Original Article:

Comparative epidemiology and factors associated with major healthcare-associated methicillin-resistant *Staphylococcus aureus* clones among interconnected acute, intermediate- and long-term healthcare facilities in Singapore

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Abstract (250 words)

Objectives

Methicillin-resistant *Staphylococcus aureus*(MRSA) has spread across countries and healthcare settings, with different ecological niches for different clones. It is crucial to understand the comparative epidemiology of MRSA clones between healthcare settings, and independent factors associated with colonization of specific clones.

Methods

We conducted annual cross-sectional surveillance studies in a network comprising an acute-care hospital and six closely-affiliated intermediate- and long-term care facilities in Singapore, in June-July, 2014-2016. 5,394 patients contributed 16,045 nasal, axillary and groin samples for culture and MRSA isolates for whole genome sequencing. Multivariable multilevel multinomial regression models were constructed to assess for independent factors associated with MRSA colonization.

Results

MRSA clonal complex(CC) 22 was more prevalent in the acute-care hospital(51.9%) and intermediate-care(54.9%) than long-term care(25.1%) facilities, with clones besides CC22 and CC45 being prevalent in intermediate- and long-term care facilities(41.0%) (*P<0.001*). Groin colonization with CC45 was 6 times that of nasal colonization(aOR 6.21, 95%CI 4.26-9.01). Prior MRSA carriage was associated with increased odds of current MRSA colonization in all settings, with a stronger association with CC22(aOR 6.45, 95%CI 3.85-10.87) than CC45(aOR 4.15, 95%CI 2.26-7.58).

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55 Conclusions

56 Colonization of MRSA clones differed between anatomic sites and across healthcare
57 settings. With CC22 having a predilection for the nares and CC45 the groin, MRSA
58 screening should include both sites. Prior MRSA carriage is a risk factor for colonization
59 with predominant MRSA clones in the acute-care hospital and intermediate- and long-
60 term care facilities. Contact precautions for prior MRSA-carriers on admission to any
61 healthcare facility could prevent intra- and inter-institutional MRSA transmission.

INTRODUCTION

Methicillin-resistant *Staphylococcus aureus* (MRSA) has disseminated globally, with many countries reporting MRSA proportions among *S. aureus* of >20% to >80% [1]. Studies have demonstrated a continuous evolution of MRSA clones, with rapid exchanges and spread across different countries and settings [2].

The first healthcare-associated MRSA (HA-MRSA) clone to emerge was that belonging to multilocus sequence type (ST) 250 ("archaic clone") [2]. The archaic clone gradually disappeared in the 1980s and was replaced by new pandemic clones [2,3]. One successful lineage was ST239, which became prevalent in the United Kingdom, United States and Australia in 1970-1980, in Europe and South America in 1980–1990, and subsequently in Asia and the Middle East in 1990–2000 [4]. In recent years, ST22-SCC*mec* IV (EMRSA-15) is the major European HA-MRSA clone [5,6].

In Asia, the major successful HA-MRSA clones were ST239 [7], ST5 (New York-Japan clone) [7], ST22 (UK-EMRSA-15) [5], and ST45 [8-10]. Between the late 1980s and 2000, virtually all HA-MRSA in Singapore were ST239 [5,11]. Around 2000, ST22 was imported into Singapore and became the dominant HA-MRSA clone by 2010 [5, 11-13]. Since 2010, ST45 has been increasing in prevalence [9]. Phylogenetic analyses have revealed interdependent evolution of clones across acute care hospitals (ACHs) [5, 12], and between interconnected acute, and intermediate- and long-term care facilities (ILTCFs) [14]. The greater diversity of MRSA clones in ILTCFs suggests that they could have stronger connectivity with the community compared with the ACH. Different ecological niches have been observed for different MRSA clones. In Australia, clonal complex (CC) 22 has been observed to be more highly associated with patients

from subacute hospitals and long-term care facilities than CC239 [15]. We therefore sought to understand the comparative epidemiology of MRSA clones between healthcare settings, and to assess for independent factors associated with the colonization of specific clones, in order to guide the design and implementation of MRSA preventive strategies.

METHODS

Study design and settings

Annual cross-sectional surveillance studies were conducted in a 1,700-bed adult tertiary-care ACH and its six most closely-affiliated ILTCFs, over six weeks in June-July, from 2014 to 2016. The ILTCs included 3 intermediate-care facilities (ITCFs) (ITCF1: 100-bed rehabilitation center, ITCF2: 116-bed community hospital, ITCF3:360-bed community hospital), and 3 long-term care facilities (LTCFs) (LTCF1: 234-bed nursing home, LTCF2: 164-bed chronic sick unit, LTCF3: 236-bed nursing home). All inpatients and residents of the ILTCFs were included in the study, and 3,040 in-patients with >48 hours stay in the ACH were randomly selected to participate in the study.

Bacterial isolates

Separate nasal, axillary, and groin swabs were obtained from study participants from the various institutions sequentially over each of the six-week periods annually. This was to capture the contemporaneity of MRSA isolates from the interconnected healthcare facilities, as the mutation rate of one core single-nucleotide polymorphism (SNP) for MRSA is estimated to be every six weeks [5, 16]. MRSA was cultured from the swabs, and DNA extracted from the isolates, using

conventional methods and subject to whole genome sequencing following previously described protocols [14].

Genomic sequencing

Multi-locus sequence types were determined from sequence reads using SRST2 [17]. Illumina reads were mapped onto a relevant reference sequences using SSAHA v2.2.1 [11]. The reference genome sequences used were: TW20 (accession number FN433596) for CC239 isolates, HO 5096 0412 (accession number HE681097) genome for CC22 isolates, CA-347 (accession number CP006044) (PUBMED; 23887918) for the CC45 isolates.

Data access

Short reads for all sequenced isolates have been submitted to the European Nucleotide Archive (ENA; http://www.ebi.ac.uk/ena/) under study accession number PRJEB9390. Individual accession numbers of sequences and assemblies for all isolates are listed in Supplementary Table 1.

Administrative, Epidemiological, and Clinical data

Administrative data from all institutions were electronically extracted. All epidemiological and clinical data from the ACH and some from the ILTCFs were obtained from the electronic medical records. Where unavailable electronically, clinical data from the ILTCFs were manually extracted from paper-based medical records by trained research assistants in a standardized manner. The complete set of variables collected is provided in Supplementary Table 2.

Data analysis

The differences in characteristics between MRSA-colonized and non-colonized patients, and between colonized patients with different types, number, and combinations of MRSA clones were compared using the Chi-square test or the Wilcoxon rank-sum test where appropriate. We explored the relationships between the various patient characteristics and anatomic sites and colonization with MRSA clones CC22, CC45, and other CCs, using multilevel multinomial logistic regression models with random intercepts, using PROC GLIMMIX in SAS version 9.4 (SAS Institute Inc, NC). We included variables selected *a priori* based on literature review and considered several multivariable multilevel multinomial logistic regression models involving the nesting of samples within patients to assess for independent factors associated with MRSA colonization. Negative 2 log-likelihood (-2LL) and likelihood-ratio tests were used to compare between models and to guide the final model selection (Supplementary Table 3).

Ethics approval

The study was approved by the Domain Specific Review Board of National Healthcare Group Singapore (DSRB e 2015/00369). Informed consent was provided by all cognitively intact participants or the legally authorized representatives (LARs) of cognitively impaired participants. A waiver of informed consent was granted for cognitively impaired participants from the ITCFs who had no LARs.

RESULTS

Over the three years, 5,394 patients were screened for MRSA, contributing to a total of 16,045 samples (Figure 1). The participation rate at the ILTCFs was 75%. Patients from the ACH, ITCF, and LTCF were similar in age and ethnicity (Table 1). Patients in the ACH had a shorter length of stay but were sicker (Charlson's Comorbidity Index >5 27.5%) than those in the ITCFs (11.7%) and LTCFs (12.8%).

The prevalence of MRSA in ITCFs (36.6%) and LTCFs (22.2%) were significantly higher than in the ACH (12.6%) (p<0.001) (Table 1). Patients who were older, male, with more comorbidities, who had a percutaneous device, longer length of stay, stayed in a room with more beds, prior and longer duration of antibiotics use, prior MRSA carriage or wound, were more likely to be MRSA colonized (Table 2). Among MRSA-colonized patients, those colonized with MRSA in more than one anatomic site included patients who had prior antibiotic exposures (P=0.04) and known MRSA carriers (P<0.001). Prior MRSA-carriers were also more likely to be colonized with different MRSA clones (P=0.05).

We sequenced 1,478 MRSA isolates from the nares (585), axillae (178), and groin (715). The predominant lineages were CC22 (n=692, 46.8%) and CC45 (n=494, 33.4%). CC22 was more prevalent in the ACH (51.9%) and ITCFs (54.9%) than LTCFs (25.1%) (*P<0.001*) (Figure 1). In contrast, LTCFs had the highest proportion (41.0%) of MRSA clones other than CC22 and CC45 (*P<0.001*). The distribution of MRSA clones in the ACH and ITCFs were similar throughout the three years, with CC22 and CC45 remaining the predominant clones in 2016. In the LTCFs, clones other than CC22 and CC45 predominated until 2016. CC22 was the most common clone colonizing the nares (54.4%), axillae (42.7%), and groin (41.7%), although CC45 had a stronger predilection for the groin (40.4%) than nares (26.2%) and axillae (29.2%) (*P<0.001*). In

patients who were colonized with more than one clone, 18 carried exclusively CC22 in the nares and CC45 in the groin. Only one patient carried more than one clone in the same anatomic site (nares, CC22 and CC8).

After adjusting for age, gender, comorbidities, prior exposures to antibiotics and percutaneous devices, presence of wound, prior MRSA colonization, and year of screening, ITCF patients were more likely than ACH patients to be colonized with CC22 (aOR 5.10, 95%CI 2.93-8.93) and CC45 (aOR 4.00, 95%CI 2.02-7.87), whilst LTCF patients were most likely to be colonized with other clones (aOR 4.24, 95%CI 1.44-12.50) (Table 3). Nares were >9 times as likely as axillae to be colonized with all clones. Groin colonization odds with CC45 was 6 times that of nasal colonization, although it was not different with CC22 and other CCs.

Stratified analysis by healthcare facility type further revealed that in ACH patients, the odds of colonization with MRSA clones other than CC45 in the nares was 2-3 times that in the groin (Table 3). For all clones, the nares was 16-100 times more colonized than the axillae. In ILTCFs, patients were more likely to be colonized on the groin than nares for MRSA clones other than CC22. Prior MRSA carriage was strongly associated with MRSA colonization in ACH patients with CC22 (aOR 14.71, 95%CI 6.17-34.48), CC45 (aOR 7.75, 95%CI 2.70-22.22) and other CCs (aOR 22.22, 95%CI 3.83-125.00), but less so in the ILTCF patients. Additionally, a length of stay of >14 days was significantly associated with colonization with CC22 (aOR 2.67, 95%CI 1.22-5.88) in the ACH but not in ILTCFs. In ILTCF patients, prior exposure to any percutaneous device was associated with CC22 colonization (aOR 2.70, 95%CI 1.19-6.17).

Almost one-in-five (18.4%) of the patients had prior MRSA carriage. Among non-prior MRSA carriers, the odds of MRSA colonization on the groin for all clones was

higher than in the nares (Table 4). In contrast, prior MRSA carriers were more likely to be colonized in the nares with all clones except CC45. Nineteen individuals were colonized with the same clones and in the same anatomic sites over 2-3 years.

DISCUSSION

We made contemporaneous comparisons of the epidemiology of MRSA clones within an interconnected healthcare network of an ACH and its closely-affiliated ITCFs and LTCFs, for three consecutive years. Ecological differences in MRSA clones were observed between facility types. Whilst CC22 and CC45 predominated in the ACH and ITCFs, other CCs circulated more in LTCFs. Similar findings on differing ecological niches of MRSA clones have been reported in Australia, where CC22 was associated with LTCF patients and CC239 with nosocomial acquisition in a tertiary hospital [15].

Regardless of lineage, prior MRSA carriage in the preceding 12 months was associated with increased odds of current MRSA colonization in both the ACH and ILTCFs. The association was stronger with CC22 than CC45. This is to be expected as CC22 has been circulating in Singapore a decade before CC45 [9]. Of interest, the difference in effect sizes was most marked in patients from the ACH, with prior MRSA carriers being almost twice as likely to be colonized with CC22 than CC45. Whilst the relationship between prior MRSA carriage and MRSA colonization in ACHs has been well described in the literature [18], the associations between prior carriage and colonization of specific MRSA clones have not been previously reported. A history of MRSA positivity has been reported to increase the odds of MRSA carriage by almost seven times among patients newly admitted to rehabilitation centres in four European

229 countries [19]. Known current MRSA carriage also independently tripled the odds of
230 MRSA colonization in nursing home residents [20].

231 A length of stay >14 days was independently associated with the increased
232 odds of colonization with CC22 in the ACH, but not in the ILTCFs. This suggests
233 potential reservoirs of CC22 in the ACH resulting in colonization. A long acute-care
234 hospital stay was also observed to similarly double the odds of MRSA carriage in
235 patients on admission to rehabilitation centres [19]. The association between the
236 increased length of stay in acute hospitals and MRSA acquisition has been previously
237 reported [21]. However, the association with a particular clone of MRSA has yet to be
238 reported. In patients from ILTCFs, prior exposure to percutaneous devices was
239 associated with an increased odds of colonization with CC22, but not CC45 and other
240 CCs. This suggests that the colonization could have occurred in the ACH, where the
241 percutaneous devices were inserted.

242 Nares are the most commonly used anatomic site for MRSA screening. We
243 observed that the nares of ACH patients were twice as likely as the groin to be
244 colonized with CC22, but 6.5 times less likely to be colonized with CC45. Among ILTCF
245 patients, the nares were similarly 6 times less likely than the groin to be colonized with
246 CC45. Additionally, CCs other than CC22 and CC45 were almost thrice as likely to be
247 colonized on the groin as in the nares. Among non-prior MRSA carriers, MRSA
248 colonization on the groin for all clones was 1.8-10.9 times as high as that in the nares.
249 As such, MRSA screening from nasal-only samples might miss detecting MRSA clones
250 that have a predilection for the groin such as CC45 which is common in ACHs and ITCFs,
251 and in non-prior MRSA carriers. In another study among HIV-infected individuals in
252 Singapore, ST45 was observed to be >24 times more likely to be associated with

perianal colonization than in nares, axillae, and groin combined [22]. The predilection for the groin has also been observed for highly transmissible strains ST36 [23] and ST228 [24]. A handful of CC45 strains has been observed to harbor the Arginine Catabolic Mobile Element (ACME) [25], which has been suggested to enhance MRSA survival on the skin. Furthermore, a high proportion of CC45 isolates has been found to be non-susceptible to antibiotics including ciprofloxacin [26]. With the growing clinical and infection control importance of CC45, MRSA screening strategies would need to include groin swabs, in addition to nasal swabs. MRSA detection by culture and rapid PCR test has been found to increase from 48% and 62% respectively from nasal swabs alone to 79% and 92% with the addition of groin swabs [27].

We observed that MRSA prevalence in ITCFs (36.6%) and LTCFs (22.2%) were thrice and twice that of the ACH (12.6%) respectively. The prevalence of MRSA in an Italian LTCF (14.8%) was similarly found to be twice that of the adjacent ACH's geriatric unit (6.0%) [28], although MRSA prevalence in rehabilitation centres were reportedly similar to ACHs in several European countries (Germany, France, Spain, Italy) [29]. Our contemporaneous comparison of MRSA prevalence across healthcare facility types highlighted the importance of infection prevention measures in ITCFs and LTCFs. Whilst active MRSA screening at-admission and isolation or cohorting is routinely implemented in many ACHs, the care delivery models in ITCFs and LTCFs where patients/residents are encouraged to ambulate and socialize would not allow for isolation and segregation between MRSA-colonized and non-colonized patients/residents. Other strategies such as antiseptic bathing and intranasal antiseptics with close monitoring of antiseptic susceptibilities could be explored in ITCFs and LTCFs to reduce MRSA transmission [30].

Our study was limited by the cross-sectional design. We acknowledge that only associational relationships can be derived from the study's findings. Nonetheless, they have provided important insights into risk factors for MRSA colonization in an interconnected healthcare network.

Our study's strengths include the ability to concurrently assess for the prevalence and epidemiology of MRSA and its specific clones across different care settings in a healthcare network, from the ACH to ITCFs and LTCFs, within the same year and across three consecutive years. Furthermore, the study was able to assess for the colonization of specific MRSA clones on various anatomic sites. To minimize ascertainment bias, standardized protocols were used for data extraction from clinical notes, sample collection, sample processing and testing, with further confirmation of colonies for MRSA using matrix-assisted laser desorption/ionization-time of flight (MALDI-TOF) mass spectrometry. The medical technologist performing the microbiologic evaluation was blinded to the patients' demographical and clinical information, rendering any detection bias negligible. Additionally, the ascertainment of prior MRSA carriage was based on laboratory records dated prior to the study screening date, making a causal relationship highly plausible. Any selection bias due to nonparticipation was highly unlikely, with the high participation rate of 80% in the ILTCFs.

In conclusion, we found that the colonization of MRSA clones differed between anatomic sites and across healthcare settings. Whilst CC22 was more likely to colonize the nares, CC45 has a predilection for the groin. Considerations should be made to include both the nares and groin for MRSA screening. Prior MRSA carriage is a

common risk factor for colonization with the predominant MRSA clones in both the ACH and ILTCFs. Hospital stay >14 days and exposure to percutaneous devices were additional risk factors for CC22 colonization in the ACH and ILTCFs respectively. Pre-emptive contact precautions for prior MRSA-carriers on admission to any healthcare facility and active screening for long-stayers in the ACH could prevent intra- and inter-institutional MRSA transmission.

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Transparency declarations. None to declare.

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Table 1. Characteristics of patients by admitted healthcare facilities

Characteristics	ACH (n = 2,985)	ITCFs (n = 1,252)	LTCFs (n = 1,157)
Age, years			
Mean ± SD	70.83 ± 15.02	70.81 ± 12.64	70.30 ± 14.07
Median (IQR)	74 (62 – 82)	73 (63 – 80)	72 (61 – 82)
Range	21 – 106	25 – 99	27 – 106
Age >65 years	2,010 (67.3)	872 (69.7)	753 (65.1)
Male	1,644 (55.1)	641 (51.2)	612 (52.9)
Ethnicity			
Chinese	2,365 (79.2)	1,013 (80.9)	744 (64.3)
Malay	277 (9.3)	123 (9.8)	317 (27.4)
Indian	257 (8.6)	88 (7.0)	73 (6.3)
Others	86 (2.9)	28 (2.2)	23 (2.0)
Charlson's Comorbidity Index – median (IQR)	3 (1 – 6)	3 (1 – 4)	2 (1 – 4)
Charlson's Comorbidity Index >5	821 (27.5)	147 (11.7)	148 (12.8)
Length of stay >14 days	972 (32.6)	856 (68.4)	1,157 (100.0)
No. of beds per room of admitted facility			
1 bed	436 (14.6)	20 (1.6)	4 (0.4)
2 – 4 beds	285 (9.6)	70 (5.6)	39 (3.4)
5 – 8 beds	2,075 (69.5)	845 (67.5)	433 (37.4)
>8 beds	189 (6.3)	317 (25.3)	681 (58.9)
Year of screening			
2014	961 (32.2)	355 (28.4)	343 (29.6)
2015	993 (33.3)	462 (36.9)	369 (31.9)
2016	1,031 (34.5)	435 (34.7)	445 (38.5)

MRSA period prevalence			
Overall	375 (12.6)	458 (36.6)	257 (22.2)
2014	115/961 (12.0)	106/355 (29.9)	70/343 (20.4)
2015	136/993 (13.7)	211/462 (45.7)	73/369 (19.8)
2016	124/1,031 (12.0)	141/435 (32.4)	114/445 (25.6)

Values are expressed in number (%) unless indicated otherwise.

Abbreviations: ACH, acute-care hospital; ITCFs, intermediate-term care facilities; IQR, interquartile range; LTCFs, long-term care facilities; SD, standard devia

Table 2. Characteristics of patients by status of MRSA colonization

Characteristics	Non-colonized (n = 4,304)	Total MRSA-colonized patients (n = 1,090)						
		Colonized (n = 1,090)	P_1	Total multiple-site colonized patients (n = 326)				
				Single site (n = 764)	Multiple sites (n = 326)	P_2	Same clones (n = 261)	Different clones (n = 65)
Demographics								
Age, years								
Mean ± SD	70.4 ± 14.5	71.7 ± 13.4	**0.01**	71.3 ± 13.4	72.8 ± 13.5	0.09	72.7 ± 13.4	73.4 ± 13.8
Median (IQR)	73 (62 - 81)	74 (63 - 82)	**0.03**	73 (62 - 81)	75 (64 - 83)	0.05	75 (64 - 83)	76 (67 - 85)
Range	21 - 106	21 - 102		21 - 102	29 - 99		29 - 99	34 - 98
Age > 65 years	2,873 (66.8)	762 (69.9)	**0.05**	525 (68.7)	237 (72.7)	0.19	188 (72.0)	49 (75.4)
Male	2,196 (51.0)	701 (64.3)	**<0.001**	491 (64.3)	210 (64.4)	0.96	165 (63.2)	45 (69.2)
Ethnicity			0.15			**0.04**		
Chinese	3,292 (76.5)	830 (76.2)		592 (77.5)	238 (73.0)		188 (72.0)	50 (76.9)
Malay	556 (12.9)	161 (14.8)		109 (14.3)	52 (16.0)		43 (16.5)	9 (13.9)
Indian	339 (7.9)	79 (7.2)		46 (6.0)	33 (10.1)		27 (10.3)	6 (9.2)
Others	117 (2.7)	20 (1.8)		17 (2.2)	3 (0.9)		3 (1.2)	0 (0.0)
Admitted healthcare facility			**<0.001**			0.21		
ACH	2,610 (60.6)	375 (34.4)		274 (35.9)	101 (31.0)		84 (32.2)	17 (26.1)
ITCFs	794 (18.5)	458 (42.0)		309 (40.4)	149 (45.7)		114 (43.7)	35 (53.9)
LTCFs	900 (20.9)	257 (23.6)		181 (23.7)	76 (23.3)		63 (24.1)	13 (20.0)
Year of screening			**<0.001**			**0.02**		
2014	1,368 (31.8)	291 (26.7)		213 (27.9)	78 (23.9)		58 (22.2)	20 (30.8)
2015	1,404 (32.6)	420 (38.5)		273 (35.7)	147 (45.1)		116 (44.4)	31 (47.7)

2016	1,532 (35.6)	379 (34.8)		278 (36.4)	101 (31.0)		87 (33.3)	14 (21.5)
Comorbidities								
CCI			**<0.001**			0.27		
Median (IQR)	3 (1 - 5)	3 (2 - 5)		3 (1 - 5)	3 (2 - 5)		3 (2 - 5)	4 (2 - 6)
CCI > 5	875 (20.3)	241 (22.1)	0.19	167 (21.9)	74 (22.7)	0.76	56 (21.5)	18 (27.7)
Cerebrovascular disease	1,554 (36.1)	477 (43.8)	**<0.001**	336 (44.0)	141 (43.3)	0.83	114 (43.7)	27 (41.5)
Congestive cardiac failure	529 (12.3)	148 (13.6)	0.25	99 (13.0)	49 (15.0)	0.36	39 (14.9)	10 (15.4)
Chronic liver disease	289 (6.7)	75 (6.9)	0.85	49 (6.4)	26 (8.0)	0.35	18 (6.9)	8 (12.3)
Chronic pulmonary disease	446 (10.4)	125 (11.5)	0.29	85 (11.1)	40 (12.3)	0.59	38 (14.6)	2 (3.1)
Chronic renal disease	1,058 (24.6)	298 (27.3)	0.06	203 (26.6)	95 (29.1)	0.38	76 (29.1)	19 (29.2)
Dementia	722 (16.8)	231 (21.2)	**<0.01**	153 (20.0)	78 (23.9)	0.15	63 (24.1)	15 (23.1)
Diabetes mellitus	1,775 (41.2)	495 (45.4)	**0.01**	343 (44.9)	152 (46.6)	0.60	115 (44.1)	37 (56.9)
HIV infection	33 (0.8)	10 (0.9)	0.59	9 (1.2)	1 (0.3)	0.30[c]	1 (0.4)	0 (0.0)
Peptic ulcer disease	261 (6.1)	80 (7.3)	0.12	51 (6.7)	29 (8.9)	0.20	25 (9.6)	4 (6.2)
Peripheral vascular disease	453 (10.5)	161 (14.8)	**<0.001**	113 (14.8)	48 (14.7)	0.98	33 (12.6)	15 (23.1)
Percutaneous devices								
Any [a]	3,492 (81.1)	922 (84.6)	**0.01**	637 (83.4)	285 (87.4)	0.09	225 (86.2)	60 (92.3)
Arterial line	627 (14.6)	144 (13.2)	0.25	99 (13.0)	45 (13.8)	0.71	40 (15.3)	5 (7.7)
Peripheral line	3,421 (79.5)	900 (82.6)	**0.02**	619 (81.0)	281 (86.2)	**0.04**	222 (85.1)	59 (90.8)
PICC	175 (4.1)	70 (6.4)	**<0.01**	46 (6.0)	24 (7.4)	0.41	17 (6.5)	7 (10.8)
Dialysis line	252 (5.9)	59 (5.4)	0.58	41 (5.4)	18 (5.5)	0.92	12 (4.6)	6 (9.2)
Endotracheal tube	523 (12.0)	134 (12.3)	0.78	83 (10.9)	51 (15.6)	**0.03**	44 (16.9)	7 (10.8)
Nasogastric tube	1,210 (28.1)	426 (39.1)	**<0.001**	293 (38.4)	133 (40.8)	0.45	109 (41.8)	24 (36.9)
Chest tube	78 (1.8)	12 (1.1)	0.10	10 (1.3)	2 (0.6)	0.53[†]	2 (0.8)	0 (0.0)

PEG tube	362 (8.4)	152 (13.9)	**<0.001**	106 (13.9)	46 (14.1)	0.92	34 (13.0)	12 (18.5)
Suprapubic catheter	33 (0.8)	6 (0.6)	0.50	4 (0.5)	2 (0.6)	1.00†	2 (0.8)	0 (0.0)
Indwelling urinary catheter	1,217 (28.3)	432 (39.6)	**<0.001**	304 (39.8)	128 (39.3)	0.87	101 (38.7)	27 (41.5)
Tracheostomy	247 (5.7)	63 (5.8)	0.96	43 (5.6)	20 (6.1)	0.74	17 (6.5)	3 (4.6)
Colostomy	54 (1.3)	18 (1.7)	0.31	11 (1.4)	7 (2.2)	0.40	7 (2.7)	0 (0.0)
Other factors								
Length of stay, days			**<0.001**			0.86		
Median (IQR)	15 (7 - 57)	32 (15 - 107)		32 (15 - 112.5)	31 (16 - 85)		31 (16 - 76)	34 (17 - 115)
Length of stay >14 days	2,153 (50.0)	832 (76.3)	**<0.001**	576 (75.4)	256 (78.5)	0.27	201 (77.0)	55 (84.6)
No. of beds per room			**<0.001**			0.19		
1 bed	403 (9.4)	57 (5.2)		44 (5.7)	13 (4.0)		12 (4.6)	1 (1.5)
2 – 4 beds	355 (8.2)	39 (3.6)		32 (4.2)	7 (2.1)		5 (1.9)	2 (3.1)
5 – 8 beds	2,673 (62.1)	680 (62.4)		475 (62.2)	205 (62.9)		163 (62.5)	42 (64.6)
>8 beds	873 (20.3)	314 (28.8)		213 (27.9)	101 (31.0)		81 (31.0)	20 (30.8)
Prior antibiotics use [b]	3,214 (74.7)	912 (83.7)	**<0.001**	628 (82.2)	284 (87.1)	**0.04**	224 (85.8)	60 (92.3)
Prior antibiotics use by days [b]			**<0.001**			0.13[c]		
None	1,066 (24.8)	164 (15.1)		128 (16.7)	36 (11.0)		32 (12.3)	4 (6.2)
1 – 3 days	306 (7.1)	42 (3.9)		29 (3.8)	13 (4.0)		12 (4.6)	1 (1.5)
4 – 7 days	598 (13.9)	99 (9.1)		69 (9.0)	30 (9.2)		23 (8.8)	7 (10.8)
>7 days	2,310 (53.7)	771 (70.7)		530 (69.4)	241 (73.9)		189 (72.4)	52 (80.0)
Unknown	24 (0.5)	14 (1.3)		8 (1.1)	6 (1.8)		5 (1.9)	1 (1.5)
Prior MRSA carriage	534 (12.4)	460 (42.2)	**<0.001**	295 (38.6)	165 (50.6)	**<0.001**	125 (47.9)	40 (61.5)
Presence of wound	1,647 (38.3)	649 (59.5)	**<0.001**	443 (58.0)	206 (63.2)	0.11	164 (62.8)	42 (64.6)

Values are expressed in number (%) unless indicated otherwise.

Single site colonization was defined as detection of an MRSA clone from one of three screening swabs (nares, axillae and groin swabs).

Multiple sites colonization was defined as detection of MRSA clone in a minimum of two out of three screening swabs (nares, axillae and groin swabs).

Multiple sites colonization was further categorized into same strain where same clone was cultured from body sites of each patient, and different strains otherwis

[a] Any percutaneous devices included procedures such as tracheostomy or colostomy, or insertion of any of the following: arterial line, dialysis line, peripherally-

PEG tube or suprapubic catheter in the preceding 12 months.

[b] Prior antibiotics use included the use of any antibiotics comprising aminoglycoside, carbapenem, cephalosporin, fluoroquinolone, penicillin, or vancomycin in

[c] Fisher's exact test

Abbreviations: ACH, acute care hospital; CCI, Charlson's comorbidity's index; ITCFs, intermediate-term care facilities; IQR, interquartile range; LTCFs, long-t

Staphylococcus aureus; PEG, percutaneous endoscopic gastrostomy; PICC, peripherally inserted central catheter; SD, standard deviation.

P_1; statistical test between MRSA-colonized and -non colonized patients

P_2; statistical test between single site and multiple sites colonized patients.

P_3; statistical test between same clones and different clones colonized patients.

Table 3. Multilevel (16,045 samples nested within 5,394 patients) multivariable multinomial models of colonization with MRSA clones including CC22, CC45 category

Variables	Model 1			Model 2			Model 3			Model 4	
	CC22 aOR (95% CI)	CC45 aOR (95% CI)	Other CC aOR (95% CI)	CC22 aOR (95% CI)	CC45 aOR (95% CI)	Other CC aOR (95% CI)	CC22 aOR (95% CI)	CC45 aOR (95% CI)	Other CC aOR (95% CI)	CC22 aOR (95% CI)	CC45 aOR (95% CI)
Age > 65 years	1.15 (0.69-1.92)	1.55 (0.84-2.86)	1.15 (0.52-2.54)	1.04 (0.63-1.72)	1.47 (0.80-2.69)	1.03 (0.48-2.24)	1.03 (0.62-1.69)	1.45 (0.79-2.65)	1.02 (0.47-2.22)	1.01 (0.61-1.67)	1.44 (0.79-2.64)
Male	1.42 (0.88-2.30)	2.26 (1.27-4.02)	2.28 (1.02-5.10)	1.18 (0.74-1.89)	1.96 (1.11-3.46)	1.95 (0.89-4.29)	1.17 (0.73-1.87)	1.96 (1.11-3.47)	1.96 (0.89-4.29)	1.18 (0.73-1.88)	1.96 (1.11-3.48)
Admitted healthcare facilities											
ACH		Reference			Reference			Reference			Reference
ITCFs	4.27 (2.58-7.09)	4.24 (2.36-8.26)	1.93 (0.71-5.26)	5.95 (3.54-10.00)	5.24 (2.79-9.90)	2.19 (0.82-5.85)	6.10 (3.57-10.42)	5.08 (2.65-9.71)	1.95 (0.72-5.29)	6.45 (3.75-10.99)	5.21 (2.70-10.00)
LTCFs	0.93 (0.46-1.88)	2.27 (1.12-4.61)	4.00 (1.72-9.26)	1.20 (0.60-2.38)	2.83 (1.39-5.75)	5.35 (2.29-12.50)	1.46 (0.70-3.03)	2.87 (1.31-6.25)	5.21 (2.04-13.33)	1.49 (0.72-3.11)	2.90 (1.32-6.37)
Year of screening											
2014		Reference			Reference			Reference			Reference
2015	1.23 (0.68-2.21)	1.62 (0.84-3.13)	1.44 (0.56-3.70)	1.36 (0.77-2.43)	1.76 (0.91-3.39)	1.53 (0.61-3.83)	1.35 (0.76-2.39)	1.78 (0.92-3.42)	1.56 (0.63-3.91)	1.33 (0.75-2.36)	1.76 (0.92-3.40)
2016	1.23 (0.68-2.19)	0.91 (0.45-1.87)	1.26 (0.49-3.27)	1.33 (0.75-2.36)	0.94 (0.46-1.91)	1.33 (0.54-3.37)	1.25 (0.70-2.22)	0.87 (0.42-1.78)	1.12 (0.44-2.89)	1.24 (0.69-2.21)	0.86 (0.42-1.76)
Anatomic sites											
Nares		Reference			Reference			Reference			Reference
Axilla	0.03	0.09	0.11	0.03	0.09	0.11	0.03	0.09	0.11	0.03	0.09

	(0.02-0.04)	(0.06-0.14)	(0.06-0.18)	(0.02-0.05)	(0.06-0.14)	(0.06-0.18)	(0.02-0.05)	(0.06-0.14)	(0.06-0.18)	(0.02-0.05)	(0.06-0.14)
Groin	0.88	6.58	1.42	0.90	6.33	1.42	0.91	6.29	1.42	0.91	6.29
	(0.67-1.17)	(4.50-9.62)	(0.92-2.18)	(0.69-1.18)	(4.33-9.17)	(0.93-2.17)	(0.69-1.18)	(4.31-9.17)	(0.93-2.17)	(0.69-1.19)	(4.31-9.17)
Prior MRSA	–	–	–	7.63	4.69	5.71	6.62	4.29	5.18	6.41	4.22
carriage				(4.59-12.66)	(2.62-8.40)	(2.67-12.20)	(3.94-11.11)	(2.34-7.87)	(2.30-11.63)	(3.82-10.75)	(2.29-7.75)
CCI > 5	–	–	–	–	–	–	1.23	1.13	0.88	1.22	1.12
							(0.70-2.16)	(0.57-2.23)	(0.35-2.25)	(0.69-2.14)	(0.56-2.20)
Prior percutaneous device use	–	–	–	–	–	–	1.61	0.88	0.81	1.36	0.80
							(0.72-3.60)	(0.40-1.95)	(0.29-2.22)	(0.59-3.13)	(0.35-1.85)
Presence of wound	–	–	–	–	–	–	1.34	1.53	2.11	1.25	1.48
							(0.83-2.17)	(0.86-2.74)	(0.95-4.72)	(0.77-2.04)	(0.82-2.66)
Prior antibiotics use	–	–	–	–	–	–	–	–	–	1.69	1.33
										(0.84-3.39)	(0.63-2.82)
LOS >14 days	–	–	–	–	–	–	–	–	–	–	–
Model assessment											
-2 log-likelihood		8982.01			8884.64			8875.00			8870.09
Likelihood ratio test P		–			<0.001			<0.01			<0.05

Table 4. Stratified multilevel multivariable multinomial models of colonization with MRSA clones including CC22, CC45 and other CC with non-colonization a

ACH (8,873 samples nested within 2,985 patients) and ILTCFs (7,172 samples nested within 2,409 patients)

Variables	ACH			
	CC22	CC45	Other CC	CC22
	aOR (95%CI)	aOR (95%CI)	aOR (95%CI)	aOR (95%CI)
Age >65 years	0.96 (0.41-2.25)	1.38 (0.45-4.20)	1.34 (0.29-6.29)	1.14 (0.61-2.10)
Male	1.02 (0.46-2.27)	1.46 (0.51-4.17)	1.19 (0.30-4.76)	1.26 (0.70-2.26)
Year of screening				
2014		Reference		
2015	1.33 (0.50-3.57)	2.16 (0.69-6.76)	2.65 (0.50-13.89)	1.34 (0.65-2.75)
2016	1.98 (0.77-5.10)	0.83 (0.22-3.09)	1.86 (0.32-10.64)	0.93 (0.44-1.97)
Anatomic sites				
Nares		Reference		
Axilla	**0.02 (0.01-0.03)**	**0.06 (0.02-0.15)**	**0.01 (0.002-0.04)**	**0.05 (0.03-0.08)**
Groin	**0.43 (0.27-0.69)**	**6.49 (3.27-12.82)**	**0.30 (0.13-0.69)**	1.35 (0.96-1.89)
Prior MRSA carriage	**14.71 (6.17-34.48)**	**7.75 (2.70-22.22)**	**22.22 (3.83-125.00)**	**2.72 (1.35-5.46)**
CCI >5	1.01 (0.45-2.29)	0.97 (0.34-2.70)	0.94 (0.24-3.70)	1.17 (0.53-2.62)
Prior percutaneous device use	1.31 (0.10-17.54)	0.74 (0.04-13.16)	0.69 (0.01-58.82)	**2.70 (1.19-6.17)**
Presence of wounds	1.07 (0.47-2.46)	2.29 (0.77-6.85)	1.41 (0.32-6.10)	1.41 (0.77-2.61)
Prior antibiotics use	1.12 (0.22-5.65)	1.05 (0.13-8.55)	1.57 (0.04-55.56)	1.64 (0.77-3.51)
LOS > 14 days	**2.67 (1.22-5.88)**	2.69 (0.99-7.30)	1.57 (0.42-5.95)	1.16 (0.55-2.46)

Abbreviations: ACH, acute care hospital; aOR; adjusted odds ratio; CCI, Charlson's comorbidity index; CI; confidence interval; ILTCFs, intermediate- and long

Table 5. Stratified multilevel multivariable multinomial models of colonization with MRSA clones including CC22, CC45 and other CC with non-colonization a

samples nested within 994 patients) or without (13,084 samples nested within 4,400 patients) prior MRSA carriage

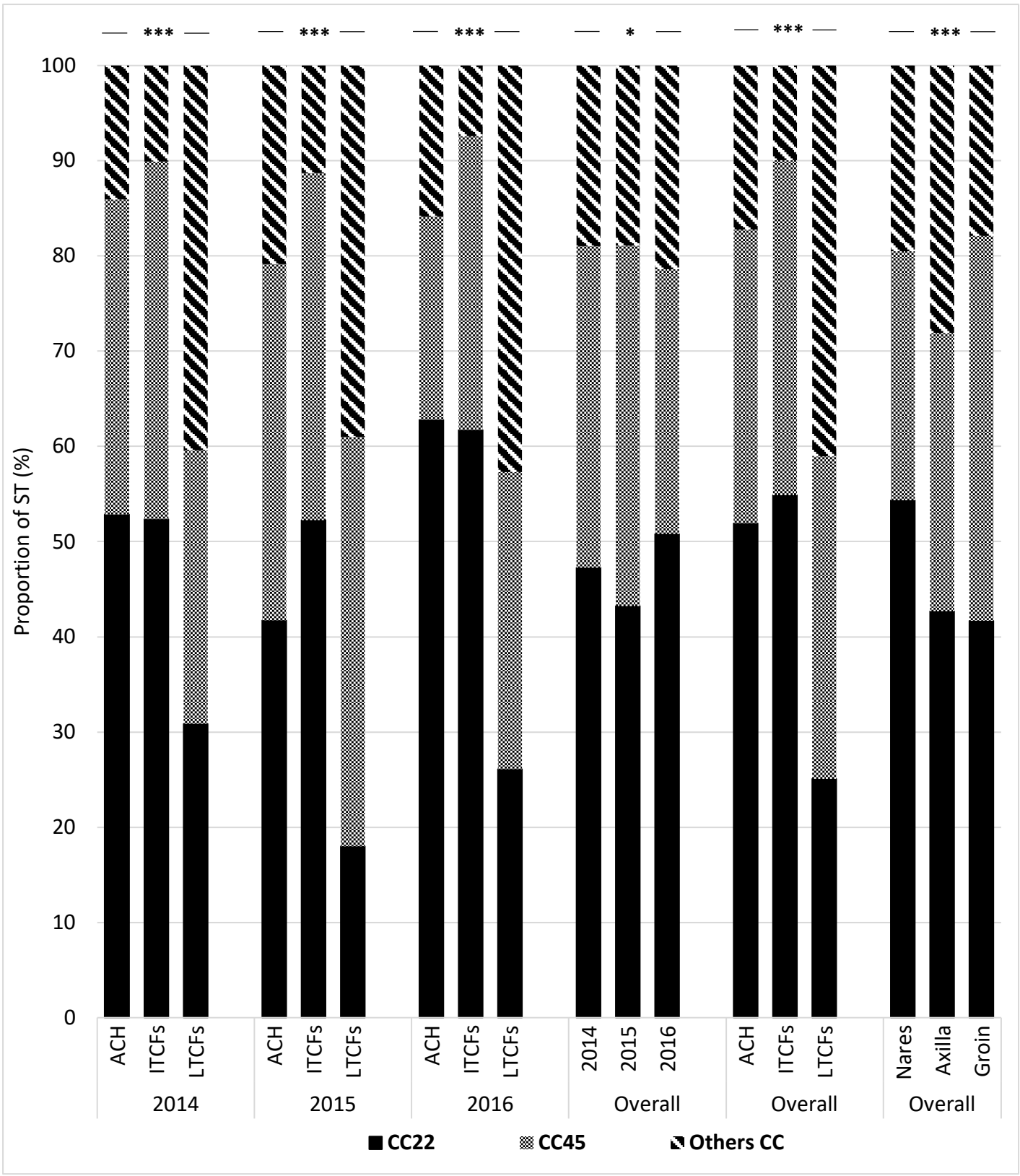
Variables	Prior MRSA carriage			
	Yes			
	CC22	CC45	Other CC	CC22
	aOR (95% CI)	aOR (95% CI)	aOR (95% CI)	aOR (95% CI)
Age >65 years	1.10 (0.56-2.18)	1.33 (0.54-3.30)	0.92 (0.29-2.87)	0.97 (0.50-1.91)
Male	0.83 (0.44-1.57)	1.16 (0.50-2.71)	1.14 (0.37-3.50)	1.39 (0.73-2.64)
Admitted healthcare facilities				
ACH		Reference		
ITCFs	**3.24 (1.46-7.14)**	**2.92 (1.11-7.69)**	1.15 (0.28-4.74)	**8.13 (3.55-18.52)**
LTCFs	0.44 (0.16-1.22)	0.77 (0.20-2.91)	1.47 (0.31-6.94)	1.61 (0.52-4.95)
Year of screening				
2014		Reference		
2015	1.75 (0.83-3.70)	2.10 (0.81-5.43)	2.49 (0.66-9.26)	1.26 (0.57-2.79)
2016	2.27 (1.07-4.81)	0.88 (0.31-2.45)	1.61 (0.40-6.45)	1.01 (0.45-2.26)
Anatomic sites				
Nares		Reference		
Axilla	**0.04 (0.02-0.10)**	**0.05 (0.02-0.10)**	**0.02 (0.01-0.06)**	**0.04 (0.02-0.07)**
Groin	**0.46 (0.31-0.70)**	**2.65 (1.58-4.46)**	**0.51 (0.27-0.97)**	**1.81 (1.24-2.63)**
CCI >5	1.15 (0.60-2.21)	1.09 (0.46-2.60)	0.95 (0.30-2.99)	1.20 (0.50-2.87)
Any percutaneous devices	3.37 (0.46-25.00)	2.56 (0.20-32.26)	1.22 (0.05-30.30)	1.47 (0.54-3.98)
Presence of wounds	0.69 (0.36-1.34)	1.25 (0.52-3.02)	1.18 (0.36-3.79)	1.37 (0.70-2.68)
Prior antibiotics use	3.94 (0.89-17.54)	1.14 (0.20-6.45)	2.51 (0.16-40.00)	1.35 (0.60-3.06)

LOS >14 days	**2.02 (1.04-3.94)**	1.72 (0.71-4.17)	1.28 (0.39-4.26)	**2.84 (1.27-6.37)**

Abbreviations: ACH, acute care hospital; aOR; adjusted odds ratio; CCI, Charlson's comorbidity index; CI; confidence interval; ITCFs, intermediate-term care f

facilities

Figure 1. Temporal distribution of MRSA clones by the healthcare facilities and anatomic sites between 2014 and 2016



Abbreviations: ACH, acute care hospital; CC, clonal complex; ITCFs, intermediate-term care facilities; LTCFs, long-term care facilities

*, $P < 0.05$; ***, $P < 0.001$