Temporal trends in respiratory care and bronchopulmonary dysplasia in very preterm infants over a 10-year period in Spain

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Abstract

Objective To evaluate trends in respiratory care practices and bronchopulmonary dysplasia (BPD) among very preterm infants born in Spain between 2010 and 2019.

Study design This was a retrospective cohort study of data obtained from a national population-based database (SEN1500 network). Changes in respiratory care and BPD-free survival of infants with gestational age (GA) of 23^0–31^6 weeks and <1500 g were assessed over two 5-year periods. Temporal trends were examined by joinpoint and Poisson regression models and expressed as the annual per cent change and adjusted relative risk (RR) for the change per year.

Results A total of 17 952 infants were included. In the second period, infants were less frequently intubated in the delivery room and during neonatal intensive care unit stay. This corresponded with an increase in use of non-invasive ventilation techniques. There were no significant differences between the periods in BPD-free survival or survival without moderate-to-severe

BPD. After adjusting for covariates, the RR for the change per year was significant for the following variables: never intubated (RR 1.03, 95% CI 1.02 to 1.04); intubation in the delivery room (RR 0.98, 95% CI 0.97 to 0.99); use of nasal intermittent positive pressure ventilation (RR 1.08, 95% CI 1.05 to 1.11); and BPD-free survival (only in the group with the lowest GA; RR 0.98, 95% CI 0.97 to 0.99).

Conclusion Our findings reveal significant changes in respiratory care practices between 2009 and 2019. Despite an increase in use of non-invasive respiratory strategies, BPD-free survival did not improve and even worsened in the group with the lowest GA (23^0–25^6).

INTRODUCTION

Among very preterm infants, bronchopulmonary dysplasia (BPD) is the most prevalent morbidity and is associated with prolonged hospitalisation in the neonatal period, growth failure, long-term pulmonary impairment, increased healthcare costs and worse neurological outcomes.[1–4]

BPD results from a complex interaction between immaturity, genetic predisposition, and perinatal or postnatal insults.[1] In this context, ventilator-induced lung injury caused by invasive respiratory support is a central factor in the BPD pathogenesis.[5,6] Avoidance of invasive mechanical ventilation (IMV) has thus became a priority in modern neonatal care, and infants today receive less invasive respiratory support compared with several decades ago.[7,8] However, emerging evidence indicates that significant improvements in mortality in recent years have not been accompanied by consistent improvements in BPD rates.[8–12] Whether this discrepancy is influenced by increased survival of the most immature infants or our inability to prevent BPD remains a matter of debate.

Over the last few decades, different modes of non-invasive ventilatory support, such as nasal intermittent positive pressure ventilation (NIPPV) and high-flow nasal cannula therapy (HFNC), as well as new techniques for surfactant adminis- tration have been progressively incorporated into clinical practice worldwide[13,14] and may have influenced the global picture of respiratory morbidity. Moreover, the availability of accurate, up-to-date trend data linked to clinical practice is essential to identify areas of improvement, facilitate ision making and optimise healthcare resources.[15,16]

In the present study we describe trends (2010–2019) in respiratory care and respiratory outcomes among very preterm and very low birthweight infants in Spain, and investigate the hypothesis that management has become less invasive and respi- ratory outcomes have improved over time.

MATERIALS AND METHODS

Study design and population

This multicentre cohort study is a retrospective analysis of data collected prospectively from the Spanish SEN1500 network database. This database was created in 2002, and a variable number of neonatal units with representation of most admin- istrative regions participate voluntarily.[17] During the study period, 79 units contributed data at some point, but only 67 did so consistently throughout the period and were included in the study. We collect approximately two-thirds of all very low birth- weight infants born in Spain, according to data from the Spanish National Institute of Statistics.

Only patients born between 23^0 and 31^6 weeks gestational age (GA) and weighing <1500 g were eligible for inclusion. Outborn patients, infants who died in the delivery room (DR), and those with chromosomal and/or major congenital anomalies were also excluded from the study. The study period comprised 10 years, from 1 January 2010 to 31 December 2019.

Outcome variables and definitions

The following variables were extracted from the original database: demographic data (GA, birth weight, sex); perinatal characteristics (antenatal steroid treatment, maternal hypertension, chorioamnionitis, mode of delivery); stabilisation in the DR (supplementary oxygen, continuous positive airway pressure (CPAP), positive pressure ventilation, intubation, chest compressions, epinephrine); respiratory support after stabilisation in the DR (surfactant, CPAP, NIPPV, HFNC, IMV); and clinical outcomes (mortality, BPD, patent ductus arteriosus (PDA), pneumothorax, sepsis).

The main exposure of interest was respiratory support without IMV (never intubated or intubated only for the purpose of surfactant administration) during the neonatal

admission. The primary respiratory outcome was survival without BPD. The secondary outcomes were survival, survival without moderate-to-severe BPD, intubation in the DR and use of NIPPV. A subgroup analysis of patients by GA strata (23^0–25^6, 26^0–28^6 and 29^0–31^6 weeks) was preplanned.

BPD was defined as the need for supplementary oxygen for at least 28 days and classified as moderate or severe depending on oxygen requirements and respiratory support at 36 weeks post- menstrual age.[18,19] Mortality was defined as death before first hospital discharge. PDA was diagnosed by echocardiography and managed according to local protocols. Closure of the PDA (phar- macological or surgical) was recorded. Small for GA (SGA) was defined as less than the 10th percentile according to Fenton's growth charts.

Statistical analysis

Descriptive data are presented as mean±SD or n/N (%). The sample was divided into two study periods (2010–2014 and 2015–2019). Respiratory practices and outcomes were compared between the two periods using the Student's t-test or Mann- Whitney U test for continuous variables and the Fisher's exact test for categorical variables. Temporal trends in respiratory care and BPD were evaluated using joinpoint regression. The Joinpoint Regression Program V.4.8 (National Cancer Institute, Bethesda, Maryland) was used to detect significant changes in the rate of events over time.[20] Default settings were employed, with up to two joinpoints, requiring at least two observations between joinpoints. A log-linear regression model was used and, in each case, the model with an optimal number of binding points was selected according to the results of the Monte Carlo permutation test. Each joinpoint in the final model corresponds to a statistically significant change in the temporal trend, and the annual per cent change (APC) is calculated to describe how the rate changes within each distinct time interval.

Trends in outcomes were further assessed using Poisson regression models with robust variance estimators, considering year as a continuous variable and accounting for clustering for hospital by using an exchangeable working correlation.[21] From these models, relative risk and 95% CI for the change per year were computed. In addition to considering the effect of the study centre, analyses were adjusted by sex, GA, SGA, prenatal steroids, multiple gestation, surfactant, chorioamnionitis and mode of delivery.

These parameters were selected as covari- ates prior to analysis based on clinical judgement and previous research.

Analyses were performed using the R statistical programming language (R Foundation for Statistical Computing, Vienna, Austria). Results were considered as statistically significant for bilateral p values <0.05.

RESULTS

A total of 20 564 neonates <1500 g and aged 23^0–31^6 weeks were born alive in the participating units during the study period. Of these, 17 952 were included in the study after applying exclusion criteria (figure 1). The entire cohort was divided into two 5-year periods: 9343 infants in period 1 (2010–2014) and 8609 infants in period 2 (2015–2019). There were no significant differences between periods in the demographic characteristics of the infants, except for a slight increase in the proportion of infants 23^0–25^6 in the second period (15.0% vs 16.4%, p=0.009; online supplemental table 1). Exposure to prenatal steroids was higher in the second period, but a high rate of steroid administration was observed in both periods (91.4% and 93.4%, respectively, p<0.001).

The univariate analysis revealed significant differences between periods for certain interventions performed in the DR and the neonatal intensive care unit (NICU; table 1). Overall, the use of CPAP and supplemental oxygen in the DR increased and the rate of intubation in the DR decreased in the second versus the first study period. Infants in the second period were less frequently intubated during the NICU admission and more frequently received respiratory support with non-invasive ventilation modes. Despite these differences in respiratory support, the univariate analysis of respiratory outcomes showed no signif- icant differences between periods in terms of survival, survival without BPD or survival without moderate-to-severe BPD (table 2). Rates of survival without BPD by GA are shown in online supplemental figure 2.

Joinpoint regression analysis for selected outcomes (figure 2 and online supplemental figure 1) showed a significant upward temporal trend during the study period for never intubated (APC 4.3, 95% CI 3.4 to 5.1) and use of NIPPV (APC 7.1, 95% CI 5.6 to 8.6), and a significant downward trend for intubation in the DR (APC −3.2, 95% CI −4 to −2.4). Again, no significant trends were observed for survival (APC 0.1, 95% CI −0.1 to 0.4) or survival without BPD (APC −0.3, 95% CI −0.6 to 0). A preplanned stratified

analysis by GA (online supplemental table 2) revealed an improvement in survival rates of infants born at 29^0–31^6 weeks GA, but not improvement in survival or even a worsening of rates of survival without BPD in the group of infants with the lowest GA (23^0–25^6 weeks).

Finally, the adjusted risk ratio for the change per year was statistically significant for never intubated, intubation in the DR, use of NIPPV and survival without BPD only in the group of infants with the lowest GA (table 3).

DISCUSSION

In this large, multicentre, national cohort study we examined secular trends in respiratory care and BPD in very low birth- weight and very preterm infants. We found that despite a significant decrease in invasive respiratory management, rates of survival without BPD did not improve over the study period, and even worsened slightly in the 23^0–25^6 weeks GA group.

NIV, together with prenatal steroids and early surfactant therapy, is considered the current mainstay treatment and standard practice in preterm infants in order to avoid IMV. We found that NIV use steadily increased during the study period in Spain, in keeping with current evidence and international recommen- dations.[7] Specifically, we observed an increase in the use of CPAP, NIPPV and HFNC, in line with previous reports.[22,23] However, there is no consistent evidence of an association between NIV use and better respiratory outcomes. In fact, early comparisons of CPAP with intubation and IMV revealed only a modest benefit in terms of the combined outcome of death or BPD at 36 weeks postmenstrual age,[24–26] and a meta-analysis involving a total of 3289 infants showed that avoiding IMV had a small but significantly beneficial impact on the incidence of BPD.[5] Moreover, most studies examining secular trends in respiratory outcomes have reported no significant improvements in BPD and other long-term respiratory outcomes over time.[8,16,23,27,28] In our last retrospective analysis of data obtained from the SEN1500 network comparing two periods (2002–2006 vs 2007–2011), we observed only a moderate increase (from 26.6% to 31.6%) in the BPD-free survival rate among infants born at 23–26 weeks GA, despite a significant increase in NIV use in the DR and NICU.[10] These findings were not confirmed in the present study, in which the

moderate-to-severe BPD-free survival rate remained constant and the BPD-free survival rate was slightly lower in the most immature infants.

Several factors have been proposed to explain this apparent lack of improvement in BPD incidence.[11] First, the definition of BPD itself is constantly evolving and is a subject of debate in the field of neonatal medicine. Most existing definitions, including that used in our database, consider BPD as a 'yes or no' phenomenon and do not account for the broad phenotypic diversity and the varying degrees of severity observed in clinical practice. Moreover, these definitions are predominantly based on the duration of supplemental oxygen requirement, without taking into account new NIV modes that are currently used.[1,29] Another factor that could contribute to our findings is the prolonged duration of overall respiratory support and supplemental oxygen described in preterm newborns receiving less invasive respiratory support.[8,23] Increased active resuscitation and increased survival of most immature babies can partially explain the findings of other series,[9] but not ours, since the survival rate remained virtually static throughout the study period.

Antenatal steroids accelerate lung maturation and reduce the need for IMV and the risk of death but, according to a recent Cochrane review,[30] do not significantly reduce rates of BPD. In our study, exposure to antenatal steroids was higher in the second period of the study, although rates remained high in both periods (over 90%) and were higher than those previously reported,[12,28,31] which may have limited their potential impact on outcomes. Given that the relationship between PDA and BPD remains a matter of debate, PDA was included as a variable in the present study. Overall, in keeping with previous reports,[28] we observed a decrease in the rate of PDA treatment. Whether this decrease may have influenced our findings for respiratory outcomes cannot be determined given the study design used. The rate of late-onset sepsis, another recognised risk factor for BPD,[32] was significantly lower in the second period of the study. Interestingly, this change was not observed in the group of infants with the lowest GA, in which rates of BPD-free survival worsened during the study period.

Finally, BPD is aetiologically complex and multifactorial in origin, resulting from a variety of sequential insults to an immature lung. Our results suggest that avoiding IMV might not be sufficient to prevent BPD in some premature infants. For this reason, modes of NIV other than CPAP are increasingly being incorporated into clinical practice.[33,34]

During the second period of our study we observed a marked increase in the use of NIPPV, although the evidence supporting its use is limited and little is known about the underlying mechanism of action.[33–35] Some studies suggest that the incidence of respiratory failure and the need for intubation are reduced by NIPPV compared with CPAP.[36,37] However, how this translates into improved respiratory morbidity is less clear, and most individual studies and meta-analyses report moderate or no effect on BPD rates.[37,38] Unfortunately, because the database used in the present study did not systematically collect precise data on NIPPV indication, timing, devices used, synchronisation, interfaces or settings, no firm conclusions could be established in this regard. Encourag- ingly, we found no significant difference in the rates of complications potentially related to NIPPV (spontaneous intestinal perforation and pneumothorax).

Apart from the lack of improvement in BPD rates, there was an increasing exposure to oxygen in the DR, which we speculate to be a consequence to the publication, after International Liaison Committee Resuscitation 2015 guidelines, of several studies in which moderate hypoxaemia and resuscitation with air were associated with adverse outcomes.[39,40] Moreover and in keeping with the policy of early rescue surfactant advocated by European guidelines, the surfactant use in the DR decreased in the second period. The observation of longer exposure to oxygen was previously reported in a trend analysis in Melbourne,[8] which in our opinion can be related to changes in oxygenation targets or prolonged periods of NIV. Finally, we do not have a clear explanation for the increased (and earlier) use of postnatal corti- costeroids for BPD, whose indication is still a matter of debate in current neonatal medicine.

The present study has some limitations. The database from which we acquired out data was hospital-based rather than population-based, and therefore may not be representative of the entire Spanish population. Not including babies who died in the DR precluded us from extracting conclusions about changes in this outcome. Furthermore, our original database lacked data on other practices that could potentially have influenced the rate of BPD and may have changed over time. The strengths of our study include a large national cohort, its multicentre nature and the detailed evaluation of standardised outcomes within the context of the SEN1500 network.

In conclusion, our findings suggest that despite increased use of NIV, BPD-free survival has not improved significantly in Spain over the last 10 years. This may indicate that avoidance of endotracheal intubation is not sufficient as a single strategy to improve respiratory outcomes. Further studies are needed to identify better strategies to improve BPD outcomes in very preterm infants.

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Contributors AA-A, CZ and FG-MR conceived the study. AA-A wrote the first draft of the manuscript. CZ, FG-MR, MS-L, MDE and MI-S edited and reviewed the manuscript and made important intellectual contributions. CZ and FG-MR contributed to data selection and extraction and presentation of the results. SP-D provided guidance in statistical analysis, preparation of figures and interpretation of results. All authors discussed, revised and approved the final manuscript.

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Research ethics approval for data collection at the first author's institution was obtained from A Coruña-Ferrol Research Ethics Committee (ref 2017/360). This study protocol has no specific ethical approval as it only gathers anonymised data.

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Data availability statement Data supporting the findings of this study (deidentified participant data) are available upon request to the corresponding author.

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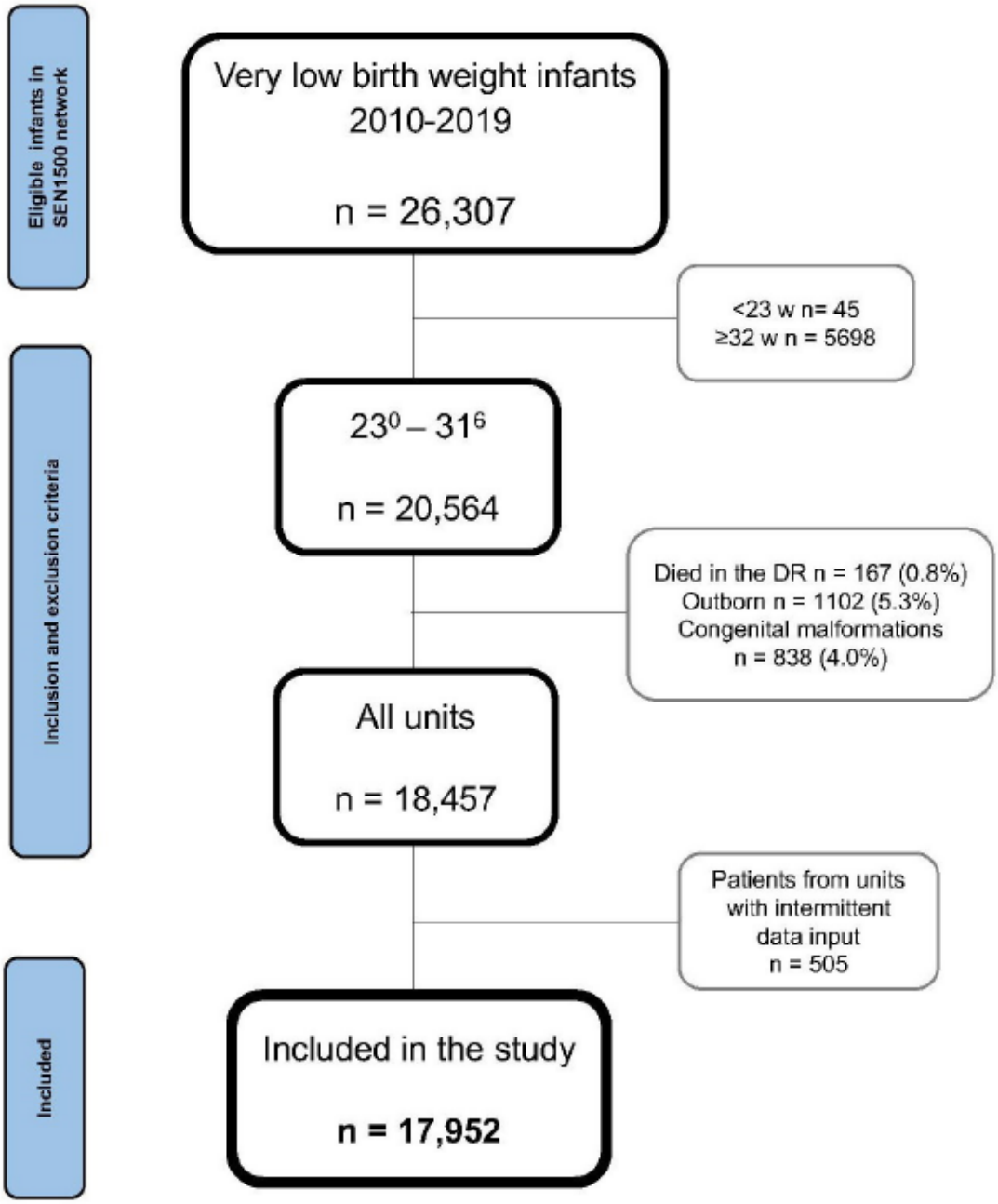


Figure 1 Flow chart depicting recruitment of the cohort. DR, delivery room.

Table 1 Interventions performed in the DR and during NICU admission in the two study periods

	2010–2014 n=9343	2015–2019 n=8609	P value
Supplemental oxygen in the DR			
23^0–25^6	1261 (90.0)	1312 (92.7)	0.009
26^0–28^6	2821 (80.7)	2782 (87.7)	<0.001
29^0–31^6	2677 (60.1)	2722 (67.6)	<0.001
Total	6759 (72.3)	6816 (79.1)	<0.001
CPAP in the DR			
23^0–25^6	335 (23.9)	544 (38.4)	<0.001
26^0–28^6	1658 (47.4)	2005 (63.2)	<0.001
29^0–31^6	2351 (52.8)	2715 (67.4)	<0.001
Total	4344 (46.4)	5264 (61.1)	<0.001
NIPPV in the DR			
23^0–25^6	1101 (78.5)	1084 (76.6)	0.222
26^0–28^6	2526 (72.3)	2152 (67.8)	<0.001
29^0–31^6	2328 (52.3)	2102 (52.2)	0.948
Total	5955 (63.7)	5338 (62)	0.017
Intubation in the DR			
23^0–25^6	1115 (79.5)	993 (70.2)	<0.001
26^0–28^6	1650 (47.2)	1244 (39.2)	<0.001
29^0–31^6	769 (17.2)	506 (12.5)	<0.001
Total	3534 (37.8)	2743 (31.8)	<0.001
Chest compressions in the DR			
23^0–25^6	156 (11.1)	148 (10.4)	0.585
26^0–28^6	277 (7.9)	209 (6.5)	0.038
29^0–31^6	144 (3.2)	124 (3.0)	0.709
Total	577 (6.1)	481 (5.5)	0.099
Epinephrine in the DR			
23^0–25^6	107 (7.6)	98 (6.9)	0.514
26^0–28^6	168 (4.8)	123 (3.8)	0.072
29^0–31^6	93 (2.0)	54 (1.3)	0.01
Total	368 (3.9)	275 (3.1)	0.008
Surfactant in the DR			
23^0–25^6	348 (24.8)	304 (21.5)	0.036
26^0–28^6	474 (13.5)	341 (10.7)	<0.001

Table 1 Interventions performed in the DR and during NICU admission in the two study periods

	2010–2014 n=9343	2015–2019 n=8609	P value
29^0–31^6	142 (3.1)	116 (2.8)	0.447
Total	964 (10.3)	761 (8.8)	0.001
Surfactant (any time)			
23^0–25^6	1249 (89.1)	1191 (84.2)	<0.001
26^0–28^6	2436 (69.7)	2014 (63.5)	<0.001
29^0–31^6	1575 (35.3)	1359 (33.7)	0.12
Total	5260 (56.3)	4564 (53.0)	<0.001
Surfactant (number of doses)			
23^0–25^6	1.41±0.73	1.43±0.77	0.564
26^0–28^6	1.15±0.76	1.08±0.81	0.002
29^0–31^6	0.63±0.72	0.59±0.68	0.038
Total	0.98±0.80	0.94±0.82	0.009
Supplemental oxygen during admission			
23^0–25^6	1268 (90.5)	1322 (93.4)	0.004
26^0–28^6	2943 (84.2)	2738 (86.3)	0.019
29^0–31^6	2963 (66.5)	2592 (64.4)	0.037
Total	7174 (76.8)	6652 (77.2)	0.445
CPAP during admission			
23^0–25^6	802 (57.2)	840 (59.4)	0.252
26^0–28^6	2903 (83.1)	2752 (86.7)	<0.001
29^0–31^6	3547 (79.7)	3404 (84.5)	<0.001
Total	7252 (77.6)	6996 (81.2)	<0.001
NIPPV during admission			
23^0–25^6	489 (34.9)	659 (46.6)	<0.001
26^0–28^6	1169 (33.4)	1457 (45.9)	<0.001
29^0–31^6	835 (18.7)	1116 (27.7)	<0.001
Total	2493 (26.6)	3232 (37.5)	<0.001
HFNC during admission			
23^0–25^6	402 (28.6)	545 (38.5)	<0.001
26^0–28^6	1103 (31.5)	1557 (49.1)	<0.001
29^0–31^6	934 (20.9)	1316 (32.7)	<0.001
Total	2439 (26.1)	3418 (39.7)	<0.001

Table 1 Interventions performed in the DR and during NICU admission in the two study periods

	2010–2014 n=9343	2015–2019 n=8609	P value
HFOV during admission			
23^0–25^6	662 (47.2)	719 (50.8)	0.059
26^0–28^6	733 (20.9)	621 (19.5)	0.161
29^0–31^6	260 (5.8)	174 (4.3)	0.002
Total	1655 (17.7)	1514 (17.5)	0.829
Never intubated			
23^0–25^6	60 (4.2)	95 (6.7)	0.005
26^0–28^6	886 (25.3)	1194 (37.6)	<0.001
29^0–31^6	2776 (62.3)	2978 (74.0)	<0.001
Total	3722 (39.8)	4267 (49.5)	<0.001
Steroids for BPD			
23^0–25^6	284 (20.2)	374 (26.4)	<0.001
26^0–28^6	369 (10.5)	379 (11.9)	0.074
29^0–31^6	77 (1.7)	90 (2.2)	0.1
Total	730 (7.8)	843 (9.7)	<0.001
Steroids for BPD, day of life			
23^0–25^6	26.8±14.4	22.6±14.6	<0.001
26^0–28^6	29.5±17.7	25.9±17.3	0.008
29^0–31^6	30.0±15.5	28.5±15.2	0.555
Total	28.5±16.3	24.7±16.1	<0.001

Mean±SD for quantitative variables and n (%) for qualitative variables.

BPD, bronchopulmonary dysplasia; CPAP, continuous positive airway pressure; DR, delivery room; HFNC, high-flow nasal cannula; HFOV, high-frequency oscillatory ventilation; NICU, neonatal intensive care unit; NIPPV, non-invasive positive pressure ventilation.

Table 2 Respiratory morbidity and related outcomes in the two study periods

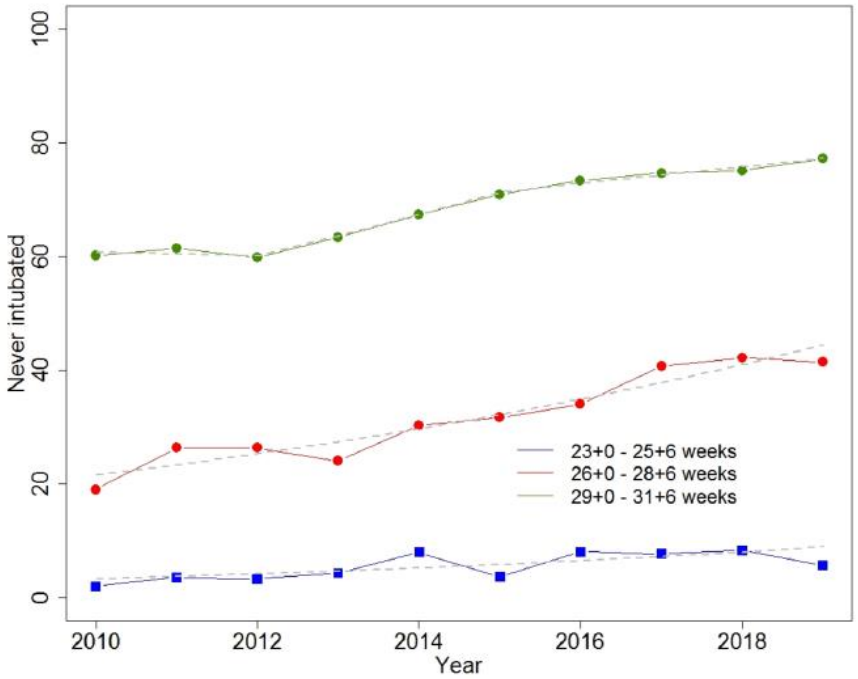
	2010–2014 n=9343	2015–2019 n=8609	P value
Survival			
23^0–25^6	735 (52.4)	753 (53.2)	0.678
26^0–28^6	3004 (86.0)	2775 (87.5)	0.076
29^0–31^6	4312 (96.9)	3925 (97.5)	0.075
Total	8051 (86.1)	7453 (86.5)	0.446
Survival without BPD			
23^0–25^6	168 (11.9)	126 (8.9)	0.008
26^0–28^6	1581 (45.2)	1443 (45.5)	0.863
29^0–31^6	3774 (84.8)	3489 (86.7)	0.013
Total	5523 (59.1)	5058 (58.7)	0.627
Survival without moderate-to-severe BPD			
23^0–25^6	390 (27.8)	381 (26.9)	0.612
26^0–28^6	2025 (57.9)	1912 (60.3)	0.058
29^0–31^6	3517 (79.0)	3243 (80.5)	0.078
Total	5932 (63.4)	5536 (64.3)	0.263
Pneumothorax			
23^0–25^6	163 (11.6)	153 (10.8)	0.512
26^0–28^6	183 (5.2)	163 (5.1)	0.868
29^0–31^6	124 (2.7)	87 (2.1)	0.07
Total	470 (5.0)	403 (4.6)	0.282
Duration of MV (hours)			
23^0–25^6	434.4±623.9	446.3±601.2	0.623
26^0–28^6	273.5±487.8	248.2±459.0	0.079
29^0–31^6	119.5±309.5	123.8±334.7	0.747
Total	267.3±495.	9 279.7±498.4	0.228
MV at 28 days			
23^0–25^6	316 (22.6)	324 (22.9)	0.93
26^0–28^6	304 (8.7)	221 (7.0)	0.003
29^0–31^6	54 (1.2)	33 (0.8)	0.023
Total	674 (7.2)	578 (6.7)	0.232
MV at 36 weeks			
23^0–25^6	28 (2.0)	24 (1.7)	0.433
26^0–28^6	40 (1.1)	28 (0.9)	0.049
29^0–31^6	31 (0.7)	18 (0.4)	0.041

Table 2 Respiratory morbidity and related outcomes in the two study periods

	2010–2014 n=9343	2015–2019 n=8609	P value
Total	99 (1.1)	70 (0.8)	0.067
Duration of supplementary oxygen (hours)			
23^0–25^6	953.3±1079.8	1195.0±1580.9	<0.001
26^0–28^6	783.2±842.9	815.0±1041.5	0.208
29^0–31^6	305.3±518.0	299.2±507.3	0.661
Total	615.8±824.3	689.5±1076.9	<0.001
Discharged home on oxygen			
23^0–25^6	152 (20.6)	173 (22.9)	0.287
26^0–28^6	229 (7.6)	219 (7.8)	0.73
29^0–31^6	76 (1.7)	65 (1.6)	0.734
Total	457 (5.6)	457 (6.1)	0.232
Surgically treated PDA			
23^0–25^6	266 (18.9)	189 (13.3)	<0.001
26^0–28^6	299 (8.5)	136 (4.2)	<0.001
29^0–31^6	49 (1.1)	20 (0.5)	0.002
Total	614 (6.5)	345 (4.0)	<0.001
Medically treated PDA			
23^0–25^6	749 (53.4)	677 (47.8)	0.003
26^0–28^6	1277 (36.5)	928 (29.2)	<0.001
29^0–31^6	612 (13.7)	318 (7.9)	<0.001
Total	2638 (28.2)	1923 (22.3)	<0.001
Late-onset sepsis			
23^0–25^6	629 (45.2)	651 (46.2)	0.613
26^0–28^6	1349 (38.6)	1072 (33.8)	<0.001
29^0–31^6	908 (20.4)	681 (16.9)	<0.001
Total	2886 (30.9)	2404 (27.9)	<0.001
Spontaneous intestinal perforation			
23^0–25^6	110 (7.8)	111 (7.8)	1
26^0–28^6	102 (2.9)	86 (2.7)	0.657
29^0–31^6	50 (1.1)	34 (0.8)	0.227
Total	262 (2.8)	231 (2.6)	0.648

Mean±SD for quantitative variables and n (%) for qualitative variables.

BPD, bronc opulmonary dysplasia; MV, mechanical ventilation; PDA, patent ductus arteriosus.



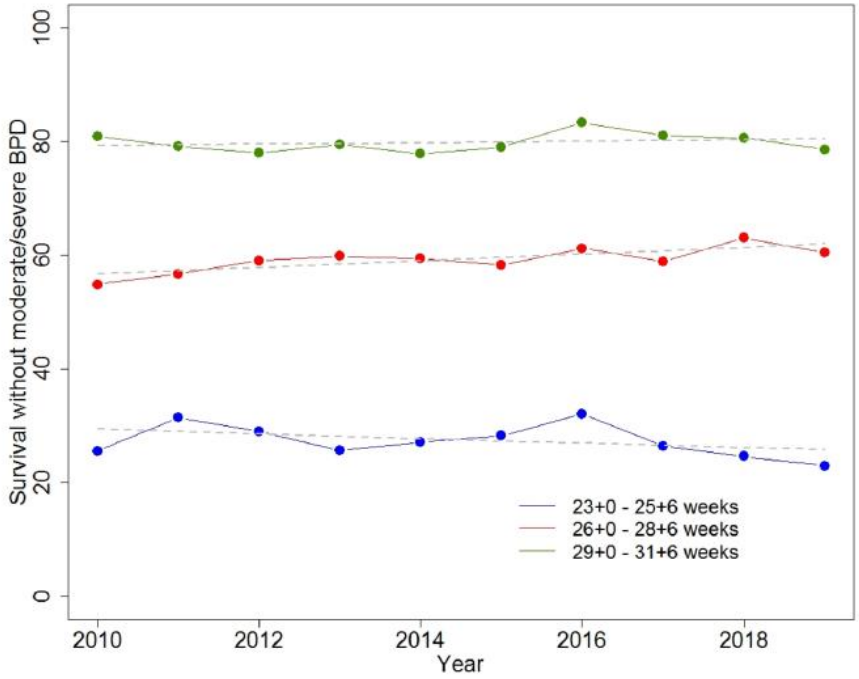


Figure 2 Trends in respiratory care and moderate-to-severe bronchopulmonary dysplaisa by gestational age (GA) strata in 2010-2019. The analysed temporal distribution is represented by continuous lines, while estimated trends are marked by dotted lines. Key: filled blue circles, GA 23+0 to 25+6 weeks; filled red circles, GA 26+0 to 28+6 weeks; filled green circles, GA 29+0 to 31+6 weeks.BPD, bronchopulmonary dysplasia.

Table 3 Adjusted risk ratio (RR) of respiratory outcomes for the change per year in 2010–2019, stratified by GA

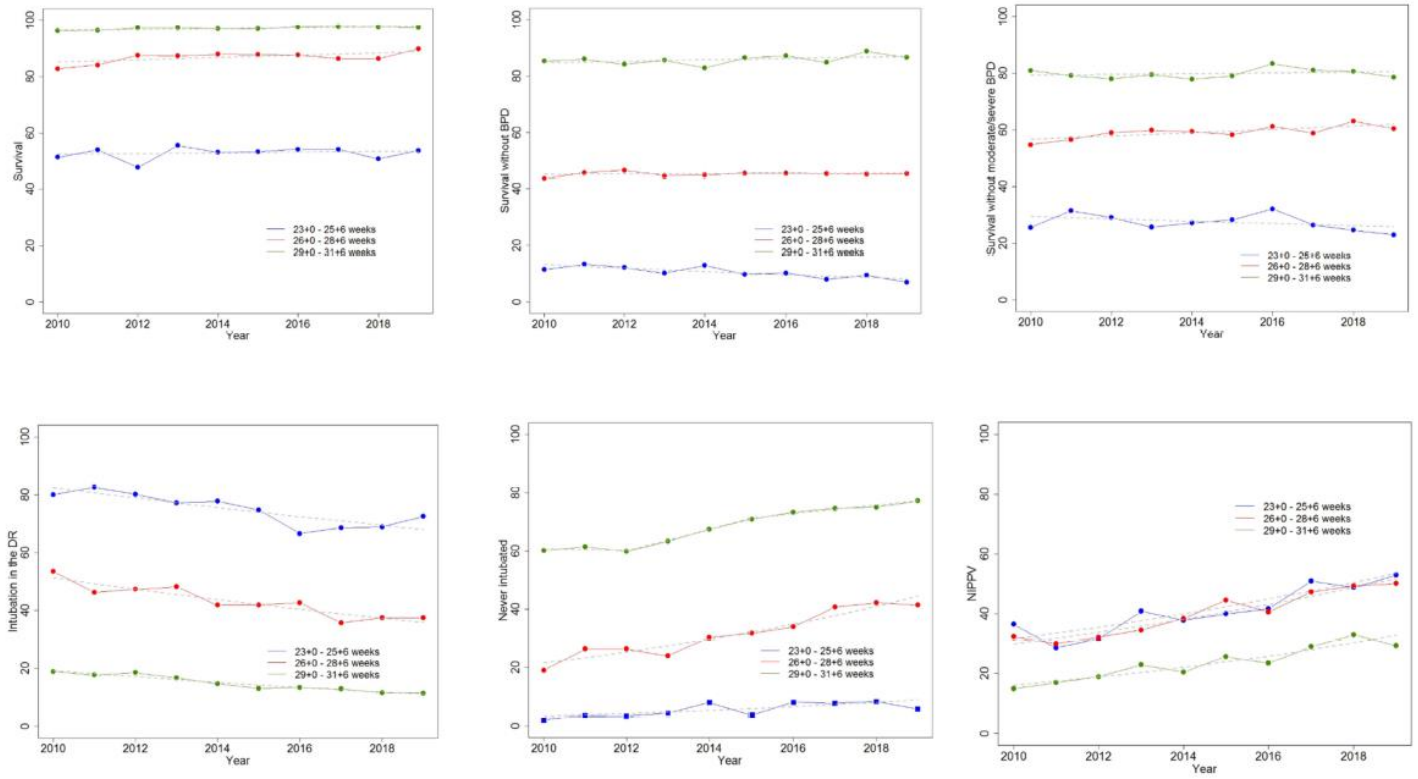
	Adjusted* RR (95% CI) for the change per year in 2010–2019			
	Total	GA 23+0 to 25+6 weeks	GA 26+0 to 28+6 weeks	GA 29+0 to 31+6 weeks
Survival	1.00 (0.99 to 1.01)	1.00 (0.99 to 1.01)	1.00 (0.99 to 1.01)	1.00 (0.99 to 1.01)
Survival without BPD	0.99 (0.98 to 1.01)	0.98 (0.97 to 0.99)†	1.00 (0.99 to 1.01)	0.99 (0.98 to 1.00)
Survival without moderate-to-severe BPD	1.00 (0.99 to 1.01)	1.00 (0.99 to 1.01)	1.00 (0.99 to 1.01)	0.99 (0.98 to 1.00)
Never intubated	1.03 (1.02 to 1.04)†	1.05 (1.03 to 1.06)†	1.04 (1.03 to 1.05)†	1.02 (1.02 to 1.03)†
Intubation in the DR	0.98 (0.97 to 0.99)†	0.98 (0.96 to 1.00)	0.97 (0.95 to 0.99)†	0.98 (0.97 to 0.99)†
NIPPV	1.08 (1.05 to 1.11)†	1.08 (1.04 to 1.13)†	1.08 (1.04 to 1.13)†	1.08 (1.04 to 1.11)†

*Adjusted for hospital centre, sex, small for GA, prenatal steroids (complete/incomplete vs none), multiple gestation, surfactant, chorioamnionitis and mode of delivery (caesarean vs vaginal).

† Statistically significant BPD, bronchopulmonary dysplasia; DR, delivery room; GA, gestational age; NIPPV, non-invasive positive pressure ventilation.

SUPPLEMENTARY MATERIAL

Supplementary Figure 1



Supplementary Table 1 Demographic and perinatal characteristics in the two study periods

	2010-2014 n = 9343	2015-2019 n = 8609	p-value
Gestational age (weeks)	28.48 ± 2.13	28.40 ± 2.19	0.013
Distribution by gestational age			
23^0 to 25^6	1401 (15.0)	1414 (16.4)	0.009
26^0 to 28^6	3492 (37.4)	3171 (36.8)	0.458
29^0 to 31^6	4450 (47.6)	4024 (46.7)	0.234
Birth weight (grams)	1060.9 ± 272.1	1051.4 ± 278.6	0.020
Female	4489 (48.0)	4168 (48.4)	0.632
Chorioamnionitis	1949 (20.8)	1913 (22.2)	0.028
Maternal arterial hypertension	1668 (17.8)	1710 (19.8)	0.001
Multiple birth	3259 (34.8)	2889 (33.5)	0.063
IVF	1857 (19.8)	1876 (21.7)	0.002
Apgar 1 minute <7	4485 (48.0)	4395 (51.0)	<0.001
Apgar 5 minutes <7	1294 (13.8)	1412 (16.4)	<0.001
SGA	1206 (12.9)	1106 (12.8)	0.911
CRIB score	3.07 ± 3.3	3.16 ± 3.4	0.066
Cesarean section			
23^0 to 25^6	755 (53.8)	791 (55.9)	0.289
26^0 to 28^6	2450 (70.1)	2250 (70.9)	0.484
29^0 to 31^6	3407 (76.5)	3075 (76.4)	0.878
Total	6612 (70.7)	6116 (71.0)	0.693
Prenatal steroids (at least one dose)			
23^0 to 25^6	1225 (88.0)	1285 (91.0)	0.011
26^0 to 28^6	3140 (90.8)	2939 (93.0)	0.001
29^0 to 31^6	4107 (93.0)	3792 (94.5)	0.005
Total	8472 (91.4)	8016 (93.4)	<0.001

Supplementary Table 2. Joinpoint regression analysis of temporal trends in respiratory care and respiratory morbidity stratified by GA.

		Total			GA 23+0 to 25+6 weeks			GA 26+0 to 28+6 weeks			GA 29+0 to 31+6 weeks		
		Years	APC	95% CI	Years	APC	95% CI	Years	APC	95% CI	Years	APC	95% CI
Survival	Trend 1	2010-2019	0.1	-0.1;0.4	2010-2019	0.2	-0.9;1.4	2010-2019	0.5	0.1;1.0	2010-2019	0.1	0.1;0.2*
Survival without BPD	Trend 1	2010-2019	-0.3	-0.6;0	2010-2019	-5.2	-8.2;-2.0*	2010-2019	0.1	-0.4;0.6	2010-2019	0.3	-0.2;0.8
Survival without moderate-to-severe BPD	Trend 1	2010-2019	0.1	-0.5;0.7	2010-2019	-1.4	-4.1;1.3	2010-2019	1.0	0.3;1.7*	2010-2019	0.2	-0.4;0.7
Never intubated	Trend 1	2010-2019	4.3	3.4;5.1*	2010-2019	11.5	1.7;22.2*	2010-2019	8.4	6.1;10.7*	2010-2012	-0.5	-4.3;3.6
	Trend 2	-	-	-	-	-	-	-	-	-	2012-2015	5.9	1.8;10.1*
	Trend 2	-	-	-	-	-	-	-	-	-	2015-2019	2.0	0.7;3.2*
Intubation in the DR	Trend 1	2010-2019	-3.2	-4.0;-2.4*	2010-2019	-2.1	-3.2;-1.1*	2010-2019	-3.9	-5.2;-2.5*	2010-2019	-5.9	-7.2;-4.7*
NIPPV	Trend 1	2010-2019	7.1	5.6;8.6*	2010-2019	6.0	3.5;8.6*	2010-2019	6.3	4.7;8.0*	2010-2019	8.3	5.8-10.8*

GA: Gestational age; APC: Annual percent change; CI: Confidence interval; BPD: Bronchopulmonary dysplasia; DR: Delivery room; NIPPV: Non-invasive positive pressure ventilation

**p<0.05*

Supplementary Figure 2

Comparison of mortality, survival with BPD and survival without BPD. Period 1 (2010 – 2014) vs Period 2 (2015 – 2019)