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Impact of transition from open bay to single room design neonatal intensive care unit on multidrug-resistant organism colonization rates

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SUMMARY

Background: The influence of the neonatal intensive care unit (NICU) design on the acquisition of multidrug-resistant organisms (MDROs) has not been well-documented.
Aim: To examine the effect of single room unit (SRU) versus open bay unit (OBU) design on the incidence of colonization with MDROs and third-generation cephalosporin-resistant bacteria (3G-CRB) in infants admitted to the NICU.
Methods: Retrospective cohort study, including all infants admitted to the NICU of a tertiary care academic hospital two years prior to and two years following the transition from OBU to SRU in May 2017. Weekly cultures of throat and rectum were collected to screen for MDRO carriership. Incidence of colonization (percentage of all infants and incidence density per 1000 patient-days) with MDROs and 3G-CRB were compared between OBU and SRU periods.
Findings: Incidence analysis of 1293 NICU infants, identified 3.2% MDRO carriers (2.5% OBU, 4.0% SRU, not significant), including 2.3% extended-spectrum β-lactamase-producing Enterobacterales carriers, and 18.6% 3G-CRB carriers (17% OBU, 20% SRU, not significant). No differences were found in MDRO incidence density per 1000 patient-days between infants admitted to OBU (1.56) compared to SRU infants (2.63).
Conclusion: Transition in NICU design from open bay to SRUs was not associated with a reduction in colonization rates with MDROs or 3G-CRB in our hospital. Further research on preventing the acquisition and spread of resistant bacteria at high-risk departments such as the NICU, as well as optimal ward design, are needed.

Introduction

Antibiotic resistance is an increasing problem, even more so in intensive care units, where patients frequently have antibiotics prescribed [1,2]. Infants admitted to the neonatal

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intensive care unit (NICU) are specifically affected by antibiotic treatment and resistance because of their newly developing gut microbiota. Antibiotic pressure drives selection towards more intrinsically resistant gut microbiota and may increase the risk for multidrug-resistant organism (MDRO) acquisition [3]. Bacterial colonization of the infant's gut is a natural process, and is influenced by dietary and medical factors [4—6]. Colonization with MDRO in infants has multiple risk factors, of which an important one is maternal MDRO colonization [7]. Other sources of MDRO acquisition for infants admitted to the NICU may be the hospital environment, healthcare workers (HCWs), and other caregivers. Other risk factors for colonization with MDROs are low gestational age, low birth weight, and extended duration of hospital stay [7]. How infants acquire microbiota from their environment is not fully understood, but admission to a NICU seems to have a sustained effect on the dynamics of gut microbial composition of infants [4—6,8]. Adapting NICU design from open bay units (OBUs) to single room units (SRUs) has been suggested to facilitate infection control, supported by a recent meta-analysis, which, among others, identified a reduction in nosocomial sepsis [9]. However, not much is known about MDRO acquisition in relation to ward design, with even less data available for NICUs. Since outbreaks with intrinsically resistant Gram-negative rods, such as *Serratia marcescens* and *Enterobacter* species, have been described in NICU settings, these may be influenced by unit design as well [10,11].

In May 2017, the NICU at our hospital was transformed from traditional OBU to SRU. This change was initiated following the need for improved family-centred care, and other possible beneficial outcomes of an SRU. This offered a unique situation to evaluate the effect of the new ward design in relation to MDRO colonization and spread among the admitted infants. Screening cultures for Gram-negative MDROs had already been implemented in our NICU before the ward transformation and enabled us to identify infants colonized with MDROs.

The aim of this study was to determine whether colonization with Gram-negative MDROs, including extended-spectrum β-lactamase-producing Enterobacterales (ESBL-E) and third-generation cephalosporin-resistant bacteria (3G-CRB) in infants admitted to the NICU would be reduced following the transition to SRUs. It was hypothesized that acquisition of colonization through the NICU environment could be an important factor, assuming walls surrounding each patient in a SRU would stimulate HCWs to consider hygiene measures more often and compliance to hygiene protocols would be higher in a SRU compared to open bay design, where medical equipment is more easily shared without disinfection. It was also hypothesized that with a decrease in colonization rate, fewer infections with MDROs would be observed.

Methods

Setting

This retrospective study was conducted at the NICU of the Leiden University Medical Center, one of the ten tertiary care NICUs in the Netherlands. The 25-bed level-III NICU admits ~600 infants per year. The new SRU ward consists of 17 single-patient rooms and four twin rooms. The nurse:infant ratio is 1:1—3 depending on illness severity. All HCWs are dedicated to the NICU. Before the transition to single rooms, the OBU ward consisted of two intensive care open bays (total of 16 beds, including one single room for isolation purposes), and one high-care open bay (nine beds), in which the nurse:infant ratio was 1:1—4. In line with national policy, if an infant reached a postpartum gestational age of 30 weeks, a weight >1000 g, and was clinically stable, the infant was transferred to another hospital for post-intensive care. Admission and transfer policies did not change during the study period. The rate of overnight stay of parents was the same during both unit layout periods. Cleaning of the space around the bed in the OBU was performed by nurses, cleaning of the room in the SRU was performed by cleaning staff, and medical equipment was in both unit types cleaned by nurses. The Institutional Ethics Review Board waived the need for formal approval because of the retrospective nature of the study (G19.071).

Standard procedures

As a standard surveillance procedure, once weekly, on the same day each week, sampling of rectum and throat was performed in each admitted infant, for Gram-negative MDRO screening by culture. MDRO was defined according to the CDC MDRO guideline, and in addition included *Escherichia* spp., *Klebsiella* spp., and *Proteus mirabilis* that were third-generation cephalosporin resistant without producing ESBL (see Supplementary Table A) [12,13]. When MDROs were identified in cultures, contact precautions were applied for the infant; however, in the open ward design no transfer to a single room was performed. If an infant was suspected of infection, clinical cultures were taken. Standard empiric therapy for late-onset sepsis of unknown origin in our NICU was a glycopeptide and a third-generation cephalosporin in combination with a single dose of an aminoglycoside, which was adjusted accordingly if an infant was colonized with MDRO. During the study period, there were no changes in empiric antibiotic therapy. There was no gut decontamination policy. Compliance to the hygiene protocol by HCWs was measured approximately every eight months, with a checklist, involving hygiene measures, performed by HCWs who were unobtrusively observing colleagues, in combination with an education and awareness programme.

Participants and design

Infants admitted to the NICU two years prior to and two years following the transition from OBUs to SRUs on May 15th, 2017, were included. Infants were divided into two groups, corresponding with the day of admission, prior to (OBU) or following (SRU) the transition day.

Data collection

All relevant patient data were retrieved from the electronic patient data management system. Microbiological data were retrieved from the laboratory information system.

Definitions

- 3G-CRB: Gram-negative rods with intrinsic or acquired third-generation cephalosporin resistance, including but not limited to ESBL-positive strains.
- Infection: Positive clinical culture with clinical signs of infection, treated as such by the treating physician.

Laboratory techniques

Screening swabs were collected from the rectum and throat, and they were inoculated in tryptic soy broth (TSB) supplemented with vancomycin (8 mg/L) and cefotaxime (2.5 mg/L) (MP products, Groningen, the Netherlands) for enrichment and selection of ESBL-E. After overnight incubation, the broth was subsequently subcultured on chromID ESBL agar (bioMérieux, Marcy-l'Etoile, France) and MacConkey agar with tobramycin (8 mg/L) (MP products). In December 2016, the laboratory procedure was changed to a non-selective broth (TSB, MP products) for improved detection of MDROs. To improve specificity, from July 2017 onwards the broth was subcultured after overnight incubation on more selective agar (chromID ESBL agar (bioMérieux) and MacConkey agar with tobramycin (8 mg/L) and ciprofloxacin (0.5 mg/L) (MP products)). Comparing the time-period one year prior to and one year following the change in procedure, a 6% increase in the overall detection rate of patients with MDRO colonization was found in our hospital, possibly related to this change in laboratory procedure. All Gram-negative rods growing on the agars were identified by matrix-assisted laser desorption–ionization time-of-flight mass spectrometry (Bruker Daltonics, Bremen, Germany) and antimicrobial drug susceptibility testing was performed by using the Vitek2 system (bioMérieux). ESBL production was phenotypically confirmed by using combination disc diffusion tests [14].

Data analysis

For analyses of infection with MDROs or 3G-CRB, all cultures collected between May 15th, 2015 and May 15th, 2019 of infants in whom screening cultures were collected, were included. For colonization analyses, only infants admitted between May 15th, 2015 and May 15th, 2019, from whom at least one MDRO screening culture set was collected, were included. To exclude possible MDRO acquisition from home or other hospitals, the following cases were excluded for colonization analyses: infants aged >72 h at admission, infants admitted on the day of unit transition, culture results of readmissions, and culture results from OBU infants after the transition day. Subanalyses were also performed in infants born at a gestational age <32 weeks from whom more than one culture set was collected, to select for the subgroup of infants needing the most intensive care (INMIC). Incidence of colonization was calculated as percentage of all infants and incidence density as incidence per 1000 patient-days. Results were analysed according to unit type. Data were presented as median with interquartile range (IQR), where appropriate. Non-normally distributed numerical data were compared using the Mann–Whitney *U*-test. Categorical outcome data were compared using Fisher's exact test. Differences in incidence density were calculated using the Poisson test. Data were analysed using R, version 3.6.3 [15].

Results

Patient and ward demographics

During the study period 2511 infants were admitted to the NICU. In 1078 infants no screening cultures were collected because their admission was shorter than a week and did not include the standard weekly culture day. In these excluded infants, no clinical cultures were positive for MDROs or 3G-CRB. Screening cultures were collected from 1433 infants, who were subsequently included in the infection analyses (759 in OBU, 673 in SRU, one infant admitted on the day of unit transition). Other exclusion criteria accounted for 140 other infants (Figure 1), resulting in 1293 infants identified for colonization analyses (675 in OBU, 618 in SRU).

Patient demographics of the infants included for colonization analyses are shown in Table I, including subgroup demographics of INMIC. No differences between the groups with different ward design were found regarding gestational age, sex, number of screening culture sets collected, time of collection of the first screening culture set, length of hospital stay and antibiotic treatment with Gram-negative coverage during admission.

Hand hygiene measure compliance measurements were recorded at three time-points during each unit period (Supplementary Table B). Focusing on hand disinfection and cleaning of surfaces, the hygiene protocol was followed more often in SRU design (203 out of 255 scored moments, 80%) compared to OBU design (67 out of 113 scored moments, 59%) ($P < 0.001$). This difference may have been due to observer bias, since it is more difficult to unobtrusively observe HCWs working in a single room, compared to observing them in a bay with co-workers.

Colonization

Multidrug-resistant organisms

MDROs were cultured from 42 infants (3.2%) in 73 screening sets. Of all MDROs, 72% were ESBL-E (30 infants, 2.3%). No carbapenemase-producing Enterobacterales were cultured. No difference was found in rates of MDRO carriership in all infants between OBU (2.5%) and SRU (4.0%) (not significant, n.s.) (Table II), nor in the INMIC subgroup (4.4% OBU, 5.2% SRU, n.s.). Also, no difference was found in the incidence density per 1000 patient-days (1.56 OBU, 2.63 SRU, n.s.). Median age until the first positive screening culture was 9.5 days (IQR: 17.5).

Of the 42 MDRO carriers, 18 (43%) infants were already positive in their first screening culture (7 OBU, 11 SRU, n.s.). Twenty infants (48%) had follow-up cultures taken after their positive culture: ten of them (50%) were persistently positive and ten of them (50%) were transient carriers (Table II). Of the ten persistent MDRO carriers, in nine infants *Escherichia coli* ($N = 6$ ESBL$^+$) were cultured, and in one infant ESBL$^+$ *Enterobacter cloacae*. In the ten transient carriers, the cultured MDRO were $N = 4$ *E. coli* ($N = 2$ ESBL$^+$), $N = 3$ ESBL$^+$ *E. cloacae*, $N = 2$ ESBL$^+$ *Klebsiella pneumoniae*, and $N = 1$ trimethoprim/sulfamethoxazole-resistant *Stenotrophomonas maltophilia*. No clear differences were observed in the patterns or onset of carriership nor the type of micro-organisms between the units.

Third-generation cephalosporin-resistant bacteria

In 540 sets from 240 infants (19%), 3G-CRB were cultured; 17% in OBU infants and 20% in SRU infants (n.s.) (Table II). Also, no difference in 3G-CRB detection rate was found between unit types in the INMIC subgroup (37% OBU, 38% SRU, n.s.). Median age until the first positive screening culture was 12 days (IQR: 16). Of the 240 3G-CRB carriers, 66 (28%) infants were positive in their first screening culture (29 in OBU, 37 in SRU, n.s.). In 131 infants (55%) follow-up cultures were taken after the positive culture; 91 of these infants (69%) were persistently positive, and 40 infants (31%) were transient carriers.

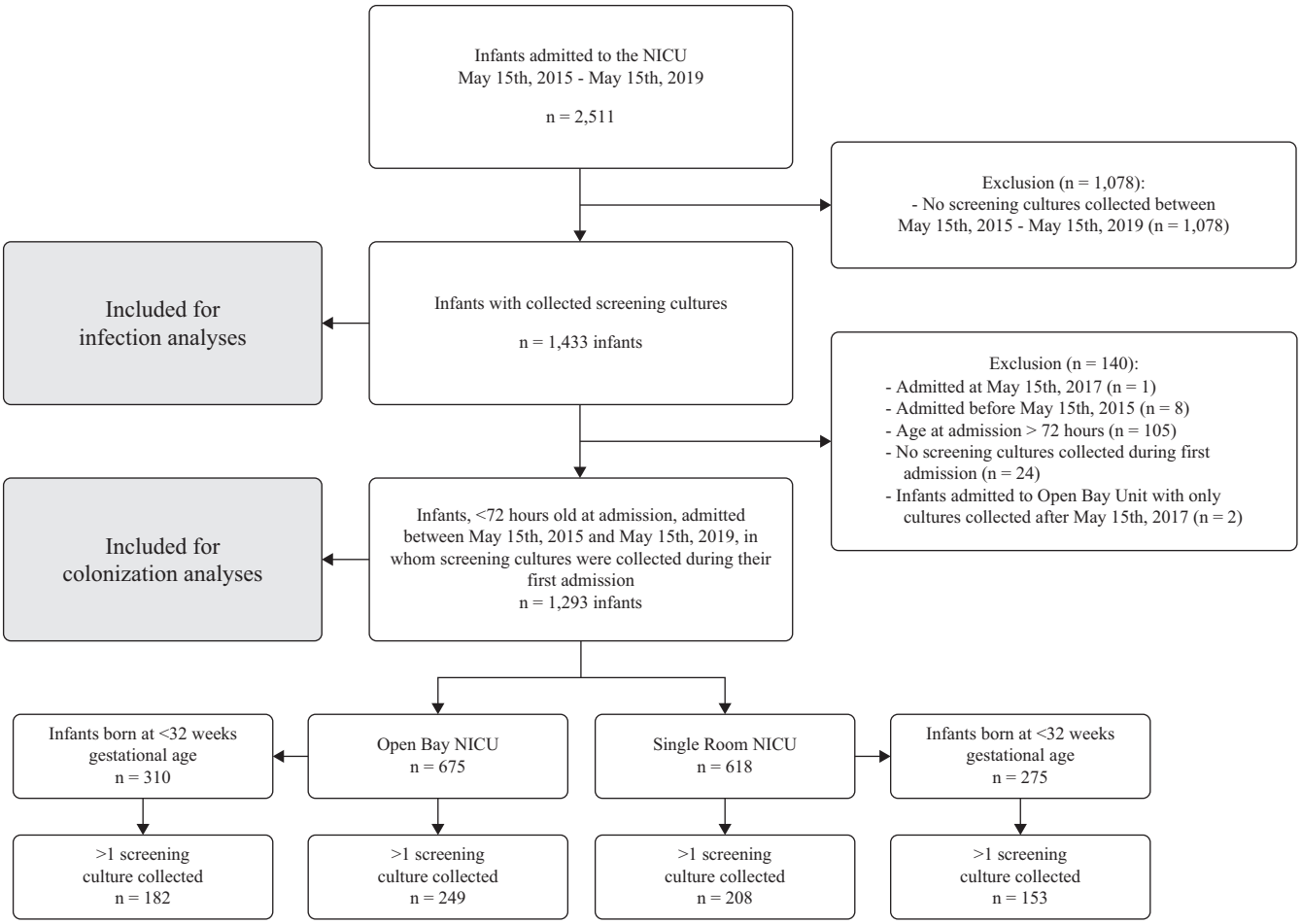

Figure 1. Flow chart. NICU, neonatal intensive care unit.

Table I
Patient demographics of infants included for colonization analyses

Variable		OBU	SRU	*P*-value
No. of infants	All	675	618	
	INMIC subgroup	182	153	
Sex (female)	All	281 (42%)	269 (44%)	0.50
	INMIC subgroup	83 (46%)	74 (48%)	0.66
Gestational age at birth (weeks)	All	32 (8)[a]	32 (8)[a]	0.67
	INMIC subgroup	28 (3)[a]	28 (2)[a]	0.73
No. of screening sets per infant	All	1 (1)[a]	1 (1)[a]	0.45
	INMIC subgroup	4 (4)[a]	3 (4)[a]	0.39
Age (days) at first culture	All	4 (3)[a]	4 (4)[a]	0.42
	INMIC subgroup	4 (3)[a]	5 (4)[a]	0.88
Total no. of patient-days	All	10,883	9516	0.49
	INMIC subgroup	6130	4781	0.71
Length of hospital stay per infant (days)	All	9 (11)[a]	9 (12)[a]	0.49
	INMIC subgroup	27 (30)[a]	25 (26)[a]	0.71
Antibiotic treatment (Gram-negative coverage) during admission	All	507 (75%)	457 (74%)	0.65
	INMIC subgroup	171 (94%)	140 (92%)	0.40

OBU, open bay unit; SRU, single room unit; INMIC, infants needing the most intensive care.
[a] Median (interquartile range).

Table II
Incidence of multidrug-resistant organisms (MDRO) and third-generation cephalosporin-resistant bacteria (3G-CRB) of infants included for colonization analyses

Micro-organism	Variable	OBU ($N = 675$)	SRU ($N = 618$)	*P*-value
MDROs	Colonization	17 (2.5%)	25 (4.0%)	0.16
	Age (days) at first culture	3 (3)[c]	4 (4)[c]	0.25
	First culture positive[a]	7 (41%)	11 (44%)	0.34
	Age (days) at first positive culture	9 (17)[c]	10 (17)[c]	0.60
	Transient carriers[b]	5 (45%)	5 (56%)	0.18
	Persistent carriers[b]	6 (55%)	4 (44%)	
3G-CRB	Colonization	114 (17%)	126 (20%)	0.12
	Age (days) at first culture	4 (3)[c]	5 (3)[c]	0.91
	First culture positive[a]	29 (25%)	37 (29%)	0.21
	Age (days) at first positive culture[a]	14 (19)[c]	12 (15)[c]	0.12
	Transient carriers[b]	19 (29%)	21 (32%)	0.72
	Persistent carriers[b]	46 (71%)	45 (68%)	

OBU, open bay unit; SRU, single room unit.
[a] Of infants with MDRO/3G-CRB carriership.
[b] Percentages based on infants with follow-up cultures available.
[c] Median (interquartile range).

Infection with MDROs or 3G-CRB

Of the 1433 infants included for infection analyses, four infants (0.28%, 3 OBU, 1 SRU, n.s.) had an infection with an MDRO (Table III). All infections were caused by MDR *E. coli*, with two infants having ESBL-positive strains and two infants having ESBL-negative, aminoglycoside- and ciprofloxacin-resistant isolates. Screening detected MDR *E. coli* in three out of four infants with an infection (range: 2—29 days between collection of positive screening culture and collection of positive clinical culture), one infant had an early onset sepsis without any preceding screening cultures being collected, and the screening cultures after treatment remained negative (Figure 2).

An infection with 3G-CRB occurred in 16 infants (1.1%, 10 OBU, 6 SRU, n.s.), of whom seven infants (44%) were known to be colonized before infection occurred. Twelve infants had a bacteraemia with 3G-CRB: 11 with Gram-negative rods intrinsically resistant for cephalosporins (*E. cloacae* $N = 4$, *Citrobacter non-koseri* spp. $N = 3$, *Serratia marcescens* $N = 2$, *Acinetobacter* spp. $N = 2$) and one infant with ESBL-positive *E. coli*. Screening cultures did not detect the 3G-CRB in six patients (50%) with bacteraemia before the bacteraemia occurred. In the other six infants, 3G-CRB were detected in the screening cultures collected between one and 20 days before the bacteraemia occurred.

Combining a third-generation cephalosporin with an aminoglycoside in our empiric treatment of in-hospital infections kept our empirical coverage adequate for all cases of unpredicted MDRO and 3G-CRB infections.

Discussion

We hypothesized that the colonization rate of MDRO in infants would be reduced following the transition to SRU. However, no decrease was found in colonization rates after transition from OBU to SRU design in our NICU. Overall, 3.2% of the infants were colonized with MDRO and 18.6% of the infants were colonized with 3G-CRB. Because MDRO screening was performed systematically throughout the entire study period, colonization rates could be precisely monitored.

Table III
Number of infants infected by multidrug-resistant organisms (MDROs) or third-generation cephalosporin resistant bacteria (3G-CRB)

Micro-organism	Variable	OBU ($N = 759$)	SRU ($N = 673$)	Total
MDROs	Colonization	26	32	58
	Infection (including bacteraemia)	3	1	4
	Infection preceded by positive screening culture	3	0	3
	Bacteraemia	1	1	2
	Bacteraemia preceded by positive screening culture	1	0	1
3G-CRB	Colonization	144	145	289
	Infection (including bacteraemia)	10	6	16
	Infection preceded by positive screening culture[a]	6	1[b]	7
	Bacteraemia	6	6	12
	Bacteraemia preceded by positive screening culture[a]	3	3[b]	6

OBU, open bay unit; SRU, single room unit.
[a] With the same or another 3G-CRB.
[b] Two infants with 3G-CRB bacteraemia, preceded by positive screening cultures, had a previous episode of infection with 3G-CRB without preceding positive cultures.

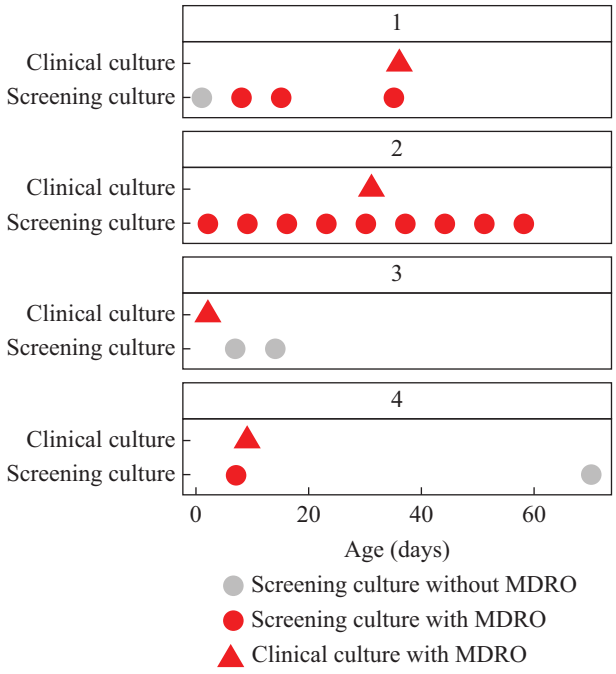

Figure 2. Clinical and screening cultures of infants (1–4) infected by a multidrug-resistant organism (MDRO). Screening detected MDROs in three of four infants with an MDRO infection. Infant 1 had sputum with *S. aureus* and multidrug-resistant (MDR) *E. coli*; the suspected focus was bronchitis. Infant 2 had a pyelonephritis with MDR *E. coli*. Infant 3 had an early onset sepsis with MDR *E. coli*. Infant 4 had bacteraemia with MDR *E. coli*, presumably from a necrotizing enterocolitis.

Only a handful of studies analysed MDRO colonization comparing single rooms with OBUs. Some studies, including one in a NICU, observed no difference in MDRO colonization after changing ward design [16–20]. Other studies did observe a decrease in MDRO colonization rates after transition to single rooms, including some studies that changed ward design because of an MDRO outbreak, in which case other critical factors that may influence MDRO colonization changed as well (e.g. increased awareness, hand hygiene, cleaning) [21–25]. Because of our transfer policy, resulting in a relatively short length of hospital stay, our colonization rates may have been lower compared to those of other NICUs. However, even in the INMIC group, no influence of ward design was detected.

Various sources may play a role in MDRO acquisition in NICU infants including caretakers, HCWs and environmental factors; however, the contribution of each factor is unknown. The lack of effect of ward design in our study suggests a smaller role for environmental factors and a larger role for parents or HCWs. According to previous studies, the rate of ESBL-E carriership in the Netherlands is 6.1–8.6% [26,27]. Combining these data with reported transmission rates from mother to child of around 14–35% leads to an expected ESBL-E carriership of approximately 0.9–3.0% in infants in our NICU if maternal transmission would be the main source, which is in accordance with the ESBL-E carrier rate of 2.3% in our cohort [7,28–30]. Since we did not screen mothers, the real contribution of maternal transmission in our population is unknown. However, although birth through vaginal delivery may be an important route of transmission, the percentage of parent-to-infant transmission is also dependent upon the duration of follow-up. Both rapid and delayed acquisition of MDRO was observed in our cohort, suggesting both acquisition through birth and later during admission through contact with parents, HCWs, or the hospital environment. Both persistent and transient carriership patterns were observed and it would be interesting to study whether the route of acquisition or other factors play a role in determining this pattern.

By conducting active surveillance, we were aiming at giving appropriate empirical therapy in case an infant becomes septic to prevent delayed treatment of sepsis. The negative predictive value of screening cultures was high (>99%) in our cohort, but the positive predictive value for MDRO infection was limited (5.2%). Unnecessary broadening of empirical therapy in all MDRO-colonized infants could also have harmful effects on resistance and microbiota development, emphasizing the need for adequate culture-taking and timely re-evaluation and cessation of empiric antibiotic therapy.

Several limitations apply to our study. Shortly after the ward transition, the laboratory improved the MDRO culturing procedure, which could have resulted in a mildly increased positivity rate in SRU infants, possibly masking a moderately positive effect of ward design. Also, the percentage of MDRO carriership in our NICU is low, requiring a large number of infants to detect a small decline. The effect of ward design may be more noticeable in high-prevalence settings. The small number of infants with MDRO colonization affected our ability to perform multivariate analysis, thereby limiting the ability to control for important potential confounding variables and making it difficult to isolate the effect of unit change.

Outbreaks were not detected in routine care, but possible transmission events (similar MDRO simultaneously cultured in different infants) were detected retrospectively in both ward design periods. These could not be evaluated, since typing results could not be obtained for most isolates of SRU infants.

In conclusion, the change from OBU to SRU did not result in a decline in colonization with resistant bacteria in our hospital. MDRO acquisition is caused by a combination of factors, including environmental factors, such as NICU design, and vertical transmission. In our setting with low MDRO colonization rates, as well as in mothers — most of whom are healthy and not pre-treated with antibiotics — standard empirical therapy is still adequate. This may change in the future with increasing colonization rates or be different in other countries with higher MDRO colonization rates. Further research on preventing the acquisition and spread of resistant bacteria at high-risk departments such as the NICU, as well as optimal ward design, are needed.

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Conflict of interest statement
None declared.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhin.2021.12.006.

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