International variations and trends in the treatment for retinopathy of prematurity

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ABSTRACT

Objective To compare the rates of retinopathy of prematurity (ROP) and treatment of ROP by laser or intravitreal anti-vascular endothelial growth factor among preterm neonates from high-income countries participating in the International Network for Evaluating Outcomes (iNeo) of neonates.

Methods A retrospective cohort study was conducted on extremely preterm infants weighing <1500 g at 24^0 to 27^6 weeks' gestation who were admitted to neonatal units in Australia/New Zealand, Canada, Finland, Israel, Japan, Spain, Sweden, Switzerland, Tuscany (Italy) and the UK between 2007 and 2013. Pairwise comparisons of ROP treatment in survivors between countries were evaluated by Poisson and multivariable logistic regression analyses after adjustment for confounders. A composite outcome of death or ROP treatment was compared between countries using logistic regression and standardised ratios.

Results Of 48 087 infants included in the analysis, 81.8% survived to 32 weeks postmenstrual age, and 95% of survivors were screened for ROP. Rates of any ROP ranged from 25.2% to 91.0% in Switzerland and Japan, respectively, among those examined. The overall rate of those receiving treatment was 24.9%, which varied from 4.3% to 30.4%. Adjusted risk ratios for ROP treatment were lower for Switzerland in all pairwise comparisons, whereas Japan displayed significantly higher ratios. Comparisons of the composite outcome between countries revealed similar, but less marked differences.

Conclusions Rates of any ROP and ROP treatment varied significantly between iNeo members, while an overall decline in ROP treatment was observed during the study period. It is unclear whether these variations represent differences in care practices, diagnosis and/or treatment thresholds.

INTRODUCTION

Retinopathy of prematurity (ROP), a disease characterised by abnormal blood vessel growth in the retina, is a significant complication of very preterm birth in high-income countries, and increasingly so in low/middle-income countries.[1] From early descriptions of the disease to the modern day, the incidence and treatment of ROP has varied considerably between hospitals.[2–5] The reasons for such variation are complex and may include differences in case-mix, case ascertainment, treatment thresholds, hospital size and variations in clinical care, among others.[2–4 6 7] Understanding the extent and causes of variation at both the local and international level may help inform future care and provide greater consistency in diagnosis and treatment thresholds.

The past two decades have witnessed a rise in national neonatal networks, which undertake ongoing audits of high-risk infants and, mainly through collaborative quality improvement efforts, have led to advances in neonatal care and better overall outcomes.[2 6] Recognising the need for international comparisons of neonatal morbidity rates, the International Network for Evaluating Outcomes (iNeo) in Neonates was formed.[7] The iNeo comprises 10 population-based national neonatal networks from 11 countries: Australia and New Zealand(ANZNN), Canada (CNN), Israel (INN), Japan (NRNJ), Sweden (SNQ), Switzerland (SwissNeoNet), Spain (SEN1500), the UK Neonatal Collaborative (UKNC), Finland (FinMBR) and Tuscany (TuscanNN). Here, our objective was to compare ROP incidence and treatment (by laser or intravitreal anti-vascular endothelial growth factor (anti-VEGF)) in very preterm neonates between networks in the iNeo consortium.

METHODS

Study design and population

This study included a retrospective comparison of data on neonates born between 24^0 and 27^6 weeks gestational age (GA) with birth weights <1500 g and admitted to a neonatal unit in a collaborating network between 2007 and 2013. Infants with major congenital anomalies were excluded, as well as extremely preterm infants <24 weeks, at which gestation neonatal intensive care provision varies considerably among iNeo networks. We included only neonates of 24^0–27^6 weeks GA because all surviving infants at this gestation are screened. Approvals for data collection and data sharing agreements were obtained by individual networks and the iNeo Coordinating Centre at Mount Sinai Hospital, Toronto, Ontario, Canada.

Outcomes and measures

Data on outcomes of eye examinations were obtained from all individual network databases. Most eye examinations were performed by fundoscopy and very few babies during the study period had wide-field retinal photography. All networks

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recorded data using the International Classification of ROP.[8] The highest stage of ROP was recorded, if present, along with any treatment for advanced stages of ROP by laser or by intravitreal anti-VEGF, but data on timing of the initial examination, frequency of examinations, zone, extent of disease (clock hours) and presence or absence of plus disease were not captured. Information on mortality prior to 32 weeks postmenstrual age (PMA) was obtained and to account for differences in mortality between networks, a composite outcome of death or treated ROP was analysed.

Statistical analysis

Rates of any ROP, stage 3 or higher ROP and treatment in surviving infants examined for ROP were calculated for each network. Data from the entire cohort were evaluated by Poisson and multivariable logistic regression models to determine risk factors for ROP treatment. Risk ratios (RRs) with 95% CIs were reported. Multivariable logistic regression and Poisson regression analyses were applied to compare ROP treatment among all networks simultaneously with adjustment for GA, birth weight z-score, multiple birth, sex, caesarean section (CS) and antenatal steroids. Adjusted RRs were estimated for all possible pairwise comparisons. Statistical significance was evaluated by applying stringent Bonferroni multiple-testing adjustments to account for 45 independent pairwise comparisons with a significance threshold of $p<0.001$ (corresponding to 99.9% CI for RR estimates). Standardised ratios (SRs) were calculated as the observed number of infants who received ROP treatment divided by the number of infants expected to receive ROP treatment, computed as the sum of predicted probabilities from a multivariable logistic regression model derived using data from all other countries. As the SR estimate is calculated in relation to all other countries combined, it is not directly comparable between contributors. The Cochran-Armitage trend test was used to assess the trend rates of ROP treatment by admission year for each network for the whole study population, as well as for various GA groups. Data management and statistical analyses were performed at the iNeo Coordinating Centre using SAS V.9.2 (SAS Institute).

RESULTS

A total of 48 087 infants of 24^0–27^6 weeks gestation were included in the analysis. Mean survival to at least 32 weeks PMA was 81.8% and varied from 91.8% in Japan to 67.8% in Spain (table 1). There was a higher proportion of the most immature (24 weeks GA) and extremely low birth weight (<1000 g) infants among survivors in Japan compared with other networks. Results of ROP screening in infants alive at 32 weeks PMA were available for 95.0% of eligible infants, with missing data varying between 0.4% and 11.4% (table 1). Among the infants examined for ROP, any ROP rates ranged from 25.2% to 91.0%, and treatment varied between 4.3% and 30.4%. The composite outcome of death or ROP treatment varied between 22.1% and 40.6% (table 1).

Analysis of the full dataset indicated that non-receipt of antenatal steroids, male sex, lower GA, lower birth weight for gestation and delivery by CS were associated with ROP treatment (table 2), whereas multiple births was not.

Table 3 highlights relative risk comparisons between pairs of networks for ROP treatment in surviving infants examined for ROP. Switzerland had a lower risk of ROP treatment in all pairwise comparisons with other countries. Similar results were obtained when caesarean delivery and antenatal steroids were not adjusted for (see online supplementary table S1). However,

Table 1 ROP in neonates of 24^0–27^6 weeks' gestation in iNeo participants between 2007 and 2013

Network	ANZNN	CNN	INN	NRNJ	SNQ	SwissNeo Net	SEN1500	UKNC*	FinMBR	TuscanNN	Total
Study infants (24^0–27^6 weeks), n	7114	7019	2889	10 244	1745	1421	5440	10 996	847	372	48 087
Surviving to 32 weeks PMA (%)	5969 (83.9)	5806 (82.7)	1998 (69.2)	9360 (91.8)	1506 (86.3)	1129 (79.5)	3686 (67.8)	8920 (81.2)	712 (86.7)	270 (72.6)	39 356 (81.8)
Screened for ROP (% of survivors)	5773 (96.7)	5142 (88.6)	1989 (99.6)	9019 (96.4)	1474 (97.9)	1107 (98.1)	3425 (92.9)	8792 (98.5)	664 (91.1)	268 (99.3)	37 653 (95.0)
GA† (weeks %)											
24	13.1	12.6	8.3	18.1	13.4	9.6	8.5	14.5	14.8	17.9	13.9
25	21.8	24.5	19.1	22.3	22.1	18.8	19.3	20.1	20.9	20.9	21.4
26	30.4	29.1	32.8	27.6	29.2	34.2	31.7	29.0	26.1	21.6	29.4
27	34.7	33.8	39.9	32.0	35.4	37.4	40.5	36.4	38.3	39.6	35.3
Birth weight†<1000 g (%)	4229 (73.3)	3832 (74.5)	1490 (74.9)	7541 (83.6)	1095 (74.3)	880 (79.5)	2471 (72.2)	6569 (74.7)	485 (73.0)	204 (76.1)	28 796 (76.5)
Retinopathy treatment, n (% of screened)	424 (7.3)	537 (10.4)	210 (10.7)	2740 (30.4)	157 (10.7)	47 (4.3)	456 (13.3)	743 (8.5)	78 (11.8)	27 (10.1)	5419 (24.9)
Death or ROP treatment (% of study infants)	1569 (22.1)	1750 (24.9)	1101 (38.1)	3582 (35.0)	396 (22.7)	339 (23.9)	2210 (40.6)	2819 (25.6)	213 (25.2)	129 (34.7)	14 108 (29.3)

*UKNC excluded infants who died <37 weeks PMA.
†Among infants surviving to 32 weeks PMA.
ANZNN, Australia and New Zealand Neonatal Network; CNN, Canadian Neonatal Network; FinMBR, Finnish Maternal Birth Register; GA, gestational age; iNeo, International Network for Evaluating Outcomes; INN, Israel Neonatal Network; NRNJ, Neonatal Research Network of Japan; PMA, postmenstrual age; ROP, retinopathy of prematurity; SEN1500, Spanish Neonatal Network; SNQ, Swedish Neonatal Quality Register; SwissNeoNet, Swiss Neonatal Network; TuscanNN, Tuscan Neonatal Network; UKNC, UK Neonatal Collaborative.

Table 2 Factors associated with ROP treatment

Risk factor	RR (95% CI)*
No antenatal steroids	1.66 (1.57 to 1.75)
Male sex	1.08 (1.03 to 1.13)
GA	
24 vs 27	5.23 (4.83 to 5.65)
25 vs 27	3.46 (3.20 to 3.74)
26 vs 27	1.89 (1.74 to 2.05)
BWZ score (per 1 unit increase—equivalent to 1 SD increase)	0.76 (0.74 to 0.78)
Caesarean section	1.26 (1.19 to 1.33)
Multiples	1.04 (0.98 to 1.10)

*Derived by Poisson analyses.
BWZ, birth weight z-score; GA, gestational age; ROP, retinopathy of prematurity; RR, risk ratio.

when death or ROP treatment was used as the outcome, Switzerland did not differ from five of the networks (see online supplementary table S2). Japan had a higher relative risk for any ROP (data not shown) and ROP treatment in comparison to all other iNeo countries.

A comparison of estimated SRs of the composite outcome of each country relative to one another is graphically displayed in figure 1. Figure 1A reveals that the SR for Japan was significantly higher, whereas Switzerland, Australia/New Zealand and the UK were significantly lower. Figure 1B illustrates the same data excluding Japan. In this analysis, the estimated SR for Spain was significantly higher compared with all others, whereas the SR for Switzerland and the UK remained significantly lower.

The rate of ROP treatment declined significantly from 2007 to 2013 within the overall collaboration, although the trend from 2008 to 2013 was stable. The trend in the latter period also remained constant in most individual networks, with the exception of the UK, where the rate of treatment increased significantly (table 4). In the full 7-year period, there was an overall significant decline in rates of treatment for infants of 26–27 weeks' gestation, but not at <26 weeks GA (see online supplementary table S3).

DISCUSSION

We have identified considerable variation in rates of treatment for ROP between countries after adjustment for risk factors. The strengths of our study include the very large sample size and ability to report on temporal trends. Weaknesses include the fact that this is a retrospective analysis of a minimum dataset. Possible explanations for the variation detected include differences in network coverage of the relevant population, differences in population and ethnic and genetic characteristics, and variations in care practices and treatment thresholds. The size of individual networks may also be a contributor, as smaller networks tend to display greater intrinsic variability due to rarity of the event of interest. To reduce bias from differences in population coverage, we only included neonates of 24^0–27^6 weeks GA, when screening is standard in all networks. Some missing data may result from back transfer of infants to a lower level neonatal unit from which data might not have been captured by most countries other than the UK.

Consistent with earlier findings, we demonstrated that receipt of antenatal corticosteroids is associated with a reduced risk of ROP treatment,[9 10] while lower GA and lower birth weight for gestation are important risk factors.[11 12] Our data also suggest

Table 3 Adjusted RR* (99.9% CI) comparing ROP treatment in survivors between pairs of countries

	ANZNN	CNN	INN	NRNJ	SNQ	SwissNeoNet	SEN1500	UKNC	FinMBR	TuscanNN
ANZNN	1	0.73 (0.60 to 0.89)	0.66 (0.51 to 0.86)	0.28 (0.23 to 0.33)	0.72 (0.54 to 0.95)	1.68 (1.04 to 2.72)	0.51 (0.41 to 0.63)	0.90 (0.74 to 1.09)	0.65 (0.45 to 0.93)	0.71 (0.39 to 1.29)
CNN	1.37 (1.12 to 1.67)	1	0.91 (0.71 to 1.16)	0.38 (0.33 to 0.44)	0.98 (0.75 to 1.29)	2.29 (1.43 to 3.69)	0.70 (0.58 to 0.84)	1.23 (1.03 to 1.47)	0.88 (0.62 to 1.27)	0.96 (0.53 to 1.75)
INN	1.51 (1.17 to 1.95)	1.10 (0.86 to 1.41)	1	0.42 (0.34 to 0.52)	1.08 (0.79 to 1.49)	2.53 (1.53 to 4.18)	0.77 (0.60 to 0.99)	1.36 (1.07 to 1.73)	0.97 (0.66 to 1.45)	1.07 (0.58 to 1.97)
NRNJ	3.61 (3.05 to 4.27)	2.64 (2.27 to 3.06)	2.39 (1.93 to 2.97)	1	2.59 (2.02 to 3.32)	6.05 (3.81 to 9.62)	1.84 (1.57 to 2.15)	3.25 (2.83 to 3.74)	2.33 (1.65 to 3.28)	2.55 (1.42 to 4.57)
SNQ	1.39 (1.05 to 1.85)	1.02 (0.78 to 1.34)	0.92 (0.67 to 1.27)	0.39 (0.30 to 0.50)	1	2.34 (1.39 to 3.92)	0.71 (0.54 to 0.94)	1.26 (0.96 to 1.64)	0.90 (0.60 to 1.36)	0.98 (0.52 to 1.84)
SwissNeoNet	0.60 (0.37 to 0.96)	0.44 (0.27 to 0.70)	0.39 (0.24 to 0.65)	0.17 (0.10 to 0.26)	0.43 (0.26 to 0.72)	1	0.30 (0.19 to 0.49)	0.54 (0.33 to 0.86)	0.38 (0.22 to 0.68)	0.42 (0.20 to 0.88)
SEN1500	1.96 (1.60 to 2.41)	1.43 (1.18 to 1.74)	1.30 (1.01 to 1.67)	0.54 (0.46 to 0.64)	1.41 (1.07 to 1.86)	3.29 (2.04 to 5.31)	1	1.77 (1.47 to 2.12)	1.27 (0.88 to 1.82)	1.38 (0.76 to 2.52)
UKNC	1.11 (0.91 to 1.34)	0.81 (0.68 to 0.97)	0.73 (0.58 to 0.93)	0.31 (0.27 to 0.35)	0.80 (0.61 to 1.04)	1.86 (1.16 to 2.99)	0.57 (0.47 to 0.68)	1	0.72 (0.50 to 1.02)	0.78 (0.43 to 1.41)
FinMBR	1.55 (1.07 to 2.24)	1.13 (0.79 to 1.62)	1.03 (0.69 to 1.52)	0.43 (0.30 to 0.61)	1.11 (0.74 to 1.68)	2.60 (1.47 to 4.59)	0.79 (0.55 to 1.14)	1.40 (0.98 to 1.99)	1	1.09 (0.56 to 2.14)
TuscanNN	1.42 (0.78 to 2.58)	1.04 (0.57 to 1.88)	0.94 (0.51 to 1.74)	0.39 (0.22 to 0.70)	1.02 (0.54 to 1.91)	2.38 (1.14 to 4.98)	0.72 (0.40 to 1.31)	1.28 (0.71 to 2.31)	0.92 (0.47 to 1.79)	1

Adjusted for antenatal steroid, sex, GA, birth weight z-score, caesarean and multiple birth using Poisson analyses.
*RR compared between row and column; green: RR significantly lower than 1; red: higher than 1.
ANZNN, Australia and New Zealand Neonatal Network; CNN, Canadian Neonatal Network; FinMBR, Finnish Maternal Birth Register; GA, gestational age; INN, Israel Neonatal Network; NRNJ, Neonatal Research Network of Japan; ROP, retinopathy of prematurity; RR, risk ratio; SEN1500, Spanish Neonatal Network; SNQ, Swedish Neonatal Quality Register; SwissNeoNet, Swiss Neonatal Network; TuscanNN, Tuscan Neonatal Network; UKNC, UK Neonatal Collaborative.

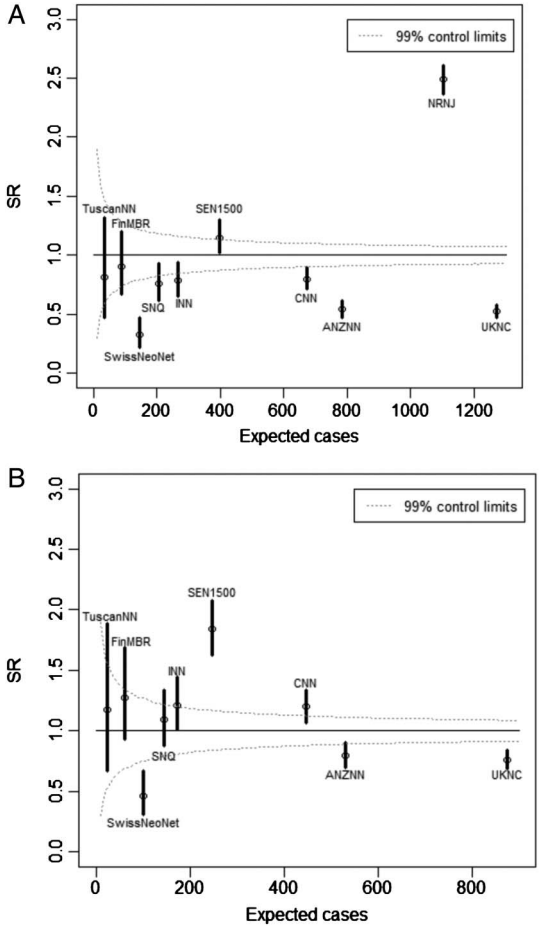

Figure 1 Standardised ratios (SRs) of the composite outcome.[a] (A) Estimated SRs (and 99% CIs) of the composite outcome of all networks included in iNeo (calculated using logistic regression analyses); (B) estimated SRs (and 99% CIs) of the composite outcome of all iNeo members, excluding Japan (calculated using logistic regression analyses). [a]SRs comparing the composite outcome of each network with all other networks combined. Vertical bars are the estimated 99% CIs of the SR. The dotted curves represent the 99% control limits expected under the null hypothesis of similar outcome rates (SR=1). ANZNN, Australian and New Zealand Neonatal Network; CNN, Canadian Neonatal Network; FinMBR, Finnish Maternal Birth Register; iNeo, International Network for Evaluating Outcomes; INN, Israel Neonatal Network; NRNJ, Neonatal Research Network of Japan; SEN1500, Spanish Neonatal Network; SNQ, Swedish Neonatal Quality Register; SwissNeoNet, Swiss Neonatal Network; TuscanNN, Tuscan Neonatal Network; UKNC, UK Neonatal Collaborative.

that males have an increased risk of ROP, similar to other studies.[5 11 13] In contrast, delivery by CS, which has become more frequent for very preterm infants during this time period,[14] has not been previously reported as a risk factor for severe ROP. The Neonatal Research Network of Japan[10] reported a significant reduction in the risk of ≥ stage 3 ROP for infants delivered by CS compared with vaginal delivery. The relationship between mode of delivery and severe ROP is likely to be complex and warrants further analysis.

Most iNeo countries, with the exception of Japan, are ethnically diverse and this may also contribute to our observed variation. A lower risk of ROP was reported among African-American infants in comparison with Caucasian infants,[15] whereas Hispanic[16] and Asian infants from the Indian subcontinent[17] display an increased risk. A study of two large cohorts from the USA revealed that a single nucleotide polymorphism in the brain-derived neurotrophic factor gene was associated with severe (threshold) ROP.[18]

Survival also impacts ROP rates, as very sick infants may not survive long enough to receive a retinal examination. When we analysed the combined outcome of death or ROP treatment, some differences between networks were no longer apparent. In high-income countries, including iNeo members, improved survival through better care practices has been frequently accompanied by stable or lower morbidity rates.[14 19] The overall trend in our dataset was a decline in treatment rates from 2007 to 2013, but stable in the last 6 years. A population-based report from Northern Ireland noted increased rates of treatment for ROP from 2000 to 2011, and indicated that earlier treatment of ROP (ET-ROP) criteria[20] was not incorporated into UK guidelines until 2008.[21] A review of hospital data from England for the years 1990–2011 also reported an increase in the rates of treatment for ROP between 2005 and 2011.[22] The UKNC has reported an annual increase in the proportion of infants meeting ROP screening criteria being examined on time; hence, the rise in treatment rates may reflect improved ascertainment.[23]

In our study, Japan had the highest survival rate at 92%, and experienced a much higher ROP treatment rate compared with all other networks. A previous study comparing the CNN and NRNJ between 2006 and 2008 revealed that Japanese infants had higher rates of severe ROP.[24] In Japan, the mean number of days of ventilation and oxygen treatment was higher than in Canada, as was the rate of bronchopulmonary dysplasia, which may have contributed to the increased risk of ROP.[24] However, another possibility is that diagnosis and treatment criteria for ROP are different in Japan.

The Cryotherapy for ROP (CRYO-ROP) study[25] established the treatment criteria of 'threshold disease' (five contiguous or eight total clock hours of stage 3 with plus disease), and this was widely used until the Early Treatment for ROP (ETROP) trial showed improved outcomes with earlier treatment at 'type 1' ROP (zone I, any ROP with plus disease; zone I, any stage 3 ROP; zone II, stage 2 or 3 with plus disease).[20] Preliminary results from our survey on current treatment practices in 10 of the 11 iNeo networks, including criteria for ROP treatment, show that 65% of neonatal intensive care units use ET-ROP type 1 criteria, 27% use the threshold and 7% use other criteria. All networks showed variation in treatment criteria and we are currently exploring this in more detail together with other practices, including oxygen saturation targets.

In our analysis, the number of infants in Japan who were treated for ROP exceeded those documented as having stage 3 ROP by 8.1%. In all other countries, except Spain and Finland, where treatment exceeded stage 3 ROP by 2.7% and 0.7%, respectively, fewer infants were treated than had stage 3 ROP. The Japanese classification of ROP is slightly different from the international classification,[8] and a subset of infants who would normally be classified with stage 2 disease would be considered stage '3 early' (see online supplementary table S4). Additionally, given the fear of litigation, it is likely that some ophthalmologists in Japan treat infants at an earlier stage than type I ROP (S. Kusuda, personal communication, 2016). Equally, in Spain and Finland it is possible that infants with 'imminent' stage 3 were treated. A major determinant of treatment using ET-ROP criteria is the presence of 'plus' disease, which is not collected by most networks.

Ascertainment bias, including subjective interpretation of the retina as seen with the indirect ophthalmoscope,[26] may be a contributing factor to the variation in severe ROP incidence rates. In the CRYO-ROP study, experts disagreed on the

Table 4 ROP treatment by year in individual participants for the entire cohort (<28 weeks GA)

Network	2007	2008	2009	2010	2011	2012	2013	p Trend	p Trend excluding 2007
ANZNN	71 (8.2)	72 (8.3)	58 (7.4)	46 (6.1)	64 (7.8)	57 (6.9)	56 (6.6)	0.13	0.26
CNN	88 (14.8)	86 (13.2)	70 (10.8)	91 (11.6)	71 (9.8)	67 (8.8)	64 (8.9)	<0.01	<0.01
INN	38 (13.9)	35 (13.0)	33 (11.4)	24 (7.8)	31 (10.7)	24 (9.3)	25 (8.3)	0.01	0.08
NRNJ	431 (36.4)	311 (26.2)	381 (30.5)	424 (30.7)	402 (29.5)	439 (31.4)	352 (28.0)	0.03	0.35
SNQ	26 (12.8)	21 (11.3)	23 (11.1)	30 (13.9)	25 (13.5)	18 (7.9)	17 (6.6)	0.02	0.05
SwissNeoNet	5 (4.0)	7 (4.7)	6 (4.2)	12 (7.3)	5 (2.8)	6 (3.1)	6 (3.9)	0.49	0.34
SEN-1500	65 (14.7)	54 (11.5)	64 (12.5)	77 (15.8)	65 (13.3)	66 (12.4)	65 (13.2)	0.83	0.68
UKNC	*	59 (5.2)	61 (5.5)	138 (9.2)	148 (8.8)	142 (8.3)	195 (11.9)	<0.01	<0.01
FinMBR	11 (12.1)	8 (7.6)	19 (20.7)	8 (9.1)	14 (12.3)	11 (11.5)	7 (9.1)	0.70	0.68
TuscanNN	*	*	8 (13.3)	4 (8.2)	5 (10.2)	4 (7.7)	6 (10.3)	0.59	0.59
Total	735 (19.4)	653 (13.0)	723 (14.2)	854 (14.9)	830 (14.1)	834 (13.7)	793 (13.7)	<0.01	0.95

*Data not available.
ANZNN, Australia and New Zealand Neonatal Network; CNN, Canadian Neonatal Network; FinMBR, Finnish Maternal Birth Register; GA, gestational age; INN, Israel Neonatal Network; NRNJ, Neonatal Research Network of Japan; ROP, retinopathy of prematurity; SEN1500, Spanish Neonatal Network; SNQ, Swedish Neonatal Quality Register; SwissNeoNet, Swiss Neonatal Network; TuscanNN, Tuscan Neonatal Network; UKNC, UK Neonatal Collaborative.

presence or absence of threshold disease for 12% of the cases, particularly regarding the presence or absence of plus disease.[27] While standard retinal examinations are performed by indirect ophthalmoscopy, digital imaging is being increasingly employed, either at the same time (to serve as a permanent record) or alone (to be interpreted locally or remotely).[28] Nonetheless, digital photographs still require interpretation and may be subject to bias.

Differences in clinical practices could also have a major impact on rates of ROP severe enough to require treatment. Nosocomial sepsis, inadequate nutrition and poor growth, prolonged supplementary oxygen and chronic neonatal lung disease have all been identified as risk factors for ROP and all potentially can be decreased through the implementation of evidence-based practices.[29] For most of the study years, there were no nationally adopted recommendations either for initial inspired oxygen concentrations at neonatal resuscitation in infants <28 weeks' gestation or for oxygen saturation targets in the neonatal intensive care unit, although the latter were typically within the range of 85%–95%.[30] Recent trials of oxygen saturation targeting indicated that infants cared for with a target at the upper end of this range (91%–95%) experienced both higher survival and higher rates of severe ROP compared with infants cared for at the lower end (85%–89%).[31] It will be important to monitor future trends in both survival and ROP as neonatologists reassess appropriate oxygen saturation targets for these high-risk patients.

We have reported considerable variation in the rates of any ROP and ROP treatment among the iNeo collaboration, although there was less variation in the composite outcome of death or ROP treatment. Differences in ascertainment of ROP and ROP treatment thresholds may contribute to the variability observed, as well as differences in care provision. Exploring care practices associated with better outcomes should benefit future generations of extremely preterm infants. To understand differences in outcomes, networks should adopt common definitions to describe pathology and improve consistency in interpretation, minimise the amount of missing data and perhaps record an expanded dataset; specifically, for ROP, this should include information on plus disease and aggressive posterior-ROP.[32] Perhaps the most important outcomes for families of extremely preterm infants beyond survival are long-term visual outcomes. Several iNeo networks now record neurodevelopmental outcomes at 18 months to 3 years and linking neonatal datasets with visual outcomes during childhood will be a major advance.

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