Project Final Report

Project Title: Comparison of outcomes of infants between 30 weeks and 0 days to 31 weeks and 6 days of gestation at birth in Ontario based on the site/level of care
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Executive Summary

Rationale/Aims: Previous studies have shown that inborn preterm infants of <32 weeks gestation born at Level III care facilities have better outcomes compared to outborn neonates delivered in non-tertiary hospitals and transferred to Level III units. However, other findings suggest that preterm infants born between 30^0 and 31^6 weeks that do not require prolonged respiratory support can be managed in Level IIc units. Therefore, as the Provincial Council for Maternal and Child Health (PCMCH) worked to develop standardized definitions for levels of maternal-newborn care in Ontario, the issue of where to manage infants born at 30^0 and 31^6 weeks gestation arose. Given the lack of available evidence to establish clear clinical practice guidelines, the PCMCH sought to compare outcomes of infants born between 30^0 and 31^6 weeks gestation cared for in different levels of NICU care in Ontario. This formed the basis of this project, which was to evaluate whether or not the outcomes of preterm infants born between 30^0 and 31^6 of gestation were similar when the intention was to deliver and care for them at Level III hospitals in the initial period versus deliver and care for them in Level IIc units in Ontario. Measured outcomes were extracted using data collection platforms of the Canadian Neonatal Network (CNN) and the Better Outcomes Registry & Network (BORN Ontario).

Comparisons were made between 805 infants born between 30^0 and 31^6 weeks gestation who were either born in Level III centres or were transferred from Level IIc centres to Level III centres within first 48 hours of age (Group A), and 264 patients who were born in Level IIc centres and were not transferred to Level III centres within first 48 hours of age but may or may not have required a later transfer to a Level III centre (Group B). Outcomes that were evaluated included 1) primary composite outcome (survival without major morbidity); 2) secondary outcomes; and 3) resource utilization.

Results: Overall, eight units from Level III hospitals contributed data to the CNN (Group A), and 16 hospitals provided data to BORN (Group B), of which 11 transferred patients within the first 48 hours. Overall, Composite outcome was significantly higher in Group A compared to Group B (Crude OR 3.32, 95% CI 1.80, 6.14). After logistic regression analysis, Group A has a higher adjusted odds ratio of 4.13 (95% CI 2.00-8.52). Components of composite outcomes such as mortality, chronic lung disease, persistent pulmonary hypertension, and air leak were higher in Group A, whereas Group B demonstrated a greater need for required oxygen and CPAP support. Apgar score at 5 minutes of <7 was identified as a significant predictor of outcome.

Important take away messages:

1. Neonates of 30 and 31 weeks GA born and/or transferred to Level III Hospitals had different baseline characteristics compared to those who were kept in Level IIC hospitals.
2. It was possible to combine data from CNN and BORN data collection systems for approximately 80-85% of neonates with probabilistic matching.
3. Antenatal steroid administration was significantly low (not only in comparison to Group A but overall as well) in Level IIc units.

4. Rates of composite outcome and individual morbidities of neonates born and/or transferred to Level III hospitals were higher compared to those admitted to Level IIC hospitals. This remained significant after adjustment of available predictors.
5. However, data on severity of illness at the time of admission to neonatal units were not available in the BORN data collection system and from baseline characteristics it appears that neonates admitted in Level IIC were less sick and more were of 31 weeks GA compared to Level III units.
6. In addition, a large number of neonatal data on resource utilization were missing in the BORN data system.
7. Despite lower severity of illness in neonates admitted to Level IIC,
    a. the proportion of neonates who received invasive ventilatory support were similar in both groups
    b. the duration of mechanical ventilation was higher
    c. the proportion who received non-invasive ventilation was higher
    d. the duration of non-invasive ventilation was higher.

Recommendations:

1. There needs to be collaborative effort to track outcomes of neonates admitted to Level III and transferred to Level IIc units in Ontario, such that proper comparisons can be made.
2. Strengthening of data collection for severity of illness and resource utilization from Level IIC is needed in order for future comparisons to result in quality improvement activities.
3. Efforts to increase antenatal steroid administration via education, feedback and constant surveillance are needed for preterm births before 34 weeks gestation in Level IIC units.
4. If Level IIC units are going to keep potentially well neonates born at 30 and 31 weeks gestation, then an extensive education package regarding neonatal resuscitation, non-invasive respiratory management, and placement of peripherally inserted central venous catheters needs to be provided to frontline health care workers, including physicians.

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Final Report

Research/Audit Question

Are the outcomes of preterm infants born between 30 weeks and 0 days (30^0) and 31 weeks and 6 days (31^6) of gestation similar when the intention was to deliver and care for them at Level III hospitals in the initial period vs. deliver and care for them in Level IIc hospitals in Ontario?

Background

Historically, it has been shown that inborn (born at a Level III care facility) preterm infants of <32 weeks gestation has better outcomes when compared to outborn neonates (those delivered at non-tertiary hospitals and then transferred to Level III hospitals). This has been shown in a number of studies from different networks.[1,2] Based on this evidence, several national guidelines suggest in-utero transfer of such mothers to tertiary hospitals when they present to non-tertiary facilities in labor. Moreover, outborn neonates are at higher risk of needing extensive resuscitation, developing hypothermia, and receiving inadequate care from respiratory, cardiovascular and hemodynamic aspects. They are at higher risk of developing immediate complications such as right main stem intubation, delay in intubation, hypothermia, hypoglycemia (due to inadequate venous access), etc. However, approximately 25-30% of infants <32 weeks gestation are delivered in non-tertiary hospitals, often because of an inability to transfer the mother due to medical reasons (advanced stages of labor) or unavailability of beds in the tertiary centre(s).

Within the preterm population, infants born between 30^0 and 31^6 weeks of gestation are unique in that many such neonates usually do not require extensive intensive care in the form of prolonged respiratory support. If the patient is stable from a respiratory point of view (not likely to need prolonged intubation beyond one-week after birth) then their care mainly involves management of nutrition, hydration, skin care, growth monitoring, breastfeeding and parental support. In Ontario, several non-tertiary hospitals are designated as Level IIc hospitals and they have the ability to provide ventilatory support for up to one week, continuous positive airway support, and the ability to provide peripherally inserted central catheters and total parenteral nutrition. Over time, these units have managed such infants from birth to discharge, unless the infant develops complications necessitating transfer to a Level III NICU.

As the Provincial Council for Maternal and Child Health (PCMCH) worked to develop standardized definitions for levels of maternal-newborn care in Ontario, which identified a clear scope of practice for each level, the issue of where to manage the infants born at 30^0 to 31^6 weeks gestation arose. Clear evidence was not available to guide practice. As a result, PCMCH committed to compare outcomes of infants born between 30^0 weeks to 31^6 weeks gestation cared for in different levels of NICU care in Ontario using the Canadian Neonatal Network (CNN) and Better Outcomes Registry & Network (BORN Ontario) data collection platforms with the understanding the limitations such project may entail particularly "confounding by indication" bias.

Methods

Population:
Preterm infants born between 30^0 and 31^6 weeks gestation in Ontario.

Setting:
Level III and Level IIc hospitals in Ontario (Please see Appendix 1 for classification).

Duration:
Infants admitted between July 1st, 2012 and June 30th, 2014 to participating hospitals in Ontario.

Data Collection Systems:
Two data collection systems were involved in this project.

A. Canadian Neonatal Network:

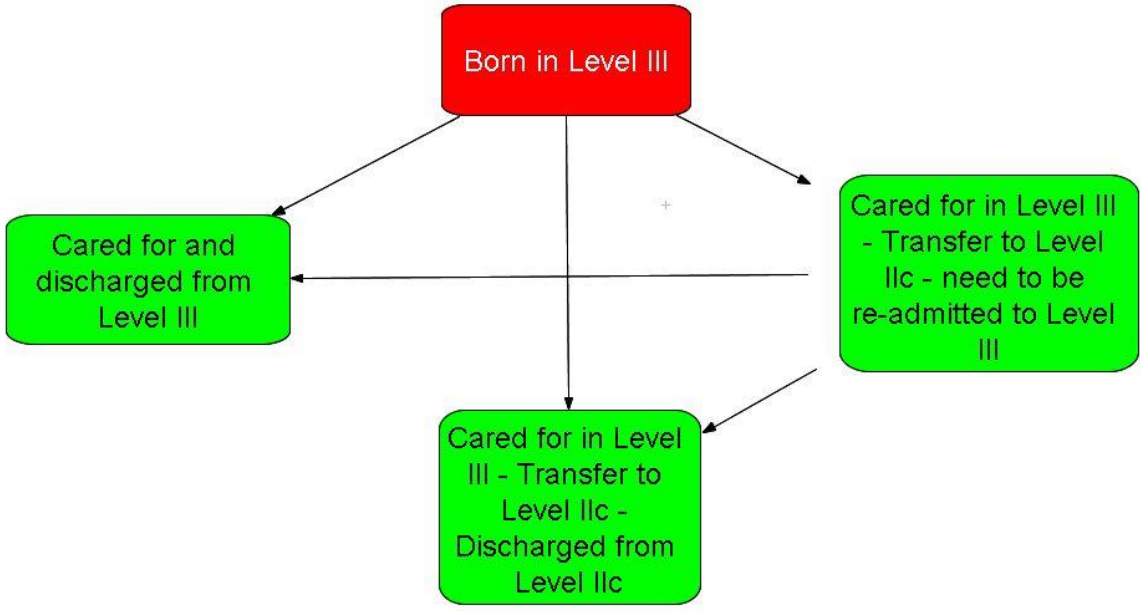
CNN maintains an established national database for the purpose of evaluation of outcomes, benchmarking and quality improvement. An initial two years-long endeavour has been extended to continue as an ongoing national data collection for benchmarking, quality improvement and research purposes. Data from eligible NICU admissions are collected and submitted after institutional approval (either from a local Research Ethics Board or an institutional quality improvement process). Since 2011, all 30 tertiary NICUs in Canada have been participating in the Network, each of which has trained research personnel who abstract data from patient charts. Details of data collection and data management have been published. Infants who were moribund on admission (*i.e.*, when a physician, in consultation with the parents, made an explicit decision not to provide life support at the time of the NICU admission) were excluded from the analyses.

B. Better Outcomes Registry & Network (BORN) Ontario registry:

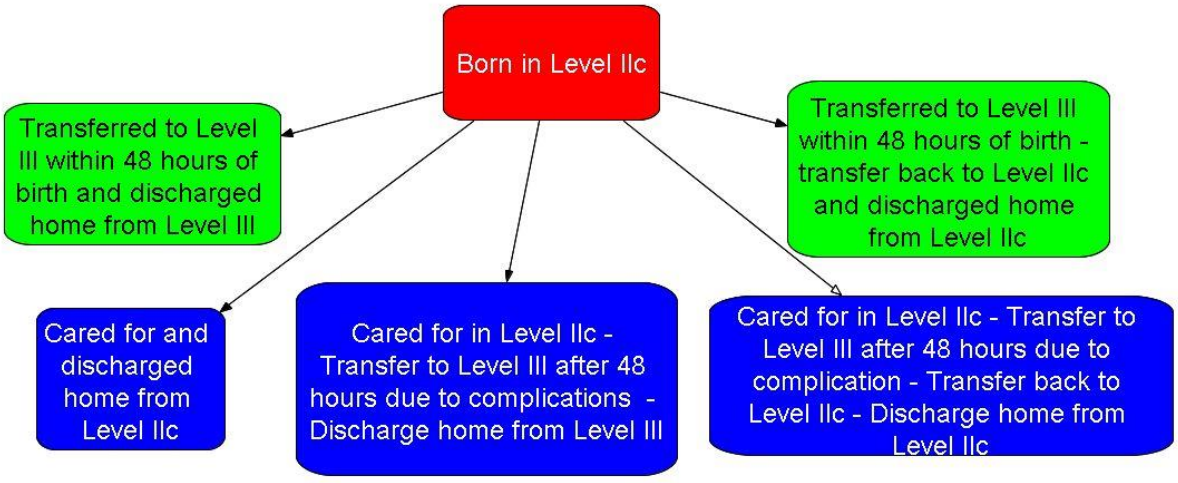
BORN is a provincial initiative developed to provide the knowledge needed for the best possible beginnings for life-long health. BORN is a *Prescribed Registry* under Ontario's Personal Health Information Protection Act. This status allows BORN to collect, use and disclose personal health information for purposes of facilitating or improving the provision of health care. Data are collected through a number of mechanisms including manual data entry and automated extraction and uploading from existing hospital and lab information systems. All Ontario facilities that provide birthing services collect and submit data on all births to BORN. The latest BORN enhancement is extensive data collection for newborn infants during their stay in Level I or Level II nurseries. This newly developed database was deployed in April 2012. Allowing for an initial period of understanding, training, etc., it was anticipated that data collection would become seamless from June 2012. Thus, data collection date for this project was targeted to begin July 1, 2012 for a total of 2-year period.

Patient flow:
Preterm infants eligible for this study in Ontario take the following care pathways prior to discharge (home or death).

Pathway 1



Pathway 2



Data collected for all neonates admitted to Level III at the time of birth or at any time during their stay in a Level III hospital in Ontario were retrieved from the CNN. Data for the remaining part of their stay were collected within the newly deployed screens for the Level IIc data collection platform of the BORN Ontario registry. The main comparison groups were:

1. **Group A:** Infants born between 30^0 and 31^6 weeks gestation who were either born in Level III centres or were transferred from Level IIc centres to Level III centres within first 48 hours of age (intention was to deliver these infants in Level III centres and provide initial care in Level III centres) – [Infants in Green coloured boxes in pathways 1 and 2]

2. **Group B:** Infants born between 30^0 and 31^6 weeks of gestation who were born in Level IIc centres and were ***not*** transferred to Level III centres within first 48 hours of age but may or may not have required a later transfer to a Level III centre (intention was to deliver these infants in Level II centres and provide initial care in Level IIc centres) – [Infants in Blue coloured boxes in pathway 2]

Outcomes:

The following outcomes were planned *a priori*.

1. Primary Composite Outcome:

Primary outcome was defined as survival without major morbidity. Thus, composite outcome was ascertained if any of the following outcomes were discovered prior to discharge home or death:

a. Mortality
b. Severe intraventricular hemorrhage (grade 3 or 4) or periventricular leukomalacia
c. Chronic lung disease defined as oxygen requirement at 36 weeks corrected gestational age
d. Nosocomial sepsis defined as isolation of bacterial/viral/fungal organism (blood or cerebrospinal fluid) after 3 days of age
e. Patent ductus arteriosus requiring surgical ligation
f. Persistent pulmonary hypertension
g. Air leak (pneumothorax/pneumomediastinum or interstitial emphysema)
h. Necrotizing enterocolitis
i. Intestinal perforation

2. Secondary outcomes:

Individual outcomes mentioned above:

a. Mortality
b. Severe intraventricular hemorrhage (grade 3 or 4) or periventricular leukomalacia
c. Chronic lung disease defined as oxygen requirement at 36 weeks corrected gestational age
d. Nosocomial sepsis defined as isolation of bacterial/viral/fungal organism (blood or cerebrospinal fluid) after 3 days of age
e. Patent ductus arteriosus requiring surgical ligation
f. Persistent pulmonary hypertension
g. Air leak (pneumothorax/pneumomediastinum or interstitial emphysema)
h. Necrotizing enterocolitis
i. Intestinal perforation

3. Resource utilization:

Data on resource utilization were compared between Groups A and B for:

a. Length of stay
b. Duration of intravenous support
c. Duration of gavage feeding
d. Duration of TPN
e. Duration of respiratory support
    i. Mechanical ventilation
        1. Number of days

2. Corrected GA on last day of support

ii. CPAP
    1. Number of days
    2. Corrected GA on last day of support

iii. Oxygen
    1. Number of days
    2. Corrected GA on last day of support

f. Duration of antibiotics

Data Management:

1. Data validation:

Both systems (CNN and BORN) have their internal checks for data validity at the time of data entry. Another set of validation by confirming ranges, SD and outliers were performed after data amalgamation from both sources. Before data matching between BORN and CNN, a deterministic linkage approach was used to clean the duplicated cases for the two datasets separately by using six key elements including birth date, gestational age, birth weight, birth hospital, baby gender, birth order and transfer hospital.

2. Data matching:

Data were collected separately in two databases and once all data collection was complete, data were matched by probabilistic matching to create one "flat file" for each patient incorporating all admissions (Level III and Level IIc NICU stay). Matching was based on 9 common variables including birth date, birth weight, birth hospital, gestational age, baby gender, delivery type, presentation type, birth order and Apgar 5 score. Before probabilistic linkage, a set of deterministic linkages were done using several rounds of possible identifiers to determine the key variables and weight score for each matching variable in probabilistic linkage. Several rounds of probabilistic linkage were repeated to find matches. The first probabilistic linkage was based on birth date, birth weight and birth hospital (that means birth date, birth weight and birth hospital must be matched first, and the rest of the variables may or may not be matched). The threshold score for matching was determined by the distribution of matching scores. Second and third probabilistic linkage was based on birth date (that means birth date must be matched first, and the rest of the variables may or may not be matched). After the probabilistic linkage, the remaining unlinked records were checked manually. Once linkage was established, all personal identifiers (that were present in BORN data but not in CNN) were stripped prior to data transfer for analyses. CNN data was sent to BORN upon execution of a data sharing agreement between Mount Sinai Hospital (CNN host institution) and Children's Hospital of Eastern Ontario (BORN Ontario host institution).

3. Database preparation for analyses:

The analyses were conducted at BORN Ontario, located at the CHEO Research Institute, Ottawa where data matching, accuracy check (if needed from source charts of individual hospitals) and preparation of database for analyses were conducted. The data at this stage were devoid of personal identifiers and only contained one file per patient (containing all admissions prior to discharge).

Data Analyses:
All analyses were stratified by study groups (A or B). Continuous variables were described by mean ± standard deviation (SD) or median (interquartile range, IQR). Categorical variables were described by count and percent (%). Baseline characteristics at first NICU admission (gestational age, baby birth weight, baby gender, maternal hypertension, maternal diabetes, any antenatal steroids use, birth location, delivery type, Apgar score at 1 minutes after birth, Apgar score at 5 minutes after birth, small for gestational age <10 percentile, baby need for chest compression or epinephrine) and resource utilization (NICU length of stay, intravenous support, parenteral nutrition, CPAP, oxygen use, invasive ventilation and non-invasive ventilation) were compared between the two study groups. Univariate analyses (chi-square or fisher's exact test for categorical variables and Student's t-test or other appropriate non-parametric test in the event of non-normal distribution for continuous variables) were performed to compare the characteristics of the study populations and to explore the association between population characteristics and clinical outcomes.

Multivariate logistic regression analyses were performed to examine composite neonatal outcomes in the two groups while controlling for potential confounding factors. Crude, adjusted odds ratios and 95% confidence intervals were calculated based on statistical significance level of a p-value ($p \leq 0.05$). The statistical software package SAS 9.4 (Cary, North Carolina, USA) was used for data analyses.

Ethics:
Approval was obtained for the project from both steering committees (CNN and BORN) for utilization of data. Ethics approval was obtained from Mount Sinai Hospital and the Children's Hospital of Eastern Ontario for analyses and dissemination. CNN participating sites have ethical approval from their hospitals regarding submission and utilization of data. Data collected in BORN can be used for the secondary purpose of research and quality improvement, provided all privacy, ethical and security regulations are met. Thus, ethical approval from individual sites was not sought.

Timeline:

Table 1. Initial and final timeline of project phases.

Phases	**Plan**	**Actual**
Preparatory phase	October 2011-June 2012	October 2011-June 2012
Proposed data collection period	July 2012- June 2014	July 2012- June 2014
Final data entry for all eligible infants	October 2014	December 2014
Data check and data cleaning	January 2015	March 2015
Data analyses	May 2015	August 2015
Report back to PCMCH	Sept-December 2015	January-March 2016

Deliverables:

1. **Regular updates:**
   The project coordinator provided regular updates (every 6 months) as to hospital participation, number of infants born and entered during the previous 6 months in both databases, and number of infants with complete and incomplete information in either database.

2. **Final report:**
   The Mother-Infant Care Research Centre at Mount Sinai Hospital is providing this as a completed project report to PCMCH.

Results

Population:
During the study period, eight units that classified as Level III hospitals contributed data to the CNN. Data from BORN came from 16 hospitals, which provided care to neonates born in their hospital and of these, 11 transferred some patients within first 48 hours contributing to both groups (Appendix 1). Initial eligible patient populations registered within the CNN and BORN systems are shown in Figures 1 and 2. Samples sizes after probabilistic linkage and those included in the final analysis are displayed in Figures 3 and 4.

Figure 1. Eligible patients registered in CNN participating hospitals during study period.

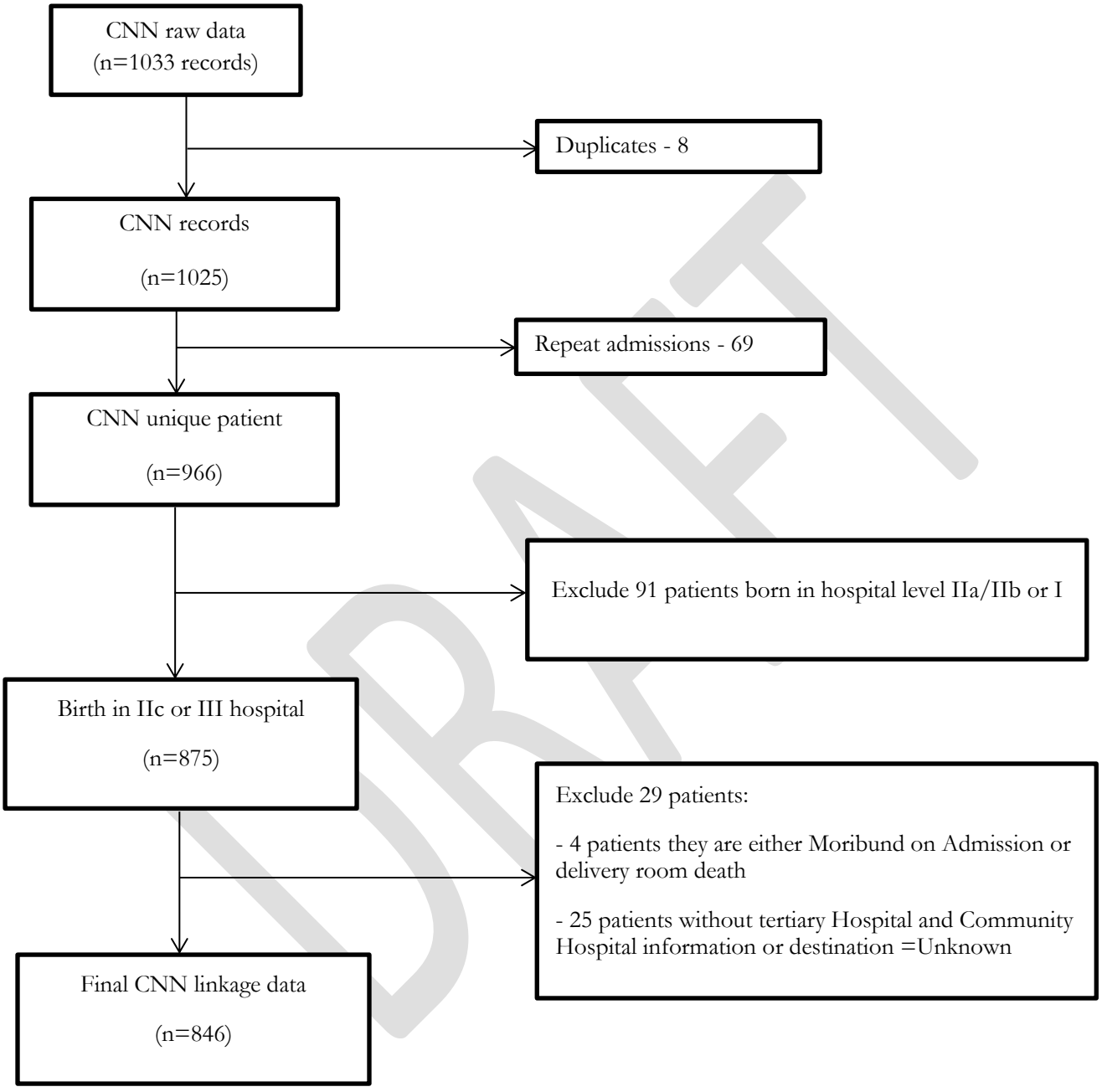


Figure 2. Patients documented in the BORN system.

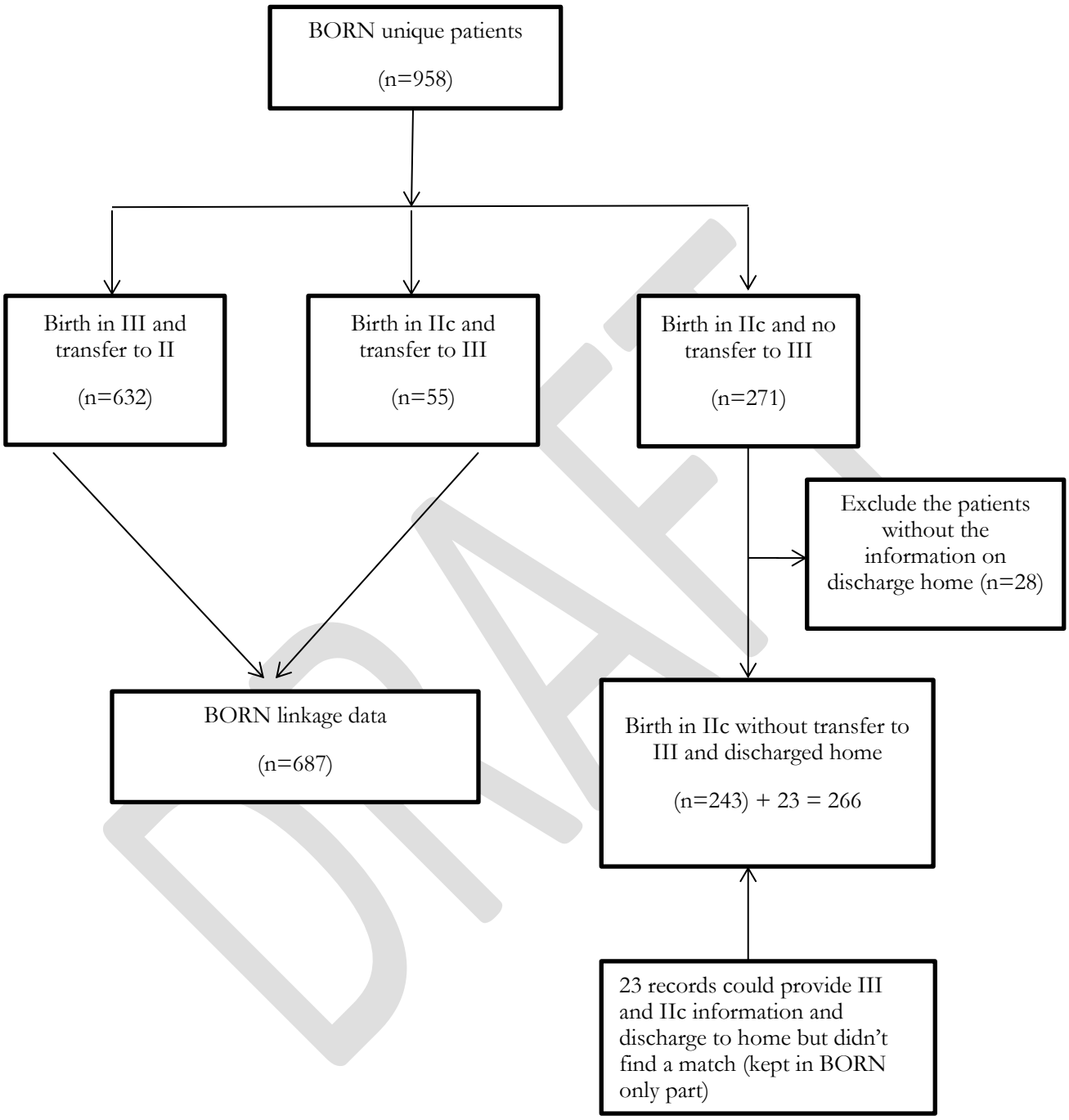


Figure 3. The probabilistic linkage process that was carried out.

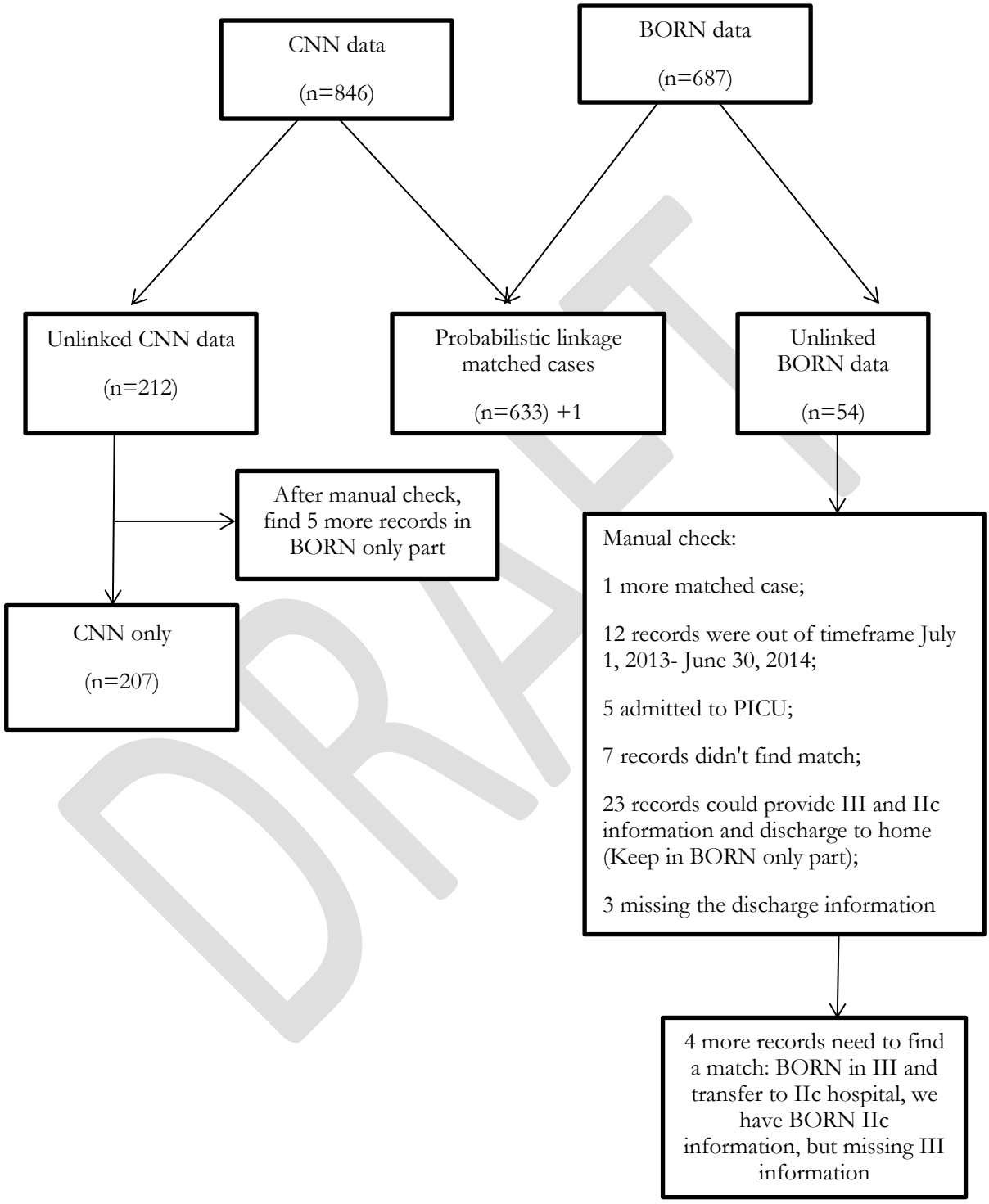
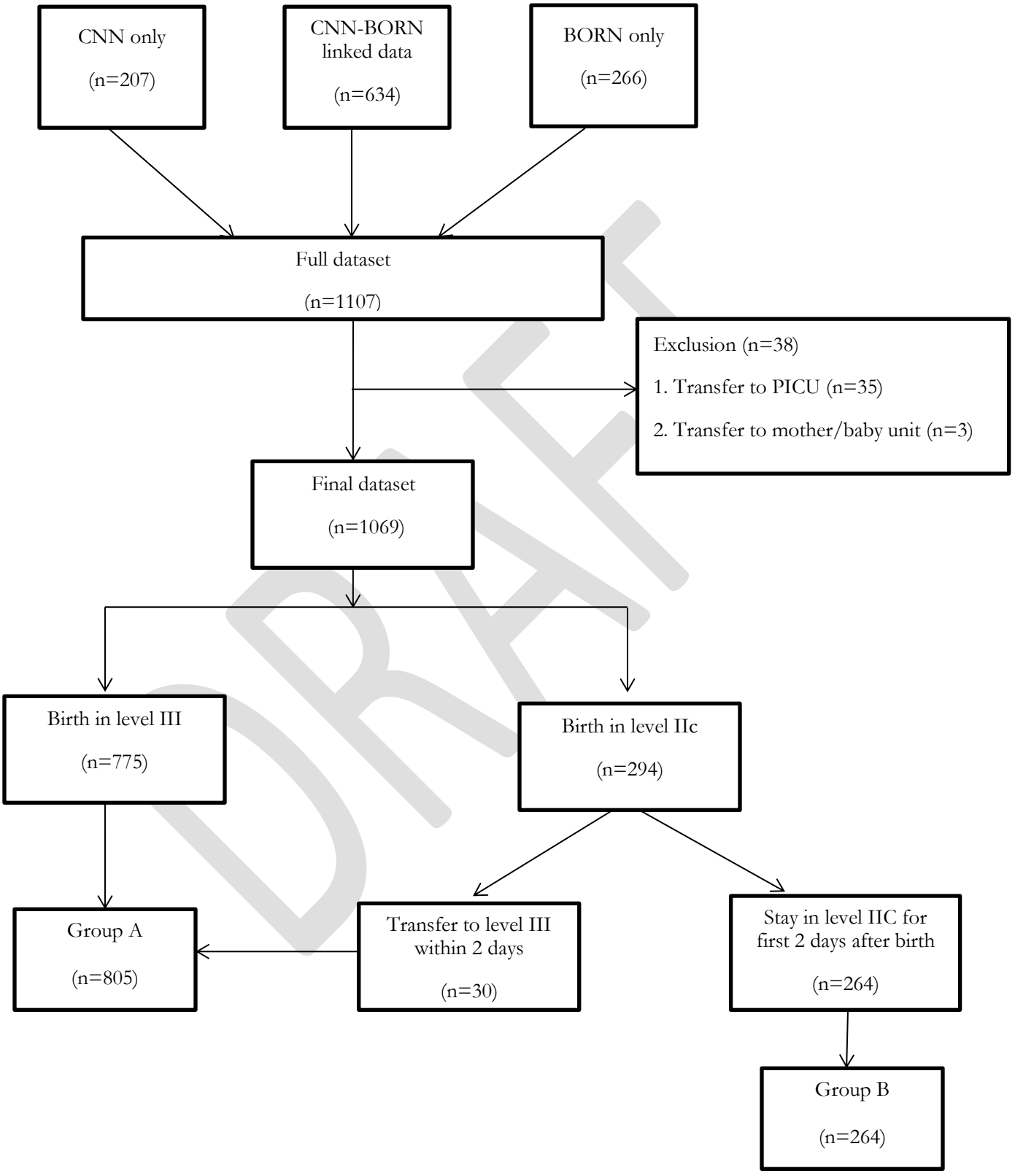


Figure 4. Final samples included in the analyses.



Thus, the final sample sizes included in the comparison contained 805 patients in Group A and 264 patients in Group B. The baseline characteristics of neonates included in the two groups are compared in Table 2.

Table 2. Characteristics of neonates included in Groups A and B.

Characteristics	**Group A (n=805)**		**Group B (N=264)**		**P-value**
	n	**%**	**n**	**%**	
Gestational age (mean ± SD)	30.6±0.50		30.7±0.50		<0.01*
GA – 30 weeks	349	43	88	33	<0.01*
GA – 31 weeks	456	57	176	67	
Birth weight (grams) (mean ± SD)	1505±316		1645±335		<0.01*
Male sex (N)	444	55	155	59	0.31
Maternal hypertension [a]	191	24	47	18	0.04*
Maternal diabetes [b]	119	15	33	13	0.36
Any Antenatal steroids	726	90	140	53	<0.01*
Complete course of antenatal steroids	607	84	89	64	<0.01*
Location of birth					
Level III hospital	775	96	0	0.0	N/A
Level 2 hospital	30	4	264	100	
Caesarean birth	506	63	140	53	<0.01*
Apgar at 1 min (median, IQR)	7 (5, 8)		7 (5, 8)		0.70
Apgar at 5 min (median, IQR)	9 (7, 9)		8 (7, 9)		0.38
Apgar <7 at 5 min	130	16	40	15	0.70
Receipt of chest compression or epinephrine	20	3	8	3	0.63
SGA <10 percentile	73	9	12	5	0.02*
SNAP score (median, IQR)[d]			NA		
SNAP score >20[d]			NA		

[a]Maternal hypertension includes gestational hypertension, pre-existing hypertension, Preeclampsia, HELLP, and eclampsia.
[b]Maternal diabetes includes pre-existing diabetes and gestational diabetes.
[c]The information is based on first NICU admission.
[d]SNAP score is not available in BORN data so comparison is not made.
*p<0.05

As it is evident from the table, patients born in Level III centers or those who were transferred to Level III centers within first 2 days of birth were of lower GA (more neonates of 30 weeks GA) and had lower birth weight. The proportion of neonates born to mothers with hypertension during pregnancy, born via caesarean delivery, and small for gestational age (BW <10th centile for GA and sex) were higher in Group A neonates. The proportion of mothers who received any steroid or

complete steroid was higher in Group A neonates. There was no difference between groups in median Apgar scores, sex, and the proportion of neonates born to mothers with diabetes. Severity of illness data were not available for neonates admitted to BORN centers (Group B).

The results of resource utilization in the form of intravenous support and respiratory support between groups are compared in Table 3. Definition of each item is available in the CNN Manual available at http://www.canadianneonatalnetwork.org/Portal/LinkClick.aspx?fileticket=krvGeUTtLck%3d&tabid=69

Table 3. Comparison of data on resource utilization among patients in two groups.

Characteristics	**Group A (n=805)**	**Group B (n=264)**	**P-value**
	n (%)	**n (%)**	
Intravenous support – defined as presence of UV, PIV, PICC	802 (100)	237 (90)	<0.01*
UVC	329 (41)	128 (49)	0.03*
PIV	724 (90)	212 (80)	<0.01*
PICC	232 (29)	40 (15)	<0.01*
Parenteral nutrition (TPN)	772 (96)	188 (71)	<0.01*
CPAP at any time	615 (76)	139 (53)	<0.01*
Oxygen at any time	441 (55)	112 (42)	<0.01*
Oxygen duration (median, IQR)[a]	1 (0, 3)	1 (1, 3)	<0.01*
Invasive ventilation (IPPV+HFV)	193 (24)	68 (26)	0.56
Duration of invasive ventilation (median, IQR)[b]	0 (0, 1)	1 (0.5, 2)	<0.01*
Non-invasive ventilation	261 (32)	145 (55)	<0.01*
Duration of non-invasive ventilation (median, IQR)[c]	0 (0, 2)	1.5 (1, 3)	<0.01*

The missing values were included in the percentage calculation.
[a]Missing data for oxygen duration in group B is high of 54.8%; results should be interpreted with caution.
[b]Missing data for duration of invasive ventilation in group B is high of 72.0%, and results should be interpreted with caution.
[c]Missing data for duration of non -invasive ventilation in group B is high of 39.8%, and results should be interpreted with caution.
Data on gavage feeding is not available in CNN data.
* $p<0.05$

The number of patients that had missing data in the BORN system is highlighted below Table 3.

Comparison of outcomes between groups is reported in Table 4.

Table 4. Neonatal outcomes: univariable comparison.

Outcome	Group A (n=805)		Group B (n=264)		P-value
	n	%	n	%	
Mortality	18	2.2	0	0.0	0.01*
Severe intraventricular hemorrhage (grade 3 or 4) or periventricular leukomalacia	23	2.9	<6	1.1	0.17
Chronic lung disease defined as oxygen requirement at 36 weeks corrected gestational age	27	3.4	NA	NA	NA
Nosocomial sepsis defined as isolation of bacterial/viral/fungal organism (blood or cerebrospinal fluid) after 3 days of age	25	3.1	NA	NA	NA
Persistent pulmonary hypertension	18	2.2	NA	NA	NA
Patent ductus arteriosus requiring surgical ligation	<6	0.1	0	0.0	1
Air leak (pneumothorax/pneumomediastinum)	27	3.4	0	0.0	<0.01*
Necrotizing enterocolitis	15	1.9	6	2.3	0.68
Intestinal perforation	<6	0.6	NA	NA	NA
Any of the above – composite outcome	110	13.7	12	4.6	<0.01*
Mild intraventricular hemorrhage (grade 1 and 2)[1]	135	16.8	13	4.9	<0.01*

* $p<0.05$
NA = not available in BORN system for major part of the study duration.
[1]Mild IVH is not included in the composite outcome.

Composite outcome was significantly higher in Group A compared to Group B (Crude OR 3.32, 95% CI 1.80, 6.14). In Group A, 30 neonates were transferred from Level IIC hospitals to Level III hospitals within first 48 hours and the composite outcome rate in that group of neonates was 20%.

Logistic regression analyses was conducted adjusting for gestational age (30 and 31 weeks), birth weight (per 50g increase), birth type (CS delivery or not), Apgar score at 5 minutes less than 7, and need for chest compression or epinephrine for composite outcome. Composite outcome was defined as any of the following: mortality, severe intraventricular hemorrhage (grade 3 or 4) or periventricular leukomalacia, chronic lung disease defined as oxygen requirement at 36 weeks corrected gestational age, nosocomial sepsis defined as isolation of bacterial/viral/fungal organism (blood or cerebrospinal fluid) after 3 days of age, patent ductus arteriosus requiring surgical ligation, persistent pulmonary hypertension, air leak (pneumothorax/pneumomediastinum), necrotizing enterocolitis and intestinal perforation. The results are presented in Table 5.

Table 5. Multivariate logistic regression model results for the composite outcome.

Parameter	Estimate	Standard Error	P-value	Adjusted OR	95% Wald Confidence Limits	
Intercept	-3.68	0.63	<0.0001		lower	upper
Group A vs B	**1.42**	**0.37**	**0.00**	**4.13**	**2.00**	**8.52**
Gestational age (30 vs 31)	0.40	0.24	0.10	1.49	0.93	2.40
Birth weight (per 50g increase)	0.00	0.02	0.96	1.00	0.97	1.04
Birth type (CS vs vaginal)	0.40	0.26	0.12	1.50	0.90	2.50
Apgar score at 5 minutes < 7 (yes vs no)	**0.74**	**0.28**	**0.01**	**2.09**	**1.21**	**3.59**
Need for chest compression or epinephrine (Yes vs no)	0.74	0.52	0.15	2.10	0.76	5.82

Two variables were identified as statistically significant after adjustment: 1) Group A had a higher adjusted odds ratio of 4.13 (95% CI 2.00, 8.52); and 2) Apgar score at 5 minutes of <7 had an odds ratio of 2.09 (95% CI 1.21, 3.59).

In order to identify which component of composite outcome was associated with higher odds, we conducted analyses of individual outcomes, which are reported in Table 6.

Table 6. Adjusted odds ratio (OR) and 95% confidence interval (95%CI) for individual outcome.

Outcome	Group A (n=805)		Group B (n=264)		Crude OR (95%CI)	Adjusted OR (95%CI)*
	n	%	n	%		
Mortality	18	2.2	0	0.0	N/A	N/A
Severe intraventricular hemorrhage (grade 3 or 4) or periventricular leukomalacia	23	2.9	<6	1.1	2.56 (0.76, 8.59)	2.75 (0.61, 12.47)
Nosocomial sepsis defined as isolation of bacterial/viral/fungal organism (blood or cerebrospinal fluid) after 3 days of age	25	3.1	N/A	N/A	N/A	N/A
Necrotizing enterocolitis	15	1.9	6	2.3	0.82 (0.31, 2.13)	0.78 (0.28, 2.18)**

*Adjusted for gestational age (30 and 31 weeks), small for gestational age at 10th percentile, Apgar score at 5 minutes less than 7, need for chest compression or epinephrine

**Validity of the model fit is questionable. The LOGISTIC procedure continues in spite of the warning. Results shown are based on the last maximum likelihood iteration.

Group B as reference group.

N/A = Not available in BORN system

Post-hoc analyses:

The finding of differences in antenatal steroid was further evaluated to check the duration of maternal admission and time of birth.

Time difference between maternal hospital admission and time of birth for Level IIc babies

Time difference between (time of birth – time of admission) of mother to hospital	Total	Those who received any antenatal steroid			Those who did not receive any antenatal steroid		
	#	n	Mean (SD)	Median (IQR)	n	Mean (SD)	Median (IQR)
<2 hours	75	30	0.9 (0.6)	0.8 (0.5-1.3)	45	0.7 (0.5)	0.6 (0.3-1.0)
2-4 hours	34	21	3.1 (0.5)	3.2 (2.5-3.5)	13	3.2 (0.6)	3.1 (2.8-3.6)
4-6 hours	21	11	4.9 (0.7)	5.0 (4.3-5.3)	10	4.9 (0.8)	4.9 (4.1-5.7)
6-12 hours	38	17	8.8 (1.8)	8.9 (7.1-10.6)	21	8.9 (1.7)	9.0 (8.1-10.5)
>12 hours	96	61	92.4 (103.9)	62.0 (24.2-125.5)	35	61.6 (91.4)	31.7 (19.8-56.0)
Total	**264**	**140**	**42.4 (81.3)**	**8.4 (2.5, 39.4)**	**124**	**19.9 (54.8)**	**4.6 (0.9-17.2)**

This table identifies that many mothers have missed opportunities for receiving antenatal steroid as >50% of mothers did not give birth within 4 hours of admission to the Level IIc hospitals.

Noteworthy results:

1. Of 1146 potential neonates born at 30 and 31 weeks gestation in the province, we were able to study 1069 (93%) patients after solving linkage issues.
2. Both databases had issues with missing information on some patients regarding where they were admitted from, which appears to be basic information that needs to be collected.
3. Probabilistic linkage was possible overall with >90% records matched and collated.
4. There were marked differences in baseline characteristics between two groups:
    a. A proportionally higher number of neonates were of 30 weeks GA in Group A compared to Group B, and the results were in the opposite direction for neonates of 31 weeks GA.
    b. Birth weight differed by ~150 g with lower birth weight in Group A.
    c. More mothers had hypertension in Group A.
    d. There were marked differences in the rate of antenatal steroids with a significantly lower proportion of mothers receiving any steroids in Group B. Post-hoc analyses of time of admission to hospital to time of birth revealed that >50% delivered >4 hours after admission.
    e. The proportion of neonates who were small for GA was higher in Group A.
    f. Severity of illness data was not available in Group B neonates; thus, admission severity of illness could not be compared.
5. Resource utilization differed between both groups:
    a. There may be data issues in Group B, where 10% of neonates were identified to have no intravenous support. Births at such low GAs are unlikely to survive without nutritional support.
    b. Similar data issues exist for TPN administration.
    c. Approximately 40-50% of neonates required oxygen or CPAP support in Group B, which is higher than expected and has resource implications.
    d. A quarter of neonates in both groups required invasive ventilator support— a finding that is of significance for Group B because it has significant resource implications.
    e. Both duration of invasive and non-invasive ventilation were higher in Group B compared to Group A. The reasons for this finding needs further exploration given those neonates in Group B were of higher GA and BW.
6. Outcomes differed between groups:
    a. Mortality, air leak and composite outcome rates were significantly higher in Group A.
    b. There was no difference in severe brain injury, PDA requiring surgical ligation or necrotizing enterocolitis between groups.
    c. The rate of composite outcome among neonates who were transferred from Level IIc to Level III in the first 48 hours was higher than those who stayed in Level IIc; however, numbers are too small for meaningful comparison.

7. Adjusted comparison between groups:
    a. In the absence of data on severity of illness, proxy measures were used to adjust analyses. This included GA, BW, route of birth, Apgar score <7 at 5 minutes and need for chest compression and epinephrine.
    b. There was significantly higher odds of composite outcome in Group A compared to Group B.
    c. Apgar score <7 at 5 minutes was another variable identified as a significant predictor of outcome.
8. Assessment of individual outcome was possible for few outcomes and indicated that odds of severe brain injury was higher in Group A. A small number of patients with outcomes led to model convergence issues for other outcomes.

Important take away messages

1. Neonates of 30 and 31 weeks GA born and/or transferred to Level III Hospitals had different baseline characteristics compared to those who were kept in Level IIC hospitals.
2. It was possible to combine data from CNN and BORN data collection systems for approximately 80-85% of neonates with probabilistic matching.
3. Antenatal steroid administration was significantly low among mothers whose neonates were cared for in Level IIc units.
4. Rates of composite outcome and individual morbidities of neonates born and/or transferred to Level III hospitals were higher compared to those admitted to Level IIC hospitals. This remained significant after adjustment of available predictors.
5. Data on severity of illness at the time of admission to neonatal units were not available in the BORN data collection system. There is tendency towards low severity of illness (assessed using proxy measures) among neonates admitted in Level IIC.
6. In addition, a large number of neonatal data on resource utilization were missing in the BORN data system.
7. Among neonates admitted to Level IIC,
    a. The proportion of neonates who received chest compression or epinephrine were not significantly
    b. the proportion of neonates who received invasive ventilatory support were similar in both groups
    c. the duration of mechanical ventilation was higher
    d. the proportion who received non-invasive ventilation was higher
    e. the duration of non-invasive ventilation was higher

Recommendations for consideration

1. There needs to be collaborative effort to track outcomes of neonates admitted to Level III and transferred to Level IIc units in Ontario, such that proper comparisons can be made.
2. Strengthening of data collection for severity of illness and resource utilization from Level IIC is needed in order for future comparisons to result in quality improvement activities.
3. Efforts to increase antenatal steroid administration via education, feedback and constant surveillance are needed for preterm births before 34 weeks gestation in Level IIc units.
4. If Level IIc units are going to keep potentially well neonates born at 30 and 31 weeks gestation, then extensive an education package regarding neonatal resuscitation, non-invasive respiratory management, and placement of peripherally inserted central venous catheters needs to be provided to frontline health care workers including physicians.
5. Further follow-up surveillance after strengthening the data collection would be needed to make final recommendations.

Reference List

(1) Chien LY, Whyte R, Aziz K et al. Improved outcome of preterm infants when delivered in tertiary care centers. *Obstet Gynecol* 2001;98:247-52.

(2) Lui K, Abdel-Latif ME, Allgood CL et al. Improved outcomes of extremely premature outborn infants: effects of strategic changes in perinatal and retrieval services. *Pediatrics* 2006;118:2076-83.

Appendices

Appendix 1: List of centers

a. List of IIc hospitals in ON in Group B

Birth hospitals	n	%
Trillium Health Partners - Credit Valley Hospital	22	8.3
Lakeridge Health Corporation - Oshawa	24	9.1
Markham Stouffville Hospital - Markham Site	10	3.8
North Bay Regional Health Centre	<6	0.4
North York General Hospital	34	12.9
Orillia Soldiers' Memorial Hospital	<6	1.5
Rouge Valley Health System - Centenary Site	19	7.2
Royal Victoria Regional Health Centre	17	6.4
Sault Area Hospital	<6	1.1
St. Michael's Hospital	29	11.0
Health Sciences North - Sudbury	7	2.7
The Ottawa Hospital - Civic Campus	38	14.4
Thunder Bay Regional Health Sciences Centre	12	4.6
Toronto East General Hospital	13	4.9
William Osler Health Centre - Brampton Civic	22	8.3
Mackenzie Health	9	3.4
Total	**264**	**100.0**

b. List of IIc hospitals which have early transfer

Birth hospitals	n	%
Trillium Health Partners - Credit Valley Hospital	<6	10.0
Lakeridge Health Corporation - Oshawa	<6	10.0
Markham Stouffville Hospital - Markham Site	<6	3.3
North Bay Regional Health Centre	<6	6.7
North York General Hospital	<6	6.7
St. Michael's Hospital	<6	3.3
The Ottawa Hospital - Civic Campus	<6	13.3
Thunder Bay Regional Health Sciences Centre	<6	3.3
Toronto East General Hospital	<6	3.3
William Osler Health Centre - Brampton Civic	11	36.7
Mackenzie Health	<6	3.3
Total	**30**	**100.0**

c. CNN sites for Group A

CNN sites	n	%
Hamilton Health Sciences Centre	118	14.7
Hospital for Sick Children	14	1.7
Kingston General Hospital	46	5.7
Mount Sinai Hospital	191	23.7
Children's Hospital of Eastern Ontario	103	12.8
St. Joseph Health Centre	109	13.5
Sunnybrook Health Sciences Centre	178	22.1
Windsor Regional Hospital	46	5.7
Total	**805**	**100.0**