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Comparison of Mortality and Morbidity of Very Low Birth Weight Infants Between Canada and Japan

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KEY WORDS

infant, very low birth weight, mortality, bronchopulmonary dysplasia, intraventricular hemorrhage, retinopathy of prematurity

ABBREVIATIONS

AOR—adjusted odds ratio
BPD—bronchopulmonary dysplasia
BW—birth weight
CI—confidence interval
CNN—Canadian Neonatal Network
GA—gestational age
IVH—intraventricular hemorrhage
NEC—necrotizing enterocolitis
NRNJ—Neonatal Research Network of Japan
PDA—patent ductus arteriosus
ROP—retinopathy of prematurity
VLBW—very low birth weight

Dr Isayama initiated the concept, designed the study, initiated the data acquisition, interpreted the data, and wrote the first draft; Dr Lee initiated the concept, designed the study, initiated the data acquisition, interpreted the data, and contributed to the final version of the manuscript; Dr Mori initiated the concept, interpreted data, reviewed results and manuscript; Dr Kusuda interpreted the results and contributed to writing manuscript; Dr Fujimura participated in interpreting data and contributed to writing manuscript; Dr Ye assisted with study design, conducted statistical analysis, and contributed to writing manuscript; and Dr Shah developed the study design, oversaw the data acquisition, analyzed and interpreted the data, and edited the final version of the manuscript.

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WHAT'S KNOWN ON THIS SUBJECT: Mortality of very low birth weight infants varies widely between regions and countries; however, the variation in morbidities after adjusting for confounders has not been adequately studied.

WHAT THIS STUDY ADDS: Composite outcome of mortality or short-term morbidity for very low birth weight infants was lower in Japan than in Canada. However, marked variations in mortality and individual morbidity exist, revealing areas for improvement in each country.

abstract

OBJECTIVE: To compare neonatal outcomes of very low birth weight (VLBW) infants admitted to NICUs participating in the Canadian Neonatal Network and the Neonatal Research Network of Japan.

METHODS: Secondary analyses of VLBW infants in both national databases between 2006 and 2008 were conducted. The primary outcome was a composite of mortality or any major morbidity defined as severe neurologic injury, bronchopulmonary dysplasia, necrotizing enterocolitis, or severe retinopathy of prematurity at discharge. Secondary outcomes included individual components of primary outcome and late-onset sepsis. Logistic regression adjusting for confounders was performed.

RESULTS: A total of 5341 infants from the Canadian Neonatal Network and 9812 infants from the Neonatal Research Network of Japan were compared. There were higher rates of maternal hypertension, diabetes mellitus, outborn, prenatal steroid use, and multiples in Canada, whereas cesarean deliveries were higher in Japan. Composite primary outcome was better in Japan in comparison with Canada (adjusted odds ratio [AOR] 0.87, 95% confidence interval [CI] 0.79–0.96). The odds of mortality (AOR 0.40, 95% CI 0.34–0.47), severe neurologic injury (AOR 0.57, 95% CI 0.49–0.66), necrotizing enterocolitis (AOR 0.23, 95% CI 0.19–0.29), and late-onset sepsis (AOR 0.22, 95% CI 0.19–0.25) were lower in Japan; however, the odds of bronchopulmonary dysplasia (AOR 1.24, 95% CI 1.10–1.42) and severe retinopathy of prematurity (AOR 1.98, 95%CI 1.69–2.33) were higher in Japan.

CONCLUSIONS: Composite outcome of mortality or major morbidity was significantly lower in Japan than Canada for VLBW infants. However, there were significant differences in various individual outcomes identifying areas for improvement for both networks. *Pediatrics* 2012;130:e957–e965

A steady improvement in neonatal mortality and morbidity was observed at the start of this century; however, more recently, several national neonatal networks have indicated variable results. Some networks have indicated a halt in the progress or worsening of outcomes, but others have reported improved outcomes.[1–6] Given the application of similar technological advances and advances in our understanding of basic pathophysiological processes, such variation is concerning. Large multicenter neonatal networks, including the National Institute of Child Health and Human Development Neonatal Research Network , Vermont Oxford Network, Neonatal Research Network of Japan (NRNJ), Canadian Neonatal Network (CNN), Australian and New Zealand Neonatal Network, and EuroNeoNet have been established, all of whom analyze network data periodically, to benchmark and assess quality improvement initiatives within their constituents.[3–9] However, the variation in outcomes between networks is striking. For example, mortality in neonates born at <25 weeks' gestation is remarkably low in Japan in comparison with other networks,[4] whereas overall mortality in infants born at <28 weeks was no different from other networks.[10] Moreover, Japan has reported ongoing improvement in mortality in recent years,[10] by contrast to other countries which report that mortality has likely already reached a plateau.[1,2]

To make further strides in the improvement of outcomes of very low birth weight (VLBW) infants, it is crucial to evaluate differences in outcomes between countries, investigate what factors are responsible for those differences, and ultimately learn from each other. The majority of previous studies have compared mortality but not morbidity outcomes of neonates between networks. The objective of this study was to examine the differences in mortality and morbidities between the CNN and the NRNJ among VLBW infants, to assess the differences in outcomes, and to identify areas of improvement, with the aim of informing collaborative learning.

METHODS

Background Information on 2 Networks

Canada has a universal health care system whereby antenatal, intrapartum, postnatal, and neonatal care are provided to all of its citizens under a national health scheme. Japanese national health insurance is limited to treatment of morbidities, not for uncomplicated obstetric and newborn care; however, the cost of care for preterm infants is fully covered by the national health scheme. The CNN was established in 1995 and is almost population-based with 28 (of total 31) tertiary NICUs in Canada participating in CNN in 2008, encompassing 95% of neonates admitted to tertiary NICUs in Canada. Among VLBW infants, ~75% were admitted to tertiary NICUs in CNN.[11] The database of the NRNJ was established in 2003, and encompasses 70 of the 75 tertiary NICUs designated by the Japanese government in 2008; however, it covered ~45% of VLBW infants born in Japan.[12] This is because many tertiary NICUs were not endorsed by Japanese government.

Population

Infants born with a birth weight <1500 g admitted to participating NICUs in the CNN and NRNJ during 3 years from January 1, 2006 to December 31, 2008 were studied. Infants who had known congenital anomalies or who were moribund (those in whom a decision was made at the time of birth not to provide resuscitative care) were excluded. An admission was defined as a stay for >24 hours in NICU, or death or transfer to another level 2 or 3 NICU within 24 hours.

Ethics and Permission

The study was approved by the steering committees of the CNN and NRNJ. For CNN, data collection was approved by either a research ethics board or appropriate quality and data control committee at each institute in Canada. The data collection in NRNJ was approved by the internal review board in Tokyo Women's Medical University. The data collections of all infants in the NRNJ were approved by parents or guardians.

Data Collection and Management in Both Networks

In the CNN, data were collected by medical chart review by trained data abstractors with use of standard definitions and protocols contained in a standard manual of operations, and were subsequently sent electronically to the CNN Coordinating Centre, located at the Maternal-Infant Care Research Centre in Mount Sinai Hospital, Toronto, Ontario.[7] In the NRNJ, data were collected by data abstractors in each NICU with use of a standard network database operation manual and were sent on a yearly basis to the NRNJ Database Center located at the Maternal and Perinatal Center in the Tokyo Women's Medical University in Tokyo. Anonymized data were transferred from Japan to Canada and analyses were performed at the CNN coordinating center in Toronto.

Definitions of Outcomes and Synchronization

Gestational age (GA) was determined by the best estimate based on early prenatal ultrasound examination, the last menstrual period, and the physical examination of infants at birth, in that order.[4,7] Maternal chorioamnionitis was diagnosed clinically during pregnancy, labor, or delivery. Prenatal steroid use was defined as administration of at least 1 dose of corticosteroid to the mother at any time before delivery to accelerate fetal lung maturity. Because there were some differences in the definitions of outcomes in the CNN and NRNJ, a consultative process was initiated to harmonize the definitions of outcomes between networks based on available data, and the consensus definitions were used in this study (Table 1). We defined a composite primary outcome of "mortality or any major morbidity" as death before discharge or survival with any 1 of the 4 major morbidities: severe neurologic injury (grade 3 or 4 intraventricular hemorrhage or periventricular leukomalacia), bronchopulmonary dysplasia (BPD), necrotizing enterocolitis (NEC), or severe retinopathy of prematurity (ROP). These 4 morbidities were included in the composite outcome, because they have been reported to have an impact on infant developmental outcome between 18 and 24 months.[13,14] Secondary outcomes included individual components of primary outcome, late-onset sepsis, patent ductus arteriosus (PDA), and PDA requiring medical or surgical treatment. We also assessed resource utilization data for infants who survived in the form of length of stay (from admission to discharge home or other level 2 or 1 institutes), duration of respiratory support, and duration of oxygen requirement between networks.

Statistical Analysis

Descriptive statistical methods were used to describe the study population. The infant characteristics and outcomes were compared between the 2 networks by using the χ^2 test for categorical variables and the t test or nonparametric test, as appropriate, for continuous variables. To further examine the differences in adverse neonatal outcomes between the 2 countries, the GA was categorized into 5 groups: 20 to 24, 25 to 26, 27 to 28, 29 to 32, and >32 weeks, and then the GA group-specific outcomes were compared between the 2 networks. Multiple logistic regression models were also used to determine the GA group-specific differences in outcomes between the 2 countries, adjusted for the potential confounders and risk factors identified in the univariable analyses. Because the use of NICU resources, including the length of hospital stay, the length of oxygen use, and the length of ventilation, was highly skewed, the differences in resource use between the 2 countries were examined by using linear regression modeling for log-transformed outcomes or zero-inflated negative binomial models, whichever was appropriate, adjusted for potential confounders and risk factors. The data management and statistical analyses were performed with use of SAS 9.2 (SAS Institute, Inc., Cary, NC). A significance level of <.05 was used without multiple comparison adjustment.

RESULTS

A total of 5385 and 9901 eligible VLBW infants were admitted to NICUs in the CNN and NRNJ, respectively, between January 1, 2006, and December 31, 2008. Of these, 44 (0.1%) from the CNN and 79 (0.1%) from the NRNJ were excluded because of moribund status at birth. In addition, 10 infants from the NRNJ were excluded because of wrong admission dates. The remaining 15 153 infants, 5341 from Canada and 9812 from Japan, composed our study population.

The comparisons of infant characteristics between the 2 countries are presented in Table 2. Of the included infants, 2021(37.9%) in CNN and 4489 (45.8%) in NRNJ were extremely low birth weight infants (<1000 g at birth). The distributions of infants in the different GA categories differed slightly between the 2 networks, especially the rates of the infants <23 weeks and >32 weeks, for

TABLE 1 The Consensus Definitions of Outcomes

Outcomes	CNN	NRNJ	Consensus
Mortality	Death before last discharge from NICU	Death before last discharge from NICU	Death before last discharge from NICU
Severe neurologic injury	IVH with ventricular enlargement or persistent parenchymal echogenicity beyond 21 d or periventricular leukomalacia	IVH grade 3 or 4 or periventricular leukomalacia	IVH grade 3 or 4 or persistent parenchymal echogenicity beyond 21 d or periventricular leukomalacia
BPD	Oxygen use at 36 wk corrected GA or at the time of discharge to level 2 hospital	Oxygen use at 36 wk corrected GA age with oxygen use on 28th day after birth	Oxygen use at 36 wk corrected GA with oxygen use on 28th day after birth
Severe ROP	Stage III or above (according to international classification)	Grade 3 (middle, late) and above (according to Japanese grading of ROP)	Stage 3 or higher (international classification) or grade 3 (middle, late) or higher
NEC	According to Bell criteria stage 2 or higher	According to Bell criteria, stage 2 or higher	According to Bell's criteria, stage 2 or higher[34]
Late-onset sepsis	Sepsis at ≥3 d of life	Sepsis at ≥7 d of life	Sepsis at ≥7 d of life
PDA	Clinical or echocardiographic diagnosis of PDA	Clinical or echocardiographic diagnosis of PDA	Clinical or echocardiographic diagnosis of PDA

TABLE 2 Comparison of VLBW Infant Characteristics Between CNN and NRNJ

Characteristics	CNN (*n* = 5341), *n* (%)	NRNJ (*n* = 9812), *n* (%)	*P*
Maternal age, mean (SD)	30.3 (6.1)	31.1 (5.2)	<.01
Maternal hypertension	1198 (23.1)	1813 (18.5)	<.01
Maternal diabetes mellitus	366 (7.1)	150 (1.5)	<.01
Chorioamnionitis	678 (14.1)	1457 (14.9)	.19
Prenatal steroid	4307 (83.9)	3932 (40.1)	<.01
Multiple pregnancy	1636 (30.7)	2612 (26.6)	<.01
Vertex presentation	3079 (63.9)	6522 (66.5)	<.01
Cesarean delivery	3379 (64.0)	7473 (76.2)	<.01
Outborn	1012 (19.1)	749 (7.6)	<.01
Gestational age, wk, mean (SD)	28.2 (2.6)	28.4 (3.2)	<.01
<23 wk	16 (0.3)	137 (1.4)	<.01
23–24 wk	443 (8.3)	1072 (10.9)	
25–26 wk	970 (18.2)	1719 (17.5)	
27–28 wk	1443 (27.0)	2141 (21.8)	
29–32 wk	2179 (40.8)	3625 (36.9)	
>32 wk	290 (5.4)	1118 (11.4)	
Birth weight, g, mean (SD)	1077 (268.4)	1029 (303.8)	<.01
<500 g	45 (0.8)	362 (3.7)	<.01
500–749 g	714 (13.4)	1840 (18.8)	
750–999 g	1262 (23.6)	2287 (23.3)	
1000–1249 g	1596 (29.9)	2375 (24.2)	
1250–1499 g	1724 (32.3)	2948 (30.0)	
Male gender	2642 (49.5)	5007 (51.0)	.08
Apgar score <7 at 5 min	1343 (25.6)	2281 (29.9)	.03

both of which there were less than half as many in the CNN as in the NRNJ. Among the other characteristics, the CNN had higher rates of maternal diabetes mellitus (>4 times as much as in NRNJ), maternal hypertension, prenatal steroid administration, and outborn birth, but had a lower rate of cesarean delivery.

Table 3 shows the comparison of the mortality and morbidities between the 2 networks for all infants and infants in each GA group. In comparison with the NRNJ, the CNN had a higher rate of mortality (10.5% vs 6.5%, $P < .0001$), especially for more premature babies at ≤28 weeks GA. The composite primary outcome of mortality or any major morbidity was significantly lower for NRNJ infants (30.3%) in comparison with CNN infants (32.2%). Moreover, the CNN had higher rates of severe neurologic injury (11.4% vs 8.0%, $P < .0001$), NEC (5.9% vs 1.6%, $P < .0001$), and late-onset sepsis (16.6% vs 5.0%, $P < .0001$), but lower rates of BPD (12.3% vs 14.6%, $P < .0001$) and severe ROP (6.2% vs 10.0%, $P < .001$) in comparison with the NRNJ. For management of PDA, the CNN had a lower rate of indomethacin administration (17.5% vs 28.9%, $P < .0001$), but a higher rate of PDA ligation (8.3% vs 5.2%, $P < .001$).

The results of multivariable analyses are shown in Table 4, adjusted for maternal hypertension, maternal diabetes mellitus, prenatal steroid, gender, GA, outborn status, Apgar score at 5 minutes of age, vertex presentation, cesarean delivery, and multiple births. The composite primary outcome of mortality or any major morbidity was significantly better in NRNJ (adjusted odds ratio [AOR] 0.87, 95% confidence interval [CI] 0.79-0.96). Analyses of secondary outcomes revealed that the NRNJ had lower odds of mortality (AOR

TABLE 3 Comparison of Outcomes Between 2 Networks

Outcomes	Network	All VLBW	<25 wk	25–26 wk	27–28 wk	29–32 wk	>32 wk
No. of infants	CNN	5341	459	970	1443	2179	290
	NRNJ	9812	1209	1719	2141	3625	1118
Mortality or any major morbidity	CNN	32.2 (1717/5341)	88.5 (406/459)	62.4 (605/970)	30.2 (436/1443)	11.8 (258/2179)	4.1 (12/290)
	NRNJ	30.3 (2968/9812)†	75.7 (915/1209)**	56.1 (964/1719)*	31.9 (683/2141)	10.6 (383/3625)	2.1 (23/1118)†
Mortality	CNN	10.5 (560/5341)	52.3 (240/459)	17.9 (174/970)	7.3 (105/1443)	1.7 (37/2179)	1.4 (4/290)
	NRNJ	6.5 (636/9812)**	27.1 (328/1209)**	9.6 (165/1719)**	4.1 (87/2141)**	1.4 (50/3625)	0.5 (6/1118)
Severe neurologic injury	CNN	11.4 (609/5341)	32.0 (147/459)	21.4 (208/970)	11.2 (161/1443)	4.1 (90/2179)	1.0 (3/290)
	NRNJ	8.0 (781/9812)**	19.5 (236/1209)**	11.7 (201/1719)**	8.3 (177/2141)*	4.3 (157/3625)	0.9 (10/1118)
BPD	CNN	12.3 (655/5341)	28.1 (129/459)	28.1 (274/970)	11.4 (165/1443)	4.0 (87/2179)	NA
	NRNJ	14.6 (1433/9812)**	36.2 (438/1209)**	30.4 (523/1719)	15.2 (326/2141)*	4.0 (146/3625)	
Severe ROP	CNN	6.2 (329/5341)	22.7 (104/459)	17.0 (165/970)	3.1 (45/1443)	0.7 (15/2179)	0 (0/290)
	NRNJ	10.0 (980/9812)**	23.7 (287/1209)	21.7 (373/1719)*	10.7 (230/2141)**	2.3 (83/3625)**	0.6 (7/1118)
NEC	CNN	5.9 (315/5341)	10.7 (49/459)	9.7 (94/970)	6.6 (95/1443)	3.3 (72/2179)	1.7 (5/290)
	NRNJ	1.6 (153/9812)**	5.7 (69/1209)*	2.7 (47/1719)**	1.3 (28/2141)**	0.2 (8/3625)**	0.1 (1/1118)**
Late-onset sepsis	CNN	16.6 (889/5341)	28.8 (132/459)	30.4 (295/970)	19.33 (279/1443)	8.1 (177/2179)	2.1 (6/290)
	NRNJ	5.0 (492/9821)**	14.6 (176/1209)**	8.1 (140/1719)**	4.3 (92/2141)**	2.1 (76/3625)**	0.7 (8/1118) †
Indomethacin for PDA	CNN	17.5 (910/5196)	30.0 (127/424)	33.2 (309/930)	23.3 (328/1411)	6.8 (145/2146)	0.35 (1/285)
	NRNJ	28.9 (2833/9812)**	44.6 (539/1209)**	41.0 (705/1719)**	38.1 (816/2141)**	19.8 (716/3625)**	5.1 (57/1118)*
PDA ligation	CNN	8.3 (430/5196)	27.8 (118/424)	23.1 (215/930)	4.6 (65/1411)	1.5 (32/2146)	0 (0/285)
	NRNJ	5.2 (508/9812)**	15.6 (189/1209)**	11.0 (189/1719)**	3.7 (80/2141)	1.3 (48/3625)	0.18 (2/1118)

** $P < .0001$; * $P < .01$; † $P < .05$.

TABLE 4 Comparison of Outcomes Between 2 Countries: Multivariable Analyses Results

Outcomes	All VLBW	<25 wk	25–26 wk	27–28 wk	29–32 wk	>32 wk
Mortality or any major morbidity	0.87 (0.79–0.96)	0.35 (0.25, 0.51)	0.76 (0.63–0.91)	1.12 (0.95–1.32)	0.92 (0.76–1.10)	0.46 (0.22–0.98)
Mortality	0.40 (0.34–0.47)	0.28 (0.22–0.37)	0.42 (0.32–0.56)	0.46 (0.33–0.64)	0.82 (0.50–1.34)	0.35 (0.09–1.40)
Severe neurologic injury	0.57 (0.49–0.66)	0.45 (0.34–0.59)	0.45 (0.35–0.58)	0.66 (0.51–0.86)	0.83 (0.62–1.12)	0.88 (0.19–4.07)
BPD	1.24 (1.10–1.42)	1.32 (1.01–1.71)	1.08 (0.89–1.32)	1.48 (1.19–1.85)	1.17 (0.87–1.58)	NA
Severe ROP	1.98 (1.69–2.33)	1.09 (0.82–1.45)	1.44 (1.14–1.82)	4.78 (3.24–7.04)	3.98 (2.11–7.52)	NA
NEC	0.23 (0.19–0.29)	0.50 (0.33–0.75)	0.26 (0.18–0.38)	0.16 (0.10–0.26)	0.07 (0.04–0.15)	0.04 (0.01–0.35)
Late-onset sepsis	0.22 (0.19–0.25)	0.35 (0.27–0.47)	0.18 (0.14–0.22)	0.17 (0.13–0.22)	0.24 (0.19–0.33)	0.41 (0.12–1.37)
Indomethacin for PDA without ligation	2.04 (1.85–2.24)	1.87 (1.43–2.43)	1.37 (1.14–1.65)	1.90 (1.61–2.24)	3.34 (2.72–4.10)	NA
PDA ligation	0.60 (0.50–0.72)	0.51 (0.38–0.69)	0.45 (0.35–0.57)	0.99 (0.68–1.45)	1.25 (0.74–2.11)	NA

The results were based on the final multiple logistic regression model derived controlled for GA, gender, Apgar score at 5 min, outborn status, prenatal steroid, vertex presentation, cesarean delivery, multiple births, maternal hypertension, and maternal diabetes. Values presented are AOR (95% CI).

0.40, 95% CI 0.34–0.47), severe neurologic injury (AOR 0.57, 95% CI 0.49–0.66), NEC (AOR 0.23, 95% CI 0.19–0.29), and late-onset sepsis (AOR 0.22, 95% CI 0.19–0.25), but it had higher odds of BPD (AOR 1.24, 95% CI 1.10–1.42) and severe ROP (AOR 1.98, 95% CI 1.69–2.33). The odds of indomethacin administration were higher in the NRNJ (AOR 2.04, 95% CI 1.85–2.24), but the odds of PDA ligation were lower (AOR 0.60, 95% CI 0.50–0.72) in NRNJ.

Data on resource utilization for infants who survived between the 2 networks revealed that days on oxygen, days on continuous positive airway pressure, days on ventilation, and length of hospital stay were longer in the NRNJ than in the CNN (Table 5).

DISCUSSION

In this comparative study of outcomes of VLBW infants in Canada and Japan, we identified that composite primary outcome of mortality or major morbidity was significantly lower for NRNJ in comparison with CNN. However, we identified significant differences between the 2 countries for individual components of the primary outcome and certain secondary outcomes. Mortality, severe neurologic injury, NEC, late-onset sepsis, and PDA ligation were higher in the CNN, whereas BPD, severe ROP, duration of hospitalization, duration of respiratory support, duration of oxygen use, and indomethacin use for PDA were higher in the NRNJ. We also identified that differences in outcomes were more striking in certain GA groups.

Previous reports have compared mortality in various countries, regions, or networks and identified that there is a wide variation (or heterogeneity) in mortality.[5,15,16] One of the key features highlighted as an issue in comparison was differences in infant characteristics (GA, birth weight [BW], multiple birth, outborn, presentation, congenital anomaly, etc), maternal characteristics (maternal age, obstetric history, socioeconomic factors, maternal complication, etc), obstetric management, viability, severity of illness on admission, definitions of outcomes, and selection bias of population.[16,17] The rate of low birth weight birth is higher in Japan than in Canada (9.6% vs 6%).[11,12,18] This results in shift of BW for GA curve to the left. This may explain higher number of >31 weeks GA infants in Japan in

TABLE 5 Comparison of Resource Usages for Infants Who Survived Between CNN and NRNJ

Resource Use	Univariable Analysis		Multivariable Analysis
	CNN	NRNJ	Estimate (SE)
Days on oxygen, median (IQR)			
All VLBW	2 (0–14)	15 (1–55)**	1.33 (0.04)**
<25 wk	25 (5–42)	91 (61–125)**	1.20 (0.12)**
25–26 wk	13 (3–30)	63 (34–87)**	1.15 (0.093)**
27–28 wk	6 (0–18)	36 (4–56)**	1.07 (0.053)**
>28 wk	0 (0–3)	4 (1–16)**	1.28 (0.05)**
Days on CPAP, median (IQR)			
All VLBW	5 (1–20)	2 (0–21)**	0.19 (0.034)**
<25 wk	19 (8–31)	15 (0–29)†	0.10 (0.07)
25–26 wk	22 (10–34)	18 (1–33)**	0.11 (0.038)*
27–28 wk	13 (4–27)	12 (0–30)	0.31 (0.037) **
>28 wk	1 (0–5)	0 (0–5)**	0.68 (0.052) **
Days on ventilation, median (IQR)			
All VLBW	2 (0–10)	4 (0–30)**	0.76 (0.037)**
<25 wk	46 (28–60)	59 (41–77)**	0.13 (0.073)
25–26 wk	22 (7–40)	38 (21–53)**	0.31(0.46) **
27–28 wk	3 (1–10)	8 (2–26)**	0.70 (0.057)**
>28 wk	0 (0–2)	0 (0–4)	0.60 (0.063)**
Length of hospital stay, median (IQR)			
All VLBW	43 (20–69)	81 (58–115)**	0.80 (0.015)**
<25 wk	109 (75–131)	145 (124–174)**	0.39 (0.060) **
25–26 wk	81 (55–105)	120 (103–142)**	0.45 (0.30)*
27–28 wk	54 (32–73)	92 (78–113)**	0.61 (0.025)**
>28 wk	27 (14–44)	60 (46–75)**	0.92 (0.02)**

Nonparametric Mood median test was used. Zero-inflated models were used for the outcome, with the exception of length of stay. Linear regression models were used for length of stay in log scale. CPAP, continuous positive airway pressure; IQR, interquartile range.
** $P < .0001$; * $P < .01$; † $P < .05$ (Japan versus Canada).

comparison with Canada in this cohort. Potential implications of higher maturity at any given BW category need further analyses and could explain some of the variation in outcomes. With a defined population base in our 2 networks and the conduct of multivariable analyses, we were able to control for some of these variations. We were also able to compare other morbidities that may come as the cost of survival of these vulnerable infants. We elected to use the composite outcome as our primary outcome because there is concern that improved survival of extremely small or immature infants may lead to higher rates of morbidities and long-term problems.[19] With our large sample size, we were able to compare outcomes individually and to identify important differences.

Mortality, especially at lower GAs, was lower in the NRNJ in comparison with the CNN. Possible explanations for this difference include the lower rates of severe neurologic injury, NEC, and late-onset sepsis in the NRNJ,[20,21] differences in philosophy of care provision with reference to lower GA infants,[19] and "referral bias" owing to the lower population coverage of NRNJ. The management of infants with borderline viability in Japan seemed to be more aggressive than in Canada.[22–24] The reduced population coverage in NRNJ may be the reason for reported improved survival rates. Smaller tertiary NICUs that are not part of national network may have different outcomes, however; it is unlikely because the mortality of extremely low birth weight infants in 2006 was 16.7% in NRNJ participating sites in comparison with 17% in a national survey in Japan in 2005 that covered ~98% of population of extremely low birth weight infants in Japan.[10] However, the effect of "referral bias" on other outcomes is unclear. Finally, it is also possible that quality of care is better in Japan than in Canada; however, it requires further exploration because, in this data set, we do not have information regarding severity of illness, other physical characteristics of units, and human factors (physician and nursing coverage ratio, on-call system, duty hours, etc).

Severe neurologic injury with severe intraventricular hemorrhage (IVH) and/or periventricular leukomalacia was an important morbidity because of its association with long-term neurodevelopmental outcomes.[20,25] Our analysis showed a much higher incidence of severe IVH and periventricular leukomalacia in the CNN than in the NRNJ, especially among more preterm infants, even after adjustment for important predictors of neurologic injury such as antenatal steroid use, cesarean delivery, outborn status, and GA.[26] Despite this adjustment, higher rates in the CNN point to differences in the management practices of such infants in the first week after birth, such as fluid management, management of PDA, and ventilator management. Unfortunately, we do not have data on ventilator management and fluid management practices. However, we are aware that many neonatologists in Japan performed functional echocardiography 2 to 3 times a day to check cardiac function and the status of PDA, to optimize the circulatory management of preterm infants.[27] This may enhance stabilization of the circulatory system and earlier treatment of PDA, both of which can reduce severe IVH.[28]

We identified that the rate of BPD was lower in the CNN than in the NRNJ. We hypothesize that this difference is mainly due to respiratory support practices between the 2 networks. The number of days of oxygen and the days of ventilation for infants who survived in the CNN were much shorter than those in the NRNJ, suggesting the possibility that early extubation and more restrictive oxygen usage may be responsible for a lower rate of BPD in CNN. This could also explain higher rates of severe ROP in the NRNJ.[29] However, it must be kept in mind that higher survival at a lower GA may also be responsible for higher rate of BPD and ROP and longer resource usage in NRNJ.[30]

The rates of NEC and late-onset sepsis in the NRNJ were much lower than in the CNN, and lower than previously reported rates from other networks or countries.[31] Although we do not have the information about management practices between countries, informal evaluation has revealed that use of breast milk, donor milk, probiotics, and prebiotics were higher in the NRNJ and may have resulted in decreased rates of NEC[32,33] and late-onset sepsis. However, these data will need to be verified by formal evaluation of practices in future. Post hoc analyses revealed that exclusion of NEC from the primary outcome of mortality or severe morbidity revealed no difference between networks (AOR 1.02, 95% CI 0.92–1.12). This suggests significant contribution of NEC in the composite outcome. Based on the importance of this outcome in overall contribution to differences between countries, this topic needs immediate and further research to illustrate fundamental differences in practice.

Strengths of our study include the large number of VLBW infants from well-established national neonatal databases of tertiary perinatal centers in Canada and Japan, with adjusted analyses at the individual patient data level and incorporation of perinatal and neonatal factors. In addition, we analyzed the morbidity in categories of GA groups to tease out differences at various GA to understand the differences more precisely. However, there are limitations to our report. This study was a retrospective observational study and we had to adjust criteria used by both networks to accommodate definitions of outcomes. Both networks had loss of data for patients not admitted to tertiary NICUs, more so in Japan than Canada. We studied only the mortality and morbidity until discharge from the NICU and did not study long-term outcomes, which are also very important; however, our composite outcome has previously been shown to have very good predictive power for long-term outcomes.[13] We do not have details regarding management practices between countries to account for differences observed. More importantly, because of noncollection of data, severity of illness could not be accounted for in our comparison.

As a next step, we should investigate why there are differences in mortality and morbidity by studying more details of clinical management and practices in each country and in each NICU to specifically target quality improvement initiatives. Moreover, it is also important to compare follow-up data to assess long-term neurodevelopmental outcomes and the quality of life of survivors. Based on this analysis, collaborative steps have already been taken and interactive learning between the 2 networks has been fostered. In future, international comparisons that include other networks will be possible by using similar methods or collaboratively developing a minimal data set and identifying areas of improvement.

CONCLUSIONS

The composite outcome of mortality or any major morbidity was significantly better in Japan than Canada for VLBW infants. However, there were significant differences in various individual outcomes identifying areas for improvement for both networks.

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Comparison of Mortality and Morbidity of Very Low Birth Weight Infants Between Canada and Japan

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