ORIGINAL ARTICLE

Active Surveillance and Decolonization of Methicillin-Resistant *Staphylococcus aureus* on Admission to Neonatal Intensive Care Units in Hong Kong: A Cost-Effectiveness Analysis

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OBJECTIVE. To examine potential clinical outcomes and cost of active methicillin-resistant *Staphylococcus aureus* (MRSA) surveillance with and without decolonization in neonatal intensive care units (NICUs) from the perspective of healthcare providers in Hong Kong.

DESIGN. Decision analysis modeling.

SETTING. NICU.

PATIENTS. Hypothetical cohort of patients admitted to an NICU.

METHODS. We designed a decision tree to simulate potential outcomes of active MRSA surveillance with and without decolonization in patients admitted to an NICU. Outcome measures included total direct medical cost per patient, MRSA infection rate, and MRSA-associated mortality rate. Model inputs were derived from the literature. Sensitivity analyses evaluated the impact of uncertainty in all model variables.

RESULTS. In the base-case analysis, active surveillance plus decolonization showed a lower expected MRSA infection rate (0.911% vs 1.759%), MRSA-associated mortality rate (0.223% vs 0.431%), and total cost per patient (USD 47,294 vs USD 48,031) compared with active surveillance alone. Sensitivity analyses showed that active surveillance plus decolonization cost less and had lower event rates if the incidence risk ratio of acquiring MRSA infections in carriers after decolonization was less than 0.997. In 10,000 Monte Carlo simulations, active surveillance plus decolonization was significantly less costly than active surveillance alone 99.9% of the time, and both the MRSA infection rate and the MRSA-associated mortality rate were significantly lower 99.9% of the time.

CONCLUSIONS. Active surveillance plus decolonization for patients admitted to NICUs appears to be cost saving and effective in reducing the MRSA infection rate and the MRSA-associated mortality rate if addition of decolonization to active surveillance reduces the risk of MRSA infection.

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The incidence of methicillin-resistant *Staphylococcus aureus* (MRSA) infections has been increasing worldwide, with the number of both hospital-acquired and community-acquired cases having been reported to rise.[1] MRSA infections cause significant morbidity and mortality in hospitalized patients.[2] In neonatal intensive care units (NICUs), MRSA is an important nosocomial pathogen for which frequent outbreaks have been reported.[3-6] According to a report from the National Nosocomial Infections Surveillance System, the incidence of MRSA colonization or infections in NICUs increased by 308% in the United States from 1995 to 2004.[7] There is also a much higher risk of infections in neonates colonized with MRSA. The most frequently reported type of infection was bacteremia,[8-11] and the mortality rate of MRSA infection in NICUs was as high as 19%–27%.[12,13] Cost-effective prevention of MRSA infections in NICUs is therefore highly warranted.

The approach of active MRSA surveillance is strongly recommended by the Society for Healthcare Epidemiology of America, and a positive impact of active surveillance has been reported.[9,12,14,15] MRSA carriers identified in NICUs by active surveillance are placed under contact isolation and receive cohorting care. Potential benefits of adding MRSA decolonization to active surveillance were recently reported in clinical trials.[10,16] The level of effectiveness of MRSA decolonization needed to achieve cost-effective outcomes in NICUs

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is yet to be determined. The objective of this study was to examine the potential cost and clinical outcomes of active MRSA surveillance with and without decolonization among patients admitted to NICUs from the perspective of healthcare providers in Hong Kong.

METHODS

Model Design

A decision tree was designed to compare the outcomes of active surveillance with and without decolonization in a hypothetical cohort of patients admitted to an NICU (Figure 1). Three tiers of outcomes were simulated by the decision model: (1) total direct medical cost, (2) MRSA infection rate, and (3) MRSA-associated mortality rate. In both study groups, active MRSA surveillance was performed for all patients admitted to the NICU by polymerase chain reaction (PCR) testing of nasal specimens obtained on admission and weekly thereafter. Patients who tested positive for MRSA would be placed under contact isolation and cared for as a cohort. Standard contact precautions would be applied to all patients and environmental contacts. In the surveillance plus decolonization group, patients testing positive for MRSA would receive decolonization interventions, including daily intranasal mupirocin ointment for 7–10 days for all test-positive patients and topical chlorhexidine baths for patients with a gestational age above 36 weeks or a chronological age above 4 weeks. Patients in both groups might acquire MRSA infections, and those who were infected might die or survive the infection.

Clinical Inputs

The clinical inputs of the model are shown in Table 1. A search of the literature on MEDLINE over the period from 2000 to 2011 was performed using the following keywords: "methicillin-resistant *Staphylococcus aureus*," "surveillance," "decolonization," and "neonatal intensive care unit." The selection criteria for clinical trials were as follows: (1) the report was written in English, (2) the prevalence of MRSA carriers in the NICU was reported, and (3) the MRSA infection rate and/or mortality rate was reported. All articles retrieved by this process were screened for relevance to our model. An article would be included if it had data pertaining to the model inputs.

MRSA prevalence in NICUs varies widely in different hospitals, depending on the infection control measures used. The base-case value for MRSA prevalence (4.3%) was estimated using the weighted average of epidemiology studies and was tested in sensitivity analysis over a broad range from 0.7% to 8.6%.[12,14,16] Data from 4 retrospective studies were used to estimate the MRSA infection rates among MRSA carriers (23.1%) and noncarriers (0.8%) with active surveillance.[8,12,13,15] The model input for the mortality rate of MRSA infections in NICUs was 24.5% (range, 19.0%–27.0%).[9,16] The incidence risk ratio (IRR) of MRSA infection (0.08; range, 0.02–1.03) among carriers in the active surveillance plus decolonization group versus the active surveillance group was obtained from an observational cohort study.[13] The MRSA infection rate in carriers after decolonization was approximated as follows: MRSA infection rate with active surveillance alone × MRSA infection IRR with active surveillance plus decolonization.

Cost Inputs

The economic analysis was conducted from the perspective of Hong Kong healthcare providers. The cost of an MRSA infection in an NICU was estimated by the change in length of stay (LOS) in an NICU as well as the increase in the daily cost of NICU care. The model input for the routine daily cost of NICU care per patient was retrieved from the *Hong Kong Government Gazette*.[17] The LOS in the NICU (20 days) and the increase in LOS for MRSA-infected patients (2.4-fold) were estimated using epidemiology studies.[5,9,11] The daily cost of NICU care for patients with MRSA infection was estimated to be 1.2-fold higher than that for noninfected patients.[9,11] The cost (including reagents and manpower) of PCR was approximated by the microbiology laboratory of a public hospital in Hong Kong.

Cost-Effectiveness Analysis and Sensitivity Analysis

If it cost less to lower infection and mortality rates in the active surveillance plus decolonization group, it would dominate the active surveillance group. If it cost more to reduce infection and mortality rates in the active surveillance plus decolonization group, the incremental costs per MRSA infection averted and life saved (incremental cost-effectiveness ratio) would be calculated using the following equations: (1) Δcost/ΔMRSA

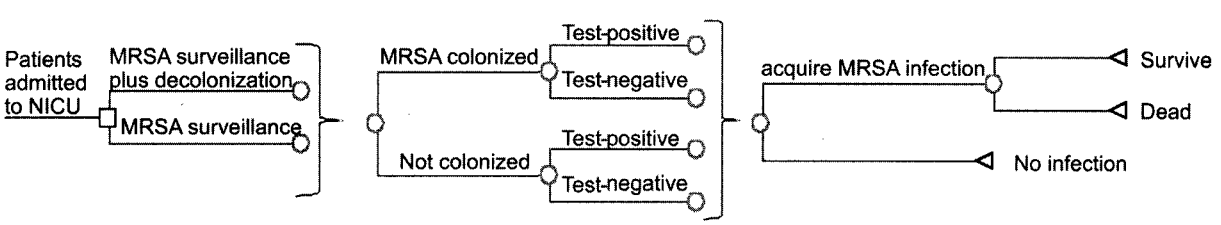


FIGURE 1. Simplified decision tree. MRSA, methicillin-resistant *Staphylococcus aureus*; NICU, neonatal intensive care unit.

TABLE 1. Model Inputs

	Base-case value	Range of sensitivity analysis	Reference(s)
Clinical inputs			
Prevalence of MRSA-colonized patients in NICU, %	4.3	0.7–8.6	Song et al,[12] Sarda et al,[14] Kim et al[16]
MRSA infection rate			
MRSA-colonized patients, %	23.1	14.7–38	Huang et al,[8] Gregory et al,[9] Milstone et al,[10] Maraqa et al[11]
Incidence risk ratio after decolonization	0.08	0.02–1.03	Milstone et al[10]
Noncolonized patients, %	0.8	0.6–1.7	Huang et al,[8] Maraqa et al[11]
Morality rate for MRSA infection in NICU, %	24.5	19–27	Song et al,[12] Gerber et al[13]
Sensitivity of PCR test, %	92.8	91.7–94.6	Nelson et al,[23] Luteijn et al,[24] Warren et al[25]
Specificity of PCR test, %	95.8	93.5–97	Nelson et al,[23] Luteijn et al,[24] Warren et al[25]
Cost inputs, USD[a]			
PCR	25	10–100	Local
Decolonization	32	15–48	Local
Daily cost of NICU care	2,320	1,856–2,784	Government of Hong Kong SAR[17]
Adjusting factor for daily cost of NICU care with MRSA infection	1.2	1–1.5	Song et al,[12] Schultz et al[15]
LOS in NICU, days	20	10–60	Khoury et al,[5] Song et al,[12] Schultz et al[15]
Adjusting factor for LOS in NICU with MRSA infection	2.4	1.4–2.5	Khoury et al,[5] Song et al,[12] Schultz et al[15]

NOTE. LOS, length of stay; MRSA, methicillin-resistant *Staphylococcus aureus*; NICU, neonatal intensive care unit; PCR, polymerase chain reaction.
[a] USD 1 = HKD 7.8.

TABLE 2. Results of Base-Case Analysis of Cost, Methicillin-Resistant *Staphylococcus aureus* (MRSA) Infection Rate, and MRSA-Associated Mortality Rate Expected for Patients Admitted to a Neonatal Intensive Care Unit

Strategy	Cost, USD	MRSA infection rate, %	MRSA-associated mortality rate, %
Active surveillance plus decolonization	47,294	0.911	0.223
Active surveillance alone	48,031	1.759	0.431

infection rate and (2) Δcost/ΔMRSA-associated mortality rate.

Sensitivity analysis was performed using TreeAge Pro 2009 (TreeAge Software) and Excel 2007 (Microsoft) to examine the robustness of the model results. All the parameters were examined over the upper and lower limits of the variables, if available. Otherwise, a range of variation of ±20% of the base-case value was used.

One-way sensitivity analysis of all variables was performed to screen for potentially influential factors. To evaluate the impact of the uncertainty of all of the variables simultaneously, a probabilistic sensitivity analysis was performed using Monte Carlo simulation. The cost, MRSA infection rate, and MRSA-associated mortality rate for each study group were recalculated 10,000 times by randomly drawing each of the model inputs from a triangular probability distribution to determine the percentage of times each strategy would be the most cost-effective option.

RESULTS

Base-Case Analysis

In the base-case analysis (Table 2), the active surveillance plus decolonization group showed a lower expected MRSA infection rate (0.911% vs 1.759%), MRSA-associated mortality rate (0.223% vs 0.431%), and total cost per patient (USD 47,294 vs USD 48,031) compared with the active surveillance group. On the basis of the expected infection rates in the 2 groups, the number of patients who would need to be decolonized to prevent 1 MRSA infection was 118.

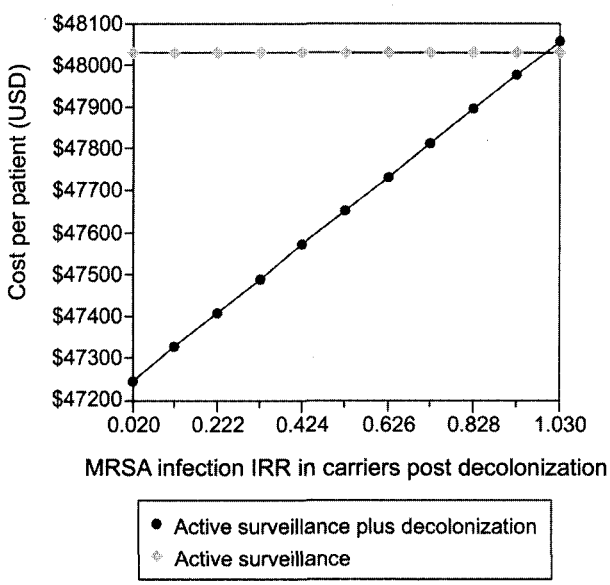


FIGURE 2. Change in cost per patient plotted against the incidence rate ratio (IRR) of methicillin-resistant *Staphylococcus aureus* (MRSA) infection in carriers after decolonization.

Sensitivity Analysis

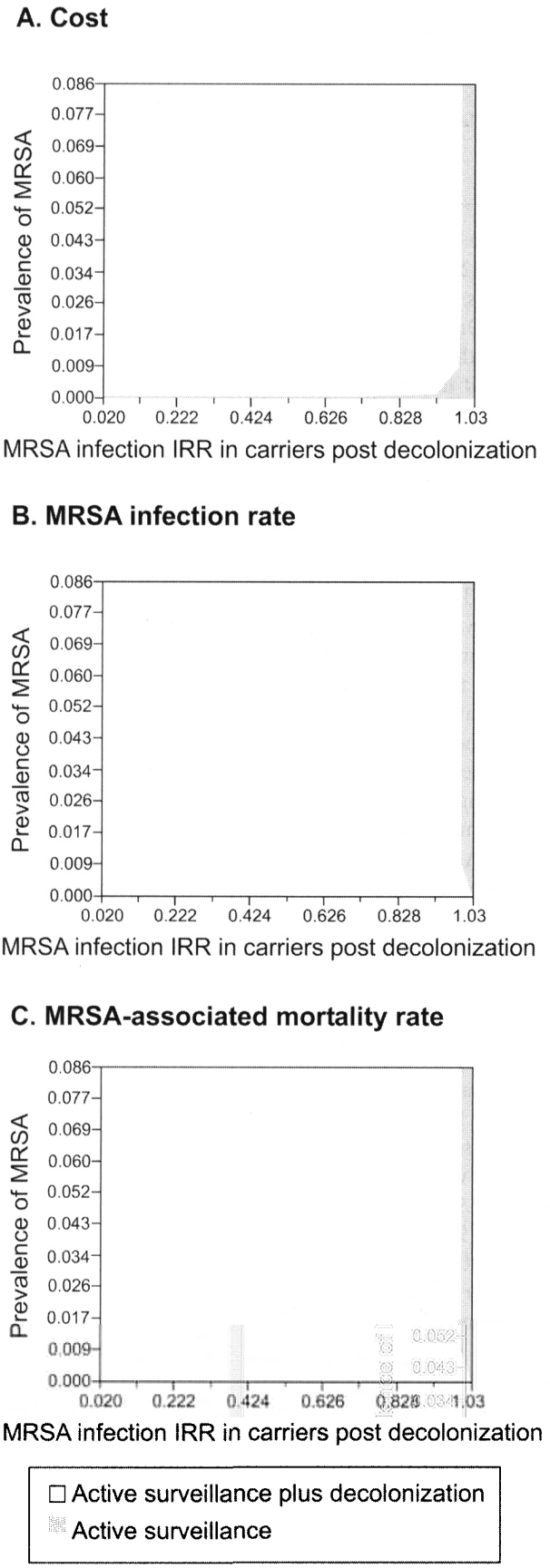
One-way sensitivity analyses of the MRSA-infection rate and the MRSA-associated mortality rate showed that active surveillance plus decolonization would remain more effective in preventing clinical events if the IRR of MRSA infection in colonized patients after decolonization (versus no decolonization) was less than 1.000. The total cost per patient in the active surveillance plus decolonization group was also sensitive to the variation in IRR of MRSA infection in MRSA carriers after decolonization. When the IRR was more than 0.997, the cost of active surveillance plus decolonization would become higher than the cost of active surveillance alone (Figure 2).

The interactions between MRSA prevalence and the IRR of MRSA infection in carriers after decolonization for the 3 outcomes were examined by 2-way sensitivity analyses (Figure 3). Active surveillance plus decolonization was found to be the preferred option in the majority of the combinations of these 2 variables. Active surveillance alone would become the preferred option only when the MRSA prevalence was extremely low (approaching zero) and the effect of active surveillance plus decolonization in preventing MRSA infection was the same as or lower than that of active surveillance alone.

In the 10,000 Monte Carlo simulations generated by probabilistic sensitivity analysis, active surveillance plus decolonization was significantly less costly than active surveillance alone 99.9% of the time, with cost savings of USD 809 per patient (95% confidence interval [CI], USD 797–821; $P < .001$). Both the MRSA infection rate and the MRSA-associated mortality rate were significantly lower ($P < .001$) in the active surveillance plus decolonization group than the active surveillance group 99.9% of the time, with absolute differences of 0.667% (95% CI, 0.660%–0.674%) and 0.156% (95% CI, 0.154%–0.158%), respectively.

DISCUSSION

This study examined the cost-effectiveness of active MRSA surveillance plus decolonization versus active surveillance alone in neonates admitted to NICUs. Our results suggest



that active surveillance plus decolonization would likely dominate active surveillance alone, with a lower total cost per patient as well as reduced MRSA infection and MRSA-associated mortality rates across the wide range of clinical and cost inputs in the decision model. The sensitivity analysis showed that these findings remained robust when the prevalence of MRSA-colonized patients admitted to NICUs was low (0.7%) or high (8.6%).

Active surveillance of MRSA colonization at admission followed by infection control measures such as isolation has been demonstrated to be cost-effective in high-risk patient groups (such as surgical patients, patients with previous MRSA, and patients admitted to ICUs), as has universal screening for adults at hospital admission.[18-20] Recently, MRSA decolonization, in addition to active surveillance and infection control measures, was shown to be effective in high-risk groups, including orthopedic surgery patients and hemodialysis patients, for prevention of MRSA infections, with an incremental cost per quality-adjusted life-year gained of less than USD 50,000.[21,22] The results of our study showed that NICU patients could benefit from active surveillance plus decolonization because of both improved clinical outcomes (reduced MRSA infection and mortality rates) and cost saving.

We found that the risk (measured as IRR) of MRSA infection in carriers who underwent decolonization (versus no decolonization) had the most influence on cost and clinical outcomes of the active surveillance plus decolonization approach. The role of decolonization in NICUs has been demonstrated only in an observational cohort study, and the findings suggested that the MRSA infection rate may be lowered by adding MRSA decolonization to routine active surveillance (with isolation and cohorting care).[13] The risk reduction gained from adding decolonization to active surveillance appears to have the highest impact on economic and clinical outcomes, and therefore further investigation is warranted in prospective clinical trials. The sensitivity analysis in our study showed that only a very modest reduction in the MRSA infection rate—0.3% or more (IRR less than 0.997)—in the active surveillance plus decolonization group would reduce MRSA-associated mortality in NICUs and produce cost savings. This finding could be explained by the high economic

Figure 3. Two-way sensitivity analysis of the prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA) and the incidence rate ratio (IRR) of MRSA infection in carriers after decolonization regarding cost (*A*), MRSA infection rate (*B*), and MRSA-associated mortality rate (*C*). Threshold lines divide the gray and white zones. Combinations of variables on the threshold line had the same outcome (cost, MRSA infection rate, or mortality rate). The white zone indicates combinations of variables for lower cost or event rate in the active surveillance plus decolonization group, and the gray zone indicates combinations of variables for lower cost or event rate in the active surveillance group.

burden caused by MRSA infections in NICUs, resulting in higher daily cost and longer length of stay. A slight reduction in the infection rate would suffice to offset the relatively small cost of active screening and decolonization.

Active surveillance with cohorting is not always possible in every NICU. The practice of MRSA decolonization is also not well standardized because of the lack of demonstrated clinical effectiveness and safety of a decolonization regimen in randomized clinical trials, and acceptance of using MRSA decolonization by clinicians should depend on future findings of prospective trials. This study is an example of a decision analysis to undertake large-scale studies by simulating the magnitude of the clinical effectiveness and cost of active MRSA surveillance plus decolonization required for such a preventive measure to translate into an effective and cost-saving strategy before initiation of a trial to compare active surveillance with and without decolonization. Our decision model also provides a framework to examine the influential factors and the corresponding threshold values for each strategy to translate into a cost-effective option. The present findings, in combination with real-time epidemiologic data acquired through continuous surveillance, may provide better insights into the cost-effectiveness of active surveillance plus decolonization for healthcare providers to consider in individual NICU settings. Despite the Hong Kong perspective that was selected in this model, it included major cost and clinical inputs that could be readily generalized to other locations by using region-specific input values.

This model was limited by sources of clinical model inputs, which were mostly obtained from retrospective observational studies. The model inputs were therefore examined over a wide range in the sensitivity analyses to identify influential factors that would alter the base-case findings. For example, the IRR of MRSA infection for active surveillance plus decolonization versus active surveillance alone was examined over a wide range (0.02–1.03) from less than 1 (risk reduced) to more than 1 (risk increased). Another limitation was the lack of cost and clinical outcomes related to toxicity of decolonization (nasal mupirocin with or without chlorhexidine bath) in the model, as the literature on decolonization safety in neonates is inadequate. It is believed that decolonization of MRSA carriers in NICUs would also reduce the risk of acquiring MRSA infections in noncarriers. Yet no estimate of the benefits to noncarriers of a decolonization program has been reported in the literature, and outcomes in this subgroup were not simulated in this model. Our results may therefore underestimate the clinical and economic benefits of adding decolonization to active surveillance in NICUs. This model simplified real-life MRSA colonization and infection in NICUs and estimated the proportion of MRSA carriers who became infected with MRSA in the study arms for weekly active surveillance with and without decolonization. The complex dynamics of MRSA decolonization and recolonization over time were not included.

In conclusion, data from our decision analysis model suggest that active MRSA surveillance plus decolonization in patients admitted to NICUs would be cost saving and effective in reducing the MRSA infection rate and the MRSA-associated mortality rate if addition of decolonization to active surveillance reduces the risk of MRSA infection from the perspective of healthcare providers in Hong Kong. Prospective clinical trials are warranted to determine the clinical impact of adding decolonization to active surveillance on the risk of MRSA infection.

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