

1 **Title:** Change in early respiratory management of infants born at less than 30 weeks' gestation
2 in England and Wales: an observational cohort study.

3

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26

27 **Abstract (248 words)**

28 **Objective:** To describe changes in early respiratory support for infants born at <30 weeks'
29 gestational age (GA) in England and Wales.

30 **Design:** Retrospective cohort study using data from the National Neonatal Research Database
31 of all infants born at <30 weeks GA, admitted to neonatal units in England and Wales from
32 2016 to 2021.

33 **Main outcome measures:** Methods of respiratory support used in the delivery room and days
34 1 and 7 of care were determined. Success of the initial non-invasive respiratory support
35 strategy was assessed by any use of mechanical ventilation in the first 7 days of care.

36 **Results:** 24,107 babies were included. Use of continuous positive airway pressure (CPAP) and
37 nasal high flow cannula (HFNC) as the highest method of respiratory support for stabilisation
38 increased during the study period (CPAP: 17.3% to 28.8%; HFNC: 0% (first recorded in 2016)
39 to 0.7%). CPAP use increased in the most preterm (<25 weeks GA; 0.7 to 4.8%), the extremely
40 preterm (<28 weeks GA; 7.2 to 17.5%) and the very preterm (28-29 weeks GA; 29.3% to
41 44.1%) cohorts. Among those initially stabilised with non-invasive ventilation in this study,
42 2,763 (48.0%) infants required mechanical ventilation in the first week.

43 **Conclusions:** In England and Wales, use of non-invasive respiratory support for initial
44 stabilisation has increased among babies born at <30 weeks GA. 48% of those stabilised with
45 non-invasive ventilation required mechanical ventilation in the first week. A higher quality
46 evidence base for interventions that reduce mechanical ventilation could improve respiratory
47 management in this population.

48

49 **What is already known on this topic** – Benefits of early, non-invasive respiratory support of
50 preterm infants include reduced incidence of bronchopulmonary dysplasia. Globally, non-
51 invasive respiratory support has become widespread practice.

52 **What this study adds** – We showed a continued increase in use of non-invasive respiratory
53 support at earlier gestations for <30 weeks' gestation infants born in England and Wales.
54 However, compared to other European nations, these data indicate that early non-invasive
55 respiratory support strategies were less frequently employed.

56 **How this study might affect research, practice or policy** – To further improve rates of BPD in
57 England and Wales, there is a need to further improve neonatal care to successfully manage
58 more preterm infants with non-invasive respiratory support. Carefully conducted clinical trials
59 are needed to establish the most appropriate respiratory support strategies to avoid
60 mechanical ventilation.

61

62 **Word count: 2916 words (3000 limit)**

63 **Introduction:**

64 Very preterm infants (born at <32 weeks' gestation) almost invariably require breathing
65 support[1]. The direct relationship between low gestational age (GA) and intensity of the
66 required respiratory support is well established, as is the relationship between GA and
67 mortality and morbidity[2]. Invasive mechanical ventilation is a major risk factor for adverse
68 respiratory outcomes, including bronchopulmonary dysplasia (BPD), which is one of the most
69 common complications of prematurity [3]. International guidelines therefore recommend
70 avoiding or minimising the duration of mechanical ventilation [4]. Based on high-quality
71 evidence[5,6] guidelines recommend that very preterm infants should if possible be stabilised
72 in the delivery room and supported with non-invasive respiratory support from birth[4,7].

73 This aims to reduce ventilator-associated lung injury, thus reducing the risk of BPD[3].
74 Consequently, use of non-invasive respiratory support as the primary method of support in
75 preterm infants has gained traction[8]. Kwok et al. studied data from a recent (2010-2020)
76 UK cohort comprising over 83,000 very preterm infants, showing a reduction in mortality rate
77 over time; however they found that the incidence of BPD increased from 28% to 33%[9].
78 Earlier studies of initial non-invasive respiratory support mainly used continuous positive
79 airway pressure (CPAP), but more recently other non-invasive methods have been tested,
80 including non-invasive intermittent positive pressure ventilation (NIPPV), high-flow nasal
81 cannula (HFNC), or nasal non-invasive high-frequency oscillation ventilation (nHFOV)[1,10–
82 15].

83 In England and Wales, between 2010 and 2017, Sand et al. reported an increasing trend in
84 the use of non-invasive respiratory support on the first day of care, but did not investigate
85 changes in the support used in the delivery room [16]. We aimed to describe changes in
86 practice in the use of respiratory support for infants <30 weeks GA in the delivery room and
87 ongoing support in the neonatal unit (on day 1 and 7 of care). We further aimed to describe
88 the incidence of the escalation of respiratory support within the first week, death before
89 discharge, chest drain requirement and BPD.

90

91 **Methods**

92 A retrospective cohort study of infants born at <30 weeks' GA in England and Wales from 01
93 January 2016 to 31 December 2021 inclusive whose data are held within the UK National
94 Neonatal Research Database (NNRD) was performed[17]. Infants were excluded if there were
95 missing data (Supplementary Figure 1).

96 The study was reviewed by the Oxford University Hospitals Joint Research Office classification
97 committee and does not require additional ethical approval as a secondary use of anonymous
98 data.

99 **Exposures**

100 Exposure to non-invasive respiratory support in the delivery room was defined as receiving
101 any mode of non-invasive ventilatory support (NIPPV, CPAP, HFNC) while in the delivery room.

102 This was derived from resuscitation information from each infant (Supplementary Table 1).

103 Modes of respiratory support were ranked in order of mechanical ventilation (most invasive,
104 or "highest:"), NIPPV, CPAP, HFNC, oxygen only (least invasive, or "lowest"). The highest mode
105 of respiratory support in the delivery room and on day 1 were defined as the highest ranked
106 on these modes in the resuscitation information and day 1 daily data record, respectively.

107 This daily respiratory data does not provide method of non-invasive ventilation and only
108 records whether an infant received non-invasive ventilation of any kind.

109 Infants who were initially stabilised on CPAP in the delivery room were further sub-grouped
110 into those who had received any mechanical ventilation by day 7 (CPAP-MV) and those who
111 remained on NIV until day 7 (CPAP-NI).

112 **Outcomes**

113 Escalation of non-invasive respiratory support was defined as any mechanical ventilation
114 within 7 days in those initially stabilised on non-invasive respiratory support in the delivery
115 room. BPD was defined as need for any supplementary oxygen or respiratory support at 36
116 weeks corrected GA[18]. Death before discharge was derived from the final outcome and/or
117 time of death variable. This was combined with BPD to create a composite death before
118 discharge/BPD variable, which accounted for infants who had died before discharge or

119 survived to discharge and were diagnosed with BPD as defined above. The presence of a chest
120 drain in daily respiratory parameters was used to assess pneumothoraces.

121

122 **Statistical analysis:**

123 Data management and analyses were performed using STATA, version 15.1 (StataCorp,
124 College Station, Tx). After exclusions, the percentage of all admissions each year was
125 quantified by highest delivery room respiratory support and the characteristics of those who
126 received CPAP, HFNC, and mechanical ventilation, were described, for all infants and for three
127 pre-specified subgroups: born at <25 weeks' gestation (most preterm), born at <28 weeks
128 (extremely preterm), and born at 28 to 29 weeks.

129 Changes in the highest method of respiratory support received on the first seven days of care
130 were then described and quantified using daily respiratory support data. Linear trend during
131 the study period was assessed using a Chi squared test for trend.

132 Escalation of respiratory support were described as those who had mechanical ventilation
133 within 7 days.

134 Infants who were initially stabilised on CPAP in the delivery room were further grouped into
135 those who had received any mechanical ventilation by day 7 (CPAP-MV) and those who
136 remained on NIV until day 7 (CPAP-NI). The characteristics of these groups are provided in
137 Supplementary Table 2.

138 The CPAP-MV group was compared to infants who were initially stabilised on MV in the
139 delivery room. A logistic regression analysis was performed to compare the odds of BPD,
140 death before discharge, and the composite outcome between the two groups. Analyses were
141 adjusted for birthweight, gestational age in days, sex, and antenatal steroid administration to
142 calculate the adjusted odds ratio (OR) with 95% confidence intervals (CI).

143

144 **Results**

145 **Highest level of respiratory support in the delivery room**

146 After exclusions (Supplementary Figure 1), 24,107 infants were included in the analysis: the
147 highest delivery room respiratory support was CPAP in 23.4%, HFNC in 0.5%, and mechanical
148 ventilation in 65.5%. The characteristics of these groups for the whole cohort and by GA
149 subgroups are given in Table 1.

150 The median (IQR) GA was 28+5 (27+5 to 29+3) weeks of infants who had CPAP and 26+5 (25+1
151 to 28+2) weeks for those who had mechanical ventilation as the highest level of respiratory
152 support in delivery room. As shown in Table 1, infants who had CPAP as the highest level of
153 respiratory support in the delivery room had a higher gestational age, a higher birthweight
154 and a higher incidence of antenatal steroid administration compared to infants who had
155 mechanical ventilation as the highest level of respiratory support in the delivery room.

156 As shown in Table 2, use of non-invasive respiratory support (either CPAP or HFNC) as the
157 highest level of delivery room respiratory support increased by 12.2% (from 17.3% in 2016 to
158 29.5% in 2021; $p<0.005$). This included an 11.5% increase in CPAP use (from 17.3% in 2016 to
159 28.8% in 2021; $p<0.005$). HFNC in delivery room was not recorded in 2016. In 2017; 14 infants
160 were supported with HFNC in the delivery room and this increased to 25 in 2021. This increase
161 was seen in all three GA subgroups.

162 Simultaneously mechanical ventilation decreased overall and in all three pre-specified GA
163 sub-groups (Table 2).

164 Key characteristics that influenced clinical decisions when deciding which respiratory support
165 would be the most suitable in the delivery room were assessed and represented in our
166 analysis by surrogate data points reliably available in the repository. These included antenatal

167 steroid administration, gestation length in days and birthweight. There was no significant
168 change during the study period in any of these parameters.

169

170 **Highest method of respiratory support in the neonatal unit, on day 1 of care**

171 The use of non-invasive respiratory support as initial support in the neonatal unit increased
172 from 869/4,412 (19.7%) in 2016 to 1,059/3,606 (29.4%) in 2021 (Table 3). There was a
173 concurrent reduction in mechanical ventilation from 3,452/4,412 (78.2%) in 2016 to
174 2,467/3,606 (68.4%) in 2021. A statistically significant increase was seen in most and
175 extremely preterm sub-groups but not in the 28-29 weeks' GA infants.

176

177 **Escalation of non-invasive respiratory support on day 1 and by day 7 of care**

178 Of the 5,762 babies who were stabilised with non-invasive respiratory support in the delivery
179 room, 1,751 (30.4%) had mechanical ventilation on day 1 and 2,783 (48.3%) had mechanical
180 ventilation within 7 days. The lowest rate of non-invasive respiratory support escalation was
181 in the 28-29 weeks GA cohort (n = 4,103; mechanical ventilation on day 1, 1,107 (27%) and by
182 day 7, 1,792 (43.7%)). The percentage needing escalation was higher for infants <28 weeks'
183 GA (n = 1,659; mechanical ventilation on day 1, 644 (38.8%) and by day 7, 991 (56.7%)) and
184 highest in <25 weeks' GA infants (n = 89; mechanical ventilation on day 1 (52.8%) and by day
185 7, 78 (87.6%)). There was no change in the percentage of infants with escalation of respiratory
186 support on day 1 or day 7 of care over the study period.

187

188 **Bronchopulmonary dysplasia, chest drain requirement, and death before discharge**

189 In the whole cohort (n = 24,107), 11,138 (46.2%) had BPD, 1,382 (5.5%) required chest drain
190 insertion, and 2,551 (10.6%) died before discharge (Table 4). Incidence of death before

191 discharge and BPD for CPAP-NI and CPAP-MV groups are shown in Table 4 whilst demographic
192 data for these cohorts is presented in Supplementary Table 2.

193 When compared to the CPAP-MV group to counterparts who were intubated in the delivery
194 room, the unadjusted odds ratio of BPD or death before discharge was 0.454 (95% CI 0.419-
195 0.494, $p < 0.005$). Adjusted for birthweight, gestational age in days, sex, and antenatal steroid
196 administration, the odds ratio was 0.880 (95% CI 0.802-0.967, $p < 0.05$).

197 **Discussion:**

198 Use of non-invasive respiratory support in stabilisation in the delivery room and as early
199 support in the neonatal unit has increased significantly for both the most and extremely
200 preterm cohorts, from 2016 to 2021 in England and Wales. Overall, these data show a
201 significant change in the care of extremely and most preterm neonates in recent time. The
202 increase in the use of non-invasive respiratory support as primary respiratory support in the
203 delivery room has been accompanied by a concurrent decrease in intubation at birth. These
204 changes in practice are understandable given the evidence relating to the efficacy and safety
205 of non-invasive respiratory support in preterm infants[4,7,19–21]. We posit that overall, the
206 increased use of non-invasive respiratory support is due to better implementation of
207 evidence from these randomised controlled trials, including COIN[21] and SUPPORT[22].

208 The increase in use of non-invasive respiratory support is proportionately most marked in the
209 most preterm cohort, with an over six-fold increase in CPAP usage from 0.7% (4/609) in 2016
210 to 4.8% (28/586) in 2021. However, the small numbers involved and our inability to adjust for
211 all confounders limit the strength of this conclusion.

212 Overall, mechanical ventilation remains the most used modality in this gestational age cohort.

213 The changes observed in our data are however worth considering, given there has been no
214 contemporaneous change in guidance around respiratory support methods in this age group

215 from national governing bodies such as the Resuscitation Council and the British Association
216 of Perinatal Medicine, nor any international guidance change. This increase represents a
217 statistically significant change in how clinicians are supporting breathing in most and
218 extremely preterm infants.

219 The hypothesis that the increase in non-invasive respiratory support was due to a reduction
220 in the use of mechanical ventilation in all age groups was formally assessed. Statistical analysis
221 showed a significant reduction in mechanical ventilation in this cohort between 2016 and
222 2021. As such, this hypothesis holds and the shift in clinical practice in neonatal units has been
223 a change from mechanical ventilation to non-invasive respiratory support.

224 Escalation of non-invasive respiratory support was assessed by requirement for mechanical
225 ventilation in the first week of life, for infants initially stabilised on non-invasive respiratory
226 support. Although more babies <28 weeks gestation were being supported with non-invasive
227 respiratory support in 2021 compared to 2016, the same proportion of this cohort required
228 escalation to mechanical ventilation over the same period.

229 Finally, outcomes were assessed at 36 weeks corrected GA. Infants who were initially
230 stabilised on non-invasive respiratory support and were escalated to mechanical ventilation
231 during their first week of life had reduced incidence of BPD compared to their peers who were
232 intubated in the delivery room.

233 The key strength of this work is that it provides the largest contemporary national study in
234 this age group focusing on non-invasive respiratory support. Whilst there have been several
235 previous trials of non-invasive respiratory support which have made significant impact on
236 clinical practice, their application to the extremely and most preterm cohorts is limited. From
237 the UK, data has been presented by Reynolds et al[11] showing the possibility of stabilising
238 some of the most premature babies using non-invasive respiratory support. Matching two UK

239 birth cohorts to RCTs in the field, Zivanovic et al[23] investigated HFNC as primary respiratory
240 support in preterm infants, but only included those >28 weeks.

241 Peart et al.[24], reviewing treatment guidelines issued by the American Academy of
242 Paediatrics, the International Liaison Committee on Resuscitation and the European
243 Consensus on the Management of RDS recently described the lack of representation of the
244 most premature infants in trials quoted in support for a non-invasive approach to
245 stabilisation. In support of Peart et al., our study, showing increased use of non-invasive
246 respiratory support in a patient cohort outside of these trial datasets, might add further
247 weight to the need for clinical trials to assess the risks and benefits of non-invasive respiratory
248 support in babies born at earlier gestations.

249 Evidence from randomised controlled trials involving NIV has, so far, not demonstrated a
250 reduction in mortality [25,26] but evolving practice such as increased and earlier use of non-
251 invasive surfactant administration and improved NIPPV delivery systems warrant high quality,
252 prospective, randomised studies to evaluate the impact of using NIV as the preferred mode
253 for even the most preterm infants.

254 A significant limitation of this study is the inability to fully analyse for confounders in the
255 association between need for non-invasive respiratory support escalation and poorer
256 outcomes. It is likely that infants who are deemed to be healthier by clinicians are those who
257 are initially supported with non-invasive respiratory support alone. Apgar scores are available
258 as part of the NNRD data set but were missing for a significant proportion of infants in this
259 study and therefore were excluded from analysis. Without adequately designed randomised
260 controlled trials, it will be challenging to unpick whether the infants who required escalation
261 to mechanical ventilation would have had similar or better outcomes had they been intubated
262 initially.

263 Whilst the NNRD remains a valued resource for research into perinatal care in the UK, its core
264 strength of large numbers and broad coverage is counterbalanced by a lack of granularity in
265 the data available. Any study drawing conclusions from large datasets, including our own, is
266 best viewed in tandem with studies from other sources including randomised controlled trials
267 that can provide a greater level of detail. Its reliance on data inputted routinely by clinicians
268 means that outside of fields designated as mandatory by the software, there is a wide variety
269 in the quality and accuracy of data inputted.

270 In addition to this, as with any study analysing large volumes of data, valid outcomes are
271 reliant on valid input. Some infants had missing outcomes for individual daily respiratory
272 parameters. Infants were excluded from analysis if they had more than 2 days' of respiratory
273 support data missing. There remains a very small proportion of infants (n=22) who were
274 included in the analysis but have missing outcomes on individual days of their first week of
275 life. We believe these are mostly accounted for by infants who were transferred to other
276 centres or who had died. Due to the small numbers of these infants and for transparency,
277 they were carried forwards in analysis.

278 Given the utility of datasets such as the NNRD, we believe that ongoing investment and
279 funding to enable these resources to best support research into improving patient care should
280 be a priority for funding bodies.

281 Another point of note is the potential increase in numbers of babies born in the most preterm
282 cohort following a change in BAPM guidelines in 2019[27]. Following this guidance, Smith et
283 al[28] clearly showed an increase in the number of infants born at 22-23 week GA receiving
284 survival-focused care. Overall, there was a decrease in the number of infants born under 30
285 weeks gestation (4,412 to 3,606) between 2016 to 2021, in keeping with a decline in birth
286 rates nationally. The proportion of most preterm infants increased from 13.8% (609/4,412) in

287 2016 to 16.3% (586/3,606) in 2021. If this trend continues, it will add weight to the need for
288 evidence-based guidelines for clinicians caring for infants at this GA. Research from other
289 countries with differing patient populations and guidelines for clinical practice still shows a
290 shift towards increasing use of non-invasive ventilation in extremely preterm infants[29],
291 further emphasising this.

292

293 **Conclusion**

294 Analysing a large national dataset, we showed that use of non-invasive respiratory support
295 continues to increase in infants born under 30 weeks gestation in England and Wales between
296 2016-2021. Whilst this has been accompanied by a decrease in escalation rates in infants born
297 between 28-30 weeks, no such concurrent change has been seen in their extremely preterm
298 counterparts. The benefits of non-invasive respiratory support are well established for
299 preterm infants born beyond 30 weeks gestation; however, further studies must focus on
300 whether there are benefits to the extremely preterm cohort. A national database evaluating
301 delivery room practice that addresses the weaknesses of NNRD and MMBRACE data would
302 also provide pertinent evidence in this field[30]. This analysis provides a strong impetus for
303 further research in the field of respiratory support of extremely preterm infants.

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305

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307 References

- 308 1. Owen LS, Manley BJ, Davis PG, Doyle LW. The evolution of modern respiratory care for
309 preterm infants. *The Lancet*. 2017 Apr 22;389(10079):1649–59.
- 310 2. Haumont D, Modi N, Saugstad OD, Antetere R, NguyenBa C, Turner M, et al. Evaluating
311 preterm care across Europe using the eNewborn European Network database. *Pediatr
312 Res*. 2020 Sept;88(3):484–95.
- 313 3. Kalikkot Thekkeveedu R, El-Saie A, Prakash V, Katakam L, Shivanna B. Ventilation-
314 Induced Lung Injury (VILI) in Neonates: Evidence-Based Concepts and Lung-Protective
315 Strategies. *J Clin Med*. 2022 Jan 22;11(3):557.
- 316 4. Sweet DG, Carnielli VP, Greisen G, Hallman M, Klebermass-Schrehof K, Ozek E, et al.
317 European Consensus Guidelines on the Management of Respiratory Distress
318 Syndrome: 2022 Update. *Neonatology*. 2023;120(1):3–23.
- 319 5. Schmolzer GM, Kumar M, Pichler G, Aziz K, O'Reilly M, Cheung PY. Non-invasive versus
320 invasive respiratory support in preterm infants at birth: systematic review and meta-
321 analysis. In: Database of Abstracts of Reviews of Effects (DARE): Quality-assessed
322 Reviews [Internet] [Internet]. Centre for Reviews and Dissemination (UK); 2013 [cited
323 2024 June 25]. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK164606/>
- 324 6. Fischer HS, Bühner C. Avoiding endotracheal ventilation to prevent bronchopulmonary
325 dysplasia: a meta-analysis. *Pediatrics*. 2013 Nov;132(5):e1351-1360.
- 326 7. Committee on Fetus and Newborn, American Academy of Pediatrics. Respiratory
327 support in preterm infants at birth. *Pediatrics*. 2014 Jan;133(1):171–4.
- 328 8. Bresesti I, Zivanovic S, Ives KN, Lista G, Roehr CC. National surveys of UK and Italian
329 neonatal units highlighted significant differences in the use of non-invasive respiratory
330 support. *Acta Paediatr Oslo Nor 1992*. 2019 May;108(5):865–9.
- 331 9. Kwok TC, Poulter C, Algarni S, Szatkowski L, Sharkey D. Respiratory management and
332 outcomes in high-risk preterm infants with development of a population outcome
333 dashboard. *Thorax*. 2023 Dec;78(12):1215–22.
- 334 10. Dargaville PA, Kamlin COF, Orsini F, Wang X, De Paoli AG, Kanmaz Kutman HG, et al.
335 Effect of Minimally Invasive Surfactant Therapy vs Sham Treatment on Death or
336 Bronchopulmonary Dysplasia in Preterm Infants With Respiratory Distress Syndrome:
337 The OPTIMIST-A Randomized Clinical Trial. *JAMA*. 2021 Dec 28;326(24):2478–87.
- 338 11. Reynolds P, Leontiadi S, Lawson T, Otunla T, Ejiwumi O, Holland N. Stabilisation of
339 premature infants in the delivery room with nasal high flow. *Arch Dis Child Fetal
340 Neonatal Ed*. 2016 July;101(4):F284-287.
- 341 12. Roberts CT, Owen LS, Manley BJ, Frøisland DH, Donath SM, Dalziel KM, et al. Nasal High-
342 Flow Therapy for Primary Respiratory Support in Preterm Infants. *N Engl J Med*. 2016
343 Sept 22;375(12):1142–51.

- 344 13. Manley BJ, Arnolda GRB, Wright IMR, Owen LS, Foster JP, Huang L, et al. Nasal High-Flow
345 Therapy for Newborn Infants in Special Care Nurseries. *N Engl J Med*. 2019 May
346 23;380(21):2031–40.
- 347 14. Lavizzari A, Colnaghi M, Ciuffini F, Veneroni C, Musumeci S, Cortinovis I, et al. Heated,
348 Humidified High-Flow Nasal Cannula vs Nasal Continuous Positive Airway Pressure for
349 Respiratory Distress Syndrome of Prematurity: A Randomized Clinical Noninferiority
350 Trial. *JAMA Pediatr*. 2016 Aug 8;
- 351 15. Roehr CC, Farley HJ, Mahmoud RA, Ojha S. Non-Invasive Ventilatory Support in Preterm
352 Neonates in the Delivery Room and the Neonatal Intensive Care Unit: A Short Narrative
353 Review of What We Know in 2024. *Neonatology*. 2024;121(5):576–83.
- 354 16. Sand L, Szatkowski L, Kwok TC, Sharkey D, Todd DA, Budge H, et al. Observational cohort
355 study of changing trends in non-invasive ventilation in very preterm infants and
356 associations with clinical outcomes. *Arch Dis Child Fetal Neonatal Ed*. 2022
357 Mar;107(2):150–5.
- 358 17. Battersby C, Statnikov Y, Santhakumaran S, Gray D, Modi N, Costeloe K, et al. The United
359 Kingdom National Neonatal Research Database: A validation study. Simeoni U, editor.
360 *PLOS ONE*. 2018 Aug 16;13(8):e0201815.
- 361 18. Jensen EA, Dysart K, Gantz MG, McDonald S, Bamat NA, Keszler M, et al. The Diagnosis
362 of Bronchopulmonary Dysplasia in Very Preterm Infants. An Evidence-based Approach.
363 *Am J Respir Crit Care Med*. 2019 Sept 15;200(6):751–9.
- 364 19. Mahmoud RA, Schmalisch G, Oswal A, Christoph Roehr C. Non-invasive ventilatory
365 support in neonates: An evidence-based update. *Paediatr Respir Rev*. 2022 Dec
366 1;44:11–8.
- 367 20. Farley H, Ojha S, Roehr CC. Non-Invasive Intermittent Positive Pressure Ventilation:
368 Addressing the “Achilles Heel” of Systematic Reviews on Non-Invasive Ventilation in
369 Premature Infants – An Argument for More Contemporaneous, Well-Conducted Trials.
370 *Neonatology*. 2025 May 23;385–7.
- 371 21. Roehr CC, Proquitté H, Hammer H, Wauer RR, Morley CJ, Schmalisch G. Positive effects
372 of early continuous positive airway pressure on pulmonary function in extremely
373 premature infants: results of a subgroup analysis of the COIN trial. *Arch Dis Child Fetal
374 Neonatal Ed*. 2011 Sept;96(5):F371-373.
- 375 22. SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research
376 Network, Finer NN, Carlo WA, Walsh MC, Rich W, Gantz MG, et al. Early CPAP versus
377 surfactant in extremely preterm infants. *N Engl J Med*. 2010 May 27;362(21):1970–9.
- 378 23. Zivanovic S, Scrivens A, Panza R, Reynolds P, Laforgia N, Ives KN, et al. Nasal High-Flow
379 Therapy as Primary Respiratory Support for Preterm Infants without the Need for
380 Rescue with Nasal Continuous Positive Airway Pressure. *Neonatology*.
381 2019;115(2):175–81.

- 382 24. Peart S, Kahvo M, Alarcon-Martinez T, Hodgson K, Eger HS, Donath S, et al. Clinical
383 Guidelines for Management of Infants Born before 25 Weeks of Gestation: How
384 Representative Is the Current Evidence? *J Pediatr*. 2025 Mar;278:114423.
- 385 25. Morley CJ, Davis PG, Doyle LW, Brion LP, Hascoet JM, Carlin JB. Nasal CPAP or Intubation
386 at Birth for Very Preterm Infants. *N Engl J Med*. 2008 Feb 14;358(7):700–8.
- 387 26. Isayama T, Iwami H, McDonald S, Beyene J. Association of Noninvasive Ventilation
388 Strategies With Mortality and Bronchopulmonary Dysplasia Among Preterm Infants: A
389 Systematic Review and Meta-analysis. *JAMA*. 2016 Aug 9;316(6):611–24.
- 390 27. British Association of Perinatal Medicine. Perinatal Management of Extreme Preterm
391 Birth Before 27 weeks of Gestation. 2019.
- 392 28. Smith LK, van Blankenstein E, Fox G, Seaton SE, Martínez-Jiménez M, Petrou S, et al.
393 Effect of national guidance on survival for babies born at 22 weeks' gestation in
394 England and Wales: population based cohort study. *BMJ Med*. 2023;2(1):e000579.
- 395 29. Boesveld M, Hemels MAC, Knol R, Logtens-Abels SAMJ, Hütten MC, Witlox RS, et al.
396 Primary respiratory support of extremely preterm neonates in the Netherlands: a
397 national survey. *Early Hum Dev*. 2025 Feb;201:106182.
- 398 30. Farley H, Roehr CC. Effect of national guidance on survival for babies born at 22 weeks'
399 gestation in England and Wales: implications for future research. *Arch Dis Child - Fetal*
400 *Neonatal Ed* [Internet]. 2025 June 19 [cited 2025 Oct 8]; Available from:
401 <https://fn.bmj.com/content/early/2025/06/19/archdischild-2025-328935>

Table 1. Characteristics of infants born at <30 weeks' gestation in England and Wales (2016 to 2021) and those who received CPAP, HFNC, or mechanical ventilation as the highest respiratory support in the delivery room

	All infants	CPAP in delivery room	HFNC in delivery room	Mechanical ventilation in delivery room
	n = 24,107	n = 5,637	n = 125	n = 15,795
GA (weeks, median (IQR))	27+4 (25+6-28+6)	28+5 (27+5-29+3)	27+4 (26+1-29+0)	26+5 (25+1-28+2)
Birth weight (grams, median (IQR))	960 (750-1,180)	1,100 (910-1,290)	845 (693-1,030)	880 (698-1,095)
Birth weight z-score (mean (SD))	-0.144 (0.99)	-0.146 (0.99)	-0.611 (1.05)	-0.156 (0.96)
Female n (%)	10,953 (45.4%)	2,567 (45.5%)	59 (47.2%)	7,156 (45.3%)
Any antenatal steroids n (%)	21,870 (72%)	5,320 (94.4%)	121 (96.8%)	14,182 (89.8%)
GA <25 weeks	n = 3,675	n = 79	n = 10	n = 3,470
GA (weeks, median (IQR))	24+1 (23+4-24+4)	24+2 (23+5-24+4)	24+3 (24+0-24+6)	24+1 (23+4-24+4)
Birth weight (grams, median (IQR))	629 (560-700)	620 (557-695)	623.5 (600-692)	630 (560-698)
Birth weight z-score (mean (SD))	-0.153 (0.77)	-0.281 (0.76)	-0.259 (0.70)	-0.153 (0.77)
Female sex n (%)	1,676 (45.6%)	35 (44.3%)	4 (40.0%)	1596 (46.0%)
Any antenatal steroids n (%)	3,184 (86.6%)	72 (91.1%)	8 (80%)	3025 (87.2%)
GA <28 weeks	n = 13,310	n = 1,585	n = 74	n = 10,844
GA (weeks, median (IQR))	26+0 (24+5-27+1)	27+0 (26+3-27+4)	26+2 (25+2-27+1)	25+6 (24+4-26+6)
Birth weight (grams, median (IQR))	800 (660-960)	915 (780-1,035)	740 (638-893)	780 (645-935)
Birth weight z-score (mean (SD))	-0.173 (0.90)	-0.199 (0.91)	-0.648 (0.89)	-0.169 (0.90)
Female sex n (%)	6,077 (45.7%)	714 (45.1%)	37 (50.0%)	4,955 (45.7%)
Any antenatal steroids n (%)	11,955 (89.8%)	1,484 (93.6%)	72 (97.3%)	9,716 (89.6%)
28-29 weeks	n = 10,797	n = 4,052	n = 51	n = 4,951
GA (weeks, median (IQR))	29+0 (28+3-29+3)	29+1 (28+4-29+4)	29+2 (28+5-29+5)	28+6 (28+3-29+3)
Birth weight (grams, median (IQR))	1,190 (1,010-1,340)	1,190 (1,003-1,345)	1,077 (862-1,265)	1,180 (1,000-1,323)
Birth weight z-score (mean (SD))	-0.107 (1.04)	-0.125 (1.02)	-0.557 (1.26)	-0.129 (1.07)
Female sex n (%)	4,876 (45.2%)	1,853 (45.7%)	22 (43.1%)	2,201 (44.5%)
Any antenatal steroids n (%)	9,915 (91.8%)	3,836 (94.7%)	49 (96.1%)	4,466 (90.2%)
CPAP, continuous positive airway pressure; GA, gestational age; IQR, interquartile range; HFNC, high flow nasal cannula oxygen; SD, standard deviation				

Table 2. Highest delivery room respiratory support in infants born at <30 weeks' gestation in England and Wales (2016 to 2021)

Highest method of support in delivery room						
	All	No support	Supplemental oxygen only	CPAP	HFNC	Mechanical ventilation
Year	Total (n)	N (%)	N (%)	N (%)	N (%)	N (%)
2016	4,412	256 (5.8)	201 (4.6)	764 (17.3)	0	3,191 (72.3)
2017	4,319	204 (4.7)	195 (4.5)	926 (21.4)	14 (0.3)	2,980 (69.0)
2018	4,058	225 (5.5)	206 (5.1)	873 (21.5)	25 (0.6)	2,729 (67.2)
2019	4,063	254 (6.3)	205 (5.0)	1,007 (24.8)	32 (0.8)	2,565 (63.1)
2020	3,649	212 (5.8)	198 (5.4)	1,029 (28.2)	29 (0.8)	2,181 (59.8)
2021	3,606	181 (5.0)	213 (5.9)	1,038 (28.8)	25 (0.7)	2,149 (59.6)
All	24,107	1,332 (5.5)	1,218 (5.1)	5,637 (23.4)	125 (0.5)	15,795 (65.5)
28-29 weeks' gestational age						
2016	2,022	188 (9.3)	147 (7.3)	593 (29.3)	0	1,094 (54.1)
2017	1,994	153 (7.7)	136 (6.8)	714 (35.8)	2 (0.1)	989 (49.6)
2018	1,770	150 (8.5)	146 (8.2)	630 (35.6)	8 (0.5)	836 (47.2)
2019	1,832	170 (9.3)	140 (7.6)	727 (39.7)	17 (0.9)	778 (42.5)
2020	1,645	147 (8.9)	135 (8.2)	712 (43.3)	13 (0.8)	638 (38.8)
2021	1,534	103 (6.7)	128 (8.3)	676 (44.1)	11 (0.7)	616 (40.2)
All	10,797	911 (8.4)	832 (7.7)	4,052 (37.5)	51 (0.5)	4,951 (45.9)
<28 weeks' gestational age						
2016	2,390	68 (2.8)	54 (2.3)	171 (7.2)	0	2,097 (87.7)
2017	2,325	51 (2.2)	59 (2.5)	212 (9.1)	12 (0.5)	1,991 (85.6)
2018	2,288	75 (3.3)	60 (2.6)	243 (10.6)	17 (0.7)	1,893 (82.7)
2019	2,231	84 (3.8)	65 (2.9)	280 (12.6)	15 (0.7)	1,787 (80.1)
2020	2,004	65 (3.2)	63 (3.1)	317 (15.8)	16 (0.8)	1,543 (77.0)
2021	2,072	78 (3.8)	85 (4.1)	362 (17.5)	14 (0.7)	1,533 (74.0)
All	13,310	421 (3.2)	386 (2.9)	1,585 (11.9)	74 (0.6)	10,844 (81.5)
<25 weeks' gestational age						
2016	609	11 (1.8)	8 (1.3)	4 (0.7)	0	586 (96.2)
2017	641	15 (2.3)	7 (1.1)	5 (0.8)	0	614 (95.8)
2018	639	8 (1.3)	5 (0.8)	8 (1.3)	1 (0.2)	617 (96.6)
2019	627	12 (1.9)	9 (1.4)	15 (2.4)	3 (0.5)	588 (93.8)
2020	573	10 (1.7)	5 (0.9)	19 (3.3)	5 (0.9)	534 (93.2)
2021	586	13 (2.2)	13 (2.2)	28 (4.8)	1 (0.2)	531 (90.6)
All	3,675	69 (1.9)	47 (1.3)	79 (2.1)	10 (0.3)	3,470 (94.4)
CPAP, continuous positive airway pressure; HFNC, high flow nasal cannula oxygen Change from 2016 to 2021 in CPAP: <25 weeks' GA p<0.005; <28 weeks' GA p<0.005; 28-29 weeks' GA, p<0.005 and in mechanical ventilation: <25 weeks' GA p<0.005; <28 weeks' GA p<0.005; 28-29 weeks' GA, p<0.005						

Table 3. Highest respiratory support on day 1 of neonatal care in infants born at <30 weeks' gestation in England and Wales (2016 to 2021)

Highest level of respiratory support in neonatal unit on day 1 of care					
	All	No support	Supplemental oxygen only	NIV	Mechanical ventilation
Year	Total (n)	N (%)	N (%)	N (%)	N (%)
2016	4,412	88 (2.0)	3 (0.1)	869 (19.7)	3,452 (78.2)
2017	4,319	83 (1.9)	3 (0.1)	925 (21.4)	3,308 (76.6)
2018	4,058	66 (1.6)	8 (0.2)	904 (22.3)	3,080 (75.9)
2019	4,063	81 (2.0)	2 (0.0)	1,049 (25.8)	2,931 (72.1)
2020	3,649	76 (2.1)	1 (0.0)	1,053 (28.9)	2,519 (69.0)
2021	3,606	77 (2.1)	3 (0.1)	1,059 (29.4)	2,467 (68.4)
All	24,107	471 (2.0%)	20 (0.1)	5,859 (24.3)	17,757 (73.7)
28-29 weeks' gestational age					
2016	2,022	56 (2.8)	2 (0.1)	690 (34.1)	1,274 (63)
2017	1,994	52 (2.6)	2 (0.1)	727 (36.5)	1,213 (60.8)
2018	1,770	37 (2.1)	5 (0.3)	658 (37.2)	1,070 (60.5)
2019	1,832	38 (2.1)	1 (0.1)	790 (43.1)	1,003 (54.7)
2020	1,645	32 (1.9)	1 (0.1)	787 (47.8)	825 (50.2)
2021	1,534	31 (2.0)	3 (0.2)	715 (46.6)	785 (51.2)
All	10,797	246 (2.3)	14 (0.1)	4,367 (40.4)	6,170 (57.1)
<28 weeks' gestational age					
2016	2,390	32 (1.3)	1 (0)	179 (7.5)	2,178 (91.1)
2017	2,325	31 (1.3)	1 (0)	198 (8.5)	2,095 (90.1)
2018	2,288	29 (1.3)	3 (0.1)	246 (10.8)	2,010 (87.8)
2019	2,231	43 (1.9)	1 (0)	259 (11.6)	1,928 (86.4)
2020	2,004	44 (2.2)	0 (0)	266 (13.3)	1,694 (84.5)
2021	2,072	46 (2.2)	0 (0)	344 (16.6)	1,682 (81.2)
All	13,310	225 (1.7)	6 (0)	1,492 (11.2)	11,587 (87.1)
<25 weeks' gestational age					
2016	609	9 (1.5)	0 (0)	6 (1.0)	594 (97.5)
2017	628	6 (1.0)	0 (0)	7 (1.1)	615 (97.9)
2018	622	10 (1.6)	0 (0)	7 (1.1)	605 (97.3)
2019	603	12 (2.0)	1 (0.2)	11 (1.8)	579 (96.0)
2020	539	18 (3.3)	0 (0)	16 (3.0)	505 (93.7)
2021	551	16 (2.9)	0 (0)	19 (3.4)	516 (93.6)
All	3,675	71 (1.9)	0 (0)	66 (1.8)	3,537 (96.2)
CPAP, continuous positive airway pressure					

Outcome	All infants	Received MV in delivery suite	Received CPAP in delivery suite	Received CPAP in delivery suite	
				Remained on non-invasive support until day 7 (CPAP-NI)	Received mechanical ventilation by day 7 (CPAP-MV)
n	24,107	15,741	5,637	2,870	2,736
BPD	11,138 (46.2%)	8,302 (52.7%)	1,923 (34.1%)	688 (24.0%)	1,233 (45.1%)
Death before discharge	2,551 (10.6%)	2,279 (14.5%)	148 (2.6%)	29 (1.0%)	116 (4.2%)
BPD or death before discharge	13,689 (56.8%)	10,581 (67.2%)	2,071 (36.7%)	717 (25.0%)	1,349 (49.3%)

Table 4: Outcomes at 36 weeks corrected gestational age for CPAP-MV and CPAP-NI groups