



Central-line-associated bloodstream infection burden among Dutch neonatal intensive care units

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SUMMARY

Background: The establishment of an epidemiological overview provides valuable insights needed for the (future) dissemination of infection-prevention initiatives.

Aim: To describe the nationwide epidemiology of central-line-associated bloodstream infections (CLABSI) among Dutch Neonatal Intensive Care Units (NICUs).

Methods: Data from 2935 neonates born at <32 weeks' gestation and/or with a birth weight <1500 g admitted to all nine Dutch NICUs over a two-year surveillance period (2019–2020) were analysed. Variations in baseline characteristics, CLABSI incidence per 1000 central-line days, pathogen distribution and CLABSI care bundles were evaluated. Multi-variable logistic mixed-modelling was used to identify significant predictors for CLABSI.

Results: A total of 1699 (58%) neonates received a central line, in which 160 CLABSI episodes were recorded. Coagulase-negative staphylococci were the most common infecting organisms of all CLABSI episodes ($N=100$, 63%). An almost six-fold difference in the CLABSI incidence between participating units was found (2.91–16.14 per 1000 line-days). Logistic mixed-modelling revealed longer central line dwell-time (adjusted odds

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ratio (aOR):1.08, $P<0.001$), umbilical lines (aOR:1.85, $P=0.03$) and single rooms (aOR:3.63, $P=0.02$) to be significant predictors of CLABSI. Variations in bundle elements included intravenous tubing care and antibiotic prophylaxis.

Conclusions: CLABSI remains a common problem in preterm infants in The Netherlands, with substantial variation in incidence between centres. Being the largest collection of data on the burden of neonatal CLABSI in The Netherlands, this epidemiological overview provides a solid foundation for the development of a collaborative platform for continuous surveillance, ideally leading to refinement of national evidence-based guidelines. Future efforts should focus on ensuring availability and extraction of routine patient data in aggregated formats.

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Introduction

Nosocomial infections (NIs) remain an important source of neonatal morbidity, mortality and added healthcare costs [1–3], with up to 25% of very-low-birthweight infants (<1500 g) experiencing at least one episode of late-onset sepsis during neonatal intensive care unit (NICU) admission [2,4]. Although forming an essential part of the provision of care to critically ill neonates, central lines pose the risk of a central-line-associated bloodstream infection (CLABSI) and have been noted to be the leading cause of NI in the NICU [5–7]. As such, continued efforts in the development and optimization of prevention strategies are needed to reduce this form of iatrogenic harm.

Over the past decade, national and international neonatal infection surveillance networks have steadily gained prominence in efforts outlining the epidemiology of neonatal NI [8–12]. Through the aggregation of data across multiple sites, interdisciplinary teamwork and shared learning, neonatal infection networks have been implemented as valuable platforms for benchmarking practice, and monitoring changes in causative micro-organisms and their antimicrobial susceptibility profiles [9]. There are, however, numerous factors which must be taken into account to ensure adequate validity and comparability of reported infection rates, including differences in CLABSI definitions, clinical practices related to central line insertion and maintenance, and unit-specific case-mix [13]. Importantly, infection reporting may be affected by variability in local data resources and surveillance methods [13]. Given that effective quality improvement collaboration requires solid epidemiological overviews based on reliable measures of performance, a better understanding of inter-facility surveillance is required.

In 2019, the Neonatal Infectious Diseases Working Group of the Dutch Society of Paediatrics decided to carry out a comparison of institution-specific CLABSI data and promote evidence-based practice to improve the effectiveness of CLABSI reduction strategies in Dutch NICUs. Previously, no neonatal CLABSI data had been shared or reported, leaving the current burden of CLABSI on a national level unknown. Recently established Dutch CLABSI surveillance criteria [14] and uncertainty regarding local data sources and surveillance methods prompted the need to gain a better understanding of the specifics and degree of variability in local CLABSI rates. The creation of a nationwide overview of neonatal CLABSI would subsequently allow us to potentially recalibrate and standardize existing surveillance reporting.

The primary aim of the present study was to describe (1) CLABSI incidence rates, (2) case-mix, (3) distribution of causative pathogens, (4) risk factors for CLABSI, and (5) central line insertion and maintenance practices in a cohort of premature infants of all nine Dutch NICUs over a two-year surveillance period.

Materials and methods

Study design and population

We conducted a nationwide, retrospective, observational cohort study in which all nine tertiary-level NICUs of The Netherlands participated. Neonates born at <32 weeks' gestation and/or with a birthweight <1500 g between 1st January 2019 and 31st December 2020 and admitted to any of the participating centres were eligible for inclusion in the study, with the exception of outborn newborns admitted >24 h postnatally or central lines inserted elsewhere prior to an infant's transfer to any of the study centres, in which case only the infant without the externally placed central line was included in the analyses. Informed consent was waived by the institutional review board (IRB) of the initiating centre (Leiden University Medical Centre, G21.010). The study was approved by the IRBs of the remaining eight sites in accordance with local regulations.

Data collection and sources

Depending upon the available digital infrastructure, data were retrieved either manually from the electronic patient medical records, a national, population-based perinatal repository or through semi-automated extraction from local digital data warehouses under the provision of stringent and detailed data specifications. Data retrieved from the repository and/or from the local digital warehouses were cross-checked for accuracy and completeness using the electronic medical records. One member of the research team (S.J.J.) collected the data and manually ascertained all CLABSI episodes for five of the nine participating units, with the remaining four units supplying the data themselves.

Extracted data included standard demographic characteristics, as well as infection- and central-line-related data for all included neonates. Due to local data privacy regulations, centre G was unable to provide specific insertion and removal dates of the central lines, providing aggregated catheter dwell-time (in days) per infant instead. Similarly, both antibiotic treatment <24 h after birth and central line type were not

available for centre E. Additional information collected included unit-specific central line insertion and maintenance protocols. All data were de-identified both on unit and patient levels.

CLABSI definition

CLABSI was defined according to the Dutch neonatal CLABSI Surveillance Criteria published previously by our research group [14]. A CLABSI was defined based on the presence of a positive blood culture obtained >72 h after birth, in combination with clinical signs and symptoms of infection and an indwelling central line. Central lines in place >2 calendar days were considered at risk for infection, up until the day after removal or hospital discharge [14]. Central lines that were inserted elsewhere prior to admission of the neonate to the respective centre were excluded from the analyses. Blood cultures positive for organisms considered to be common commensals according to the National Healthcare Safety Network (NHSN) Master Organism List [15] were classified as true bloodstream infections in case of a single blood culture in combination with a single C-reactive protein measurement of >10 mg/L obtained in the first 36 h after blood culture sampling, or in case the micro-organism had been isolated from two or more blood cultures sampled on the same or consecutive day.

Statistical analysis

Data were reported as mean and standard deviation (SD), median and interquartile range (IQR) or absolute number and percentage, as appropriate. Distribution of baseline neonatal and central line characteristics were stratified by participating centre over the entire two-year study period. Crude CLABSI incidence rates were normalized per 1000 central-line days, with cumulative incidence rates normalized per 100 infants. Catheter dwell-time was determined by tallying the number of calendar days a central line was *in situ*, for each participating unit alike. Distribution of causative micro-organisms associated with CLABSI over the study period are shown as bar-charts with stratification according to participating unit.

To investigate the association between several factors and CLABSI, a multi-variable logistic mixed-model analysis was performed. A one-level hierarchy was employed, indicating that observations are nested within centres. Through the use of a random intercept, the model included centre as a random effect to express the notion that individual patient observations within the same centre are correlated. The following candidate predictors, selected based on expert opinion, the literature and availability in the dataset, were included in the model: gestational age, sex, central line duration, central line type (i.e., PICC and umbilical lines), unit type (i.e., open-bay and single rooms) and provision of surgical procedures. Results of the fixed effects (measures of association) are presented as regression coefficients with standard errors (SEs), including the corresponding adjusted odds ratios (aORs) and *P*-values. Random effects (measures of variation) include the random intercept variance (var). Fixed and random effects estimates were estimated using the restricted maximum likelihood procedure (REML). Considering one centre (centre E) did not have complete data on central line type, only eight centres were included in the model.

All analyses were performed using R, version 4.0 (R Foundation for Statistical Computing, <http://rgg.rforge.r-project.org>).

Results

Unit and patient characteristics

Seven of the nine participating NICUs units were situated in university-affiliated academic teaching hospitals, with two units being part of a community medical centre. Likewise, two NICUs were designed as single-room units, and the remaining seven as open-bay wards. Neonatal abdominal surgery was provided in seven of the nine units.

Over the two-year study period, a total of 2935 neonates were admitted to the participating centres, with admission numbers varying from 179 to 499 between centres (Table I). Considerable variation was seen in the number of neonates exposed to invasive mechanical ventilation (27%–48%) and delivery by caesarean section (35%–64%). Comparatively, the median admission duration ranged between 13 and 24 days, with the median length of stay over all centres combined being 16 days (IQR 7.9–35.8). Proportions of antibiotic use within the first 24 h after birth ranged between 53% and 80%.

Central line characteristics and CLABSI outcomes

Central line characteristics and CLABSI outcomes of all participating units are illustrated in Tables II and III. Over the two-year study period, 3101 central lines covering a total 23,905 central-line days were placed in 1699 neonates. Of the eight units with available data on central line types, four centres placed peripherally inserted central catheters (PICC) most often, and the remaining four units umbilical-venous catheters (UVC). The number of neonates with at least one central line varied from 46% to 75%, with the median catheter dwell-time per line varying from eight to 12 days. No variability was observed in the age at central line insertion between the units. On average, 9.4% of neonates with a central line developed at least one episode of CLABSI, with the variation between the centres being 4.0%–18.6%. Concomitantly, substantial variation was found in the CLABSI incidence (varying from 2.91 to 16.14 per 1000 central-line days), with the mean CLABSI incidence rate across all participating NICUs being 6.69 per 1000 central-line days. None of the neonates experienced more than one CLABSI episode during NICU admission.

Microbial aetiology

Gram-positive bacteria were responsible for 80% (128/160) of all CLABSI episodes, with Gram-negative organisms and fungi representing 18.7% (30/160) and 1.3% (2/160) of infections, respectively. The majority of CLABSI episodes were caused by coagulase-negative staphylococci (*N*=100, 63%), followed by *Staphylococcus aureus* (*N*=19, 11.9%). Only one centre reported two CLABSI episodes caused by *Candida albicans*. Moreover, three centres showed little internal variation in the spectrum of causative pathogens, with three genera of micro-organisms being responsible for all infection episodes. Overall, no marked variation in the distribution of reported pathogens was observed between the units (Supplementary Figure S1).

Table I
Demographic characteristics of included neonates per participating centre

	A	B	C	D	E	F	G	H	I
Neonates, <i>N</i>	499	314	255	379	343	375	363	228	179
Sex, <i>N</i> (%)									
Male	288 (58%)	174 (55%)	146 (57%)	194 (51%)	183 (53%)	199 (53%)	192 (53%)	119 (52%)	93 (52%)
Female	211 (42%)	140 (45%)	109 (43%)	185 (49%)	160 (47%)	176 (47%)	171 (47%)	109 (48%)	86 (48%)
GA, median [IQR]	29 [27–31]	29 [28–31]	29 [27–30]	29 [28–31]	29 [28–31]	29 [27–31]	29 [28–31]	29 [27–30]	30 [28–31]
<28 weeks, <i>N</i> (%)	155 (31%)	89 (28%)	84 (33%)	96 (25%)	98 (29%)	110 (29%)	102 (28%)	72 (32%)	49 (27%)
BW, mean (SD)	1205 (386)	1244 (369)	1274 (398)	1230 (363)	1229 (342)	1240 (375)	1224 (389)	1164 (348)	1204 (422)
Caesarean section, <i>N</i> (%)	308 (62%)	201 (64%)	110 (43%)	212 (56%)	120 (35%)	208 (55%)	223 (61%)	108 (47%)	104 (58%)
Apgar at 5 min, median [IQR]	8 [7–9]	8 [7–9]	8 [7–8]	8 [7–9]	8 [7–9]	8 [7–9]	8 [7–9]	8 [7–9]	9 [8–9]
Invasive mechanical ventilation, <i>N</i> (%) ^a	195 (39%)	101 (32%)	122 (48%)	141 (37%)	100 (29%)	117 (31%)	139 (38%)	70 (31%)	49 (27%)
Antibiotic therapy < 24 h postpartum, <i>N</i> (%)	401 (80%)	165 (53%)	182 (71%)	253 (67%)	–	270 (72%)	243 (67%)	157 (69%)	128 (72%)
Length of hospital stay per infant, median [IQR]	13 [6–36]	13 [7–28]	13 [8–30]	13 [7–30]	14 [8–35]	13 [6–34]	24 [12–46]	16 [7–31]	23 [12–53]
In-hospital mortality, <i>N</i> (%)	44 (8.8%)	17 (5.4%)	23 (9.0%)	16 (4.2%)	27 (7.8%)	26 (6.9%)	29 (7.9%)	15 (6.6%)	13 (7.3%)

BW, birth weight; GA, gestational age; IQR, interquartile range; SD, standard deviation. Data for the proportion of neonates treated with antibiotics <24 h postpartum not available for centre E.

^a Invasive mechanical ventilation comprises conventional mechanical ventilation and/or high frequency oscillatory ventilation.

Multi-variable multi-level logistic analyses

Multi-variable logistic mixed-modelling revealed that umbilical central lines were associated with a statistically significant increased risk of CLABSI as compared with PICCs (aOR: 1.85, $P=0.03$; Table IV). Similarly, for every one additional day a central line remained inserted, the odds of acquiring CLABSI increased by approximately 8% (aOR: 1.08, $P<0.001$). Moreover, the odds of CLABSI was almost four-fold higher for single-room units compared with multi-bed units (aOR: 3.63, $P=0.02$). All other included candidate predictors were not significantly associated with CLABSI.

Central line insertion and maintenance bundles

Key components of central line insertion and maintenance bundles for each participating NICU are listed in Supplementary Table S1. The use of maximal barrier precautions, performance of hand hygiene according to surgical standards as well as the use of skin disinfection prior to central line insertion were uniform components across all units. The use of a checklist as an additional means of procedure standardization was reported in four of nine centre-specific procedure guidelines. Although seven of nine centres reported performing assessment of central line indication, only one centre cited

Table II
Central-line characteristics per participating centre

	A	B	C	D	E	F	G	H	I
Central-lines, <i>N</i>	673	318	238	329	280	301	538	249	175
UAC, <i>N</i> (%)	89 (13%)	49 (15%)	62 (26%)	79 (24%)	–	57 (19%)	92 (17%)	46 (19%)	43 (25%)
UVC, <i>N</i> (%)	198 (30%)	124 (39%)	93 (39%)	132 (40%)	–	90 (30%)	226 (42%)	88 (35%)	74 (43%)
PICC, <i>N</i> (%)	386 (57%)	145 (46%)	83 (35%)	118 (36%)	280 (100%)	154 (51%)	220 (41%)	115 (46%)	58 (33%)
Neonates with a central-line, <i>N</i> (%)	375 (75%)	167 (53%)	118 (46%)	177 (47%)	183 (53%)	190 (51%)	254 (70%)	113 (50%)	122 (68%)
Line-days per neonate, median [IQR]	10 [7–17]	9 [6–16]	12 [7–19]	12 [7–18]	9 [7–13]	8 [6–13]	11 [7–19]	12 [7–23]	10 [8–13]
Line-days per line, median [IQR]	8 [4–10]	6 [4–8]	8 [5–10]	7 [6–9]	7 [4–9]	7 [5–8]	7 [5–9]	7 [3–10]	9 [6–11]
Total line-days, <i>N</i>	5705	1912	1958	2393	2387	1996	3917	1917	1720
Age at insertion, median [IQR]	1 [0–3]	1 [0–4]	1 [0–2]	1 [0–4]	1 [0–6]	1 [0–2]	1 [0–4]	1 [0–8]	0 [0–2]
Age at removal, median [IQR]	8 [5–13]	7 [5–10]	8 [6–10]	8 [6–10]	8 [5–13]	7 [5–9]	7 [5–11]	8 [4–18]	9 [7–13]

IQR, interquartile range; PICC, peripherally inserted central catheter; UAC, umbilical-arterial catheter; UVC, umbilical-venous catheter.

Table III
Central-line associated bloodstream infection (CLABSI) outcomes per participating centre

	A	B	C	D	E	F	G	H	I
Neonates with a central-line, <i>N</i>	375	167	118	177	183	190	254	113	122
Total line-days, <i>N</i>	5705	1912	1958	2393	2387	1996	3917	1917	1720
CLABSI episodes, <i>N</i>	29	31	11	23	11	9	23	18	5
Neonates with CLABSI, <i>N</i> (%)	29 (7.7%)	31 (18.6%)	11 (9.3%)	23 (12.9%)	11 (6.0%)	9 (4.7%)	23 (9.0%)	18 (15.9%)	5 (4.0%)
<28 weeks GA	19 (66%)	16 (52%)	9 (82%)	14 (61%)	5 (45%)	6 (67%)	11 (48%)	11 (61%)	5 (100%)
<750 g BW	12 (41%)	3 (9.7%)	2 (18%)	9 (39%)	4 (36%)	5 (56%)	4 (17%)	8 (44%)	1 (20%)
Cumulative incidence rate	7.73	18.56	9.32	12.99	6.01	4.74	9.06	15.93	4.10
Incidence per 1000 line-days	5.08	16.14	5.62	9.61	4.61	4.51	5.87	9.39	2.91

BW, birth weight; GA, gestational age. Cumulative incidence rate represents the CLABSI incidence per 100 neonates.

documentation thereof in the patient medical records. All units except for centre G reported assessing the integrity of the central line and dressings, with the frequency of assessment varying from one to eight times daily. Some variation was present with regards to general intravenous (IV) tubing care, including scrubbing of the IV connectors. The recommendation with regards to catheter dwell-time for umbilical lines ranged between seven and 14 days, with three centres mentioning having no maximum duration. A recommendation for the duration of a PICC was not made for the majority of units, and only two were based on reaching a certain enteral feed level. Other frequently reported components included the placement of screens around the incubator, restricting the number of visitors during the procedure and the use of the double-glove technique. Centre C reported administering antibiotic prophylaxis in case of belated (i.e., >3 days) umbilical-arterial catheter (UAC) insertion, although type and duration were not mentioned. Similarly, centre D reported administration of amoxicillin/clavulanic acid in case of UAC/UVC insertion >24 h postpartum as well as administration of a single doses of

vancomycin immediately before and after central line removal. Centres F and G likewise reported the use of two doses of prophylactic cefazoline upon central line removal.

Discussion

This is the first formal initiative of a Dutch, nationwide collaboration to describe neonatal CLABSI data as a first step in determining the feasibility of a continued, prospective CLABSI surveillance initiative. This national study provides a unique insight into the current national burden of neonatal CLABSI and allows participating units to evaluate their own performance and set quantifiable targets for further quality improvement. In the current study, 9.4% of preterm neonates with a central line admitted to a Dutch NICU developed CLABSI, with considerable variation present in incidence, central line usage and duration of catheter dwell-time between units. Increased central line dwell-time, umbilical lines and the single-room design were found to be risk factors for CLABSI. Additionally, the most common bundle elements were hand hygiene, skin disinfection and the use of maximal barrier precautions, with disparity identified in general IV tubing care, duration policy of catheter dwell-time and administration of antibiotic prophylaxis for belated line insertion and/or removal.

Incidence rates pertaining to neonatal CLABSI specifically have only sporadically been investigated by large surveillance networks [16–20]. Reported incidence rates from single-centre studies range from 3.2 to 21.8 per 1000 central-line days [21], demonstrating that our national rate of 6.39 per 1000 central-line days lies at the lower end of this spectrum. The variation in reported CLABSI rates probably reflects the substantial heterogeneity in the surveillance definition of CLABSI, as well as variations in local practice patterns and infection prevention guidelines. However, by using the Dutch neonatal CLABSI surveillance criteria under standardized data collection methods, we were able to ascertain all CLABSI episodes in an accurate and reliable manner. This not only enhances the validity of our reported rates, but also facilitates the current interfacility comparison initiative. An intriguing and important finding from this study is the substantial variation in CLABSI rates between units, with the difference between the lowest and highest reported incidences being almost six-fold. One may speculate that this variation is primarily caused by differences in case-mix, as we observed considerable variations in the use of invasive mechanical ventilation and antibiotic use within 24 h after birth. Certain imperative case-mix-related characteristics such as the presence of surgical pathology, congenital

Table IV
Multivariable multi-level model of factors associated with central-line associated bloodstream infection (CLABSI)

Fixed parameters	Coefficient (SE)	aOR	<i>P</i>
Intercept	-1.85 (1.79)	—	0.30
Gestational age	-0.08 (0.06)	0.92	0.30
Sex	—	—	—
Female (ref)	—	1	—
Male	-0.20 (0.26)	0.82	0.43
Central-line duration	0.07 (0.02)	1.08	<0.001
Central-line type	—	—	—
PICC (ref)	—	1	—
UAC/UVC	0.61 (0.28)	1.85	0.03
Unit type	—	—	—
Open-bay (ref)	—	1	—
Single-room	1.29 (0.54)	3.63	0.02
Provision of surgical procedures	0.04 (0.57)	1.04	0.94
Random effects parameters			
Random intercept variance	0.22	—	—

aOR, adjusted odds ratio; PICC, peripherally inserted central catheter; SE, standard error; UAC, umbilical-arterial line; UVC, umbilical-venous line.

anomalies, use of total parenteral nutrition and duration of mechanical ventilation, all of which are measured on the patient level, as well as adherence to and individual interpretation of local infection-prevention protocols, were not uniformly available across all NICUs and thereby not collected, indicating that residual bias due to these other, unavailable parameters may still be present in the reported CLABSI rates. We nevertheless believe that our study captured the most important variation in case-mix between the NICUs required for interpreting CLABSI outcomes.

In line with previous studies, our results indicate that increased central line dwell-time is associated with an increased risk of CLABSI, suggesting that timely removal remains an important prevention strategy [22–24]. Umbilical lines were furthermore found to carry a higher CLABSI risk compared with PICCs, which is in contrast to other studies reporting either no difference in CLABSI risk between central line types or a higher risk for PICCs [25–27]. A possible explanation may be that umbilical lines are primarily inserted during the first week of life in all participating units, during which the overall infection risk may be different and a high prevalence of antibiotic treatment (which typically does not cover coagulase-negative staphylococci (CoNS)) is present. Insertion sites of umbilical lines are likewise not always covered with dressings, thereby increasing the risk of extraluminal colonization.

Somewhat surprisingly, single-room units were found to be a risk factor for CLABSI. The effect of single-room care on the risk of infection nevertheless remains controversial, with previous studies from our group indicating that single-room care does not necessarily result in a lower incidence of NI or multi-drug-resistant organism colonization [28,29]. Moreover, participating units with single-rooms had higher CLABSI rates, clarifying the regression results and indicating that local differences in and adherence to evidence-based practice guidelines may be of greater importance.

Comparison of best practice recommendations is known to help in the reformation and improvement of care bundles [30]. Even though we did not attempt to associate specific bundle features with differences in CLABSI rates, we identified the most frequently reported components and variations between the centres. Disparity within bundled elements was present, although the most common and critical elements such as hand hygiene, skin antisepsis and the use of maximum barrier precautions were reported by all units. Given that the success of a care bundle often lies in the extent to which all components are consistently executed by all healthcare workers [31–33], an essential next step is to evaluate the implementation process taking into account the organizational context and overall compliance with individual CLABSI prevention bundle elements.

Benchmarking strategies are increasingly being used to improve the quality of care and describe the variability in infection rates between healthcare institutions. Such efforts are however often subject to several pitfalls, including the variability in data collection methods, distribution of key risk factors and definitions and application thereof to measure and assess CLABSI. Moreover, difficulties in attributing positive blood cultures to a central line and differences in measuring the number of central-line days (i.e., in calendar days or hours) may increase the risk of measurement bias and

local interpretation [34]. Although the primary aim of this study was not to explicitly compare incidence rates between units, our results lay the foundation for future comparison. Ongoing improvements aimed at optimizing digital infrastructures, data availability, accessibility and completeness are currently being carried out to further improve the sensitivity and efficiency of forthcoming neonatal CLABSI surveillance initiatives by our research team.

Our study has several limitations. First, due to COVID-19 and time-related restrictions, data collection and case-finding for four of the nine units were performed by the respective local investigators, signifying that we cannot guarantee systematic application of the surveillance criteria. Second, although CLABSIs are one of the most common types of NI and thereby an appropriate proxy measure for NI in the NICU, they do not provide an all-encompassing overview of NI, as central line exposure accounts for only a limited proportion of the at-risk period in the NICU. Lastly, we were unable to determine the extent to which peripheral-intravenous catheters (PIVs) contribute to the overall burden of CLABSI, especially in infants with both a central line and PIV *in situ*. Centres with high centre-specific CLABSI rates may reflect the predominance of (undetected) PIV-related infections. As such, further determination of the relative contribution of PIVs to the overall NI burden is needed.

Despite the above limitations, the strengths of this study are that it is the largest evaluation of neonatal CLABSI in The Netherlands with data collected under the provision of an appropriate and detailed definition.

In conclusion, CLABSI remains a common problem in preterm infants in the Netherlands, with substantial variation in incidence between centres. Common risk factors identified were increased central line dwell-time, umbilical lines and the single-room design. The results of our national study support the notion that establishing an epidemiological overview provides valuable insights which work towards dissemination of improvement initiatives among Dutch NICUs, under the premise of accurate and reliable data availability. An important challenge that remains is implementing strategies which will facilitate data collection and improve the standardization of surveillance to further build upon the first steps that have been taken towards meaningful comparability.

Author contributions

S.J.J.: conceptualization, methodology, data curation, analysis, writing – original and final draft preparation. S.D.L.B.: Methodology, Analysis, Writing- Reviewing and Editing. M.A.C.H.: Conceptualization, Data curation, Writing- Reviewing and Editing. D.H.V.: Conceptualization, Data curation, Writing – Reviewing and Editing. T.A.J.A.: Conceptualization, Data curation, Writing – Reviewing and Editing. I.E.H.: Conceptualization, Writing – Reviewing and Editing. K.A.B.: Conceptualization, Writing – Reviewing and Editing. J.U.M.T.: Conceptualization, Writing – Reviewing and Editing. M.C.H.: Conceptualization, Data curation, Writing – Reviewing and Editing. J.P.F. vd.S: Conceptualization, Writing – Reviewing and Editing. E.J.d’H.: Conceptualization, Data curation, Writing- Reviewing and Editing. R.F.K.: conceptualization, writing – reviewing and editing. E.L.: conceptualization, writing – reviewing and editing. V.B.: conceptualization, writing – reviewing and editing, study oversight.

Conflict of interest statement

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Appendix A. Supplementary data

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References

- [1] Payne NR, Carpenter JH, Badger GJ, Horbar JD, Rogowski J. Marginal increase in cost and excess length of stay associated with nosocomial bloodstream infections in surviving very low birth weight infants. *Pediatrics* 2004;114:348–55.
- [2] Fanaroff AA, Korones SB, Wright LL, Verter J, Poland RL, Bauer CR, et al. Incidence, presenting features, risk factors and significance of late onset septicemia in very- low-birthweight infants. The National Institute of Child Health and Human Development Neonatal Research Network. *Pediatr Infect Dis J* 1998;17:593–8.
- [3] Stoll BJ, Hansen N, Fanaroff AA, Wright LL, Carlo WA, Ehrenkranz RA, et al. Late-onset sepsis in very low birth weight neonates: the experience of the NICHD neonatal research network. *Pediatrics* 2002;110:285–91.
- [4] Wojkowska J, Gulczynska E, Nowiczewski M, Borszewska-Kornacka M, Domanska J, Merritt TA, et al. Late-onset bloodstream infections of very-low-birth-weight infants: data from the Polish Neonatology Surveillance Network in 2009–2011. *BMC Infect Dis* 2014;14:339.
- [5] Bizzarro MJ, Raskind C, Baltimore RS, Gallagher PG. Seventy-five years of neonatal sepsis at Yale: 1928-2003. *Pediatrics* 2005;116:595–602.
- [6] Smulders CA, van Gestel JP, Bos AP. Are central line bundles and ventilator bundles effective in critically ill neonates and children? *Intensive Care Med* 2013;39:1352–8.
- [7] Schulman J, Stricof RL, Stevens TP, Holzman IR, Shields EP, Angert RM, et al. Development of a statewide collaborative to decrease NICU central line-associated bloodstream infections. *J Perinatol* 2009;29:591–9.
- [8] Cailles B, Kortsalioudaki C, Buttery J, Pattanayak S, Greenough A, Matthes J, et al. Epidemiology of UK neonatal infections: the neonIN infection surveillance network. *Arch Dis Fetal Neonatal Ed* 2018;103:F547–53.
- [9] Vergnano S, Menson E, Kennea N, Embleton N, Russell AB, Watts T, et al. Neonatal infections in England: the NeonIN surveillance network. *Arch Dis Child Fetal Neonatal* 2011;96:F9–14.
- [10] Leistner R, Piening B, Gastmeier P, Geffers C, Schwab F. Nosocomial infections in very low birthweight infants in Germany: current data from the National Surveillance System NEO-KISS. *Klin Padiatr* 2013;225:75–80.
- [11] Giannoni E, Agyeman PKA, Stocker M, Posfay-Barbe KM, Heining U, Spycher BD, et al. Neonatal sepsis of early onset, and hospital-acquired and community-acquired late onset: a prospective population-based cohort study. *J Pediatr* 2018;201:106–14.
- [12] Escalante MJ, Ceriani-Cernadas JM, D'Apremont Y, Bancalari A, Webb V, Genes L, et al. Late onset sepsis in very low birth weight infants in the South American NEOCOSUR Network. *Pediatr Infect Dis J* 2018;37:1022–7.
- [13] Niedner MF and the 2008 National Association of Children's Hospitals and Related Institutions Pediatric Intensive Care Unit Patient Care FOCUS Group. The harder you look, the more you find: Catheter-associated bloodstream infection surveillance variability. *Am J Infect Control* 2010;38:585–95.
- [14] Heijting IE, Antonius TAJ, Tostmann A, de Boode WP, Hogeveen M, Hopman J, et al. Sustainable neonatal CLABSI surveillance: consensus towards new criteria in the Netherlands. *Antimicrob Resist Infect Control* 2021;10:31.
- [15] Centers for Disease Control and Prevention (CDC). Centers for Disease Control and Prevention (CDC)/National Healthcare Safety Network (NHSN) patient safety component manual. https://www.cdc.gov/nhsn/pdfs/pscmanual/pscmanual_current.pdf; 2022 [last accessed February 2023].
- [16] Hornik CP, Fort P, Clark RH, Watt K, Benjamin DK, Smith PB, et al. Early and late onset sepsis in very-low-birth-weight infants from a large group of neonatal intensive care units. *Early Human Dev* 2012;88(Suppl 2):S69–74.
- [17] Ronnestad A, Abrahamson TG, Medbo S, Regstad H, Lossius K, Kaarens PI, et al. Late-onset septicemia in a Norwegian national cohort of extremely premature infants receiving very early human milk feeding. *Pediatrics* 2005;115:e269–76.
- [18] Morioka I, Morikawa S, Miwa A, Minami H, Yoshii K, Kugo M, et al. Culture-proven neonatal sepsis in Japanese neonatal care units in 2006–2008. *Neonatology* 2012;102:75–80.
- [19] Piazza AJ, Brozanski B, Provost L, Grover TR, Chuo J, Smith JR, et al. SLUG bug: quality improvement with orchestrated testing leads to NICU CLABSI reduction. *Pediatrics* 2016;137.
- [20] Schulman J, Stricof R, Stevens TP, Horgan M, Gase K, Holzman IR, et al. Statewide NICU central-line-associated bloodstream infection rates decline after bundles and checklists. *Pediatrics* 2011;127:436–44.
- [21] Folgori L, Bielicki J, Sharland M. A systematic review of strategies for reporting of neonatal hospital-acquired bloodstream infections. *Arch Dis Child Fetal Neonatal Ed* 2013;98:F518–23.
- [22] Sengupta A, Lehmann C, Diener-West M, Perl TM, Milstone AM. Catheter duration and risk of CLABSI in neonates with PICCs. *Pediatrics* 2010;125:648–53.
- [23] Sanderson E, Yeo KT, Wang AY, Callander I, Bajuk B, Bolisetty S, et al. Dwell time and risk of central-line-associated bloodstream infection in neonates. *J Hosp Infect* 2017;97:267–74.
- [24] Butler-O'Hara M, D'Angio CT, Hoey H, Stevens TP. An evidence-based catheter bundle alters central venous catheter strategy in newborn infants. *J Pediatr* 2012;160(6):972–977.e2.
- [25] Shalabi M, Adel M, Yoon E, Aziz K, Lee S, Shah PS, et al. Risk of infection using peripherally inserted central and umbilical catheters in preterm neonates. *Pediatrics* 2015;136:1073–9.
- [26] Arnts IJ, Bullens LM, Groenewoud JM, Liem KD. Comparison of complication rates between umbilical and peripherally inserted central venous catheters in newborns. *J Obstet Gynecol Neonatal Nurs* 2014;43:205–15.
- [27] de Brito CS, de Brito DV, Abdallah VO, Gontijo Filho PP. Occurrence of bloodstream infection with different types of central vascular catheter in critically neonates. *J Infect* 2010;60:128–32.
- [28] Jansen SJ, Lopriore E, Berkhout RJM, van der Hoeven A, Saccoccia B, de Boer JM, et al. The effect of single-room versus open-bay care on the incidence of bacterial nosocomial infections in pre-term neonates: a retrospective cohort study. *Infect Dis Ther* 2021;10:373–86.
- [29] van der Hoeven A, Bekker V, Jansen SJ, Saccoccia B, Berkhout RJM, Lopriore E, et al. Impact of transition from open bay to single room design neonatal intensive care unit on multi-drug resistant organism colonization rates. *J Hosp Infect* 2021;120:90–7.
- [30] Bierlaire S, Danhaive O, Carkeek K, Piersigilli. How to minimize central line-associated bloodstream infections in a neonatal

- intensive care unit: a quality improvement intervention based on a retrospective analysis and the adoption of an evidence-based bundle. *Eur J Pediatr* 2021;180:449–60.
- [31] Gupta P, Thomas M, Patel A, George R, Mathews L, Alex S, et al. Bundle approach used to achieve zero central line-associated bloodstream infections in an adult coronary intensive care unit. *BMJ Open Qual* 2021;10:e001200.
- [32] Mahieu L, van Damme K, Mertens K, Pierart J, Tackoen M, Cossey V. Compliance with international prevention guidelines for central-line-associated bloodstream infections in neonatal intensive care units in Belgium: a national survey. *J Hosp Infect* 2022;129:49–57.
- [33] Zachariah P, Furuya EY, Edwards J, Dick A, Liu H, Herzig C, et al. Compliance with prevention practices and their association with central line-associated blood stream infections in neonatal intensive care unit. *Am J Infect Control* 2014;42:947–51.
- [34] Dixon-Woods M, Leslie M, Tarrant C, Bion J. Explaining Matching Michigan: an ethnographic study of a patient safety program. *Implement Sci* 2013;8:70.