable
Thakur 2015	3	40	0	50	1.2%	9.43 [0.47, 188.05]
Subtotal (95% CI)		**40**		**50**	**1.2%**	**9.43 [0.47, 188.05]**
Total events	3		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.47 (P = 0.14)						
3.3.2 RCT with bundle interventions						
El–Chimi 2017	8	57	11	55	10.3%	0.65 [0.24, 1.77]
Te Pas 2007	21	104	16	103	18.3%	1.38 [0.67, 2.82]
Subtotal (95% CI)		**161**		**158**	**28.6%**	**1.03 [0.51, 2.10]**
Total events	29		27			
Heterogeneity: $Tau^2 = 0.08; Chi^2 = 1.41, df = 1 (P = 0.23); I^2 = 29\%$						
Test for overall effect: Z = 0.08 (P = 0.93)						
3.3.3 cohort studies						
Guinsburg 2018	350	1456	121	506	70.2%	1.01 [0.79, 1.28]
Ng 2015	0	0	0	0		Not estimable
Subtotal (95% CI)		**1456**		**506**	**70.2%**	**1.01 [0.79, 1.28]**
Total events	350		121			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.06 (P = 0.95)						
Total (95% CI)		**1657**		**714**	**100.0%**	**1.05 [0.75, 1.47]**
Total events	382		148			
Heterogeneity: $Tau^2 = 0.03; Chi^2 = 3.57, df = 3 (P = 0.31); I^2 = 16\%$						
Test for overall effect: Z = 0.28 (P = 0.78)						
Test for subgroup differences: $Chi^2 = 2.13, df = 2 (P = 0.34), I^2 = 6.2\%$						



IVH[28–30,32]

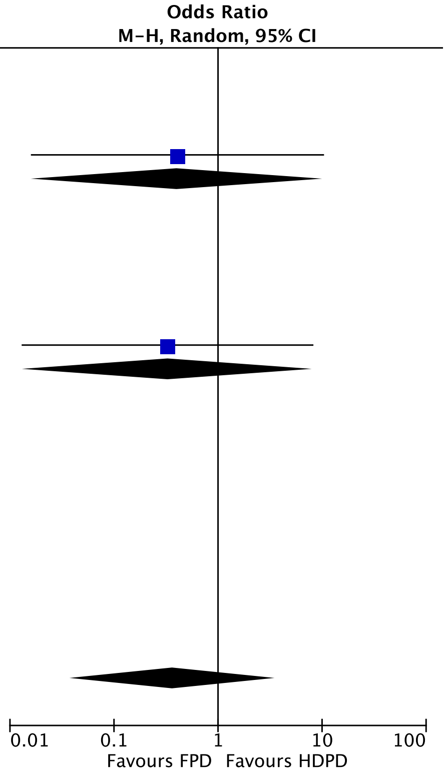
Study or Subgroup	FPD Events	FPD Total	HDPD Events	HDPD Total	Weight	Odds Ratio M–H, Random, 95% CI
3.4.1 RCT						
Dawson 2011	0	0	0	0		Not estimable
Menakaya 2014	0	0	0	0		Not estimable
Szyld 2014	0	0	0	0		Not estimable
Thakur 2015	2	40	0	50	3.7%	6.56 [0.31, 140.60]
Subtotal (95% CI)		**40**		**50**	**3.7%**	**6.56 [0.31, 140.60]**
Total events	2		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.20 (P = 0.23)						
3.4.2 RCT with bundle interventions						
El–Chimi 2017	10	57	12	55	25.7%	0.76 [0.30, 1.94]
Te Pas 2007	7	104	3	103	15.0%	2.41 [0.60, 9.57]
Subtotal (95% CI)		**161**		**158**	**40.7%**	**1.21 [0.40, 3.63]**
Total events	17		15			
Heterogeneity: $Tau^2 = 0.30; Chi^2 = 1.83, df = 1 (P = 0.18); I^2 = 45\%$						
Test for overall effect: Z = 0.33 (P = 0.74)						
3.4.3 cohort studies						
Guinsburg 2018	145	1218	60	376	55.6%	0.71 [0.51, 0.99]
Ng 2015	0	0	0	0		Not estimable
Subtotal (95% CI)		**1218**		**376**	**55.6%**	**0.71 [0.51, 0.99]**
Total events	145		60			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.04 (P = 0.04)						
Total (95% CI)		**1419**		**584**	**100.0%**	**0.94 [0.51, 1.73]**
Total events	164		75			
Heterogeneity: $Tau^2 = 0.14; Chi^2 = 4.74, df = 3 (P = 0.19); I^2 = 37\%$						
Test for overall effect: Z = 0.19 (P = 0.85)						
Test for subgroup differences: $Chi^2 = 2.73, df = 2 (P = 0.26), I^2 = 26.6\%$						



ROP[28,30]

Study or Subgroup	FPD Events	FPD Total	HDPD Events	HDPD Total	Weight	Odds Ratio M-H, Random, 95% CI
3.6.1 RCT						
Dawson 2011	0	0	0	0		Not estimable
Menakaya 2014	0	0	0	0		Not estimable
Szyld 2014	0	0	0	0		Not estimable
Thakur 2015	0	40	1	50	49.8%	0.41 [0.02, 10.27]
Subtotal (95% CI)		**40**		**50**	**49.8%**	**0.41 [0.02, 10.27]**
Total events	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.55 (P = 0.59)						
3.6.2 RCT with bundle interventions						
El-Chimi 2017	0	0	0	0		Not estimable
Te Pas 2007	0	104	1	103	50.2%	0.33 [0.01, 8.12]
Subtotal (95% CI)		**104**		**103**	**50.2%**	**0.33 [0.01, 8.12]**
Total events	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.68 (P = 0.50)						
3.6.3 cohort studies						
Guinsburg 2018	0	0	0	0		Not estimable
Ng 2015	0	0	0	0		Not estimable
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**144**		**153**	**100.0%**	**0.36 [0.04, 3.55]**
Total events	0		2			

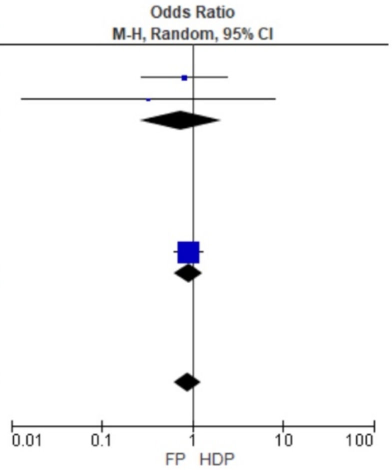
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.01$, df = 1 (P = 0.92); $I^2 = 0\%$
Test for overall effect: Z = 0.87 (P = 0.39)
Test for subgroup differences: $Chi^2 = 0.01$, df = 1 (P = 0.92), $I^2 = 0\%$



NEC[29,30,32]

Study or Subgroup	Fixed pressure Events	Fixed pressure Total	Hand driven pressure Events	Hand driven pressure Total	Weight	Odds Ratio M-H, Random, 95% CI
3.16.1 RCT - bundle interventions						
EL-Chimi, 2017	7	57	8	55	10.3%	0.82 [0.28, 2.45]
Te Pas, 2007	0	104	1	103	1.2%	0.33 [0.01, 8.12]
Subtotal (95% CI)		**161**		**158**	**11.4%**	**0.75 [0.27, 2.10]**
Total events	7		9			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.28$, df = 1 (P = 0.59); $I^2 = 0\%$						
Test for overall effect: Z = 0.55 (P = 0.58)						
3.16.2 Cohort						
Guinsburg, 2018	110	1456	42	506	88.6%	0.90 [0.62, 1.31]
Subtotal (95% CI)		**1456**		**506**	**88.6%**	**0.90 [0.62, 1.31]**
Total events	110		42			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.54 (P = 0.59)						
Total (95% CI)		**1617**		**664**	**100.0%**	**0.88 [0.62, 1.25]**
Total events	117		51			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.40$, df = 2 (P = 0.82); $I^2 = 0\%$
Test for overall effect: Z = 0.69 (P = 0.49)
Test for subgroup differences: $Chi^2 = 0.11$, df = 1 (P = 0.74), $I^2 = 0\%$



cPVL[28,30,32]

Study or Subgroup	FPD Events	FPD Total	HDPD Events	HDPD Total	Weight	Odds Ratio M-H, Random, 95% CI
3.5.1 RCT						
Dawson 2011	0	0	0	0		Not estimable
Kookna 2019	0	0	0	0		Not estimable
Menakaya 2014	0	0	0	0		Not estimable
Szyld 2014	0	0	0	0		Not estimable
Thakur 2015	0	40	0	50		Not estimable
Subtotal (95% CI)		**40**		**50**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
3.5.2 RCT with bundle interventions						
El-Chimi 2017	0	0	0	0		Not estimable
Te Pas 2007	2	104	5	103	4.8%	0.38 [0.07, 2.03]
Subtotal (95% CI)		**104**		**103**	**4.8%**	**0.38 [0.07, 2.03]**
Total events	2		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.13 (P = 0.26)						
3.5.3 cohort studies						
Guinsburg 2018	95	1209	46	373	95.2%	0.61 [0.42, 0.88]
Ng 2015	0	0	0	0		Not estimable
Subtotal (95% CI)		**1209**		**373**	**95.2%**	**0.61 [0.42, 0.88]**
Total events	95		46			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.63 (P = 0.009)						
Total (95% CI)		**1353**		**526**	**100.0%**	**0.59 [0.41, 0.85]**
Total events	97		51			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.28$, df = 1 (P = 0.60); $I^2 = 0\%$

Test for overall effect: Z = 2.81 (P = 0.005)

Test for subgroup differences: $Chi^2 = 0.27$, df = 1 (P = 0.60), $I^2 = 0\%$