

ORIGINAL ARTICLE

Methicillin-Resistant *Staphylococcus aureus*: Site of Acquisition and Strain Variation in High-Risk Nursing Home Residents with Indwelling Devices

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OBJECTIVE. Characterize the clinical and molecular epidemiology of new methicillin-resistant *Staphylococcus aureus* (MRSA) acquisitions at nasal and extranasal sites among high-risk nursing home (NH) residents.

DESIGN. Multicenter prospective observational study.

SETTING. Six NHs in southeast Michigan.

PARTICIPANTS. A total of 120 NH residents with an indwelling device (feeding tube and/or urinary catheter).

METHODS. Active surveillance cultures from the nares, oropharynx, groin, perianal area, wounds (if present), and device insertion site(s) were collected upon enrollment, at day 14, and monthly thereafter. Pulsed-field gel electrophoresis and polymerase chain reaction for *SCCmec*, *agr*, and Panton-Valentine leukocidin were performed.

RESULTS. Of 120 participants observed for 16,290 device-days, 50 acquired MRSA (78% transiently, 22% persistently). New MRSA acquisitions were common in extranasal sites, particularly at device insertion, groin, and perianal areas (27%, 23%, and 17.6% of all acquisitions, respectively). Screening extranasal sites greatly increases the detection of MRSA colonization (100% of persistent carriers and 97.4% of transient carriers detected with nares, groin, perianal, and device site sampling vs 54.5% and 25.6%, respectively, for nares samples alone). Colonization at suprapubic urinary catheter sites generally persisted. Healthcare-associated MRSA (USA100 and USA100 variants) were the dominant strains (79.3% of all new acquisition isolates). Strain diversity was more common in transient carriers, including acquisition of USA500 and USA300 strains.

CONCLUSION. Indwelling device insertion sites as well as the groin and perianal area are important sites of new MRSA acquisitions in NH residents and play a role in the persistency of MRSA carriage. Clonal types differ among persistent and transient colonizers.

Infect Control Hosp Epidemiol 2014;35(12):1458-1465

Nursing home (NH) residents represent a unique, vulnerable, and growing population. Approximately 1.4 million people in the United States reside in over 15,000 NHs. These numbers are expected to increase due to an aging population and the rapid expansion of postacute care in NHs.¹ Residence in a NH has long been identified as an important risk factor for methicillin-resistant *Staphylococcus aureus* (MRSA) carriage, and MRSA carriage in NH residents is associated with increased morbidity.²⁻⁴ NH residents with an indwelling device, such as a urinary catheter or feeding tube, share many characteristics with high-risk hospitalized populations, be-

cause the improper maintenance of these devices presents opportunities for pathogen acquisition. NH residents typically exhibit multiple comorbidities and greater functional dependence, requiring more hands-on contact care from healthcare workers.^{5,6}

There are 3 well-known carriage patterns for MRSA: persistent carriage, intermittent or transient carriage, and non-carriage.^{4,7} The transmission dynamics of MRSA are difficult to assess in acute care because of the short length of stay and the inherent variability within the population.⁸ Because residents typically reside in NHs longer than hospitalized pa-

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Received May 1, 2014; accepted July 31, 2014; electronically published November 5, 2014.

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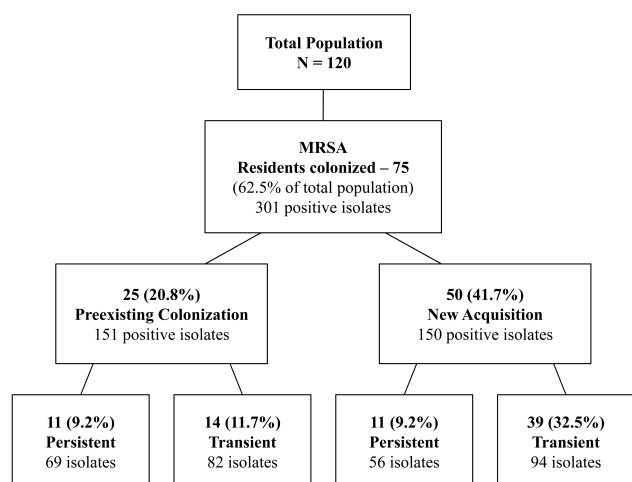


FIGURE 1. Flow chart displaying the study participants with a new methicillin-resistant *Staphylococcus aureus* (MRSA) acquisition, along with the percentage of colonization. The percentages in parentheses represent the percentage of residents colonized out of the total number of participants ($n = 120$).

tients reside in hospitals and are exposed to more healthcare worker interactions, they represent an ideal population for investigating the colonization patterns of MRSA.

The goal of this study was to identify determinants of new MRSA acquisitions (persistent or transient carriage) among high-risk NH residents. We were particularly interested in defining the common anatomic sites of new MRSA acquisitions as well as the genotype of these pathogens. The clinical importance of understanding the relative contribution of different anatomic sites over time, along with the clone-specific patterns of colonization, lies in the ability to understand MRSA transmission in NHs as well as in other healthcare settings that care for older adults and to intervene through infection prevention programs.

METHODS

Study Population and Design

This study included in-depth analyses of samples collected as part of our larger parent study. The goal of the parent study was to design, implement, and evaluate the efficacy of a multi-component targeted infection prevention (TIP) program in reducing multidrug-resistant organism (MDRO) prevalence and infections in a high-risk NH population.⁹ This was a cluster-randomized intervention trial conducted in 12 community-based NHs (6 control NHs and 6 intervention NHs) in Michigan. The parent project was approved by the University of Michigan and Veterans Affairs Ann Arbor Healthcare System institutional review boards. Study inclusion criteria were (a) any short- or long-stay resident with an indwelling urinary catheter (Foley or suprapubic) and/or a

feeding tube (nasogastric or percutaneous endoscopic gastrostomy tube) for more than 72 hours and (b) informed consent. Residents receiving end-of-life care were excluded. Enrolled residents from both intervention and control NHs had samples collected at the time of enrollment, on day 14, and monthly thereafter for a maximum of 1 year (or until death, discharge, or device discontinuation) for outcome measurements. Clinical and demographic data on the participants were obtained from the source documents at the participating facility or chart review conducted by trained research staff.

To investigate whether molecular type and site of acquisition influence the carriage pattern (persistent vs transient), only residents of control NHs with at least 30 days of follow-up were included in the analysis. Residents of intervention NHs were excluded to avoid any influence due to intervention effects.

Laboratory Methods

Participant samples to assess potential colonization with MRSA were obtained from the nares, oropharynx, suprapubic (SP) urinary catheter or enteral feeding tube insertion site(s), groin, perianal area, and wounds (if present) for all participants using swabs. Swabs were streaked onto mannitol salt agar and incubated at 35°C for 48 hours. Bright yellow colonies suggestive of *S. aureus* were streaked onto trypticase soy agar with 5% sheep blood, and growth was confirmed to be *S. aureus* by catalase positivity and agglutination with a rapid test for protein A (Fisher HealthCare, Houston, TX). All suspected colonies were tested for methicillin resistance by growth on Mueller-Hinton agar containing oxacillin (6 µg/mL) and 4% NaCl. Colonies identified as MRSA were further typed using molecular methods.

Molecular Typing

Pulsed-field gel electrophoresis (PFGE) was performed to characterize the relatedness of newly acquired MRSA strains. Genomic DNA was prepared and digested with *Sma*I (New England BioLabs, Ipswich, MA) using a previously described method.¹⁰ *Sma*I fragments were separated using a CHEF-DR II apparatus (BioRad, Hercules, CA) and compared using BioNumerics software (Applied Maths, Belgium). Polymerase chain reaction (PCR) was performed to detect the Pantone-Valentine leukocidin (PVL) cytotoxin.¹¹ Multiplex PCR was performed using previously described methods to determine staphylococcal cassette chromosome *mec* (SCC*mec*) types I, II, III, IV, and V and to determine accessory gene regulator (*agr*) types I, II, III, and IV.¹²⁻¹⁶

The PFGE-based dendrogram was created using the Dice coefficient and the unweighted pair group method using arithmetic averages. All MRSA isolates were also compared with MRSA strains USA100–1100, as described elsewhere.^{10,17} Isolates were considered to be in the same PFGE strain group

TABLE 1. Characteristics of Nursing Home Residents with a New Methicillin-Resistant *Staphylococcus aureus* (MRSA) Acquisition Stratified by Carrier Status

Characteristic	All new acquisitions (<i>n</i> = 50)	Persistent carriers (<i>n</i> = 11)	Transient carriers (<i>n</i> = 39)	<i>P</i> ^a
Time to new acquisition, days	77 (84.7)	49.8 (79.5)	84.7 (85.5)	.23
Follow-up days in study	195 (133.4)	158.2 (127.3)	205.4 (134.8)	.30
Device type at acquisition, no. (%) of residents				.28 ^b
FT	18 (36)	6 (54.5)	12 (30.8)	
UC	20 (40)	4 (36.4)	16 (41)	
Both	12 (24)	1 (9)	11 (28.2)	
MRSA-positive samples per resident	3 (2.5)	5.1 (3.1)	2.4 (2.0)	<.001
No. body sites colonized at acquisition	1.96 (1.1)	2.4 (1.4)	1.8 (1.0)	.11

NOTE. Data are mean (\pm standard deviation), unless otherwise indicated. FT, feeding tube; SD, standard deviation; UC, urinary catheter.

^a $P \leq .05$ is considered statistically significant. *P* values obtained using Student *t* test, unless otherwise indicated.

^b χ^2 test.

if their *Sma*I restriction patterns were 80% similar or more as determined by the Dice coefficient. Clones were defined using 80% genetic similarity and 1% tolerance by PFGE.

Definitions

One or more MRSA-positive cultures from any anatomic site indicated MRSA colonization. Colonized participants were divided into the following 2 categories: (1) preexisting colonization, which included those in whom MRSA was present at enrollment, and (2) new acquisition, which included those who were not colonized at enrollment and acquired MRSA.¹⁸

For each category, the status of the colonization was defined as either persistent or transient carriage. We used the definitions established by Muder et al,⁴ which are appropriate for prospective studies in the NH setting. Transient carriage is defined as 2 or more MRSA-negative cultures after a single MRSA-positive culture from any site, whereas persistent carriage is defined as 2 or more MRSA-positive cultures from any site, separated by fewer than 2 MRSA-negative cultures. If no sample was collected after a single positive MRSA culture, it was conservatively classified as a transient colonization. The time to acquisition was calculated for each new MRSA acquisition, measured by the visit day that the organism was first identified.

Statistical Analyses

Our main outcome of interest was the frequency of extranasal versus nasal colonization in an NH resident with a new acquisition of MRSA. We were also interested in determining whether specific anatomic sites of acquisition, molecular strain type, and type of indwelling device led to persistent MRSA carriage. Data were analyzed using SAS 9.0. Categorical variables were compared using the χ^2 test, and continuous variables were compared using Student *t* test. *P* values less than .05 were considered to be statistically significant.

RESULTS

Study Population

In the 6 control NHs, 641 residents were assessed for eligibility. Of these, 245 residents were not eligible (unable to reach family or guardian, 46; discharged from the NH before enrollment, 112; indwelling device was removed before enrollment, 67; died before enrollment, 10; other reasons, 10). Of the 396 residents eligible for study participation, 181 residents or their family or guardian refused consent, and 215 residents or their family or guardian provided consent and were enrolled. To achieve our study objective, we included only those residents with at least 30 days of follow-up in the analysis, resulting in a total of 120 residents. The number and percentages of participants in which a preexisting or new colonization of MRSA was detected are shown in Figure 1. One hundred and fifty MRSA samples were collected from the 50 participants with a new MRSA acquisition over 9,750 device-days. There were no major differences between the persistent and transient carriers with respect to their age, weight, sex, race, comorbidity score, or functional status score. Time to new acquisition of MRSA, follow-up time, number of positive samples, device type, and number of positive body sites are shown in Table 1 for persistent and transient carriers.

Anatomic Sites of Colonization

The majority (64%) of participants with a new MRSA acquisition became colonized at a single body site; 26% became colonized at 2 body sites, 8% at 3 body sites, and 2% at 4 body sites. To determine where new MRSA acquisitions most commonly occur in persistent and transient carriers, the site of new acquisition was classified into 2 groups: (1) extranasal only (newly acquired MRSA colonization at any site other than the nares, including the oropharynx, groin, perianal area,

TABLE 2. Comparison of Anatomic Site of New Methicillin-Resistant *Staphylococcus aureus* Acquisitions between Persistent and Transient Carriers

Anatomic site of acquisition	No. (%) of residents		Total	P ^a
	Persistent carriers	Transient carriers		
Nares (<i>n</i> = 16)	6 (37.5)	10 (62.5)	16 (100)	.15
Exclusively (<i>n</i> = 7)	3 (43)	4 (57)	7 (100)	
+1 extranasal site (<i>n</i> = 6)	2 (33)	4 (67)	6 (100)	
+2 extranasal sites (<i>n</i> = 2)	...	2 (100)	2 (100)	
+3 extranasal sites (<i>n</i> = 1)	1 (100)	...	1 (100)	
Extranasal only (<i>n</i> = 34)	5 (14.7)	29 (85.3)	34 (100)	
Single site (<i>n</i> = 25)	4 (16)	21 (84)	25 (100)	
2 sites (<i>n</i> = 8)	...	8 (100)	8 (100)	
3 sites (<i>n</i> = 1)	1 (100)	...	1 (100)	
Overall (<i>n</i> = 50)	11 (22)	39 (78)	50 (100)	

^a $P \leq .05$ is considered statistically significant. *P* values were obtained using Fischer exact test.

device site, and/or wound) and (2) nares (exclusively or in addition to extranasal sites). This dichotomous classification was chosen to establish how many MRSA acquisitions would have been missed if MRSA screening had been restricted to the nares only.

Most participants with a new MRSA acquisition became colonized exclusively at extranasal sites, and the majority were transient MRSA carriers (Table 2). The most common extranasal sites of acquisition included device insertion sites, constituting 27% of all new acquisition isolates, followed by the groin (23%) and the perianal area (17.6%). The most common anatomic sites for new transient MRSA acquisition were the groin (21.4%), enteral feeding tube (21.4%), perianal area (17.9), and nares (17.9%). The most common anatomic sites for new persistent MRSA acquisition were the nares (33.3%), groin (27.9%), perianal area (16.7%), and SP catheter (11.1%).

If screening for MRSA colonization in these participants had been performed on the nares only, 5 persistent carriers (45.5%) and 29 transient carriers (74.4%) would have been missed at the time of acquisition. If screening for MRSA colonization in these participants had been conducted at both the nares and the groin at the time of screening, 3 persistent carriers (27.3%) and 20 transient carriers (51.3%) would have been missed. Screening participants at device insertion sites in addition to the nares and groin would have improved screening outcomes, detecting 90.9% of persistent carriers and 84.6% of transient carriers. Screening participants at 1 additional site—the perianal area—would have detected 100% of the persistent carriers and 97.4% of the transient carriers.

MRSA Acquisition at Device Sites

Of the 120 residents included in this analysis, 54 (45%) had a urinary catheter, 45 (37.5%) had a feeding tube, and 21

(17.5%) had both devices in place at baseline. Twenty (40%) of the 50 participants with a new MRSA acquisition became colonized at their tested device site, including 7 (63.6%) of the 11 participants with an SP catheter and 13 (44.8%) of the 29 participants with an enteral feeding tube. New MRSA acquisitions occurring at the SP catheter were more likely to persist, colonizing 7 participants for a mean (\pm standard deviation) of 3.4 ± 2.5 visits during follow-up (range, 1–8 visits; Figure 2).

Molecular Typing

Molecular typing was conducted on 115 MRSA isolates from 39 participants available for further analysis. Twenty-eight (71.8%) of the participants included in the molecular analysis were transient carriers, whereas 11 (28.2%) were persistent carriers.

Of the 115 MRSA isolates analyzed, 58 isolates were from samples collected on the visit at which a new acquisition was identified, and 57 isolates were from samples collected at subsequent visits. Genotypically, 46 new MRSA acquisition isolates (79.3%) were SCC*mecII*, which typically represents healthcare-associated (HA) MRSA; these included 23 USA100 isolates from 13 participants, 22 USA100 variants from 17 participants, and 1 isolate belonging to a PFGE group other than USA100–1100. All SCC*mecII* isolates were PVL negative and *agr II*. Six (10.3%) of the new acquisition isolates from 6 participants were SCC*mecIVa*, which is usually community-acquired (CA) MRSA.⁸ All of these strains were USA300, PVL positive, and *agr I*. Four (6.9%) of the isolates from 2 participants were identified as SCC*mecIV*, not a–d; 2 of these were USA500: 1 was USA100 variant, and 1 was a non

Resident No.	Visit (in days)													
	0	14	30	60	90	120	150	180	210	240	270	300	330	360
1		X												
2				X										
3		X												
4		X												
5		X	X											
6					X									
7				X										
8		X												
9					X									
10			X									X		
11									X					
12						X								
13										X				
14		O	O	O	O		O	O	O			O	O	O
15			O	O								O	O	O
16				O	O			O						O
17							O							
18														O
19			O		O							O		
20		O	O											

FIGURE 2. Temporal trends of methicillin-resistant *Staphylococcus aureus* (MRSA) acquisition at indwelling device sites. Each row corresponds to a different nursing home resident, and each column represents a follow-up visit (in days). White squares correspond to a follow-up day during which residents were not colonized with MRSA at their device insertion site; gray squares correspond to days for which that resident was lost to follow-up. X represents colonization at the enteral feeding tube site, and O represents colonization at the suprapubic urinary catheter site.

USA100–1100. All 4 isolates were PVL negative and *agr* I. Two (3.4%) of the final isolates from 2 participants were untypeable, giving results characteristic of mixed *SCCmec* types (*SCCmed* and *SCCmedI*) and were both typed as non USA100–1100 strains, PVL negative, and *agr* II.

The PFGE band patterns for the 58 strains included in the study are shown in Figure 3. PFGE analysis clustered these strains into 11 groups. Five different clusters were USA100 variants, because they were slightly less than 80% similar to the typical USA100 strain. Three additional clusters were identified as non USA100–1100 strains.

Notable differences were seen between persistent and transient carriers in terms of the MRSA strains they acquired. Overall, more diversity was seen in transient carriers, because they were more likely than persistent carriers to acquire a USA100, a USA500, or a USA300 strain. In fact, persistent carriers never acquired nor were they colonized at any time during follow-up with a USA300 or a USA500 strain type. The majority (72.7%) of persistent carriers acquired a USA100 variant strain of MRSA and exhibited chronic carriage of the same strain as opposed to transient acquisition of new strains.

This preponderance of USA100 and USA100 variant strains was maintained even when analyzing single NHs. Facilities tended to harbor either predominantly USA100 strains—57% at facility G, 63.6% at facility I, and 66.7% at facility J—or predominantly USA100 variant strains—50% at facility B and 75% at facility E. An equal proportion of USA100 and USA100 variants were found at facility K. Additionally, among the less common strains, there were no indications of an outbreak, with no single particular strain circulating among any particular NH. The 6 USA300 isolates were from 6 participants at 4 different facilities (B, E, J, and K); 4 isolates belonging to PFGE groups other than USA100–1100 were from 4 participants at 3 different facilities (E, I, and K); 2 USA500 isolates were from 1 participant at 1 facility (I). Each NH facility had 2–4 different circulating USA strain types.

DISCUSSION

In this study, we show that a large proportion of NH residents with an indwelling device acquire MRSA, usually at extranasal anatomic sites and with a preponderance of HA-MRSA strains. Extranasal sites appear to play an important role in the detection process of new MRSA acquisitions among transient carriers. Additionally, certain characteristics at the time of MRSA acquisition distinguished persistent carriage from transient carriage, including acquisition at the nares or the SP catheter and acquisition of a USA100 variant.

Based on single nares surveillance swab samples at admission for all patients, prevalence of MRSA colonization at admission to 2 acute care hospitals located in Detroit, Michigan, ranged from 13% to 23%.¹⁹ Similar to our earlier work,^{5,20,21} MRSA prevalence was higher in our study, likely because of our high-risk population and multianatomic site

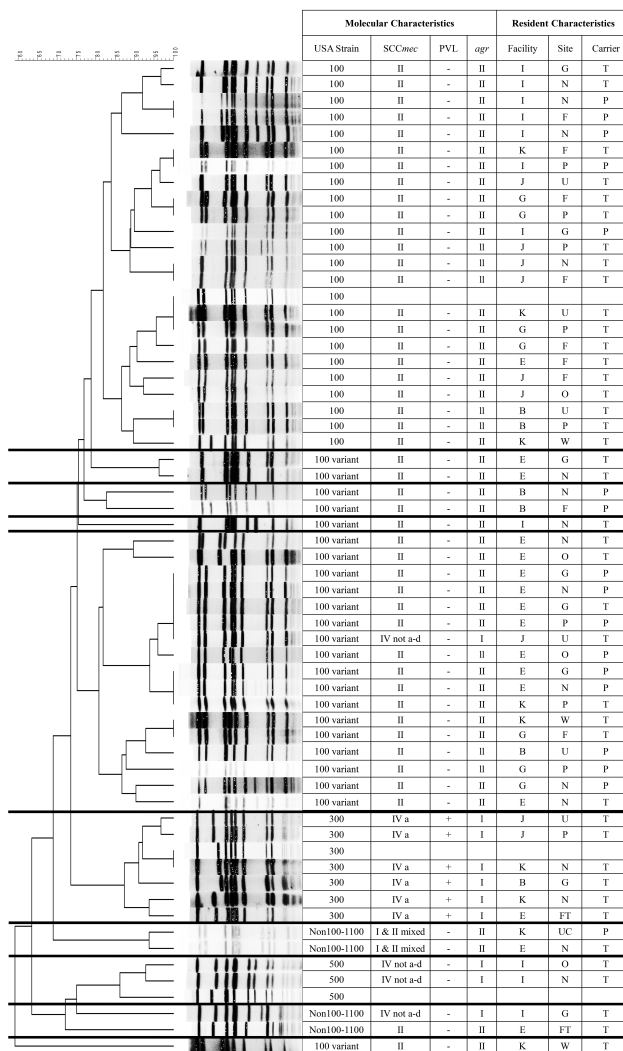


FIGURE 3. Dendrogram of *Sma*I restriction profiles of 58 methicillin-resistant *Staphylococcus aureus* (MRSA) isolates from 39 nursing home residents at the time of MRSA acquisition. Molecular and epidemiologic characteristics of the isolates exhibiting these pulsed field gel electrophoresis (PFGE) patterns are summarized to the right of the PFGE gel results. The scale shows the similarity index. Extended horizontal lines separate the 11 clusters that maintained 80% or greater similarity. *agr*, accessory gene regulator; FT, feeding tube; G, groin; N, nares; O, oropharynx; P, perianal area (under “site” column) or persistent (under “carrier” column); PVL, Pantone-Valentine leukocidin; *SCCmec*, staphylococcal cassette chromosome *mec*; T, transient; UC, urinary catheter; W, wound.

sampling. Residents with indwelling devices are more commonly colonized with MRSA than those without devices,²⁰ often with a shorter time to new acquisition and more persistent carriage.²¹ Therefore, interventions aimed at preventing acquisition and, once colonized, transmission from residents with indwelling devices are needed to reduce MRSA reservoirs in the NH. Appropriate screening protocols for

MRSA in this high-risk population can be an important component of these interventions.

Although nares colonization was once thought to be the primary reservoir for *S. aureus*,²² recent studies have shown the emerging role of screening both nasal and extranasal sites for MRSA colonization.^{23,24} A 2013 literature review found that extranasal testing would increase the number of patients identified as MRSA carriers by 33%–55%, with the oropharynx, rectum, and wounds playing significant roles in increasing pathogen detection.²³ A prospective study of NH residents with an indwelling device identified the perianal area, the oropharynx, and the groin as significant extranasal sites, colonizing 27%, 26%, and 25% of residents ($n = 105$), respectively.²⁴ In our study, only 16 participants (32%) newly acquired MRSA in the nares; 68% of participants with a new MRSA acquisition would have been missed if sample collection had been confined to the nares only. Therefore, screening additional extranasal anatomic sites greatly increases the detection of MRSA colonization.

The groin, perianal area, and device insertion sites all appear to be important extranasal sites of new MRSA acquisition, with the SP catheter in particular playing a role in persistent carriage. It has been shown that the bacterial load of *S. aureus* is highest in persistent carriers, which results in increased bacterial dispersal and a higher risk of infection.^{25,26} Thus, identifying key features of persistent MRSA carriage can be helpful in decreasing its transmission and preventing infection. The presence of nasal colonization alone or together with extranasal colonization appear to be more likely to lead to persistent colonization in our study participants, although no single site or combination of sites was highly predictive (>50%) of persistent colonization.

Emergence of CA-MRSA has become a major problem in many settings; however, NH residents are more often colonized with HA-MRSA, typically SCC*me*II.²⁴ Moreover, we found that persistent carriers in particular are far more likely to acquire HA-MRSA. A recent prospective study that identified MRSA from nasal surveillance cultures of residents of 26 NHs in Orange County, California, found the USA100 variant to be predominant.²⁷ We found an equal proportion of new acquisitions to be of the USA100 or USA100 variant type, although the USA100 variant type was more common among persistent carriers. If results correlating the USA100 variant strain to carriage persistency can be reproduced in larger investigations, identifying strain type at acquisition may be helpful in predicting subsequent carriage, especially given that the majority of persistent carriers remain colonized with the same strain of MRSA throughout their carriage.

Our study does have limitations. Our sample included a relatively small number of NHs in a single region; therefore, the results need to be replicated in a larger, more diverse sample of NHs. Variations in bacterial burden at the tested anatomical sites over time could have affected our rates of isolation, thereby resulting in an overrepresentation of transient carriers who may in fact have been persistent carriers.

These variations remain a challenge in many studies evaluating colonization patterns of various MDROs. We enrolled newly admitted residents as well as those already residing at the facility; therefore, new MRSA acquisition may also have been overestimated if residents had a preexisting colonization that was not identified on the initial sampling. However, our definition is similar to that used in other studies.¹⁸

A major strength of our study was that we prospectively cultured specimens from multiple anatomic sites of NH residents for extended periods of time. Our study is reflective of the population that resides in NHs, with length of stay measured in months to years, compared with acute care studies, in which length of stay is usually measured in days. As a result, we have been able to perform a more comprehensive assessment of new MRSA acquisition and thereby MRSA transmission in the NH population. Our findings may also be used to strengthen the surveillance programs for NH residents transferred to acute care. Prevalence rates of MRSA colonization have been extensively described, but the studies have often been performed at a single nursing facility, used clinical cultures, or described colonization at a single anatomic site.^{28–31} Our study focuses on residents from multiple community-based NHs, making it more generalizable to other NH populations. Lastly, we employed extensive molecular typing of MRSA strains, allowing us to observe strain patterns among persistent and transient carriers. Our findings show that extranasal sites offer improved sensitivity in detecting new MRSA acquisitions. New MRSA acquisitions at extranasal sites tend to occur transiently and may play an important role in the transmission of MRSA.

ACKNOWLEDGMENTS

We thank the Infectious Disease laboratory at the Henry Ford Healthcare System for their assistance in the molecular analysis of samples; the leadership and healthcare personnel at all participating nursing home facilities; and the members of the TIP Study Team, including Suzanne Bradley, MD; Kay Cherman, MSc; Jay Fisch, MSc; James T. Fitzgerald, PhD; Andrzej Galecki, MD; Mohammed Kabeto, MS; Carol A. Kauffman, MD; Evonne Koo, MS, MPH; Sarah L. Krein, PhD; Bonnie Lansing, LPN; Lillian Min, MD; Ana Montoya, MD; Tisha Moore, BA; Russell Olmsted, MPH; Ruth Anne Rye, BS; Sanjay Saint, MD; Kathleen Symons, BA; and Linda Wang, BS.

Financial support. This work was supported by grants from the Veterans Affairs Healthcare System Geriatric Research Education and Clinical Care Center (to L.M.), National Institute on Aging (NIA) Pepper Center (to L.M.), and the National Institutes of Health (NIA R01AG032298 and R01AG041780 to L.M.).

Potential conflicts of interest. All authors report no conflicts of interest relevant to this article. All authors submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest, and the conflicts that the editors consider relevant to this article are disclosed here.

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