

ORIGINAL ARTICLE

An Integrated Approach to Methicillin-Resistant *Staphylococcus aureus* Control in a Rural, Regional-Referral Healthcare Setting

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OBJECTIVE. To curtail the prevalence and cross-transmission of methicillin-resistant *Staphylococcus aureus* (MRSA) in a rural healthcare setting.

DESIGN. Before-after, quasi-experimental quality improvement study.

SETTING. A regional-referral hospital, 5 affiliated nursing homes, and an outpatient MRSA clinic.

INTERVENTIONS. Residents of the 5 nursing homes were screened for MRSA at baseline and 1 year later. Active surveillance cultures were performed on subsequently admitted nursing home residents, "high-risk" patients admitted to the hospital, and household contacts of clinic patients. The decolonization regimen consisted of systemic therapy with minocycline and rifampin and topical therapy with nasal mupirocin ointment and 5% tea tree oil body wash. Three separate samples for cultures to document clearance of MRSA colonization were obtained at 1-week intervals 1 month after the completion of decolonization therapy. Samples for follow-up cultures were obtained at month 6 and month 12 after the completion of decolonization therapy.

RESULTS. After intervention and follow-up for 12 months or more, the prevalence of MRSA carriage at the nursing homes decreased by 67% ($P < .001$), and 120 (82%) of 147 nursing home residents and 111 (89%) of 125 clinic patients remained culture-negative for MRSA. Twenty-three (24%) of 95 new clinic patients had at least 1 MRSA-positive contact. Mupirocin resistance did not develop. In the hospital, the incidence rate of nosocomial MRSA infection decreased from 0.64 infections per 1,000 patient-days before the interventions to 0.40 infections per 1,000 patient-days 1 year after the interventions and to 0.32 infections per 1,000 patient-days 2 years after the intervention ($P < .01$).

CONCLUSIONS. Use of active surveillance cultures and decolonization therapy was effective in decreasing the prevalence of asymptomatic carriage, the incidence of nosocomial infection, and the overall prevalence of MRSA in our rural healthcare setting.

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Over the past decade, the incidence rates of and the morbidity and mortality associated with healthcare-acquired methicillin-resistant *Staphylococcus aureus* (MRSA) infection and community-acquired MRSA infection have progressively increased.¹ Asymptomatic colonization with MRSA is often unrecognized and generally precedes the development of MRSA infection. In addition, by way of colonization pressure, asymptomatic colonization plays a major role in the dissemination of this organism within and between healthcare facilities, particularly in settings where adherence to hand hygiene standards is suboptimal.^{2,3} MRSA colonization increases a patient's risk of subsequent MRSA infection by 4-fold to 13-fold, compared with colonization with methicillin-susceptible *S. aureus* or no *S. aureus* colonization. As many as one-third of patients who are found to be colonized with MRSA on admission to the hospital will develop an MRSA infection, frequently severe, during the subsequent 12–18 months, and the attributable mortality is as high as 17%.⁴⁻⁷ Patients harboring MRSA are placed under contact precautions during their

hospital stay, which results in increased costs and inconvenience, an increase in the number of adverse events, and significant patient dissatisfaction, compared with those for control patients.⁸⁻¹⁰

We undertook an integrated quality improvement project across the continuum of care, utilizing active surveillance cultures and whole-body decolonization therapy with both topical and systemic antimicrobial agents. Our aim was to decrease the prevalence and nosocomial transmission of MRSA in our rural, regional-referral healthcare system, utilizing methods that could be applied in other resource-limited community settings.

METHODS

Setting and Study Population

The study was performed at Aspirus Wausau Hospital and Clinics, a 235-bed, regional-referral center averaging 57,000 patient-days annually, with 5 affiliated local nursing homes

From Aspirus Wausau Hospital, Wausau, Wisconsin.

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(with a total of 725 beds) and an outpatient MRSA Clinic. Patients and nursing home residents aged 10 years or more who had a culture positive for MRSA were eligible for participation. Informed consent was obtained. Because of limited resources, genotypic differentiation of MRSA strains is not available in the community setting, and we therefore did not differentiate between healthcare-associated strains of MRSA and community-associated strains.

Decolonization Regimen

The initial phase of decolonization consisted of therapy with minocycline (100 mg orally twice per day for 5 days), rifampin (600 mg orally once daily for 5 days), 2% mupirocin ointment applied to the anterior nares twice per day for 7 days, and a bath or shower with a 5% tea tree oil body wash once per day for 7 days. During a continuation phase of decolonization, patients were directed to apply 2% mupirocin ointment to the anterior nares twice per day and to apply tea tree oil bodywash once per day for the first 5 days of each of the next 5 calendar months. Although individuals' use of tea tree oil was not quantified, patients were encouraged to use the tea tree oil bodywash frequently, beyond the prescribed minimum, paying particular attention to cleansing of the axillae, groin, and perineum.

Tea tree oil is obtained by the steam distillation of the leaves of *Melaleuca alternifolia*, a tree native to Australia. It is a popular "natural" antiseptic with a variety of purported uses. Tea tree oil has a broad spectrum of antimicrobial activity and is active against MRSA.¹¹⁻¹³ Cutaneous and systemic toxicity appears to be minimal, and tea tree oil may be used on a long-term basis. There is minimal published evidence on the value of tea tree oil in medical settings; however, in one trial, a 5% tea tree oil body wash was more effective than chlorhexidine at clearing MRSA from superficial skin sites and skin lesions.¹⁴ In its guidelines for clinical management and control of community-acquired MRSA, the Wisconsin Division of Public Health suggests use of tea tree oil as a means of eradicating MRSA colonization.¹⁵

Interventions

Nursing homes. In May 2006, the point prevalence of MRSA colonization was determined by screening all residents at each of 5 local nursing homes. The body sites sampled for culture included the anterior nares, open skin lesions or ulcers, and exit sites of indwelling catheters. Residents with a positive culture result underwent decolonization, and their rooms were decontaminated according to established institutional terminal-cleaning protocols. Four weeks after the completion of the initial phase of decolonization, 3 separate samples for culture to determine whether MRSA colonization had been cleared (hereafter, "clearance cultures") were obtained at 1-week intervals from the nares and body sites that previously tested positive. To avoid obtaining culture samples during the course of mupirocin application, samples for clearance cul-

tures were not collected during the first calendar week of any month. Samples for follow-up cultures were obtained at months 6, 12, and 24 after the start of decolonization therapy. Residents who had treatment failure or a relapse of colonization were reevaluated and sometimes re-treated, at the discretion of the project director. Subsequent to May 2006, all individuals admitted to the nursing homes underwent active surveillance culture for MRSA and underwent decolonization if the culture result was positive. In May 2007, screening to determine the point prevalence of MRSA colonization at each nursing home was repeated.

Hospital. Beginning July 2006, "high-risk" patients admitted to the hospital underwent active surveillance cultures for MRSA; samples from the anterior nares and any cutaneous lesions were obtained. Patients were considered at high risk for MRSA colonization if they were aged greater than 65 years, had been hospitalized within the previous year, had any prior residence in a nursing home, had previously received any treatment in a wound clinic, had a skin ulcer or infection on admission, were undergoing hemodialysis, and/or were admitted to the intensive care unit. Approximately 50% of all patients admitted to the hospital fell into one of these high-risk categories.

A patient was considered to have clinical infection with MRSA if culture of a sputum, wound, urine, or blood specimen was positive for MRSA. Patients were defined as having nosocomial MRSA infection according to standard Centers for Disease Control and Prevention definitions¹⁶ and if an extensive review of their medical records indicated no other likely source for acquisition.

MRSA Clinic

To evaluate MRSA carriers identified in the hospital or other outpatient sources, an MRSA Clinic began operation in July 2006. Individuals with ongoing MRSA infections were not assigned to the clinic until their infection had resolved. Patients with a history of MRSA infection or carriage more than 2 months prior to their assignment were rescreened to re-establish their status as carriers and were considered "permanent" carriers. We did not further differentiate between transient and permanent MRSA carriers. Intimate household contacts of new ("index") clinic patients were screened, and, if a culture was positive for MRSA, they were decolonized concurrently with the index patient. Patients undergoing decolonization therapy were instructed to concurrently perform thorough environmental decontamination in their home with any commercial disinfectant that specified activity against "*Staphylococcus*." Samples for clearance and follow-up cultures were obtained according to the same protocol used in the nursing homes.

Additionally, beginning the second year of the project, in both the MRSA Clinic and the nursing homes, performance of "skin survey" cultures (of samples from the axillae and groin) was added to the performance of clearance cultures

TABLE 1. Prevalence of Asymptomatic Colonization with Methicillin-Resistant *Staphylococcus aureus* (MRSA) among Nursing Home Residents

Nursing home (size)	June 2006			June 2007			Decrease in prevalence of asymptomatic colonization from 2006 to 2007, %
	Point prevalence of MRSA positivity ^a	No. of residents with known previous MRSA positivity	Prevalence of asymptomatic colonization ^a	Point prevalence of MRSA positivity ^a	No. of residents with known previous MRSA positivity	Prevalence of asymptomatic colonization ^a	
A (52 beds)	8/50 (16.0)	0	8/50 (16.0)	1/49 (2.0)	0	1/49 (2.0)	88 ^b
B (88 beds)	15/82 (18.3)	2	13/80 (16.3)	5/79 (6.3)	2	3/77 (3.9)	76 ^b
C (148 beds)	7/137 (5.1)	0	7/137 (5.1)	6/140 (4.2)	2	4/138 (2.9)	43
D (320 beds)	40/303 (13.2)	10	30/293 (10.2)	13/257 (5.1)	2	11/255 (4.3)	58 ^b
E (150 beds)	34/139 (24.5)	12	22/127 (17.3)	9/136 (6.6)	2	7/134 (5.2)	70 ^b
Overall (<i>n</i> = 758 beds)	104/711 (14.6)	24	80/687 (11.6)	34/661 (5.1)	8	26/653 (4.0)	65 ^c

^a No. of residents who tested positive for MRSA / no. of residents screened.

^b $P \leq .05$.

^c $P < .001$ for comparison of 2007 with 2006.

and follow-up cultures. The “skin survey” culture was also performed for intimate household contacts of patients in the clinic but, because of resource limitations, was not included as part of active surveillance cultures in the hospital or in the nursing homes.

Laboratory Methods

Specimens were inoculated onto BBL CHROMagar MRSA medium (BD Diagnostics) and inspected 24 and 48 hours after the start of incubation for the presence of mauve-colored colonies indicative of MRSA, in accordance with the manufacturer’s guidelines. Results of this test were accepted as accurate, and no additional laboratory testing was undertaken to confirm the presence of MRSA. Antimicrobial susceptibility testing was not routinely performed on isolates from surveillance, clearance, or follow-up cultures.

MRSA isolates were stored for mupirocin susceptibility testing and pulsed-field electrophoresis (PFGE) analysis. For each patient for whom initial decolonization failed or who later had relapse after successful initial decolonization, the paired isolates from the baseline cultures and from the cultures performed to determine treatment failure and/or colonization relapse were tested for mupirocin susceptibility by means of the E-test (AB Biodisk) and were tested for strain-relatedness by PFGE using *Sma*I digests of DNA fragments, according to published guidelines.¹⁷ Strains that differed by fewer than 3 bands on PFGE were considered similar, and those differing by more than 3 bands were considered to be different.

Data Analysis

Patients with at least 1 positive or 2 negative clearance culture results were included in the analysis (only 7 patients had 2, rather than 3, negative clearance culture results). The outcome of MRSA decolonization was considered successful if there was a negative result for the most recently available clearance culture or for a follow-up culture performed more

than 12 months after initial decolonization for the nursing home cohort or for a follow-up culture performed more than 6 months after decolonization for the clinic cohort. Treatment failure was considered to have occurred if a clearance culture was positive for MRSA; colonization relapse was considered to have occurred if 3 clearance cultures were negative for MRSA but a follow-up culture performed 6, 12, or 24 months after decolonization therapy was positive.

Statistical Analysis

Statistical analysis was performed using InStat, version 3.0b (GraphPad). The proportions of nursing home residents colonized with MRSA in 2007 and in 2006 were compared by the Fisher exact test. The Student *t* test was used to compare data on reductions in the number of nosocomial MRSA infections.

RESULTS

Nursing Homes

The baseline prevalence of MRSA colonization (in 2006) at the 5 nursing homes was 12% (80 of 687 residents). After 12 months of active surveillance cultures and decolonization therapy, the prevalence of MRSA colonization decreased by 67%, to 4% (26 of 653 residents) (relative risk, 0.48 [95% confidence interval, 0.34–0.68]; $P < .001$ (Table 1). From June 2006 through July 2008, there were 147 nursing home residents who underwent decolonization therapy (Figure 1). Forty-eight residents whose most recently available clearance culture or 6-month follow-up culture was negative for MRSA were lost to follow-up by month 12 because of death or discharge. Including the residents who were lost to follow-up but whose most recent screening culture was negative, the residents who had treatment failure or relapse of colonization who were re-treated and whose colonization was cleared, and the residents whose 12-month follow-up culture was negative for MRSA, the overall rate of successful decolonization in the

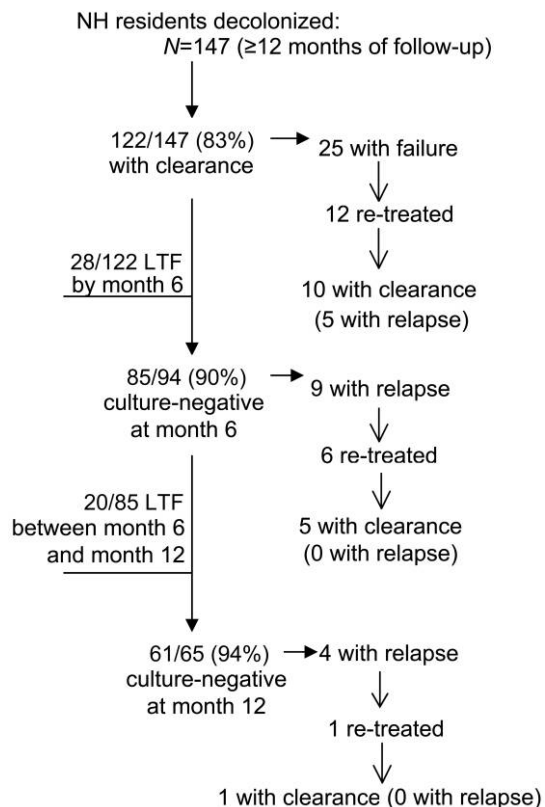


FIGURE 1. Results of the methicillin-resistant *Staphylococcus aureus* (MRSA) decolonization regimen among nursing home residents. Clearance of colonization was considered achieved if cultures of 3 separate samples obtained at 1-week intervals 1 month after the completion of the decolonization regimen (hereafter, “clearance cultures”) were negative for MRSA; failure of treatment was considered to have occurred if 1 clearance culture was positive for MRSA; relapse of colonization was considered to have occurred if there was initial clearance but a follow-up culture at month 6 or month 12 after the end of decolonization was positive for MRSA; Lost to follow-up (LTF) indicates a resident who died or was discharged whose most recent available surveillance culture was negative for MRSA.

nursing home cohort was 82% (120 of 147 residents) (Table 2). In addition, 27 of 28 surviving residents who were screened in 2006 had a negative follow-up culture result at 24 months.

Hospital

From July 2006 through June 2007 in the hospital, 93 (1.5%) of 6,232 “high risk” patients who had active surveillance cultures performed were identified as previously unknown MRSA carriers; these 93 patients represented 25% of all admitted patients who had MRSA detected during the year.

The incidence rate for the aggregate of nosocomial clinical MRSA infections (ie, pneumonia, bloodstream infection, urinary tract infection, and wound infection) declined from 0.64

infections per 1,000 patient-days in the year prior to project implementation (July 2005 through June 2006) to 0.40 infections per 1,000 patient-days in the year July 2006 through June 2007, and to 0.32 infections per 1,000 patient-days during the year July 2007 through June 2008 (for the comparison of the first period with the third period, $P < .01$).

MRSA Clinic

Among MRSA Clinic patients, the success rate for the initial course of decolonization therapy was 92% (115 of 125 patients) (Figure 2). Although the number of patients lost to follow-up was high, approximately 90% of those who returned for follow-up at both 6 months and 12 months remained negative for MRSA; at 12 months, the overall rate of decolonization success was 89% (111 of 125 patients) (Table 2). Screening of intimate contacts of index patients revealed 30 individuals asymptotically colonized with MRSA; these contacts were associated with 23 (24%) of the 95 index patients. There were 5 family clusters in which 2–3 household contacts were detected to be carriers.

Antimicrobial Susceptibility and PFGE Testing

Routine antibiotic susceptibility testing was not performed for isolates recovered from surveillance, clearance, or follow-up cultures. However, the annual hospital antibiogram has shown that, between 2000 and 2008, 96% or more of clinical MRSA isolates have retained susceptibility to tetracycline, and 97% or more have retained susceptibility to rifampin. The percentage of MRSA isolates with susceptibility to tetracycline increased from 96% in 2006 to 99% in 2008.

Paired MRSA isolates from patients who either had treatment failure or had relapse after initially successful decolonization were examined for the development of mupirocin resistance (38 isolates) and strain-relatedness (37 isolates). Baseline isolates from 5 patients exhibited low-level resistance to mupirocin (defined as a minimum inhibitory concentration of 8–256 $\mu\text{g}/\text{mL}$); the median minimum inhibitory concentration was 12 $\mu\text{g}/\text{mL}$, and the mean was 28 $\mu\text{g}/\text{mL}$. Apparent development of low-level resistance was seen in 2 isolates (5.2%) from patients for whom initial decolonization therapy failed; however, PFGE testing revealed these isolates to be different strains. High-level mupirocin resistance was not seen in any pair of isolates recovered from patients who had treatment failure or relapse of colonization. PFGE analysis revealed that a new, unrelated strain of MRSA was recovered from 7 (19%) of the 37 patients who had treatment failure or relapse of colonization (6 nursing home residents and 1 MRSA Clinic patient).

DISCUSSION

The aim of our quality improvement project was to attempt to curtail the rising prevalence of MRSA colonization and infection in our rural healthcare system. This is, to our knowledge, the first report of the comprehensive use of whole-body

TABLE 2. Overall Results at Month 12 of Follow-Up After Completion of the Initial Decolonization Regimen for Methicillin-Resistant *Staphylococcus aureus* (MRSA) among Nursing Home Residents and Patients at the MRSA Clinic

Setting	No. of subjects						
	Who underwent decolonization	With culture negative for MRSA at month 12	Lost to follow-up	With culture negative for MRSA at month 6 with pending	With failure who were re-treated and had clearance	With relapse who were re-treated and had clearance	Total no. of subjects with clearance (%)
Nursing home	147	61	48	0	5	6	120 (82)
MRSA Clinic	125	36	54	14	3	4	111 (89)
Total	272	86	105	25	8	10	231 (85)

NOTE. Clearance of colonization was considered achieved if cultures of 3 separate samples obtained at 1-week intervals 1 month after the completion of the decolonization regimen (hereafter, “clearance cultures”) were negative for MRSA; failure of treatment was considered to have occurred if 1 clearance culture was positive for MRSA; relapse of colonization was considered to have occurred if there was initial clearance but a follow-up culture at month 6 or month 12 after the end of decolonization was positive for MRSA; Lost to follow-up indicates a resident who died or was discharged whose most recent available surveillance culture was negative for MRSA.

MRSA decolonization therapy in a large, diverse population of patients across the continuum of care. Our comprehensive program, similar to the successful “search and destroy” protocols utilized in the Netherlands and Nordic countries, placed emphasis on patient education, on the screening of intimate contacts, and on the concurrency of decolonization among index patients, their intimate contacts, and on environmental decontamination.^{18,19}

The incidence of MRSA infection and colonization in US hospitals continues to increase at alarming rates.²⁰ As a result, many hospitals have adopted active surveillance culture protocols, either universally applied to all patients admitted or targeted at patients who are at high risk, in an attempt to identify MRSA colonization and implement contact precautions earlier during hospitalization. However, despite identification and isolation of MRSA carriers, the reservoir of MRSA remains and exerts colonization pressure that increases the risk of nosocomial cross-transmission.³ In addition, the implementation of active surveillance cultures and contact precautions alone is unlikely to lead to eradication of this established reservoir of endemic MRSA colonization, nor does it address the individual patient’s subsequent risk for the development of active infection related to colonization.⁴⁻⁷

The role of decolonization regimens as an infection control intervention to decrease this reservoir and decrease the rate of nosocomial transmission of MRSA remains controversial.²¹ However, more recent studies suggest that whole-body decolonization regimens may be beneficial. In a study similar to ours, Simor et al²² utilized a combination of oral doxycycline and rifampin therapy, nasal administration of mupirocin ointment, and body washing with 2% chlorhexidine gluconate to achieve a statistically significant rate of eradication of MRSA carriage among hospitalized patients at month 3 and month 8 of follow-up, and only 5% of MRSA isolates demonstrated emergence of mupirocin resistance. Ridenour et al²³ implemented decolonization therapy among all MRSA-colonized patients in a medical-coronary ICU in

which an active surveillance culture program was already in place. The number of incident cases of MRSA colonization or infection was reduced by 47.6%, suggesting an additional benefit of decolonization therapy beyond that seen with use of active surveillance cultures alone. In the nursing home setting, Kotilainen et al²⁴ and Harberg²⁵ used both topical therapy and systemic therapy, which eradicated MRSA in 83%

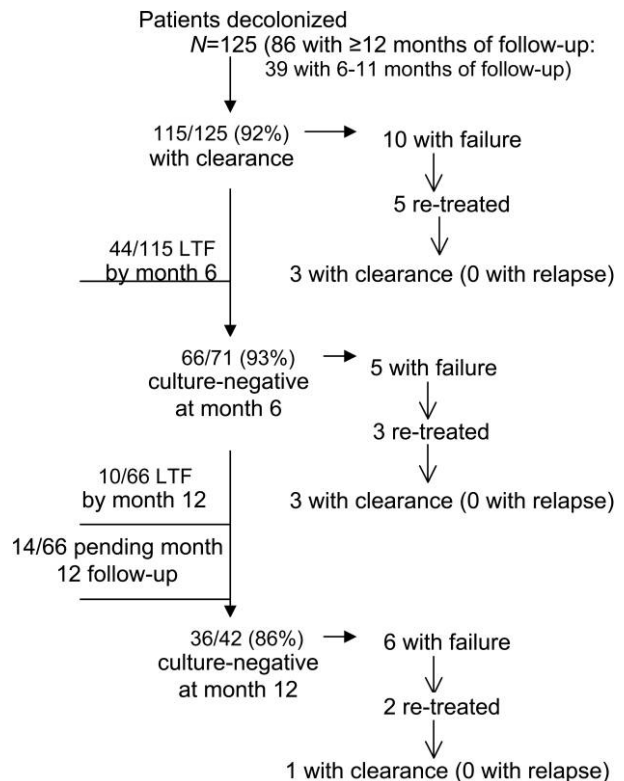


FIGURE 2. Results of the methicillin-resistant *Staphylococcus aureus* (MRSA) decolonization regimen among patients at the MRSA Clinic. Definitions are as in Figure 1.

and 70% of nursing home residents, respectively, at month 6 of follow-up.

Ours is the first report on the use of tea tree oil as a major component of a whole-body MRSA decolonization regimen. Although further, more rigorous studies of tea tree oil are needed, the frequent use of this skin antiseptic may be an important method for the maintenance of long-term MRSA decolonization, especially among patients with recurrent community-acquired MRSA infection, among whom extranasal colonization may play a significant role.²⁶ Because we believed it to be a critical component of our decolonization regimen, we encouraged patients to use the tea tree oil body wash on a frequent basis, beyond that prescribed in the protocol. The tea tree oil body wash was well tolerated; it is less irritating to the skin with prolonged use than chlorhexidine, and, indeed, only 2 patients developed a skin eruption likely caused by the body wash. Overall, our decolonization regimen was well tolerated with minimal adverse effects.

Similar to other investigators, we found that a significant percentage (24%) of new patients in the MRSA Clinic had an asymptotically colonized spouse or other intimate household contact.^{27,28} Failure to identify and concurrently decolonize these close contacts may be responsible for the high rates of colonization relapse seen in other studies. In addition, MRSA can persist for long periods on fomites (eg, faucet handles, doorknobs, and tabletops) in the home or hospital environment.²⁹ Recent data suggest that skin-fomite contact may be an important route of transmission and of recolonization after initially successful decolonization therapy, unless aggressive environmental decontamination is undertaken concurrently with medicinal decolonization.²⁶ Decolonization efforts must therefore include concurrent treatment of any MRSA-positive household contacts and concurrent decontamination of the home environment.

Limitations of our project include (1) the failure to detect and isolate carriers because active surveillance cultures were performed only for "high risk" patients admitted to the hospital, rather than for all patients admitted ("universal" surveillance); (2) the absence of ongoing hospital surveillance; and (3) the potential limited sensitivity of performing screening cultures only of specimens from the nares, open skin lesions, and device exit sites to identify patients colonized with MRSA. Screening by culture of throat swab specimens and specimens from other extranasal sites has been found to increase the sensitivity of detecting carriers of *Staphylococcus aureus* by 25%–50%, compared with culture of nares samples alone. This has been found also among nursing home residents; according to one report, one-third of MRSA-colonized residents would have been missed if screening cultures had been confined to nares samples alone.^{30–32} Although we did not quantify the effect of including the results of the "skin survey" cultures with the results of the clearance cultures and follow-up cultures, the number of false-negative findings of successful decolonization at month 6 and month 12 was likely

decreased. Nonetheless, it is possible that our approach failed to detect significant numbers of carriers in the hospital and the nursing homes. These missed carriers could account for a significant number of hospital-days or nursing home-days in which contact precautions were not in place for MRSA-colonized residents, which, through colonization pressure, could increase the risk of cross-transmission. A final limitation of our project is that it was conducted in a relatively small, geographically rural healthcare system, and our findings may not be generalizable to larger metropolitan areas with overlapping healthcare systems in which resource allocation and coordination would likely be more difficult.

In summary, our quality improvement project represents a potential model for control of MRSA in routine clinical practice and is the first report of the comprehensive use of whole-body decolonization therapy across the continuum of care. We were able to achieve sustained rates of MRSA eradication, and we decreased the incidence of nosocomial MRSA infection in our hospital through a comprehensive program of active surveillance culture, contact evaluation, and whole-body decolonization of MRSA-positive patients and their MRSA-positive contacts, in conjunction with concurrent environmental decontamination. Although further studies are needed to address the relative contribution and cost-effectiveness of each modality, successful control of the spread of MRSA will likely require a "bundle" approach that utilizes the concurrent application of these multiple components, as well as continued efforts to optimize adherence to established hand hygiene protocols.

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Potential conflicts of interest. All authors report no conflicts of interest relevant to this study.

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