

Effectiveness of Methicillin-resistant *Staphylococcus aureus* surveillance among exposed roommates in community hospitals: Conventional culture vs direct PCR

ABSTRACT

Background: Roommates of unrecognized nosocomial Methicillin-Resistant *Staphylococcus aureus* (MRSA) cases are at higher acquisition risk; however, optimal surveillance strategies are unknown.

Methods: Using simulation, we analyzed surveillance testing and isolation strategies for MRSA among exposed hospital roommates. We compared isolating exposed roommates until conventional culture testing on day six (Cult6) and a nasal polymerase chain reaction (PCR) test on day three (PCR3) with/without day zero culture testing (Cult0). The model represents MRSA transmission in medium-sized hospitals using data and recommended best practices from the literature and Ontario community hospitals.

Results: Cult0+PCR3 incurred a slightly lower number of MRSA colonizations and 38.9% lower annual cost in the base case compared to Cult0+Cult6 because the reduced isolation cost compensated for the increased testing cost. The reduction in MRSA colonizations was due to 54.5% drop in MRSA transmissions during isolation as PCR3 reduced exposure of MRSA-free roommates to new MRSA carriers. Removing the day zero culture test from Cult0+PCR3 increased total cost, the number of MRSA colonization, and missed cases by \$1,631, 4.3%, and 50.9%, respectively. Improvements were higher under aggressive MRSA transmission scenarios.

Discussion and Conclusions: Adopting direct nasal PCR testing for determining post-exposure MRSA status reduces transmission risk and costs. Day zero culture would still be beneficial.

Key Words: Methicillin-resistant *Staphylococcus aureus*, PCR test, culture test, exposed roommates, MRSA surveillance, computer simulation.

BACKGROUND

Around 120,000 and 14,000 methicillin-resistant *Staphylococcus aureus* (MRSA) cases are reported in the U.S.¹ and Canada, respectively, per year.² This translates into a significant burden for society: i) MRSA is associated with 20%-30% increased mortality due to life-threatening infections; ii) prevention and control of MRSA imposes a significant cost.^{1,2} MRSA incidence had been steadily increasing over the years (e.g., 35-fold between 1995-2009 in Canada). Although the increase in Canadian MRSA incidence had recently stopped due to improved infection control,² it may increase again as the recent pandemic (SARS-CoV-2) caused increases in hospital stays and antibiotic use.³ Thus, testing at-risk individuals and management of colonized patients cost-effectively remains important.

One scenario is the recognition of a new MRSA case (unrecognized nosocomial MRSA) in a multi-bedded room (of n patients), placing roommates at risk for acquisition.^{2,4} Ideally, this index case (primary transmission; infected or colonized) is removed from the room, leaving $(n - 1)$ exposed roommates. Guidelines from Ontario's Provincial Infectious Diseases Advisory Committee specify that exposed roommates are placed in contact isolation until the results of surveillance tests (generally baseline and 7 days since last exposure with conventional culture at a minimum) are known.⁴ MRSA acquisitions could occur from the pre-intervention exposure to the index case and/or from unrecognized cohorted roommates during isolation and testing (secondary transmission).

However, the optimal post-exposure testing schedule and test modality, i.e., culture vs polymerase chain reaction (PCR) tests, remain uncertain.⁴ Ensuring sufficient new case detection prior to releasing exposed roommates from isolation is critical to interrupt future transmissions.⁴⁻⁶ This must be balanced against the organizational (i.e., cost, impeded bed flow) and patient-centric (i.e., decreased care, increased psychological distress) drawbacks of longer isolation.^{5,7} Leveraging the sensitivity of PCR testing may avoid prolonged isolation if cases are not missed and cost-effectiveness is demonstrated.

Most studies analyzed universal versus targeted testing practices on admission for detecting MRSA cases.⁸⁻¹⁰ Only a few studies analyzed post-exposure MRSA incidence in acute care among exposed roommates under various surveillance strategies.^{4,11,12} For instance, using data from a community teaching hospital in Ontario-Canada, Ng et al. showed that accelerated detection via direct PCR testing rather than culture may help reduce isolation duration.⁴ However, detailed analyses of the optimal MRSA surveillance strategy among exposed roommates across all relevant performance metrics are needed.

METHODS

Computer Simulation Model

We built a stochastic agent-based computer simulation model in ARENA 15. Using simulation, we evaluated the performances of MRSA surveillance strategies with direct nasal PCR and conventional chromogenic culture among exposed roommates. The computer simulation mimicked the MRSA transmission and progression among the exposed roommates of the index case (primary transmission). The model was applied to the case of a 400-bed community acute care hospital for one year. The input parameters were determined using data from the literature, the facility's Infection Prevention and Control (IPAC) department, and through model calibration based on benchmark statistics from a community teaching hospital in Ontario.⁴ The performances of the surveillance strategies were evaluated in terms of the expected annual number of MRSA colonizations/transmissions during and before isolation, missed MRSA cases, the number of days spent in isolation, and the total cost. We ran 1,000 simulation replications for each considered surveillance strategy.

MRSA Progression and Transmission among Exposed Roommates

As commonly done, we assumed index MRSA carriers are detected in the hospital according to a Poisson arrival process, i.e., the time between two consecutive detections of index cases is exponentially distributed.^{10,13} In the model, upon the recognition of an index case, all exposed roommates are placed into contact isolation and undergo follow-up testing. The number of exposed roommates in isolation depends on the room size in which the index case is diagnosed, i.e., three and one exposed roommate/s for the ward and semi-private rooms, respectively. At any time, there could be multiple isolations in different rooms based on the recognition times of index cases.

The MRSA transmission/progression follows a Markov transition framework (Supplementary Figure 1). We defined the MRSA statuses of exposed roommates as non-colonized (no colonization), colonized (MRSA colonization), and infected (MRSA infection) as true patient states (not test results). MRSA transmissions lead to MRSA colonizations, which may later progress to infection. Thus, we used MRSA colonization and transmission interchangeably hereafter. In the model, each exposed roommate may become MRSA colonized on day zero of the isolation with a probability equal to the MRSA colonization prevalence (P_{prv}) due to exposure to the index case before isolation starts (primary transmission). During each isolation day, newly colonized roommates may transmit MRSA to each non-colonized roommate (secondary transmissions) with a probability $P_{col}(N_t) = 1 - (1 - P_{iso})^{N_t}$, where N_t is the number of MRSA

colonized roommates in the room and P_{iso} is the daily probability of MRSA transmission from each colonized roommate to a non-colonized one. In addition, on each isolation day, the MRSA status of a colonized roommate may progress into (clinical) infection with a probability P_{inf} . Mortality during isolation was not explicitly modeled due to the limited time window (i.e., one week); however, indirectly considered in the treatment cost of MRSA colonization.

MRSA Surveillance and Isolation Strategies Based on Test Results

We compared performances of two surveillance strategies on exposed roommates: i) Best practices recommending 7-day isolation with day zero and six culture tests (Cult0+Cult6); ii) 3-day isolation with day zero culture test and day three direct nasal PCR test (Cult0+PCR3). We also analyzed the performances of both strategies without the recommended day zero testing to address the controversy around its cost-benefit, which was questioned due to the low sensitivity.⁴ In the model, the exposed roommates with positive PCR or culture tests at any time are removed from the shared space but kept in isolation.^{8,14,15} Those with negative Cult0 remain in contact isolation, until a negative PCR3 or Cult6 result (for both true and false negatives). However, patients with false negative test results risk new MRSA cases amongst newly exposed roommates as precautions are removed.

Data for Model Parameters

We derived the rate of recognizing nosocomial MRSA cases, room setting, and room-type distributions based on the data from our acute care site. We modeled the time until the recognition of missed MRSA cases after the isolation using a discrete distribution with a mean of seven days based on observations in the acute care hospital. Progression and test parameters, i.e., MRSA colonization prevalence, transmission probabilities, and test sensitivities were calibrated specifically for exposed roommates using benchmark statistics from the literature. Benchmark statistics were derived from a study analyzing culture and PCR testing outcomes among a cohort of exposed roommates in a community teaching hospital in Ontario (see Table 1 for more details).⁴ Both the benchmark statistics and calibrated model parameters were reported in Table 1. The remaining parameters including the ratio between MRSA transmission probabilities during and before isolation (e ; the ratio of isolation effectiveness), test specificities, and costs were collected from the medical literature (see Table 1 and Supplementary Materials I for more details).

Table 1. Input parameters and data sources for the computer simulation model

Description	Base-case value	Low value	High value	Estimation method and data source
Arrival times				
Interarrival time of index cases	Exponential (0.255) [†]	–	–	IPAC of the acute care site*
Interarrival time of missed cases (T_{miss})	DISC (0.1,6,0.9,7,1,8) ^{††}	–	–	IPAC of the acute care site*
Room setting				
Percentage of ward rooms (4 people)	80%	–	–	IPAC of the acute care site*
Percentage of semi-private rooms (2 people)	20%	–	–	IPAC of the acute care site*
Benchmark statistics				
MRSA conversion rate among exposed roommates	8%	–	–	Based on data from literature ⁴
MRSA conversion rate detected on days 0-1 by culture test	30%	–	–	Based on data from literature ⁴
MRSA conversion rate detected on days 2-4 by culture test	50%	–	–	Based on data from literature ⁴
MRSA conversion rate detected on days 2-4 by PCR test	55%	–	–	Based on data from literature ⁴
MRSA conversion rate detected on days 5-10 by culture test	56%	–	–	Based on data from literature ⁴
MRSA progression and transmission parameters				
MRSA colonization prevalence at the beginning of isolation (P_{prv})	7.5%	4.4%	12.6%	Calibration based on data from literature ^{4,11,16}
Transmission probability during isolation per patient per day (P_{iso})	0.84%	0	4.8%	Calibration based on data from literature ^{4,15,17}
Infection probability during isolation per patient per day (P_{inf})	0	–	–	Calibration based on data from literature ⁸
The ratio of effectiveness (e)	2.423	1.691	3.154	Based on data from literature ^{15,17}
Test characteristics				
Sensitivity of culture test on day zero	31.7%	27.9%	35.5%	Calibration based on data from literature ⁴
Sensitivity of culture test on day six	56.2%	49.5%	62.9%	Calibration based on data from literature ⁴
Specificity of culture test	100%	–	–	Based on data from literature ^{15,17}
Sensitivity of the PCR test on day three	57%	52%	62%	Calibration based on data from literature ⁴
Specificity of PCR test	97.5%	–	–	Based on data from literature ^{15,17}
Turnaround time of culture test	24 hrs	–	–	Based on data from literature ¹⁷⁻¹⁹
Turnaround time of PCR test (assay time)	1-2 hrs	–	–	Based on data from literature ¹⁷⁻¹⁹
Costs				
Cost of a PCR test	\$41.11	\$23.38	\$60.30	Based on data from literature ^{14,17-19}
Cost of a culture test	\$13.85	\$4.61	\$22.14	Based on data from literature ^{14,17-19}
Cost of isolation (per patient per day)	\$73.31	\$58.52	\$81.42	Based on data from literature ^{14,17,20}
Cost of MRSA colonization (per patient)	\$1,316.41	\$706.16	\$1,926.67	Based on data from literature ^{14,20}
Cost of MRSA infection (per patient)	\$12,308.32	\$9,372.7	\$19,094.38	Based on data from literature ^{17,20,21}

Base-case and low/high parameter values specify the mean and ranges of input parameters for the base-case and sensitivity analyses, respectively. MRSA colonization prevalence at the beginning of isolation refers to the proportion of exposed roommates with MRSA colonization on day 0 and is calibrated using benchmark statistics from a similarly exposed roommate cohort along with the other transmission/progression probabilities and test sensitivities. Costs are attributable to hospital expenses associated with MRSA testing, isolation, and management. The studies reporting MRSA colonization and infection costs calculated those costs based on mean lengths of stays varying between 8-19 and 10-28 days, respectively. Costs were converted into the year 2022 Canadian dollars using exchange rates and the consumer price index in health care. *Data on index case arrival and room settings were provided by the IPAC department of Grand River and St. Mary's hospitals (GRH & SMH) in Kitchener-ON, Canada. [†] Exponentially distributed with an interarrival rate of 0.255 per day. ^{††} Discrete distribution representing $P(T_{miss} = 6) = 0.1$, $P(T_{miss} = 7) = 0.8$, and $P(T_{miss} = 8) = 0.1$.

Costs were considered from the hospital's perspective. Therefore, considered costs include only the direct costs borne by individual departments within the hospital budget, which are publicly funded. Considering the hospital perspective is reasonable as there is an agreement within the hospital governance programs that permits added funding for lab testing to recognize savings in infection prevention and control expenses. The cost of isolation for the hospital mainly includes isolation materials (gloves, gowns, masks, etc.) and additional isolation cleaning. The costs of MRSA colonization and infection for the hospital include all relevant expenses for MRSA management after detection such as isolation, materials, cleaning/housekeeping, and additional follow-up tests. Kim et al. reported the colonization cost in such a form; however, Roth et al. reported the expenses related to MRSA colonization individually.^{14,20} Thus, we combined these individual expenses to be consistent with the colonization cost estimate from Kim et al.^{14,20} All cost estimates were converted to the year 2022 Canadian dollars.

Reported MRSA transmission rates and test sensitivities significantly vary due to differences in nosocomial MRSA prevalences, compliance to infection prevention/control guidelines, and bacterial load changing over time.^{14,15} We estimated MRSA transmission probability, MRSA colonization prevalence on day 0, and test sensitivities for exposed roommates via model calibration for the acute care community hospital with benchmark statistics from an observational study conducted at a similar-sized Ontario community teaching hospital.⁴ We systematically searched for the parameter combinations that produce model outputs matching the selected benchmark statistics with the minimum mean squared error (See Supplementary Materials II for details). As benchmark statistics, we used 8% cumulative rate of MRSA colonization as well as 30%, 56%, and 55% MRSA conversion rates (i.e., the percentage of test-detected MRSA cases) for conventional culture tests at the beginning and end of the isolation, and a nasal PCR test in the middle of the isolation, respectively.⁴ The estimates from the calibrated model for these benchmark statistics, i.e., 7.96% (CI:7.87%-8.04%), 29.92% (CI:29.31%-30.53%), 56.57% (CI:55.48%-57.67%), and 55.44% (CI:54.21%-56.67%), respectively, had the reported rates in Ng et al. within the confidence intervals (CIs).⁴

Model Validation and Sensitivity Analysis

The simulation model was face validated by our contacts in the IPAC department of the considered acute care site, who confirmed the clinical relevance and reasonability of the model, parameters, and results. Also, the simulation results for the case of our acute care site were consistent with the historical records on the number of exposed roommates and the cumulative MRSA colonization in the site (see Table 2), providing a partial external validation.

We conducted one-way sensitivity analyses by varying each model parameter to its lower and upper limits (see ranges in Table 1) while keeping the others at their base-case values to explore the individual effect of each parameter on the selection of the ideal MRSA surveillance strategy. We also conducted a multi-way sensitivity analysis by varying test sensitivities and disease transmission parameters simultaneously because they may vary and affect the strategy selection. We ran our model under PCR- and culture-based MRSA surveillance strategies for all the selected test sensitivity and transmission probability combinations, derived from the calibration and literature (See Supplementary Materials III for details). For brevity, we excluded the MRSA colonization prevalence from the multi-way analysis as its effect on model outcomes was similar to that of transmission probability, i.e., making MRSA propagation more/less aggressive.

RESULTS

Performances of Surveillance Strategies in the Base-case Scenario

MRSA Surveillance with Culture vs PCR Test

Table 2 shows the base-case performances of post-exposure MRSA surveillance with Cult0+Cult6 and Cult0+PCR3 strategies. The current MRSA surveillance practice among the exposed roommates (Cult0+Cult6) led to a mean cumulative MRSA colonization (both primary and secondary transmissions) of 7.9% (CI:7.7-8.1%) among an average of 301.9 (CI:299.1-304.0) exposed roommates in our acute care site in a year. These values complied with the 2011-2012 statistics collected from the same acute care hospital, which had 301 exposed roommates in MRSA isolation in 2011 and a cumulative MRSA colonization rate of 8.1% in the 2011-2012 period.

Both surveillance strategies resulted in 23-24 MRSA colonizations, i.e., 7.7-7.9% cumulative MRSA colonization, among around 300 exposed roommates. Most colonizations resulted from primary transmissions before the index case was removed from the room. Both strategies detected around 68-70% of MRSA colonizations before isolation ends. Replacing Cult0+Cult6 with Cult0+PCR3 reduced the MRSA colonization due to secondary transmissions during isolation by 54.5% ($P<0.01$) as PCR-negative roommates would leave ward rooms thus limiting the exposure to those with yet-to-be-documented MRSA cases. As a result, Cult0+PCR3 was associated with 3.1% and 5.3% fewer MRSA cases and missed colonizations, respectively ($P<0.01$). In exchange for enhanced MRSA detection, Cult0+PCR3 led to a false-positive result for 6.75 exposed roommates on average based on the specificity of direct nasal PCR testing. This result shows that replacing Cult6 with PCR3 may result in at least comparable if not better surveillance outcomes.

Table 2. Expected performances of the MRSA surveillance strategies for the base-case scenario

Performance measures	Cult0+Cult6		Cult0+PCR3	
	Average	Half-width	Average	Half-width
Number of exposed roommates	301.91	< 2.08	300.61	< 2.07
Number of MRSA colonizations*	23.93		23.20	
Transmissions before isolation	22.39	< 0.34	22.51	< 0.34
Transmissions during isolation*	1.54		0.70	
Transmitted (day 0-1)	0.27	< 0.03	0.27	< 0.03
Transmitted (day 1-6 or day 1-3)	1.13	< 0.07	0.43	< 0.04
Transmitted (day 6-7)	0.13	< 0.02	-	-
Number of true-positives	16.32	< 0.27	16.18	< 0.26
Detected by/at day zero testing	7.19	< 0.17	7.12	< 0.17
Detected by/at day six (three) testing	9.14	< 0.20	9.08	< 0.20
Number of false-positives	-	-	6.75	< 0.17
Number of missed cases*	7.30	< 0.19	6.91	< 0.18
Costs				
Testing cost	\$7,911		\$15,820	
Isolation cost	\$146,557		\$66,570	
MRSA colonization cost	\$31,502		\$31,075 (\$40,116) [†]	
Total cost	\$185,970		\$113,465 (\$122,506) [†]	

Significances of the performance differences were assessed by the Paired T-Test and * refers to significant performance metric differences with $P < 0.01$. [†]The cost estimations inside and outside of the parenthesis refer to the estimations by including and not including an MRSA colonization cost after a false-positive test result, respectively.

Replacing Cult0+Cult6 with Cult0+PCR3 would also significantly reduce costs by improving resource consumption and bed flow associated with shorter isolation requirements. Cult0+PCR3 resulted in a 99.9% higher expected testing expense driven by PCR prices (compared to conventional culture) and confirmatory testing to exclude false-positive PCR cases. However, by removing isolation sooner, PCR3 reduced isolation costs by more than half. When the interventions for roommates with false-positive PCR were ignored (i.e., assuming that false-positive cases only incur additional isolation and follow-up costs), PCR3 also slightly decreased the MRSA colonization costs. Cult0+PCR3's reduction of expenditures related to isolation was more than enough to compensate for the increase in the testing cost, and thus, reduced the expected annual total cost by \$72,505 (i.e., 39% of the total cost). Even when the false-positive PCR results were included in the MRSA colonization costs, replacing Cult6 with PCR3 saved \$63,464 (i.e., \$185,970-\$122,506), a 34.1% reduction in total cost.

Marginal Benefits of the Day Zero Culture Test

Cult0 facilitates the removal of unrecognized MRSA cases from the isolation room at time zero, and thus, helps minimize secondary transmission risk. Therefore, removing Cult0 would reduce the sensitivity of MRSA surveillance testing. Table 3 highlights the performances of both MRSA surveillance strategies when the day zero culture is removed. We observed a 37% (41.4%) increase in secondary transmissions during isolation and a 5.4% (4.3%)

increase in the total number of MRSA colonizations when Cult6 (PCR3) was applied without Cult0. Cult6-only and PCR3-only were also associated with 49.3% and 50.9% more missed MRSA cases, respectively. Removing Cult0 from both MRSA surveillance strategies led to a \$3,809 and \$3,311 reduction in testing costs, respectively. However, these cost savings were lost due to higher isolation and MRSA colonization costs, resulting in higher total costs for the culture- and PCR-based MRSA surveillance strategies (by \$3,349 and \$1,631, respectively).

Table 3. Comparison of MRSA surveillance strategies with and without day zero culture test

Performance measures	Cult0+Cult6	Cult6	Difference (%)*	Cult0+PCR3	PCR3	Difference (%)*
Number of MRSA colonizations	23.93	25.24	5.5	23.20	24.19	4.3
MRSA transmissions during isolation	1.54	2.11	37	0.7	0.99	41.4
Number of missed cases	7.30	10.90	49.3	6.91	10.43	50.9
Total cost	\$185,970	\$189,319	1.8	\$113,465	\$115,096	1.4
Testing cost	\$7,911	\$4,102	-48.1	\$15,820	\$12,509	-20.9
Isolation cost	\$146,557	\$151,991	3.7	\$66,570	\$70,186	5.4
MRSA colonization cost	\$31,502	\$33,226	5.5	\$31,075	\$32,401	4.3

* % differences are calculated relative to the strategies with the day zero test, e.g., $(\text{Cult6} - (\text{Cult0} + \text{Cult6})) / (\text{Cult0} + \text{Cult6})$.

Sensitivity Analyses

The one-way sensitivity analysis in Figure 1 illustrates that the performance ranges of Cult0+PCR3 due to the variability in each model parameter were narrower and left-shifted compared to those for Cult0+Cult6 for all outcomes. The changes in isolation and colonization costs and MRSA colonization prevalence parameters caused the highest variability in the expected total costs of both strategies (See Figure 1a). The variability in testing costs had a relatively limited effect on the total expenses due to higher contributions of isolation and MRSA colonization costs. Moreover, the total cost ranges for Cult0+PCR3 did not overlap with those for Cult0+Cult6. These results imply that Cult0+PCR3 may be cost-saving compared to Cult0+Cult6 in most model parameter scenarios.

Figure 1b-d illustrates that MRSA colonization prevalence and transmission probability significantly affected the reduction in the numbers of MRSA colonizations, missed cases, and secondary transmissions because these parameters specify transmission risk during the exposure to the index case and the undetected roommates carrying MRSA. The range of the total number of MRSA colonization and missed cases due to variability in the MRSA colonization prevalence was higher than that due to the variability in transmission probability; whereas, the new cases during isolation showed greater variability to the changes in the transmission probability.

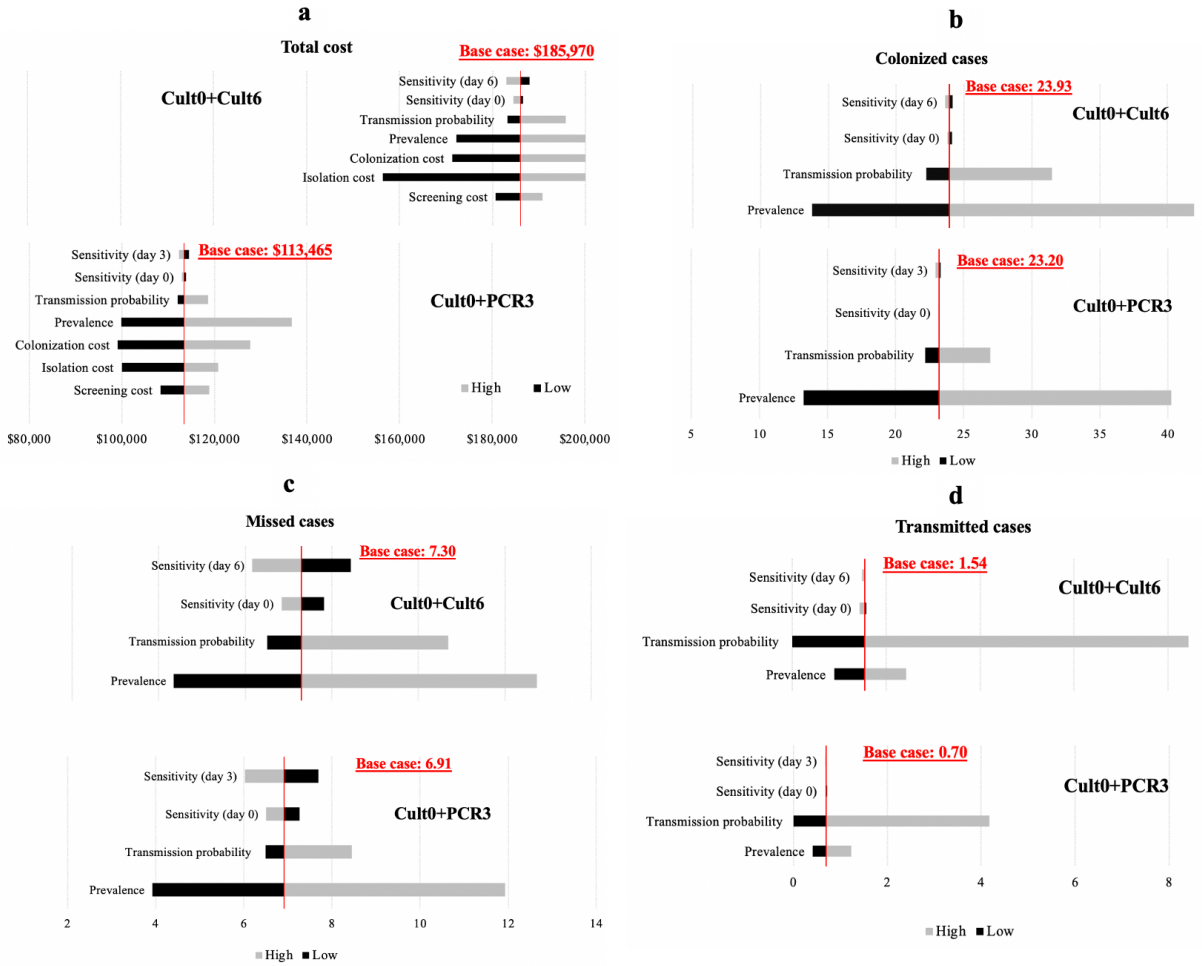


Figure 1. One-way sensitivity analysis measuring the effects of model parameters on performances of considered surveillance strategies: a) Total cost, b) Number of MRSA colonizations, c) Number of missed cases, and d) Number of MRSA transmissions during isolation.

Unlike other outcomes, the number of missed cases was quite sensitive to the test accuracies. The one-way sensitivity ranges of each surveillance outcome for Cult0+PCR3 and Cult0+Cult6 significantly overlapped. This warrants a joint analysis of disease transmission and sensitivity parameters to verify that Cult0+PCR3 may outperform Cult0+Cult6 in surveillance outcomes.

Figure 2 shows the reduction in MRSA colonization and missed cases achieved by Cult0+Cult6 and Cult0+PCR3 when MRSA transmission probability and test sensitivities varied simultaneously. For instance, when the transmission probability was 0.84%, conventional culture test sensitivity was 56.2% on day six, and nasal PCR test sensitivity was 62% on day three (i.e., PCR sensitivity – culture sensitivity = 5.8%), Cult0+PCR3 prevented 0.98 (4.1%) more MRSA colonization (i.e., secondary transmissions) and 1.28 (17.5%) more missed MRSA cases compared to Cult0+Cult6. The reductions in MRSA transmissions and missed cases achieved by Cult0+PCR3 increased from -0.37 to 5.11 (i.e.,

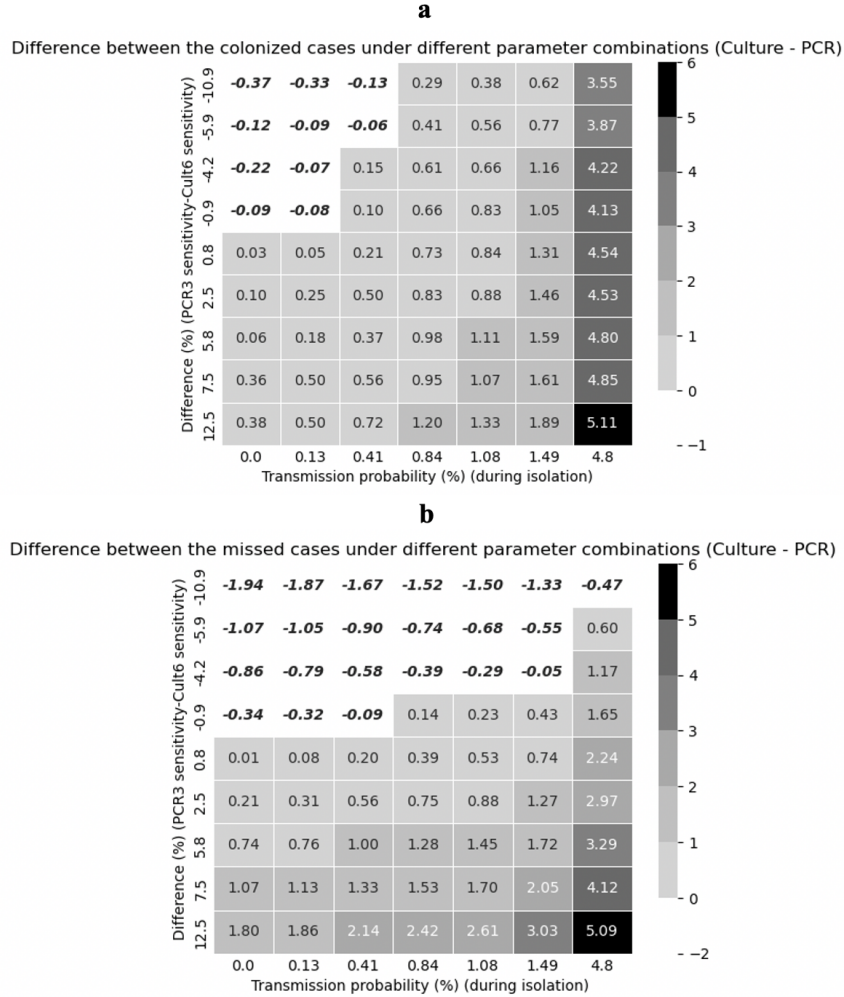


Figure 2. a) Difference between the numbers of MRSA colonizations and b) the missed cases under Cult0+PCR3 and Cult0+Cult6 for different combinations of transmission probabilities and sensitivity levels. Cells represent outcomes for Cult0+ Cult6 minus those for Cult0+ PCR3. Sensitivity combinations were presented in the increasing order of the difference between the sensitivity values, i.e., PCR test sensitivity - culture test sensitivity. The white cells highlighted in bold italic font represent the parameter combinations for which the PCR test did not reduce the number of MRSA colonizations or/and missed MRSA cases. The total number of MRSA colonization and missed MRSA cases were given in Supplementary Materials VI.

up to 16.1% reduction) and from -1.94 to 5.09 (i.e., up to 40.7% reduction), respectively, as transmission probability and the test sensitivity differences increased. Surprisingly, Cult0+PCR3 reduced the disease burden by preventing more MRSA colonization and missed cases compared to Cult0+Cult6 in most transmission probability values, sometimes even when the culture test sensitivity was higher than that of PCR. Note that, when Cult0+PCR3 failed to produce a lower number of MRSA colonization than Cult0+Cult6, the difference was negligible in most cases.

DISCUSSION

Studies on the optimal MRSA surveillance strategies among exposed roommates are limited even though it is a known scenario in acute care hospitals. A few studies reported a comparable performance of MRSA surveillance using conventional culture and direct PCR tests based on post-secondary data because of similar test sensitivities and conversion rates for these two strategies.^{4,22} However, they did not provide a detailed comparison in terms of the number of transmissions during isolation, missed cases, and cost savings. We presented a comprehensive comparison of culture- and PCR-based MRSA surveillance for the exposed roommates considering these metrics and show that a day zero conventional culture combined with day three direct nasal PCR improves surveillance outcomes and saves costs.

The simulation model used for this analysis was developed and calibrated using reported data on MRSA isolation/colonization counts and room settings from two Ontario community hospitals and data from the literature. The model estimated the cumulative MRSA colonization rate as 7.96%, and PCR (on day three) and culture (on day six) sensitivities as 55.44% and 56.57%, which were consistent with the reported value ranges in the literature, i.e., 4.4-12.6%, 52-62%, and 49.5-62.9%, respectively.^{4,11,15,16} Therefore, we concur that the simulation model reflects the MRSA transmission in middle-sized community hospitals in Ontario. In addition, based on the sensitivity analyses, our results can be generalized to other settings, as many Canadian hospitals have a high proportion of ward rooms compared to private/semi-private ones.²³ Moreover, the MRSA transmission rate in Canadian hospitals remains important especially when there is poor adherence to infection control practices and/or colonization pressure.^{2,24} Furthermore, the reported MRSA colonization and transmission rates are generally higher in the U.S. than those in Canada.²⁴ Our results would apply to those Canadian and U.S. settings with higher MRSA transmission risk, given that Figure 2 highlights the good performance of PCR-based surveillance in such aggressive MRSA transmission cases. However, we recommend caution in assessing the applicability of our results to small hospitals and those with high private/semi-private room proportions as those factors limit MRSA transmission and exposed roommate population, and thus, reduce the benefits of PCR-based MRSA surveillance compared to a culture-based one.

According to our results, the main benefit of the PCR-based MRSA surveillance was reducing the isolation duration by four days per case, which leads to significant improvements in direct costs attributable to the hospital, bed flow, and patient care. This strategy reduced days with isolation by 1,174 patient-days and led to 54.6% savings in isolation

cost, which compensated for i) additional laboratory expense for surveillance testing due to switching from culture to PCR testing, and ii) the costs of addressing PCR false positives (assuming all received interventions). In addition, in the base-case scenario, i.e., with low daily MRSA transmission probability (0.84%/day) and comparable Cult6 and PCR3 sensitivities (56.2% and 57%, respectively), Cult0+PCR3 reduced the cumulative MRSA colonization rate by 3.1% and prevented 5.3% of the missed MRSA colonization cases compared to Cult0+Cult6. Cult0+PCR3 achieved these improvements by decreasing the exposure of the MRSA-free roommates to potential carriers by four days and reducing secondary MRSA transmissions by 54.5%. The increase in PCR false positives (2.3% of around 300 exposed roommates isolated) to save around one MRSA colonization per year may seem alarming for increasing the negative impact of isolation and additional testing costs. However, Cult0+PCR3 significantly reduced total isolation days which may easily compensate for the negative effects of increased false positives, i.e., the additional isolation days caused by the 6.75 false positives is around 4% of the isolation reduction (i.e., 1,174 patient-days) achieved by Cult0+PCR3. These results suggest that Cult0+PCR3 is cost-saving and slightly improves surveillance outcomes compared to Cult0+Cult6.

The above results would apply to other likely parameter scenarios. Figure 1 shows that the contribution of the isolation cost to the total cost was several times higher than those of the other cost components; therefore, Cult0+PCR3 would be cost-saving compared to Cult0+Cult6 even if the costs and disease characteristics vary. Note that, our analysis considered conservative isolation cost estimates by including only the direct costs from the hospital perspective such as isolation and cleaning materials.^{14,20} Other studies reported higher isolation costs by including indirect costs from the patient and societal perspectives such as those related to the loss of revenue for private rooms, staff times, and productivity. When such indirect costs are included, the actual cost-effectiveness of Cult0+PCR3 would be further pronounced. Figure 2 also shows that unless the transmission rate was very low and direct PCR sensitivity inferior to conventional culture test, Cult0+PCR3 was associated with lower MRSA colonization and missed MRSA cases among the exposed roommates. Furthermore, Figure 2 and Supplementary Table 3 show that as the transmission rate increased, the outcome improvements associated with Cult0+PCR3 also increased. For instance, the percentage of MRSA colonizations prevented by the PCR-based surveillance compared to a culture-based one increased from 5% (for base case) to 16.1% (for the scenario of 12.5% sensitivity difference and 4.8% daily transmission rate). These findings are in line with studies supporting the use of PCR-based MRSA surveillance.^{4,11}

Our results also reinforce the benefits of day zero testing for MRSA surveillance among exposed roommates that are in line with the current best practices.⁶ An earlier study recommended removing the day zero culture test from surveillance based on its low sensitivity (i.e., 27.9%-35.5%) to save laboratory resources.^{4,16} However, focusing only on test sensitivity could be short-sighted because the reduced knowledge of baseline status may cause more MRSA colonizations due to increased secondary transmissions during isolation. Table 3 shows that removing the day zero culture test from Cult0+PCR3 and Cult0+Cult6 led to 4.3% and 5.4% more MRSA colonizations, respectively, and increased the missed MRSA cases by around 50%. As a result, removing Cult0 from Cult0+PCR3 and Cult0+Cult6 increased the total cost by \$1,631 and \$3,349 in the base-case scenario. These findings support the cost-effectiveness and surveillance value of day zero testing among MRSA-exposed roommates, especially for institutions with lower compliance to infection prevention/control practices and higher regional/institutional nosocomial MRSA prevalence.

Our analyses have a few limitations. First, we selected the test sensitivities, cost values, and rate of observing index cases from pre-pandemic (SARS-CoV-2) studies. Since the pandemic, the cost and performance of PCR testing for MRSA may have improved, which would further amplify the surveillance performance and cost-effectiveness of a PCR3 strategy. Conversely, bed pressures (from increased respiratory isolations) may have increased the proportion of ward rooms and prevented access to private rooms which may weaken preventative measures.^{3,25} Hence, these pandemic-related trends would only make the benefits of Cult0+PCR3 stronger and not change our conclusions. Second, we assumed that all missed cases can cause a new chain of transmissions in the hospital. Here, due to limited data, we could not incorporate into the model that an unknown portion of the missed cases may be diagnosed elsewhere or caught by admission tests due to their history. Thus, our results may overestimate the effects of the missed cases. However, the effect of this assumption on our conclusions would be limited given that; i) the considered hospital is the largest acute care in the region (so missed cases were likely to return to our site), and ii) the compared culture- vs PCR-based surveillance strategies had similar base-case numbers of missed cases, so the effects of a reduced return rate of missed cases in the performances of the two strategies would offset each other in most parameter settings. Third, in our analysis, we do not consider the individual risk of MRSA acquisition (i.e., from underlying medical conditions or length of stay) of the exposed roommates. Their incorporation required estimating all disease characteristics based on these factors, which was not possible given the scarcity of available data and the lack of these factors in studies reporting outcomes for exposed roommates.^{4,11} Finally, it may have been prudent to consider an alternative schedule for the direct PCR test, (e.g., day two or day four), or replace the day 0 culture test with a day 0

PCR test as well. Nevertheless, analyzing these alternatives would require information on PCR sensitivity at different time points, which was not available in the literature, and therefore left for future research.

Note that the 1-2 hour turnaround time considered in our analysis mainly refers to the assay time. This turnaround time estimation makes sense for a hospital laboratory with the ability to process priority PCR specimens on-demand. However, due to practical considerations with laboratory workflow (i.e., specimen transportation, operation hours, PCR capacity), longer turnaround times of up to 24 hours could occur.¹⁵ This may slightly reduce the cost-effectiveness of PCR-based surveillance. For example, if the turnaround time of the PCR test was around 24 hours and would lead to completion of isolation at the end of day 3 rather than in the morning of the same day (turnaround time = 1-2 hours) for test negatives, the total cost of Cult0+PCR3 in the base case would increase from \$113,465 to \$125,679 which is still much lower than that of Cult0+Cult6 (\$185,970). Therefore, PCR-based MRSA surveillance would be still cost-saving and associated with similar (if not better) health outcomes compared to culture-based surveillance even if PCR turnaround times would be longer.

The results from modeling of nosocomial MRSA transmission within shared rooms show that the strategy of Cult0+PCR3 required fewer days of isolation without negatively affecting infection control outcomes, compared to the conventional strategy or those omitting the baseline test (i.e., day zero culture). Despite the initial higher unit cost for direct PCR testing, there is a significant net saving from expenditures directly associated with isolation. It is also advantageous for patients in lowering their risk of MRSA acquisition (and therefore infection) and improving care/wellness from shorter isolation requirements. Our results are in line with studies highlighting the potential of the PCR test to replace the conventional culture test for MRSA surveillance among exposed roommates in the North American setting.^{4,11} In hospitals, which have a large percentage of multibed rooms and/or frequent nosocomial transmission, this strategy can help alleviate the financial implications of isolation requirement interrupting transmission risk at earlier stages. Guidelines should consider the use of this strategy in some situations, after careful analysis of local MRSA epidemiology and financial implications.

This study focused on only a particular part of the patient population subject to MRSA risk and management activities, i.e., the exposed roommates predominantly in four-bedded ward rooms in hospitals. However, exposed roommates have a high risk of MRSA acquisition, and studies focusing on the cost-effectiveness of MRSA testing among them are very limited. Therefore, our study significantly contributes to the medical literature. Our results also provide

partial/indirect insights for other population settings, e.g., the good performance of early PCR-based MRSA testing for scenarios with higher transmission risk suggests a potential use during MRSA outbreaks in hospitals and nursing homes. The proposed model can be easily extended to settings of other populations under heightened MRSA acquisition risk for future studies.

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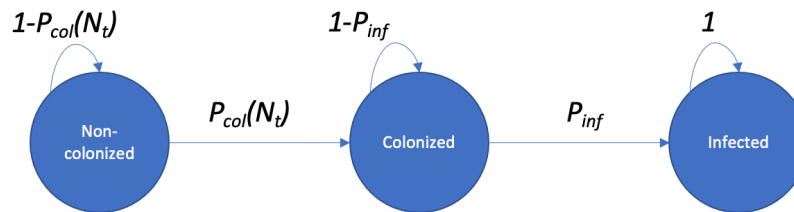
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Supplementary Materials

Supplementary Materials I: Derivation of Model Parameters

This section provides further details about model parametrization to facilitate understanding and interpretation of the input parameters reported in Table 1. As shown in **Supplementary Figure 1**, MRSA statuses of exposed roommates transition from non-colonized (no colonization) to colonized (MRSA colonization), and from colonized to infected (MRSA infection) randomly based on daily MRSA transmission and progression probabilities. This transition and progression scheme starts with the diagnosis of an MRSA index case. We derived the rate of diagnosis for MRSA index cases, room settings, and room-type distributions based on the data provided by the Infection Prevention and Control (IPAC) department in Grand River and St. Mary's hospitals (GRH & SMH). The rate of diagnosis for the MRSA index cases (e.g., exposed roommate isolations) was 0.255 diagnoses per day in the GRH & SMH. We also derived the isolation room type distribution based on the 4:1 cohort to semi-private room ratio in the GRH & SMH. We modeled the time till the diagnosis of missed MRSA cases after the isolation using a discrete distribution with a mean of seven days based on follow-up practices for the discharged roommates in GRH & SMH.



Supplementary-Figure 1: Transmission and progression sub-model during isolation: $P_{col}(N_t)$ refers to the probability of MRSA transmission to each disease-free roommate on day t (i.e., developing MRSA colonization) given that there are N_t patients with MRSA colonization in the room. $P_{col}(N_t) = 1 - (1 - P_{iso})^{N_t}$; P_{iso} : daily probability of MRSA transmission from an infected/colonized patient to an uncolonized roommate. P_{inf} : daily probability of MRSA

progression from colonization to infection. Mortality during isolation was not explicitly modeled due to the limited time window (i.e., one week); however, indirectly considered in the treatment cost of MRSA colonization.

The reported estimations of MRSA transmission/infection rate and test sensitivities in the literature significantly differ due to changing MRSA prevalence and control practices at different hospitals and regions, and bacterial load changing over time. Therefore, we estimated MRSA prevalence, transmission probabilities, and test sensitivities via model calibration for the case of GRH & SMH in Ontario-Canada based on benchmark statistics from a retrospective study conducted in North York General Hospital (NYGH), ON-Canada; a similar-sized Ontario community teaching hospital.⁴ The calibrated model parameters are reported in Table 1, and the calibration process is explained in Supplementary Materials II.

The remaining parameters including the ratio between MRSA transmission probability before and during isolation, test specificities, costs, and the benchmark statistics for the model calibration were collected from the medical literature (see Table 1). The culture and PCR specificities were reported as 100% and 97.5% in the literature, respectively.^{14,16} Costs were estimated for screening (culture and PCR), isolation, and colonization management (including costs associated with treatments, medications, further follow-up, and mortality) from the literature, and converted to the 2022 Canadian dollars using exchange rates from the correspondent years and the consumer price index (CPI) in health care.^{13,14,16-20}

Supplementary Materials II: Details Related to the Model Calibration Process

The calibration process included specifying search intervals for each parameter, discretizing these intervals to derive candidate parameter values, and methodologically searching these values for the combination that produces model outputs matching the selected benchmark statistics with the minimum mean squared error. Ng et al. (2012) reported an 8% cumulative rate of MRSA colonization as well as 30%, 56%, and 55% MRSA conversion rates in NYGH for culture tests at the beginning and end of the isolation period, and a PCR test in the middle of the isolation, respectively.⁴ We took these rates as benchmark statistics and determined the calibrated model parameters estimating these benchmark statistics with minimum mean squared error as 7.96% (CI:7.87%-8.04%), 29.92% (CI:29.31%-30.53%), 56.57% (CI:55.48% - 57.67%), and 55.44% (CI:54.21%-56.67%), respectively.

For computational efficiency, we calibrated a single parameter for MRSA prevalence on day 0 and MRSA transmission rates during isolation by assuming that MRSA transmission rates during the exposure of the roommates

to the index case, and the post-exposure period are proportional with a ratio e , an indicator of isolation effectiveness. Thus, we only calibrated the latter based on the proportion of patients with short (48 hrs) and long (96 hrs) contact duration reported in Ng et al. (2012) (i.e., 62.9% and 37.1%, respectively).⁴ We derived low, medium, and high isolation effectiveness values for Canadian hospitals from the literature (see Table 1 and Supplementary Table 1).^{14,16} We used the high isolation effectiveness ratio as our base case given i) the high compliance to isolation protocols in NYGH and GRH & SMH, and ii) recent reports indicating reducing healthcare-associated MRSA incidence rates in Ontario due to improvements in hospital infection control.²⁵

We assumed that MRSA transition can occur from each unrecognized colonized roommate independently with the same probability $p_{pre-iso}$ before isolation starts. Given $p_{pre-iso}$ (MRSA transmission probability from each colonized to non-colonized patient before isolation), we calculated the MRSA prevalence among the roommates as the probability of having k colonized roommates in the room by the diagnosis of the index case, i.e., $P(N_c = k)$. We calculated these prevalence probabilities using a Markov Chain, X_n , which kept track of the numbers of colonized and non-colonized patients on the n^{th} day of the pre-isolation contact with the index case based on the one-step transition probability given in Equation 1:

$$P(X_{n+1} = \{(N_{nc} - l), (N_c + l)\} | X_n = \{N_{nc}, N_c\}) = \binom{N_{nc}}{l} (p_{pre-iso}(N_c))^l (1 - p_{pre-iso}(N_c))^{N_{nc}-l}$$

$$\text{for } N_{nc}, N_c \geq 0, \text{ and } 0 \leq l \leq N_{nc} \quad (\text{Eq. 1})$$

Equation 1 calculates the probability of having l MRSA conversions among roommates in contact each day before the isolation starts, where N_{nc} and N_c denote the number of non-colonized and colonized cases, and $p_{pre-iso}(N_c) = 1 - (1 - p_{pre-iso})^{N_c}$. Using Equation 1, we calculated the probability of having k colonized roommates on the n^{th} day of the pre-isolation contact as $P_n(N_c = k) = P(X_n = \{K - k - 1, k + 1\} | X_0 = \{K - 1, 1\})$, where K refers to the room size and $X_0 = \{K - 1, 1\}$ represents the situation that initially only the index cases carry MRSA in the room. Then, we calculated the final prevalence probabilities as follows:

$$P(N_c = k) = 0.629P_2(N_c = k) + 0.371P_4(N_c = k) \quad (\text{Eq. 2})$$

Finally, given $P(N_c = k)$, we specified the probability that each exposed roommate may have MRSA colonization on day 0 (P_{prv}) as follows:

$$P_{prv} = \sum_k \frac{k}{K-1} P(N_c = k) \quad (\text{Eq. 3})$$

Supplementary Table 1 illustrates the calibrated model outcomes mimicking the settings in NYGH as described in Ng et al. (2012).⁴ Note that the CIs of the model outcomes in the following table cover the point estimates of benchmark statistics from Ng et al. (2012).⁴

Supplementary-Table 1
Calibrated results under different e values

Ratio e	1.69		2.42		3.15	
	Average	Half-width	Average	Half-width	Average	Half-width
Total exposed roommates	842.66	< 2.02	842.19	< 2.09	840.71	< 2.03
Total conversions	67.33	< 0.82	67.34	< 0.82	66.99	< 0.81
Total conversion rate (benchmark 1)	8%		8%		8%	
Total conversion rate (95% CI)	7.98% (7.89%-8.07%)		7.98% (7.89%-8.07%)		7.96% (7.87%-8.04%)	
Total transmitted	7.14		5.48		4.22	
Total detected	45.32	< 0.59	45.44	< 0.61	45.49	< 0.60
Missed cases	21.72	< 0.43	21.63	< 0.44	21.26	< 0.43
T1 culture screening						
Total conversions	44.33	< 0.62	44.61	< 0.63	44.11	< 0.62
True positive	13.31	< 0.33	13.33	< 0.31	13.17	< 0.32
Conversion rate (benchmark 2)	30%		30%		30%	
Conversion rate (95% CI)	30.13% (29.48%-30.78%)		29.99% (29.40% - 30.57%)		29.92% (29.31% -30.53%)	
T2 PCR screening						
False positive	5.49	< 0.21	5.08	< 0.20	5.08	< 0.20
Total conversions	14.51	< 0.34	14.63	< 0.34	14.49	< 0.34
True positive	7.93	< 0.24	8.06	< 0.25	8.02	< 0.25
Conversion rate (benchmark 3)	55%		55%		55%	
Conversion rate (95% CI)	54.88% (53.65% - 56.11%)		55.11% (53.95% - 56.27%)		55.44% (54.21% - 56.67%)	
T3 culture screening						
Total conversions	17.19	< 0.39	16.94	< 0.38	16.82	< 0.36
True positive	9.68	< 0.28	9.55	< 0.28	9.5	< 0.26
Conversion rate (benchmark 4)	56%		56%		56%	
Conversion rate (95% CI)	56.38% (55.35% - 57.41%)		56.30% (55.19% - 57.41%)		56.57% (55.48% - 57.67%)	

Supplementary Materials III: Derivations of Sensitivity Analysis Scenarios

For one-way sensitivity analysis, we set the upper and lower limits for the daily MRSA transmission rate based on Tübbicke et al. (2012).^{14,16} The range of MRSA prevalence (i.e., 4.4%-12.6%) was derived from the papers analyzing MRSA incidences among the exposed roommates.^{10,15} Upper and lower limits for the costs were set based on the ranges reported in the literature.^{13,14,16-20} The ranges for test sensitivities for particular test days were not available. Therefore, we calculated the proportion of CI half-width from a study on the sensitivity of the general-purpose MRSA culture test and apply the same proportion to our sensitivity point estimates from model calibration to derive their upper/lower limits. Specifically, Tübbicke et al. (2012) estimated the sensitivity of the culture test for diagnosing

index cases as 92.4% with a CI of 78.1%-100%.^{14,16} Thus, we determined the proportion of CI half-width as 11.85% (i.e., $11.85\% = (100\% - 78.1\%) / 92.4\%$). Then, for instance, the range of the culture test sensitivity on day 6 was calculated as 49.5%-62.9% (i.e., $56.2\% \pm 11.85\% \times 56.2\%$).

For the multi-way sensitivity analysis, we measured the performances of the considered MRSA surveillance strategies for various combinations of test sensitivities and disease transmission parameters. To efficiently analyze the joint effect of variabilities in these parameters, we run our model for all combinations of i) the difference between the selected PCR and culture test sensitivity values (i.e., PCR sensitivity – culture sensitivity) and ii) transmission probability. We derived the parameter combinations from the calibration results and literature. For example, the transition probabilities of 0.84%, 1.08%, and 1.49% were derived from calibrating the model outcomes to match the results from Ng et al. (2012) for low, medium, and high (base-case) isolation effectiveness rates from the literature (e.g., 1.691, 2.423, and 3.154) respectively.⁴ The rest of the transition probability values (e.g., 0.013%, 0.041%, and 4.8%) were derived from the literature to better populate the parameter range.^{14,16}

Supplementary Materials IV: Detailed One- and Multi-way Sensitivity Analysis Results

Supplementary-Table 2 provides the details of the one-way sensitivity analysis in Figure 1 of the manuscript by specifying the exact lower and upper limits in the Tornado charts. Similarly, Supplementary Table 3 provides more details on the multi-way sensitivity analysis illustrated in Figure 2 of the main manuscript by specifying average counts of MRSA colonization and missed MRSA cases for each combination of transmission rate and test sensitivities.

Supplementary-Table 2

One-way sensitivity analysis results for the Cult0+Cult6 and Cult0+PCR3 strategies

	Cult0+Cult6		Cult0+PCR3	
	Lower bound	Upper bound	Lower bound	Upper bound
Total Cost	Base-case =\$185,970		Base-case =\$113,465	
Screening cost	\$180,694	\$190,704	\$108,422	\$118,922
Isolation cost	\$156,395	\$202,183	\$100,031	\$120,829
Colonization cost	\$171,367	\$200,574	\$99,209	\$127,722
Prevalence	\$172,177	\$210,372	\$99,972	\$136,687
Transmission probability (during isolation)	\$183,195	\$195,794	\$112,132	\$118,615
Sensitivity (day 0)	\$186,558	\$184,528	\$113,962	\$113,043
Sensitivity (day 6 or 3)	\$187,978	\$182,989	\$114,502	\$112,365
Number of colonized cases	Base-case 23.93		Base-case =23.20	
Prevalence	13.769	41.960	13.234	40.248
Transmission probability (during isolation)	22.212	31.490	22.181	26.951

Sensitivity (day 0)	24.113	23.761	23.233	23.145
Sensitivity (day 3 or 6)	24.150	23.610	23.318	22.950
Number of missed cases	Base-case 7.30		Base-case 6.91	
Prevalence	4.349	12.737	3.925	11.931
Transmission probability (during isolation)	6.505	10.690	6.495	8.450
Sensitivity (day 0)	7.818	6.836	7.258	6.509
Sensitivity (day 3 or 6)	8.442	6.159	7.694	6.023
Number of transmitted cases	Base-case 1.54		Base-case 0.70	
Prevalence	0.888	2.429	0.413	1.224
Transmission probability (during isolation)	0.000	8.442	0.000	4.170
Sensitivity (day 0)	1.580	1.435	0.716	0.680
Sensitivity (day 3 or 6)	1.522	1.480	0.684	0.677

Supplementary-Table 3

The number of colonized and missed cases under different combinations of transmission probabilities and sensitivity levels

PCR sensitivity-Culture sensitivity			Transmission probability (during isolation)						
			0%	0.13%	0.41%	0.84%	1.08%	1.49%	4.8%
Sensitivities (%)	Difference (%)		The number of colonized cases under different parameter combinations						
PCR3	52	-10.9	22.44	22.52	22.83	23.32	23.71	24.05	27.27
Cult6	62.9		22.07	22.18	22.71	23.61	24.08	24.67	30.82
PCR3	57	-5.9	22.18	22.27	22.77	23.20	23.52	23.90	26.95
Cult6	62.9		22.07	22.18	22.71	23.61	24.08	24.67	30.82
PCR3	52	-4.2	22.44	22.52	22.83	23.32	23.71	24.05	27.27
Cult6	56.2		22.21	22.45	22.98	23.93	24.36	25.21	31.49
PCR3	62	-0.9	22.15	22.26	22.61	22.95	23.26	23.62	26.69
Cult6	62.9		22.07	22.18	22.71	23.61	24.08	24.67	30.82
PCR3	57	0.8	22.18	22.27	22.77	23.20	23.52	23.90	26.95
Cult6	56.2		22.21	22.32	22.98	23.93	24.36	25.21	31.49
PCR3	52	2.5	22.44	22.52	22.83	23.32	23.71	24.05	27.27
Cult6	49.5		22.54	22.77	23.33	24.15	24.59	25.51	31.80
PCR3	62	5.8	22.15	22.26	22.61	22.95	23.26	23.62	26.69
Cult6	56.2		22.21	22.45	22.98	23.93	24.36	25.21	31.49
PCR3	57	7.5	22.18	22.27	22.77	23.20	23.52	23.90	26.95
Cult6	49.5		22.54	22.77	23.33	24.15	24.59	25.51	31.80
PCR3	62	12.5	22.15	22.26	22.61	22.95	23.26	23.62	26.69
Cult6	49.5		22.54	22.77	23.33	24.15	24.59	25.51	31.80
Sensitivities (%)	Difference (%)		The number of missed cases under different parameter combinations						
PCR3	52	-10.9	7.36	7.40	7.48	7.69	7.85	8.02	9.52
Cult6	62.9		5.43	5.53	5.81	6.17	6.34	6.69	9.05
PCR3	57	-5.9	6.50	6.58	6.71	6.91	7.03	7.23	8.45
Cult6	62.9		5.43	5.53	5.81	6.17	6.34	6.69	9.05
PCR3	52	-4.2	7.36	7.40	7.48	7.69	7.85	8.02	9.52
Cult6	56.2		6.51	6.61	6.91	7.30	7.56	7.97	10.69
PCR3	62	-0.9	5.77	5.85	5.90	6.02	6.11	6.25	7.40
Cult6	62.9		5.43	5.53	5.81	6.16	6.34	6.69	9.05
PCR3	57	0.8	6.50	6.58	6.71	6.91	7.03	7.23	8.45
Cult6	56.2		6.51	6.66	6.91	7.30	7.56	7.97	10.69
PCR3	52	2.5	7.36	7.40	7.48	7.69	7.85	8.02	9.52
Cult6	49.5		7.57	7.70	8.04	8.44	8.72	9.28	12.49
PCR3	62	5.8	5.77	5.85	5.90	6.02	6.11	6.25	7.40
Cult6	56.2		6.51	6.61	6.91	7.30	7.56	7.97	10.69
PCR3	57	7.5	6.50	6.58	6.71	6.91	7.03	7.23	8.45
Cult6	49.5		7.57	7.70	8.04	8.44	8.72	9.28	12.57
PCR3	62	12.5	5.77	5.85	5.90	6.02	6.11	6.25	7.40
Cult6	49.5		7.57	7.70	8.04	8.44	8.72	9.28	12.49

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