ORIGINAL ARTICLE

Methicillin-Resistant *Staphylococcus aureus* (MRSA) Nasal Carriage in Residents of Veterans Affairs Long-Term Care Facilities: Role of Antimicrobial Exposure and MRSA Acquisition

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OBJECTIVE. To identify risk factors associated with methicillin-resistant *Staphylococcus aureus* (MRSA) acquisition in long-term care facility (LTCF) residents.

DESIGN. Multicenter, prospective cohort followed over 6 months.

SETTING. Three Veterans Affairs (VA) LTCFs.

PARTICIPANTS. All current and new residents except those with short stay (<2 weeks).

METHODS. MRSA carriage was assessed by serial nares cultures and classified into 3 groups: persistent (all cultures positive), intermittent (at least 1 but not all cultures positive), and noncarrier (no cultures positive). MRSA acquisition was defined by an initial negative culture followed by more than 2 positive cultures with no subsequent negative cultures. Epidemiologic data were collected to identify risk factors, and MRSA isolates were typed by pulsed-field gel electrophoresis (PFGE).

RESULTS. Among 412 residents at 3 LTCFs, overall MRSA prevalence was 58%, with similar distributions of carriage at all 3 facilities: 20% persistent, 39% intermittent, 41% noncarriers. Of 254 residents with an initial negative swab, 25 (10%) acquired MRSA over the 6 months; rates were similar at all 3 LTCFs, with no clusters evident. Multivariable analysis demonstrated that receipt of systemic antimicrobials during the study was the only significant risk factor for MRSA acquisition (odds ratio, 7.8 [95% confidence interval, 2.1–28.6]; $P = .002$). MRSA strains from acquisitions were related by PFGE to those from a roommate in 9/25 (36%) cases; 6 of these 9 roommate sources were persistent carriers.

CONCLUSIONS. MRSA colonization prevalence was high at 3 separate VA LTCFs. MRSA acquisition was strongly associated with antimicrobial exposure. Roommate sources were often persistent carriers, but transmission from roommates accounted for only approximately one-third of MRSA acquisitions.

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Long-term care facilities (LTCFs) may be reservoirs for methicillin-resistant *Staphylococcus aureus* (MRSA) strains.[1] One study in Department of Veterans Affairs (VA) LTCF residents demonstrated an MRSA colonization prevalence of 48%.[2] Though prior data suggested that VA LTCFs had a higher MRSA prevalence than community nursing homes,[3] studies have shown similar MRSA colonization prevalence (40%) among community nursing homes residents.[4]

The risk of progression from colonization to infection has been demonstrated in a variety of patient populations.[5] With a high prevalence of MRSA carriage in the long-term care setting, there is concern about the transmission of this organism in these facilities. In acute care hospitals, control efforts have focused on reducing transmission of MRSA from known carriers to noncarriers by active surveillance, isolation precautions, and cohorting.[6,7] However, aggressive institution of these measures in elderly, frail LTCF residents may have unintended, serious consequences (eg, social isolation, depression). A study of elderly patients receiving inpatient rehabilitation demonstrated higher rates of depression and anxiety among individuals in contact precautions for MRSA compared with matched controls not in isolation.[8] Therefore,

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a better understanding of MRSA transmission is needed in the long-term care setting.

This study examined the epidemiology of MRSA carriage among 3 geographically distinct VA LTCFs over a 6-month time period to identify risk factors associated with MRSA acquisition.

METHODS

Study Population

The 3 participating VA LTCFs, also know as community living centers, cared for a mixture of residents; some received short stay rehabilitation, while others received long stay, skilled, or dementia care. The Atlanta VA LTCF is a 100-bed nursing home care unit physically connected to an acute care hospital. The Augusta VA LTCF is a 132-bed unit located within a larger complex with outpatient clinics and inpatient mental health and rehabilitation units, with a VA acute care hospital 3 miles away. The Tuscaloosa VA LTCF has 178 nursing home beds but no local VA hospital; residents are transferred to a community hospital for acute care needs. Study participants were followed for 6 months; however, enrollment dates were staggered at each site, so the data collection period was from October 2006 until August 2007. All residents of the LTCFs were included in the study except respite care residents, whose shortened length of stay (<2 weeks) was not sufficient to determine carrier status. The study was approved with a waiver of informed consent by the Emory University Institutional Review Board, the Medical College of Georgia Institutional Review Board, and the local VA Research and Development Committees for each site.

Study Design

Eligible residents had MRSA carrier status defined by serial nares swab cultures obtained once a week for 3 times during the first month, followed by once a month for 5 months. A minimum of 3 cultures was required for defining MRSA carrier status and inclusion in the risk factor analyses. MRSA carriage was classified into 3 groups: persistent (all cultures positive), intermittent (at least 1 but not all cultures positive), and noncarrier (no cultures positive). MRSA acquisition was defined as an initial negative culture followed by more than 1 positive culture, with no subsequent negative cultures. Predictor variables were collected for both MRSA carriage and MRSA acquisition risk factor analysis. These variables included demographics; prior medical conditions calculated into a Charlson comorbidity index[9] on a scale from 0 to 37 (higher score indicates increasing comorbidity); standardized evaluations of functional status extracted to calculate an activities of daily living index on a scale from 4 to 18 (higher score indicates increasing dependence); previous MRSA identified by surveillance/clinical cultures; antimicrobial exposure in the 3 months before study entry and during the study; hospitalizations in the prior year and during the study; presence of a skin wound or pressure ulcer during the study; and presence during the study of any medical device, including urinary catheters, intravenous devices, and percutaneous gastrostomy tubes.

Lab Methods

Using a polyurethane-tipped swab (BD BBL CultureSwab EZ), samples for culture were obtained from the anterior nares (1 swab for both nostrils). MRSA was isolated by plating swabs directly on MRSA CHROMagar (BD Diagnostics). During the first month, susceptible *S. aureus* carriage was assessed by also plating the nares swabs on a mannitol salt agar plate (Remel). If cultures on CHROMagar MRSA remained negative while mannitol salt agar plates grew, then a colony from the mannitol plate was tested for methicillin susceptibility by disk diffusion using a cefoxitin disk. Culture plates were incubated at 35°C for 48 hours, and bacterial growth at 24 hours was graded on a semiquantitative scale from 0 to 6, using previously described methods.[2] A growth score was calculated for each participant by averaging the growth from all cultures obtained to estimate burden of nasal carriage. For intermittent carriers, an additional growth score calculation was performed by taking the average from only positive swab cultures. A representative colony from each positive MRSA nares culture underwent molecular strain characterization by pulsed-field gel electrophoresis (PFGE). Digital images of all PFGE gels were analyzed using Gelcompar II (Applied Maths). Percent similarities were identified on a dendrogram based on Dice coefficients, as previously described.[10]

Statistical Analysis

An a priori sample size calculation estimated that 204 MRSA carriers and 141 noncarriers should be enrolled to demonstrate differences in risk factor distribution of 6% or more between the 2 groups, with a significance level of $\alpha = 0.05$ and 80% power. Univariate analyses were conducted using the χ^2 test for categorical variables and the Mann-Whitney test or Kruskal-Wallis test for continuous variables. Those variables significant at $\alpha = 0.05$ on univariate analyses were entered into multivariable logistic regression models along with other clinically meaningful variables to identify risk factors independently associated with MRSA colonization or acquisition. For multivariable models, goodness-of-fit statistics were calculated and variables were checked for multicollinearity using conditional indices. All statistical analyses were carried out using SAS (ver. 9.1).

RESULTS

There were 445 residents enrolled in the study among the 3 VA LTCFs: 107 from Atlanta, 139 from Augusta, and 199 from Tuscaloosa. Overall, 329 residents were present in the facilities from the start of the study (inception cohort), while 116 (26%) were new admissions over the study period. All 3 study facilities had a similar proportion of new admissions

(range, 23%–29%) during the study period. The mean age of residents was 72.3 (range, 23–101), and 98% of the study population was male, consistent with current demographics of the VA long-term care population. The comorbidity and functionality indices of the population were similar across the 3 study sites, but the time spent in the facility before the study inception was shorter for residents in Atlanta compared with the other sites (Table 1).

The overall prevalence of MRSA carriage (ie, combining prevalence on study entry and those identified during the study) was 58%, and there was no statistically significant difference in the prevalence of carriage among the 3 facilities (χ^2 test, $P = .64$). On the basis of first culture obtained at study entry, MRSA prevalence was higher among the inception cohort compared with the new admission cohort (44% vs 22%; $P < .001$). There was not a significant difference in the prevalence of MRSA carriage between residents being admitted to the LTCF from home compared with those coming from other healthcare facilities (25% vs 22%; $P = .76$). The distribution of MRSA carriage was similar at all 3 facilities (χ^2 test, $P = .16$), with 20% persistent carriers, 39% intermittent, and 41% noncarriers among the 412 residents who had 3 or more cultures. Thirty-three (7%) residents had fewer than 3 cultures and therefore could not have carrier status defined. Among the noncarriers, only 24% were found to carry methicillin-susceptible *S. aureus*, while 76% did not carry *S. aureus* at all.

The analysis to identify risk factors predictive of MRSA carriage (ie, positive nares culture at any time during the study) included 412 residents, 242 MRSA carriers (83 persistent and 159 intermittent), and 170 noncarriers. In univariate analysis, factors significantly associated with MRSA carriage included prior antimicrobial exposure in the 3 months before study entry ($P < .001$), prior hospitalization in the 12 months before study entry ($P = .04$), prior isolation of MRSA in a surveillance/clinical culture before study entry ($P < .001$), presence of a skin wound or pressure ulcer ($P < .001$), presence of any medical device during the study ($P < .001$), receipt of systemic antimicrobials during the study ($P < .001$), and activities of daily living index ($P = .006$; Table 2). The multivariable model included these significant risk factors as well as a facility variable, given the possibility that there were facility-level risk factors that could not be otherwise assessed in our study. There was no evidence of multicollinearity among the variables in the final model. The strongest predictor of overall MRSA carriage during the study was prior isolation of MRSA in a surveillance/clinical culture before study entry (risk ratio, 3.5; $P < .001$), although presence of a device and receipt of systemic antimicrobials during the study were also significant risk factors (Table 3).

Comparing risk factors that might differentiate persistent carriage ($n = 83$) from intermittent carriage ($n = 159$), most risk exposures, such as systemic antibiotic use during the study (54% vs 50%; $P = .57$), were similar. Only prior isolation of MRSA in a surveillance/clinical culture before study entry (57% vs 33%; $P < .001$) was statistically different between the 2 groups. However, the mean growth score from swabs obtained over the study period was significantly lower in the intermittent carriage cohort compared with the persistent cohort (1.2 vs 3.4; t test, $P < .001$), and this finding was similar across all 3 facilities. This difference in growth score remained statistically significant even when limited to the average score among only positive swabs obtained from the intermittent cohort compared with the persistent carriers (ie, removing the effect of growth scores of 0; 2.4 vs 3.4; $P < .001$).

Among the 412 residents included in the initial analysis, 254 (62%) had no MRSA recovered from their first nares swab culture. Of these, 25 (10%) acquired MRSA during the study period. The distribution of MRSA acquisition was similar among the 3 facilities: 6/64 (9%) in Atlanta, 9/79 (11%) in Augusta, and 10/101 (10%) in Tuscaloosa. The incidence density of acquisition was approximately 1 acquisition per 1,000 facility-days. Mean time to acquisition was 49 days (range, 7–147), but the mean time to acquisition among the 6 residents who were new admissions to the facilities and acquired MRSA was 25 days. The mean time the noncarriers were followed during the study was 140 days.

Univariate analysis identified several exposures that were associated with residents who acquired MRSA ($n = 25$) ver-

TABLE 1. Characteristics of Residents within Each of the 3 Veterans Affairs Long-Term Care Facilities Enrolled in the Study

Variable	Range	Atlanta ($n = 107$)	Augusta ($n = 139$)	Tuscaloosa ($n = 199$)	Total ($n = 445$)	P[a]
Age, mean, years	23–101	71	72.8	72.5	72.3	.63
Sex, male, %		95	98	99	98	.10
Length of stay in facility before study entry, mean, days	1–7,977	472	781	824	726	**.02**
Charlson index, mean	0–11	3.27	3.39	2.99	3.18	.29
Activities of daily living index, mean[b]	4–18	9.3	10.9	10.2	10.3	**.04**
Facility-days per resident during study period, mean	1–365	244.6	286.3	248.3	259.2	.06
No. of deaths during 1-year study (%)		31 (29)	35 (25)	73 (37)	139 (31)	.07

NOTE. Boldface indicates results that met statistical significance of $P \leq .05$.

[a] Kruskal-Wallis for continuous variables; χ^2 or Fisher exact for dichotomous variables.

[b] Higher score indicates increasing dependence.

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TABLE 2. Univariate Analysis of Risk Factors for Methicillin-Resistant *Staphylococcus aureus* (MRSA) Carriage during the Study

Variable	MRSA carriers (n = 242)	Noncarriers (n = 170)	OR (95% CI)	P[a]
Antimicrobial use in prior 3 months	122 (50)	55 (32)	2.1 (1.4–3.2)	**<.001**
Hospitalization in prior 12 months	129 (53)	73 (43)	1.5 (1.0–2.3)	**.04**
Previous MRSA in culture	100 (41)	26 (15)	3.9 (2.4–6.4)	**<.001**
Presence of a wound	90 (37)	36 (21)	2.2 (1.4–3.5)	**<.001**
Presence of any device during study	154 (64)	65 (38)	2.8 (1.9–4.2)	**<.001**
Antimicrobial use during study	153 (63)	72 (42)	2.3 (1.6–3.5)	**<.001**
Hospitalization during study	40 (17)	18 (11)	1.7 (0.9–3.0)	.09
Age, mean, years[b]	72.5	71.8		.48
Length of stay in facility before study, mean, days[b]	830	690		.13
Charlson index, mean[b]	3.12	3.05		.51
Activities of daily living index, mean[b]	10.7	9.4		**.006**

NOTE. Data are no. (%), unless otherwise indicated. CI, confidence interval; OR, odds ratio. Boldface indicates results that met statistical significance of $P \leq .05$.

[a] χ^2 for dichotomous variables.

[b] Mann-Whitney for continuous variables.

sus noncarriers (n = 170), including prior antimicrobial exposure in the 3 months before study entry (odds ratio [OR], 6.6; $P < .001$), presence of any medical device during the study (OR, 2.4; $P = .04$), presence of an intravenous line (peripheral or central) during the study (OR, 10.4; $P < .001$), receipt of systemic antimicrobials during the study (OR, 9.9; $P < .001$), and a higher Charlson comorbidity index ($P = .03$). In the multivariable model, only the receipt of systemic antimicrobials during the study period was a significant predictor of MRSA acquisition, after controlling for the presence of an intravenous line, Charlson comorbidity index, and transfer to a hospital during the study (Table 4). There was no evidence of multicollinearity among the variables in the final model.

Further evaluation of antimicrobial exposure during the study revealed that those who acquired MRSA had a longer duration of antimicrobial exposure (22 vs 8 days for noncarriers; t test, $P < .0001$). Furthermore, fluoroquinolone agents were used with greater frequency in this group relative to the total study population (68% in the acquisition group vs 27% of the total population). This difference in use among the acquisition cohort compared with the general population was not seen for other antimicrobials, such as trimethoprim-sulfamethoxazole or cephalosporins.

Among the 25 residents who acquired MRSA, 12 had either no primary roommate or a roommate who was a noncarrier, making it less likely that MRSA was acquired from a roommate. Of the 13 whose roommates were MRSA carriers, 9 acquired a strain that was possibly related to their roommate's strain by PFGE typing; 5 of these were highly related (Figure 1). Among the 9 individuals who may have acquired MRSA from their roommate, 5 (56%) were new admissions to the facility. Of the 9 potential roommate sources, 6 (67%) were persistent carriers whose mean growth score was 4 (range, 3.6–4.5).

Three residents developed MRSA infections while in the LTCF during the 6-month study period: 1 bloodstream infection and 2 wound infections. All 3 residents were intermittent carriers; none of the infections occurred in individuals who had acquired MRSA carriage during the study.

DISCUSSION

We found MRSA nasal carriage to be highly prevalent (58%), with similar rates of carriage demonstrated among 3 geographically distinct VA LTCFs. The primary independent risk factors for MRSA carriage were previous isolation of MRSA in a surveillance/clinical culture before study entry, presence of a medical device, and receipt of systemic antimicrobials during the study. Similar risk factors for MRSA carriage in the long-term care setting have previously been described in the literature.[11-14] The patterns of MRSA carrier status (persistent, intermittent, and noncarrier), previously described in

TABLE 3. Multivariable Analysis of Risk Factors Predictive of Methicillin-Resistant *Staphylococcus aureus* (MRSA) Carriage among Long-Term Care Facility Residents (n = 412)

Risk factor	RR (95% CI)	P
Resident in Augusta[a]	1.17 (0.64–2.17)	.60
Resident in Tuscaloosa[a]	1.36 (0.74–2.50)	.33
Antimicrobial use in prior 3 months	1.20 (0.70–2.06)	.50
Hospitalization in prior 12 months	0.95 (0.59–1.52)	.82
Previous MRSA in culture	3.45 (2.03–5.94)	**<.001**
Presence of a wound	1.66 (0.99–2.76)	.05
Presence of any device during study	1.83 (1.05–3.17)	**.03**
Antimicrobial use during study	1.72 (1.03–2.86)	**.04**
Activities of daily living index	1.01 (0.96–1.06)	.71

NOTE. CI, confidence interval; RR, risk ratio. Boldface indicates results that met statistical significance of $P \leq .05$.

[a] Resident in Atlanta is reference group.

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TABLE 4. Multivariable Analysis of Risk Factors Predictive of Methicillin-Resistant *Staphylococcus aureus* Acquisition among Long-Term Care Facility Residents ($n = 195$)

Risk factor	RR (95% CI)	*P*
Antimicrobial use during study	7.76 (2.1–28.56)	**.002**
Hospitalization during study	1.51 (0.48–4.72)	.48
Intravenous line during study	3.44 (0.87–13.58)	.08
Charlson index	1.20 (0.98–1.47)	.08

NOTE. CI, confidence interval; RR, risk ratio. Boldface indicates results that met statistical significance of $P \leq .05$.

the literature,[2,11,15] were confirmed in this larger cohort, with similar distributions at all 3 LTCFs. There were more intermittent carriers in this 6-month study compared with an 8-week longitudinal pilot performed previously at the Atlanta LTCF (36% vs 23%);[2] this may be a result of the longer duration of surveillance. Previous isolation of MRSA in a surveillance/clinical culture and mean growth score of nasal cultures were the only distinguishing characteristics between the persistent and intermittently positive carriers. Though previous work demonstrated the importance of bacterial burden in distinguishing persistent and intermittent carriers,[2] our study confirms this finding in 3 distinct sites.

The acquisition rate of MRSA in the LTCFs was 0.42% per week. The rate of acquisition was similar across all 3 LTCFs, despite the fact that each facility was regionally distinct and had different geographical relationships to acute care hospitals. The major risk factor for acquiring MRSA during the study was systemic antimicrobial exposure. Although prior antimicrobial exposure is a well-described risk factor for MRSA carriage and infection,[16-18] this study highlights the role of antimicrobial use in predisposing LTCF residents to acquisition of MRSA following a documented negative culture.

Several studies have suggested a relationship between fluoroquinolone exposure and MRSA colonization. During a hospital outbreak of MRSA, a case-control study demonstrated that fluoroquinolone exposure was independently associated with hospital-acquired MRSA even when controlling for other risk factors in a multivariable model.[19] A study examining the risk for hospital acquisition of MRSA among patients with known MRSA-colonized roommates showed that acquisition was independently associated with exposure to levofloxacin.[20]

Although active surveillance cultures tend to be the primary focus of many recent MRSA prevention strategies, antimicrobial stewardship is also mentioned in recommendations for addressing MRSA transmission in the healthcare setting.[6] Despite the emphasis in guidelines on preventing MRSA transmission among roommates, most of the acquisition events seen in this study could not be linked back to a roommate. Among the 254 residents initially at risk, only 9 (3.5%) were likely to have acquired MRSA from their roommate. This finding was comparable to the study by Bradley et al,[11] which found that 3% of transmission events were due to roommates, although the MRSA carrier prevalence in Bradley's cohort was significantly lower than in our study. Unique in our study was the finding that the majority of roommates who were probable sources of transmission were persistent carriers with a mean growth score of 4. A recent study evaluating *S. aureus* carrier dynamics also demonstrated that median colony-forming units per swab sample from na-

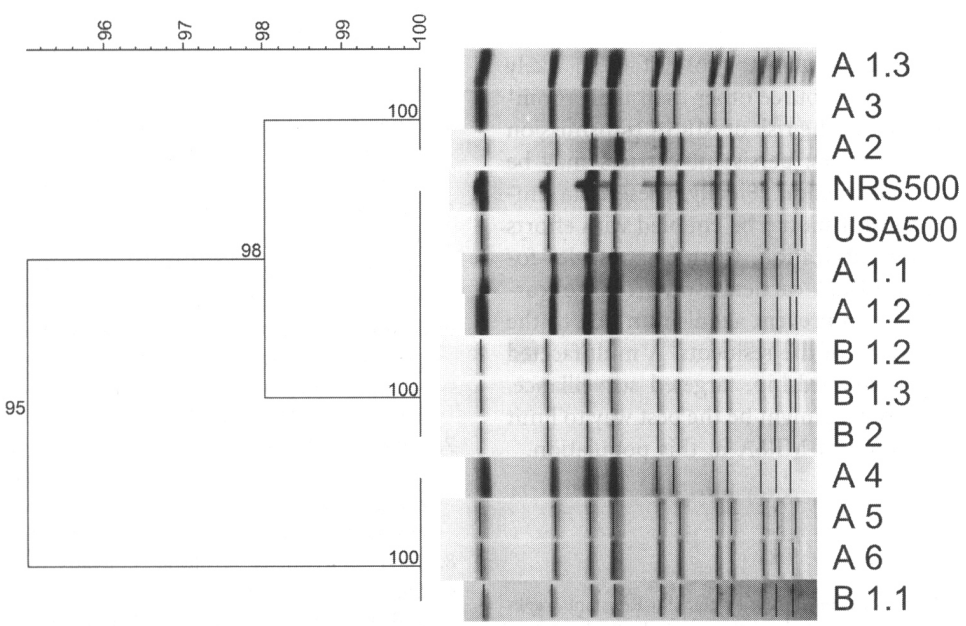

FIGURE 1. Pulsed-field gel electrophoresis (PFGE) image demonstrating percent relatedness of methicillin-resistant *Staphylococcus aureus* strains isolated from 2 roommates (A and B). Also present on gel are PFGE standards for USA500 type strain (USA500 and NRS500).

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sal cultures of persistent carriers are significantly higher than those of both intermittent and noncarriers.[21] The relationship between high bacterial burden of nasal carriage and persistent MRSA carriage raises the possibility that persistent carriers may be more likely to be a source of transmission to noncarriers.

There were a few limitations to this study. Findings in the VA population may not be more broadly generalizable. Because the majority of residents (74%) enrolled were present in the LTCFs for an average of 2 years before the study inception, the study captured only a small portion of the total period at risk for this cohort. This could have caused misclassification in the assignment of MRSA carrier cohorts. Misclassification would be particularly relevant to the small cohort of 25 new acquisitions (ie, a false negative initial swab), given that only 6 residents were new to the facilities during the study. Censored swab results due to residents leaving the facility may have also resulted in misclassification. Limiting surveillance to nasal carriage may have missed individuals with only extranasal MRSA colonization. There was also potential for decreased sensitivity in detecting MRSA nasal carriage using the culture technique compared with polymerase chain reaction–based systems; however, repeating cultures should have increased the likelihood of identifying MRSA carriers. Although we identified risk factors at the time of MRSA surveillance swabbing, except for antimicrobial exposure during the study, we did not capture the total length of time a risk factor was present. Therefore, we were not able to incorporate the duration of exposure to most risk factors into the analysis. Despite these limitations, this study provides some important information about the risk factors for MRSA carriage and acquisition in LTCFs.

In these LTCFs, prevalence of MRSA was high, but documented transmission was less than 1 episode per week. Of those residents who acquired MRSA, most of them likely acquired the organism from a source other than their roommate. Our study suggests that the risk of MRSA transmission is not the same for all carriers; persistent carriers may be responsible for more transmission. Finally, these data emphasize that infection control should be coupled with efforts to optimize antimicrobial utilization. Current strategies focused only on cohorting MRSA carriers away from noncarriers may not be adequate to prevent acquisition due to the communal living conditions of the residents. A multifaceted strategy of antimicrobial stewardship, targeted surveillance, and selected resident cohorting might be the best way to limit transmission and acquisition of MRSA in this population.

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