CLINICAL RESEARCH ARTICLE

Family integrated care in single family rooms for preterm infants and late-onset sepsis: a retrospective study and mediation analysis

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BACKGROUND: During hospital stay after birth, preterm infants are susceptible to late-onset sepsis (LOS).
OBJECTIVE: To study the effect of family integrated care in single family rooms (SFRs) compared to standard care in open bay units (OBUs) on LOS. Peripheral or central venous catheters (PVCs/CVCs) and parenteral nutrition (PN) were investigated as potential mediators. Secondary outcomes were length of stay, exclusive breastfeeding at discharge, and weight gain during hospital stay.
METHODS: Single-center retrospective before-after study with preterm infants admitted ≥3 days.
RESULTS: We studied 1,046 infants (468 in SFRs, 578 in OBUs, median gestational age 35 weeks). SFRs were associated with less LOS (adjusted odds ratio (OR) 0.486, 95% confidence interval (CI): 0.293; 0.807, $p = 0.005$). PVCs (indirect effect −1.757, 95% CI: −2.738; −1.068), CVCs (indirect effect −1.002, 95% CI: −2.481; 0.092), and PN (indirect effect −1.784, 95% CI: −2.688; −1.114) were possible mediators of the effect. PN was the main mediator of the effect of SFRs on LOS. We found shorter length of stay (median length of stay in SFRs 10 days and in OBUs 12 days, adjusted β −0.088, 95% CI: −0.159; −0.016, $p = 0.016$), but no differences in weight gain or exclusive breastfeeding at discharge.
CONCLUSIONS: SFRs were associated with decreased incidences of LOS and shorter length of hospital stay. The positive effect of SFRs on LOS was mainly mediated through a decreased use of PN in SFRs.

IMPACT:

- Family integrated care (FICare) in single family rooms for preterm infants was associated with less late-onset sepsis events during hospital stay and a shorter length of hospital stay after birth.
- FICare in single family rooms was associated with less use of peripheral or central venous catheters and parenteral nutrition.
- Mediation analysis provided insights into the mechanisms underlying the effect of FICare in single family rooms on late-onset sepsis and helped explain the differences observed in late-onset sepsis between FICare in single family rooms and open bay units.
- The reduction in late-onset sepsis in FICare in single family rooms was mediated by a reduced use of intravenous catheters and parenteral nutrition.

INTRODUCTION
Background
Each year ~15 million children are born preterm, and the largest proportion (85%) is born moderate or late preterm (between 32 and 37 weeks of gestation).[1] Even moderate or late preterm infants can spend a considerable time in the neonatal intensive care unit (NICU) after birth, and in this environment they are susceptible to late-onset sepsis (LOS, occurring ≥72 h after birth).[2,3] LOS has a multifactorial origin, and risk factors for LOS include biological immaturity of immunological defense mechanisms, frequent disruptions of natural barriers (skin and mucous membranes), the presence of peripheral (PVCs) or central venous

catheters (CVCs), poor hygiene practices, or prolonged and widespread initial empirical antibiotic treatment.[4,5]

In the technological environment of the modern-day NICU, parents cannot always be present, and emotional and physical closeness is impaired as preterm infants are cared for in open bay units (OBUs).[6] The European Standards of Care for Newborn Health recommend that each unit should strive for an optimal design to support family-centered care, thereby facilitating parent participation in care and optimizing outcomes (including LOS) in this vulnerable patient population.[7,8] Supporting these recommendations, a recent meta-analysis (including 9 studies and 4,165 patients) revealed that hospitalizing preterm infants in single

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family rooms (SFRs) was associated with a reduced incidence of LOS during hospital stay relative to OBUs.[9]

However, in these previous studies, the mechanisms underlying the decrease in LOS events have remained unidentified and the participation and presence of parents and the association with infections remain unclear.[10,11] Specifically, no studies have described the association between the use of PVCs, CVCs, or parenteral nutrition (PN) and the incidence of LOS when infants are cared for in different environments.

In 2014, our neonatal level 2 department was rebuilt to SFRs, thereby allowing parents to be present 24 h per day, with complete couplet care for mother–infant dyads.[12] Also, we simultaneously started a complementary family integrated care (FICare) program.[13] In this program, parents provide most of the care for their infants, they are invited to participate in family-centered rounds, and have educational group sessions to learn about various aspects of prematurity.

Objective
We studied the effect of hospitalizing preterm infants in SFRs with a complementary FICare program compared to standard care in OBUs on the incidence of LOS in our level 2 neonatal ward. Additionally, we studied PVCs, CVCs, and PN as potential mediators in the pathway between SFRs and LOS. Secondary outcome measures were length of hospital stay, exclusive breastfeeding at discharge, and weight gain during hospital stay.

METHODS
We used the TREND (Transparent Reporting of Evaluations with Nonrandomized Designs) checklist[14] and the STROBE-NI (Strengthening the Reporting of Observational Studies in Epidemiology for Newborn Infection) case-ascertainment methods.[15]

Study design
This was a single-center retrospective study, with a before-after design. We studied preterm infants admitted during the period of standard neonatal care in OBUs (January 2012 through June 2014) vs. preterm infants admitted to FICare in SFRs (January 2015 through December 2016). An information specialist, independent of the objective of this research, was asked to provide all cases of preterm infants admitted to the hospital during the study period. Data collectors were blinded to the objective of this research and collected data of all preterm infants from January 2012 through December 2016. Due to the construction of the new ward, FICare implementation, and training of healthcare professionals, data between June 2014 and January 2015 were not used for this study. Data were collected from medical records during the years 2017 and 2018.

Population
Eligible patients were all infants born in or transferred to the level 2 neonatal ward in a teaching hospital in Amsterdam, the Netherlands. Preterm infants (<37 weeks gestation) with a length of hospital stay ≥3 days were included. For a detailed explanation on the population of preterm infants studied and levels of neonatal care in the Netherlands, see Supplementary information (page 2 (online)).

Intervention
Family integrated care.   In the FICare model, parents were trained to be the primary caregiver of their infant, and nurses supported, instructed, and counseled parents. Parents were invited but not obligated to be present ≥8 h per day, and rooming-in facilities were present if they wanted to stay during the night. Parents were actively encouraged to participate in their infant's care by providing feedings by nasogastric tube, breast or bottle, providing skin-to-skin care (by mothers and fathers), weighing, and regulating temperature control.

Family-centered rounds were implemented and included active parental participation in medical decision making on daily medical rounds and involving them in the process of patient management together with the nurses and doctors.[16,17] Weekly, parents had group sessions to learn and talk about prematurity and their infant's hospital stay, guided by healthcare professionals or veteran parents.[13]

Nurses provided cardiorespiratory monitoring as well as treatments such as intravenous fluids or antibiotics, placing nasogastric tubes, providing respiratory support, and phototherapy.[13,18,19]

Single family rooms.   The new neonatal, maternity, and obstetric ward of the hospital allowed mothers and their infants to always stay together in one family room. They were never separated, even when one or both needed medical care (providing complete couplet care, Supplementary Fig. S1 (online)).[12] Other family members could also be present 24 h per day. With this new architectural design of the mother–child center, maternity and neonatology services were fully integrated, with trained professionals with special skills to provide simultaneous medical care for ill mothers and/or preterm infants.

Control/reference treatment
Standard neonatal care in OBUs.   Standard neonatal care in OBUs was provided before October 2014. In this ward, infants stayed together in an open bay ward (a maximum of 18 infants in the ward), with incubators and beds lined up next to each other separated by curtains (Supplementary Fig. S2 (online)). The OBUs were close to, but physically separated from the maternity ward. Parents could visit their child, participate in routine infant care, and provide skin-to-skin contact. Due to the setting, the duration mothers and fathers could stay at the bedside of their infant was limited. Rooming-in facilities were not present.

During the hospital stay of their infant, parents were stimulated by the nurses to take part in the basic care of their infant. Medical rounds were done in a separate room from the OBUs, attended by the nurses and the doctors, without the parents. Approximately 2 days before discharge, parents could room-in with their infant in a family room near the neonatal ward.

Inclusion and exclusion criteria
Infants were included if they were born between 24 and 36 6/7 weeks gestation, with a post-conceptional age <44 weeks on admission and if they had a length of hospital stay in the level 2 ward of ≥3 days. Infants were excluded if they were born abroad (not in the Netherlands) or had a congenital anomaly (e.g., severe congenital heart defects requiring surgery or Down's syndrome).

Case ascertainment
LOS was defined as a clinical suspicion of sepsis with the physician's decision to do diagnostic testing because of symptoms of illness, to examine and culture bodily fluids (blood, urine, and cerebrospinal fluid) for the presence of bacterial micro-organisms, and to start antibiotics. The clinical signs should present between ≥72 h and 90 days after birth, during hospitalization for prematurity. The local hospital protocol defined the following signs to be present to consider a bacterial infection in the infant: increased, decreased, or instable temperature, respiratory problems, including tachypnea, nasal flaring, grunting, labored breathing, cyanosis, and apneas. Other possible signs were circulatory instability, feeding problems (feeding intolerance and vomiting), lethargy, or irritability.

The following definitions were used:

Total group of LOS: If signs were present of LOS, cultures were drawn, and antibiotics were started.

Group 1: Culture-proven LOS: When cultures were positive, independent of the duration of treatment for sepsis.

Group 2: Clinical suspected but not confirmed LOS: If diagnostics were done, and the antibiotic treatment was given for a maximum of 3 days with negative cultures.

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Group 3: LOS treated ≥7 days with antibiotics: When the infant was treated with antibiotics ≥7 days after clinical signs of LOS, and cultures were negative.

We defined LOS as probable and treated with infants either in *Group 1* or *Group 3*.

A minimum of 0.5 to 1 mL of blood was required for culture on clinical indication as defined by the local hospital protocol. Cultures were drawn before antimicrobial administration. We only considered the first LOS episode during hospital stay in the department for the primary outcome and did not analyze relapse episodes.

One author (A.A.M.W.v.K.) reviewed cases of children who developed LOS within 3 days after transfer from the level 3 NICU. These cases were checked anonymously and blinded to their allocation to OBUs or SFRs for case ascertainment (assigned to LOS developed in our hospital, or LOS developed in the referring NICU). We calculated LOS events per 1,000 hospital days.

Potential mediators
We considered PVCs, CVCs, and PN as possible mediators in the pathway between SFRs and LOS. In infants who developed LOS, mediators were only coded as present (yes/no) if they were started up to 1 day before the development of LOS. If infants received PVCs, PN, or CVCs after development of clinical signs of LOS, mediators were not coded as present. In children who did not develop LOS, mediators were coded as present ever (yes/no) during hospital stay. All potential mediators were analyzed in simple mediation models.

Additionally, mediators were analyzed in multiple mediation models if they were identified as a mediator in the simple mediation model. As PN can be given over PVCs or CVCs, we researched two different models. In *Model 1*, we investigated PVCs (without PN), CVCs (without PN) and PN. In *Model 2*, we analyzed PVCs (without PN), CVCs (without PN), and PN over PVCs, PN over CVCs, or PN over both PVCs and CVCs.

Secondary outcome measures
The secondary outcomes evaluated were rate of weight gain during hospital stay (average weight gain as calculated by Cormack,[20] using the following formula as an indicator of child health during hospital stay: $1,000 \times (\ln(\text{discharge weight/birthweight})/(\text{date of discharge} - \text{date of birth})))$, length of hospital stay (in days, from admission to discharge), and exclusive breastfeeding (100% breastfeeds or expressed breastmilk) during the 24 h before discharge.[21]

Sample size calculation
In a pilot study, we found LOS in ~10% of preterm infants admitted to our OBUs. We hypothesized that FICare in SFRs would reduce the incidence of LOS to 5%. With a power of $(1 - \beta)$ 80%, and a significance level of (a) 0.05, we needed 436 patients in OBUs, and 436 patients in SFRs.

Statistical analysis
For continuous variables, we evaluated if these were normally distributed using histograms. If normally distributed, mean and standard deviation (SD) were calculated. If variables were non-normally distributed, median and interquartile range (IQR) were calculated. For non-normally distributed data, we first applied a (natural) logarithmic or square root transformation to obtain normal distribution. We performed an independent t test or Mann–Whitney test as appropriate.

For binary variables (e.g., sex and singleton), number and percentages were calculated. We calculated the χ^2 to test for differences. If expected cell counts were <5, we calculated differences with the Fisher's exact test.

Missing data. For missing data the proposed guidance as explained by Sterne et al.[22] was applied. Little's MCAR (missing completely at random) test was used to test the MCAR assumption for continuous variables. We applied the multivariate imputation by chained equations (mice) procedure to missing data, with 30 imputations and 50 iterations to obtain a dataset for further analyses.[23] Pooled estimates were derived applying Rubin's rules.[24] Convergence was checked graphically with iteration plots.

Evaluation of the primary and secondary outcomes. To evaluate the association between SFRs and binary outcomes (LOS, exclusive breastfeeding at discharge), we calculated odds ratios (ORs) with multivariable logistic regression analyses. For continuous outcome variables (length of stay and weight gain), multivariable linear regression analyses were performed. The crude regression models were adjusted for confounders identified in the literature or if the β-regression coefficient differed at least 10% from the crude β-coefficient. The following variables were assessed and included in the adjusted model: birthweight (in g), post-intensive care status, sex and previous treatment with antibiotics for early-onset sepsis (<72 h after birth), and culture-proven LOS for secondary outcomes. If collinearity was present, the strongest confounder (with the largest change in crude β-coefficient) was used to adjust for. For the difference in incidence of sepsis (per 1,000 hospital days) between SFRs and OBUs, we calculated incidence rate ratios (IRRs).

Mediation analysis. Mediation analyses on the imputed dataset were applied to analyze, identify, and explain the underlying mechanisms of the observed total effect of SFRs on LOS (i.e., the c path).[25] In addition to the total effect model, two logistic regression models were fitted. In single mediator models, PVCs, CVCs, and PN were included as individual potential mediators. In the first regression model, the effect of SFRs on the mediator was estimated (a path). In the second regression model, the effect of the mediator on LOS (b path) and the direct effect of SFRs on LOS (c' path) were calculated. Crude and adjusted mediation analyses were performed. In the adjusted analyses, confounders were added to all paths. We calculated the indirect effect as the product of the a and b coefficients. We used bootstrap 95% confidence intervals (CIs) based on 1,000 bootstrap resamples around the indirect effects.[26]

Additionally, we included all identified mediators in a multiple mediator model. Again, indirect effects were calculated as the product of the a and b coefficients. To summarize information provided by the multiple mediator models, we calculated proportions mediated. The proportion mediation was calculated by dividing the indirect effect of the separate mediators through the sum of the indirect and the direct effect.

Statistical packages and software. We used R for statistical analyses (version 3.6.1)[27] and specifically for multiple imputation the "mice" package,[23] for analyzing missing data patterns the "VIM" package,[28] the "epiR" package for the IRR,[29] for Little's MCAR test the "BaylorEdPsych" package,[30] and for the 95% bootstrap CI the "boot" package.[31] For all tests, a p value <0.05 was considered statistically significant.

RESULTS
A total of 1,152 preterm infants were admitted during the entire study period. From this cohort, 1,046 preterm infants without exclusion criteria (468 in SFRs and 578 in OBUs) were admitted for ≥3 days in our hospital (Fig. 1). The baseline characteristics of infants admitted to SFRs or OBUs are shown in Table 1. Infants admitted to SFRs had a higher median gestational age than infants in OBUs (35^{+2} vs. 34^{+6} weeks, respectively).

The proportion of males was larger in SFRs (53.8% vs. 47.9%). Infants were more likely to be treated with antibiotics for early-onset sepsis in the OBU group (21.2% vs. 14.5%). No differences were found in other baseline characteristics.

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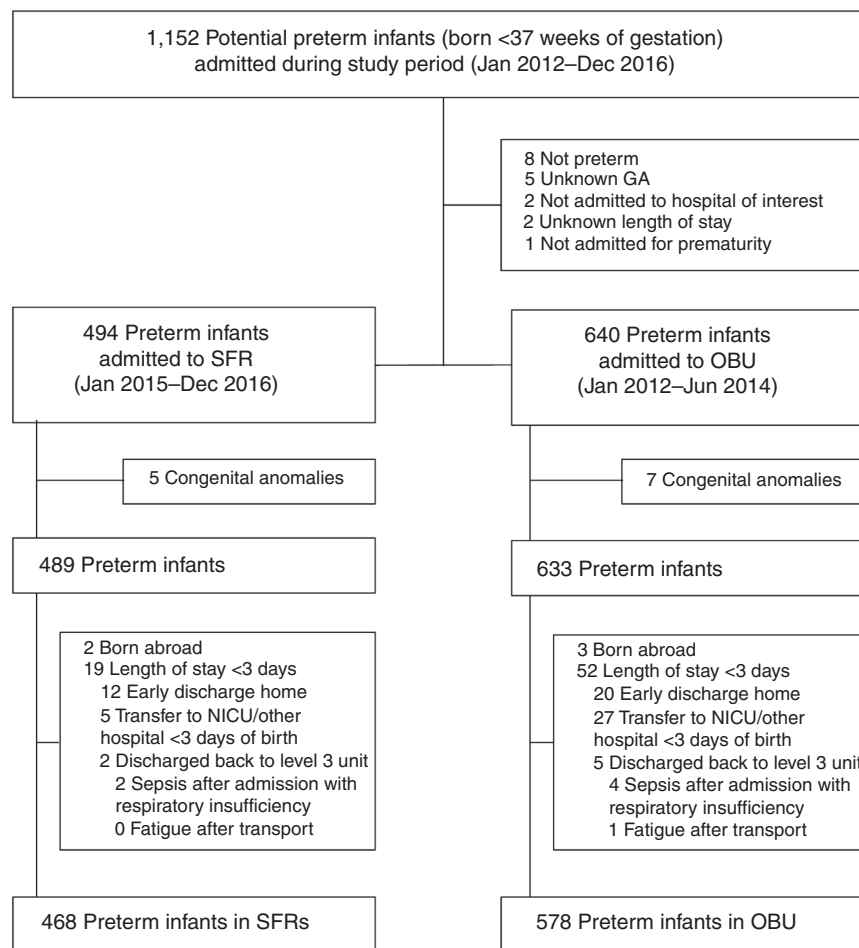
Fig. 1 Flow diagram. *GA* gestational age, *NICU* neonatal intensive care unit, *SFRs* single family rooms, *OBU* open bay unit.

Table 1. Baseline characteristics.				
Characteristic	SFR infants (*n* = 468)	Missing (*n* (%))	OBU infants (*n* = 578)	Missing (*n* (%))
Gestational age (weeks^{+days}, median (IQR), range (min to max))	35^{+2} (32^{+2}–36^{+2})* 24^{+2} to 36^{+6}	0	34^{+6} (32^{+6}–36^{+1})* 24^{+2} to 36^{+6}	0
Birthweight (g, mean (SD))	2145 (708)	0	2143 (656)	1 (0.2)
Male (*n* (%))	252 (53.8)	0	277 (47.9)	0
Apgar score at 1 min (median (IQR))	9 (7–9)	4 (0.8)	8.5 (7–9)	8 (1.4)
Apgar score at 5 min (median (IQR))	9 (8–10)	3 (0.6)	9 (8–10)	9 (1.6)
Inborn (*n* (%))	313 (66.9)	0	415 (71.9)	1 (0.2)
Post-intensive care status (transferred from level 3 NICU) (*n* (%))	146 (31.2)	0	153 (26.4)	1 (0.2)
Received surfactant previously	40 (8.5)	1 (0.2)	54 (9.3)	0
Maternal age (years, mean (SD))	33.3 (4.7)	4 (0.8)	33.3 (5.2)	8 (1.4)
Primipara (*n* (%))	251 (53.6)	0	337 (58.0)	1 (0.2)
Singleton (*n* (%))	322 (68.8)	0	392 (67.8)	0
Vaginal delivery (*n* (%))	277 (59.2)	0	333 (57.6)	2 (0.3)
Antenatal corticosteroids (*n* (%))	153 (32.7)	1 (0.2)	196 (33.9)	6 (1.0)
Treated for early-onset sepsis (*n* (%))	68 (14.5)*	82 (17.5)	123 (21.2)*	85 (14.7)
Had culture-proven LOS previously in referral center (*n* (%))	28 (6.0)	7 (1.5)	20 (3.5)	12 (2.1)

IQR interquartile range, *LOS* late-onset sepsis, *n* number, *NICU* neonatal intensive care unit, *OBU* open bay unit, *SD* standard deviation, *SFR* single family rooms.
*$p < 0.05$.

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Table 2. Presence of mediators in infants with and without late-onset sepsis in different hospital environments.

Mediator	SFR infants				OBU infants			
	Total ($n = 468$)	With LOS ($n = 25$)	Without LOS ($n = 443$)	Missing (n (%))	Total ($n = 578$)	With LOS ($n = 54$)	Without LOS ($n = 524$)	Missing (n (%))
PVC	145 (31.0)	18 (72.0)	127 (28.7)	6 (1.3)	322 (55.7)	47 (87.0)	275 (52.3)	13 (2.2)
CVC	11 (2.4)	1 (4.0)	10 (2.3)		40 (6.9)	9 (16.7)	31 (5.9)	
PN	96 (20.5)	15 (60.0)	81 (18.3)		222 (38.4)	44 (81.5)	178 (34.0)	

CVC central venous catheter, *PVC* peripheral venous catheter, *n* number, *LOS* late-onset sepsis, *OBU* open bay unit, *PN* parenteral nutrition, *SFR* single family room.

Table 3. The association between single family rooms and late-onset sepsis in the imputed dataset.

Outcome	SFR infants ($n = 468$)	OBU infants ($n = 578$)	OR	95% CI	OR[a]	95% CI[a]
Overall LOS (*Total group*), n (%)	25 (5.3)	54 (9.3)	0.548	0.335; 0.895*	0.486	0.293; 0.807**
Culture-proven LOS (*Group 1*), n (%)	17 (3.6)	25 (4.3)	0.834	0.444; 1.564	0.739	0.387; 1.410
Symptoms of LOS, maximum of 2–3 days of antibiotics, culture negative (*Group 2*), n (%)	2 (0.4)	11 (1.9)	0.221	0.049; 1.005	0.235	0.051; 1.082
LOS treated ≥7 days of antibiotics, culture negative (*Group 3*), n (%)	6 (1.3)	18 (3.1)	0.404	0.159; 1.027	0.337	0.133; 0.907*
LOS probable and treated (*Groups 1 and 3*), n (%)	23 (4.9)	43 (7.4)	0.643	0.381; 1.084	0.558	0.324; 0.961*

95% CI 95% confidence interval, *LOS* late-onset sepsis, *OBU* open bay unit, *OR* odds ratio, *SFR* single family room.
*$p < 0.05$.
**$p < 0.01$.
[a]Adjusted for post-intensive care status, previous treatment with antibiotics for early-onset sepsis, birthweight, and sex.

Fewer infants received PVCs (31.2% in SFRs vs. 55.7% in OBUs), CVCs (2.4% vs. 6.9%), and PN (21.4% vs. 38.4%) during their stay in SFRs compared to OBUs (Table 2).

Little's MCAR test revealed that data were not MCAR ($\chi^2 = 130.9$, $p < 0.00001$) and 10 missing data patterns were present for continuous outcomes (and 36 if including all variables).

SFRs and the association with LOS
We analyzed a total of 17,443 days of hospitalization (7,821 in SFRs and 9,622 in OBUs). Twelve children had a clinical suspicion of LOS within 3 days after transfer from another level 3 NICU. Eight events (4 in SFRs and 4 in OBUs) were assigned to the NICU of origin, and not included in the analyses. In SFRs, 25 (5.3%) infants had a clinical suspicion of LOS and were started on treatment with antibiotics compared to 54 (9.3%) infants in OBUs (adjusted OR 0.486, 95% CI: 0.293; 0.807, $p = 0.005$). Also, when analyzing this per hospital day it was lower in SFRs than in OBUs (3.2/1,000 vs. 5.6/1,000, IRR 0.570, 95% CI: 0.340; 0.930, $p = 0.019$). This association was also present for LOS treated for ≥7 days (Group 3). Although not significant, in SFRs, infants were less often started on antibiotics for ≥2–3 days with negative cultures (adjusted OR 0.235, 95% CI: 0.051; 1.082, $p = 0.063$), and overall, less LOS events were probable in SFRs (adjusted OR 0.558, 95% CI: 0.324; 0.961, $p = 0.036$, Table 3).

On average, infants developed LOS symptoms and were started on antibiotics 6 days after hospital admission, and this was not different in the SFRs and OBUs group. In total, 42 infants had a culture-proven LOS (Group 1), 17 (3.6%) in SFRs and 25 (4.3%)) in OBUs during hospital stay (adjusted OR 0.739, 95% CI 0.387; 1.410, $p = 0.348$). The incidence in SFRs was 2.2/1000 compared to 2.6/1000 hospital days in OBUs (IRR 0.836, 95% CI 0.424; 1.611, $p = 0.570$). If infants had a culture-proven sepsis, sepsis was more often associated with a focal infection in SFRs (14/17 (82%)) compared to OBUs (7/25 (28%)) (Supplementary Table S2 (online)).

Mediation analysis
The relationship between SFRs and LOS was mediated by PVCs, CVCs, and PN individually, independent of the definition of LOS (Fig. 2 and Supplementary Table S3 (online)). Fewer infants received PVCs (31.2% in SFRs vs. 55.7% in OBUs), CVCs (2.4% vs. 6.9%), and PN (21.4% vs. 38.4%, Table 2) during their stay in SFRs compared to OBUs also when adjusting for confounding factors (*a* path, Fig. 2 and Supplementary Table S3 (online)). PVCs, CVCs, and PN were positively associated with culture-proven, LOS treated for ≥7 days and clinically suspected but not confirmed LOS (*b* path, Supplementary Table S3 (online)).

The indirect mediating effect of PVCs and PN on LOS was present in single mediation analysis, also after adjusting for all possible confounders (indirect effect (*ab*), Fig. 2, Supplementary Table S3 (online)). The 95% CI of the indirect effect of CVCs included zero in all analyses, indicating a non-significant indirect effect in the pathway between SFRs and LOS. The total proportion of mediation through PVCs, CVCs, and PN after adjustment for confounders was 83.7%, 59.8%, and 84.7%, respectively, in the single mediation models (Supplementary Table S3 (online)).

Within multiple mediation models (*Model 1*), the effect of SFRs on LOS was mainly mediated by PN and less through PVCs without PN (Supplementary Table S5, Supplementary Fig. S3 (online)). As none of the infants received CVCs without PN, CVCs in itself were not a mediator in the pathway between SFRs and LOS (Supplementary Table S4 (online)). In *Model 2*, CVCs without PN were not a mediator, PVCs without PN were a moderate mediator, and PN was a strong mediator of the effect of SFRs on LOS. The three different pathways by which PN could be given were all mediators of the effect of SFRs on LOS (Fig. 3). Within *Model 2*, the effect of PN through PVCs was stable over different definitions of LOS with narrow 95% bootstrap CIs of the indirect (*ab*) effect. PN over CVCs, or PN over both were also mediators, but CIs were very wide (Supplementary Table S6 (online)).

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SFRs and the association with length of stay, exclusive breastfeeding at discharge, and weight gain
The median length of stay in SFRs was 10 days (IQR 5–24) and in OBUs it was 12 days (IQR 5–22). After adjusting for confounding factors, SFRs were associated with a shorter length of stay (adjusted β after natural logarithmic (ln) transformation: −0.088,

95% CI: −0.158; −0.016, $p = 0.016$). After adjusting for confounders, SFRs were associated with higher exclusive breastfeeding at discharge and weight gain, but this was statistically not significant (Supplementary Table S7 (online)).

DISCUSSION
Key findings
In this study, PVCs, CVCs, and PN were potential mediators in the pathway between SFRs and LOS. The positive effect of SFRs on LOS was mainly mediated through a decreased use of PN in SFRs, and—to a lesser extent—decreased use of PVCs.

These findings are consistent with our previous systematic review of SFRs and the incidence of LOS.[9] We show similar results in the rate of clinically suspected LOS events and proven LOS events per 1,000 hospital days. Also in line with previous research, PVCs and CVCs used in our population were associated with LOS,[5] and we found a strong association between PN and the development of LOS.[5,32,33] Due to the retrospective nature of our study, we did not culture PN for contamination and therefore it remains unclear if PN itself caused LOS, or if PN predisposed for LOS. Interestingly, even though lower usage of PN was present, no differences in weight gain were measured between the two groups.

The reason for the decreased use of PVCs, CVCs, and PN in SFRs remains to be further elucidated. Also, after correcting for gestational age, birthweight, and previous treatment for early-onset sepsis, this lower usage of catheters and PN was present. Previous research has shown that parents are often stressed and concerned about painful procedures in their infant.[34] Parents were often more present during hospital stay in SFRs, participated in family-centered rounds, and aided in the caregiving and decision making in this vulnerable patient population.[17,35,36] They could have gathered more knowledge in the education sessions and had more parenting experiences during hospital stay with their infant.[13,19] One could consider that family-centered rounds invited to more elaborate discussions with the parents on the necessity of the use of catheters and PN.[35] Previous research and observations from our research group showed that, if parents were present in SFRs, clinicians were more likely to discontinue after multiple attempts to start interventions, including PN and catheters, despite the local hospital protocol.[37,38] As this was not measured
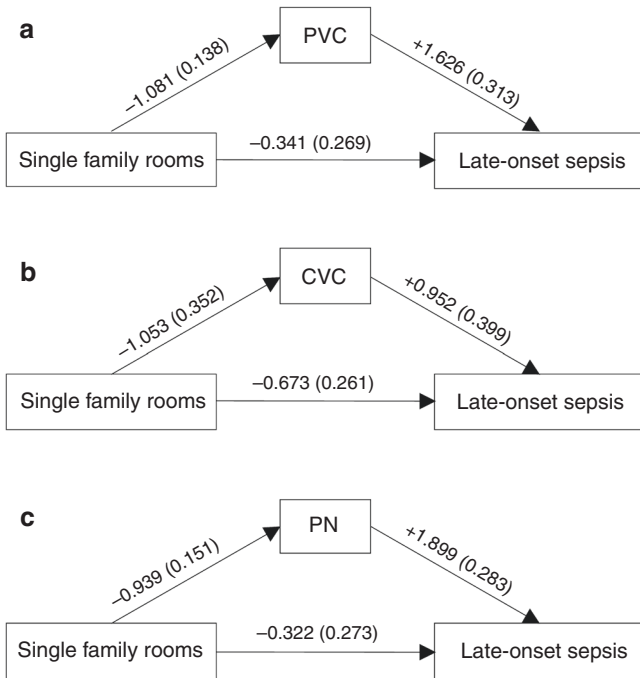
Fig. 2 Single mediation models of FICare in SFRs on late-onset sepsis. All analyses are adjusted for birthweight, post-intensive care status, previously treated for early-onset sepsis and sex. **a** Peripheral venous catheters (PVCs) as a mediator of the effect of FICare in SFRs on late-onset sepsis in preterm infants. **b** Central venous catheters (CVCs) as a mediator of the effect of FICare in SFRs on late-onset sepsis in preterm infants. **c** Parenteral nutrition (PN) as a mediator of the effect of FICare in SFRs on late-onset sepsis in preterm infants.
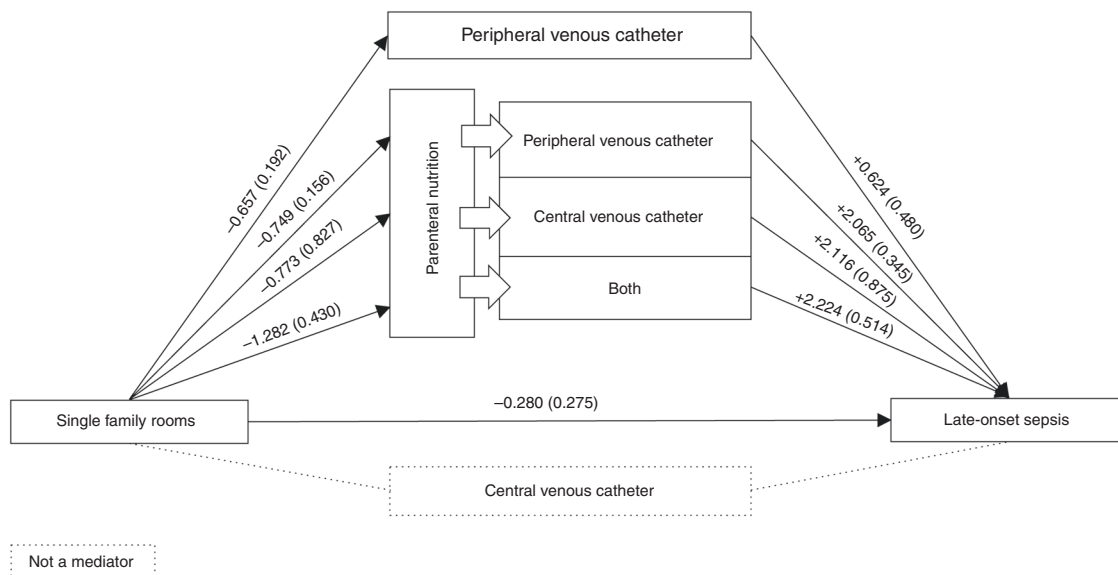
Fig. 3 Multiple mediation model of FICare in SFRs on late-onset sepsis. Analysis is adjusted for post-intensive care status, previous treatment with antibiotics for early-onset sepsis, birthweight, and sex.

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in this retrospective study, this should be addressed in future research.

In previous studies, parental participation was a mediator of the effect of SFRs on clinical outcomes in children, including weight gain and short- and long-term neurodevelopment.[36,38,39] One could consider that SFRs facilitated parental presence and participation in our population as well. Parents could have provided healthcare professionals with important information on the clinical condition of their infant, and might have aided physicians in their suspicion and/or diagnosis of LOS (through their parental experience and knowledge of their child's normal behavior).[13,19,40] This could have resulted in less use of antibiotics in our population, and also this is reflected by the higher percentage of culture-proven LOS in the SFR infants when compared to OBU infants. This might possibly represent the difference in reading clinical cues between parents and professionals, as symptoms of LOS can sometimes be difficult to interpret.[41] Obviously, the role of the parents and subsequent actions of the healthcare professionals in these SFRs, and the effect on the use of PN, catheters, and (diagnosis of) outcomes needs to be explored in future (preferably prospective) research.

In line with previous studies, we found that SFRs are associated with a shorter length of stay.[42,43] This is specifically important to healthcare policy makers, as costs per patient are high.[44] Decreasing length of stay in large proportions of patients can save money and support the decision of hospitals to redesign their hospitals to SFRs. However, this should be more elaborately studied in cost-effectiveness analyses.

Strengths
For the first time, we have done mediation analyses on the effect of an intervention on the usage of intravenous catheters and PN and the outcome LOS in this vulnerable patient group. Mediation analysis provides insight into the mechanisms underlying the effect of SFRs on LOS and therefore helps explain the differences observed in LOS between SFRs and OBUs.

In contrast to previous studies concerning this area of research, we have transparently shown where the data are missing, and how we dealt with this.[9] Multiple imputation has been shown to be robust when dealing with missing data.[23] As missing values are a problem in bootstrapping, and may lead to biased outcomes, multiple imputation also accounted for this.[26] The non-imputed outcome was more extreme (association of SFRs with LOS; adjusted OR 0.378, 95% CI: 0.198; 0.688, $p = 0.002$), and therefore the imputed dataset could give a more realistic measure of association.

As the information specialist and data collectors were blinded to the objective of this study, selection bias into the study was minimized. Also, as we asked a researcher to classify infants developing LOS in our facility <3 days after transfer from the NICU, independent and blinded to group assignment, misclassification of LOS was minimized.

Limitations
As randomization was not possible due to the construction of the hospital, the non-randomization of this study should be considered when studying the associations between SFRs and LOS. A possible explanation for a decreased incidence of LOS and decreased use of PN or PVCs and CVCs could also be the effect of time itself. As we studied two different time periods (before and after start of SFRs), it might be possible that over time we reduced the use of PVCs, CVCs, and PN or became more conservative in starting and/or more liberal in discontinuing antibiotics, which would be in concordance to previous studies.[45] Preferably randomized trials should be conducted to study this more thoroughly. One randomized trial did find that LOS was (non-significantly) decreased; however, no information was given on the use of PVCs, CVCs, or PN.[42]

Due to the high proportion of late preterm infants (≥35 weeks gestation) in this study, we were unable to provide the age of full enteral or oral feedings in our population, as the volume of feedings often did not meet the criteria at the time of discharge (volume of feedings >130 mL/kg per day). For the subpopulation of children born <35 weeks of gestation in our facility (72 in SFRs and 143 in OBUs), the median number of days to full enteral feedings and removal of nasogastric tube was not significantly different ($p = 0.107$ and $p = 0.327$, respectively).

In the absence of consensus on the quantification of breastfeeding and breastmilk rates, and due to the retrospective nature of our study, we used a previous reported measure for breastfeeding rates.[21] Future research should prospectively document and analyze breastfeeding rates with a standardized and validated scoring system that preferably also incorporates the quality and efficiency of breastfeeding preterm infants.[46]

Other etiological factors that might have reduced the need for catheters and PN during hospital stay, including feeding (in)tolerance and frequency, parental presence and participation, and duration of skin-to-skin care during hospital stay were not measured in this study.[47] Also, we did not include other predisposing and possible mediators for LOS, for instance, the amount of skin breaks (for blood sampling or venous catheters), compliance to (hand)hygiene protocols, and the cumulative amount of human milk given during hospital stay.[4,5] Future studies should include these variables in their analyses.

Practice implications
Our study shows that FICare in SFRs is associated with less LOS events and a shortened hospital stay for preterm infants after birth, which can reduce costs. Also, we found less use of catheters and PN during hospital stay, which potentially explained the decrease of infections in our department. Our study therefore supports the development of SFRs and implementation of FICare for the neonatal ward and can help policy makers and healthcare professionals decide on how to (re)construct hospital wards in the future and specifically level 2 neonatal wards. The population we studied was a relatively healthy level 2 neonatal population, with concurrent low incidences of LOS in the two different environments. This study is applicable for level 2 neonatal wards, and specifically for those infants admitted for at least 3 days in a facility that is situated in a developed country such as the Netherlands.

This study is also meaningful for hospitals that may not be able to reconstruct their facilities to SFRs, as they might be able to consider more discretely the need for PN, PVCs, and CVCs in the care of preterm infants.

CONCLUSION
This study contributes to existing knowledge on the beneficial effect of FICare and SFRs in preterm infants. We identified less LOS events, a shorter hospital stay, and less use of PVCs, CVCs, and PN in preterm infants admitted to SFRs with a complementary FICare program, with similar weight gain. By using mediation analysis, we identified that the reduction in LOS in SFRs was mediated by a reduced use of intravenous catheters and PN.

AUTHOR CONTRIBUTIONS
N.R.v.V., S.R.D.v.d.S., A.A.M.W.v.K., and J.B.v.G. developed the design and database of this study. N.R.v.V. performed acquisition of the data. N.R.v.V. performed the data

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analysis. J.J.M.R. provided insights into the use of mediation models, M.W.H. provided insights into the multiple imputation model. M.W.H. provided the script for the bootstrapping of indirect effects in the imputed database. A.A.M.W.v.K. reviewed infants with sepsis events. J.W.R.T. and W.H.H. provided insight into the use of regression models and conduct of the study and data analysis. N.R.v.V. drafted the first version of the manuscript. N.R.v.V., S.R.D.v.d.S., W.H.H., J.J.M.R., M.W.H., J.W.R.T., J. B.v.G., and A.A.M.W.v.K. all contributed to revising the manuscript critically for important intellectual content and approving this paper to be published. N.R.v.V., S.R. D.v.d.S., and A.A.M.W.v.K. are the guarantors of this study; they accept full responsibility for the work and the conduct of the study, had full access to the data, and controlled the decision to publish. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

ADDITIONAL INFORMATION

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