Epidemiol. Infect. (2016), **144**, 1248–1256. © Cambridge University Press 2015
doi:10.1017/S0950268815002733

Length of stay an important mediator of hospital-acquired methicillin-resistant *Staphylococcus aureus*

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Received 13 July 2015; Final revision 23 September 2015; Accepted 19 October 2015; first published online 5 November 2015

SUMMARY

Hospital-acquired methicillin-resistant *Staphylococcus aureus* (HA-MRSA) is becoming increasingly established in Asian hospitals. The primary aim of this study was to decompose the risk factors for HA-MRSA based on conceptual clinical pathways. The secondary aim was to show the amount of effect attributable to antibiotic exposure and total length of stay before outcome (LBO) so that institutions can manage at-risk patients accordingly. A case-control study consisting of 1200 inpatients was conducted in a large tertiary hospital in Singapore between January and December 2006. Results from the generalized structural equation model (GSEM) show that LBO [adjusted odds ratio (aOR) 14·9, 95% confidence interval (CI) 8·7–25·5], prior hospitalization (aOR 6·2, 95% CI 3·3–11·5), and cumulative antibiotic exposure (aOR 3·5, 95% CI 2·3–5·3), directly affected HA-MRSA acquisition. LBO accounted for the majority of the effects due to age (100%), immunosuppression (67%), and surgery (96%), and to a lesser extent for male gender (22%). Our model enabled us to account and quantify effects of intermediaries. LBO was found to be an important mediator of age, immunosuppression and surgery on MRSA infection. Traditional regression approaches will not only give different conclusions but also underestimate the effects. Hospitals should minimize the hospital stay when possible to reduce the risk of MRSA.

Key words: Generalized structural equation model, hospital-acquired (nosocomial) infections, indirect effects, mediator, *Staphylococcus aureus*.

INTRODUCTION

Since the introduction of antibiotics, there has been a global emergence of multi-drug resistance and its spread from the West to Asia [1]. Methicillin-resistant *Staphylococcus aureus* (MRSA) has been a major cause of infections in hospitals and nursing homes, and is associated with increased morbidity and mortality [2]. It is estimated that 25–35% of healthy individuals carry *S. aureus* on their skin or mucous membranes [3]. Globally, the proportion of MRSA in hospital-acquired *S. aureus* infections are among the highest (>50%) in East Asian countries like Sri Lanka, South Korea, Thailand, Vietnam, Hong Kong and Singapore [4, 5]. Increased resistance will imply that more people are in need of second-line drugs which are more expensive and/or toxic [6]. The high risk of death and large excess hospitalization costs due to MRSA has led hospitals in Singapore to roll out infection prevention and control programmes

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targeting healthcare workers (HCWs) and visitors [7, 8].

Several risk factors have been associated with infection by MRSA. Prior antibiotic exposure, nursing-home exposure, surgery, length of intensive-care unit (ICU) and hospital stay, presence of co-morbidities, use of intravascular devices, exposure to an MRSA-colonized patient, diagnosis of skin or soft-tissue infection at admission, and immunosuppression were found to be associated with MRSA colonization and infection [9–13]. Furthermore, the association between MRSA prevalence and antibiotic exposure appears to be dose-dependent and varies with antimicrobial class [14]. More recently patients with healthcare-associated community-onset (CO-)MRSA were more likely to have a history of renal failure, haemodialysis, residence in a long-term care facility, long-term invasive devices, and higher rate of MRSA relapse [15]. Patients infected by MRSA in an outpatient setting are unlikely to be exposed to the same factors as those infected in an inpatient setting. Prior hospitalization and male gender were identified as risk factors for CO-MRSA [16, 17].

Patient-level risk factors of MRSA have been widely studied. Antibiotic prescription and length of hospitalization stay are often the predominant factor or confounder of the exposure of interest [12, 13]. A confounder must be a risk factor of the disease and associated with the exposure but cannot be affected by the exposure or disease [18]. A mediator is defined as a third variable that intervenes in the relationship between independent and dependent variables, transmitting the effect of the independent variable on the dependent variable. Statistically, a third variable is considered a significant mediator when the relationship between the independent and dependent variable is completely or partially accounted for by the mediator [19]. For example, patients who had undergone surgery are more likely to experience longer hospital stay, which then increases the risk of nosocomial MRSA. Assuming this relationship is true, adjusting for total length of stay before outcome (LBO) will underestimate the effect of surgery. In our opinion, they are mediators, and correcting for confounding will give misleading results [18]. We propose the use of generalized structural equation models (GSEM) to address this issue.

To our knowledge there has been only one study that uses SEM to address the complex relationships among the risk factors of nosocomial pathogens, but the population of interest were patients in intensive care [20]. We examine direct and indirect effects of various risk factors through the LBO and antibiotic exposure on MRSA infection while controlling for the presence of other confounding and mediating factors. In traditional regression analysis, one needs to build different models for different outcomes given a set of covariates. This makes drawing conclusions difficult and probably inaccurate. We propose pathways to explore these effects. We also show that using the traditional approach yields different conclusions from the GSEM.

Our primary objective is to decompose the risk factors of CO-MRSA and hospital-acquired (HA-) MRSA infections through clinical pathways and derive the total effect of each predictor on the outcomes. We hypothesize cumulative antibiotic exposure (CUMABXEXP) and LBO to be the main mediators of MRSA infection. Hence, our secondary objective is to ascertain the percentage of effects that were attributable to CUMABXEXP and LBO.

METHODS

Study population and design

We conducted a case-control study on patients admitted to Tan Tock Seng Hospital (TTSH), a 1600-bed acute tertiary-care general hospital and Singapore's second largest general hospital. It has 63 ICU beds, and 1574 beds for medical and surgical disciplines.

The study population consisted of patients admitted to TTSH between January and December 2006, who had clinical cultures taken for the investigation of infections and who did not have a positive MRSA clinical culture in the preceding 5 years. Case patients included 600 patients randomly selected from patients who had a positive MRSA clinical culture for the first time. Control patients were 600 patients randomly selected from those without a *Staphylococcus aureus* (non-SA) infection. Ethical approval was obtained from the National Healthcare Group's Domain Specific Review Board (DSRB Reference No. B/6/323).

Outcome definition

We further classified case patients into CO-MRSA and HA-MRSA. Patients with a positive MRSA clinical culture 2 days after admission were defined as HA-MRSA. The remaining case patients were classified as CO-MRSA. There were three outcome groups: 0 = Non-SA, 1 = CO-MRSA and 2 = HA-MRSA.

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Dependent variables

Epidemiological and clinical data including age, gender, comorbidities (cardiovascular disease, chronic lung disease, diabetes mellitus, liver disease, renal disease, organ transplant), history of smoking, alcohol intake and use of intravenous drugs, exposure to nursing-home or healthcare facilities, number of hospitalizations in the preceding year, and antibiotic and procedural exposures, were obtained through review of patients' medical records. Patients were classified as immunosuppressive if they had undergone renal dialysis or had one of the following: renal, liver, or immunosuppressive disorder, or cancer.

Detailed information on antibiotics including the route, dosage, and frequency of administration were obtained. Additionally, cumulative days of exposure to antibiotics prior to onset of infection during current admission were calculated (CUMABXEXP). Data were collected on surgeries and procedures, urinary catheter usage, presence of central venous catheter, tracheostomy, and LBO. LBO was divided into five groups (0 = 0, 1 = 1, 2 = 2–7, 3 = 8–14, 4 = >14) while CUMABXEXP was categorized into four groups (0 = 0–1, 1 = 2–7, 2 = 8–14, 3 = >14).

Microbiology laboratory data were extracted from laboratory databases, the hospital's infection control, and administrative databases and medical records. A medically qualified research associate reviewed patient medical records and compiled the data into a single dataset using the Microsoft Access Database Management System.

Statistical analysis

SEM is a collection of statistical techniques that can examine complex relationships between dependent and independent variables, and answer questions that involve multiple regression analyses of factors. Unlike standard regression models, SEM can simultaneously predict more than one outcome in a single analysis. SEM is usually used in the social sciences, but is now being increasingly applied in epidemiology, public health, and the medical sciences. SEM has been further extended to the generalized form (GSEM) for the evaluation of categorical and time-to-event outcomes [21]. In this paper, the model was analysed using the multinomial distribution and logit link.

Univariate analyses were performed using the χ^2 test for categorical variables and Kruskal–Wallis test for continuous variables. Multinomial logistic regression and GSEM were performed for the multivariate analysis. The GSEM was modelled with a multinomial logit, and adjusted odds ratios were compared to the referent Non-SA group. The results were compared to illustrate how intermediaries affect interpretation and conclusion. Indirect effects were calculated by multiplying the slope coefficients on each path. They were then summed to obtain the overall indirect effect of the variable. Total effects were calculated as a sum of the direct and indirect effects and reported in terms of odds ratios. The mediation proportion was calculated by dividing the indirect over the total effect [22]. These values were obtained using the *nlcom* command and decomposed into percentages. Using Stata MP v. 13 (StataCorp., USA), all analyses were performed at a 5% significance level.

Model specification

Direct effects

We hypothesized that sex, age, ethnicity, residence in community care (CC), any surgery during admission period (surgery), exposure to invasive procedures (IV), immunosuppression, prior hospitalization, LBO and CUMABXEXP to be direct risk factors of MRSA infection. (Fig. 1)

Indirect effects

On top of being direct effects, LBO, CUMABXEXP, CC, immunosuppression, surgery, smoker, alcohol or drug abuse (ALC_DRUG) and IV were modelled as intermediate variables.

Age, immunosuppression, and surgery were hypothesized to precede LBO. CC was hypothesized to be preceded by age. Immunosuppression was hypothesized to be preceded by age, ethnicity, sex, smoker, and ALC_DRUG. Surgery was hypothesized to be preceded by age, immunosuppression, smoker, and ALC_DRUG. Being a smoker and ALC_DRUG was hypothesized to be preceded by ethnicity and sex. CUMABXEXP was hypothesized to be preceded by age, immunosuppression and surgery. (Fig. 1)

RESULTS

Description of cohort

There were 263 CO-MRSA, 337 HA-MRSA and 600 Non-SA patients. The median age of our cohort was 69 years (57% male). The racial spread was representative of the local population with 898 (75%) Chinese, 109 (9%) Indian, 156 (13%) Malay and 37 (3%) others.

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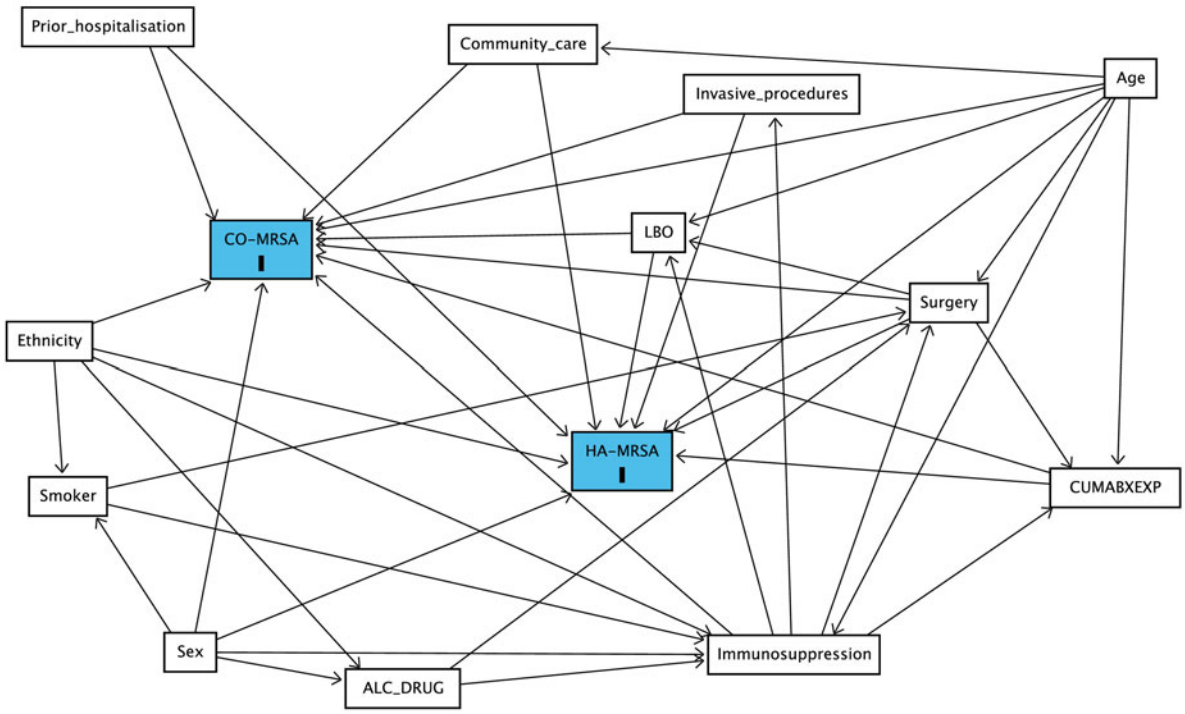

Fig. 1. Model specification of the generalized structural equation model. LBO, Length of stay prior to infection; CUMABXEXP, cumulative antibiotic exposure; ALC_DRUG, alcohol or drug abuse; Community_care, living in community care.

Table 1. *Univariate analysis of risk factors associated with MRSA*

Variable	Non-SA ($n = 600$)	CO-MRSA ($n = 263$)	HA-MRSA ($n = 337$)	P value
Age	69 (26–92)	70 (30–93)	69 (29–89)	0·17
Male	308 (51·3)	156 (59·3)	219 (65·0)	<0·01
Ethnicity				
Chinese	429 (71·5)	205 (78)	264 (78·3)	
Indian	53 (8·8)	26 (9·9)	30 (8·9)	
Malay	96 (16)	27 (10·3)	33 (9·8)	
Others	22 (3·7)	5 (1·9)	10 (3·0)	0·06
Immunosuppressive*	135 (22·5)	93 (35·4)	119 (35·3)	<0·01
Smoker	90 (15·0)	32 (12·2)	41 (12·2)	0·36
Alcohol or drug abuse	25 (4·2)	14 (5·3)	26 (7·7)	0·07
Community care	44 (7·3)	48 (18·3)	20 (5·9)	<0·01
Surgery during hospitalization	33 (5·5)	11 (4·2)	148 (43·9)	<0·01
Invasive procedures	304 (50·7)	149 (56·7)	326 (96·7)	<0·01
Length of stay	1 (0–5)	1 (0–2)	14 (3–67)	<0·01
Prior hospitalization	143 (23·8)	206 (78·3)	148 (43·9)	<0·01
CUMABXEXP	0 (0–3)	0 (0–5)	15 (0–69)	<0·01

SA, *Staphylococcus aureus*; CUMABXEXP, cumulative antibiotic exposure.
* Includes one or more of the following: HIV, on prednisolone, systemic lupus erythematosus, rheumatoid arthritis.

Univariate analysis

A higher proportion of males developed HA-MRSA compared to Non-SA and CO-MRSA groups (65% *vs.* 51·3% and 59·3%, $P < 0·01$) (Table 1). There was a higher proportion of immunosuppressive patients in MRSA infections, compared to Non-SA infections ($P < 0·001$). The percentage of CO-MRSA patients in

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Table 2*a*. *Direct effects of the generalized structural equation model (HA-MRSA and CO-MRSA outcomes)*

	HA-MRSA		CO-MRSA	
Variable	aOR (95% CI)	*P*	aOR (95% CI)	*P*
Length of stay	14·9 (8·7–25·5)	<0·01	0·8 (0·5–1·1)	0·16
Age	0·998 (0·98–1·02)	0·86	0·99 (0·98–1)	0·18
Ethnicity				
Chinese	Reference			
Malay	0·6 (0·2–1·7)	0·34	0·6 (0·4–1·1)	0·08
Indian	1·7 (0·7–4·2)	0·24	1·3 (0·7–2·3)	0·43
Others	0·6 (0·1–3·5)	0·56	0·7 (0·2–2·3)	0·56
Male	1·6 (0·9–2·9)	0·11	1·6 (1·1–2·2)	0·01
Community care	1·3 (0·4–3·7)	0·6	2·6 (1·5–4·5)	<0·01
Immunosuppression	1·5 (0·8–2·7)	0·21	1·3 (0·9–1·9)	0·15
Invasive procedures	0·9 (0·3–2·6)	0·59	1·8 (1·03–3)	0·04
Surgery during hospitalization	1·4 (0·7–3·1)	0·38	0·8 (0·4–1·8)	0·63
CUMABXEXP	3·5 (2·3–5·3)	<0·01	1·6 (1·1–2·4)	0·01
Prior hospitalization	6·2 (3·3–11·5)	<0·01	12·3 (8·4–17·9)	<0·01

aOR, Adjusted odds ratio; CI, confidence interval; CUMABXEXP, cumulative antibiotic exposure.

CC was more than twice that of the other groups (18·3% *vs.* 7·3% and 5·9%, $P < 0·01$). Patients who had prior hospitalization had much higher incidence of CO-MRSA infections diagnosed during subsequent hospital admissions (78·3% *vs.* 23·8% *vs.* 43·9%). Surgery was much more common in HA-MRSA infections, with 43·9% of patients receiving surgery compared to 5·5% in Non-SA and 4·2% in CO-MRSA ($P < 0·01$). As expected, exposure to IV (96·7% *vs.* 50·7% and 56·7%, $P < 0·01$) and LBO (median: 14 *vs.* 1 and 1, $P = < 0·01$) were also found to be significantly higher in HA-MRSA infections. Exposure to antibiotics was uncommon, although patients with HA-MRSA infections tended to have extended durations of antibiotic exposure.

GSEM results

Direct effects

Being male [odds ratio (OR) 1·6, 95% confidence interval (CI) 1·1–2·2], CC exposure (OR 2·6, 95% CI 1·5–4·5), IV (OR 1·8, 95% CI 1·03–3·0), prior hospitalization (OR 12·3, 95% CI 8·4–17·9 and CUMABXEXP (OR 1·6, 95% CI 1·1–2·4) were directly associated with CO-MRSA infection. Similarly, for HA-MRSA, CUMABXEXP (OR 3·5, 95% CI 2·3–5·3) increased the risk of infection. In addition, prior hospitalization (OR 6·2, 95% CI 3·3–11·5) and prolonged LBO (OR 14·9, 95% CI 8·7–25·5) was associated with increased risk of HA-MRSA infection. Age, ethnicity, immunosuppression, and surgery had no significant direct effect on MRSA infection (Table 2*a*).

Older age (OR 1·010, 95% CI 1·003–1·014), immunosuppression (OR 1·30, 95% CI 1·01–1·60) and surgery (OR 16, 95% CI 12–22) were associated with increased LBO. Odds of immunosuppression and surgery were directly affected only by age (OR 1·002, 95% CI 1·001–1·004 and OR 0·998, 95% CI 0·997–0·999, respectively). Males had increased odds of smoking or ALC_DRUG (OR 1·18, 95% CI 1·14–1·23 and OR 1·07, 95% CI 1·04–1·10, respectively). Indians had a higher tendency for ALC_DRUG (OR 1·06, 95% CI 1·01–1·10).

Effect on CUMABXEXP was increased by age (OR 1·01, 95% CI 1·002–1·01), immunosuppression (OR 1·3, 95% CI 1·02–1·7) and surgery (OR 10·4, 95% CI 7·6–14·2) (Table 2*b*).

Total and indirect effects

Being male [total effect (TE) 1·6, 95% CI 1·1–2·2], CC exposure (TE 2·6, 95% CI 1·5–4·5) and IV exposure (TE 1·75, 95% CI 1·03–2·98) were significantly associated with CO-MRSA, with 99% of the gender effect being direct (Table 3).

Male patients (TE 1·84, 95% CI 1·01–3·36), those who were older (TE 1·03, 95% CI 1·01–1·06), immunosuppressed (TE 3·2, 95% CI 1·1–9·3), or had surgery (OR 7311, 95% CI 1126–47 466) were more likely to develop HA-MRSA infections. All of the age effect

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Table 2*b*. *Direct effect of the generalized structural equation model*

	aOR (95% CI)	*P*
Outcome: Length of stay		
Age	1·01 (1·003–1·014)	<0·01
Immunosuppression	1·30 (1·01–1·60)	0·04
Surgery during hospitalization	16 (12–22)	<0·01
Outcome: Community care		
Age	1·003 (1·0029–1·004)	<0·01
Outcome: Immunosuppression		
Age	1·002 (1·001–1·004)	<0·01
Ethnicity		
Chinese	Reference	
Malay	0·96 (0·89–1·04)	0·33
Indian	0·98 (0·89–1·07)	0·60
Others	1 (0·9–1·1)	0·88
Male	1·03 (0·97–1·09)	0·28
Alcohol or drug abuse	1·1 (1–1·3)	0·05
Smoker	0·96 (0·89–1·04)	0·33
Outcome: Surgery during hospitalization		
Age	0·998 (0·997–0·999)	0·01
Immunosuppression	1·01 (0·96–1·06)	0·73
Alcohol or drug abuse	1·05 (0·95–1·2)	0·33
Smoker	1·05 (1–1·1)	0·11
Outcome: CUMABXEXP		
Age	1·01 (1·002–1·01)	<0·01
Immunosuppression	1·3 (1·02–1·7)	0·04
Surgery during hospitalization	10·4 (7·6–14·2)	<0·01
Outcome: Smoker		
Ethnicity		
Chinese	Reference	
Malay	1·03 (0·98–1·10)	0·21
Indian	0·99 (0·92–1·06)	0·73
Others	1·03 (0·92–1·15)	0·58
Male	1·18 (1·14–1·23)	<0·01
Outcome: Alcohol or drug abuse		
Ethnicity		
Chinese	Reference	
Malay	0·99 (0·95–1·02)	0·46
Indian	1·06 (1·01–1·10)	0·02
Others	0·97 (0·91–1·05)	0·51
Male	1·07 (1·04–1·10)	<0·01

aOR, Adjusted odds ratio; CI, confidence interval; CUMABXEXP, cumulative antibiotic exposure.

was indirect (29% CUMABXEXP, 71% LBO) while 67% of the immunosuppressive effect was indirect (6% CUMABXEXP, 61% LBO) and 96% of the surgery effect was indirect (11% CUMABXEXP, 85% LBO).

Prolonged exposure to antibiotics increased the risk of both CO-MRSA (TE 1·6, 95% CI 1·1–2·4) and HA-MRSA (TE 3·5, 95% CI 2·3–5·3) infections.

DISCUSSION

Our results showed that while the effects of CO-MRSA were mostly direct, HA-MRSA was largely mediated through length of hospital stay followed by CUMABXEXP. We have also shown that the effects of age, immunosuppression, and surgery would have been underestimated had we used traditional logistic regression due to the presence of significant mediators (Supplementary Table S1).

The use of SEM in infectious diseases to model potential pathways is new compared to the fields of psychology and chronic diseases where there are common needs to analyse latent factors from quality-of-life data or questionnaires [23, 24]. Together with other studies, we have shown that the exposure effect will

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Table 3. *Total effects and percentage of effects explained by the total indirect, CUMABXEXP and LBO*

	Direct effect (coeff.)	Total effect (coeff.)	Total effect (95% CI)	% Indirect explained	% CUMABXEXP explained	% LBO explained
CO-MRSA						
Male	0·45 (0·09 to 0·81)	0·45 (0·09–0·81)	1·6 (1·1–2·2)**	1%	n.a.	n.a.
Community care	0·94 (0·39 to 1·50)	0·94 (0·39–1·50)	2·6 (1·5–4·5)**	n.a.	n.a.	n.a.
Invasive procedures	0·60 (0·03 to 1·10)	0·60 (0·03–1·10)	1·75 (1·03–2·98)*	n.a.	n.a.	n.a.
HA-MRSA						
Age	−0·002 (−0·02 to 0·02)	0·03 (0·01–0·06)	1·03 (1·01–1·06)**	100	29	71
Male	0·47 (−0·12 to 1·06)	0·61 (0·01–1·21)	1·84 (1·01–3·36)*	22	13	28
Immunosuppression	0·38 (−0·22 to 0·98)	1·16 (0·10–2·20)	3·20 (1·10–9·30)*	67	6	61
Surgery during hospitalization	0·35 (−0·43 to 1·14)	8·90 (7·03–10·8)	7311 (1126–47 466)**	96	11	85

CUMABXEXP, Cumulative antibiotic exposure; LBO, length of stay; CI, confidence interval.
* Significant at 5% level; ** significant at 1% level; n.a., not applicable.

be underestimated if a true mediator is adjusted for as a confounder in a traditional regression framework [25, 26].

Surgery was not directly associated with HA-MRSA and CO-MRSA infections. However, intermediaries play an important role with 96% of its effect explained by indirect effects, with length of hospital stay taking up the majority (85%) of these effects. Patients who had surgery were likely to have a longer length of hospital stay, and hence an increased risk for acquiring MRSA infection.

Exposure to antibiotics was found to affect CO-MRSA and HA-MRSA. As it is unlikely for individuals to acquire MRSA infection within 48 h of antibiotic or hospital exposure, we attempted to explain this result by performing a sensitivity analysis, excluding those who were prescribed antibiotics prior to admission ($n = 24$), but found no significant change in the results. It is highly plausible that patients were infected during previous hospitalizations but only manifested the infection during the current admission, as prior hospitalization was shown to be a direct effect of both CO- and HA-MRSA infections. Data on prior medication history was not available. However, the observed incremental effect of antibiotic exposure in HA-MRSA is to be expected, as this group of patients were more likely to have been exposed to antibiotics post-admission than CO-MRSA patients. Length of hospital stay had a large direct effect on HA-MRSA and a stronger indirect effect than CUMABXEXP on both HA- and CO-MRSA infections. This is likely to be through increased exposure to MRSA contamination in the hospital environment.

Only one study has demonstrated higher susceptibility of males to CO-MRSA infection but this involved a group of patients who experienced IV [17]. A German study found that HA-MRSA acquisition was significantly higher in male ICU patients [27]. Additional analysis from our data did not show any significant association between gender with residence in CC, IV, immunosuppression and surgery. To our knowledge, there are no studies linking genetics to gender and MRSA acquisition. Further research in this area is needed to explain the gender differences in MRSA infections.

Our study has some limitations. Some data were not available and proxies were used. For example, exposure to endotracheal tube ($n = 102$) was used as a proxy for mechanical ventilation in ICU. Measurement error, if any, is likely be minimal as mechanical ventilation

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would only be possible in patients who had endotracheal tubes. Any misclassification is also likely to be non-differential, as the determination of exposure was independent of ascertainment of the infection. MRSA colonization on admission has been found in other studies to be a risk factor for developing infection. Unfortunately, screening for MRSA colonization on admission was not available during the study period. Prior hospitalization, however, could be used as a proxy for colonization on admission.

While we attempted to perform our analysis on as many characteristics known to affect MRSA as possible, there are other hospital and external factors which we did not taken into account (e.g. baseline ward infection rate, bed occupancy). Our study was also not designed for risk profiling for the different infection sites. We also made the assumption of no effect modification in our analysis.

Nonetheless, our study has several strengths. The main strength of our study is the ability to model the dependency of different covariates and quantify the indirect effects leading to patient-level MRSA acquisition. We had separately classified community-associated and hospital-acquired infections to assess their differences, all modelled simultaneously from a single population source. The large sample size of our study also allowed a comprehensive analysis on the data, including subgroup analyses. Last, we have shown that length of hospital stay and CUMABXEXP are important mediators of MRSA infection. To conclude, the effects of CO- and HA-MRSA are very different. While the effect of CO-MRSA was mainly direct, modelling HA-MRSA was made complicated due to various possible pathways. We have identified length of hospital stay and CUMABXEXP to be important mediators of HA-MRSA. Interventions to reduce exposures to these factors are crucial to reduce the risk of HA-MRSA infection.

SUPPLEMENTARY MATERIAL

For supplementary material accompanying this paper visit http://dx.doi.org/10.1017/S0950268815002733.

ACKNOWLEDGEMENTS

This work was supported by the National Healthcare Group's Small Innovative Grant- SIG/07027, Singapore.

DECLARATION OF INTEREST

None.

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