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Neonatal Outcomes of Very Low Birth Weight and Very Preterm Neonates: An International Comparison

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Objective To compare rates of a composite outcome of mortality or major morbidity in very-preterm/very low birth weight infants between 8 members of the International Network for Evaluating Outcomes.

Study design We included 58 004 infants born weighing <1500 g at 24^0–31^6 weeks' gestation from databases in Australia/New Zealand, Canada, Israel, Japan, Spain, Sweden, Switzerland, and the United Kingdom. We compared a composite outcome (mortality or any of grade ≥3 peri-intraventricular hemorrhage, periventricular echodensity/echolucency, bronchopulmonary dysplasia, or treated retinopathy of prematurity) between each country and all others by using standardized ratios and pairwise using logistic regression analyses.

Results Despite differences in population coverage, included neonates were similar at baseline. Composite outcome rates varied from 26% to 42%. The overall mortality rate before discharge was 10% (range: 5% [Japan]-17% [Spain]). The standardized ratio (99% CIs) estimates for the composite outcome were significantly greater for Spain 1.09 (1.04-1.14) and the United Kingdom 1.16 (1.11-1.21), lower for Australia/New Zealand 0.93 (0.89-0.97), Japan 0.89 (0.86-0.93), Sweden 0.81 (0.73-0.90), and Switzerland 0.77 (0.69-0.87), and nonsignificant for Canada 1.04 (0.99-1.09) and Israel 1.00 (0.93-1.07). The adjusted odds of the composite outcome varied significantly in pairwise comparisons.

Conclusions We identified marked variations in neonatal outcomes between countries. Further collaboration and exploration is needed to reduce variations in population coverage, data collection, and case definitions. The goal would be to identify care practices and health care organizational factors, which has the potential to improve neonatal outcomes. *(J Pediatr 2016;177:144-52)*.

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Infants born very preterm (<32 weeks' gestation) and very low birth weight (birth weight <1500 g) are at an increased risk of mortality and multiple morbidities.[1] In high-resourced countries, complications of preterm birth are the leading cause of mortality in children younger than 5.[2] The need to continually improve the care of these infants has led to the establishment of national, population-based and academic/open-membership initiatives to benchmark, identify trends,[3-12] and improve neonatal outcomes, with variable success.[4,13-18]

Understanding international variations in outcomes is very important because all countries aim to provide the best possible health care to their residents without significant impact on budget or other initiatives.[19] This idea underpins the premise that medicine is universal and, thus, advances in biomedical research should span borders and yield similar results regardless of the organization of health care. Potential threats to this concept include the role of quality of care, health care organization, and access to health care. Identifying outcome variations in very preterm/very low birth weight infants across countries can provide impetus for identifying areas of improvement for each country. The International Network for Evaluating Outcomes (iNeo) of Neonates is a multinational

iNeo	International Network for Evaluating Outcomes
NEC	Necrotizing enterocolitis
SR	Standardized ratio
UKNC	United Kingdom Neonatal Collaborative

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Funding for iNeo of Neonates has been provided by a Canadian Institutes of Health Research (FRN87518) Chair in Reproductive and Child Health Services and Policy Research (to P.S.). Additional funding is available at www.jpeds.com (**Appendix 2**). The authors declare no conflicts of interest.

Portions of the study were presented at the meeting of the Pediatric Academic Societies, Baltimore, MD, April 30-May 3, 2016.

0022-3476/$ - see front matter.
http://dx.doi.org/10.1016/j.jpeds.2016.04.083

collaboration between 9 high-resource countries, including the Australian and New Zealand Neonatal Network,[3] Canadian Neonatal Network,[9] Israel Neonatal Network,[20] Neonatal Research Network of Japan,[8] Spanish Neonatal Network,[10] Swedish Neonatal Quality Register,[5] Swiss Neonatal Network,[6] and United Kingdom Neonatal Collaborative (UKNC).[11] The structure, design, and overall objectives of iNeo of Neonates have been reported elsewhere.[21] Our objective was to compare rates of a composite outcome of mortality or major morbidity in very preterm/very low birth weight infants between the iNeo of Neonates members.

Methods

This retrospective cohort study included infants born weighing <1500 g at 24^0 to 31^6 weeks' gestation and admitted to the contributing neonatal units of participating countries during 2007-2010 (2008-2010 for the UKNC). We excluded infants born at <24 weeks' gestation because culture, practices, and guidelines[22,23] concerning resuscitation differed at lower gestational ages, which was reflected in widely differing rates of neonates born at <24 weeks' gestation admitted to networks. This was a post-hoc deviation from protocol. We excluded neonates born weighing ≥1500 g/at ≥32 weeks' gestation because some networks did not collect data on such infants, neonates with major congenital anomalies,[24] those admitted after 36 weeks' postmenstrual age, and those who died in the delivery room without receiving resuscitation.

Data on infant characteristics and outcomes for this study were extracted by participating networks from their existing databases according to predetermined definitions.[21] For most networks, data for defined data elements were either collected from patient records by designated abstractors according to network policies and sent to coordinating centers or entered directly into a central online database by the participating neonatal units. UKNC data were obtained from the National Neonatal Research Database managed by the Neonatal Data Analysis Unit, which contains a predefined extract from the Electronic Patient Record used in UK neonatal units regardless of designation and is updated quarterly. All iNeo of Neonates collaborators obtained research ethics approval for their primary data collection. For the purpose of iNeo of Neonates, separate data-sharing agreements were obtained from the Executive Committees of each network and the iNeo of Neonates Coordinating Centre.

Table I presents an overview of the organization of perinatal-neonatal health care services obtained by surveying directors of the databases and publicly available perinatal information from country's vital statistics. There were variations in how health services are organized, especially in the United Kingdom, where neonatal services are organized in a networked basis with infants moving to higher or lower designation units according to clinical need.

Outcomes

We defined our primary composite outcome as mortality (all cause after neonatal unit admission until discharge or transfer) or any of grade ≥3 peri-intraventricular hemorrhage,[25] persistent periventricular echodensity/echolucency; bronchopulmonary dysplasia, defined as infants receiving oxygen at 36 weeks postmenstrual age[26]; or retinopathy of prematurity[27] requiring treatment by laser or cryotherapy. Necrotizing enterocolitis (NEC) was included in the composite outcome in the protocol but was later excluded because data from one of the networks were not available.

Covariate Definitions

Gestational age was determined by the best estimate based on early prenatal ultrasound, last menstrual period, or physical examination of infants at birth, in that order. Prenatal steroid use was defined as any administration before birth, regardless of the time interval. Birth weight z scores were calculated relative to population- and sex-specific birth weight for gestational age references selected by each network as most appropriate for the comparison.

With respect to specific practices, the majority of women in the participating countries (>90%) received prenatal care. Resuscitation and management of infants at each site was according to local unit guidelines. No data were available regarding artificial reproductive technology. None of the neonates included in the study period received injection treatment for retinopathy. The frequency of head ultrasound examination, eye examination, threshold stage of retinopathy used for treatment, and oxygen saturation targets were according to local guidelines and not available for comparison.

Statistical Analyses

Infant characteristics were summarized and compared by the use of either the Pearson χ^2 test or the ANOVA F test for categorical variables and continuous measures, respectively. Standardized ratios (SRs) were computed by use of the "indirect standardization" approach.[28] For each country, the SR was calculated as the observed number of infants with the composite outcome divided by the number of infants expected to develop this outcome, computed as the sum of predicted probabilities from a multivariable logistic regression model, with adjustment for gestational age (linear), birth weight z score (linear and quadratic), multiple birth, sex, antenatal steroids, cesarean delivery, and the interaction between birth weight z score and multiple birth, derived with the use of data from all other countries. SR estimates were displayed graphically to identify countries with outcome rates above and below the average rate of all others at the 99% confidence level. Because the SR estimate is calculated in relation to all other countries combined, it is not directly comparable between contributors.[29]

Using multivariable logistic regression including country-specific fixed effects, we compared the composite outcome for all countries simultaneously (using same variables as mentioned previously except cesarean delivery; variables were selected based on $P < .1$ in univariate analyses). Hosmer-Lemeshow test and c-statistic were used to check model fit. aORs were estimated for all possible pair-wise comparisons. We evaluated statistical significance by