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The attributable mortality, length of stay, and health care costs of methicillin-resistant *Staphylococcus aureus* infections in Singapore

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ABSTRACT

Objectives: We used a multi-state model, which mitigates time-dependent bias, to estimate the mortality, length of stay (LOS), and costs of methicillin-resistant *Staphylococcus aureus* (MRSA) infections in Singapore.
Methods: We conducted a retrospective study in a hospital in Singapore from 2018 to 2022. Patients with MRSA infections were matched 1:1:3 to patients with MRSA colonization and patients without MRSA by age, gender, specialty, and intensive care admission, respectively. A multi-state model was used to derive excess LOS and mortality hazard ratios. The attributable cost of infections was estimated in 2022 Singapore dollars (SGDs) from the health care perspective.
Results: We matched 536 patients with MRSA infections to 536 patients with MRSA colonization, and to 1608 patients without MRSA. The excess LOS due to MRSA infection was 2.11 (95% confidence interval [CI] 2.05-2.17) days compared with MRSA colonization and 3.75 (95% CI 3.69-3.80) days compared with no MRSA, which translated to an excess cost of SGD $1825 and SGD $3238, respectively. Of the different MRSA infection types, pneumonia had the highest mortality risk (hazard ratio 4.13; 95% CI 2.28-7.50) compared with patients without MRSA.
Conclusions: MRSA infections increased hospital LOS and health care costs in Singapore. Our estimates can inform future economic analyses of management strategies against MRSA.

Introduction

Methicillin-resistant *Staphylococcus aureus* (MRSA) is a major nosocomial pathogen associated with a wide range of potentially life-threatening infections. It is endemic in many hospitals worldwide, with several countries reporting MRSA proportions of more than 20% of *S. aureus* infections [1]. Patients who are colonized or infected with MRSA act as reservoirs for spread within hospitals. Nosocomial transmission of MRSA occurs either via direct patient-to-patient contact or indirectly through the hands of health care workers or contaminated fomites [2]. In hospitals in Singapore, MRSA remains endemic despite sustained and considerable infection prevention and control (IPC) efforts [3]. In a point prevalence survey in 2015, it was reported that MRSA is the most common multi-drug–resistant organism associated with nosocomial infections in acute care hospitals in Singapore, with approximately 58% of all *S. aureus* infections found to be resistant to methicillin [4]. In a more recent report, it appears that although MRSA remains entrenched in Singapore hospitals, infection rates have somewhat been declining in the recent years [5].

It is well-recognized that IPC strategies play a vital role in reducing MRSA transmission in hospitals [2]. Several IPC strategies have shown effectiveness in reducing MRSA transmission, but it is not possible to adopt all effective strategies because health care resources are limited. Economic evaluations, such as cost-effectiveness analyses, can be used to inform IPC policies against MRSA. Such evaluations examine the relative costs and outcomes of two or more IPC strategies to determine which

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options provide reasonable value for money and should be adopted. To perform economic analyses of IPC strategies against MRSA, robust estimates of costs and consequences of MRSA infections are needed. Accurate estimates for excess length of stay (LOS) of MRSA infections are especially important for deriving infection costs because a major component for increased health care costs associated with MRSA infection is the prolongation of hospital stay [6].

At present, studies that describe the excess LOS associated with MRSA infections in Singapore have not accounted for the biases associated with the time-varying nature of nosocomial infections [7]. This can result in overestimation in excess LOS [8]. Multi-state models include time as a continuous phenomenon within the model to avoid time-dependent bias and address the competing risks of death and discharge [9]. These models have been used to provide estimates of excess LOS associated with health care–associated infections and infections caused by drug-resistant organisms, including MRSA [10,11]. In this study, we used a multi-state model to estimate the attributable LOS and mortality risk associated with MRSA infections in Singapore, compared with patients who are asymptomatically colonized with MRSA and patients without MRSA. We also estimated the economic impact of MRSA infections on Singapore health care institutions.

Methods

Study setting

We conducted a retrospective case-cohort study in all patients admitted to Singapore's largest tertiary acute care hospital over a 5-year period from January 2018 to December 2022. The hospital has 1939 beds, which accounted for approximately 15% of all acute care hospital beds in Singapore in 2022 [12]. In 2018-2019, the incidence of MRSA acquisition in the hospital was 11.7 cases per 10,000 patient-days; the incidence of MRSA bacteremia was 0.36 cases per 10,000 patient-days [13]. The hospital's MRSA prevention and control policies follows the National Infection Prevention and Control Guidelines stipulated by the Ministry of Health, Singapore [14]. These include nasal and axillary swabs for MRSA in all patients at point of admission, followed by every fortnight; tagging of patients with MRSA colonization or patients with MRSA infection; contact precautions for all patients with MRSA colonization or patients with MRSA infection; and decolonization of MRSA carriers using a 5-day regimen of nasal mupirocin and chlorhexidine gluconate 4% or octenidine wash [5,14].

Study design

We matched patients with active MRSA infection and patients who are asymptomatically colonized with MRSA to a common group of patients without positive clinical or surveillance culture for MRSA by age, gender, admitting specialty, and presence of intensive care unit admission during hospital stay to account for potential confounders in demographics, baseline medical conditions, and clinical severity. Three patients without MRSA were matched to one patient with MRSA infection and one patient with MRSA colonization. We excluded all patients with positive clinical cultures of MRSA but with antibiotic treatment for MRSA for ≤2 days, as well as all patients with MRSA cultures from urinary tract because primary MRSA urinary tract infections are uncommon and it was difficult to differentiate clinical infection from asymptomatic urinary colonization based on available data for these patients. We considered patients with one or more positive clinical cultures of MRSA and initiated on antibiotic treatment for MRSA for ≥3 days within a 5-day period from culture date as having an active MRSA infection [15]. Patients with positive nasal and axillary MRSA surveillance swabs but without positive clinical cultures of MRSA were considered to be asymptomatically colonized with MRSA. MRSA was defined as *S. aureus* isolates with a methicillin or oxacillin minimum inhibitory concentration ≥4 μg/mL, in accordance with the Clinical Laboratory Susceptibility Institute guidelines [16]. Antibiotic susceptibilities for *S. aureus* were determined through disk susceptibility testing, supplemented by the VITEK 2 system (bioMérieux, Marcy l'Etoile, France). We defined the onset of MRSA infection as the time of first clinical culture; for patients with multiple clinical cultures, only the first MRSA clinical culture was analyzed. The onset of MRSA colonization was defined as the date of first positive nasal or axillary MRSA surveillance swab.

Data collection

Relevant data were derived from an anonymized data set provided by the hospital's infection prevention and epidemiology team, extracted from the hospital's electronic database. These included demographics, admission details, laboratory results, and antibiotic use details. We obtained the yearly incidence of clinical MRSA infections from the hospital's infection prevention and epidemiology team for calculating cost estimates. Patient outcomes on in-hospital all-cause mortality and time to discharge were collected.

Data analysis

Each patient's admission was modeled using five states in a multi-state model: no MRSA colonization or infection, asymptomatically colonized with MRSA, active MRSA infection, discharged alive, or died (Figure 1). Such models consider the time-dependent and the competing risks nature of the different events. Excess LOS due to MRSA infections compared with patients asymptomatically colonized with MRSA and patients with no MRSA was derived with the use of transition probabilities, estimated non-parametrically using the Aalen–Johansen estimator [17]. Additional analyses were performed for each infection type and for the subset of patients with MRSA infections that developed ≥72 hours from admission. To derive 95% confidence intervals (CIs) for excess LOS, we used 500 bootstrap resamples from random selection with replacement based on approximate normality. The hazards of death or discharge over the course of time were calculated using an extended Cox proportional hazard model, presented as hazard ratios (HRs) and 95% CIs. The proportional hazards assumption was evaluated by the test for proportional hazards assumption (cox.zph) and visual inspection of the plot. We censored long hospitalizations at 60 days to reduce the influence of outliers because these long stays are often most associated with social barriers to discharge (e.g. caregiver stress, inability to find post-discharge long-term care placement) and are less likely attributable to acute MRSA infections [18].

We calculated the excess costs of a MRSA infection compared to patients with no MRSA and to patients asymptomatically colonized with MRSA from the health system perspective by multiplying the prolongation of LOS with a monetary value of a bed-day. Cost of a bed-day was obtained from the study by Graves *et al.* [19], adjusted to the 2022 Singapore dollar (SGD) using the Singapore Consumer Price Index [20]. Uncertainties around bed-day cost, incidence, and LOS were modeled using Monte Carlo resampling of 500 iterations based on previous distributions. All statistical analyses were conducted using "MatchIt," "survival," "etm," and "glm" package in R software [21]. A final two-sided $P \leq 0.05$ was considered significant.

Results

Patient characteristics

We included a total of 2680 patients, composed of 536 patients with MRSA infections, 536 patients colonized asymptomatically with MRSA, and 1608 patients without MRSA colonization or infection (Table 1). The mean age of patients was 65.9 ± 11.9 years; the proportion of patients admitted to the intensive care unit during hospital stay was 12.5% in all three groups. Of the 536 patients with MRSA infections,

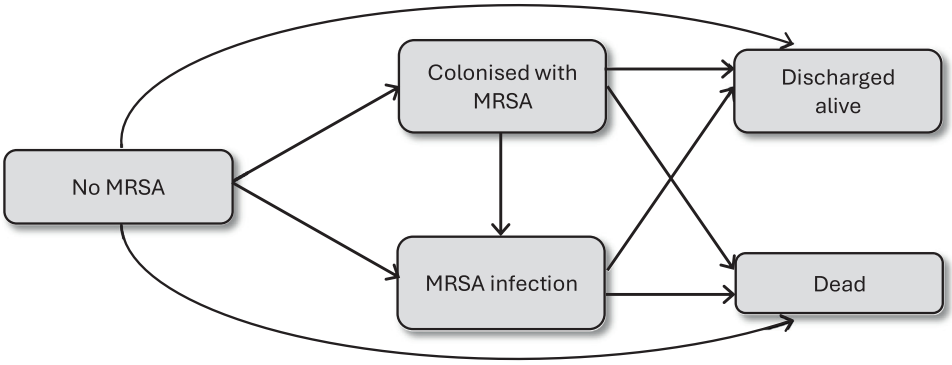

Figure 1. Multi-state model depicting the different states of a patient within a hospital admission. MRSA, methicillin-resistant *S. aureus*.

Table 1
Baseline characteristics, MRSA colonization and infection details, and outcomes of included patients.

Characteristics (Mean ± SD or number [%])	Patients with MRSA infections (n = 536)	Patients with MRSA colonization but without infection (n = 536)	Patients with no MRSA colonization or infection (n = 1608)
Demographics and admission details			
Age (year)	65.9 ±11.9	65.9 ±11.9	65.9 ±11.9
Male gender	391 (72.9)	391 (72.9)	1173 (72.9)
Admitting specialty			
General surgery/vascular	84 (15.7)	84 (15.7)	252 (15.7)
Internal medicine	120 (22.4)	120 (22.4)	360 (22.4)
Orthopedics	60 (11.2)	60 (11.2)	180 (11.2)
Renal	66 (12.3)	66 (12.3)	198 (12.3)
Oncology/Hematology	47 (8.8)	47 (8.8)	141 (8.8)
Other specialties	159 (29.7)	159 (29.7)	477 (29.7)
Intensive care unit admission during stay	67 (12.5)	67 (12.5)	201 (12.5)
MRSA colonization and infection details			
Colonized with MRSA	417 (77.8)	536 (100.0)	
Infection type			
Skin/soft tissue	279 (52.1)	-	-
Bloodstream	122 (22.8)	-	-
Lower respiratory tract	45 (8.4)	-	-
Others[a]	90 (16.8)	-	-
Developed MRSA infection ≥72 hours from admission	349 (65.1)	-	-
MRSA treatment details			
Antibiotic use[b]			
Vancomycin	503 (93.8)	-	-
Daptomycin	78 (14.6)	-	-
Sulfamethoxazole/ trimethoprim	79 (14.7)	-	-
Patient outcomes			
Length of hospital stay	42.0 ± 46.2	16.9 ± 30.9	8.3 ± 15.9
All-cause mortality	65 (12.1)	17 (3.2)	56 (3.5)

[a] Other infections include infection of the eye, ear, nose or throat (n = 31), peritoneal/abdominal cavity (19), infection of the perineum or genitalia (n = 16), bone and joint infection (n = 12) and line/tip without bloodstream infection (n = 12).
[b] A total of 114 (21.3%) patients used two antibiotics for MRSA treatment, and five (0.9%) patients used three antibiotics for MRSA treatment in the treatment course.Abbreviations: MRSA, methicillin-resistant *S. aureus*.

349 (65.1%) developed MRSA infection ≥72 hours from hospital admission. The most common MRSA infections were skin and soft tissue (52.1%) and bloodstream infections (22.8%). The most common antibiotic prescribed for treatment was vancomycin (93.8%). Overall, the all-cause mortality in patients with MRSA infection, MRSA colonization, and without MRSA were 65 of 536 (12.1%) 17 of 536 (3.2%), and 56 of 1608 (3.5%), respectively. The crude mean hospital LOS was the longest in patients with MRSA infections (42.0 ± 46.2 days), followed by patients colonized with MRSA (16.9 ± 30.9 days).

Hazards of mortality and being discharged alive

In the Cox regression analysis, patients with MRSA infections had significantly higher hazards of mortality than patients with MRSA colonization (HR 2.09; 95% CI 1.13-3.69) when all infection sites were considered, but not when compared with patients with no MRSA (HR 0.94; 95% CI 0.60-1.43) (Table 2). Across the different MRSA infection types, hazards of mortality were the highest in patients with lower respiratory tract infections, followed by bloodstream infections. The findings remained similar in the subset of patients who developed MRSA infections ≥72 hours from hospital admission. The presence of an MRSA infection at any site significantly reduced the daily likelihood of discharged alive when all infection sites were considered compared with patients with MRSA colonization (0.57, 95% CI 0.49-0.66) and patients with no MRSA (0.34, 95% CI 0.30-0.39). The hazards of being discharged alive was also significantly lower when each infection type was separately analyzed and in the subset of patients who developed MRSA infection ≥72 hours from hospital admission.

Excess length of stay

From the multi-state model, MRSA infections resulted in an additional hospital LOS of 2.11 days (95% CI 2.05-2.17) and 3.75 days (95% CI 3.69-3.80) compared with patients with MRSA colonization and pa-

Table 2
Hazard ratio for in-hospital all-cause mortality and being discharged alive in (i) patients with MRSA colonization only, compared to those with no MRSA infection or colonization; and (ii) patients with MRSA infections, compared to those with no MRSA infection or colonization; and (iii) patients with MRSA infections, compared to those with MRSA colonization only.

Patient type	All-cause mortality		Discharged alive	
	Hazard ratio (95% CI)	*P*-value	Hazard ratio (95% CI)	*P*-value
MRSA colonization only *vs* no MRSA infection or colonization				
All colonized with MRSA	0.61 (0.32-1.12)	0.787	0.79 (0.71-0.88)	<0.001
MRSA infection *vs* no MRSA infection or colonization				
All MRSA infections	0.94 (0.60-1.43)	0.223	0.34 (0.30-0.39)	<0.001
Skin/soft tissue	0.56 (0.13-1.47)	0.075	0.57 (0.46-0.71)	<0.001
Bloodstream	2.02 (1.24-3.30)	0.002	0.33 (0.26-0.41)	<0.001
Lower respiratory tract	4.13 (2.28-7.50)	<0.001	0.27 (0.17-0.44)	<0.001
Others	0.70 (0.23-1.31)	0.271	0.43 (0.35-0.53)	<0.001
MRSA infections ≥72 hours from admission	0.92 (0.59-1.43)	0.389	0.34 (0.30-0.39)	<0.001
Skin/soft tissue	0.37 (0.03-1.25)	0.082	0.46 (0.38-0.56)	<0.001
Bloodstream	2.31 (1.20-4.46)	0.001	0.32 (0.23-0.45)	<0.001
Lower respiratory tract	3.89 (2.10-7.17)	<0.001	0.40 (0.16-0.89)	<0.001
Others	0.67 (0.27-1.71)	0.376	0.44 (0.31-0.60)	<0.001
MRSA infection *vs* MRSA colonization only				
All MRSA infections	2.09 (1.13-3.69)	0.011	0.57 (0.49-0.66)	<0.001
Skin/soft tissue	0.70 (0.33-1.54)	0.385	0.58 (0.50-0.67)	<0.001
Bloodstream	3.44 (1.88-6.32)	<0.001	0.41 (0.33-0.52)	<0.001
Lower respiratory tract	5.92 (2.97-11.79)	<0.001	0.29 (0.19-0.43)	<0.001
Others	1.29 (0.50-3.32)	0.592	0.63 (0.50-0.79)	<0.001
MRSA infections ≥72 hours from admission	2.10 (1.15-3.85)	<0.001	0.46 (0.40-0.54)	<0.001
Skin/soft tissue	0.59 (0.24-1.45)	0.182	0.51 (0.43-0.61)	<0.001
Bloodstream	3.27 (1.68-6.34)	<0.001	0.49 (0.28-0.64)	<0.001
Lower respiratory tract	6.47 (3.23-12.96)	<0.001	0.27 (0.43-0.61)	<0.001
Others	1.50 (0.55-4.12)	0.171	0.57 (0.43-0.76)	<0.001

CI, confidence interval; MRSA, methicillin-resistant *S. aureus*.

Table 3
Mean excess length of stay and healthcare costs in 2022 SGD dollar with 95% CI, in (i) patients with infections, compared to those with no MRSA infection or colonization; and (ii) patients with MRSA infections, compared to those with MRSA colonization only.

Infection type	Incidence per 100,000 admissions	Mean excess length of stay per infection (95% CI)		Cost per infection (95% CI)		Cost per 100,000 admissions (95% CI)	
		Compared to no MRSA	Compared to MRSA colonized patients	Compared to no MRSA	Compared to MRSA colonized patients	Compared to no MRSA	Compared to MRSA colonized patients
All MRSA infections	210.30 (209.59-211.02)	3.75 (3.69-3.80)	2.11 (2.05-2.17)	3238 (3126-3351)	1825 (1746-1905)	680,646 (656,997-704,295)	383,427 (366,844-400,011)
Skin/soft tissue	108.51 (108.01-109.02)	5.78 (5.71-5.86)	4.14 (4.06-4.22)	5009 (4836-5182)	3597 (3460-3733)	543,458 (524,888-562,358)	390,076 (375,173-404,979)
Bloodstream	46.25 (45.90-46.61)	6.78 (6.66-6.85)	5.12 (5.02-5.22)	5846 (5645-6046)	4433 (4269-4597)	270,598 (261,016-280,180)	205,114 (197,333-212,896)
Lower respiratory tract	21.56 (21.32-21.80)	2.56 (2.32-2.80)	0.92 (0.68-1.16)	2197 (1964-2429)	784 (561-1007)	47,464 (42,363-52,566)	16,996 (12,131-21,860)
Others	33.87 (33.58-34.16)	7.53 (7.37-7.64)	5.87 (5.73-6.00)	6484 (6250-6718)	5071 (4872-5270)	219,577 (211,377-227,776)	171,756 (164,791-178,721)
MRSA infections MRSA infections ≥72 hours from admission	137.27 (136.65-137.90)	3.90 (3.87-3.99)	2.29 (2.23-2.36)	3399 (3278-3520)	1986 (1898-2075)	467,079 (450,240-483,917)	272,924 (260,704-285,143)
Skin/soft tissue	68.52 (68.10-68.94)	6.10 (6.02-6.18)	4.46 (4.37-4.55)	5268 (5090-5446)	3855 (3712-3999)	360,959 (348,575-373,343)	264,198 (254,269-274,128)
Bloodstream	28.39 (28.12-28.67)	6.65 (6.48-6.74)	4.97 (4.83-5.11)	5702 (5492-5912)	4290 (4111-4468)	161,661 (155,578-167,745)	121,566 (116,438-126,695)
Lower respiratory tract	18.40 (18.19-18.62)	3.20 (2.77-3.25)	1.38 (1.13-1.62)	2616 (2378-2853)	1203 (974-1432)	48,419 (43,808-53,031)	22,374 (17,984-26,764)
Others	22.13 (21.89-22.38)	8.01 (7.75-8.06)	6.26 (6.10-6.42)	6846 (6583-7110)	5434 (5204-5664)	151,177 (145,277-157,076)	119,901 (114,803-125,000)

CI, confidence interval; MRSA, methicillin-resistant *S. aureus*.

tients with no MRSA, respectively (Table 3). When the subset of patients who developed an MRSA infection ≥72 hours from hospital admission were analyzed, the excess LOS were 2.29 days (95% CI 2.23-2.36) and 3.90 days (95% CI 3.87-3.99) compared with patients with MRSA colonization and patients with no MRSA, respectively. Across the different infection types, lower respiratory tract infection was associated with the lowest excess LOS.

Attributable health care costs

The excess health care cost of a single MRSA infection to the health system was SGD $1825 (95% CI SGD $1746-1905) compared with patients with MRSA colonization and SGD $3238 (95% CI SGD $3126-3351) compared with patients with no MRSA (Table 3). After accounting for the incidence of MRSA infections in the hospital, we estimated

that MRSA infections will have an excess attributable health care cost of SGD $383,427 (95% CI SGD $366,844-400,011) per 100,000 inpatient admissions compared with patients with asymptomatic MRSA colonization and SGD $680,646 (95% CI, SGD $656,997-704,295) per 100,000 inpatient admissions compared with patients with no MRSA. When the incidence of different MRSA infections was considered, MRSA skin and soft tissue infections was associated with the highest excess costs to the health system among the different infection types.

Discussion

To the best of our knowledge, this is the first multi-state modeling study to estimate the excess LOS and attributable costs of MRSA infections in Singapore hospitals. Compared with patients with MRSA colonization and with patients with no MRSA, MRSA infections were associated with excess hospital LOS and increased health care costs. Of the different MRSA infection types, pneumonia and bloodstream infections were associated with the highest increased risks of mortality. The estimates derived in our study will be useful to inform future model-based economic analyses of IPC strategies against MRSA.

In our study, we opted to compare the outcomes of patients with MRSA infections with a no-infection counterfactual, as opposed to a susceptible infection (i.e. methicillin-susceptible *S. aureus*) counterfactual. This is because MRSA spread within hospitals occurs principally via horizontal transmission, which is consistent with addition-type epidemiology, where MRSA infections add to the total infection burden of *S. aureus*, as opposed to replacing the methicillin-susceptible infections [2,22]. An important advantage of our study is that we provided outcome estimates against the comparator groups of "MRSA-colonized only" and "no MRSA." We advise that both estimates will be useful for future economic analyses, depending on the IPC strategy being evaluated [22]. For instance, for interventions that identify patients for MRSA decolonization to reduce risk of MRSA infection, estimates against the comparator group of MRSA-colonized should be used. On the other hand, estimates against the comparator group of no MRSA are more applicable for IPC measures that limit MRSA spread, such as enhanced surveillance with patient isolation or cohorting.

Due to limited data availability on the patients' clinical symptoms, we used the surrogate measure of positive clinical MRSA culture plus MRSA-active antibiotic prescriptions, in accordance with the methods described by Branch-Elliman *et al.* [15]. In the study, the authors showed that the surrogate measure of MRSA culture plus receipt of MRSA-active antibiotics had excellent sensitivity and good specificity in detecting MRSA infections. To minimize the likelihood of including patients colonized with MRSA without active infection in the infection group, we excluded patients who were treated with an MRSA-active antibiotic for less than 3 days. We also excluded patients with MRSA from the urinary tract because MRSA is a relatively uncommon cause of active urinary tract infection, but frequently identified as a colonizer in patients in long-term care [23].

After accounting for the time-varying nature of MRSA infections, we found that MRSA infections resulted in an excess hospital LOS of approximately 4 days. Our estimates are substantially shorter than the findings in a previous local study that did not consider the time-varying nature of MRSA infections, which found that MRSA infections increased hospital LOS by approximately 25 days [7]. Our results concurred with findings from a previous multi-state model on health care–associated infections in Singapore, which found that health care–associated infections due to multi-drug–resistant organisms resulted in an excess LOS of 3.9 days [24]. Overall, MRSA infections were not associated with higher mortality risk, compared with patients without MRSA. We postulate that our observations were due to the high proportion of patients with skin and soft tissue infections (>50%), which tended to have lower mortality risk than other more invasive MRSA infections [25]. To explore whether hospital-onset MRSA infections were associated with substantially different mortality risk or excess LOS, we performed a sub-analysis on patients who developed MRSA infection ≥72 hours from hospital admission. Interestingly, we did not observe substantial differences in excess LOS or mortality risk compared with all patients with MRSA infections, although the literature has suggested that community-acquired MRSA is different from hospital-acquired MRSA in terms of fitness, virulence, and disease presentation [26]. We surmise that this is because a substantial proportion of patients who developed MRSA infection within 72 hours from admission had been exposed to community hospitals or long-term care facilities, where major hospital MRSA strains have been shown to reside [27,28]. Across the different infection types, MRSA pneumonia was associated with the shortest excess LOS and consequently economic burden, although the hazards of being discharged alive is substantially lower than other MRSA infection types. This is because patients with MRSA pneumonia had substantially higher hazards of death than patients with other MRSA infections in our study, which inevitably resulted in an overall shorter excess hospital LOS.

Our cost estimates adopted the health system perspective and focused on excess costs associated with increase in-hospital stay. Although using the cost of a bed-day was reasonable because bed-day costs traditionally represented the largest proportion of the costs, a direct costing approach might be more appropriate if a substantial portion of the costs was incurred for treatment, such as if newer and more expensive antibiotics (e.g. daptomycin, ceftaroline) were prescribed for the management of MRSA infections. A direct costing approach estimates the direct costs of consumables and treatment costs that may be used by other patients and can differ for different infection types, depending on the choice of antibiotics and instrumentation procedures [29]. In a study by Cai *et al.*, the authors used both approaches to estimate the excess costs associated with a carbapenem-resistant Enterobacterales health care–associated infection in Singapore [30]. They found that although overall infections costs were arguably similar when the two approaches are used, estimates for individual infection types differed appreciably between the two approaches.

Our study has limitations. First, we defined MRSA infections based on presence of positive MRSA culture and antibiotic use. Due to the reliance on a positive clinical MRSA culture, some patients with suspected MRSA infection but who did not have a culture sent might have been misclassified as having no MRSA. In a previous study, it was suggested that 6% of cases of infections may be missed if infections were defined using positive cultures or presence of antibiotic administration [31]. Second, our cost estimates of a bed-day did not differentiate between the bed costs for the different ward types. Given that patients with certain infection types such central line–associated bloodstream infections and ventilator-associated pneumonia more likely occurred in the intensive care unit setting, the economic impact of these infections may have been somewhat underestimated.

Conclusion

The use of multi-state modeling that estimates the attributable health and cost outcomes for resistant infections has previously been recommended because standard regression techniques may overstate the attributable LOS for hospital-onset infections. Using a multi-state model to mitigate time-dependent bias, we found that MRSA infections resulted in additional hospital LOS of almost 4 days and was associated with substantial excess health care costs in Singapore. Our methods can be applied to other multi-drug–resistant organisms in hospitals in Singapore to elucidate their health and economic burden. We believed that the findings in our study highlighted target areas for future IPC initiatives and provided data for future cost-effectiveness studies and budget impact analyses of these initiatives.

Declaration of competing interest

The authors have no competing interests to declare.

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Author contributions

All author contributed to the conception and design or analysis and interpretation of data and the writing of the paper. All authors have each approved the version being submitted.

Ethical approval

Our study was reviewed by the institutional ethics review board (CIRB 2017/2576). Given the use of de-identified data exclusively, informed consent was waived.

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References

[1] World Health Organization *Antimicrobial resistance: global report on surveillance.* Geneva: World Health Organization; 2014.
[2] Muto CA, Jernigan JA, Ostrowsky BE, Richet HM, Jarvis WR, Boyce JM, et al. SHEA guideline for preventing nosocomial transmission of multidrug-resistant strains of *Staphylococcus aureus* and *Enterococcus*. *Infect Control Hosp Epidemiol* 2003;**24**:362–86. doi:10.1086/502213.
[3] Pereira LA, Fisher DA. Methicillin-resistant *Staphylococcus aureus* control in Singapore: moving forward. *Ann Acad Med Singap* 2008;**37**:891–6. doi:10.47102/annals-acadmedsg.V37N10p891.
[4] Cai Y, Venkatachalam I, Tee NW, Tan TY, Kurup A, Wong SY, et al. Prevalence of healthcare-associated infections and antimicrobial use among adult inpatients in Singapore acute-care hospitals: results from the first national point prevalence survey. *Clin Infect Dis* 2017;**64**:S61–7. doi:10.1093/cid/cix103.
[5] Hong F, Salmon S, Ong XY, Liew K, Koh Y, Young A, et al. Routine antiseptic baths and MRSA decolonization: diverse approaches across Singapore's acute-care hospitals. *J Hosp Infect* 2021;**112**:87–91. doi:10.1016/j.jhin.2021.03.025.
[6] Graves N, Harbarth S, Beyersmann J, Barnett A, Halton K, Cooper B. Estimating the cost of health care-associated infections: mind your p's and q's. *Clin Infect Dis* 2010;**50**:1017–21. doi:10.1086/651110.
[7] Pada SK, Ding Y, Ling ML, Hsu LY, Earnest A, Lee TE, et al. Economic and clinical impact of nosocomial meticillin-resistant *Staphylococcus aureus* infections in Singapore: a matched case-control study. *J Hosp Infect* 2011;**78**:36–40. doi:10.1016/j.jhin.2010.10.016.
[8] Wolkewitz M, Allignol A, Harbarth S, de Angelis G, Schumacher M, Beyersmann J. Time-dependent study entries and exposures in cohort studies can easily be sources of different and avoidable types of bias. *J Clin Epidemiol* 2012;**65**:1171–80. doi:10.1016/j.jclinepi.2012.04.008.
[9] Pan J, Kavanagh K, Stewart S, Robertson C, Kennedy S, Manoukian S, et al. Comparison of multistate model, survival regression, and matched case-control methods for estimating excess length of stay due to healthcare-associated infections. *J Hosp Infect* 2022;**126**:44–51. doi:10.1016/j.jhin.2022.04.010.
[10] Stewardson AJ, Allignol A, Beyersmann J, Graves N, Schumacher M, Meyer R, et al. The health and economic burden of bloodstream infections caused by antimicrobial-susceptible and non-susceptible *Enterobacteriaceae* and *Staphylococcus aureus* in European hospitals, 2010 and 2011: a multicentre retrospective cohort study. *Euro Surveill* 2016;**21**. doi:10.2807/1560-7917.ES.2016.21.33.30319.
[11] Lee XJ, Stewardson AJ, Worth LJ, Graves N, Wozniak TM. Attributable length of stay, mortality risk, and costs of bacterial health care-associated infections in Australia: a retrospective case-cohort study. *Clin Infect Dis* 2021;**72**:e506–14. doi:10.1093/cid/ciaa1228.
[12] Duke SH. NUS Academic Medical Centre. SingHealth Duke-NUS Academic Medical Centre annual report 2021/2022 - spearheading the future, 2022.
[13] Wee LEI, Conceicao EP, Tan JY, Magesparan KD, Amin IBM, Ismail BBS, et al. Unintended consequences of infection prevention and control measures during COVID-19 pandemic. *Am J Infect Control* 2021;**49**:469–77. doi:10.1016/j.ajic.2020.10.019.
[14] Ministry of Health – Singapore. The national infection prevention control guidelines for acute healthcare facilities, https://www.moh.gov.sg/resources-statistics/guidelines/infection-control-guidelines/national-infection-prevention-and-control-guidelines-for-acute-healthcare-facilities; 2017 [accessed 28 June 2024].
[15] Branch-Elliman W, Strymish J, Gupta K. Development and validation of a simple and easy-to-employ electronic algorithm for identifying clinical methicillin-resistant *Staphylococcus aureus* infection. *Infect Control Hosp Epidemiol* 2014;**35**:692–8. doi:10.1086/676437.
[16] Clinical and Laboratory Standards Institute (CLSI) *CLSI M100-ED29: 2021. Performance standards for antimicrobial susceptibility testing.* 30th ed. Wayne: CLSI; 2020.
[17] Allignol A, Schumacher M, Beyersmann J. Empirical Transition Matrix of Multi-State Models: the etm Package. *J Stat Softw* 2011;**38**:1–15.
[18] Toh HJ, Lim ZY, Yap P, Tang T. Factors associated with prolonged length of stay in older patients. *Singapore Med J* 2017;**58**:134–8. doi:10.11622/smedj.2016158.
[19] Graves N, Cai Y, Mitchell B, Fisher D, Kiernan M. Cost effectiveness of temporary isolation rooms in acute care settings in Singapore. *PLoS One* 2022;**17**:e0271739. doi:10.1371/journal.pone.0271739.
[20] Department of Statistics Singapore. Consumer price index, Singapore, https://www.singstat.gov.sg/modules/infographics/consumer-price-index; 2023 [accessed 28 June 2024].
[21] R Core Team *R: A Language and Environment for Statistical Computing.* Vienna: R Foundation for Statistical Computing; 2022.
[22] de Kraker MEA, Lipsitch M. Burden of antimicrobial resistance: compared to what? *Epidemiol Rev* 2022;**43**:53–64. doi:10.1093/epirev/mxab001.
[23] Muder RR, Brennen C, Rihs JD, Wagener MM, Obman A, Stout JE, et al. Isolation of Staphylococcus aureus from the urinary tract: association of isolation with symptomatic urinary tract infection and subsequent staphylococcal bacteremia. *Clin Infect Dis* 2006;**42**:46–50. doi:10.1086/498518.
[24] Cai Y, Venkatachalam I, Kwa AL, Tambyah PA, Hsu LY, Marimuthu K, et al. Estimating the excess bed days and economic burden of healthcare-associated infections in Singapore public acute-care hospitals. *Infect Control Hosp Epidemiol* 2022;**43**:1245–8. doi:10.1017/ice.2021.165.
[25] Klevens RM, Morrison MA, Nadle J, Petit S, Gershman K, Ray S, et al. Invasive methicillin-resistant *Staphylococcus aureus* infections in the United States. *JAMA* 2007;**298**:1763–71. doi:10.1001/jama.298.15.1763.
[26] Otto M. Community-associated MRSA: what makes them special? *Int J Med Microbiol* 2013;**303**:324–30. doi:10.1016/j.ijmm.2013.02.007.
[27] Tambyah PA, Habib AG, Ng TM, Goh H, Kumarasinghe G. Community-acquired methicillin-resistant *Staphylococcus aureus* infection in Singapore is usually "healthcare associated". *Infect Control Hosp Epidemiol* 2003;**24**:436–8. doi:10.1086/502228.
[28] Chow A, Lim VW, Khan A, Pettigrew K, Lye DCB, Kanagasabai K, et al. MRSA transmission dynamics among interconnected acute, intermediate-term, and long-term healthcare facilities in Singapore. *Clin Infect Dis* 2017;**64**:S76–81. doi:10.1093/cid/cix072.
[29] Page K, Graves N, Halton K, Barnett AG. Humans, 'things' and space: costing hospital infection control interventions. *J Hosp Infect* 2013;**84**:200–5. doi:10.1016/j.jhin.2013.03.006.
[30] Cai Y, Hoo GSR, Lee W, Tan BH, Yoong J, Teo YY, et al. Estimating the economic cost of carbapenem resistant *Enterobacterales* healthcare associated infections in Singapore acute-care hospitals. *PLoS Glob Public Health* 2022;**2**:e0001311. doi:10.1371/journal.pgph.0001311.
[31] Gastmeier P, Bräuer H, Hauer T, Schumacher M, Daschner F, Rüden H. How many nosocomial infections are missed if identification is restricted to patients with either microbiology reports or antibiotic administration? *Infect Control Hosp Epidemiol* 1999;**20**:124–7. doi:10.1086/501600.