



Trends in Outcomes for Neonates Born Very Preterm and Very Low Birth Weight in 11 High-Income Countries

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Objective To evaluate outcome trends of neonates born very preterm in 11 high-income countries participating in the International Network for Evaluating Outcomes of neonates.

Study design In a retrospective cohort study, we included 154 233 neonates admitted to 529 neonatal units between January 1, 2007, and December 31, 2015, at 24^{0/7} to 31^{6/7} weeks of gestational age and birth weight <1500 g. Composite outcomes were in-hospital mortality or any of severe neurologic injury, treated retinopathy of prematurity, and bronchopulmonary dysplasia (BPD); and same composite outcome excluding BPD. Secondary outcomes were mortality and individual morbidities. For each country, annual outcome trends and adjusted relative risks comparing epoch 2 (2012-2015) to epoch 1 (2007-2011) were analyzed.

Results For composite outcome including BPD, the trend decreased in Canada and Israel but increased in Australia and New Zealand, Japan, Spain, Sweden, and the United Kingdom. For composite outcome excluding BPD, the trend decreased in all countries except Spain, Sweden, Tuscany, and the United Kingdom. The risk of composite outcome was lower in epoch 2 than epoch 1 in Canada (adjusted relative risks 0.78; 95% CI 0.74-0.82) only. The risk of composite outcome excluding BPD was significantly lower in epoch 2 compared with epoch 1 in Australia and New Zealand, Canada, Finland, Japan, and Switzerland. Mortality rates reduced in most countries in epoch 2. BPD rates increased significantly in all countries except Canada, Israel, Finland, and Tuscany.

Conclusions In most countries, mortality decreased whereas BPD increased for neonates born very preterm. (*J Pediatr* 2019;215:32-40).

Neonates born very preterm at <32 weeks of gestational age or at a very low birth weight (<1500 g) have a high risk of mortality and morbidity, including neurodevelopmental problems.¹⁻³ Adverse long-term health outcomes contribute significantly to increased financial costs to both health systems and families.⁴ Many countries have established national registries and networks that benchmark outcomes of neonates born very preterm.⁵⁻¹⁰ Evaluating mortality and morbidity trends within specific populations over time can help identify targets for improvement.¹¹⁻¹³ Furthermore, quality improvement initiatives using registries for site-level reports, trend analysis, and case review can foster collaborative learning, improve outcomes, and reduce costs.^{14,15}

The International Network for Evaluation of Outcomes (iNeo) of neonates was established to develop collaboration between networks/registries that have population-based or national datasets. Eleven high-income countries/regions with neonatal datasets agreed to participate and contribute data to iNeo with the goal to identify care practices that improve neonatal outcomes and identify

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BPD	Bronchopulmonary dysplasia
iNeo	International Network for Evaluation of Outcomes of neonates
NICU	Neonatal intensive care unit
ROP	Retinopathy of prematurity
SNI	Severe neurologic injury

areas for possible improvement.¹¹ Previously, we reported a significant variation in outcomes between the participating iNeo countries¹⁶ as well as differences in some practices.¹⁷⁻²¹ In this study, our aim was to analyze trends in the health outcomes of neonates born very preterm in 11 high-income countries. The impetus for this comparison came from iNeo objectives to understand variation, foster discussion and collaboration, and identify areas for improvement through the assessment of changes in neonatal outcomes within countries over time.

Methods

In our retrospective cohort study, neonates born between January 1, 2007, and December 31, 2015, weighing <1500 g at 24^{0/7} to 31^{6/7} weeks of gestational age, and admitted to a neonatal intensive care unit (NICU) participating in a national neonatal network/registry included in iNeo were eligible. Neonates who were born at <24 weeks of gestational age, ≥32 weeks of gestational age, or had major congenital anomalies were excluded. Neonates <24 weeks of gestational age were excluded because resuscitation practices for neonates who are 22 and 23 weeks of gestational age vary within both units and countries.²² The cohort data from 2007 to 2015 were divided in 2 epochs of approximately similar number of neonates to assess change over time. The 2 epochs were used instead of year as a continuous variable because fluctuations in annual outcome rates in smaller countries/region may have a large effect on statistical estimates unless data from a few years were combined together.

Our study included data from 11 high-income countries with 10 independent neonatal networks/registries that participate in the iNeo. The iNeo dataset contains deidentified individual patient data for neonates admitted to 29 Australian and New Zealand Neonatal Network units, 28 Canadian Neonatal Network units, 28 Finnish Medical Birth Register units, 27 Israel Neonatal Network units, 159 Neonatal Research Network Japan units, 50 Spanish Neonatal Network units, 37 Swedish Neonatal Quality Register units, 10 Swiss Neonatal Network units, 4 Tuscany Neonatal Network units, and 103 United Kingdom Neonatal Collaborative units. Data were only available from 2008 to 2015 for the United Kingdom Neonatal Collaborative and from 2009 to 2015 for the Tuscany Neonatal Network.

Data Source and Definitions

The countries participating in iNeo agreed to share a defined set of variables.¹¹ Gestational age was defined according to the best available information within each country. Early ultrasound scan or last menstrual period were used in majority of cases to determine gestational age. We compared proportions of total admissions at each gestational age in weeks in each country to check distribution of patients. Any administration of corticosteroids before birth, regardless of drug, timing, or dose, was classified as receipt of antenatal steroids. A country-specific birth weight standard was used to calculate the birth weight z score for each neonate.²³

Outcome Measures

We evaluated 2 composite outcomes, 1 with BPD and 1 without because the diagnosis of BPD was the most variable outcome definition between countries: in-hospital mortality or any of 3 major morbidities including severe neurologic injury (SNI), treated retinopathy of prematurity (ROP), and bronchopulmonary dysplasia (BPD); and the same composite outcome but excluding BPD. We evaluated SNI, ROP, and BPD in our composite outcome because they were reported consistently by all networks and associated with neurodevelopmental outcomes. We did not include necrotizing enterocolitis or infection in the composite outcome because debate around their diagnosis led to high variability among countries.

Secondary outcomes were mortality, SNI, treated ROP, or BPD individually. Mortality was defined as death before discharge. Delivery room deaths were not included because of differential data collection methods. SNI included grade 3 or greater peri-intraventricular hemorrhage²⁴ or persistent periventricular echodensity/echolucency, but not cerebellar hemorrhage or injury as they were not consistently evaluated by all units. Receipt of either laser surgery or intraocular injections of antivascular endothelial growth factor agents was classified as treated ROP.²⁵ BPD was defined as a supplementation of oxygen at 36 weeks of postmenstrual age or discharge.

Statistical Analyses

We divided the cohort in 2 epochs with a similar number of neonates: epoch 1 included births between January 1, 2007, and December 31, 2011; epoch 2 included births between January 1, 2012, and December 31, 2015. We evaluated annual adjusted trends for the outcomes within each country using the Cochran–Armitage trend test and reported these as a significant ($P < .05$) increase or decrease. We compared baseline characteristics and composite and individual outcomes within each country between the 2 epochs and reported the frequency (percentage) or mean (\pm SD). We assessed differences between the epochs by Pearson χ^2 for categorical variables and Student t test for continuous variables. We applied multivariable Poisson regressions to assess the epoch effect across countries with adjustments. We estimated adjusted risk ratios and 95% CIs for outcome change between epoch 1 and epoch 2 for both composite outcomes. We adjusted for birth weight z score (calculated using country-specific birthweight charts for gestational age and sex), sex, and multiple births and did not include any practice related variables (eg, cesarean delivery, antenatal steroid administration, or Apgar scores).

We calculated standardized ratios for the composite outcome using the “indirect standardization” approach, stratified by epoch. The expected numbers of neonates with outcomes for each individual country were calculated from the multivariable logistic regression model constructed on the rest of the dataset. We applied Bonferroni correction for pairwise comparisons across countries. Standardized ratio estimates and the 99% CI for both epochs for each individual country were displayed graphically. We conducted all analyses using SAS 9.4 (SAS Institute Inc, Cary, North Carolina).

Research Ethics Approval

The data collection methods and analyses were approved by the research ethics boards of the participating countries and by the iNeo steering committee.

Results

Of the total 200 472 neonates in the dataset, 154 233 were eligible for this study. A total of 46 239 neonates were excluded from the analysis: 6970 were <24 weeks of gestational age, 33 379 were ≥32 weeks of gestational age, and 5890 had major congenital anomalies. The rates of multiple births and outborn neonates were significantly lower in epoch 2 (2012 and 2015) than epoch 1 (2007-2011), and rates of cesarean delivery, antenatal steroid use, and Apgar score of <7 at 5 minutes were significantly greater in epoch 2 than epoch 1 (**Table I**). Given the known variation in care practices and outcomes at <26 weeks of gestational age, we identified that Switzerland and Tuscany had a lower percentage of neonates admitted at <26 weeks of gestational age than other countries (**Table II**; available at www.jpeds.com). Tuscany also had the greatest percentage of neonates admitted at 30 and 31 weeks of gestational age of all countries. There was no clinically significant change in distribution of neonates at each gestational age over the years (**Table III**; available at www.jpeds.com).

The composite outcome rate including BPD increased by 1.9% across all countries in epoch 2, whereas the composite outcome excluding BPD decreased by 1.8% (**Table IV**). The mortality rate decreased between the epochs by 1.7 percentage points, and all countries except Israel reduced their mortality rate between epoch 1 and epoch 2. All individual outcomes were lower in epoch 2 than epoch 1 except for BPD, which increased by 4.2%. The rate of BPD increased in epoch 2 in all countries except Canada and Finland.

Analysis of outcome trends over the study period showed that the composite outcome including BPD decreased in Canada and Israel over the study period, whereas it increased in Australia and New Zealand, Japan, Spain, Sweden, and the United Kingdom (**Figure 1** and **Table V** [available at www.jpeds.com]). The trend for Switzerland, Finland, and Tuscany did not significantly change throughout the study period; however, Switzerland had the lowest composite outcome rates of all countries for most of the study period. For the composite outcome excluding BPD a decreasing trend was observed in all countries except Spain, Sweden, Tuscany, and the United Kingdom, where there was no significant difference. The trends for mortality and individual morbidities also were analyzed (**Figures 2-5** and **Tables VI-IX**; available at www.jpeds.com).

For the composite outcome including BPD, Canada had a significantly lower adjusted relative risk in epoch 2 than epoch 1; however, the risk of the composite outcome was greater in Australia–New Zealand, Japan, Spain, Sweden, and the United Kingdom (**Table X**). For the composite

outcome excluding BPD, Australia–New Zealand, Canada, Finland, Japan, and Switzerland had a significantly lower risk in epoch 2 than epoch 1, whereas there was no statistically significant change in the rest of the countries.

The risk of mortality was lower in epoch 2 than in epoch 1 in all countries, but the improvement was insignificant in Israel, Sweden, Switzerland, and Tuscany (**Table X**). The risk of SNI was significantly lower in epoch 2 than epoch 1 in Australia–New Zealand and Japan but greater in Spain and the United Kingdom. Spain and United Kingdom had a significantly greater risk of treated ROP in epoch 2 than epoch 1, whereas Canada, Israel, and Japan had a lower risk of treated ROP. The risk of BPD was lower in epoch 2 than epoch 1 in Canada but higher in Australia–New Zealand, Japan, Spain, Sweden, and the United Kingdom, which was the driver for the increased composite outcome including BPD in those countries.

Overall, the standardized ratio of the composite outcome improved in Canada and Israel in epoch 2 compared with epoch 1 (**Figure 6**; available at www.jpeds.com). The United Kingdom and Spain had a high standardized ratio in both epochs, whereas Australia and New Zealand, Finland, Japan, and Tuscany had low standardized ratios.

Discussion

In this large international cohort from 11 countries, we identified that mortality and major morbidities decreased between 2007 and 2015 in most countries. However, there was an increase in BPD in most countries except Canada. Subtle differences in population characteristics were identified that may or may not explain these differences.

The strengths of our study are a high-risk, large, international, multiple country cohort; a standardized reporting system within each country; and a focus on within country comparisons. In addition, we used both composite outcome (including and excluding BPD) and individual outcomes for comparison, as it may be possible that a unit/country may have a lower morbidity rate but greater mortality rate. Without the use of a composite outcome such detail will be missed, and it is important that neonates survive without any morbidity.

Our study has limitations. First, due to inconsistencies in data availability between the countries, our composite outcome did not include 2 other commonly reported and important outcomes: necrotizing enterocolitis and late-onset sepsis. Second, we excluded neonates born at <24 weeks of gestational age. This was pre-planned because there are marked variations in resuscitation and active care in neonates at these gestational ages. However, we must acknowledge that minor differences in rates of neonates admitted at 24-26 weeks of gestational age persisted, which may have resulted in baseline differences in outcome rates as this gestational age group is at high risk of adverse outcomes. Third, because some countries did not collect these data, we excluded neonates who were stillborn, not admitted to a

Table I. Infant characteristics in countries participating in iNeo

Characteristics	Epoch	ANZNN	CNN	FinMBR	INN	NRNJ	SEN1500	SNQ	SwissNeoNet	Tuscan NN	UKNC	Total	P value
Number of infants	Total	22 331	20 783	2627	10 050	30343	18 257	5351	4895	1465	38 131	154 233	NA
	1*	12 161	11 068	1560	5577	16 633	10 273	2700	2575	675	17 584	80 806	
	2†	10 170	9715	1067	4473	13 710	7984	2651	2320	790	20 547	73 427	
Gestational age, wk, mean (SD)	Total	27.9 (2.1)	27.7 (2.1)	27.9 (2.1)	28.1 (2.1)	27.8 (2.1)	28.1 (2.1)	27.7 (2.1)	28.0 (2.0)	28.2 (2.2)	27.8 (2.1)	27.9 (2.1)	<.01
	1*	27.8 (2.1)	27.7 (2.0)	27.9 (2.0)	28.1 (2.1)	27.8 (2.1)	28.1 (2.1)	27.8 (2.1)	28.0 (2.0)	28.2 (2.2)	27.8 (2.1)	27.9 (2.1)	
	2†	27.9 (2.1)	27.7 (2.1)	27.9 (2.1)	28.1 (2.1)	27.8 (2.1)	28.1 (2.1)	27.7 (2.0)	28.1 (2.1)	28.3 (2.2)	27.9 (2.1)	27.9 (2.1)	
Birth weight, g, mean (SD)	Total	1064 (264)	1050 (261)	1062 (270)	1065 (266)	1012 (281)	1059 (265)	1054 (270)	1045 (273)	1048 (274)	1047 (262)	1046 (268)	.05
	1*	1061 (264)	1048 (259)	1059 (271)	1066 (264)	1012 (280)	1060 (263)	1058 (272)	1048 (272)	1042 (269)	1044 (260)	1045 (267)	
	2†	1069 (265)	1052 (263)	1066 (270)	1065 (269)	1012 (283)	1057 (267)	1050 (269)	1042 (274)	1052 (279)	1050 (263)	1048 (269)	
Birth weight z score, mean (SD)	Total	-0.20 (0.96)	-0.25 (0.85)	-0.38 (0.90)	-0.26 (0.79)	-0.28 (0.94)	-0.32 (0.99)	-0.27 (0.85)	-0.32 (0.80)	-0.18 (0.94)	-0.32 (0.92)	-0.28 (0.92)	<.01
	1*	-0.19 (0.96)	-0.26 (0.85)	-0.39 (0.89)	-0.27 (0.77)	-0.27 (0.94)	-0.32 (0.99)	-0.26 (0.85)	-0.30 (0.81)	-0.17 (0.94)	-0.31 (0.93)	-0.27 (0.92)	
	2†	-0.21 (0.96)	-0.25 (0.86)	-0.35 (0.92)	-0.25 (0.81)	-0.30 (0.95)	-0.33 (1.00)	-0.27 (0.85)	-0.36 (0.79)	-0.19 (0.94)	-0.32 (0.91)	-0.29 (0.92)	
Males, n (%)	Total	11 621 (52.1)	10 914 (52.6)	1345 (51.2)	5195 (51.7)	15 800 (52.1)	9430 (51.7)	2881 (53.9)	2519 (51.5)	740 (50.5)	19 764 (51.9)	80 209 (52.0)	.87
	1*	6274 (51.6)	5782 (52.3)	806 (51.7)	2882 (51.7)	8739 (52.6)	5364 (52.2)	1441 (53.4)	1319 (51.2)	341 (50.5)	9059 (51.6)	42 007 (52.0)	
	2†	5347 (52.6)	5132 (52.9)	539 (50.5)	2313 (51.7)	7061 (51.5)	4066 (50.9)	1440 (54.3)	1200 (51.8)	399 (50.5)	10 705 (52.1)	38 202 (52.1)	
Multiple births, n (%)	Total	6648 (29.8)	6136 (29.5)	797 (30.3)	4200 (41.8)	6855 (22.6)	6000 (32.9)	1572 (29.4)	1665 (34.0)	517 (35.4)	10 494 (27.6)	44 884 (29.1)	<.01
	1*	3705 (30.5)	3361 (30.4)	486 (31.2)	2349 (42.1)	3886 (23.4)	3441 (33.5)	794 (29.4)	879 (34.1)	218 (32.3)	4969 (28.3)	24 088 (29.8)	
	2†	2943 (28.9)	2775 (28.6)	311 (29.1)	1851 (41.4)	2969 (21.7)	2559 (32.1)	778 (29.3)	786 (33.9)	299 (37.9)	5525 (26.9)	20 796 (28.3)	
Cesarean delivery, n (%)	Total	14 824 (65.4)	13 014 (63.1)	1901 (72.5)	7443 (74.1)	23 724 (79.6)	12 573 (68.9)	3887 (72.8)	4058 (82.9)	1144 (78.1)	21 180 (60.0)	103 448 (68.7)	<.01
	1*	7832 (64.9)	6874 (62.7)	1142 (73.3)	4090 (73.3)	12 842 (77.9)	6920 (67.4)	1928 (71.4)	2159 (83.8)	519 (76.9)	9258 (58.8)	53 564 (68.1)	
	2†	6692 (66.0)	6140 (63.4)	759 (71.2)	3353 (75.0)	10 882 (81.8)	5653 (70.8)	1959 (74.1)	1899 (81.9)	625 (79.1)	11 922 (61.0)	49 884 (69.3)	
Antenatal steroids, ‡ n (%)	Total	20 030 (90.9)	17 805 (88.7)	2482 (95.5)	7893 (78.6)	16 644 (56.8)	15 812 (88.1)	4415 (82.5)	4436 (92.0)	1290 (88.6)	31 868 (88.7)	122 675 (82.1)	<.01
	1*	10 890 (90.8)	9371 (87.9)	1478 (95.5)	4211 (75.6)	8464 (51.9)	8663 (86.2)	2223 (82.3)	2293 (91.2)	588 (87.9)	13 981 (87.2)	62 162 (79.6)	
	2†	9140 (91.1)	8434 (89.5)	1004 (95.5)	3682 (82.3)	8180 (63.0)	7149 (90.4)	2192 (82.7)	2143 (92.8)	702 (89.2)	17 887 (89.9)	60 513 (84.6)	
Outborn, n (%)	Total	2873 (12.9)	3400 (16.4)	134 (5.1)	95 (1.0)	1818 (6.0)	1140 (6.2)	451 (8.5)	238 (4.9)	185 (12.6)	NA	10 334 (8.9)	<.01
	1*	1576 (13.0)	1925 (17.4)	93 (6.0)	56 (1.0)	1117 (6.7)	722 (7.0)	173 (6.4)	122 (4.7)	102 (15.1)	NA	5886 (9.3)	
	2†	1297 (12.8)	1475 (15.2)	41 (3.8)	39 (0.9)	701 (5.1)	418 (5.2)	278 (10.5)	116 (5.0)	83 (10.5)	NA	4448 (8.4)	
Apgar at 5 min <7, n (%)	Total	4675 (21.1)	6534 (32.0)	942 (36.9)	1081 (11.0)	8174 (27.6)	2568 (14.4)	1350 (25.7)	1582 (32.5)	225 (15.6)	NA	27 131 (23.9)	<.01
	1*	2591 (21.5)	3368 (30.9)	521 (34.5)	559 (10.4)	4159 (25.6)	1384 (13.8)	626 (23.5)	708 (27.7)	93 (14.1)	NA	14 009 (22.6)	
	2†	2084 (20.7)	3166 (33.2)	421 (40.3)	522 (11.8)	4015 (30.0)	1184 (15.1)	724 (27.9)	874 (37.8)	132 (16.8)	NA	13 122 (25.2)	

ANZNN, Australia/New Zealand; CNN, Canada; FinMBR, Finland; INN, Israel; NA, not available; NRNJ, Japan; SEN1500, Spain; SNQ, Sweden; SwissNeoNet, Switzerland; Tuscan NN, Tuscany, Italy; UKNC, United Kingdom.

*Epoch 1 is 2007-2011 except United Kingdom (2008-2011) and Tuscany (2009-2011).

†Epoch 2 is 2012-2015.

‡Any antenatal steroids.

Table IV. Outcome rates in countries participating in iNeo

Outcomes	Epoch	ANZNN N = 22331	CNN N = 20783	FinMBR N = 2627	ININ N = 10050	NRNJ N = 30343	SEN1500 N = 18257	SNQ N = 5351	SwissNeoNet N = 4895	TuscanNN N = 1465	UKNC N = 38131	Total N = 154233	P value
Composite outcome with BPD,* n (%)	Total	8051 (37.6)	6615 (35.7)	828 (34.2)	3178 (32.1)	11002 (37.7)	6680 (39.0)	1781 (34.9)	1272 (26.2)	419 (28.7)	17414 (45.7)	57240 (38.8)	<.01
	1 [†]	4134 (35.3)	3884 (39.9)	514 (36.0)	1780 (32.5)	5945 (36.5)	3716 (38.2)	831 (31.4)	666 (26.1)	197 (29.3)	7707 (43.9)	29374 (37.8)	
Composite outcome without BPD,§ n (%)	Total	3917 (40.4)	2731 (31.1)	314 (17.7)	1398 (31.6)	5057 (39.3)	2964 (40.1)	950 (38.6)	606 (26.4)	222 (28.2)	9707 (47.3)	27886 (39.7)	<.01
	1 [†]	3188 (14.3)	3797 (18.3)	464 (17.7)	2380 (23.7)	6732 (22.2)	5130 (28.1)	876 (16.4)	760 (15.5)	328 (22.4)	7102 (18.6)	30757 (20.8)	
Mortality, n (%)	Total	1836 (15.1)	2168 (19.6)	303 (19.4)	1359 (24.7)	4012 (24.1)	2873 (28.0)	456 (16.9)	434 (16.9)	160 (23.7)	3236 (18.4)	16837 (20.8)	<.01
	1 [†]	1352 (13.3)	1629 (16.8)	161 (15.1)	1021 (22.8)	2720 (19.8)	2257 (28.3)	420 (15.8)	326 (14.1)	168 (21.3)	3866 (18.8)	13920 (19.0)	
SNI, n (%)	Total	1797 (8.1)	1816 (8.7)	206 (7.8)	1361 (13.5)	1266 (4.2)	2783 (15.2)	414 (7.8)	464 (9.5)	167 (11.4)	3735 (9.8)	14010 (9.1)	<.01
	1 [†]	1048 (8.6)	1049 (9.5)	143 (9.2)	754 (13.5)	799 (4.8)	1748 (17.0)	214 (7.9)	258 (10.0)	83 (12.3)	1890 (10.8)	7986 (9.9)	
Treated ROP, n (%)	Total	749 (7.4)	767 (7.9)	63 (5.9)	607 (13.6)	467 (3.4)	1035 (13.0)	201 (7.6)	206 (8.9)	84 (10.6)	1845 (9.0)	6024 (8.2)	.06
	1 [†]	1393 (6.6)	2018 (10.6)	237 (9.0)	1357 (14.1)	2052 (7.0)	2635 (15.8)	377 (7.5)	406 (8.3)	186 (13.0)	2981 (7.8)	13642 (9.3)	
BPD, n (%)	Total	801 (6.9)	1086 (10.9)	155 (9.9)	779 (14.6)	1224 (7.5)	1423 (15)	186 (7.1)	232 (9.1)	95 (14.4)	1300 (7.4)	7281 (9.4)	.01
	1 [†]	592 (6.2)	932 (10.3)	82 (7.7)	578 (13.5)	828 (6.4)	1212 (16.8)	191 (8.0)	174 (7.5)	91 (11.8)	1681 (8.2)	6361 (9.1)	
BPD, n (%)	Total	635 (2.8)	719 (3.5)	95 (3.6)	312 (3.1)	4324 (14.3)	1020 (5.6)	238 (4.5)	62 (1.3)	48 (3.3)	1579 (4.1)	9032 (5.9)	<.01
	1 [†]	364 (3.0)	444 (4.0)	62 (4.0)	191 (3.4)	2565 (15.4)	436 (4.2)	134 (5.0)	39 (1.5)	23 (3.4)	591 (3.4)	4849 (6.0)	
BPD, n (%)	Total	271 (2.7)	275 (2.8)	33 (3.1)	121 (2.7)	1759 (12.8)	584 (7.3)	104 (3.9)	23 (1.0)	25 (3.2)	988 (4.8)	4183 (5.7)	<.01
	1 [†]	5781 (28.1)	3807 (21.2)	462 (21.0)	1234 (14.0)	6536 (23.2)	2409 (15.8)	1171 (23.6)	612 (13.7)	143 (10.8)	12872 (37.1)	35027 (25.5)	
BPD, n (%)	Total	2774 (25.0)	2298 (24.5)	276 (21.7)	675 (13.8)	3121 (20.0)	1279 (15.3)	509 (20.3)	294 (12.7)	64 (10.6)	5484 (34.7)	16774 (23.3)	<.01
	2 [‡]	3007 (31.7)	1509 (17.6)	186 (20.1)	559 (14.3)	3415 (27.3)	1130 (16.5)	662 (26.8)	318 (14.9)	79 (11.0)	7388 (39.2)	18253 (27.5)	

*Composite outcome included mortality or any of the following 3 morbidities: SNI, treated ROP, or BPD.
[†]Epoch 1 is 2007-2011 except UKNC (2008-2011) and Tuscan NN (2009-2011).
[‡]Epoch 2 is 2012-2015.
[§]Composite outcome included mortality or either of the following 2 morbidities: SNI or treated ROP.

NICU, or died in the delivery room. Fourth, there are variations in the definitions of variables and different data collection mechanisms between countries. However, as we compared results within each country rather than between countries, the variable data collection mechanisms should not be a major limiting factor. Finally, although data from the entire country/network are requested in iNeo, Japan (~60%) and Spain (~50-60%) collected partial population data and United Kingdom (~60%) submitted a partial data set because only a proportion of neonatal units chose to participate in iNeo. Despite these limitations, we believe our interpretation of the results has significant implications because we did not directly compare data from one country with another, but instead analyzed the data of each individual country over time.

One important finding was a reduction in mortality in all countries except Israel, where it was static (Figure 2 and Table VI). The Vermont Oxford Network reported a similar decreased mortality rate for neonates born between 501 and 1500 g at birth from 13.7% in 2007 to 10.9% in 2014,²⁶ and data from England identified an increase in survival from 88% to 91.3% between 2008 and 2014 for neonates of 22-32 weeks of gestational age.²⁷ We identified a significant increase in antenatal steroid use in epoch 2 that may have contributed to the decrease in mortality. In addition, of the 9 countries with outborn rates available, 7 reported a decrease in outborn neonates in epoch 2, which previous reports showed was associated with decreased mortality.²⁸⁻³⁰ However, the observed practice changes only partly explains the differences in outcomes rates between and within countries. Socioeconomic circumstances among countries may differ and external economic impacts on national scales also may have contributed to the changes in services available and outcome changes observed.³¹

Despite decreasing mortality, there was less improvement in morbidity (Figures 3-5 and Tables VII-IX). The most striking finding of our study was that the rate of BPD in the iNeo collaborative countries increased between epoch 1 and epoch 2, with the exception of Canada (6.9% absolute reduction) and Finland (1.6% absolute reduction; Figure 5 and Table IX). The lack of improvement in BPD was a surprise, given the increasing use of gentle respiratory support care practices, including greater use of noninvasive ventilation, continuous positive airway pressure, and availability of different ventilatory modes that are supposed to be synchronous, patient-friendly, and associated with less barotrauma.³² The Canadian Neonatal Network reported concern over static BPD rates between 1996-1997 and 2006-2007 in their participating NICUs. Stoll et al reported that BPD increased in the US Neonatal Network Research Center units between 2009 and 2012 for infants at 26 to 27 weeks of gestational age.³ Chen et al reported that in Switzerland, the rate of BPD was higher during years 2009 to 2012 than during years 2005 to 2008 for infants born at <32 weeks of gestational age.³³ In contrast, Garcia-Munoz et al from Spain reported that survival without

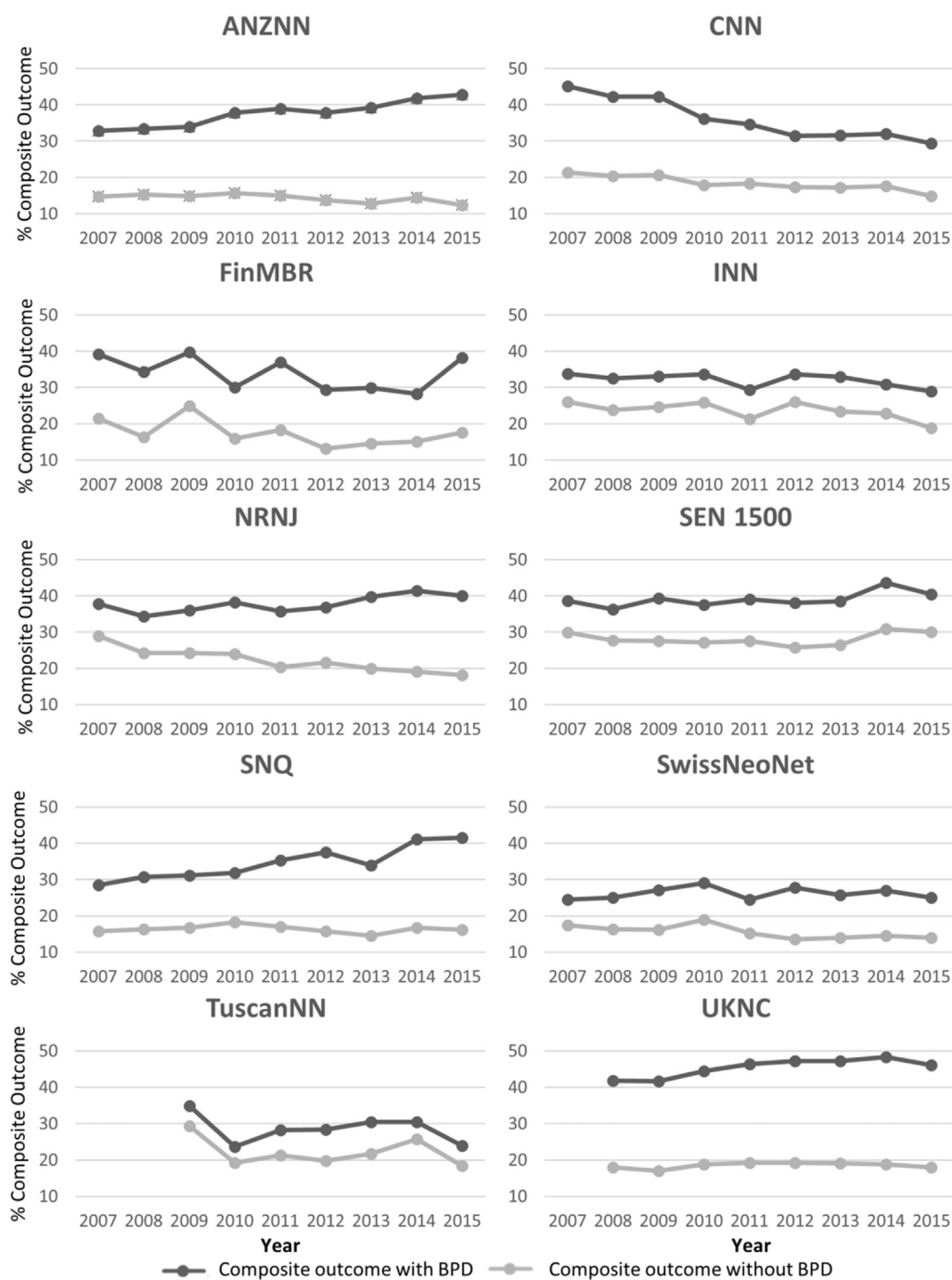


Figure 1. Trends of composite outcomes (including and excluding BPD) between 2007 and 2015. ANZNN, Australia/New Zealand; CNN, Canada; FinMBR, Finland; INN, Israel; NRNJ, Japan; SEN1500, Spain; SNQ, Sweden; SwissNeoNet, Switzerland; Tuscan NN, Tuscany, Italy; UKNC, United Kingdom. The X-axis represents year; Y-axis represents percentage. The P values for trend were adjusted for birth weight z score, sex, and multiple births. Black lines represent composite outcomes including mortality or any of the following 3 morbidities: SNI, treated ROP, or BPD. Gray lines represent composite outcomes including mortality or any of the following 2 morbidities: SNI or treated ROP.

BPD increased from 26.8% between 2002 and 2006 to 32.1% between 2007 and 2011 for neonates born at 22 to 26 weeks of gestational age. However, in subsequent analyses, they reported that the rate of BPD increased in neonates >27 weeks of gestational age.^{31,34}

It is unclear what potentially contributed to our observed increase in BPD. The first possibility is the definition of BPD, which is a topic of intense debate.^{20,22} If the definition of BPD was consistent within the study period within country, it should not affect the interpretation of our analyses;

Table X. Adjusted risk ratios of outcomes from Epoch 2* compared with Epoch 1†

Outcomes	ANZNN	CNN	FinMIBR	INN	NRNJ	SEN1500	SNQ	SwissNeoNet	TuscanNN	UKNC
Composite outcome‡	1.14 (1.09-1.19)	0.78 (0.74-0.82)	0.88 (0.76-1.01)	0.97 (0.91-1.04)	1.08 (1.04-1.12)	1.05 (1.00-1.10)	1.23 (1.12-1.35)	1.0 (0.89-1.11)	0.96 (0.80-1.17)	1.07 (1.04-1.11)
Composite outcome§	0.88 (0.82-0.94)	0.85 (0.80-0.91)	0.78 (0.64-0.94)	0.94 (0.86-1.02)	0.82 (0.78-0.86)	1.01 (0.96-1.07)	0.94 (0.82-1.07)	0.83 (0.72-0.95)	0.90 (0.73-1.12)	1.02 (0.97-1.07)
Mortality	0.85 (0.77-0.93)	0.83 (0.76-0.91)	0.66 (0.49-0.88)	1.00 (0.90-1.12)	0.70 (0.62-0.78)	0.76 (0.70-0.82)	0.96 (0.79-1.16)	0.87 (0.72-1.04)	0.86 (0.64-1.17)	0.83 (0.78-0.89)
SNI	0.89 (0.8-0.99)	0.94 (0.86-1.03)	0.77 (0.59-1.00)	0.92 (0.82-1.02)	0.87 (0.79-0.95)	1.13 (1.05-1.22)	1.13 (0.92-1.38)	0.84 (0.69-1.03)	0.83 (0.62-1.11)	1.11 (1.03-1.19)
Treated ROP	0.89 (0.76-1.04)	0.71 (0.61-0.82)	0.78 (0.51-1.19)	0.79 (0.63-0.99)	0.83 (0.78-0.88)	1.72 (1.52-1.95)	0.79 (0.61-1.01)	0.64 (0.38-1.07)	0.92 (0.52-1.63)	1.43 (1.29-1.58)
BPD	1.26 (1.20-1.33)	0.72 (0.67-0.77)	0.93 (0.77-1.12)	1.04 (0.93-1.17)	1.36 (1.29-1.43)	1.08 (1.0-1.17)	1.32 (1.17-1.48)	1.15 (0.98-1.35)	1.02 (0.73-1.42)	1.13 (1.09-1.17)

All outcomes are reported as adjusted risk ratio (95% CI) comparing epoch 2 vs epoch 1 after adjustment for birth weight z score, sex, and multiple birth.

*Epoch 2 is 2012-2015.

†Epoch 1 is 2007-2011 except United Kingdom (2008-2011) and Tuscany (2009-2011).

‡Composite outcome includes mortality or any of the following 3 morbidities: SNI, treated ROP, or BPD.

§Composite outcome includes mortality or any of the following 2 morbidities: SNI or treated ROP.

however, in database studies like ours, we have no way of checking the consistency of the BPD definition over time. Second, it is possible that oxygen saturation targets have changed as new evidence emerged over the study period, which may have contributed to the apparent increase in BPD. Third, it was reported that high use of noninvasive continuous positive airway pressure leads to increased time of ventilation and use of supplemental oxygen.³⁵ Fourth, high BPD rates could reflect increased survival of these neonates. Fifth, we did not adjust data for altitude of the unit; however, this is unlikely to have changed during study period. Finally, strategies including postnatal steroids, vitamin A,³⁶ caffeine,³⁷ avoidance of mechanical ventilation,³⁸ and administration of steroids and surfactant in combination³⁹ have been associated with reduced BPD, yet their use in practice is variable.⁴⁰ For example, during the study period, the postnatal use of steroids reduced significantly because of concerns about increased risk of neurodevelopmental outcomes.⁴¹ Vitamin A is not used in a majority of NICUs because of availability issues and administration concerns. Caffeine was studied in a large randomized study during this period. Respiratory management, including avoidance of mechanical ventilation, is practiced widely; however, postextubation management is variable between both countries and units within countries.¹⁷ Evidence for simultaneous administration of steroid and surfactant has recently emerged; therefore, the practice was not in use in any country 2015. Future studies are needed to determine which management factors are associated with non-improvement or increases in BPD rates.²²

The consistent success of Canada at reducing adverse outcomes over the study period suggests there may be care practices that drove this change. One major difference between Canada and the other countries in iNeo during the study period was a national program of continuous quality improvement.^{14,15} In 2008, Canada implemented a national Evidence-based Practice for Improving Quality-2 initiative in 25 of 30 tertiary NICUs¹⁴ that was continued as Evidence-based Practice for Improving Quality-3 between 2013 and 2017.¹⁵ These programs were associated with a significant reduction in composite outcomes in Canada, and these improvements may be reflected in the current comparison. However, because the quality improvement programs were multifaceted and unit-driven, we were unable to pinpoint specific changes that led to improvement. These results reinforce the importance of national networks and registries to be active facilitators of a culture of continuous quality improvement.⁴²

In conclusion, mortality significantly improved in almost all countries participating in iNeo; however, the risk of BPD also increased over the study period in most countries, except Canada. Within-country comparisons revealed improvement in the composite outcome including BPD over years in some countries, but the composite outcome either remained static or worsened in a majority of iNeo countries. Our results provide an opportunity for each country to investigate the reasons for differences in outcome rates and change over time and work together to harmonize

definitions, streamline data collection, and identify practice differences between countries that are associated with improvement in outcomes. ■

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Data Statement

Data sharing statement available at www.jpeds.com.

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50 Years Ago in *THE JOURNAL OF PEDIATRICS*

Vitamin A and Mucopolysaccharidosis: A clinical and biochemical evaluation

Madsen JA, Linker A. *J Pediatr* 1969;75:843-52

In vitro studies in the mid-1960s suggested that vitamin A had a beneficial effect in cells from patients with mucopolysaccharidosis (MPS) I and II by altering the synthesis and degradation of glycosaminoglycans (GAGs).¹ Following this publication, several laboratories tested the hypothesis, alas, arriving at conflicting results. Thus, Madsen and Linker performed a clinical study to evaluate the effects of vitamin A in patients with MPS I, II, III, and IV. Patients were treated with the highest nontoxic dose of vitamin A for a period between 4 and 14 months, and they were followed up routinely and evaluated biochemically and clinically. This clinical study revealed adverse effects of vitamin A in patients with MPS I-III contrary to what was suggested by the in vitro studies.¹ Among the harmful effects of vitamin A observed in patients were increased GAGs in urine, hepatosplenomegaly, hyperactivity, and increased frequency of seizures. These effects were reduced after the termination of the vitamin A treatment. Because many physicians were prescribing long-term treatment with vitamin A, Madsen and Linker advised caution in the interpretation and translation of in vitro results into the clinic.

Since the publication of these reports, the field of MPS research has grown substantially. Scientists have generated and characterized animal models for MPS, produced in vitro recombinant enzymes, developed novel treatment strategies, and gained better insight on the natural history of MPS disorders.

Currently there is enzyme replacement therapy for patients with MPS I, II, IVA, VI, and VII. Enzyme replacement therapy has shown to decrease GAG storage and ameliorates systemic manifestations of the MPS. However, there are still challenges that include lack of correction of neurologic manifestations, heart and bone disease, and the high immune response toward the treatment. It is hoped that 50 years later we would be in a time where all these challenges are solved and other mysteries of this group of diseases are uncovered paving the way for more effective and accessible treatments for all patients.

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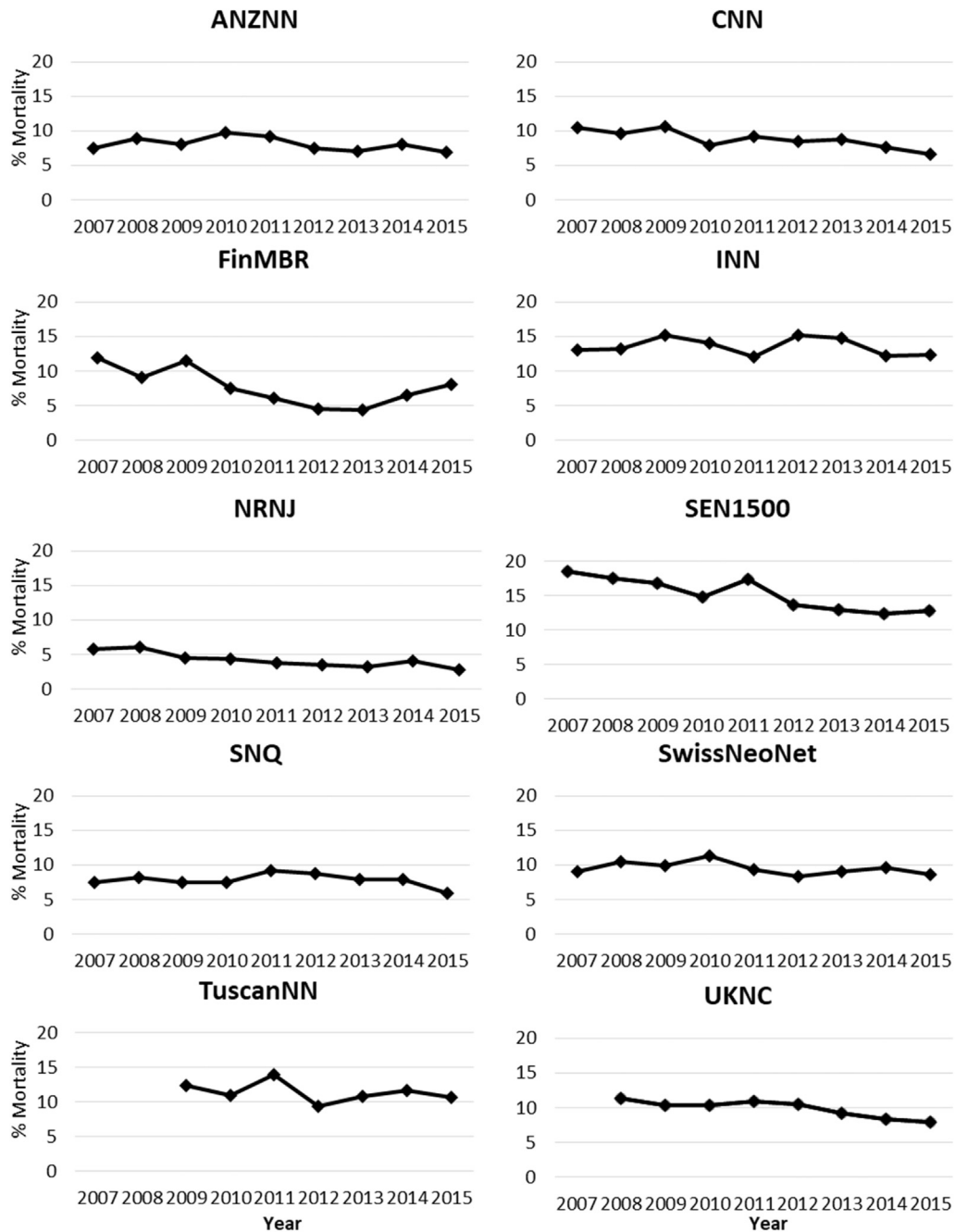


Figure 2. Trends of mortality between 2007 and 2015.

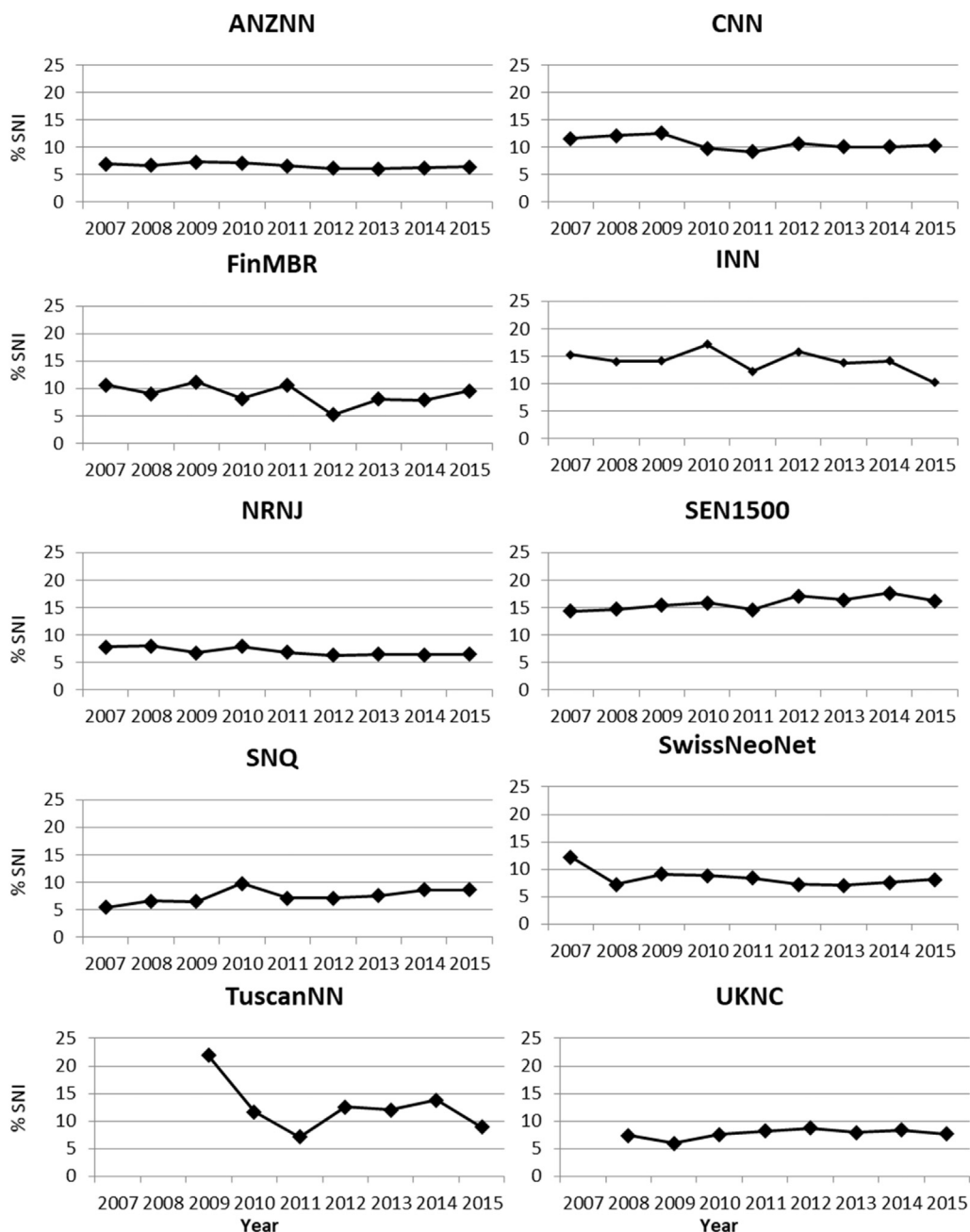


Figure 3. Trends of SNI between 2007 and 2015.

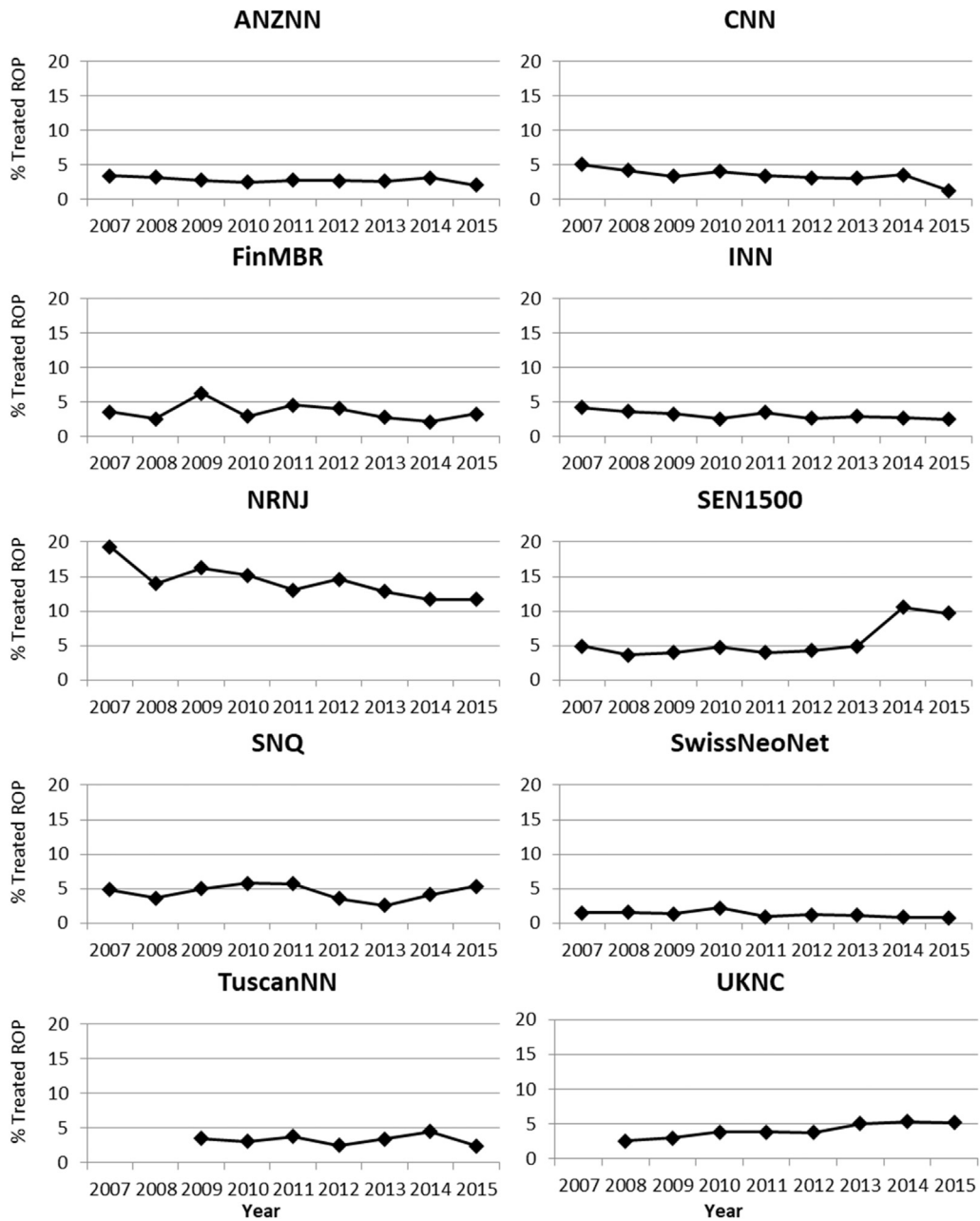


Figure 4. Trends of treated ROP between 2007 and 2015.

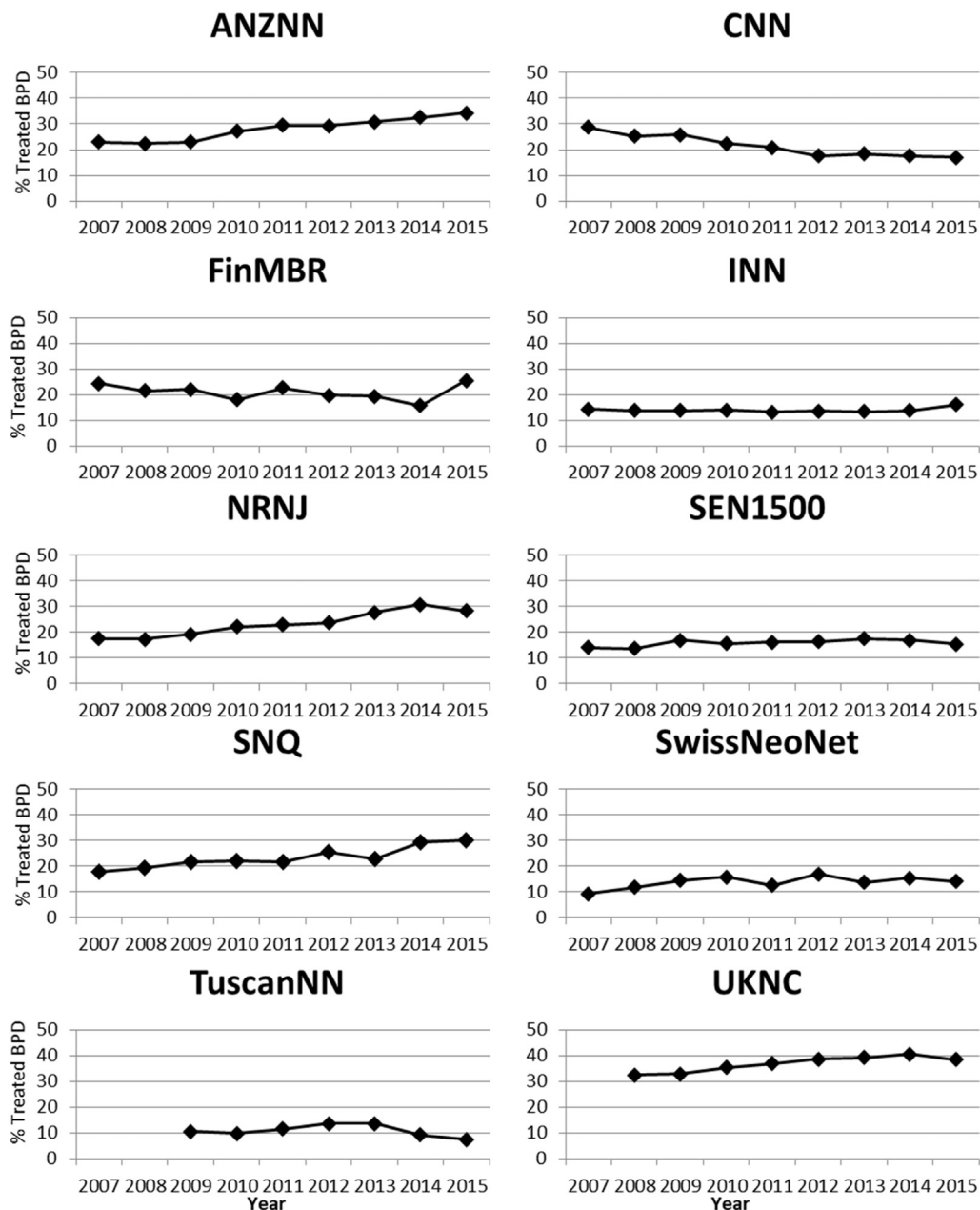


Figure 5. Trends of BPD between 2007 and 2015.

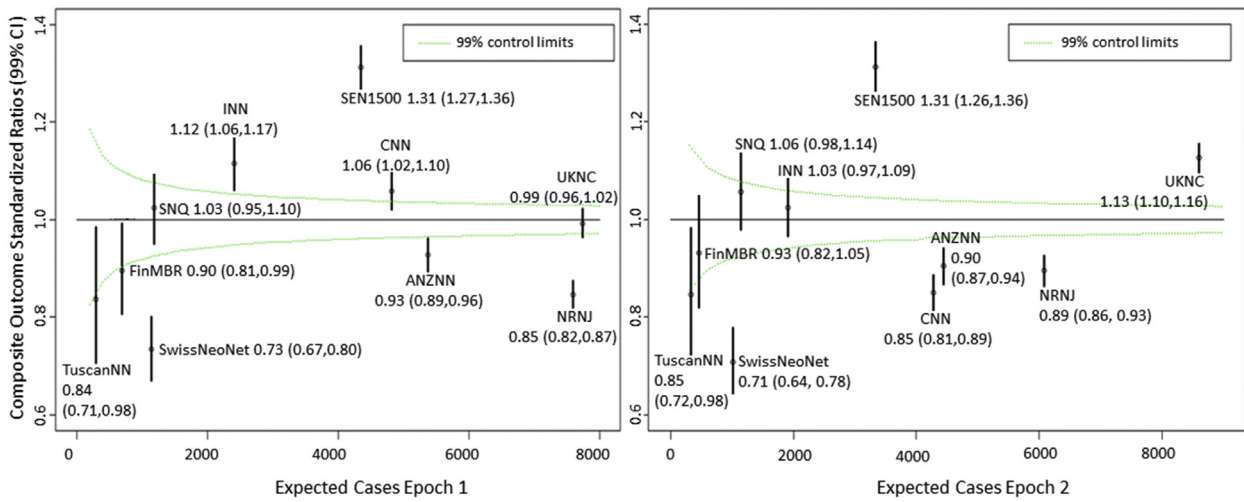


Figure 6. Standardized ratios* of composite outcomes for Epoch 1† and Epoch 2‡. *Adjusted for gestational age, birth weight z score, sex, and multiple births. †Epoch 1 is 2007-2011 except for UKNC (2008-2011) and TuscanNN (2009-2011). ‡Epoch 2 is 2012- 2015.

Table II. Population gestational age distribution

Gestational age	ANZN N = 22 331	CNN N = 20 783	FINMBR N = 2627	INN N = 10 050	NRNJ N = 30 343	SEN1500 N = 18 257	SNQ N = 5351	SwissNeoNet N = 4895	Tuscan NN N = 1465	UKNC N = 38 131	Total N = 154 233
24 wk, n (%)	1552 (6.9)	1531 (7.4)	180 (6.9)	652 (6.5)	2567 (8.5)	1072 (5.9)	397 (7.4)	262 (5.4)	118 (8.1)	2971 (7.8)	11 302 (7.3)
25 wk, n (%)	2081 (9.3)	2233 (10.7)	232 (8.8)	798 (7.9)	2921 (9.6)	1553 (8.5)	525 (9.8)	419 (8.6)	106 (7.2)	3427 (9.0)	14 295 (9.3)
26 wk, n (%)	2643 (11.8)	2533 (12.2)	267 (10.2)	1064 (10.6)	3494 (11.5)	1961 (10.7)	656 (12.3)	572 (11.7)	117 (8.0)	4322 (11.3)	17 629 (11.4)
27 wk, n (%)	2918 (13.1)	2928 (14.1)	396 (15.1)	1219 (12.1)	3987 (13.1)	2333 (12.8)	760 (14.2)	630 (12.9)	167 (11.4)	5151 (13.5)	20 489 (13.3)
28 wk, n (%)	3754 (16.8)	3368 (16.2)	421 (16.0)	1464 (14.6)	4593 (15.1)	2754 (15.1)	893 (16.7)	742 (15.2)	191 (13.0)	6312 (16.6)	24 492 (15.9)
29 wk, n (%)	3707 (16.6)	3389 (16.3)	422 (16.1)	1663 (16.5)	4741 (15.6)	3078 (16.9)	892 (16.7)	850 (17.4)	235 (16.0)	6317 (16.6)	25 294 (16.4)
30 wk, n (%)	3290 (14.7)	2866 (13.8)	416 (15.8)	1697 (16.9)	4613 (15.2)	3037 (16.6)	712 (13.3)	788 (16.1)	287 (19.6)	5425 (14.2)	23 131 (15.0)
31 wk, n (%)	2386 (10.7)	1935 (9.3)	293 (11.2)	1493 (14.9)	3427 (11.3)	2469 (13.5)	516 (9.6)	632 (12.9)	244 (16.7)	4206 (11.0)	17 601 (11.4)
Total	22 331	20 783	2627	10 050	30 343	18 257	5351	4895	1465	38 131	154 233

ANZN, Australian and New Zealand Neonatal Network; CNN, Canadian Neonatal Network; FINMBR, Finnish Medical Birth Register; INN, Israel Neonatal Network; NRNJ, Neonatal Research Network Japan; SEN1500, Spanish Neonatal Network; SNQ, Swedish Neonatal Quality Register; SwissNeoNet, Swiss Neonatal Network; Tuscan NN, Tuscany Neonatal Network; UKNC, United Kingdom Neonatal Collaborative.

Table III. Distribution of gestational age over study years

Gestational age	2007 N = 11 669	2008 N = 16 039	2009 N = 16 650	2010 N = 17 845	2011 N = 18 603	2012 N = 19 149	2013 N = 18 403	2014 N = 18 229	2015 N = 17 646	Total N = 152 333
24 wk, n (%)	849 (7.3)	1169 (7.3)	1199 (7.2)	1277 (7.2)	1364 (7.3)	1371 (7.2)	1375 (7.5)	1375 (7.5)	1323 (7.5)	11 302 (7.3)
25 wk, n (%)	1120 (9.6)	1561 (9.7)	1519 (9.1)	1631 (9.1)	1707 (9.2)	1798 (9.4)	1682 (9.1)	1662 (9.1)	1615 (9.2)	14 295 (9.3)
26 wk, n (%)	1405 (12.0)	1847 (11.5)	1931 (11.6)	2150 (12.0)	2143 (11.5)	2104 (11.0)	2065 (11.2)	2020 (11.1)	1964 (11.1)	17 629 (11.4)
27 wk, n (%)	1531 (13.1)	2208 (13.8)	2255 (13.5)	2414 (13.5)	2473 (13.3)	2555 (13.3)	2421 (13.2)	2367 (13)	2265 (12.8)	20 489 (13.3)
28 wk, n (%)	1828 (15.7)	2588 (16.1)	2607 (15.7)	2765 (15.5)	3008 (16.2)	3100 (16.2)	2871 (15.6)	2899 (15.9)	2826 (16.0)	24 492 (15.9)
29 wk, n (%)	1846 (15.8)	2630 (16.4)	2749 (16.5)	2948 (16.5)	3086 (16.6)	3156 (16.5)	3043 (16.5)	2955 (16.2)	2881 (16.3)	25 294 (16.4)
30 wk, n (%)	1753 (15.0)	2330 (14.5)	2496 (15.0)	2622 (14.7)	2689 (14.5)	2910 (15.2)	2787 (15.1)	2804 (15.4)	2740 (15.5)	23 131 (15.0)
31 wk, n (%)	1337 (11.5)	1706 (10.6)	1894 (11.4)	2038 (11.4)	2133 (11.5)	2155 (11.3)	2159 (11.7)	2147 (11.8)	2032 (11.5)	17 601 (11.4)

Table V. Annual composite outcome rates between 2007 and 2015 for countries participating in iNeo

Countries	Outcome	2007 N = 11 669	2008 N = 16 039	2009 N = 16 650	2010 N = 17 845	2011 N = 18 603	2012 N = 19 149	2013 N = 18 403	2014 N = 18 229	2015 N = 17 646	P trend*
ANZNN	Composite [†]	773/2351 (32.9)	809/2425 (33.4)	792/2337 (33.9)	822/2176 (37.8)	938/2413 (38.9)	949/2512 (37.8)	947/2416 (39.2)	1022/2446 (41.8)	999/2333 (42.8)	<.01 (i)
	Composite [‡]	359/2447 (14.7)	389/2539 (15.3)	360/2426 (14.8)	353/2248 (15.7)	375/2501 (15.0)	356/2607 (13.7)	322/2539 (12.7)	370/2573 (14.4)	304/2451 (12.4)	<.01 (d)
CNN	Composite [†]	735/1626 (45.2)	820/1943 (42.2)	849/2005 (42.3)	758/2093 (36.2)	722/2078 (34.7)	703/2233 (31.5)	697/2205 (31.6)	712/2226 (32.0)	619/2111 (29.3)	<.01 (d)
	Composite [‡]	395/1849 (21.4)	446/2200 (20.3)	466/2260 (20.6)	440/2453 (17.9)	421/2306 (18.3)	428/2472 (17.3)	423/2460 (17.2)	436/2478 (17.6)	342/2305 (14.8)	<.01 (d)
FinMBR	Composite [†]	109/278 (39.2)	94/274 (34.3)	113/284 (39.8)	86/287 (30.0)	112/303 (37.0)	76/259 (29.3)	67/224 (29.9)	72/254 (28.3)	99/259 (38.2)	.08 (d)
	Composite [‡]	67/311 (21.5)	51/311 (16.4)	76/304 (25.0)	49/306 (16.0)	60/328 (18.3)	35/268 (13.1)	36/249 (14.5)	42/278 (15.1)	48/272 (17.6)	.01 (d)
INN	Composite [†]	349/1034 (33.8)	358/1101 (32.5)	384/1161 (33.1)	371/1102 (33.7)	318/1080 (29.4)	385/1145 (33.6)	339/1026 (33.0)	339/1096 (30.9)	335/1155 (29.0)	.03 (d)
	Composite [‡]	272/1044 (26.1)	268/1126 (23.8)	293/1188 (24.7)	291/1123 (25.9)	235/1096 (21.4)	303/1163 (26.1)	246/1050 (23.4)	253/1103 (22.9)	219/1157 (18.9)	<.01 (d)
NRNJ	Composite [†]	1143/3024 (37.8)	1011/2945 (34.3)	1108/3078 (36.0)	1362/3562 (38.2)	1321/3694 (35.8)	1379/3746 (36.8)	1376/3468 (39.7)	1289/3111 (41.4)	1013/2533 (40.0)	<.01 (i)
	Composite [‡]	873/3025 (28.9)	718/2949 (24.3)	747/3082 (24.2)	884/3692 (23.9)	790/3885 (20.3)	849/3936 (21.6)	728/3654 (19.9)	634/3325 (19.1)	509/2795 (18.2)	<.01 (d)
SEN1500	Composite [†]	743/1925 (38.6)	750/2065 (36.3)	809/2056 (39.3)	675/1799 (37.5)	739/1889 (39.1)	741/1947 (38.1)	705/1833 (38.5)	799/1831 (43.6)	719/1781 (40.4)	<.01 (i)
	Composite [‡]	592/1983 (29.9)	596/2150 (27.7)	608/2211 (27.5)	519/1910 (27.2)	558/2019 (27.6)	543/2108 (25.8)	517/1956 (26.4)	623/2015 (30.9)	574/1905 (30.1)	.34
SNQ	Composite [†]	153/537 (28.5)	170/552 (30.8)	163/523 (31.2)	183/575 (31.8)	162/459 (35.3)	214/569 (37.6)	209/617 (33.9)	254/618 (41.1)	273/656 (41.6)	<.01 (i)
	Composite [‡]	85/537 (15.8)	91/554 (16.4)	88/523 (16.8)	105/575 (18.3)	87/511 (17.0)	97/612 (15.8)	98/669 (14.6)	110/659 (16.7)	115/711 (16.2)	.69
SwissNeoNet	Composite [†]	114/466 (24.5)	128/509 (25.1)	136/502 (27.1)	156/536 (29.1)	132/538 (24.5)	161/580 (27.8)	135/526 (25.7)	152/562 (27.0)	158/629 (25.1)	.97
	Composite [‡]	83/473 (17.5)	84/516 (16.3)	82/507 (16.2)	103/541 (19.0)	82/538 (15.2)	79/581 (13.6)	74/529 (14.0)	83/569 (14.6)	90/641 (14.0)	.01 (d)
TuscanNN	Composite [†]	NA	NA	90/258 (34.9)	54/228 (23.7)	53/187 (28.3)	57/201 (28.4)	62/203 (30.5)	54/177 (30.5)	49/205 (23.9)	.18
	Composite [‡]	NA	NA	76/259 (29.3)	44/229 (19.2)	40/187 (21.4)	40/202 (19.8)	44/203 (21.7)	46/179 (25.7)	38/206 (18.4)	.10
UKNC	Composite [†]	NA	1543/3683 (41.9)	1620/3882 (41.7)	2116/4764 (44.4)	2428/5231 (46.4)	2462/5200 (47.3)	2406/5092 (47.3)	2439/5050 (48.3)	2400/5202 (46.1)	<.01 (i)
	Composite [‡]	NA	665/3694 (18.0)	664/3890 (17.1)	895/4768 (18.8)	1012/5232 (19.3)	1000/5200 (19.2)	975/5094 (19.1)	954/5050 (18.9)	937/5203 (18.0)	.28

*The *P* trend was adjusted for birth weight z score, sex, and multiple births; (i) denote increasing trend and (d) denote decreasing trend.

[†]Composite outcome included mortality or any of the following 3 morbidities: SNI, treated ROP, or BPD.

[‡]Composite outcome included mortality or any of the following 2 morbidities: SNI or treated ROP.

Table VI. Mortality rates between 2007 and 2015 in countries participating in iNEO

Countries/regions	2007 N = 11 669	2008 N = 16 039	2009 N = 16 650	2010 N = 17 845	2011 N = 18 603	2012 N = 19 149	2013 N = 18 403	2014 N = 18 229	2015 N = 17 646	P trend*
ANZNN, n/N (%)	181/2447 (7.4)	226/2539 (8.9)	194/2426 (8.0)	219/2248 (9.7)	228/2501 (9.1)	196/2607 (7.5)	179/2539 (7.1)	205/2573 (8.0)	169/2451 (6.9)	.04
CNN, n/N (%)	193/1849 (10.4)	211/2200 (9.6)	238/2260 (10.5)	194/2453 (7.9)	213/2306 (9.2)	210/2472 (8.5)	214/2460 (8.7)	190/2478 (7.7)	153/2305 (6.6)	<.01
FinMBR, n/N (%)	37/311 (11.9)	28/311 (9.0)	35/304 (11.5)	23/306 (7.5)	20/328 (6.1)	12/268 (4.5)	11/249 (4.4)	18/278 (6.5)	22/272 (8.1)	.06
INN, n/N (%)	136/1044 (13.0)	148/1126 (13.1)	181/1188 (15.2)	157/1123 (14.0)	132/1096 (12.0)	176/1163 (15.1)	155/1050 (14.8)	134/1103 (12.1)	142/1157 (12.3)	.42
NRNJ, n/N (%)	174/3025 (5.8)	180/2949 (6.1)	138/3082 (4.5)	163/3692 (4.4)	144/3885 (3.7)	138/3936 (3.5)	118/3654 (3.2)	134/3325 (4.0)	77/2795 (2.8)	<.01
SEN1500, n/N (%)	366/1983 (18.5)	377/2150 (17.5)	372/2211 (16.8)	283/1910 (14.8)	350/2019 (17.3)	289/2108 (13.7)	253/1956 (12.9)	249/2015 (12.4)	244/1905 (12.8)	<.01
SNQ, n/N (%)	40/537 (7.4)	45/554 (8.1)	39/523 (7.5)	43/575 (7.5)	47/511 (9.2)	54/612 (8.8)	53/669 (7.9)	52/659 (7.9)	42/711 (5.9)	.48
SwissNeoNet, n/N (%)	43/473 (9.1)	54/516 (10.5)	50/507 (9.9)	61/541 (11.3)	50/538 (9.3)	48/581 (8.3)	48/529 (9.1)	55/569 (9.7)	55/641 (8.6)	.32
TuscanNN, n/N (%)	NA	NA	32/259 (12.4)	25/229 (10.9)	26/187 (13.9)	19/202 (9.4)	22/203 (10.8)	21/179 (11.7)	22/206 (10.7)	.57
UKNC, n/N (%)	NA	420/3694 (11.4)	405/3890 (10.4)	493/4768 (10.3)	572/5232 (10.9)	542/5200 (10.4)	471/5094 (9.2)	421/5050 (8.3)	411/5203 (7.9)	<.01

*The P trend was adjusted for birth weight z score, sex, and multiple births.

Table VII. SNI rates between 2007 and 2015 in countries participating in iNEO

Countries/regions	2007	2008	2009	2010	2011	2012	2013	2014	2015	P trend*
ANZNN, n/N (%)	163/2355 (6.9)	161/2405 (6.7)	168/2308 (7.3)	153/2142 (7.1)	156/2377 (6.6)	150/2453 (6.1)	146/2394 (6.1)	149/2400 (6.2)	147/2299 (6.4)	.08
CNN, n/N (%)	184/1594 (11.5)	232/1912 (12.1)	246/1961 (12.5)	225/2297 (9.8)	199/2178 (9.1)	248/2314 (10.7)	230/2278 (10.1)	231/2293 (10.1)	223/2168 (10.3)	.01
FinMBR, n/N (%)	33/311 (10.6)	28/311 (9.0)	34/304 (11.2)	25/306 (8.2)	35/328 (10.7)	14/268 (5.2)	20/249 (8.0)	22/278 (7.9)	26/272 (9.6)	.20
INN, n/N (%)	154/1008 (15.3)	151/1076 (14.0)	159/1121 (14.2)	185/1075 (17.2)	130/1056 (12.3)	175/1106 (15.8)	136/989 (13.8)	152/1074 (14.2)	115/1128 (10.2)	.01
NRNJ, n/N (%)	237/3019 (7.9)	234/2940 (8.0)	207/3074 (6.7)	285/3602 (7.9)	261/3801 (6.9)	238/3775 (6.3)	227/3486 (6.5)	199/3102 (6.4)	164/2546 (6.4)	<.01
SEN1500, n/N (%)	272/1896 (14.3)	296/2014 (14.7)	306/1989 (15.4)	279/1767 (15.8)	270/1852 (14.6)	322/1884 (17.1)	291/1780 (16.3)	316/1793 (17.6)	283/1747 (16.2)	<.01
SNQ, n/N (%)	29/537 (5.4)	36/552 (6.5)	34/523 (6.5)	56/575 (9.7)	31/439 (7.1)	39/550 (7.1)	45/597 (7.5)	52/601 (8.7)	55/636 (8.6)	.03
SwissNeoNet, n/N (%)	57/468 (12.2)	37/513 (7.2)	46/504 (9.1)	47/534 (8.8)	45/538 (8.4)	42/579 (7.3)	37/528 (7.0)	43/566 (7.6)	52/638 (8.2)	.04
TuscanNN, n/N (%)	NA	NA	56/256 (21.9)	26/223 (11.7)	13/182 (7.1)	25/199 (12.6)	24/200 (12.0)	24/174 (13.8)	18/201 (9.0)	.54
UKNC, n/N (%)	NA	275/3694 (7.4)	234/3890 (6.0)	363/4768 (7.6)	428/5232 (8.2)	454/5200 (8.7)	405/5094 (8.0)	423/5050 (8.4)	399/5203 (7.7)	.01

*The P trend was adjusted for birth weight z score, sex, and multiple births.

Table VIII. ROP treatment rates between 2007 and 2015 in countries participating in iNEO

Countries/regions	2007	2008	2009	2010	2011	2012	2013	2014	2015	P trend*
ANZNN, n/N (%)	84/2447 (3.4)	83/2539 (3.3)	69/2426 (2.8)	57/2248 (2.5)	71/2501 (2.8)	71/2607 (2.7)	67/2539 (2.6)	81/2573 (3.1)	52/2451 (2.1)	.02
CNN, n/N (%)	94/1849 (5.1)	94/2200 (4.3)	76/2260 (3.4)	101/2453 (4.1)	79/2306 (3.4)	79/2472 (3.2)	77/2460 (3.1)	89/2478 (3.6)	30/2305 (1.3)	<.01
FinMBR, n/N (%)	11/311 (3.5)	8/311 (2.6)	19/304 (6.3)	9/306 (2.9)	15/328 (4.6)	11/268 (4.1)	7/249 (2.8)	6/278 (2.2)	9/272 (3.3)	.38
INN, n/N (%)	44/1044 (4.2)	41/1126 (3.6)	39/1188 (3.3)	29/1123 (2.6)	38/1096 (3.5)	31/1163 (2.7)	31/1050 (3.0)	30/1103 (2.7)	29/1157 (2.5)	.01
NRNJ, n/N (%)	585/3025 (19.3)	411/2949 (13.9)	500/3082 (16.2)	562/3692 (15.2)	507/3885 (13.1)	576/3936 (14.6)	468/3654 (12.8)	388/3325 (11.7)	327/2795 (11.7)	<.01
SEN1500, n/N (%)	97/1983 (4.9)	78/2150 (3.6)	89/2211 (4.0)	91/1910 (4.8)	81/2019 (4.0)	90/2108 (4.3)	96/1956 (4.9)	213/2015 (10.6)	185/1905 (9.7)	<.01
SNQ, n/N (%)	26/537 (4.8)	20/554 (3.6)	26/523 (5.0)	33/575 (5.7)	29/511 (5.7)	22/612 (3.6)	17/669 (2.5)	27/659 (4.1)	38/711 (5.3)	.62
SwissNeoNet, n/N (%)	7/467 (1.5)	8/509 (1.6)	7/502 (1.4)	12/539 (2.2)	5/537 (0.9)	7/580 (1.2)	6/527 (1.1)	5/563 (0.9)	5/628 (0.8)	.08
TuscanNN, n/N (%)	NA	NA	9/259 (3.5)	7/229 (3.1)	7/187 (3.7)	5/201 (2.5)	7/203 (3.4)	8/179 (4.5)	5/206 (2.4)	.88
UKNC, n/N (%)	NA	93/3694 (2.5)	114/3890 (2.9)	183/4768 (3.8)	201/5232 (3.8)	194/5200 (3.7)	258/5094 (5.1)	267/5050 (5.3)	269/5203 (5.2)	<.01

*The P trend was adjusted for birth weight z score, sex, and multiple births.

Table IX. BPD rates between 2007 and 2015 in countries participating in iNEO

Countries/regions	2007	2008	2009	2010	2011	2012	2013	2014	2015	P trend*
ANZNN, n/N (%)	518/2253 (23.0)	515/2301 (22.4)	512/2235 (22.9)	557/2041 (27.3)	672/2270 (29.6)	713/2426 (29.4)	731/2375 (30.8)	776/2378 (32.6)	787/2294 (34.3)	<.01
CNN, n/N (%)	456/1586 (28.8)	481/1897 (25.4)	504/1942 (26.0)	451/2013 (22.4)	406/1943 (20.9)	377/2145 (17.6)	393/2143 (18.3)	385/2194 (17.5)	354/2077 (17.0)	<.01
FinMBR, n/N (%)	59/242 (24.4)	52/242 (21.5)	54/245 (22.0)	47/262 (17.9)	64/282 (22.7)	48/244 (19.7)	41/211 (19.4)	37/235 (15.7)	60/236 (25.4)	.43
INN, n/N (%)	133/922 (14.4)	136/988 (13.8)	141/1021 (13.8)	136/975 (13.9)	129/975 (13.2)	137/1001 (13.7)	122/905 (13.5)	135/975 (13.8)	165/1027 (16.1)	.45
NRNJ, n/N (%)	499/2873 (17.4)	485/2798 (17.3)	571/2963 (19.3)	753/3421 (22.0)	813/3568 (22.8)	858/3628 (23.6)	932/3379 (27.6)	926/3007 (30.8)	699/2485 (28.1)	<.01
SEN1500, n/N (%)	219/1574 (13.9)	238/1745 (13.6)	304/1805 (16.8)	250/1602 (15.6)	268/1659 (16.2)	294/1794 (16.4)	292/1679 (17.4)	292/1733 (16.8)	252/1637 (15.4)	.01
SNQ, n/N (%)	88/498 (17.7)	98/510 (19.2)	106/489 (21.7)	117/537 (21.8)	100/468 (21.4)	142/561 (25.3)	140/622 (22.5)	178/612 (29.1)	202/675 (29.9)	<.01
SwissNeoNet, n/N (%)	39/431 (9.0)	54/464 (11.6)	65/456 (14.3)	75/480 (15.6)	61/494 (12.3)	91/538 (16.9)	66/484 (13.6)	79/517 (15.3)	82/590 (13.9)	.02
TuscanNN, n/N (%)	NA	NA	24/227 (10.6)	21/213 (9.9)	19/166 (11.4)	25/184 (13.6)	25/183 (13.7)	15/162 (9.3)	14/188 (7.4)	.54
UKNC, n/N (%)	NA	1072/3304 (32.4)	1155/3512 (32.9)	1522/4311 (35.3)	1735/4696 (36.9)	1817/4697 (38.7)	1827/4656 (39.2)	1895/4663 (40.6)	1849/4818 (38.4)	<.01

*The P trend was adjusted for birth weight z-score, sex, and multiple births.