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Late-Onset Sepsis among Extremely Preterm Infants of 24–28 Weeks Gestation: An International Comparison in 10 High-Income Countries

Gil Klinger[a, b] Brian Reichman[b, c] Mikael Norman[d, e] Satoshi Kusuda[f] Malcolm Battin[g] Kjell Helenius[h, i] Tetsuya Isayama[j] Kei Lui[k] Mark Adams[l] Maximo Vento[m] Stellan Hakansson[n] Marc Beltempo[o] Chiara Poggi[p] Laura San Feliciano[q] Liisa Lehtonen[h, i] Dirk Bassler[k] Junmin Yang[r] Prakesh S. Shah[r]

on behalf of the International Network for Evaluating Outcomes of Neonates (iNeo)

[a]Department of Neonatal Intensive Care, Schneider Children's Medical Center of Israel, Petah Tikva, Israel; [b]School of Medicine, Tel Aviv University, Tel Aviv, Israel; [c]Women and Children's Health Research Unit, Gertner Institute, Chaim Sheba Medical Center, Tel Hashomer, Israel; [d]Karolinska Institutet, Department of Clinical Science, Intervention, and Technology, Stockholm, Sweden; [e]Department of Neonatal Medicine, Karolinska University Hospital, Stockholm, Sweden; [f]Department of Pediatrics, Kyorin University, Tokyo, Japan; [g]Newborn Service, Te Whatu Ora, Te Toka Tumai, Auckland, New Zealand; [h]Department of Paediatrics and Adolescent Medicine, Turku University Hospital, Turku, Finland; [i]Department of Medicine, University of Turku, Turku, Finland; [j]Division of Neonatology, National Center for Child Health and Development, Tokyo, Japan; [k]Department of Newborn Care, Royal Hospital for Women and School of Women's and Children's Health, Faculty of Medicine, University of New South Wales, Sydney, NSW, Australia; [l]Newborn Research, Department of Neonatology, University of Zurich and University Hospital Zurich, Zurich, Switzerland; [m]Instituto de Investigación Sanitaria (Health Research Institute) La Fe Valencia, Valencia, Spain; [n]Department of Clinical Sciences/Pediatrics, Umeå University, Umeå, Sweden; [o]Department of Pediatrics, McGill University, Montreal, QC, Canada; [p]Neonatal Intensive Care Unit, Department of Mother and Child Care, Careggi University Hospital, Florence, Italy; [q]Unidad de Neonatología, Hospital Universitario de Salamanca, Salamanca, Spain; [r]Department of Pediatrics, Mount Sinai Hospital and University of Toronto, Toronto, ON, Canada

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Abstract
Introduction: Despite advances in neonatal care, late-onset sepsis remains an important cause of preventable morbidity and mortality. Neonatal late-onset sepsis rates have decreased in some countries, while in others they have not. Our

karger@karger.com
www.karger.com/neo

Correspondence to:
Prakesh S. Shah, prakeshkumar.shah@sinaihealth.ca

objective was to compare trends in late-onset sepsis rates in 9 population-based networks from 10 countries and to assess the associated mortality within 7 days of late-onset sepsis. ***Methods:*** We performed a retrospective population-based cohort study. Infants born at 24–28 weeks' gestation between 2007 and 2019 were eligible for inclusion. Late-onset sepsis was defined as a positive blood or cerebrospinal fluid culture. Late-onset sepsis rates were calculated for 3 epochs (2007–11, 2012–15, and 2016–19). Adjusted risk ratios (aRRs) for late-onset sepsis were calculated for each network. ***Results:*** Of a total of 82,850 infants, 16,914 (20.4%) had late-onset sepsis, with Japan having the lowest rate (7.1%) and Spain the highest (44.6%). Late-onset sepsis rates decreased in most networks and remained unchanged in a few. Israel, Sweden, and Finland showed the largest decrease in late-onset sepsis rates. The aRRs for late-onset sepsis showed wide variations between networks. The rate of mortality temporally related to late-onset sepsis was 10.9%. The adjusted mean length of stay for infants with late-onset sepsis was increased by 5–18 days compared to infants with no late-onset sepsis. ***Conclusions:*** One in 5 neonates of 24–28 weeks' gestation develops late-onset sepsis. Wide variability in late-onset sepsis rates exists between networks with most networks exhibiting improvement. Late-onset sepsis was associated with increased mortality and length of stay.

Introduction

Neonatal late-onset sepsis remains an important cause of neonatal morbidity and mortality [1, 2] and is associated with adverse neurodevelopmental outcomes [3]. The rate of neonatal late-onset sepsis is inversely related to gestational age (GA) and birth weight (BW) [4, 5] and varies between countries [6–8]. For extremely preterm (EPT) or extremely low birth weight infants, rates range between 8% and 38% [7, 9–15], and for very low birth weight (VLBW) infants rates range from 7.4% to 30% [2, 6, 14–21].

Many countries have reported a decrease in late-onset sepsis rates among VLBW or EPT infants [10, 12, 14, 16, 18, 22–24], while others have not [2, 13]. Factors that may influence change in late-onset sepsis rates include how it is defined, baseline rate, and implementation of quality improvement programs.

It is unclear whether the reduction in late-onset sepsis rates has been translated to decreased mortality. This issue is compounded by the fact that changes in mortality directly related to late-onset sepsis are difficult to quantify because infants who develop late-onset sepsis may have comorbidities increasing mortality risk. Greenberg et al. [10] reported that a decreased late-onset sepsis rate was not accompanied by decreased mortality. In contrast, Hornik et al. [2] reported a decrease in mortality related to late-onset sepsis, compared to previous cohorts.

The International Network for Evaluating Outcomes of Neonates (iNeo) has reported large variations in the survival of VLBW infants [25] as well as temporal improvements in mortality rates [26]. The present study's aim was to assess temporal trends of late-onset sepsis in neonates of 24–28 weeks' gestation and to evaluate late-onset sepsis-associated mortality.

Methods

We performed a retrospective cohort study of preterm infants included in the iNeo database to evaluate temporal trends of late-onset sepsis and the effect of late-onset sepsis on mortality and length of stay. The study was approved by the Research Ethics Board of Mount Sinai Hospital, Toronto, and by the iNeo collaboration directors. The STROBE methodology (online suppl. checklist appended; for all online suppl. material, see https://doi.org/10.1159/000539245) was followed for all available data [27].

International Network for Evaluating Outcomes of Neonates

The iNeo data set contains deidentified data for neonates admitted to 10 independent networks or registries. The present study included data from 9 of the networks, representing 10 countries or regions: Australian and New Zealand Neonatal Network (ANZNN), Canadian Neonatal Network (CNN), Finnish Medical Birth Register (FinMBR), Israel Neonatal Network (INN), Neonatal Research Network Japan (NRNJ), Spanish Neonatal Network (SEN1500), Swedish Neonatal Quality Register (SNQ), Swiss Neonatal Network (SNN), and Tuscany Neonatal Network (Tuscan NN). Six networks cover the entire population (CNN, ANZNN, INN, SNQ, FMBR, and SNN), 2 networks cover 50–60% of the population (NRNJ and SEN1500), and one network (Tuscan NN) is regional. Comparative information on the networks participating in the iNeo collaboration has previously been published [28].

Population

The study cohort included neonates of 24–28 weeks' gestation admitted to a neonatal intensive care unit (NICU) between January 1, 2007, and December 31, 2019. Infants who died prior to 4 days of age, who had major congenital malformations, who had necrotizing enterocolitis (NEC stage 2 or 3), or infants with missing data were excluded.

Definitions

Late-onset sepsis was defined as a positive blood or cerebrospinal fluid culture for bacterial or fungal pathogens in infants suspected of sepsis. A positive blood culture within 7 days of a previous positive blood culture and without antibiotic discontinuation was considered the same episode. Most

networks defined late-onset sepsis as occurring >3 days after birth; however, two networks used different cutoff ages: the Japanese network used >7 days and the Australian-New Zealand network used >2 days as the cutoff. All late-onset sepsis episodes were included in the study. Data on pathogens were not routinely collected by networks. Overall mortality until discharge included mortality occurring >7 days after delivery as immediate mortality in the first 7 days of life was most commonly due to extreme prematurity, intraventricular hemorrhage, and refractory hypoxemic respiratory failure. Mortality temporally related to late-onset sepsis was defined as death within 7 days of onset of a sepsis episode. Length of stay was defined as admission day to discharge day or transfer to a level 2 facility or to death. Bronchopulmonary dysplasia (BPD) was defined as supplemental oxygen therapy or respiratory support at 36 weeks' postmenstrual age or at discharge.

Statistics

Baseline characteristics were reported in the form of frequency (percentage) or mean (standard deviation) values. Late-onset sepsis rates across networks were stratified by GA in weeks. For pairwise comparisons of late-onset sepsis between networks, general linear regression analysis with Poisson distribution was applied and adjusted risk ratios (aRRs) with 95% confidence intervals (CIs) were estimated adjusting for GA, gender, multiple births, and BW z-score (calculated using country-specific charts used by individual networks for GA and sex). BPD, mortality, and length of stay for each network were compared for late-onset sepsis versus no late-onset sepsis groups after adjusting for GA, gender, multiple births, and BW z-score.

The study population was divided into three birth epochs (2007–11, 2012–15, and 2016–19), and the late-onset sepsis rates for each epoch across networks were determined. To have an effective representation of the current state, we calculated standardized ratios (SRs) for late-onset sepsis for the 2016–19 epoch using the "indirect standardization" approach [29]. The expected numbers of neonates with outcomes for each individual network were calculated from the multivariable logistic regression model (adjusting for GA, gender, multiple births, and BW z-score) constructed on the rest of the data set. SR estimates and the 95% CI for each individual country were displayed graphically for all networks in an SR plot. All analyses were conducted using SAS 9.4 (SAS Institute Inc., Cary, NC, USA) with a two-sided significance level of 0.05. SR plot was conducted by R (version 4.1.1).

Results

A total of 97,982 infants of 24–28 weeks' GA were identified. Excluded were 3,703 infants with major congenital malformations, 3,690 infants who died prior to 4 days of age, 6,132 infants with NEC, and 1,607 infants with missing data, resulting in a final study cohort of 82,850 infants. Table 1 shows the characteristics of the study population by individual networks. Comparison of mean BW by epoch for all networks did not show any significant difference. Late-onset sepsis rates by GA for each network are presented in Table 2 and show an inverse relationship to GA. In infants of 24, 25, 26, 27, and 28 weeks' GA, the late-onset sepsis rates were 31.8%, 28.4%, 22.9%, 17.5%, and 12.6%, respectively. Across all GAs, Japan consistently exhibited the lowest late-onset sepsis rates compared to all other networks. This lower rate was not attributable to differences in the definition of sepsis as it persisted even when combining both early-onset and late-onset sepsis rates (10.5%) for the Japanese network. Spain, Italy (Tuscany), and Israel had higher rates of late-onset sepsis compared to all other countries. Among the study cohort, 16,914 infants (20.4%) had at least one late-onset sepsis episode and 2,210 (4.5% of the total with data) infants had multiple late-onset sepsis episodes. Pairwise comparisons of the aRRs for late-onset sepsis between the iNeo networks are shown in Figure 1. Japan had significantly lower aRRs compared to all other networks (range 0.14–0.41), while Spain had higher aRRs compared to all other networks (range 1.56–6.92).

The mean rates of late-onset sepsis for the iNeo networks over three time epochs (2006–11, 2012–15, and 2016–19) are shown in Figure 2. For the entire iNeo network, late-onset sepsis rates decreased from 24.6% to 17.7% over the study period. Most networks observed a decrease in late-onset sepsis rates with the Israel, Swedish, and Finnish networks experiencing greater decreases. Conversely, late-onset sepsis rates remained stable in the Japanese network at very low levels and in the Tuscany network at a high level. Figure 3 presents SRs (99% CI) for late-onset sepsis for each network compared to all others combined during the last epoch (2016–2019). The Spain and Tuscany networks had significantly higher SRs, while the Japanese, Finnish, and Australian-New Zealand networks had significantly lower SRs than all other networks.

Late-onset sepsis rates and aRRs for selected outcomes by the iNeo networks are presented in Table 3. Mortality, temporally associated with late-onset sepsis, was observed in 10.9% of the infants (865/7,962 infants; data from 6 networks with available data) and varied from 5.9% to 16.3%. In the entire cohort, the overall mortality rate to discharge was higher for infants with late-onset sepsis compared to those without (aRR 1.51; 95% CI, 1.44–1.59). The aRR for BPD was significantly higher in infants with late-onset sepsis compared to those without across all networks (aRRs ranging from 1.14 to 1.79). The adjusted mean NICU length of stay among infants with versus without late-onset sepsis was increased in the iNeo networks by 5–18 days.

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Table 1. Baseline characteristics of the study populations of iNeo networks

	ANZNN	CNN	FinMBR	INN	NRNJ	SEN1500	SNQ	SNN	Tuscan NN	All networks
Data included, years	2007–19	2007–19	2010–19	2007–19	2007–19	2007–19	2007–19	2007–19	2009–19	–
Participating units, *n*	29	32	5	24	234	8	11	86	4	433
Total included in database, *n*	19,266	19,678	1,596	7,573	25,391	14,236	5,147	4,005	1,090	97,982
Major congenital anomalies, *n* (%)	697 (3.62)	884 (4.49)	57 (25.91)	159 (2.95)	1,183 (4.87)	526 (4.22)	101 (1.96)	77 (1.92)	19 (1.74)	3,703 (4.04)
Death in first 3 days, *n* (%)	634 (3.41)	620 (3.30)	60 (3.90)	550 (7.42)	374 (1.54)	961 (7.01)	210 (4.16)	190 (4.84)	91 (8.50)	3,690 (3.91)
NEC, *n* (%)	1,165 (6.52)	1,455 (8.04)	122 (8.43)	647 (9.43)	581 (2.54)	1,504 (11.80)	410 (8.48)	195 (5.22)	53 (5.45)	6,132 (6.85)
Missing data, *n* (%)	24 (0.14)	318 (1.90)	1 (0.07)	90 (1.45)	953 (4.10)	118 (1.05)	5 (0.11)	56 (1.58)	42 (4.53)	1,607 (1.90)
Study population, *n*	**16,746**	**16,401**	**1,356**	**6,127**	**22,300**	**11,127**	**4,421**	**3,487**	**885**	**82,850**
Antenatal steroids, *n* (%)	15,192 (91.6)	14,283 (89.2)	1,293 (96.1)	4,976 (81.2)	13,475 (61.3)	8,721 (87.6)	3,759 (90.3)	3,190 (92.3)	796 (90.2)	65,685 (81.6)
Cesarean birth, *n* (%)	10,091 (60.5)	9,846 (60.4)	808 (65.9)	4,337 (70.8)	17,559 (79.0)	7,041 (63.3)	3,019 (68.7)	2,823 (81)	591 (66.8)	56,115 (68.1)
Multiple births, *n* (%)	4,391 (26.2)	4,414 (26.9)	355 (26.2)	2,278 (37.2)	4,357 (19.5)	3,903 (35.1)	1,142 (25.8)	1,009 (28.9)	269 (30.5)	22,118 (26.7)
Mean GA, weeks (SD)	26.5 (1.3)	26.4 (1.3)	26.6 (1.3)	26.6 (1.3)	26.3 (1.4)	26.6 (1.3)	26.4 (1.4)	26.5 (1.3)	26.5 (1.4)	26.4 (1.4)
Median GA (IQR) in weeks	27 (25,28)	27 (25,28)	27 (26, 28)	27 (26, 28)	26 (25, 28)	27 (26, 28)	27 (25, 28)	27 (26, 28)	27 (25, 28)	27 (25, 28)
Mean BW (SD)	953 (237)	954 (248)	954 (247)	931 (217)	866 (227)	935 (251)	934 (247)	906 (234)	906 (239)	922 (241)
Median BW (IQR) in grams	940 (777, 1,120)	940 (770, 1,120)	930 (765, 1,140)	930 (760, 1,098)	856 (699, 1,029)	925 (765, 1,096)	920 (751, 1,110)	900 (730, 1,060)	880 (723, 1,070)	910 (748, 1,090)
ELBW (<1,000g), *n* (%)	9,875 (59.0)	9,637 (58.8)	765 (56.4)	3,732 (60.9)	15,985 (71.7)	6,840 (61.5)	1,617 (61.8)	2,310 (66.8)	572 (64.6)	51,354 (63.4)
Small for GA, *n* (%)	1,489 (8.9)	1,337 (8.2)	137 (10.1)	508 (8.3)	3,025 (13.6)	1,061 (9.5)	1,008 (22.8)	361 (10.4)	70 (7.9)	8,996 (10.9)

ANZNN, Australian and New Zealand Neonatal Network; CNN, Canadian Neonatal Network; FinMBR, Finnish Medical Birth Register; INN, Israel Neonatal Network; NRJ, Neonatal Research Network Japan; SEN1500, Spanish Neonatal Network; SNQ, Swedish Neonatal Quality Register; SNN, Swiss Neonatal Network; Tuscan NN, Tuscany Neonatal Network; NEC, necrotizing enterocolitis; ELBW, extremely low birth weight. The bold values indicate the final study cohort.

Discussion

In this multicenter, multicountry cohort study, one in 5 neonates of 24–28 weeks' GA developed late-onset sepsis. Moreover, a significant variation in late-onset sepsis rates across iNeo networks was identified. Most networks showed a trend toward a decrease in late-onset sepsis rates, whereas in a few countries the rate remained stable. Late-onset sepsis was temporally associated with mortality in 1 of 9 infants.

The vision of the iNeo collaboration is to improve patient-oriented outcomes for preterm infants. This goal can be achieved by comparing outcomes at the country or regional level [25, 26]. We identified a significant variation in the rates of late-onset sepsis between countries, serving as an incentive to evaluate risk factors, epidemiology, and preventative aspects. Countries such as Japan with significantly lower aRRs compared to other countries and countries that have achieved the largest decrease in late-onset sepsis provide an opportunity to learn effective strategies. Three countries, Finland, Sweden, and Israel, showed a large decrease in late-onset sepsis rates. In Finland and Sweden, we speculate that an important change over time was a shift in NICU architecture from rooms that housed multiple infants to single family-oriented rooms. Lehtonen et al. [30] showed that neonates from units with versus without infant-parent rooms had lower odds of mortality and sepsis (adjusted OR 0.80; 95% CI, 0.66–0.97). In this study, Finland and Sweden had the highest rates of NICUs with single rooms. The implementation of a family-centered setting has been shown by Pricoco et al. [31] to significantly decrease the rate of late-onset sepsis among VLBW infants from 10.7% to 2.5% (p = 0.005). Quality improvement programs in Israel and Sweden most likely led to the observed decrease in late-onset sepsis rates in these countries. In Israel, a national quality improvement program to decrease late-onset sepsis rates was implemented. The program monitored the rate and targeted multiple factors related to late-onset sepsis, leading to a sustained reduction in rates [23].

Considerable variation in late-onset sepsis rates was shown between iNeo networks. In some networks, rates remained unchanged. The Japanese network consistently displayed the lowest and most stable rates among iNeo networks. The very low baseline rate accompanied by the high survival rate in Japan likely explains the difficulty in achieving further decreases. Networks with an initially high late-onset sepsis rate have the most potential for improvement. This was demonstrated in the Israel network that achieved a large reduction in rate throughout the study period.

Variation in length of stay between iNeo networks of up to 3 weeks was shown by Seaton et al. [32]. This variation is partly related to neonatal morbidities such as BPD [33] and

Table 2. Percentage of late-onset sepsis by gestational age for participating networks in 2007–2019

GA	ANZNN	CNN	FinMBR	INN	NRNJ	SEN1500	SNQ	SNN	Tuscan NN	All networks
24 wks, *n*/*N* (%)	623/1,748 (35.6)	684/1,779 (38.4)	44/142 (31.0)	247/569 (43.4)	414/3,127 (13.2)	594/993 (59.8)	208/523 (39.8)	83/325 (25.5)	63/115 (54.8)	**2,960/9,321 (31.8)**
25 wks, *n*/*N* (%)	706/2,472 (28.6)	849/2,726 (31.1)	48/176 (27.3)	337/848 (39.7)	321/3,670 (8.8)	979/1,639 (59.7)	224/678 (33.0)	135/500 (27.0)	43/117 (36.8)	**3,642/12,826 (28.4)**
26 wks, *n*/*N* (%)	672/3,357 (20.0)	745/3,253 (22.9)	52/253 (20.6)	370/1,213 (30.5)	344/4,453 (7.7)	1,103/2,164 (51.0)	270/882 (30.6)	162/740 (21.9)	53/161 (32.9)	**3,771/16,476 (22.9)**
27 wks, *n*/*N* (%)	571/4,002 (14.3)	681/3,857 (17.7)	41/354 (11.6)	368/1,554 (23.7)	270/5,143 (5.3)	1,172/2,835 (41.3)	203/1,037 (19.6)	114/853 (13.4)	45/221 (20.4)	**3,465/19,856 (17.5)**
28 wks, *n*/*N* (%)	450/5,167 (8.7)	572/4,786 (12.0)	61/431 (14.2)	359/1,943 (18.5)	229/5,907 (3.9)	1,112/3,496 (31.8)	174/1,301 (13.4)	71/1,069 (6.6)	48/271 (17.7)	**3,076/24,371 (12.6)**
All GA, *n*/*N* (%)	3,022/16,746 (18.1)	3,531/16,401 (21.5)	246/1,356 (18.1)	1,681/6,127 (27.4)	1,578/22,300 (7.1)	4,960/11,127 (44.6)	1,079/4,421 (24.4)	565/3,487 (16.2)	252/885 (28.5)	**16,914/82,850 (20.4)**

ANZNN, Australian and New Zealand Neonatal Network; CNN, Canadian Neonatal Network; FinMBR, Finnish Medical Birth Register; INN, Israel Neonatal Network; NRNJ, Neonatal Research Network Japan; SEN1500, Spanish Neonatal Network; SNQ, Swedish Neonatal Quality Register; SNN, Swiss Neonatal Network; Tuscan NN, Tuscany Neonatal Network. The bold values indicate the final study cohort.

	Australia New Zealand ANZNN	Canada CNN	Finland FinMBR	Israel INN	Japan NRNJ	Sweden SNQ	Switzerland SNN	Spain SEN1500	Tuscany TuscanNN
ANZNN	1.00	**0.86** (0.83,0.9)	1.00 (0.89, 1.12)	**0.66** (0.63.0.69)	**2.80** (2.65, 2.97)	**0.82** (0.77, 0.87)	**1.15** (1.06, 1.24)	**0.40** (0.39, 0.52)	**0.63** (0.57, 0.70)
CNN	**1.16** (1.11, 1.21)	1.00	**1.16** (1.03, 1.30)	**0.76** (0.73, 0.80)	**3.25** (3.07, 3.43)	0.95 (0.90. 1.01)	**1.33** (1.23, 1.44)	**0.47** (0.45, 0.49)	**0.73** (0.66, 0.81)
FinMBR	1.00 (0.89, 1.13)	**0.87** (0.77, 0.97)	1.00	**0.66** (0.59, 0.74)	**2.81** (2.49, 3.17)	**0.82** (0.73, 0.93)	**1.15** (1.01, 1.31)	**0.41** (0.36, 0.45)	**0.63** (0.55, 0.74)
INN	**1.52** (1.44, 1.60)	**1.31** (1.25, 1.38)	**1.51** (1.34, 1.71)	1.00	**4.25** (3.99, 4.52)	**1.24** (1.17, 1.33)	**1.74** (1.60, 1.89)	**0.61** (0.59, 0.64)	0.96 (0.86, 1.07)
NRNJ	**0.36** (0.34, 0.38)	**0.31** (0.29, 0.33)	**0.36** (0.32, 0.40)	**0.24** (0.22, 0.25)	1.00	**0.29** (0.27, 0.32)	**0.41** (0.38, 0.45)	**0.14** (0.14, 0.15)	**0.23** (0.20, 0.25)
SNQ	**1.22** (1.15, 1.30)	1.05 (0.99, 1.12)	**1.22** (1.08, 1.38)	**0.80** (0.75, 0.86)	**3.41** (3.18, 3.65)	1.00	**1.40** (1.28, 1.53)	**0.49** (0.47, 0.52)	**0.77** (0.69, 0.86)
SNN	**0.87** (0.81, 0.95)	**0.75** (0.70, 0.82)	**0.87** (0.76, 0.99)	**0.58** (0.53, 0.63)	**2.44** (2.24, 2.66)	**0.72** (0.65, 0.78)	1.00	**0.35** (0.33, 0.38)	**0.55** (0.49, 0.62)
SEN1500	**2.48** (2.38, 2.57)	**2.13** (2.06, 2.21)	**2.47** (2.20, 2.76)	**1.63** (1.56, 1.70)	**6.92** (6.57, 7.29)	**2.03** (1.92, 2.14)	**2.83** (2.63, 3.06)	1.00	**1.56** (1.41, 1.73)
TuscanNN	**1.59** (1.43, 1.76)	**1.37** (1.23, 1.52)	**1.58** (1.36, 1.83)	1.04 (0.94, 1.16)	**4.44** (3.98, 4.96)	**1.30** (1.16, 1.45)	**1.82** (1.60, 2.06)	**0.64** (0.58, 0.71)	1.00

Fig. 1. Pairwise comparison of late-onset sepsis between iNeo networks. The table compares pairs of countries. Countries on the left side of the table are compared to countries listed above by aRRs (adjusted for GA, gender, multiple births, and BW z-score). Dark gray indicates the corresponding country in the row has better results than the corresponding country in the column. Light gray indicates vice versa. No color indicates no statistically significant difference. ANZNN, Australian and New Zealand Neonatal Network; CNN, Canadian Neonatal Network; FinMBR, Finnish Medical Birth Register; INN, Israel Neonatal Network; NRNJ, Neonatal Research Network Japan; SEN1500, Spanish Neonatal Network; SNQ, Swedish Neonatal Quality Register; SNN, Swiss Neonatal Network; Tuscan NN, Tuscany Neonatal Network.

sepsis. Our study revealed a substantial, network-dependent decrease in adjusted hospital length of stay for infants with late-onset sepsis compared to those without. This difference varied between networks from 5 to 18 days, representing a large potentially reducible healthcare burden.

We observed a marked variation in late-onset sepsis-associated mortality between networks. The network with the highest late-onset sepsis rate had the lowest aRR for mortality (Spain), and the network with the lowest late-onset sepsis rate (Japan) had the highest sepsis-associated mortality rate. Potential explanations for this contradictory finding could lie in the method of detection of sepsis (one vs. two culture methods), the inclusion or exclusion of coagulase-negative staphylococcal sepsis in late-onset sepsis, or the overall mortality within networks. Japan had overall the lowest mortality, whereas Spain had the highest, which may be reflected in the higher mortality in Spain even among non-late-onset sepsis neonates giving lower odds of sepsis-associated mortality. Flannery et al. [5] reported that infants with late-onset sepsis had lower survival (78.2% vs. 94.9%; aRR 0.89; 95% CI, 0.87–0.90). However, determining whether mortality in an infant is related or not to late-onset sepsis is challenging. In some infants, late-onset sepsis may be the cause of death, while in others death may be due to preexisting comorbidities [34]. Although NEC is commonly diagnosed by Bell's criteria, there are differences in definitions between networks [35]. Infants with NEC were excluded because death occurring in proximity to NEC is likely related to NEC, and including the infants would have led to the overestimation of late-onset

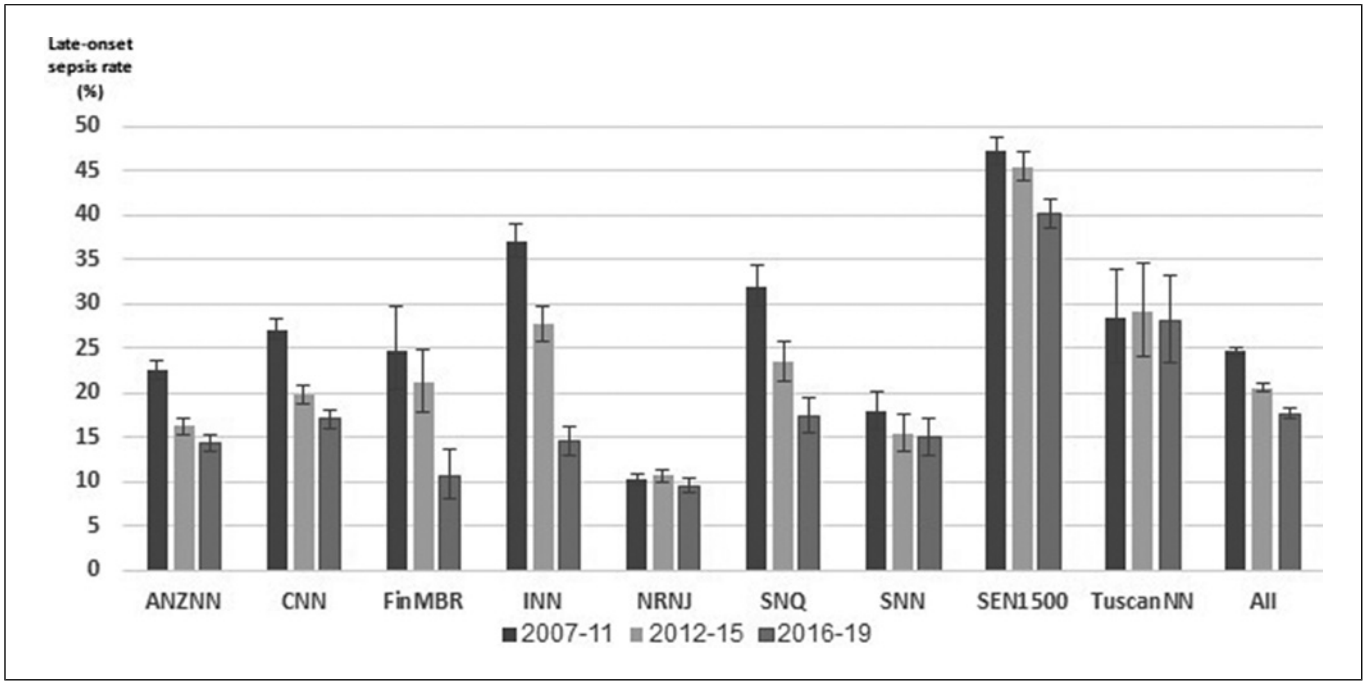

Fig. 2. Late-onset sepsis rates over 3 epochs by iNeo networks. Mean late-onset sepsis rates for each network are shown for 3 time epochs with standard deviations. ANZNN, Australian and New Zealand Neonatal Network; CNN, Canadian Neonatal Network; FinMBR, Finnish Medical Birth Register; INN, Israel Neonatal Network; NRNJ, Neonatal Research Network Japan; SEN1500, Spanish Neonatal Network; SNQ, Swedish Neonatal Quality Register; SNN, Swiss Neonatal Network; Tuscan NN, Tuscany Neonatal Network.

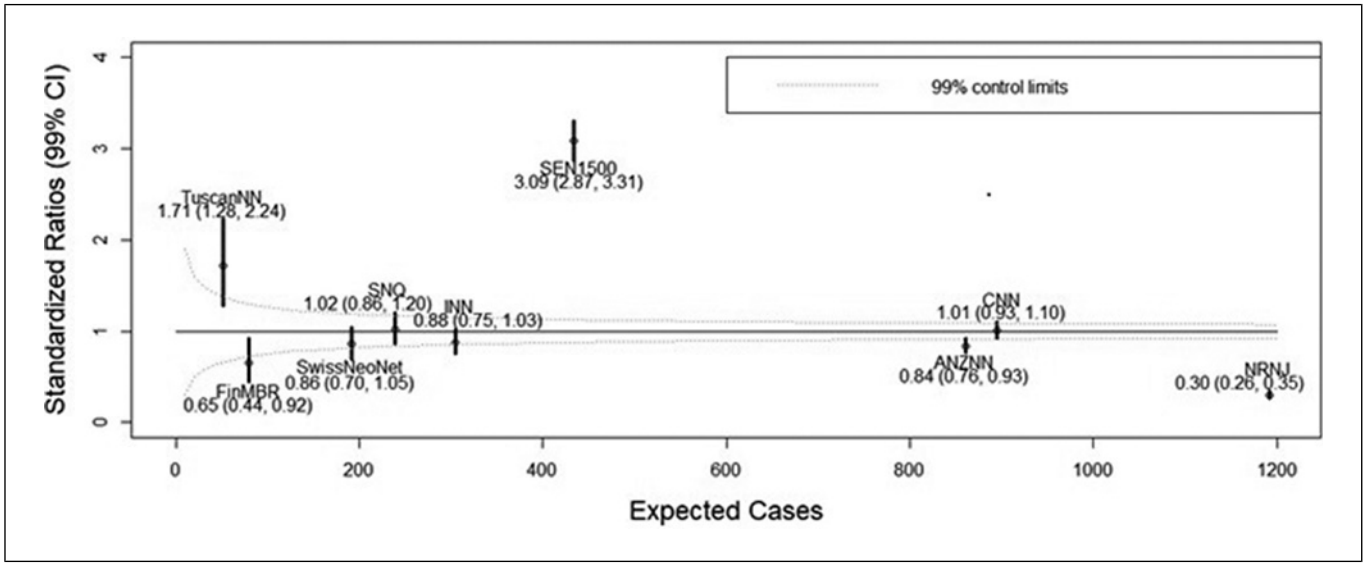

Fig. 3. Standardized ratios (SR) comparing the Late-onset sepsis of each network to all other networks combined. Vertical bars are the estimated 99% confidence intervals of the SR. The dotted curves represent the 99% confidence limits expected under the null hypothesis of similar outcome rates (SR = 1). ANZNN, Australia and New Zealand Neonatal Network; CNN, Canadian Neonatal Network; FinMBR, Finland Medical Birth Register; INN, Israel Neonatal Network; NRNJ, Neonatal Research Network of Japan; SEN1500, Spanish Neonatal Network; SNQ, Swedish Neonatal Quality register; SwissNeoNet, Swiss Neonatal Network; TuscanNN, Tuscany Neonatal Network.

Table 3. Outcomes of EPT infants of the iNeo networks by each network

		ANZNN	CNN	FinMBR	INN	NRNJ	SEN1500	SNQ	SNN	Tuscan NN	All networks
Study population		16,746	16,401	1,356	6,127	22,300	11,127	4,421	3,487	885	82,850
Late-onset sepsis, *n* (%)		3,022 (18.1)	3,531 (21.5)	246 (18.1)	1,681 (27.4)	1,578 (7.1)	4,960 (44.6)	1,079 (24.4)	566 (16.2)	252 (28.5)	16,914 (20.4)
Death within 7 days of late-onset sepsis episode, *n/N* (%)		242/ 2,432 (9.9)	313/ 2,836 (11.0)	NA	192/ 1,292 (14.9)	NA	NA	51/ 858 (5.9)	52/ 452 (11.5)	15/92 (16.3)	865/ 7,962 (10.9)
Mortality up to discharge, *n* (%)	Late-onset sepsis – yes	346 (11.4)	418 (11.8)	13 (5.3)	315 (18.7)	753 (15.2)	200 (12.7)	66 (6.1)	85 (15.0)	43 (17.1)	2,239 (13.2)
	Late-onset sepsis – no	849 (6.2)	811 (6.3)	52 (4.7)	460 (10.3)	998 (16.2)	607 (2.9)	182 (5.4)	192 (6.6)	51 (8.1)	4,202 (6.4)
	aRR (95% CI)	1.15 (1.02, 1.30)	1.20 (1.07, 1.34)	0.85 (0.46, 1.56)	1.20 (1.06, 1.36)	0.68 (0.63, 0.74)	2.84 (2.42, 3.33)	0.75 (0.59, 0.99)	1.46 (1.16, 1.85)	1.32 (0.92, 1.91)	1.51 (1.44, 1.59)
BPD, *n* (%)	Late-onset sepsis – yes	1,717 (63.3)	1,759 (55.5)	95 (42.4)	456 (32.4)	1,506 (36.5)	728 (52.2)	476 (46.0)	212 (43.4)	71 (33.5)	7,020 (47.5)
	Late-onset sepsis – no	5,164 (40.0)	4,267 (35.4)	230 (23.1)	845 (21.1)	773 (15.3)	7,044 (35.6)	941 (29.6)	484 (17.7)	93 (16.0)	19,841 (32.4)
	aRR (95% CI)	1.20 (1.16, 1.25)	1.23 (1.18, 1.28)	1.44 (1.19, 1.73)	1.14 (1.04, 1.25)	1.79 (1.65, 1.94)	1.15 (1.10, 1.22)	1.20 (1.10, 1.31)	1.76 (1.55, 2.00)	1.55 (1.18, 2.04)	1.21 (1.18, 1.23)
NICU days, mean (SD)	Late-onset sepsis – yes	100.1 (44.5)	89.1 (46.1)	84.6 (29.8)	83.3 (44.5)	78.0 (38.7)	124.3 (57.0)	93.8 (37.6)	90.1 (46.6)	93.9 (45.6)	90.8 (46.0)
	Late-onset sepsis – no	83.3 (33.1)	67.6 (39.5)	72.3 (28.7)	72.5 (33.0)	59.3 (32.0)	108.2 (43.6)	79.5 (37.4)	76.8 (33.1)	80.1 (36.2)	84.4 (41.9)
	Adj. mean difference (95% CI)	9.1 (7.8, 10.5)	13.3 (11.8, 14.7)	6.6 (2.7, 10.5)	7.8 (5.7, 9.8)	17.6 (16.2, 18.9)	5.9 (3.8, 8.0)	7.4 (4.9, 9.9)	7.3 (4.1, 10.5)	5.3 (−0.3, 10.9)	NA

ANZNN, Australian and New Zealand Neonatal Network; CNN, Canadian Neonatal Network; FinMBR, Finnish Medical Birth Register; INN, Israel Neonatal Network; NRNJ, Neonatal Research Network Japan; SEN1500, Spanish Neonatal Network; SNQ, Swedish Neonatal Quality Register; SNN, Swiss Neonatal Network; Tuscan NN, Tuscany Neonatal Network; BPD, bronchopulmonary dysplasia; NICU, neonatal intensive care unit; aRR, adjusted relative risk (adjusted for gestational age, gender, multiple births, birth weight, z-score).

sepsis-associated mortality [34]. Due to the difficulty in attribution, there is a paucity of data directly linking mortality to late-onset sepsis among EPT infants. The temporal relationship between late-onset sepsis and mortality in our study suggested that a mortality rate of nearly 11% was associated with late-onset sepsis.

Our study is one of the largest to date to evaluate late-onset sepsis among EPT infants. Only infants with culture-confirmed sepsis were included, and suspected or "clinical" sepsis was excluded. We only included infants ≥24 weeks old as all participating networks provide active resuscitation at 24 weeks' gestation [28]. Infants who died prior to day 4 of life were excluded because they could not meet the 3-day definition of late-onset sepsis and their inclusion would increase mortality in the "no-late-onset sepsis" group. There were no infants who died prior to 4 days who had late-onset sepsis. This is a retrospective study with known limitations; however, this is mitigated to a large extent because data are prospectively collected. Two networks used different definitions which can result in late-onset sepsis rates being underestimated for Japan and overestimated for Australia-New Zealand. Blood culture practices, which are the basis for confirmation

of late-onset sepsis, may differ between networks, as may antibiotic practices [36]. The rates of late-onset sepsis are affected by the definition of sepsis used for the most common pathogen, coagulase-negative staphylococci, because its diagnosis may require one or two positive blood cultures, depending on the network [23]. Coagulase-negative staphylococci account for approximately 50% of cases, and if a stringent definition is used, the incidence of late-onset sepsis will be lower. Networks that take more blood cultures probably have higher antibiotic therapy use. We have surveyed sites to ask about their preferences/practices and identified that the majority practice single blood culture collection considering the size of the baby and the amount of blood needed. Microbiological data were not available for all networks; thus we could not evaluate the effect of causative pathogens on outcomes or trends. Information regarding prophylactic therapies is not routinely collected by our network. We do not have information from all countries regarding outcomes after transfer to level 2 units. However, the majority of units which transfer babies to level 2 units do so after the initial acute period; thus the occurrence of late-onset sepsis at level 2 units is rare.

In conclusion, one in 5 neonates of 24–28 weeks' gestation developed late-onset sepsis. Wide variability in rates exists between networks with most networks exhibiting a trend toward decreased rates. Late-onset sepsis was associated with increased morbidity and mortality. The marked decrease in late-onset sepsis rates in some networks suggests that interventions may be effective in preventing late-onset sepsis.

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Statement of Ethics

Data collection and data transfer from individual networks were approved by the research ethics boards of the participating networks in the respective countries and by the iNeo steering committee. Specific ethics approval for this project was obtained from the Mount Sinai Hospital Research Ethics Board and the iNeo Steering Committee. This study protocol was reviewed and approved by the Research Ethics Board (approval number 22-0047-C). Informed consent from individual patients was waived due to the retrospective nature of this database study.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Drs. Gil Klinger and Prakesh S. Shah were involved in the conception and design of the study; the acquisition, analysis, and interpretation of data; drafting the article; and revising it critically for important intellectual content. All other authors (Brian Reichman, Mikael Norman, Satoshi Kusuda, Malcolm Battin, Kjell Helenius, Tetsuya Isayama, Kei Lui, Mark Adams, Max Vento,

Stellan Hakansson, Marc Beltempo, Chiara Poggi, Laura San Feliciano, Liisa Lehtonen, Dirk Bassler, and Junmin Yang) were involved in the conception and design of the study, interpretation of results, and critical revision of the article for important intellectual content. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Data Availability Statement

Prakesh S. Shah, Mount Sinai Hospital, Toronto, ON, Canada, has full access to the data. He takes responsibility for the integrity of the data and the accuracy of the data analysis. The data analyses were conducted by Junmin Yang. Data are confidential and not available for public access. Further inquiries can be directed to the corresponding author.

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