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Evaluating a neonatal intensive care unit MRSA surveillance programme using agent-based network modelling

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SUMMARY

Background: Surveillance for meticillin-resistant *Staphylococcus aureus* (MRSA) in neonatal intensive care units (NICUs) is a commonplace infection prevention strategy, yet the optimal frequency with which to monitor the unit is unknown.

Aim: To compare various surveillance frequencies using simulation modelling.

Methods: One hundred NICU networks of 52 infants were simulated over a six-month period to assess MRSA transmission. Unit-wide surveillance occurred every N weeks where $N=\{1,2,3,4\}$, and was compared with the current NICU policy of dynamic surveillance (i.e. weekly when at least one positive screen, otherwise every three weeks). For each surveillance period, colonized infants received a decolonization regimen (56% effective) and were moved to isolation rooms, if available.

Findings: As the surveillance frequency increased, the mean number of MRSA-colonized infants decreased, from a high of 2.9 (four-weekly monitoring) to a low of 0.6 (weekly monitoring) detected per episode. The mean duration of colonization decreased from 307 h (four-weekly monitoring) to 61 h (weekly monitoring). Meanwhile, the availability of isolation rooms followed an inverse relationship: as surveillance frequency increased, the availability of isolation rooms decreased (61% isolation success rate for four-weekly monitoring vs 49% success rate for weekly monitoring). The dynamic policy performed similar to a biweekly programme.

Conclusions: An effective MRSA surveillance programme needs to balance resource availability with potential for harm due to longer colonization periods and opportunity for development of invasive disease. While more frequent monitoring led to greater use of a decolonization regimen, it also reduced the likelihood of isolation rooms being available.

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Introduction

Preventing meticillin-resistant *Staphylococcus aureus* (MRSA) colonization in neonates is a key infection prevention strategy, given that approximately 30% develop invasive disease with potential for serious sequela [1]. Current practices for preventing invasive disease due to MRSA in the neonatal intensive care unit (NICU) include a 'seek and destroy' infection control programme, whereby periodic surveillance cultures are obtained and colonized infants are decolonized and/or isolated [2]. Decolonization procedures are unit based, gestational and chronological age specific, and may include intranasal mupirocin and chlorhexidine gluconate baths; the youngest neonates are particularly vulnerable to invasive infection due to their immature skin and immune systems, and invasive devices and procedures. Isolation procedures include placing infants on contact precautions and moving them into isolation rooms, if available. In an MRSA outbreak setting, cohorting may also be employed, where infants are grouped together within the general NICU based on their colonization status.

A central question of these infection control programmes centres around surveillance frequency. The frequency with which units monitor for MRSA varies in the published literature, most commonly upon admission and/or weekly [3]. The authors' literature review did not reveal any rigorous analysis evaluating the frequency of surveillance with control of MRSA colonization in the NICU. Acknowledging that surveillance programmes need to balance limited resources with potential harm to infants from subsequent MRSA infection, this study sought to evaluate the infection control programme in an NICU using a mathematical modelling approach explicitly varying the surveillance frequency.

Methods

Overview of the agent-based network model

Goldstein *et al.* previously developed an agent-based network model of horizontal (infant to infant via healthcare worker) transmission of MRSA in the NICU to evaluate the effectiveness of hand hygiene [4]. This model served as the basis for the current analysis and will only be described in brief here. The model simulated patient care patterns of an actual NICU, whereby individual infants were linked together by common providers creating a patient care network. The resulting network was dependent upon individual characteristics of the infants (infants of greater acuity had more connections than infants of lower acuity) and environmental characteristics (infants were clustered together by the configuration of the NICU floor plan). This NICU network model was simulated over a nine-day period (the median length of stay) and was evaluated hourly for the potential of horizontal transmission of MRSA via the patient care network, allowing for hand hygiene to mitigate the occurrence. The authors noted that despite optimal compliance with hand hygiene, MRSA colonization can still persist in the NICU via horizontal transmission [3,4].

To adapt this model to evaluate an MRSA surveillance programme, it was extended in four ways. First, the duration of the simulation was extended from nine days to six months (4392 h) to allow for varying surveillance frequencies. Second, infants admitted to the NICU were allowed to have prevalent

MRSA colonization, either through birth or shortly thereafter. This rate was set to 2.5% of all admissions [5,6]. All infants who, at any time during the simulation, were colonized with MRSA, whether prevalent or incident, were potential sources for horizontal transmission. Third, based on the NICU design, two isolation rooms were added to the NICU floor plan, allowing up to four infants to be isolated at any given time. At the start of simulation, no infants were in isolation or were colonized with MRSA. Fourth, the NICU was capped to a maximum of 70 infants, based upon current capacity. Additional model details can be found in Table A (see online supplementary material).

Description of the dynamic surveillance programme

Current NICU policy is weekly monitoring for MRSA colonization of the nares when at least one infant is detected, and this is continued each week until all infants are screened negative. Subsequently, to conserve resources, the unit is monitored once every three weeks until another MRSA colonization is detected. Space permitting, infants who are colonized with MRSA are isolated in one of the two isolation rooms. Each room can accommodate up to two infants. Infants may be eligible for a decolonization regimen dependent upon gestational and chronological age: infants >36 weeks gestational age or >4 weeks chronological age receive two 2% chlorhexidine gluconate baths separated by 48 h. All colonized infants receive 2% intranasal mupirocin twice per day for five days. A similar regimen has been documented to eliminate colonization in 56% of infants [7], and served as the expected effectiveness of decolonization in the model. As implemented in the mathematical model, at each surveillance time point, the algorithm updates the known colonization status of each infant, moves colonized infants to an isolation room if available, and probabilistically decolonizes.

Statistical analysis

To evaluate the effectiveness of the surveillance programme at reducing MRSA colonization, the current dynamic policy (described previously and considered as the baseline) was simulated and contrasted with a generalized approach of monitoring every week (168 h), every two weeks (336 h), every three weeks (504 h) and every four weeks (672 h) for five distinct models. In the baseline scenario, acknowledging the absence of any MRSA-colonized infants at the start of simulation, the first unit-wide monitor occurred after three weeks.

All simulations also employed a hand hygiene intervention to control horizontal transmission. This intervention was considered to be 87% effective at stopping horizontal MRSA transmission, and was calculated as the product of 88% hygiene efficacy [8] combined with near-perfect compliance (99%) observed in the study NICU. To acknowledge uncertainty in hand hygiene, in a sensitivity analysis, all five simulation models were repeated with hand hygiene set to 54% effectiveness as the product of 88% hygiene efficacy combined with 61% compliance observed in a systematic review [9].

All analyses were performed using R Version 3.4.3 (R Foundation for Statistical Computing, Vienna, Austria) with Epi-Model Version 1.5.0 [10]. Estimates correspond to the mean statistic with corresponding 95% confidence intervals (CIs) based upon 100 runs of the simulated NICU network. Annotated model source code is available for download at <https://doi.org/10.5281/zenodo.1227270>.

Results

Baseline per-policy scenario

In the baseline scenario, an average of one MRSA-colonized infant was present in the NICU over the duration of the simulation. With a mean census of 53 infants, this equated to an average prevalence of 2.2%, which fluctuated over the simulation (Figure 1). The current surveillance policy resulted in 14 surveillance episodes occurring, which closely matched the number of episodes that occurred with a biweekly surveillance programme (Table I). At each surveillance period, an average of 1.2 infants (95% CI 0.6–2.1) screened positive for MRSA colonization. At the end of the six-month simulation, a total of 16 colonizations (95% CI 7–28) were identified through surveillance efforts. Employing the decolonization and isolation policies resulted in an expected reduction in prevalence. On average, 0.9

infants (95% CI 0.4–1.6) were decolonized successfully during the surveillance episode (56% effectiveness), with a mean duration of colonization of 151 h (six days; 95% CI 60–258). An average of 0.3 infants (95% CI 0.1–0.7) were moved to an isolation room during each surveillance period. As isolation rooms were unavailable due to maximum occupancy (50% mean availability during the simulation; 95% CI 25–79%), approximately half of MRSA-colonized infants were isolated *in situ*.

Varying the frequency of surveillance

Decreasing the surveillance frequency resulted in fewer surveillance episodes during the simulation (Table I), while a greater average number of infants screened positive for MRSA colonization at each surveillance episode (Figure 1 and Table I). As a consequence of monitoring less frequently, the mean duration of MRSA colonization increased from a low of 61

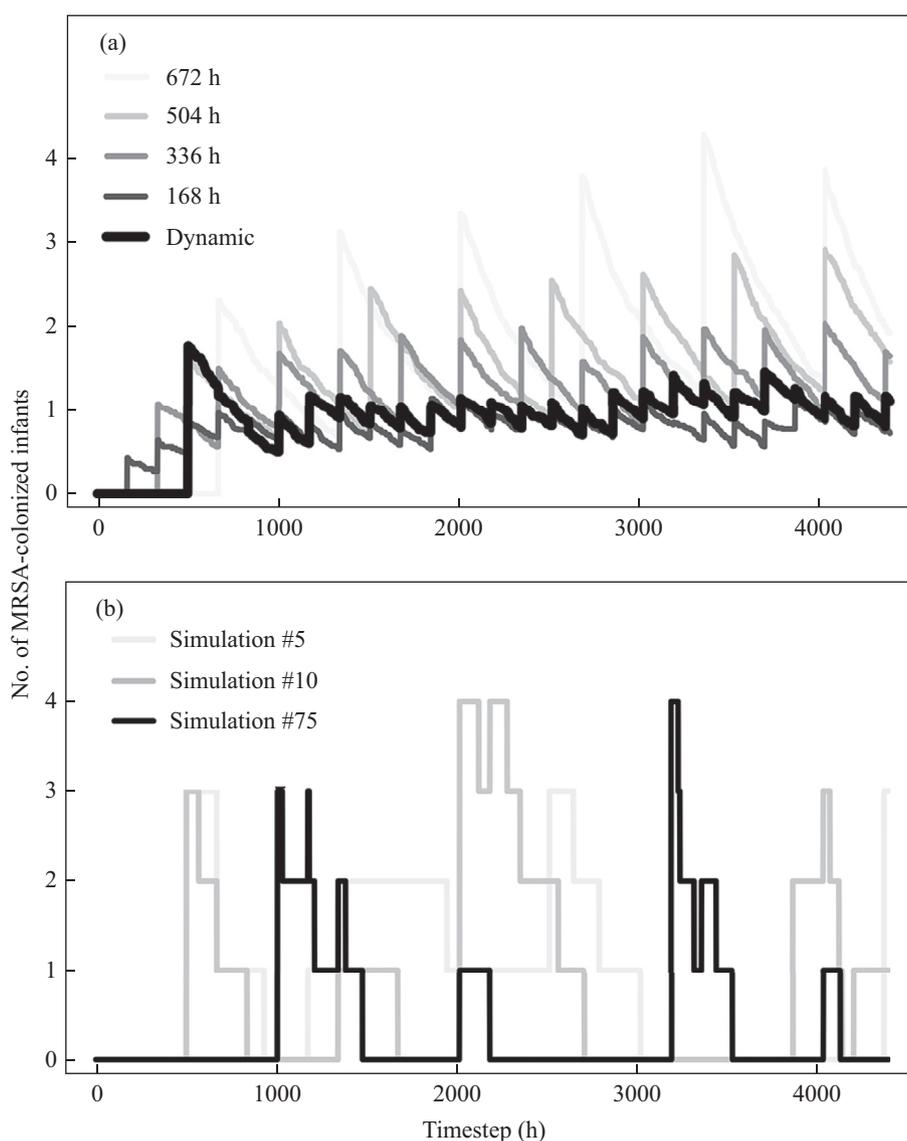


Figure 1. Meticillin-resistant *Staphylococcus aureus* (MRSA)-colonized infants detected through the simulated neonatal intensive care unit surveillance programme assuming 87% hand hygiene effectiveness. Results presented as averaged across all simulations (a) and three individual runs of the dynamic policy model* (b). *The individual surveillance time variations under the dynamic policy become masked when averaged across all 100 simulation runs; therefore, three individual runs of the dynamic model are also depicted.

Table I

Results of varying the frequency of a meticillin-resistant *Staphylococcus aureus* (MRSA) surveillance programme in a simulated neonatal intensive care unit (NICU) assuming 87% hand hygiene effectiveness

| Surveillance programme evaluation metric | Per policy ^a | Surveillance frequency (h) | | | |
|--|-------------------------|--------------------------------|---------------|---------------|---------------|
| | | 168 | 336 | 504 | 672 |
| Average number of surveillance episodes during the six-month simulation | 14 | 26 | 13 | 8 | 6 |
| | | Mean (95% confidence interval) | | | |
| Mean census of NICU | 53 (48–57) | 53 (49–57) | 53 (47–57) | 54 (48–59) | 54 (49–59) |
| Mean number colonized at each surveillance episode | 1.2 (0.6–2.1) | 0.6 (0.2–1.0) | 1.3 (0.6–2.1) | 1.9 (0.7–3.6) | 2.9 (1.2–5.4) |
| Total number of colonizations identified over six-month period | 16 (7–28) | 16 (6–25) | 16 (8–28) | 15 (5–29) | 17 (7–33) |
| <i>Decolonization</i> | | | | | |
| Mean number decolonized at each surveillance episode | 0.9 (0.4–1.6) | 0.5 (0.2–0.8) | 1.0 (0.5–1.7) | 1.3 (0.4–2.5) | 1.9 (0.7–3.8) |
| Mean proportion successfully decolonized at each surveillance episode ^b | 56% (35–76%) | 57% (36–81%) | 58% (37–83%) | 55% (30–87%) | 57% (31–91%) |
| Mean duration of colonization (h) | 151 (60–258) | 61 (18–128) | 160 (58–278) | 212 (62–436) | 307 (90–514) |
| <i>Isolation</i> | | | | | |
| Mean number in isolation, colonized | 0.3 (0.1–0.7) | 0.3 (0.1–0.6) | 0.4 (0.0–1.0) | 0.5 (0.0–1.2) | 0.5 (0.0–1.2) |
| Mean number in isolation, decolonized | 1.9 (0.6–3.6) | 2.2 (0.7–4.1) | 1.9 (0.6–3.5) | 1.5 (0.3–3.1) | 1.4 (0.5–2.8) |
| Mean number isolated at each surveillance episode | 0.8 (0.4–1.1) | 0.4 (0.2–0.6) | 0.8 (0.5–1.2) | 1.2 (0.6–1.8) | 1.6 (0.9–2.4) |
| Mean proportion successfully isolated at each surveillance episode ^{c,d} | 50% (25–79%) | 49% (20–78%) | 57% (27–94%) | 61% (22–95%) | 61% (32–96%) |

^a Weekly when at least one infant is detected, and continues each week until all infants in the NICU are screened negative; subsequently, the unit is monitored once every three weeks until another MRSA colonization is detected.

^b Although treated as a fixed effectiveness of 56%, sampling variability resulted in fluctuations.

^c Contingent upon an isolation room being available.

^d Multiple factors can affect isolation room availability, including staffing, census and other neonatal morbidities.

h (three days; 95% CI 18–128) for a weekly programme to a high of 307 h (13 days; 95% CI 90–514) for a four-weekly programme. While the mean number of infants in an isolation room remained consistent across the varying surveillance frequencies, on average, more infants were successfully moved to an isolation room when the surveillance frequency was lower (49% success for a weekly programme vs 61% success for a four-weekly programme), resulting in fewer colonized infants being isolated *in situ*. Compared with the baseline scenario, in terms of detecting colonized infants, a biweekly programme performed comparably (mean of 1.2 vs 1.3 colonized infants at each surveillance episode for the dynamic and biweekly programme, respectively).

After undertaking a sensitivity analysis lowering the effectiveness of hand hygiene, the number of MRSA transmissions and subsequent colonizations increased as expected (Figure 2 and Table II). The relative comparisons remained: more frequent surveillance resulted in fewer colonized infants with a shorter duration of colonization. Contrary to models with greater effectiveness of hand hygiene, a lower surveillance frequency resulted in the availability of fewer isolation rooms (36% success for a weekly programme vs 21% success for a four-weekly programme). An effect of the models using lower surveillance frequency was a steady increase in the mean census of the NICU, from a low of 53 infants to a high of 58 infants, as a result of a greater number of MRSA-colonized infants with multiple factors contributing to longer lengths of stay.

Discussion

This simulation study sought to compare and contrast an MRSA surveillance programme using empiric NICU data by

varying the surveillance period. More frequent surveillance was seen to result in fewer MRSA-colonized infants with shorter mean colonization times. Under the 87% hand hygiene effectiveness models, increased surveillance resulted in resource limitations as the isolation rooms achieved maximum occupancy more frequently compared with a less frequent surveillance programme. As the data indicated, the majority of infants in isolation had been decolonized successfully, perhaps suggesting an opportunity to refine the protocol and consider transferring infants out of isolation. Assuming a lower level of hand hygiene effectiveness reached similar conclusions, except the availability of isolation rooms was generally greater with more frequent surveillance periods. This is attributed to a greater number of MRSA-colonized infants present in the unit between longer surveillance periods, resulting in a greater demand for isolation rooms.

Surveillance for MRSA colonization is commonplace in NICUs with varying frequency and success [1–3]. Lyles *et al.* examined the epidemiology of MRSA colonization in 10 NICUs in Chicago following a state-wide legislative approach to mandating screening [11]. The legislation did not dictate a frequency, and consequently the implementation varied widely. Most commonly used was admission-only screening or weekly screening, but some hospitals employed a two-weekly programme or a fixed time post admission. They did not detect any difference in MRSA colonization post legislation, nor when examining differences by surveillance frequency. From this study, it is hypothesized that the reduction in MRSA-colonized infants with more frequent surveillance resulted from the decolonization regimen, which was not studied in the work by Lyles *et al.* The present study provides a framework for NICUs to model different surveillance strategies and develop

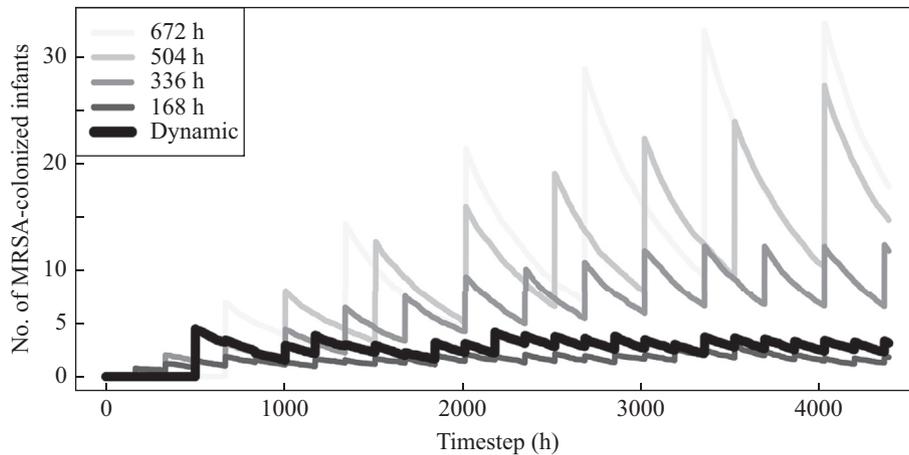


Figure 2. Meticillin-resistant *Staphylococcus aureus* (MRSA)-colonized infants detected through the simulated neonatal intensive care unit surveillance programme assuming 54% hand hygiene effectiveness. Results presented as averaged across all simulations.

Table II

Results of varying the frequency of a meticillin-resistant *Staphylococcus aureus* (MRSA) surveillance programme in a simulated neonatal intensive care unit (NICU) assuming 54% hand hygiene effectiveness

| Surveillance programme evaluation metric | Per policy ^a | Surveillance frequency (h) | | | |
|--|-------------------------|--------------------------------|----------------|-----------------|-----------------|
| | | 168 | 336 | 504 | 672 |
| Average number of surveillance episodes during the six-month simulation | 16 | 26 | 13 | 8 | 6 |
| | | Mean (95% confidence interval) | | | |
| Mean census of NICU | 53 (48–58) | 53 (48–59) | 55 (49–61) | 57 (49–62) | 58 (51–63) |
| Mean number colonized at each surveillance episode | 3.0 (1.0–6.0) | 1.2 (0.3–2.4) | 5.9 (1.0–12.4) | 12.2 (2.4–21.4) | 17.9 (4.9–27.2) |
| Total number of colonizations identified over six-month period | 49 (16–99) | 32 (9–62) | 77 (13–161) | 98 (19–172) | 107 (29–163) |
| <i>Decolonization</i> | | | | | |
| Mean number decolonized at each surveillance episode | 2.6 (1.0–4.7) | 1.1 (0.3–2.3) | 5.0 (0.8–11.0) | 9.3 (1.9–18.0) | 13.0 (3.2–20.2) |
| Mean proportion successfully decolonized at each surveillance episode ^b | 57% (42–75%) | 58% (41–79%) | 56% (38–70%) | 55% (41–69%) | 57% (41–76%) |
| Mean duration of colonization (h) | 159 (59–256) | 79 (29–155) | 186 (60–272) | 253 (142–352) | 301 (156–405) |
| <i>Isolation</i> | | | | | |
| Mean number in isolation, colonized | 0.5 (0.1–1.0) | 0.4 (0.1–0.8) | 0.8 (0.2–1.5) | 1.0 (0.2–1.6) | 1.1 (0.1–2.2) |
| Mean number in isolation, decolonized | 2.6 (1.1–4.0) | 2.8 (1.2–4.8) | 2.3 (0.8–4.3) | 1.9 (0.8–3.1) | 1.6 (0.5–3.0) |
| Mean number isolated at each surveillance episode | 0.8 (0.4–1.3) | 0.4 (0.2–0.7) | 1.0 (0.5–1.5) | 1.5 (0.8–2.1) | 1.8 (0.7–2.6) |
| Mean proportion successfully isolated at each surveillance episode ^{c,d} | 27% (7–56%) | 36% (11–72%) | 29% (9–64%) | 24% (5–62%) | 21% (6–64%) |

^a Weekly when at least one infant is detected, and continues each week until all infants in the NICU are screened negative; subsequently, the unit is monitored once every three weeks until another MRSA colonization is detected.

^b Although treated as a fixed effectiveness of 56%, sampling variability resulted in fluctuations.

^c Contingent upon an isolation room being available.

^d Multiple factors can affect isolation room availability, including staffing, census and other neonatal morbidities.

unit-specific interventions based on real-world data on colonization rates, handwashing and isolation strategies. Outside of the NICU, universal MRSA decolonization has been studied in adult intensive care units, which would obviate the need for surveillance [12]. However, neonates may experience adverse outcomes as the result of routine skin antiseptics, especially preterm infants, plus overuse of antiseptic practices may further promote bacterial resistance [13].

Intuitively, a more frequent surveillance programme sounds appealing, but must be balanced with its corresponding risks and drawbacks. *In situ* cohorting practices in the NICU may act as a buffer between colonized and non-colonized infants by modifying the patient care network, whereas isolation rooms, if available, provide a physical barrier as an additional means of protection. However, having more infants isolated *in situ* results in MRSA-colonized infants present in the general

population, which can lead to a greater potential for horizontal transmission if cohorting procedures and contact precautions are not followed [3]. Moreover, a frequent programme is resource intensive, in terms of time, personnel and costs.

Data on screening costs are limited, but reported amounts range between a low of US\$11 per screen to a high of US\$71 per screen [14]. Applying data from the present study, a weekly surveillance programme conducted over six months results in a corresponding range of culture costs between US\$15,158 and US\$97,838. Meanwhile, a four-weekly programme conducted over six months ranges between US\$3564 and US\$23,004. Of course, these numbers do not factor in the subsequent costs of nursing time, decolonization regimen, isolation rooms or potential for harm from invasive disease. When evaluating the cost of screening, the cost per MRSA colonization with its potential for morbidity must also be considered. Schultz *et al.* calculated that each MRSA-colonized infant in their level III–IV NICU resulted in an additional cost of US\$116,969 for the total hospitalization, mainly due to the additional length of stay due to development of invasive disease [15]. Examining the total number of colonizations in the present results under an 87% hygiene effectiveness scenario revealed that varying the surveillance period did not result in a meaningful shift in the number of MRSA-colonized infants. However, if one assumes a suboptimal level of hygiene effectiveness at 54%, the total number of colonizations at the end of the six-month period was in excess of three-fold greater ($N=75$) when comparing a four-weekly surveillance programme with a weekly programme. This could potentially incur costs up to US\$8,772,675 over a six-month period, representing a substantial amount of money to the healthcare system, especially when compared with the estimated weekly surveillance costs. The models used in this study also demonstrate the potential for poor hand hygiene to increase healthcare costs dramatically.

This approach to network modelling makes several assumptions. First, the models were initialized without any MRSA-colonized infants, with the assumption of being in a non-outbreak setting. Starting with existing colonizations would result in the per-policy programme effectively mirroring the weekly programme, defeating one of the inferential goals. Second, the horizontal transmission model did not consider visitor–infant or fomite–healthcare worker interactions, which can harbour MRSA. This may have resulted in underestimation of actual colonization and per-contact probabilities of infection transmission. Further, the study NICU has an open pod design, and recent evidence suggests that private patient rooms may limit the risk for MRSA [16]. Third, non-isolation room barrier protection, such as use of an incubator, was not considered. It is conceivable that an incubator may impede exposure, assuming effective hand and environmental hygiene, although in a case–control study of MRSA transmission in the NICU, incubator use was not identified as a factor [17]. The use of incubators in the study NICU is governed by temperature regulation, gestational age and birthweight. Fourth, apart from MRSA, there are other medical indications for use of isolation rooms that were not considered, such as respiratory syncytial virus infection. In the study NICU, these other indications are infrequent and the primary reason for isolation is MRSA colonization.

Despite these limitations, this study had notable strengths. The NICU network model was based on empiric data, minimizing the need for assumptions. The network model

framework is flexible to allow testing of various scenarios over the same data; that is, a counterfactual ‘what-if’ analysis was conducted, examining what would have happened under a more or less frequent surveillance programme in the same group of patients. To examine this in a real patient population would have required five otherwise equivalent NICUs in a prospective study – a significant undertaking.

In conclusion, this study quantified aspects of an MRSA surveillance programme in the NICU, and can be applied in other hospitals and settings to compare and contrast the effects of screening for MRSA according to different schedules. This study found that the institution’s dynamic policy errs on the side of a more frequent surveillance programme, which attempts to minimize the mean duration of colonization at the expense of more infants being isolated. There is no ‘one-size-fits-all’ approach, and each institution must balance the availability of resources with the costs of different strategies, potential for longer colonization periods, and subsequent risk for invasive disease.

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Conflict of interest statement

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Appendix A. Supplementary data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.jhin.2018.05.002>.

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