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ARTICLE

Spatial and environmental correlates of organism colonization and infection in the neonatal intensive care unit

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Abstract

Objective To examine organism colonization and infection in the neonatal intensive care unit as a result of environmental and spatial factors.

Study design A retrospective cohort of infants admitted between 2006 and 2015 ($n = 11\,428$), to assess the relationship between location and four outcomes: methicillin-resistant *Staphylococcus aureus* (MRSA) colonization; culture-confirmed late-onset sepsis; and, if intubated, endotracheal tube colonization with *Pseudomonas aeruginosa* or *Klebsiella pneumonia*. Independent risk factors were identified with mixed-effects logistic regression models and Moran's I for spatial autocorrelation.

Result All four outcomes statistically clustered by location; neighboring colonization also influenced risk of MRSA ($p < 0.05$). For *P. aeruginosa*, being in a location with space for more medical equipment was associated with 2.61 times the odds of colonization (95% CrI: 1.19, 5.78).

Conclusion Extrinsic factors partially explained risk for neonatal colonization and infection. For *P. aeruginosa*, infection prevention efforts at locations with space for more equipment may lower future colonization.

Introduction

Traditional clinical risk factors for pathogen colonization and infection of the infant focus on characteristics of the mother, such as inflammation or infection during pregnancy, labor, or delivery; and characteristics of the infant, such as prematurity resulting in immature skin and an underdeveloped immune system [1–4]. These characteristics are intrinsic and a focus of clinical management of the infant. Yet there are also important extrinsic factors that can influence exposure to potentially harmful organisms. These extrinsic factors can be environmental, with reservoirs of organisms residing on equipment, devices, or other surfaces [5], and may affect the health of the infant either through direct contact with the fomites [6], or indirectly through the health-care worker or visitor serving as an intermediary to spread the organisms [7].

Infectious disease epidemiology has focused on the triad of disease transmission (i.e., host, agent, and environment, possibly with a vector passing in between) [8], and is useful in determining pathways of colonization and infection in a congregant setting of vulnerable individuals, such as within a hospital's neonatal intensive care unit (NICU). We can view the host as the intrinsic factors of the infant, the agent as the potentially pathogenic organism, the environment as the NICU, and the vector being the health-care worker or visitor. Consequently understanding the environmental and spatial correlates of colonization and infection is necessary for targeted infection prevention practices, such as hygienic cleaning or sterilization [5]. In this study, we sought to accurately model the NICU environment, assess spatial dependency of transmission, and establish whether certain areas of our NICU were more likely to lead to organism colonization and infection of the infant. We hypothesized that the distribution of organisms would not be random, and may in fact be related to certain environmental features.

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Materials and methods

Study setting

The Christiana Hospital NICU is a regional perinatal referral center with ~1100 admissions per year. The level III NICU is an open pod design, with up to three cribs per pod (28 total pods), and a maximum capacity of 70 infants. The NICU is designed in a U-shaped pattern with three main hallways and two isolation rooms in the middle. Due to this design, certain pods within the NICU can accommodate infants requiring higher levels of care, allowing for more medical equipment, such as devices used for therapeutic hypothermia, high-frequency ventilation, or inhaled nitric oxide. Several pods also include refrigerators for medications and nutritional supplies. Clinical staff include attending neonatologists, fellows, residents, and medical students; neonatal nurse practitioners, bedside nurses, and nursing students; and ancillary health-care providers, including respiratory, physical, and occupational therapists. Visitors frequent the unit as well, and are instructed in proper hand hygiene before entering the patient care areas. The study was approved by the hospital's institutional review board. Informed consent was not required as this study used existing data collected during clinical care and no patients nor families were contacted.

Patient population and variables

We assembled a retrospective cohort of all initial admissions to the unit between 2006 and 2015. A sub-cohort was created based on the presence of an endotracheal tube used for mechanical ventilation, and one or more surveillance cultures were obtained from the endotracheal tube. Infants contributed time to the cohort until death, discharge, or transfer, or one or more of the following four primary outcomes occurred: methicillin-resistant *Staphylococcus aureus* (MRSA) colonization of the nares or late-onset sepsis (full cohort); and *Pseudomonas aeruginosa* or *Klebsiella pneumoniae* endotracheal tube colonization (sub-cohort). We specifically focused on these three organisms as they have historically been present in our unit, convey substantial risk for serious invasive infection, and have corresponding surveillance cultures. Late-onset sepsis was defined as bacteremia confirmed by laboratory isolation of an infectious organism after 72-h NICU admission. As of 2013, surveillance for MRSA occurred weekly, when ≥1 infant was colonized up until all infants in the NICU screened negative, and then, to conserve resources, once every 3 weeks until another MRSA colonization was detected. Prior to 2013, screening for MRSA was variable by unit policy. All outborn infants received at least one screening for MRSA colonization at the time of admission. Surveillance for endotracheal tube isolates occurred every Monday, therefore all infants who were intubated on that day were screened. Individual (infant)-level covariates included year of birth, gestational age in weeks, birthweight in grams, presence of a central line, antibiotic exposure, average census during stay (a proxy for staff workload [9]), outborn birth, ventilation days (sub-cohort), and markers of maternal inflammation or infection including premature rupture of membranes and clinical chorioamnionitis.

Infants were tracked by crib number for the spatial analysis, and the pod where the infant resided the longest during the NICU admission served as the spatial unit of analysis. Infants are maintained in the same pod throughout their stay based on NICU policy; on occasion, they are moved to a different pod in the NICU based on family requests or nursing assignments.

Contexual (pod)-level covariates included being in a pod with a single crib, more space for equipment, or containing a refrigerator. Whereas eight pods can house only a single crib, six of these met the criteria of "more space for equipment" as their square footage per crib was greater than multiple crib pods. For example, one such pod had an area of 127 square feet for a single crib, while a three-crib pod had an area of 174 square feet (or 58 square feet per crib). Three pods contained a refrigerator. Contextual factors were modeled as indicator variables indicating presence or absence of a pod-level exposure.

Statistical analysis

Descriptive statistics assessed the overall characteristics of cohort, as well as crude associations between the primary outcomes and pods. Choropleth maps were created to visualize the spatial distribution of the outcomes. As our outcomes are all communicable in nature and presence of an outcome in one pod may influence a neighboring pod, spatial autocorrelation was assessed via Moran's I [10]. A neighbor matrix was created with input from nursing staff and defined the typical patient load and workflow of the bedside nurses who provide the majority of infant care (eFig. 1). A spatial correlogram with four lags depicted the extent to which a given pod's outcomes influenced neighboring pods' outcomes.

To isolate the independent effects of the individual and contextual factors associated with the primary outcomes, we fit Bayesian mixed-effects multilevel logistic regression models. The use of Bayesian models allowed for incorporation of prior knowledge on how the individual and contextual factors may influence the outcome [11]; we assumed flat priors on all variables. The first level included the infant characteristics and outcomes, and the second level included the contextual factors. The pod was treated as a random intercept; all other covariates were fixed effects.

Birth year and gestational age were grand mean centered in the multilevel models for model fit and interpretability [12], and ventilation days was log-transformed. If spatial autocorrelation was detected for each outcome, eigenvectors were computed and included as fixed effects in a multilevel spatial model to account for the spatial dependency [13]. Fixed effect estimates as presented as odds ratios (ORs), with corresponding 95% credible intervals (CrI). The impact of location in the unit is described via the median OR (MOR), which can be interpreted as the change in odds moving from one pod to another with greater outcomes [14].

All analyses were conducted in R version 3.2.1 (R Foundation for Statistical Computing, Vienna, Austria). Analytic codes are available for download at https://doi.org/10.5281/zenodo.1040301.

Sensitivity analyses

We conducted three separate sensitivity analyses to ensure our results were robust to data assumptions. In the first sensitivity analysis, we limited the full cohort years to 2013–2015 for the MRSA colonization outcome, acknowledging that our surveillance program has grown more robust over time, and in particular in 2013 following an outbreak of MRSA in the unit. In the second sensitivity analysis, we stochastically added cases of MRSA colonization to the uncolonized full cohort, acknowledging our surveillance program will not capture all colonizations. Our range of MRSA prevalence was set to a low of 0.9% of the cohort to a high of 2.2% of the cohort, informed from 2014 meta-analysis of MRSA colonization in various NICUs over a 12-year period [15]. In the third set of sensitivity analyses for both the full and sub-cohorts, we excluded infants who were not born at Christiana Hospital (i.e., outborn; 10% of full cohort and 18% of sub-cohort), acknowledging that some of these infants may have been colonized prior to admission to the NICU.

Results

Between 2006 and 2015, there were 11 428 initial admissions to the NICU, among which MRSA colonization was detected in 77 (0.7%) and late-onset sepsis was lab-confirmed in 151 (1.3%) infants. *S. aureus* was cultured in 19 (12.6%) of late-onset sepsis cases; data were not accessible to classify MRSA bacteremia. Among those whose trachea was intubated ($n = 2670$, 23.4%), routine surveillance cultures were performed in 1215 infants (45.5%). *P. aeruginosa* grew in 49 (4.0%) and *K. pneumonia* grew in 106 (8.7%) of the endotracheal tube isolates.

Table 1 Characteristics of the full cohort and sub-cohort of infants admitted to the neonatal intensive care unit between 2006 and 2015

Characteristic	Full cohort ($n = 11\,428$)	Sub-cohort ($n = 1215$)
Individual level		
Gestational age, wks, median (IQR)	37 (5)	29 (9)
Birthweight, g, mean (SD)	2638 (975)	1678 (1059)
Central line, *n* (%)	2042 (18%)	869 (72%)
Infant antibiotics, *n* (%)	8939 (78%)	1197 (99%)
PROM, *n* (%)	1706 (15%)	311 (26%)
Clinical chorioamnionitis, *n* (%)	1253 (11%)	74 (6%)
Maternal antibiotics, *n* (%)	5073 (44%)	593 (49%)
Outborn, *n* (%)	1124 (10%)	217 (18%)
Average census during stay, mean (SD)	49 (7)	49 (6)
Vent days, median (IQR)	—	6 (19)
Outcomes		
MRSA colonization, *n* (%)	77 (1%)	—
Late-onset sepsis, *n* (%)	151 (1%)	—
P. aeruginosa colonization	—	49 (4%)
K. pneumonia colonization	—	106 (9%)
Contextual level		
Single crib pod, *n* (%)	1506 (14%)	199 (17%)
Space for equipment pod, *n* (%)	1340 (12%)	186 (16%)
Refrigerator pod, *n* (%)	623 (6%)	58 (5%)

The sub-cohort included infants whose tracheas were intubated for mechanical ventilation and at least one surveillance culture was obtained

PROM premature rupture of membranes, *MRSA* methicillin-resistant *Staphylococcus aureus*, *IQR* interquartile range

In the full cohort, the median gestational age was 37 weeks (interquartile range: 5) and the mean birthweight was 2638 g (SD: 975). Approximately 90% of infants ($n = 10\,299$) were born at Christiana Hospital, and the average census during the NICU stay was 49 occupied beds (SD: 7). For the sub-cohort of intubated infants where at least one surveillance culture was obtained, the median gestational age was 29 weeks (interquartile range: 9) and mean birthweight was 1678 g (SD: 1059). The median length of intubation was 6 days (interquartile range: 19), and was heavily skewed right. For both the full and sub-cohorts, ~15% of infants were in a pod that had space for more medical equipment. Additional characteristics can be found in Table 1.

Table 2 presents the results of the regression analyses. MRSA colonization, late-onset sepsis, *P. aeruginosa* colonization, and *K. pneumonia* colonization clustered significantly by pod with the respective MORs: 3.87 (95% CrI:

Table 2 Mixed effect multilevel logistic regression model results for MRSA colonization of the nares or lab-confirmed late-onset sepsis (full cohort), and *Pseudomonas aeruginosa* or *Klebsiella pneumoniae* endotracheal tube colonization (sub-cohort)

Characteristic	Full cohort outcomes ($n = 11\,428$)		Sub-cohort outcomes ($n = 1215$)	
	MRSA colonization[a] ($n = 77$)	Late-onset sepsis ($n = 151$)	*P. aeruginosa* colonization ($n = 49$)	*K. pneumonia* colonization ($n = 106$)
Estimates of fixed effects: OR (95% CrI)				
Individual level				
Birth year[b]	**1.30 (1.18, 1.43)**	**0.91 (0.86, 0.97)**	1.09 (0.97, 1.22)	**1.16 (1.06, 1.27)**
Gestational age, wks[c]	**0.78 (0.73, 0.83)**	**0.79 (0.75, 0.83)**	1.03 (0.93, 1.13)	0.96 (0.87, 1.05)
Central line	1.62 (0.82, 3.18)	**7.75 (4.38, 13.71)**	2.82 (0.36, 22.33)	2.21 (0.48, 10.15)
Infant antibiotics[c]	1.39 (0.52, 3.67)	1.61 (0.57, 4.58)	—	—
Vent days[d]	—	—	**3.56 (2.30, 5.53)**	**5.00 (3.47, 7.19)**
PROM	0.87 (0.50, 1.51)	0.80 (0.53, 1.19)	0.96 (0.46, 2.01)	1.11 (0.65, 1.92)
Chorioamnionitis	0.73 (0.28, 1.91)	0.64 (0.31, 1.32)	1.29 (0.46, 3.65)	0.79 (0.34, 1.83)
Average census during stay[b]	1.01 (0.97, 1.05)	1.01 (0.98, 1.04)	1.02 (0.96, 1.09)	1.03 (0.98, 1.08)
Contextual level				
Equipment pod	0.67 (0.25, 1.83)	0.75 (0.36, 1.56)	**2.61 (1.19, 5.78)**	0.92 (0.45, 1.87)
Estimates of random effects and test for spatial autocorrelation				
MOR (95% CrI)[e]	**3.87 (2.90, 5.61)**	**2.07 (1.68, 2.62)**	**2.29 (1.53, 4.01)**	**2.06 (1.44, 3.21)**
Moran's *I* statistic	−0.08 (0.20)[f]	<0.01	−0.10	−0.12
Moran's *I* *p*-value	0.60 (0.05)[f]	0.33	0.62	0.71

OR odds ratio,*MOR* median odds ratio, *CrI* credible interval, *PROM* premature rupture of membranes, *MRSA* methicillin-resistant *Staphylococcus aureus*

[a]A multilevel spatial model using eigenvectors was fit to the data to account for observed spatial autocorrelation

[b]Variable grand mean centered for modeling

[c]Due to near-complete antibiotic exposure among the sub-cohort, this variable was omitted from modeling

[d]Variable log-transformed for modeling; only available for sub-cohort

[e]Precision estimates based on 1000 bootstrap replicates

[f]Moran's *I* in parentheses depicts original multilevel model without eigenvectors, indicating presence of spatial autocorrelation

Bold values denote statistically significant estimates.

2.90, 5.61); 2.07 (95% CrI: 1.68, 2.62); 2.29 (95% CrI: 1.52, 4.01); and 2.06 (95% CrI: 1.44, 3.21), suggesting that location in the NICU mattered for all studied outcomes. Figure 1 shows the corresponding choropleth maps. Only MRSA colonization demonstrated spatial autocorrelation (Moran's *I*: 0.20; *p*-value: 0.05) implying that neighboring pods influenced risk of becoming colonized (see eFig. 2 for spatial correlogram).

Among the contextual-level variables considered, being in a pod with more space for equipment increased risk 2.61 times (95% CrI: 1.19, 5.78) for *P. aeruginosa* endotracheal tube colonization compared to being in a pod without the available equipment space, controlling for factors relating to infant acuity. On the individual level, younger gestation was a risk factor for both MRSA colonization and late-onset sepsis, and having a central line increased risk of sepsis nearly eight-fold (OR: 7.75; 95% CrI: 4.38, 13.71). The greatest risk factor for endotracheal tube colonization was length of ventilator support, where each log increase in vent days increased the odds of *P. aeruginosa* 3.56 times (95% CrI: 2.30, 5.53) and *K. pneumonia* 5.00 times (95% CrI: 3.47, 7.19). Over the study period, MRSA colonization and *K. pneumonia* colonization statistically increased (average of 30% and 16% per year, respectively), while late-onset sepsis decreased (average of 9% per year).

The sensitivity analysis for MRSA surveillance improvements demonstrated a slight underestimation of the spatial clustering (MOR: 5.34; 95% CrI: 3.40, 10.95), while the gestational age effect remained similar (OR: 0.80; 95% CrI: 0.74, 0.88). Birth year was no longer an independent predictor due to the limited cohort years. Stochastically increasing detection of MRSA colonization from the observed prevalence of 0.7% to 0.9%, 1.5%, and 2.2% correspondingly attenuated the clustering effect, with respective MORs of 2.87 (95% CrI: 2.28, 3.83), 2.16 (95% CrI: 1.83, 2.63), and 1.93 (95% CrI: 1.65, 2.30). The sensitivity analyses excluding outborn infants demonstrated the results were robust to this potential selection bias, as point

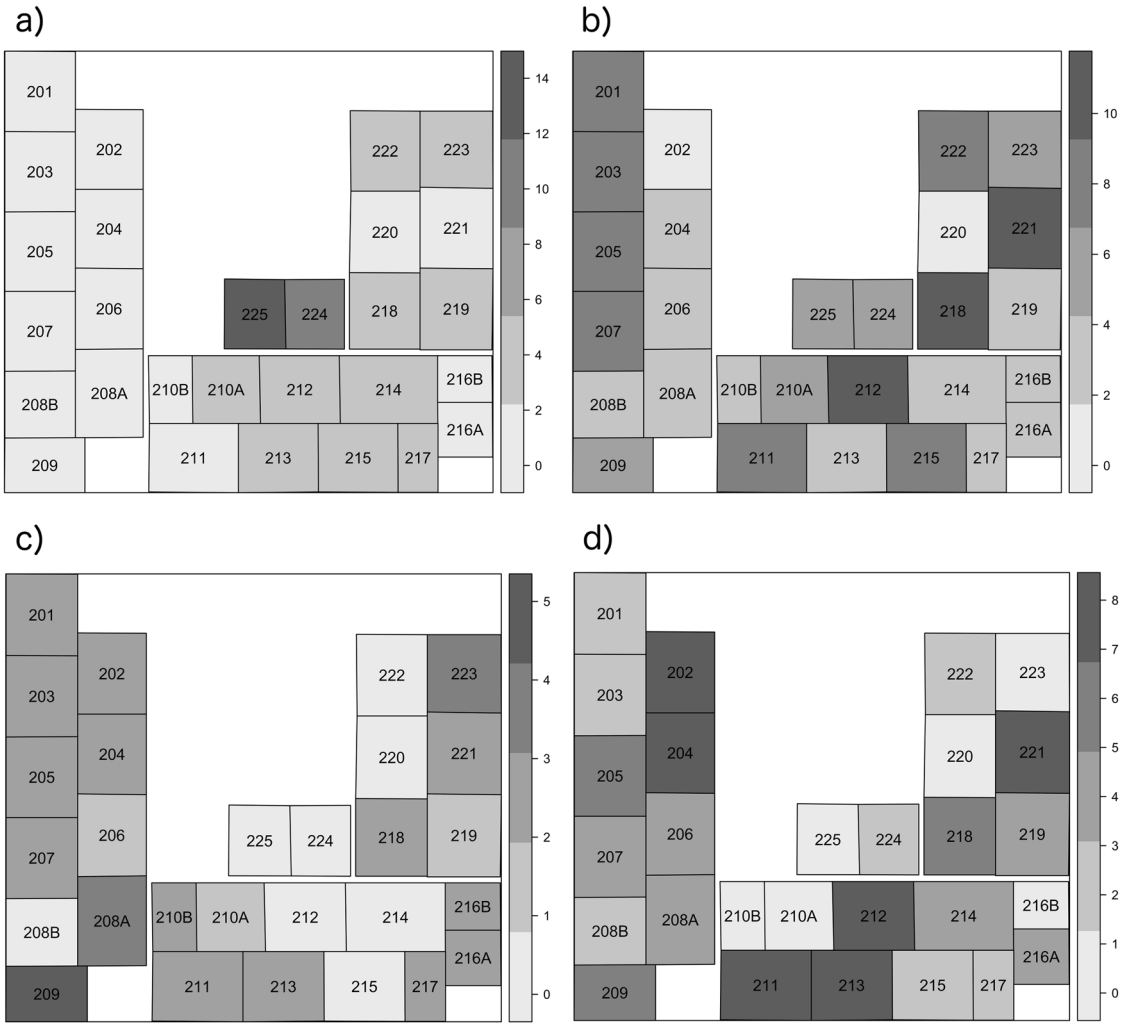

Fig. 1 Choropleth maps of methicillin-resistant *Staphylococcus aureus* (MRSA) colonization of the nares (**a**), lab-confirmed late-onset sepsis (**b**), *Pseudomonas aeruginosa* colonization of the endotracheal tube (**c**), and *Klebsiella pneumoniae* colonization of the endotracheal tube (**d**) in the neonatal intensive care unit. Lighter shades of gray indicate a fewer number of cases, while darker shades indicate a greater number of cases

estimates did not meaningfully differ from the full analyses and statistical inference remained consistent (results not shown).

Discussion

In this retrospective analysis of pathogenic organism colonization and infection in the NICU, we observed that location of care in the NICU appeared to correlate with all four studied outcomes. Additionally and among those infants whose trachea was intubated, being in a pod with space for more equipment had higher odds of *P. aeruginosa* colonization of the endotracheal tubes. Using a framework such as the epidemiological triad of infectious disease transmission allowed us to consider extrinsic factors that otherwise may not be included in a traditional clinical study.

The NICU environment is a reservoir for a variety of organisms, both pathogenic and commensal [16], and can influence the microbiome of the infant [17]. A variety of environmental correlates of infection have been found in other NICUs. For example, a *Serratia marcescens* outbreak was believed to be the result of clutter within the unit and inappropriate sterilization of shared breast pumps [18], while a *Pseudomonas aeruginosa* outbreak in another unit was caused by a contaminated water supply [19]. Recently a 2016 outbreak of *P. aeruginosa* linked to contaminated water sources, including sinks led to the temporary closure of a NICU [20]. Consequently as others have stated, prevention of health-care-associated infections needs to focus on extrinsic as well as intrinsic factors [21].

In addition to extrinsic factors explaining some of the outcome risk, the data in our study suggest that the primary correlates of colonization and infection were intrinsic

neonatal factors, such as younger gestational age, presence of a central line, or, among those intubated, the length of ventilation required. These attributes are well described in the literature [1–3]. While some pathogens may be vertically transmitted during pregnancy and birth, the amount of care required of an infant (i.e., their acuity) in an ICU setting potentially implicates health-care workers (as well as visitors) as vectors for horizontal transmission. Previous work examining the interplay of patient care networks among babies in the NICU has demonstrated that intrinsic factors such as being preterm or intubated increases risk for MRSA colonization [22].

Our finding that MRSA colonization for a given infant depended in some part upon a neighboring colonized infant may partially be explained by cohorting in our NICU. That is, when infants test positive for MRSA colonization, they may be moved to certain areas of the NICU with other MRSA-colonized infants. However, depending on the time period and room availability, infants may have also been isolated in situ, supporting the need for early identification of MRSA colonization, single room isolation, and clustered care practices given potential for horizontal transmission [23–25]. Previous research indicates that 20–40% of a patient's flora may be the result of cross-contamination via the health-care worker [26], and ~30% of infants colonized with MRSA develop invasive infection [27].

There are several limitations to this work. First, historic data do not necessarily reflect the current state of risk in the NICU. For example, various infection control policies have been temporally implemented in our NICU in response to outbreak conditions, such as universal gloving when handling infants. If there were an environmental correlate—e.g., a cooling device contaminated with *P. aeruginosa* that has since been sterilized—we may no longer note equipment space as a risk factor in analysis. Second, the finding of equipment space as an independent risk factor does not necessarily implicate actual medical devices as the causative agent, as we did not have a measure of amount of equipment used. There may be unmeasured or unaccounted for factors that explained the observed association. Further, infants requiring advanced care may have been admitted to these areas in our NICU and thus at greater risk for the outcomes, although we did attempt to control for markers of acuity. Third, we did not have timing of the outcomes in relation to the individual or spatial components. We made the simplifying assumption that where the infant resided the longest was the location of the outcome occurring. Similarly, some of our variables, namely presence of a central line, intubation, and antibiotic exposure, lacked timing data as well and therefore may have occurred after the outcome developed. The notion of spatial misclassification is an important epidemiologic concept, and techniques are needed to account for this potential information bias [28]. Fourth, critical care management of infants and spatial design differs from institution to institution, therefore generalizability needs to be considered for other NICUs. Colonization findings reflect our unit's surveillance program. Outcomes have likely been undercounted as every infant is not screened, although the sensitivity analyses did not alter our conclusions.

There are several important strengths to this work. The use of a multilevel analysis allowed for detection of pod-level factors, as opposed to a typical individual-level regression model that would fail to take into account the contextual correlation. Furthermore, by applying a spatial multilevel model we were able to account for the auto-correlation demonstrated in the MRSA model. A second strength was the use of a Bayesian framework, which allows prior information to be incorporated into the model. Third, creating choropleth maps allowed us to visualize patterning of these outcomes and intervene in specific areas of our NICU. Fourth and finally, all data derived from a database with nurse-reviewed clinical data, as opposed to billing data.

In summary, we observed that extrinsic factors partially explained risk for neonatal colonization and infection of pathogenic organisms, but intrinsic factors were the primary drivers, possibly through the health-care worker as an intermediary. Infection control and prevention researchers should nonetheless still consider spatial and environmental correlates of infection, as there are many opportunities for horizontal organism transmissions in a NICU setting.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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