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

Kei Lui, MD[1], Shoo K. Lee, MBBS, FRCPC, PhD[2,3,4], Satoshi Kusuda, MD[5], Mark Adams, PhD[6], Maximo Vento, MD, PhD[7], Brian Reichman, MB, ChB[8], Brian A. Darlow, MD[9], Liisa Lehtonen, MD[10,11], Neena Modi, MD[12], Mikael Norman, MD, PhD[13,14], Stellan Håkansson, MD[15], Dirk Bassler, MD, MSc[6], Franca Rusconi, MD[16], Abhay Lodha, MD, MSc[17], Junmin Yang, MSc[3], Prakesh S. Shah, MD, MSc[2,3], on behalf of the International Network for Evaluation of Outcomes (iNeo) of neonates Investigators*

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

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

From the [1]Department of Newborn Care, Royal Hospital for Women and School of Women's and Children's Health, Faculty of Medicine, University of New South Wales, Sydney, NSW, Australia; [2]Department of Pediatrics, Sinai Health System, University of Toronto, Ontario, Canada; [3]Maternal-Infant Care Research Centre, Sinai Health System, [4]Department of Obstetrics and Gynecology, Dalla Lana School of Public Health, University of Toronto, Toronto, Ontario, Canada; [5]Division of Neonatology, National Center for Child Health and Development, Tokyo, Japan; [6]Swiss Neonatal Network, Department of Neonatology, University Hospital Zurich, University of Zurich, Zurich, Switzerland; [7]Spanish Neonatal Network, Health Research Institute La Fe, Avenida Fernando Abril Martorell, Valencia, Spain; [8]Israel Neonatal Network, Gertner Institute for Epidemiology and Health Policy Research, Tel Hashomer, Israel; [9]Department of Paediatrics, University of Otago, Christchurch, Canterbury, New Zealand; [10]Department of Pediatrics and Adolescent Medicine, Turku University Hospital, [11]Department of Clinical Medicine, University of Turku, Turku, Finland; [12]UK Neonatal Collaborative, Neonatal Data Analysis Unit, Section of Neonatal Medicine, Department of Medicine, Imperial College London, Chelsea and Westminster Hospital campus, London, United Kingdom; [13]Department of Clinical Science, Intervention and Technology, Karolinska Institutet, [14]Department of Neonatal Medicine, Karolinska University Hospital, Stockholm, [15]Department of Clinical Science/Pediatrics, Umeå University, Umeå, Sweden; [16]Unit of Epidemiology Meyer Children's University Hospital and Regional Health Agency, Florence, Italy; and [17]Pediatrics & Community Health Sciences, University of Calgary, Calgary, Alberta, Canada

*List of iNeo investigators can be found in the **Appendix** (www.jpeds.com).

Funding and disclosure information is available at www.jpeds.com.

Portions of this study were presented at the Pediatric Academic Society Meeting, May 5-8, 2018, Toronto, Ontario, Canada; and the congress of Joint European Neonatal Societies (jENS), October 31 – November 4, 2017, Venice, Italy.

https://doi.org/10.1016/j.jpeds.2019.08.020

areas for possible improvement.[11] Previously, we reported a significant variation in outcomes between the participating iNeo countries[16] 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 hemorrhage[24] 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 (±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)	
	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)	<.01
	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)	
	1*	1061 (264)	1048 (259)	1059 (271)	1066 (264)	1012 (280)	1060 (263)	1058 (272)	1048 (272)	1042 (269)	1044 (260)	1045 (267)	.05
	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)	
	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)	<.01
	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)	
	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)	.87
	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)	
	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)	<.01
	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)	
	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)	<.01
	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)	
	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)	<.01
	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)	
	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)	<.01
	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)	
	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)	<.01
	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 = 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	TuscanNN N = 1465	UKNC N = 38 131	Total N = 154 233	*P* value
Composite outcome with BPD,* n (%)	Total	8051 (37.6)	6615 (35.7)	828 (34.2)	3178 (32.1)	11 002 (37.7)	6680 (39.0)	1781 (34.9)	1272 (26.2)	419 (28.7)	17 414 (45.7)	57 240 (38.8)	
	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)	29 374 (37.8)	<.01
	2‡	3917 (40.4)	2731 (31.1)	314 (31.5)	1398 (31.6)	5057 (39.3)	2964 (40.1)	950 (38.6)	606 (26.4)	222 (28.2)	9707 (47.3)	27 886 (39.7)	
Composite outcome without BPD,§ n (%)	Total	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)	30 757 (20.0)	
	1†	1836 (15.1)	2168 (19.6)	303 (19.4)	1359 (24.4)	4012 (24.1)	2873 (28.0)	456 (16.9)	434 (16.9)	160 (23.7)	3236 (18.4)	16 837 (20.8)	<.01
	2‡	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)	13 920 (19.0)	
Mortality, n (%)	Total	1797 (8.1)	1816 (8.7)	206 (7.8)	1361 (13.5)	1266 (4.2)	2783 (15.2)	415 (7.8)	464 (9.5)	167 (11.4)	3735 (9.8)	14 010 (9.1)	
	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)	<.01
	2‡	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)	
SNI, n (%)	Total	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)	13 642 (9.3)	
	1†	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)	.06
	2‡	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)	
Treated ROP, 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)	
	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)	.01
	2‡	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)	
BPD, n (%)	Total	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)	12 872 (37.1)	35 027 (25.5)	
	1†	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)	16 774 (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)	18 253 (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

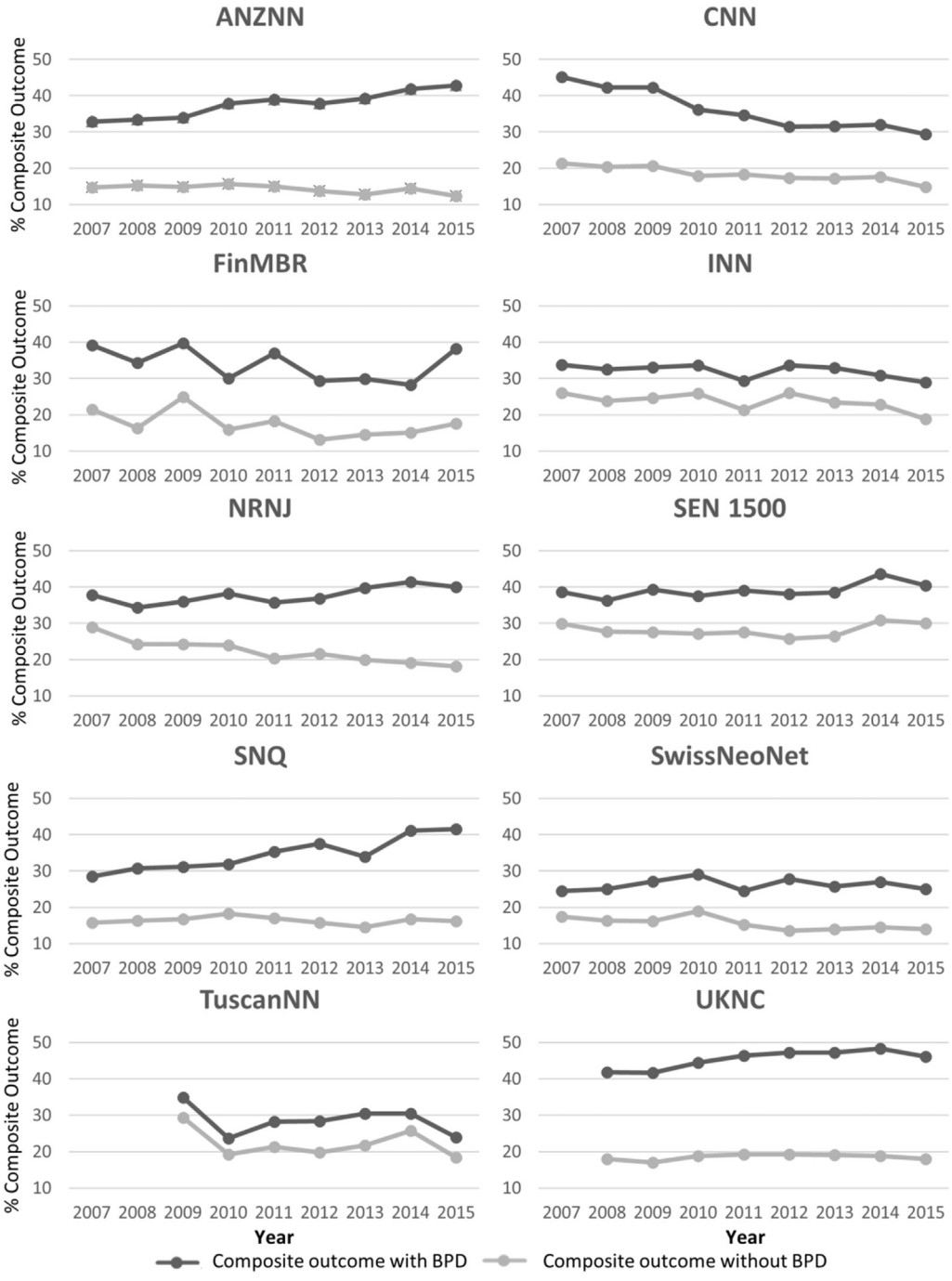

Figure 1. Trends of composite outcomes (including and excluding BPD) between 2007 and 2015. *ANZNN*, Australia/New Zealand; *CNN*, Canada; *FinMBR*, Finland; *INN*, Israel; *NRNJ*, Japan; *SEN1500*, Spain; *SNQ*, Sweden; *SwissNeoNet*, Switzerland; *Tuscan NN*, Tuscany, Italy; *UKNC*, United Kingdom. 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	FinMBR	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 combination[39] 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 NICUs[14] 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. ■

We thank all investigators and data abstractors of the networks participating in the iNeo consortium for their diligent work. We thank Sarah Hutchinson, PhD, from the Maternal-Infant Care Research Centre (MiCare) in Toronto, Ontario, Canada, for editorial support for this manuscript and other MiCare staff for organizational and statistical support.

Submitted for publication Jun 6, 2019; last revision received Jul 4, 2019; accepted Aug 8, 2019.

Data Statement

Data sharing statement available at www.jpeds.com.

References

1. Patel RM, Kandefer S, Walsh MC, Bell EF, Carlo WA, Laptook AR, et al. Causes and timing of death in extremely premature infants from 2000 through 2011. N Engl J Med 2015;372:331-40.
2. Liu L, Oza S, Hogan D, Perin J, Rudan I, Lawn JE, et al. Global, regional, and national causes of child mortality in 2000-13, with projections to inform post-2015 priorities: an updated systematic analysis. Lancet 2015;385:430-40.
3. Stoll BJ, Hansen NI, Bell EF, Walsh MC, Carlo WA, Shankaran S, et al. Trends in care practices, morbidity, and mortality of extremely preterm neonates, 1993-2012. JAMA 2015;314:1039-51.
4. Johnston KM, Gooch K, Korol E, Vo P, Eyawo O, Bradt P, et al. The economic burden of prematurity in Canada. BMC Pediatr 2014;14:93.
5. Bader D, Kugelman A, Boyko V, Levitzki O, Lerner-Geva L, Riskin A, et al. Risk factors and estimation tool for death among extremely premature infants: a national study. Pediatrics 2010;125:696-703.
6. Cust AE, Darlow BA, Donoghue DA. Australian New Zealand Neonatal Network. Outcomes for high risk New Zealand newborn infants in 1998-1999: a population based, national study. Arch Dis Child Fetal Neonatal Ed 2003;88:F15-22.
7. Gale C, Santhakumaran S, Nagarajan S, Statnikov Y, Modi N. Neonatal Data Analysis Unit and the Medicines for Neonates Investigator Group. Impact of managed clinical networks on NHS specialist neonatal services in England: population based study. BMJ 2012;344:e2105.
8. EXPRESS Group Fellman V, Hellström-Westas L, Norman M, Westgren M, Kallen K, Lagercrantz H, et al. One-year survival of extremely preterm infants after active perinatal care in Sweden. JAMA 2009;301:2225-33.
9. Kusuda S, Fujimura M, Sakuma I, Aotani H, Kabe K, Itani Y, et al. Morbidity and mortality of infants with very low birth weight in Japan: center variation. Pediatrics 2006;118:e1130-8.
10. Lee SK, McMillan DD, Ohlsson A, Pendray M, Synnes A, Whyte R, et al. Variations in practice and outcomes in the Canadian NICU network: 1996-1997. Pediatrics 2000;106:1070-9.
11. Shah PS, Lee SK, Lui K, Sjors G, Mori R, Reichman B, et al. The International Network for Evaluating Outcomes of very low birth weight, very preterm neonates (iNeo): a protocol for collaborative comparisons of international health services for quality improvement in neonatal care. BMC Pediatr 2014;14:110.
12. Evans N, Hutchinson J, Simpson JM, Donoghue D, Darlow B, Henderson-Smart D. Prenatal predictors of mortality in very preterm infants cared for in the Australian and New Zealand Neonatal Network. Arch Dis Child Fetal Neonatal Ed 2007;92:F34-40.
13. Hossain S, Shah PS, Ye XY, Darlow BA, Lee SK, Lui K, et al. Outcome comparison of very preterm infants cared for in the neonatal intensive care units in Australia and New Zealand and in Canada. J Paediatr Child Health 2015;51:881-8.
14. Lee SK, Shah PS, Singhal N, Aziz K, Synnes A, McMillan D, et al. Association of a quality improvement program with neonatal outcomes in extremely preterm infants: a prospective cohort study. CMAJ 2014;186:E485-94.
15. Shah PS, Dunn M, Aziz K, Shah V, Deshpandey A, Mukerji A, et al. Sustained quality improvement in outcomes of preterm neonates with a gestational age less than 29 weeks: results from the Evidence-based Practice for Improving Quality Phase 3. Can J Physiol Pharmacol 2019;97:213-21.
16. Shah PS, Lui K, Sjors G, Mirea L, Reichman B, Adams M, et al. Neonatal outcomes of very low birth weight and very preterm neonates: an international comparison. J Pediatr 2016;177:144-52.e6.
17. Beltempo M, Isayama T, Vento M, Lui K, Kusuda S, Lehtonen L, et al. Respiratory management of extremely preterm infants: an international survey. Neonatology 2018;114:28-36.
18. Darlow BA, Lui K, Kusuda S, Reichman B, Hakansson S, Bassler D, et al. International variations and trends in the treatment for retinopathy of prematurity. Br J Ophthalmol 2017;101:1399-404.
19. Darlow BA, Vento M, Beltempo M, Lehtonen L, Hakansson S, Reichman B, et al. Variations in oxygen saturation targeting, and retinopathy of prematurity screening and treatment criteria in neonatal intensive care units: an international survey. Neonatology 2018;114:323-31.
20. Hines D, Modi N, Lee SK, Isayama T, Sjors G, Gagliardi L, et al. Scoping review shows wide variation in the definitions of bronchopulmonary dysplasia in preterm infants and calls for a consensus. Acta Paediatr 2017;106:366-74.
21. Kelly LE, Shah PS, Hakansson S, Kusuda S, Adams M, Lee SK, et al. Perinatal health services organization for preterm births: a multinational comparison. J Perinatol 2017;37:762-8.
22. Nelin LD, Shepherd EG. Disappointing results: a call to action. J Thorac Dis 2018;10:631-3.
23. Martin LJ, Sjors G, Reichman B, Darlow BA, Morisaki N, Modi N, et al. Country-specific vs. common birthweight-for-gestational age references to identify small for gestational age infants born at 24-28 weeks: an international study. Paediatr Perinat Epidemiol 2016;30:450-61.
24. Papile LA, Burstein J, Burstein R, Koffler H. Incidence and evolution of subependymal and intraventricular hemorrhage: a study of infants with birth weights less than 1,500 gm. J Pediatr 1978;92:529-34.
25. International Committee for the Classification of Retinopathy of Prematurity. The International Classification of Retinopathy of Prematurity revisited. Arch Ophthalmol 2005;123:991-9.
26. Horbar JD, Edwards EM, Greenberg LT, Morrow KA, Soll RF, Buus-Frank ME, et al. Variation in performance of neonatal intensive care units in the United States. JAMA Pediatr 2017;171:e164396.
27. Santhakumaran S, Statnikov Y, Gray D, Battersby C, Ashby D, Modi N, et al. Survival of very preterm infants admitted to neonatal care in England 2008-2014: time trends and regional variation. Arch Dis Child Fetal Neonatal Ed 2018;103:F208-15.
28. Amer R, Moddemann D, Seshia M, Alvaro R, Synnes A, Lee KS, et al. Neurodevelopmental outcomes of infants born at <29 weeks of gestation admitted to Canadian neonatal intensive care units based on location of birth. J Pediatr 2018;196:31-7.e1.
29. Boland RA, Davis PG, Dawson JA, Doyle LW. Outcomes of infants born at 22-27 weeks' gestation in Victoria according to outborn/inborn birth status. Arch Dis Child Fetal Neonatal Ed 2017;102:F153-61.
30. Thompson K, Gardiner J, Resnick S. Outcome of outborn infants at the borderline of viability in Western Australia: a retrospective cohort study. J Paediatr Child Health 2016;52:728-33.
31. Garcia-Munoz Rodrigo F, Diez Recinos AL, Garcia-Alix Perez A, Figueras Aloy J, Vento Torres M. Changes in perinatal care and outcomes in newborns at the limit of viability in Spain: the EPI-SEN Study. Neonatology 2015;107:120-9.
32. Greenough A, Lingam I. Invasive and non-invasive ventilation for prematurely born infants—current practice in neonatal ventilation. Expert Rev Respir Med 2016;10:185-92.
33. Chen F, Bajwa NM, Rimensberger PC, Posfay-Barbe KM, Pfister RE , Swiss Neonatal Network. Thirteen-year mortality and morbidity in

preterm infants in Switzerland. Arch Dis Child Fetal Neonatal Ed 2016;101:F377-83.
34. Garcia-Munoz Rodrigo F, Losada Martinez A, Elorza Fernandez MD, Moreno Hernando J, Figueras Aloy J, Vento Torres M. The burden of respiratory disease in very-low-birth-weight infants: changes in perinatal care and outcomes in a decade in Spain. Neonatology 2017;112:30-9.
35. Doyle LW, Carse E, Adams AM, Ranganathan S, Opie G, Cheong JLY, et al. Ventilation in extremely preterm infants and respiratory function at 8 years. N Engl J Med 2017;377:329-37.
36. Araki S, Kato S, Namba F, Ota E. Vitamin A to prevent bronchopulmonary dysplasia in extremely low birth weight infants: a systematic review and meta-analysis. PLoS One 2018;13:e0207730.
37. Schmidt B, Roberts RS, Davis P, Doyle LW, Barrington KJ, Ohlsson A, et al. Caffeine therapy for apnea of prematurity. N Engl J Med 2006;354:2112-21.
38. Fischer HS, Schmolzer GM, Cheung PY, Buhrer C. Sustained inflations and avoiding mechanical ventilation to prevent death or bronchopulmonary dysplasia: a meta-analysis. Eur Respir Rev 2018;27:180083.
39. Yeh TF, Chen CM, Wu SY, Husan Z, Li TC, Hsieh WS, et al. Intratracheal administration of budesonide/surfactant to prevent bronchopulmonary dysplasia. Am J Respir Crit Care Med 2016;193:86-95.
40. Kennedy KA, Cotten CM, Watterberg KL, Carlo WA. Prevention and management of bronchopulmonary dysplasia: lessons learned from the neonatal research network. Semin Perinatol 2016;40:348-55.
41. Watterberg KL , American Academy of Pediatrics Committee on Fetus and Newborn. Policy statement—postnatal corticosteroids to prevent or treat bronchopulmonary dysplasia. Pediatrics 2010;126:800-8.
42. Shah V, Warre R, Lee SK. Quality improvement initiatives in neonatal intensive care unit networks: achievements and challenges. Acad Pediatr 2013;13:S75-83.

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.

Adriana M. Montaño, PhD
Departments of Pediatrics, and Biochemistry and Molecular Biology
School of Medicine
Saint Louis University
St. Louis, Missouri

Reference

1. Danes BS, Bearn AG. Hurler's syndrome. Effect of retinol (vitamin A alcohol) on cellular mucopolysaccharides in cultured human skin fibroblasts. J Exp Med 1966;124:1181-98.

Appendix

Additional members of iNeo Investigators

ANZNN (Australian and New Zealand Neonatal Network): Kei Lui* Chair of ANZNN. Flinders Medical Centre, SA: Peter Marshall. Gold Coast University Hospital, QLD: Peter Schmidt. Blacktown District Hospital, NSW: Anjali Dhawan*. John Hunter Children's Hospital, NSW: Paul Craven, Koert de Waal*. King Edward Memorial and Perth Children's Hospitals, WA: Karen Simmer, Andy Gill*, Jane Pillow*. Liverpool Hospital, NSW: Jacqueline Stack. Mater Mothers' Hospital, QLD: Pita Birch, Neonatal Retrieval Service, QLD: Lucy Cooke*. Mercy Hospital for Women, VIC: Dan Casalaz, Jim Holberton*. Monash Medical Centre, VIC: Alice Stewart. Nepean Hospital, NSW: Lyn Downe. Newborn Emergency Transport Service (VIC): Michael Stewart. NSW Pregnancy and Newborn Services Network: Barbara Bajuk*. NSW Newborn & Paediatric Emergency Transport Service: Andrew Berry. Royal Children's Hospital, VIC: Rod Hunt. Royal Darwin Hospital, NT: Charles Kilburn. Royal Hobart Hospital, Tasmania: Tony De Paoli. Royal Hospital for Women, NSW: Kei Lui*, Srinivas Bolisetty. Royal North Shore Hospital, NSW: Mary Paradisis. Royal Prince Alfred Hospital, NSW: Ingrid Rieger. Royal Brisbane and Women's Hospital, QLD: Pieter Koorts. Royal Women's Hospital, VIC: Carl Kuschel, Lex Doyle. Sydney Children's Hospital, NSW: Andrew Numa. The Canberra Hospital, ACT: Hazel Carlisle. The Children's Hospital at Westmead, NSW: Nadia Badawi, Alison Loughran-Fowlds. The Townsville Hospital, QLD: Guan Koh. Western Australia Neonatal Transport Service: Jonathan Davis. Westmead Hospital, NSW: Melissa Luig. Women's & Children's Hospital, SA: Chad Andersen*. National Perinatal Epidemiology and Statistics Unit, University of New South Wales: Georgina Chambers*. New Zealand: Christchurch Women's Hospital: Nicola Austin, Adrienne Lynn. University of Otago, Christchurch: Brian Darlow. Dunedin Hospital: Liza Edmonds. Middlemore Hospital: Lindsay Mildenhall. Auckland City Hospital: Mariam Buksh, Malcolm Battin*. North Shore and Waitakere Hospitals: Jutta van den Boom*. Waikato Hospital: David Bourchier. Wellington Women's Hospital: Vaughan Richardson, Fiona Dineen*. Singapore: KK Women's and Children's Hospital, Singapore: Victor Samuel Rajadurai*. Hong Kong: Prince of Wales Hospital: Simon Lam. United Christian Hospital: Genevieve Fung. (* Denotes the ANZNN Executive Committee).

CNN (Canadian Neonatal Network): Prakesh S. Shah, MD, MSc (Director, Canadian Neonatal Network and site investigator), Mount Sinai Hospital, Toronto, Ontario; Adele Harrison, MD, MBChB, Victoria General Hospital, Victoria, British Columbia; Anne Synnes, MDCM, MHSC, and Joseph Ting, MD, B.C. Women's Hospital and Health Centre, Vancouver, British Columbia; Zenon Cieslak, MD, Royal Columbian Hospital, New Westminster, British Columbia; Rebecca Sherlock, MD, Surrey Memorial Hospital, Surrey, British Columbia; Wendy Yee, MD, Foothills Medical Centre, Calgary, Alberta; Khalid Aziz, MBBS, MA, MEd, and Jennifer Toye, MD, Royal Alexandra Hospital, Edmonton, Alberta; Carlos Fajardo, MD, Alberta Children's Hospital, Calgary, Alberta; Zarin Kalapesi, MD, Regina General Hospital, Regina, Saskatchewan; Koravangattu Sankaran, MD, MBBS, and Sibasis Daspal, MD, Royal University Hospital, Saskatoon, Saskatchewan; Mary Seshia, MBChB, Winnipeg Health Sciences Centre, Winnipeg, Manitoba; Ruben Alvaro, MD, St Boniface General Hospital, Winnipeg, Manitoba; Amit Mukerji, MD, Hamilton Health Sciences Centre, Hamilton, Ontario; Orlando Da Silva, MD, MSc, London Health Sciences Centre, London, Ontario; Chuks Nwaesei, MD, Windsor Regional Hospital, Windsor, Ontario; Kyong-Soon Lee, MD, MSc, Hospital for Sick Children, Toronto, Ontario; Michael Dunn, MD, Sunnybrook Health Sciences Centre, Toronto, Ontario; Brigitte Lemyre, MD, Children's Hospital of Eastern Ontario and Ottawa General Hospital, Ottawa, Ontario; Kimberly Dow, MD, Kingston General Hospital, Kingston, Ontario; Ermelinda Pelausa, MD, Jewish General Hospital, Montréal, Québec; Keith Barrington, MBChB, Hôpital Sainte-Justine, Montréal, Québec; Christine Drolet, MD, and Bruno Piedboeuf, MD, Centre Hospitalier Universitaire de Québec, Sainte Foy Québec; Martine Claveau, MSc, LLM, NNP, and Marc Beltempo, MD, McGill University Health Centre, Montréal, Québec; Valerie Bertelle, MD, and Edith Masse, MD, Centre Hospitalier Universitaire de Sherbrooke, Sherbrooke, Québec; Roderick Canning, MD, Moncton Hospital, Moncton, New Brunswick; Hala Makary, MD, Dr Everett Chalmers Hospital, Fredericton, New Brunswick; Cecil Ojah, MBBS, and Luis Monterrosa, MD, Saint John Regional Hospital, Saint John, New Brunswick; Akhil Deshpandey, MBBS, MRCPI, Janeway Children's Health and Rehabilitation Centre, St. John's, Newfoundland; Jehier Afifi, MB BCh, MSc, IWK Health Centre, Halifax, Nova Scotia; Andrzej Kajetanowicz, MD, Cape Breton Regional Hospital, Sydney, Nova Scotia; Shoo K. Lee, MBBS, PhD (Chairman, Canadian Neonatal Network), Mount Sinai Hospital, Toronto, Ontario.

FinMBR (Finnish Medical Birth Register): Sture Andersson, MD, Helsinki University Hospital, Helsinki; Liisa Lehtonen, MD, Turku University Hospital, Turku; Outi Tammela, MD, Tampere University Hospital, Tampere; Ulla Sankilampi, MD, Kuopio University Hospital, Kuopio; Timo Saarela, MD, Oulu University Hospital, Oulu.

ILL (Illinois Neonatal Network): Preetha Prazad, MD, Advocate Children's Hospital, Park Ridge, Illinois; Akihiko Noguchi, MD, SSM Cardinal Glennon/St Mary's Hospital, St Louis Missouri; Kamlesh McWan, MD, Children's Hospital of Illinois, Peoria, Illinois; Beau Button, MD, St John's Hospital, Springfield, Illinois; William Stratton, MD, Carle Foundation Hospital, Urbana, Illinois; Aaron Hamvus, MD, Northwestern University Hospitals, Chicago, Illinois; Aarti Raghaven, MD, University Illinois Chicago Hospital, Chicago, Illinois; Matthew Derrick, MD, Evanston Northshore Hospital, Evanston, Illinois; Radley Hadley, MD, Advocate Illinois Masonic Hospital, Chicago, Illinois; Robert

Covert, MD, Edward Hospital, Naperville, Illinois; Omar Lablanc, MD, John H. Stroger Cook County Hospital, Chicago, Illinois; Marc Weiss, MD, RMCH Loyola University Hospital, Maywood, Illinois; Anthony Bell, MD, Adventist Hinsdale Hospital, Hinsdale, Illinois; Maliha Shareef, MD, St Alexius Hospital, Hoffman Estates, Illinois; Jean Silvestri, MD, Rush University Hospital, Chicago, Illinois.

INN (Israel Neonatal Network): Eli Heymann, MD, Assaf Harofeh Medical Center, Tzrifin; Shmuel Zangen, MD, Barzilai Medical Center, Ashkelon; Tatyana Smolkin, MD, Baruch Padeh Medical Center, Poriya; Francis Mimouni, MD, Bikur Cholim Hospital, Jerusalem; David Bader, MD, Bnai Zion Medical Center, Haifa; Avi Rothschild, MD, Carmel Medical Center, Haifa; Zipora Strauss, Chaim Sheba Medical Center, Ramat Gan; Clari Felszer, MD, Emek Medical Center, Afula; Hussam Omari, MD, French Saint Vincent de Paul Hospital, Nazareth; Smadar Even Tov-Friedman, MD, Hadassah University Hospital-Ein Karem, Jerusalem; Benjamin Bar-Oz, MD, Hadassah University Hospital-Har Hazofim, Jerusalem; Michael Feldman, MD, Hillel Yaffe Medical Center, Hadera; Nizar Saad, MD, Holy Family (Italian) Hospital, Nazareth; Orna Flidel-Rimon, MD, Kaplan Medical Center, Rehovot; Meir Weisbrod, MD, Laniado Hospital, Netanya; Daniel Lubin, MD, Mayanei Hayeshua Medical Center, Bnei Brak; Ita Litmanovitz, MD, Meir Medical Center, Kfar Saba; Amir Kugelman, MD, Rambam Medical Center; Eric Shinwell, MD, Rivka Ziv Medical Center, Safed; Gil Klinger, MD, Schneider Children's Medical Center of Israel, Rabin Medical Center (Beilinson Campus), Petah Tikva; Yousif Nijim, MD, Scottish (EMMS) Hospital, Nazareth; Alona Bin-Nun, MD, Shaare-Zedek Medical Center, Jerusalem; Agneta Golan, MD, Soroka Medical Center, Beersheba; Dror Mandel, MD, Sourasky Medical Center, Tel Aviv; Vered Fleisher-Sheffer, MD, Western Galilee Medical Center, Nahariya; David Kohelet, MD, Wolfson Medical Center, Holon; Lev Bakhrakh, MD, Yoseftal Hospital, Eilat.

NRNJ (Neonatal Research Network Japan): Satoshi Hattori, MD, Sapporo City Hospital, Sapporo, Hokkaido; Masaru Shirai, MD, Asahikawa Kosei Hospital, Asahikawa, Hokkaido; Toru Ishioka, MD, Engaru Kosei Hospital, Engaru, Hokkaido; Toshihiko Mori, MD, NTT East Sappro Hospital, Sapporo, Hokkaido; Takasuke Amizuka, MD, Aomori Prefecture Central Hospital, Aomori, Aomori; Toru Huchimukai, MD, Iwate Prefecture Ohfunato Hospital, Ofunato, Iwate; Hiroshi Yoshida, MD, Tsuruoka City Shonai Hospital, Tsuruoka, Yamagata; Ayako Sasaki, MD, Yamagata University, Yamagata, Yamagata; Junichi Shimizu, MD, Tsuchiura Kyodo Hospital, Tsuchiura, Ibaraki; Toshihiko Nakamura, MD, National Nishisaitama Central Hospital, Tokorozawa, Saitama; Mami Maruyama, MD, Jichi Medical University Saitame Medical Center, Omiya, Saitama; Hiroshi Matsumoto, MD, Asahi Central Hospital, Asahi, Chiba; Shinichi Hosokawa, MD, National International Medical Center, Shinjuku, Tokyo; Atsuko Taki, MD, Tokyo Medical and Dental University, Bunkyo, Tokyo; Machiko Nakagawa, MD, Saint Luku Hospital, Chuo, Tokyo; Kyone Ko, MD, Sanikukai Hospital, Sumida, Tokyo; Azusa Uozumi, MD, Odawara City Hospital, Odawara, Kanagawa; Setsuko Nakata, MD, Iida City Hospital, Iida, Nagano; Akira Shimazaki, MD, National Shinshu Ueda Medical Center, Ueda, Nagano; Tatsuya Yoda, MD, Saku General Hospital, Saku, Nagano; Osamu Numata, MD, Nagaoka Red Cross Hospital, Nagaoka, Niigata; Hiroaki Imamura, MD, Koseiren Takaoka Hospital, Takaoka, Toyama; Azusa Kobayashi, MD, Kanazawa Medical University, Kanazawa, Kanazawa; Shuko Tokuriki, MD, Fukui University, Fukui, Fukui; Yasushi Uchida, MD, National Nagara Medical Center, Nagara, Gifu; Takahiro Arai, MD, Takayama Red Cross Hospital, Takayama, Gifu; Mitsuhiro Ito, MD, Fujieda City Hospital, Fujieda, Shizuoka; Kuniko Ieda, MD, Koritsu Tosei Hospital, Toyota, Aichi; Toshiyuki Ono, MD, Komaki City Hospital, Komaki, Aichi; Masashi Hayashi, MD, Okazaki City Hospital, Okazaki, Aichi; Kanemasa Maki, MD, Yokkaichi City Hospital, Yokkaichi, MieToru Yamakawa, MD, Japan Baptist Hospital, Kyoto, Kyoto; Masahiko Kawai, MD, Kyoto University, Kyoto, Kyoto; Noriko Fujii, MD, Fukuchiyama City Hospital, Fukuchiyama, Kyoto; Kozue Shiomi, MD, Kyoto City Hospital, Kyoto, Kyoto; Koji Nozaki, MD, Mitubishi Kyoto Hospital, Kyoto, Kyoto; Hiroshi Wada, MD, Yodogawa Christian Hospital, Osaka, Osaka; Taho Kim, MD, Osaka City Sumiyoshi Hospital, Osaka, Osaka; Yasuyuki Tokunaga, MD, Toyonaka City Hospital, Toyonaka, Osaka; Yasuyuki Tokunaga, MD, National Cerebral and Cardiovascular Center, Suita, Osaka; Akihiro Takatera, MD, Chifune Hospital, Osaka, Osaka; Toshio Oshima, MD, Bell Land General Hospital, Sakai, Osaka; Hiroshi Sumida, MD, Rinku General Hospital, Izumisano, Osaka; Yae Michinomae, MD, Yao City Hospital, Yao, Osaka; Yoshio Kusumoto, MD, Osaka General Medical Center, Osaka, Osaka; Seiji Yoshimoto, MD, Kobe Children's Hospital, Kobe, Hyogo; Takeshi Morisawa, MD, Kakogawa City Hospital, Kakogawa, Hyogo; Tamaki Ohashi, MD, Hyogo Prefectural Awaji Hospital, Sumoto, Hyogo; Yukihiro Takahashi, MD, Nara Prefecture Medical University, Kashiwara, Nara; Moriharu Sugimoto, MD, Tsuyama Central Hospital, Tsuyama, Okayama; Noriaki Ono, MD, Hiroshima University, Hiroshima, Hiroshima; Shinichiro Miyagawa, MD, National Kure Medical Center, Kure, Hiroshima; Takahiko Saijo, MD, Tokushima University, Tokushima, Tokushima; Takashi Yamagami, MD, Tokushima City Hospital, Tokushima, Tokushima; Kosuke Koyano, MD, Kagawa University, Kida, Kagawa; Shoko Kobayashi, MD, Shikoku Medical Center for Children and Adults, Zentsuji, Kagawa; Takeshi Kanda, MD, National Kyushu Medical Center, Fukuoka, Fukuoka; Yoshihiro Sakemi, MD, National Kokura Medical Center, Kitakyushu, Fukuoka; Mikio Aoki, MD, National Nagasaki Medical Center, Nagasaki, Nagasaki; Koichi Iida, MD, Oita Prefectural Hospital, Oita, Oita; Mitsushi Goshi, MD, Nakatsu City Hospital, Nakatsu, Oita; Yuko Maruyama, MD, Imakyure General Hospital, Kagoshima, Kagoshima.

SEN1500 (Spanish Neonatal Network): Alejandro Avila-Alvarez, MD, and José Luis Fernandez-Trisac, MD, Complexo Hospitalario Universitario De A Coruña, A Coruña;

Mª Luz Couce Pico, MD, and María José Fernández Seara, MD, Hospital Clínico Universitario de Santiago, Santiago de Compostela; Andrés Martínez Gutiérrez, MD, Complejo Hospitalario Albacete, Albacete; Carolina Vizcaíno, MD, Hospital General Universitario de Elche, Alicante; Miriam Salvador Iglesias, MD, and Honorio Sánchez Zaplana, MD, Hospital General Universitario de Alicante, Alicante; Belén Fernández Colomer, MD, and José Enrique García López, MD, Hospital Universitario Central de Asturias, Oviedo, Asturias; Rafael García Mozo, MD, and M. Teresa González Martínez, MD, Hospital Universitario de Cabueñes, Gijón, Asturias; Mª Dolores Muro Sebastián, MD, and Marta Balart Carbonell, MD, Clínica Corachán, Barcelona; Joan Badia Barnusell, MD, and Mònica Domingo Puiggròs, MD, Corporacio Parc Taulí, Sabadell, Barcelona; Josep Figueras Aloy, MD, and Francesc Botet Mussons, MD, Hospital Clínic de Barcelona, Barcelona; Israel Anquela Sanz, MD, Hospitalario De Granollers, Granollers; Gemma Ginovart Galiana, MD, H. De La Santa Creu I Sant Pau, Barcelona; W. Coroleu, MD, Hospital Universitari Germans Trias I Pujol, Badalona; Martin Iriondo, MD, Hospital Sant Joan de Déu Barcelona, Esplugues de Llobregat, Barcelona; Laura Castells Vilella, MD, Hospital General de Cataluña, Barcelona; Roser Porta, MD, Institute Dexeus, Barcelona; Xavier Demestre, MD, and Silvia Martínez Nadal, MD, Scias-Hospital Barcelona, Barcelona; Cristina de Frutos Martínez, MD, Hospital Universitario de Burgos, Burgos; María Jesús López Cuesta, MD, H. San Pedro de Alcántara, Cáceres; Dolores Esquivel Mora, MD, and Joaquín Ortiz Tardío, MD, Hospital Jerez, Cádiz; Isabel Benavente, MD, and Almudena Alonso, MD, Hospital Universitario Puerta Del Mar, Cádiz; Ramón Aguilera Olmos, MD, Hospital General de Castellón, Castellón; Miguel A. García Cabezas, MD, and Mª Dolores Martínez Jiménez, MD, Hospital General Universitario de Ciudad Real, Ciudad Real; Mª Pilar Jaraba Caballero, MD, and Mª Dolores Ordoñez Díaz, MD, Hospital Universitario Reina Sofía, Córdoba; Alberto Trujillo Fagundo, MD, and Lluis Mayol Canals, MD, Hospital Universitari de Girona Dr. Josep Trueta, Girona; Fermín García-Muñoz Rodrigo, MD, and Lourdes Urquía Martí, MD, H.M.I. Las Palmas, Las Palmas, Gran Canaria; María Fernanda Moreno Galdo, MD, and José Antonio Hurtado Suazo, MD, Hospital Universitario Virgen De Las Nieves, Granada; Eduardo Narbona López, and José Uberos Fernández, MD, Hospital Universitario San Cecilio, Granada; Miguel A. Cortajarena Altuna, MD, and Oihana Muga Zuriarrain Hospital, MD, Donostia, Gipuzkoa; David Mora Navarro, MD, Hospital Juan Ramón Jiménez, Huelva; María Teresa Domínguez, MD, Hospital Costa De La Luz, Huelva; Mª Yolanda Ruiz del Prado, MD, and Inés Esteban Díez, MD, Hospital San Pedro, Logroño, La Rioja; María Teresa Palau Benavides, MD, and Santiago Lapeña, MD, Hospital de León, León, León; Teresa Prada, MD, Hospital del Bierzo, Ponferrada, León; Eduard Soler Mir, MD, Hospital Arnau De Vilanova, Lleida; Araceli Corredera Sánchez, MD, Enrique Criado Vega, MD, Náyade del Prado, MD, and Cristina Fernández, MD, Hospital Clínico San Carlos, Madrid; Lucía Cabanillas Vilaplana, MD, and Irene Cuadrado Pérez, MD, Hospital Universitario De Getafe, Madrid; Luisa López Gómez, MD, Hospital De La Zarzuela, Madrid; Laura Domingo Comeche, MD, Hospital Universitario de Fuenlabrada, Fuenlabrada, Madrid; Isabel Llana Martín, MD, Hospital Madrid-Torrelodones, Madrid, Madrid; Carmen González Armengod, MD, and Carmen Muñoz Labián, MD, Hospital Universitario Puerta De Hierro, Majadahonda, Madrid; Mª José Santos Muñoz, MD, Hospital Severo Ochoa, Leganés, Madrid; Dorotea Blanco Bravo, MD, and Vicente Pérez, MD, Hospital Gregorio Marañón, Madrid; Mª Dolores Elorza Fernández, MD, Celia Díaz González, MD, and Susana Ares Segura, MD, H.U. La Paz, Madrid; Manuela López Azorín, MD, Hospital Universitario Quirónsalud Madrid, Madrid; Ana Belén Jimenez MD, Hospital Universitario Fundación Jiménez Díaz, Madrid; Tomás Sánchez-Tamayo, MD, and Elías Tapia Moreno, MD, Hospital Carlos Haya, Málaga; María González, MD, and José Enrique Sánchez Martínez, MD, Hospital Parque San Antonio De Málaga, Málaga; José María Lloreda García, MD, Hospital Universitario Santa Lucia De Cartagena, Murcia; Concepción Goñi Orayen, MD, Hospital Virgen Del Camino De Pamplona, Pamplona, Navarra; Javier Vilas González, MD, Complexo Hospitalario Pontevedra, Pontevedra; María Suárez Albo, MD, and Eva González Colmenero, MD, Hospital Xeral De Vigo, Pontevedra; Elena Pilar Gutiérrez González, MD, and Beatriz Vacas del Arco, MD, Hospital Universitario de Salamanca, Salamanca; Josefina Márquez Fernández, MD, and Laura Acosta Gordillo, MD, Hospital Valme, Sevilla; Mercedes Granero Asensio, MD, Hospital Virgen De La Macarena, Sevilla; Carmen Macías Díaz, MD, Hospital Universitario Virgen Del Rocío, Sevilla; Mar Albújar, MD, Hospital Universitari de Tarragona Joan XXIII, Tarragona; Pedro Fuster Jorge. MD, Hospital Universitario De Canarias, San Cristóbal de La Laguna, Santa Cruz de Tenerife; Sabina Romero, MD, and Mónica Rivero Falero, MD, Hospital Universitario Nuestra Señora De Candelaria, Santa Cruz de Tenerife; Ana Belén Escobar Izquierdo, Hospital Virgen De La Salud, Toledo; Javier Estañ Capell, MD, Hospital Clinico Universitario De Valencia, Valencia; Mª Isabel Izquierdo Macián, MD, Hospital Universitari La Fe, Valencia; Mª Mar Montejo Vicente, MD, and Raquel Izquierdo Caballero, MD, Hospital Universitario Río Hortega, Valladolid; Mª Mercedes Martínez, MD, and Aintzane Euba, MD, Hospital de Txagorritxu, Vitoria-Gasteiz; Amaya Rodríguez Serna, MD, and Juan María López de Heredia Goya, MD, Hospital de Cruces, Baracaldo; Alberto Pérez Legorburu, MD, and Ana Gutiérrez Amorós, MD, Hospital Universitario de Basurto, Bilbao; Víctor Manuel Marugán Isabel, MD, and Natalio Hernández González, MD, Hospital Virgen De La Concha - Complejo Asistencial De Zamora, Zamora; Segundo Rite Gracia, MD, Hospital Miguel Servet, Zaragoza; Mª Purificación Ventura Faci, MD, and Mª Pilar Samper Villagrasa, MD, Hospital Clínico Universitario Lozano Blesa, Zaragoza.

SNQ (Swedish Neonatal Quality Register): Jiri Kofron, MD, Södra Älvsborgs Sjukhus, Borås; Katarina Strand Brodd, MD, Mälarsjukhuset, Eskilstuna; Andreas Odlind, MD, Falu

Lasarett, Falun; Lars Alberg, MD, Gällivare Sjukhus, Gällivare; Sofia Arwehed, MD, Gävle Sjukhus, Gävle; Ola Hafström, MD, SU/Östra, Göteborg; Anna Kasemo, MD, Länssjukhuset, Halmstad; Karin Nederman, MD, Helsingborgs Lasarett, Helsingborg; Lars Åhman, MD, Hudiksvalls Sjukhus, Hudiksvall; Fredrik Ingemarsson, MD, Länssjukhuset Ryhov, Jönköping; Henrik Petersson, MD, Länssjukhuset, Kalmar; Pernilla Thurn, MD, Blekingesjukhuset, Karlskrona; Eva Albinsson, MD, Centralsjukhuset, Karlstad; Bo Selander, MD, Centralsjukhuset, Kristianstad; Thomas Abrahamsson, MD, Universitetssjukhuset, Linköping; Ingela Heimdahl, MD, Sunderby sjukhus, Luleå; Kristbjorg Sveinsdottir, MD, Skånes Universitetssjukhus, Malmö/Lund; Erik Wejryd, MD, Vrinnevisjukhuset, Norrköping; Anna Hedlund, MD, Skellefteå Lasarett, Skellefteå; Maria Katarina Söderberg, MD, Kärnsjukhuset Skaraborg, Skövde; Boubou Hallberg, MD, Karolinska Sjukhuset, Stockholm; Thomas Brune, MD, Södersjuhuset, Stockholm; Jens Bäckström, MD, Länssjukhuset, Sundsvall; Johan Robinson, MD, Norra Älvsborgs Länssjukhus, Trollhättan; Aijaz Farooqi, MD, Norrlands Universitetssjukhus, Umeå; Erik Normann, MD, Akademiska Barnsjukhuset, Uppsala; Magnus Fredriksson, MD, Visby Lasarett, Visby; Anders Palm, MD, Västerviks Sjukhus, Västervik; Urban Rosenqvist, MD, Centrallasarettet, Västerås; Bengt Walde, MD, Centrallasarettet, Växjö; Cecilia Hagman, MD, Lasarettet, Ystad; Andreas Ohlin, MD, Universitetssjukhuset, Örebro; Rein Florell, MD, Örnsköldsviks Sjukhus, Örnsköldsvik; Agneta Smedsaas-Löfvenberg, MD, Östersunds Sjukhus, Östersund.

Swiss NeoNet (Switzerland Neonatal Network): Philipp Meyer, MD, and Claudia Anderegg, MD, Cantonal Hospital, Children's Clinic, Aarau; Sven Schulzke, MD, University Children's Hospital, Basel; Mathias Nelle, MD, University Hospital, Berne; Bendicht Wagner, MD, University Hospital, Berne; Thomas Riedel, MD, Children's Hospital, Chur; Grégoire Kaczala, MD, Cantonal Hospital, Fribourg; Riccardo E. Pfister, MD, University Hospital (HUG), Geneva; Jean-François Tolsa, MD, and Matthias Roth, MD, University Hospital (CHUV), Lausanne; Martin Stocker, MD, Children's Hospital, Lucerne; Bernhard Laubscher, MD, Cantonal Hospital, Neuchatel; Andreas Malzacher, MD, Cantonal Hospital, St Gallen; John P. Micallef, MD, Children's Hospital, St Gallen; Lukas Hegi, MD, Cantonal Hospital, Winterthur; Dirk Bassler, MD, and Romaine Arlettaz, MD, University Hospital (USZ), Zurich; Vera Bernet, MD, University Children's Hospital, Zurich.

TIN Toscane on-line Network (Tuscan NN): Carlo Dani, MD, Careggi University Hospital, Florence, Italy; Patrizio Fiorini, MD, Anna Meyer Children's University Hospital, Florence, Italy; Antonio Boldrini, MD, University Hospital of Pisa, Pisa, Italy; Barbara Tomasini, MD, University Hospital of Siena, Siena, Italy.

UKNC (UK Neonatal Collaborative): Anita Mittal, MBChB, Bedford Hospital, Bedford, Bedfordshire; Jonathan Kefas, MBChB, Lister Hospital, Stevenage, Hertfordshire; Anand Kamalanathan, MBChB, Arrowe Park Hospital, Wirral, Merseyside; Jayachandran, MBChB, Leighton Hospital, Crewe, Cheshire; Bill Yoxall, MBChB, Liverpool Women's Hospital, Liverpool, Merseyside; Tim McBride, MBChB, Ormskirk District General Hospital, Ormskirk, Lancashire; Delyth Webb, MBChB, Warrington Hospital, Warrington, Cheshire; Ross Garr, MBChB, Whiston Hospital, Prescot, Merseyside; Ahmed Hassan, MBChB, Broomfield Hospital, Chelmsford, Essex; Priyadarshan Ambadkar, MBChB, James Paget Hospital, Gorleston, Norfolk; Mark Dyke, MBChB, Norfolk & Norwich University Hospital, Norwich, Norfolk; Katharine McDevitt, MBChB, Peterborough City Hospital, Peterborough, Cambridgeshire; Glynis Rewitzky, MBChB, Queen Elizabeth Hospital, King's Lynn, Birmingham, West Midlands; Angela D'Amore, MBChB, Rosie Maternity Hospital, Addenbrookes, Cambridge, Cambridgeshire; Nagesh Panasa, MBChB, North Manchester General Hospital, Manchester, Greater Manchester; Paul Settle, MBChB, Royal Bolton Hospital, Bolton, Lancashire; Natasha Maddock, MBChB, Royal Oldham Hospital, Manchester, Greater Manchester; Ngozi Edi-Osagie, MBChB, St Mary's Hospital, Manchester, Greater Manchester; Christos Zipitis, MBChB, The Robert Albert Edward Infirmary, Wrightington, Greater Manchester; Carrie Heal, MBChB, Stepping Hill Hospital, Stockport, Cheshire; Jacqeline Birch, MBChB, Tameside General Hospital, Ashton-under-Lyne, Lancashire; Abdul Hasib, MBChB, Darent Valley Hospital, Dartford, Kent; Aung Soe, MBChB, Medway Maritime Hospital, Gillingham, Kent; Niraj Kumar, MBChB, Queen Elizabeth The Queen Mother Hospital, Margate, Kent; Hamudi Kisat, MBChB, Tunbridge Wells Hospital, Tunbridge Wells, Kent; Vimal Vasu, MBChB, William Harvey Hospital, Ashford, Kent; Meera Lama, MBChB, Lancashire Women & Newborn Centre, Burnley, Lancashire; Richa Gupta, MBChB, Royal Preston Hospital, Preston, Lancashire; Chris Rawlingson, MBChB, Victoria Hospital, Blackpool, Blackpool, Lancashire; Tim Wickham, MBChB, Barnet Hospital, Barnet, Hertfordshire; Marice Theron, MBChB, The Royal Free Hospital, Hampstead, London; Giles Kendall, MBChB, University College Hospital, Fitzrovia, London; Aashish Gupta, MBChB, Basildon Hospital, Basildon, Essex; Narendra Aladangady, MBChB, Homerton Hospital, Hackney, London; Imdad Ali, MBChB, Newham General Hospital, Newham, London; Lesley Alsford, MBChB, North Middlesex University Hospital, Edmonton, London; Wilson Lopez, MBChB, Queen's Hospital, Romford, Essex; Vadivelam Murthy, MBChB, The Royal London Hospital, Whitechapel, London; Caroline Sullivan, MBChB, Whipps Cross University Hospital, Whipps Cross, London; Mark Thomas, MBChB, Chelsea & Westminster Hospital, Chelsea, London; Tristan Bate, MBChB, Hillingdon Hospital, Hillingdon, London; Sunit Godambe, MBChB, Queen Charlotte's Hospital, East Acton, London; Sunit Godambe, MBChB, St Mary's Hospital, Westminister, London; Timothy Watts, MBChB, Guy's & St Thomas' Hospital, Lambeth, London; Jauro Kuna, MBChB, University Hospital Lewisham, Lewisham, London; John Chang, MBChB, Croydon University Hospital, Croydon,

Surrey; Vinay Pai, MBChB, Kingston Hospital, Kingston, London; Charlotte Huddy, MBChB, St George's Hospital, Wandsworth, London; Salim Yasin, MBChB, St. Helier Hospital, Merton, London; Richard Nicholl, MBChB, Northwick Park Hospital, Brent, London; Poornima Pandey, MBChB, Kettering General Hospital, Kettering, Northhamptonshire; Jonathan Cusack, MBChB, Leicester General Hospital, Leicester, Leicestershire; Venkatesh Kairamkonda, MBChB, Leicester Royal Infirmary, Leicester, Leicestershire; Dominic Muogbo, MBChB, Queen's Hospital, Burton On Trent, Burton-on-Trent, Staffordshire; Liza Harry, MBChB, Alexandra Hospital, Redditch, Worcestershire; Phil Simmons, MBChB, Birmingham Heartlands Hospital, Birmingham, West Midlands; Julie Nycyk, MBChB, City Hospital, Birmingham, West Midlands; Phil Simmons, MBChB, Good Hope Hospital, Birmingham, West Midlands; Andrew Gallagher, MBChB, Worcestershire Royal Hospital, Worcester, Worcestershire; Tilly Pillay, MBChB, New Cross Hospital, Wolverhampton, West Midlands; Sanjeev Deshpande, MBChB, Royal Shrewsbury Hospital, Shrewsbury, Shropshire; Mahadevan, MBChB, Russells Hall Hospital, Dudley, West Midlands; Alison Moore, MBChB, University Hospital of North Staffordshire, Hartshill, Staffordshire; Simon Clark, MBChB, The Jessop Wing, Sheffield, South Yorkshire; Mehdi Garbash, MBChB, Darlington Memorial Hospital, Darlington, County Durham; Mithilesh Lal, MBChB, James Cook University Hospital, Middlesborough, North Yorkshire; Majd Abu-Harb, MBChB, Sunderland Royal Hospital, Sunderland, Tyne and Wear; Mehdi Garbash, MBChB, University Hospital Of North Durham, Durham, Durham; Alex Allwood, MBChB, Derriford Hospital, Plymouth, Devon; Michael Selter, MBChB, North Devon District Hospital, Barnstaple, Devon; Paul Munyard, MBChB, Royal Cornwall Hospital, Truro, Cornwall; David Bartle, MBChB, Royal Devon & Exeter Hospital, Exeter, Devon; Siba Paul, MBChB, Torbay Hospital, Torquay, Devon; Graham Whincup, MBChB, Conquest Hospital, St Leonards-on-sea, East Sussex; Abdus Mallik, MBChB, Frimley Park Hospital, Frimley, Surrey; Philip Amess, MBChB, Princess Royal Hospital, Telford, Shropshire; Charles Godden, MBChB, Royal Surrey County Hospital, Guildford, Surrey; Philip Amess, MBChB, Royal Sussex County Hospital, Brighton, East Sussex; Peter Reynolds, MBChB, St Peter's Hospital, Chertsey, Surrey; Indranil Misra, MBChB, Milton Keynes Foundation Trust Hospital, Milton Keynes, Buckinghamshire; Peter De Halpert, MBChB, Royal Berkshire Hospital, Reading, Berkshire; Sanjay Salgia, MBChB, Stoke Mandeville Hospital, Aylesbury, Buckinghamshire; Rekha Sanghavi, MBChB, Wexham Park Hospital, Slough, Berkshire; Ruth Wigfield, MBChB, Basingstoke & North Hampshire Hospital, Basingstoke, Hampshire; Abby Deketelaere, MBChB, Dorset County Hospital, Dorchester, Dorset; Minesh Khashu, MBChB, Poole Hospital NHS Foundation Trust, Poole, Dorset; Michael Hall, MBChB, Princess Anne Hospital, Southampton, Hampshire; Charlotte Groves, MBChB, Queen Alexandra Hospital, Portsmouth, Hampshire; Nick Brown, MBChB, Salisbury District Hospital, Salisbury, Wiltshire; Nick Brennan, MBChB, St Richard's Hospital, Chichester, West Sussex; Katia Vamvakiti, MBChB, Worthing Hospital, Worthing, West Sussex; John McIntyre, MBChB, Royal Derby Hospital, Derby, Derbyshire; Simon Pirie, MBChB, Gloucestershire Royal Hospital, Gloucester, Glourcestershire; Stephen Jones, MBChB, Royal United Hospital, Avon, Somerset; Paul Mannix, MBChB, Southmead Hospital, Westbury-on-Trym, Bristol; Pamela Cairns, MBChB, St Michael's Hospital, Bristol, Bristol; Megan Eaton, MBChB, Yeovil District Hospital, Yeovil, Somerset; Karin Schwarz, MBChB, Calderdale Royal Hospital, Halifax, West Yorkshire; David Gibson, MBChB, Pinderfields General Hospital., Dewsbury, West Yorkshire; Lawrence Miall, MBChB, Leeds Neonatal Service, Leeds, Yorkshire; David Gibson, MBChB, Pinderfields General Hospital, Wakefield, West Yorkshire; Krishnamurthy, MBChB, Walsall Manor Hospital, Walsall, West Midlands.

Funding and Conflicts of Interest Disclosure

Funding for iNeo has been provided by a Canadian Institutes of Health Research Chair in Reproductive and Child Health Services and Policy Research (APR-126340 [to P.S.]). The Australian and New Zealand Neonatal Network is predominantly funded by membership contributions from participating centers. The Canadian Neonatal Network is supported by a team grant from the Canadian Institutes of Health Research (CTP 87518), the Ontario Ministry of Health, and individual participating centers. The Finnish Medical Birth Register is governmentally funded and kept by the National Institute for Health and Welfare (to T.L.). The Israel Neonatal Network very low birth weight infant database is partially funded by the Israel Center for Disease Control and the Ministry of Health. The Neonatal Research Network of Japan is partly funded by a Health Labour Sciences Research Grant from the Ministry of Health, Labour and Welfare of Japan. SEN1500 is supported by funds from the Spanish Neonatal Society (SENeo). The Swedish Neonatal Quality Register is funded by the Swedish Government (Ministry of Health and Social Affairs) and the body of regional health care providers (County Councils). SwissNeoNet is partially funded by participating units in the form of membership fees. Tuscany Neonatal Network is funded by the Tuscany Region. The United Kingdom Neonatal Collaborative receives no core funding. M.V. received a research grant from the Instituto de Investigación Sanitaria Carlos III (Ministry of Science, Innovation and Universities; Kingdom of Spain) (FIS17/0131) and RETICS funded by the PN 2018-2021 (Spain), ISCIII- Sub-Directorate General for Research Assessment and Promotion and the European Regional Development Fund (FEDER) (RD16/0022). The other authors declare no conflicts of interest.

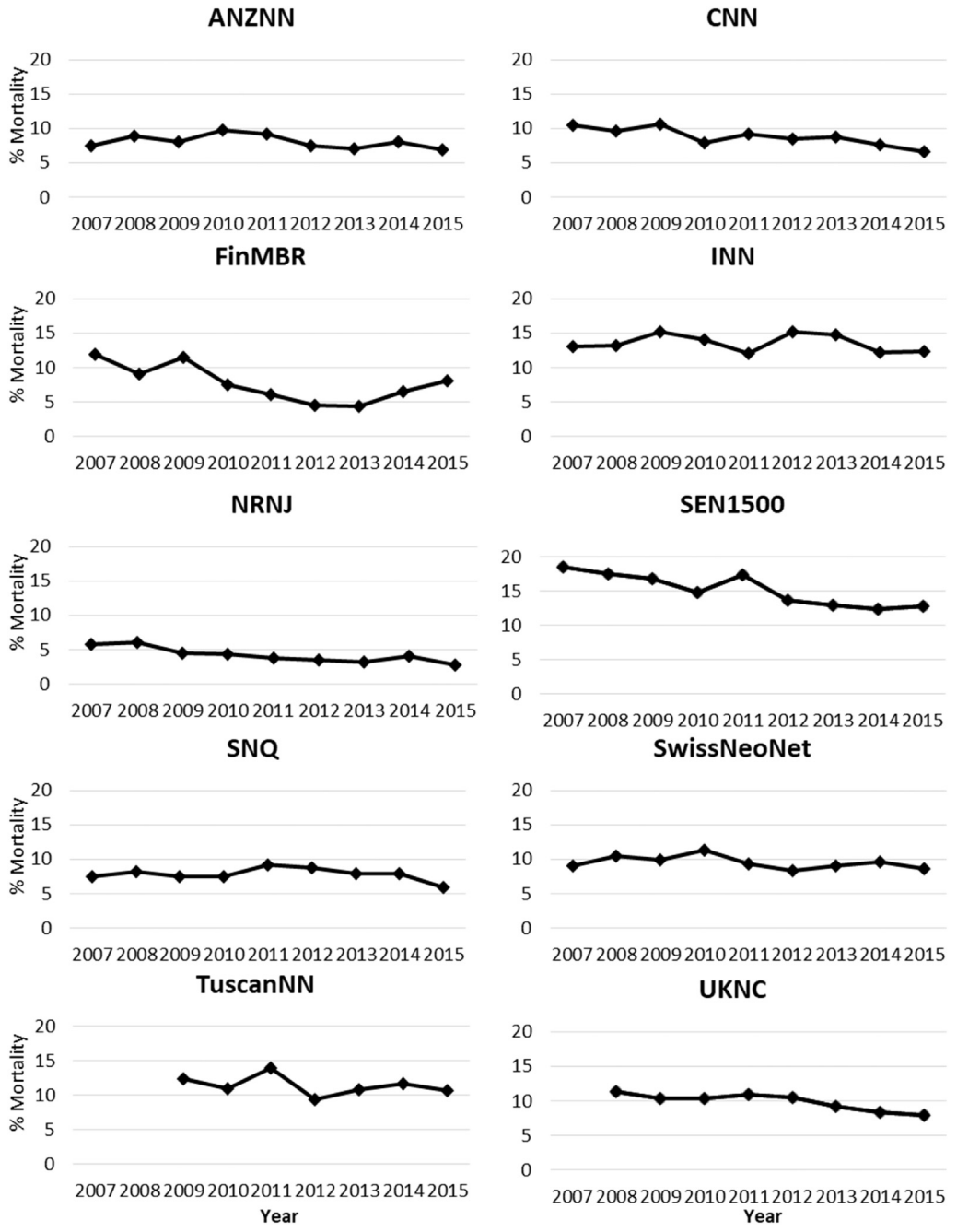

Figure 2. Trends of mortality between 2007 and 2015.

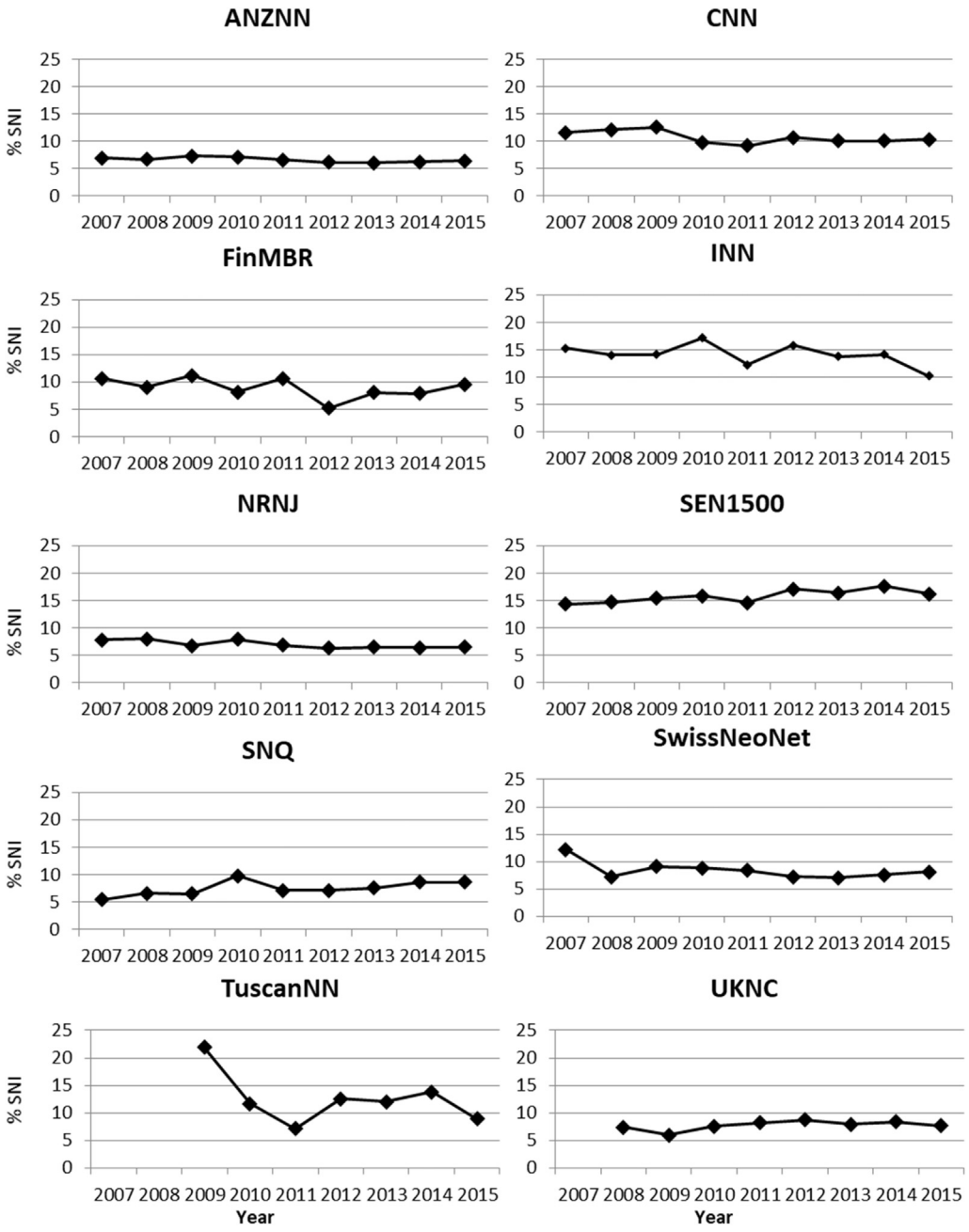

Figure 3. Trends of SNI between 2007 and 2015.

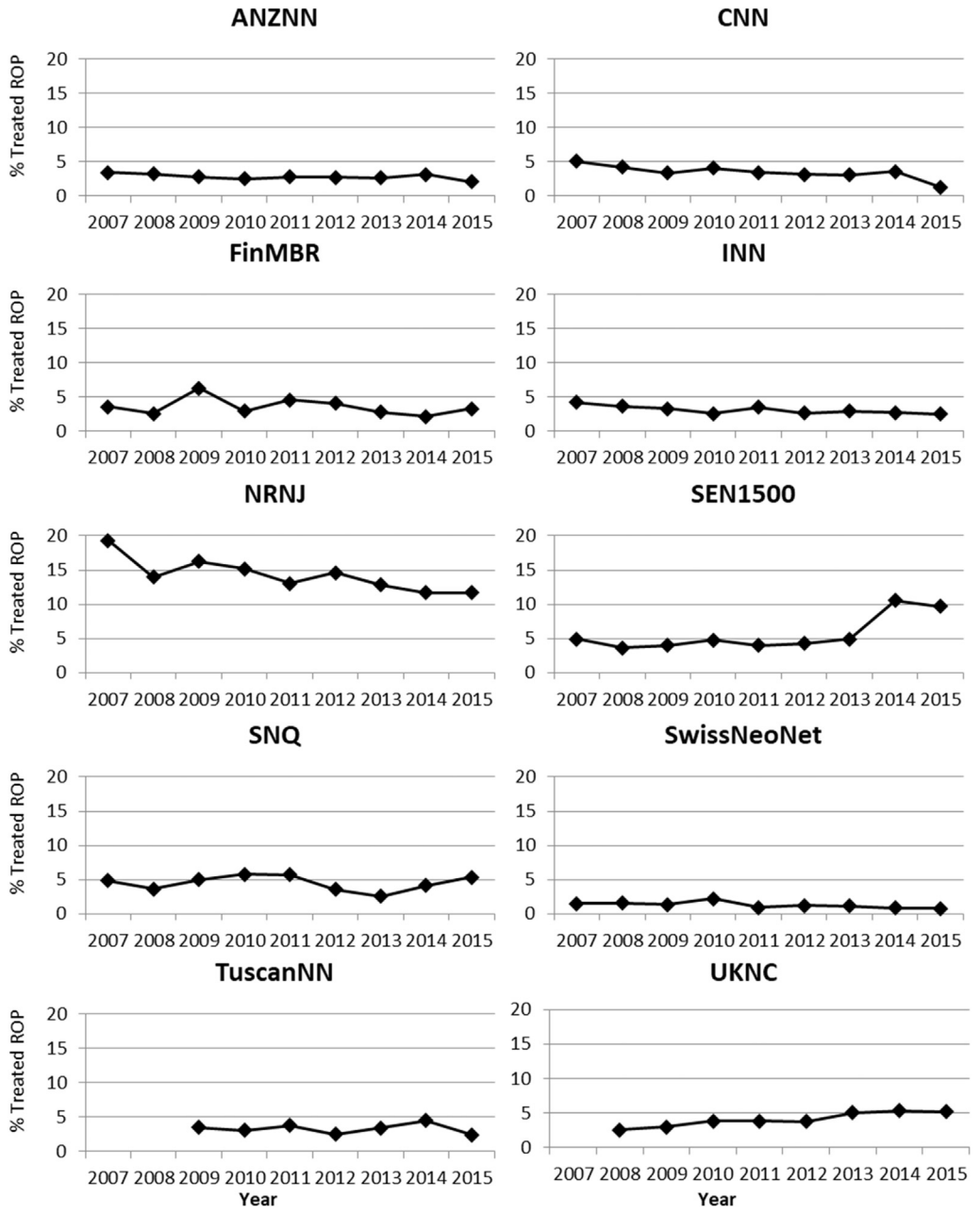

Figure 4. Trends of treated ROP between 2007 and 2015.

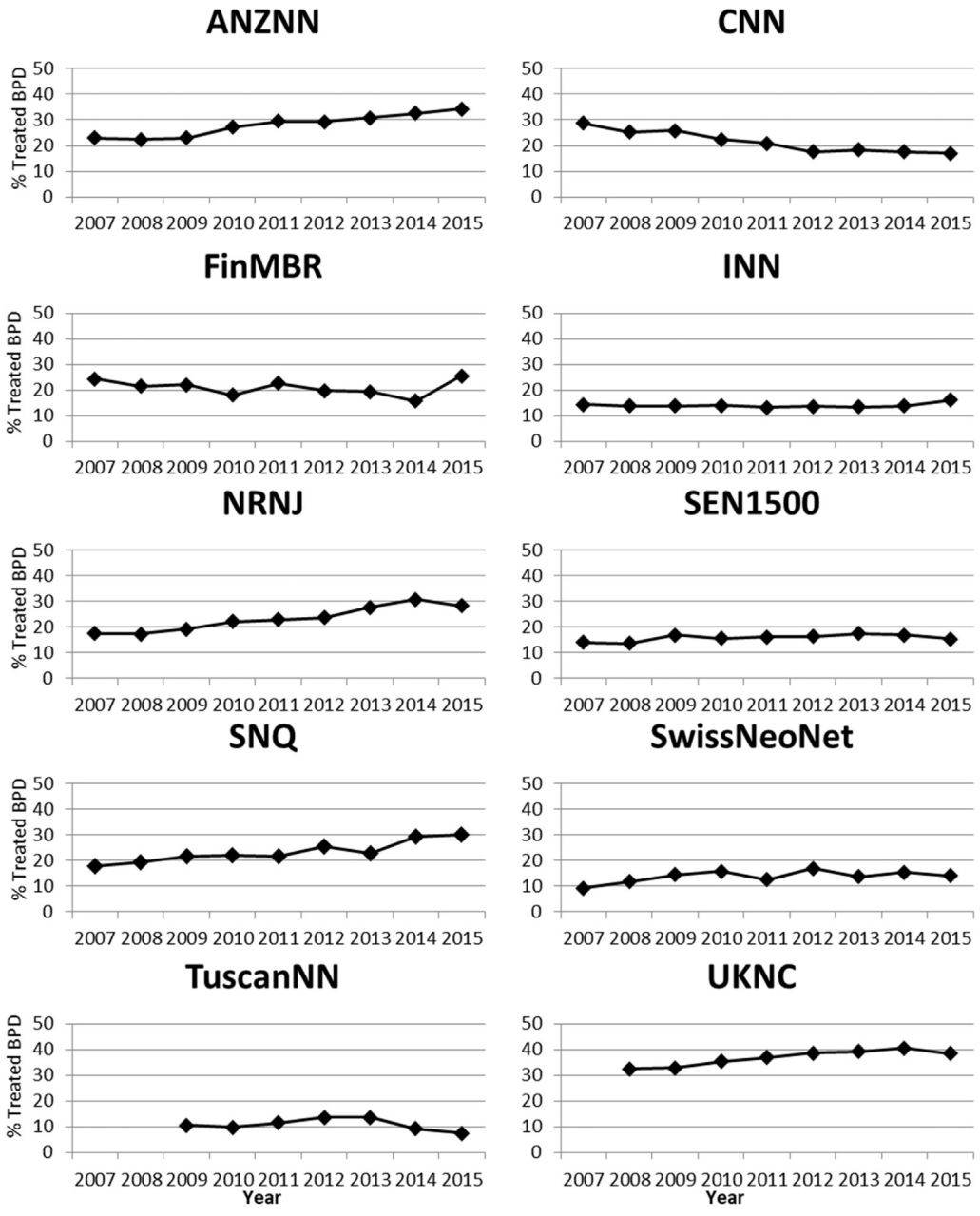

Figure 5. Trends of BPD between 2007 and 2015.

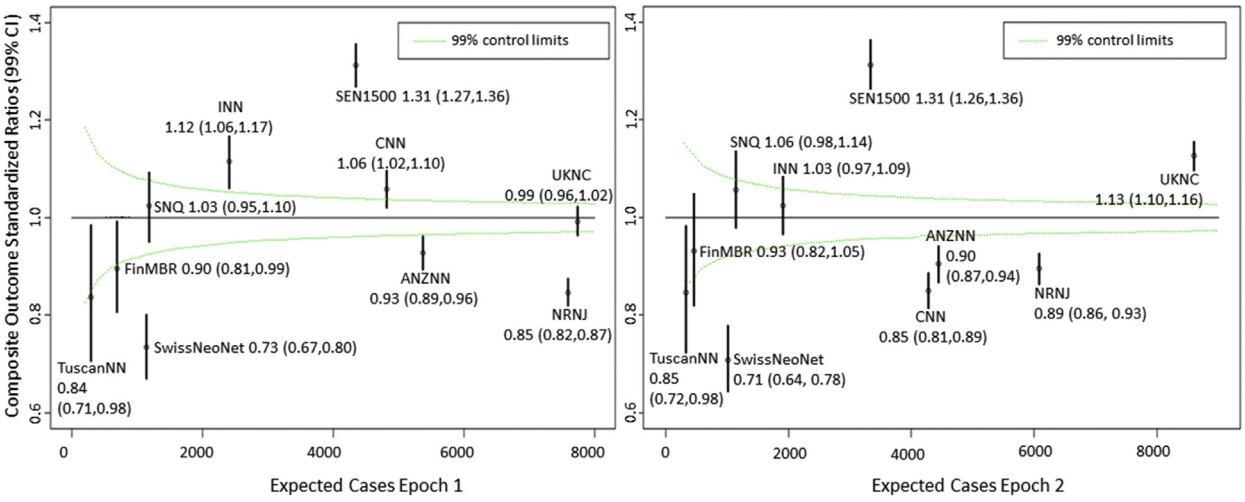

Figure 6. Standardized ratios* of composite outcomes for Epoch 1† and Epoch 2‡. *Adjusted for gestational age, birth weight z score, sex, and multiple births. †Epoch 1 is 2007-2011 except for UKNC (2008-2011) and TuscanNN (2009-2011). ‡Epoch 2 is 2012- 2015.

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 = 15 233
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.