Targeted Intranasal Mupirocin To Prevent Colonization and Infection by Community-Associated Methicillin-Resistant \textit{Staphylococcus aureus} Strains in Soldiers: a Cluster Randomized Controlled Trial\textsuperscript{v}

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Community-associated methicillin-resistant \textit{Staphylococcus aureus} (CA-MRSA) is an emerging pathogen that primarily manifests as uncomplicated skin and soft tissue infections. We conducted a cluster randomized, double-blind, placebo-controlled trial to determine whether targeted intranasal mupirocin therapy in CA-MRSA-colonized soldiers could prevent infection in the treated individual and prevent new colonization and infection within their study groups. We screened 3,447 soldiers comprising 14 training classes for CA-MRSA colonization from January to December 2005. Each training class was randomly assigned to either the mupirocin or placebo study group, and the participants identified as CA-MRSA colonized were treated with either mupirocin or placebo. All participants underwent repeat screening after 8 to 10 weeks and were monitored for 16 weeks for development of infection. Of 3,447 participants screened, 134 (3.9%) were initially colonized with CA-MRSA. Five of 65 (7.7%; 95% confidence interval [95% CI], 4.0% to 11.4%) placebo-treated participants and 7 of 66 (10.6%; 95% CI, 7.9% to 13.3%) mupirocin-treated participants developed infections; the difference in the infection rate of the placebo- and mupirocin-treated groups was −2.9% (95% CI, −7.5% to 1.7%). Of those not initially colonized with CA-MRSA, 63 of 1,459 (4.3%; 95% CI, 2.7% to 5.9%) of the placebo group and 56 of 1,607 (3.5%; 95% CI, 2.6% to 5.2%) of the mupirocin group developed infections; the difference in the infection rate of the placebo and mupirocin groups was 0.8% (95% CI, −1.0% to 2.7%). Of 3,447 participants, 3,066 (89%) were available for the second sampling and completed follow-up. New CA-MRSA colonization occurred in 24 of 1,459 (1.6%; 95% CI, 0.05% to 2.8%) of the placebo group participants and 23 of 1,607 (1.4%; 95% CI, 0.05% to 2.3%) of the mupirocin group participants; the difference in the infection rate of the placebo and mupirocin groups was 0.2% (95% CI, −1.3% to 1.7%). Despite CA-MRSA eradication in colonized participants, this study showed no decrease in infections in either the mupirocin-treated individuals or within their study group. Furthermore, CA-MRSA eradication did not prevent new colonization within the study group.

Once considered to be an unusual occurrence, infections with community-associated methicillin-resistant \textit{Staphylococcus aureus} (CA-MRSA) have become increasingly common, emerging as a growing public health concern (13, 20). The majority of CA-MRSA infections manifest as uncomplicated skin and soft tissue infections; however, severe infections resulting in considerable morbidity and mortality have been reported (4, 19, 20, 22, 34, 36). The scope of the problem with CA-MRSA continues to expand with infections occurring across a broad epidemiological spectrum that includes neonates (24) and professional athletes (26). Indeed, some groups, among whom soldiers are included, appear to be at increased risk (1, 3, 5, 6, 23, 33, 40, 53).

With mounting concern over CA-MRSA infections, many authors have displayed considerable interest in determining the best strategy to prevent CA-MRSA colonization and infection. Many have posited that the best method may be to identify and decolonize nasal carriers of CA-MRSA who appear at highest risk for infection (7, 10, 30, 32, 46, 47). Although other anatomical sites may be colonized, the anterior nares are the principal reservoir for \textit{S. aureus}, and nasal colonization is associated with an increased risk of subsequent infection with the endogenous strain (12, 28, 45, 47, 49, 51, 52). Similarly, in a prospective observational study, we found that nasal colonization with CA-MRSA strains was associated with a significantly increased risk of subsequent soft tissue infections (15).

Mupirocin is a topical antimicrobial agent that decolonizes \textit{S. aureus} from the anterior nares and reduces colonization at extranasal sites (14, 21, 42). The eradication of \textit{S. aureus} colonization with mupirocin in order to prevent infections has been studied in various populations and has been shown to be...
effective in some groups (32, 43). The efficacy of intranasal mupirocin targeted at CA-MRSA-colonized individuals to prevent subsequent infections has yet to be determined.

Topical mupirocin avoids the potential adverse effects of systemic antimicrobial agents and can be easily administered in a directly observed manner. The widespread use of mupirocin in a community is not without consequence, as its indiscriminate use may result in the development of mupirocin-resistant strains, especially among MRSA (9, 29, 37). Additionally, in our recent natural history study of CA-MRSA colonization, we noted no new colonization in participants who were already colonized with methicillin-susceptible *Staphylococcus aureus* (MSSA), suggesting that occupying the ecological niche with a less virulent strain may be salutary (15, 28). For these reasons, a strategy of blanket administration to at-risk populations to prevent infections may be unwise; instead, a targeted approach aimed at only CA-MRSA carriers who are at higher risk for infection may be the most prudent strategy. Reducing the number of CA-MRSA-colonized people in a population also carries the potential benefit of reducing new colonization and infection in those not currently colonized.

We conducted this cluster randomized, double-blind, placebo-controlled trial to determine whether targeted and rapidly administered intranasal mupirocin in CA-MRSA-colonized soldiers would reduce the risk of infection in the treated individual, prevent new colonization within the larger, noncolonized population with whom they have direct contact (their study group), and reduce the risk of infection within the study group.

**MATERIALS AND METHODS**

**Study design and participants.** This was a cluster randomized, double-blind, placebo-controlled trial approved by the Brooke Army Medical Center Institutional Review Board (C.2004.163) designed to determine whether selective CA-MRSA decolonization with mupirocin reduces infection in treated participants and prevents new colonization and infection within the treated individual’s study group. U.S. Army personnel enrolled in the Health Care Specialist Course from 10 January 2005 to 16 December 2005 were eligible for the trial. This course is a 16-week program that trains soldiers (both women and men) to become combat and prevents new colonization and infection within the treated individual's study group. The pharmacy randomized classes with block randomization defined CA-MRSA colonization as occurring in any study participant who was given. During the consent process, CA-MRSA-colonized participants were instructed and prevent new colonization and infection in those not currently colonized.

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**Statistical analysis and sample size.** This was a modified intent-to-treat analysis of all participants who completed follow-up. The null hypotheses were that eradication of CA-MRSA colonization will not prevent new soft tissue infections in mupirocin-treated participants and will not prevent new colonization or infection within their study group. Based on the natural history study conducted in this population, we anticipated a CA-MRSA prevalence of 3.0% and an infection rate of 38% in colonized carriers (15). We calculated that 42 CA-MRSA-colonized participants were needed in each group to detect a reduction in infection rate from 38% to 10%. According to this estimate, at least 1,400 participants per group (2,800 total) would be needed to detect this decrease with a level of confidence of 95% and a power of 80% assuming an intracluster correlation coefficient of 0.0. The intracluster correlation coefficient describes the correlation among subjects within a training class (18). We estimated an overall infection rate within the entire study sample of 3.57% (15). According to this estimate, we calculated that at least 1,094 participants per group (2,188 total) would be needed to detect a 2% decrease (to 1.57%) with a level of confidence of 95% and a power of 80% assuming an intracluster correlation coefficient of 0.0. The intracluster correlation coefficient describes the correlation among subjects within a training class (18). We estimated an overall infection rate within the entire study sample of 1.6% (15). Based on this estimate, we calculated that at least 1,529 participants per group (3,058 total) would be needed to detect a decrease to 0.005% with a significance level of 0.05 and a power of 80%. Based on an anticipated average class size of 250 soldiers, we estimated that 14 classes would be needed for the investigation. Proportions (culture results and infection rates) were compared, accounting for correlation within classes, following the method given by Fleiss et al. (18). We used SPSS statistical software, version 14.0 (SPSS, Chicago, IL) and SAS software (SAS Institute, Cary, NC) for our analyses.

**RESULTS**

**Population characteristics.** Of the 4,003 soldiers eligible for the study, 3,447 (86.1%) volunteered to participate and 556 declined. Seven classes (1,669 participants) were randomized...
to the placebo-treated group, and seven classes (1,778 participants) were randomized to the mupirocin-treated group (Fig. 1). Overall, at the initial anterior nares culture, 134 participants (3.9%) were colonized with CA-MRSA, 1,316 participants (38.2%) were colonized with MSSA, and 1,997 participants (57.9%) did not have *S. aureus* recovered on screening culture. Initial colonization with CA-MRSA was noted in 66 of 1,669 participants (4.0%) in the placebo group and 68 of 1,778 participants (3.8%) in the mupirocin group. Of the 134 CA-MRSA-colonized participants initially identified, 62 were treated with placebo and 64 were treated with mupirocin (Fig. 2). These treated CA-MRSA-colonized participants are hereafter referred to as placebo-treated or mupirocin-treated participants. Four CA-MRSA-colonized participants (three from the same class and one from another class) from the placebo group declined treatment, and four CA-MRSA-colonized participants (three from the same class and one from another class) from the mupirocin group declined treatment. All of those who declined were men.

Demographic data for the two study groups (Table 1) and for the placebo-treated and the mupirocin-treated CA-MRSA-colonized participants are shown in the tables (Table 2). Placebo-treated and mupirocin-treated participants received their first dose on average 42 h after the initial anterior nares culture (range, 33 to 81 h). In the placebo-treated participants, 99.5% of possible doses were given, and in the mupirocin-treated participants, 99.2% possible doses were administered. One placebo-treated participant missed two doses, and two mupirocin-treated participants missed two doses. Medication doses were missed due to intervening military training requirements. All treated CA-MRSA-colonized participants completed the 16-week follow-up.

**Infections.** During the 16-week follow-up, 5 of 65 (7.7%; 95% confidence interval [95% CI], 4.0% to 11.4%) placebo-treated and 7 of 66 (10.6%; 95% CI, 7.9% to 13.3%) mupirocin-treated participants developed infections (Table 3). The estimated intraclass correlation coefficients for placebo- and mupirocin-treated groups were −0.034 and −0.057, respectively. The difference in the infection rate for the placebo and mupirocin groups was 2.9% (95% CI, 7.5% to 1.7%). None of the eight CA-MRSA-colonized participants who declined treatment with either placebo or mupirocin developed an infection. Overall, 119 of 3,066 (3.9%; 95% CI, 3.2% to 4.6%) study participants developed infections during the 16-week follow-up period: 63 of 1,459 (4.3%; 95% CI, 3.2% to 4.6%) placebo-treated and 56 of 1,607 (3.5%; 95% CI, 2.6% to 5.2%) in the mupirocin group (Table 4). The estimated intraclass correlation coefficients for the placebo and mupirocin groups were 0.006 and 0.0001, respectively. The difference in infection rate for the placebo and mupirocin groups was 0.8% (95% CI, −1.0% to 2.7%). Based on initial nares culture results, 22 of 548 (4.0%; 95% CI, 2.8% to 5.3%) MSSA-colonized participants declined treatment.
nized participants in the placebo group and 20 of 645 (3.1%; 95% CI, 1.7% to 4.5%) in the mupirocin group developed skin and soft tissue infections; the difference in the infection rate of placebo and mupirocin group was 0.9% (95% CI, 0.9% to 2.8%). The estimated intraclass correlation coefficients were 0.0052 and 0.0009 for the placebo group and mupirocin group, respectively.

In the participants for whom no S. aureus was recovered, 36 of 846 (4.3%; 95% CI, 2.3% to 6.2%) in the placebo group and 29 of 896 (3.2%; 95% CI, 2.6% to 3.9%) in the mupirocin group developed skin and soft tissue infections; the difference in the infection rate of the placebo and mupirocin groups was 1.1% (95% CI, −1.0% to 3.1%). The estimated intraclass correlation coefficients were 0.0081 and −0.005 for the placebo group and mupirocin group, respectively. There were no bacteremias detected in either group.

**TABLE 1. Characteristics of the 3,447 study participants by assigned study group**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value for group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Both (overall)</td>
</tr>
<tr>
<td>No. of study classes</td>
<td>14</td>
</tr>
<tr>
<td>Mean class size (range)</td>
<td>246 (124–373)</td>
</tr>
<tr>
<td>Mean age (yr) (SD)</td>
<td>22.6 (5)</td>
</tr>
</tbody>
</table>

**Gender**

|                               | Placebo (n = 1,669) | Mupirocin (n = 1,778) |
| No. of males (%)              | 2,493 (72.3)        | 1,262 (75.6)          |
| No. of females (%)            | 954 (27.7)          | 407 (24.4)            |

*a The percentages may not total 100 due to rounding. See Materials and Methods for the differences noted between the study groups.

**TABLE 2. Characteristics of the treated participants**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo (n = 62)</th>
<th>Mupirocin (n = 64)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (yr) (SD)</td>
<td>21.3 (3.3)</td>
<td>21.6 (4.2)</td>
</tr>
</tbody>
</table>

**Gender**

|                               | Placebo (n = 62) | Mupirocin (n = 64) |
| No. of males (%)              | 45 (72.6)       | 39 (60.9)          |
| No. of females (%)            | 17 (27.4)       | 25 (39.1)          |

<table>
<thead>
<tr>
<th>First drug administration (h) (range)</th>
<th>Placebo (n = 62)</th>
<th>Mupirocin (n = 64)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Possible no. of doses delivered (%)</td>
<td>617/620 (99.5)</td>
<td>635/640 (99.2)</td>
</tr>
</tbody>
</table>

*Data for the 62 of 65 placebo-treated participants and 64 of 66 mupirocin-treated participants included in the analysis who actually received treatment.

Ten possible doses of study medication per participant. See Materials and Methods for the dosing regimen.
TABLE 3. Infections in treated participants

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value for group</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of participants completing follow-up(^a)</td>
<td>65</td>
</tr>
<tr>
<td>No. of infections/no. of participants (%)(^b)</td>
<td>5/65 (7.7)</td>
</tr>
<tr>
<td>Total abscesses</td>
<td>4</td>
</tr>
<tr>
<td>CA-MRSA abscess</td>
<td>2</td>
</tr>
<tr>
<td>MSSA abscess</td>
<td>0</td>
</tr>
<tr>
<td>Abscess not cultured(^c)</td>
<td>2</td>
</tr>
<tr>
<td>Folliculitis</td>
<td>0</td>
</tr>
<tr>
<td>Cellulitis</td>
<td>1</td>
</tr>
</tbody>
</table>

| No. of hospital admissions            | 0               |

\(^a\) Participants who were assigned to the placebo-treated or mupirocin-treated group who completed follow-up and were included in the analysis.
\(^b\) Data based on infections identified during the 16-week follow-up period.
\(^c\) Describes an abscess that was incised and drained but no specimen was sent for bacterial culture.

action, military reassignment, and personal emergencies. Those who did not complete the study were excluded from the analysis. The initial colonization results and demographic characteristics (age and gender) of those who completed the study and those who did not complete the study did not differ. Three CA-MRSA-colonized participants, one in the placebo group and two in the mupirocin group, left the course prematurely and did not have a final nares culture. Thus, for the colonization analysis, data from 131 (65 placebo-treated and 66 mupirocin-treated) participants of the 134 (97.8%) initially CA-MRSA-colonized participants were available and included in the analysis. At the 8- to 10-week follow-up anterior nares culture, CA-MRSA colonization decreased from 4.0% (95% CI, 1.1% to 6.9%) to 3.2% (95% CI, 1.0% to 5.5%) in the placebo group; the estimated intraclass correlation coefficients in the placebo and mupirocin groups were 0.035 and 0.032, respectively (Table 5). In the mupirocin group, CA-MRSA colonization decreased from 3.8% (95% CI, 1.9% to 5.7%) to 1.9% (95% CI, 1.1% to 2.8%); the estimated intraclass correlation coefficients in the placebo and mupirocin groups were 0.012 and 0.002, respectively. In CA-MRSA-colonized participants in the placebo group, CA-MRSA colonization was eliminated in 42 of 65 (64.6%; 95% CI, 52.5% to 75.1%). In CA-MRSA-colonized participants in the mupirocin group, colonization was eliminated in 58 of 66 participants (87.9%; 95% CI, 77.9% to 93.7%). In the placebo-treated group, new colonization was noted in 24 of 1,459 participants (1.6%; 95% CI, 0.5% to 2.8%). The estimated intraclass correlation coefficient was 0.01. Among these 24 participants, 8 had previously been colonized with MSSA and 16 had previously been colonized but S. aureus had not been recovered. In the mupirocin-treated group, new colonization was noted in 23 of 1,607 (1.4%; 95% CI, 0.05% to 2.3%). The estimated intraclass correlation coefficient was 0.006. Among the 23 participants who were newly colonized with CA-MRSA, 7 had previously been colonized with MSSA and 16 had previously been colonized but S. aureus had not been recovered. The difference in new CA-MRSA colonization rate for the placebo and mupirocin groups was 0.2% (95% CI, 1.3% to 1.7%). At the follow-up anterior nares culture, MSSA colonization in the entire study population (placebo and mupirocin groups combined) decreased from 38.2% to 30.2%.

During the study period, a total of 13 CA-MRSA-colonized participants also received trimethoprim-sulfamethoxazole (TMP-SMX), a drug that was active against all colonizing strains. Seven placebo-treated participants received TMP-SMX for soft tissue infections (four participants) or urinary tract infections (UTIs) (three participants). Only one of these seven had a positive CA-MRSA screening culture at the second sampling. Likewise, six mupirocin-treated participants received TMP-SMX for soft tissue infections (three participants) or UTIs (three participants), all of whom had a negative CA-MRSA screening culture at the second sampling.

The difference in the number of infections for the placebo and mupirocin groups was 0.8% (95% CI, 1.1% to 6.9%) to 3.2% (95% CI, 1.0% to 5.5%) in the placebo and mupirocin groups, respectively (Table 5). In the mupirocin group, CA-MRSA colonization decreased from 3.8% (95% CI, 1.9% to 5.7%) to 1.9% (95% CI, 1.1% to 2.8%); the estimated intraclass correlation coefficients in the placebo and mupirocin groups were 0.012 and 0.002, respectively. In CA-MRSA-colonized participants in the placebo group, CA-MRSA colonization was eliminated in 42 of 65 (64.6%; 95% CI, 52.5% to 75.1%). In CA-MRSA-colonized participants in the mupirocin group, colonization was eliminated in 58 of 66 participants (87.9%; 95% CI, 77.9% to 93.7%).

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Molecular analysis and mupirocin resistance. The predominant colonizing PFT in our study was USA 300 (54% of CA-MRSA colonizing isolates [34 of 66 in the placebo-treated group and 38 of 68 in the mupirocin-treated group]), and the second most common was USA 800 (40% of CA-MRSA colonizing isolates). Only one of the 134 colonizing isolates was PFT USA 100. Of the 31 study participants who were CA-MRSA colonized at both the initial and terminal culture, all but 2 participants remained colonized with the identical strain. The two participants colonized with different strains had received no antimicrobial therapy and had had no hospital exposure. All CA-MRSA-colonized participants who developed soft tissue abscesses were infected with their original colonizing strain.

No mupirocin resistance was detected by disk diffusion in the 199 CA-MRSA isolates tested (165 colonizing isolates and 34 abscess isolates).

Of the 62 placebo-treated participants, 20 (32.3%) noted at least one adverse effect, and of the 64 mupirocin-treated participants, 9 (14.1%) noted at least one adverse effect. The primary adverse effect was rhinorrea. No adverse effects that were deemed significant were noted in either treated group.

DISCUSSION

In this cluster randomized, double-blind, placebo-controlled trial of mupirocin-based intranasal decolonization of CA-MRSA-colonized soldiers, we found that despite intranasal decolonization, there was no decrease in the incidence of soft tissue infection in either the mupirocin-treated participants or within the mupirocin-treated study group. Additionally, treatment with mupirocin did not reduce new CA-MRSA colonization within the mupirocin study group.

Our study is unique because it is the first mupirocin-based eradication effort aimed at affecting CA-MRSA colonization and infection in a general population. The majority of mupirocin-based intervention studies have focused on preventing nosocomial infections or infections in patients undergoing dialysis (32, 43). Previous studies of intranasal mupirocin have shown benefit only in the subset of patients with S. aureus colonization (7, 39, 42). For example, Perl et al. showed a decrease from 7.7% to 4% in postoperative wound infections in patients who were colonized with S. aureus (42). Our investigation did not show a similar benefit in individual participants colonized with CA-MRSA, and there did not appear to be an impact on the study group. Several recently conducted trials demonstrated similar results, showing no benefit for either orthopedic patients (25) or nonsurgical patients (50).

There were significantly fewer infections in the placebo-treated group than we had anticipated despite the fact that CA-MRSA prevalence was similar to our previous study conducted in this population (15). The infection rate of 7.7% in the placebo-treated participants was considerably lower than the rate of 38% noted in our natural history study (15). This is the study's principal limitation. There are several possible reasons why we observed fewer infections. First, during the consent process, CA-MRSA-colonized participants were informed of their colonization status and educated about their possible increased risk for skin and soft tissue infections. Despite being blind to their treatment, it is possible that with their awareness of CA-MRSA colonization and the education provided by investigating physicians that participants may have altered personal hygiene practices in a manner that affected both colonization and subsequent infections. Additionally, the study group consisted of combat medic trainees, a group of individuals whose training includes the basic management of skin infections. It is possible that they used the information given in the study introduction and their training to institute hygiene changes or other interventions on their own that altered the measured outcomes. Another possibility is that the overall virulence of the colonizing strains in this study was somehow different. Evidence of this has been demonstrated in recent investigations that showed that PFT USA 300 is the principal cause of suppurative soft tissue infections in some urban areas and university-affiliated emergency departments (27, 38). In our study, PFT USA 300 represented only 54% of the initial isolates colonizing the anterior nares, although there was no difference in the number of PFT USA 300-colonized participants between both treatment groups. Further investigation using molecular techniques assessing virulence factors may further clarify reasons for this observation.

The point prevalence of CA-MRSA colonization at the initial anterior nares culture was 3.9%, similar to the 3.0% in our previous investigation in this population (15). This finding is considerably higher than a recent report that noted a national MRSA prevalence of 0.8% for the years 2001 and 2002; however, the authors of that study suggest that their work might underestimate the current MRSA prevalence (30). At the 8- to 10-week follow-up anterior nares culture, CA-MRSA colonization in the mupirocin-treated group decreased from 3.8% to 1.9%. In the placebo-treated group, CA-MRSA colonization decreased from 4.0% to 3.2% over the study period. Interestingly, in the initially CA-MRSA-colonized participants in the placebo group, only 23 of the 65 remained colonized at the terminal sampling. The seven CA-MRSA-colonized participants who received TMP-SMX (four for soft tissue infection and three for UTI) during the study period do not account for this reduction. There are several possible explanations for this decrease. The subjects' awareness of their CA-MRSA colonization status may have encouraged other hygiene interventions. It may be that overall personal hygiene improved after the earlier basic training environment and affected colonization overall (28). This notion is supported by the fact that during this investigation we observed a decrease in MSSA colonization from 38.2% to 30.2%, mirroring the decrease in CA-MRSA colonization. Likewise, in our prior investigation in this study population, we noted a similar decrease in MSSA colonization from 28% to 20% (15). Additionally, less crowding and fewer skin abrasions than probably occurred during the earlier basic training experience may also have had some impact (28, 31, 53). Some of the CA-MRSA-colonized participants whom we identified may have only been intermittent carriers, as S. aureus carriage is itself a dynamic process (28, 51). Weekly cultures of the anterior nares may have helped to describe the natural history of the carrier state in our study population; however, we were limited by military training requirements to the number of cultures that could be done (41). Likewise, the intermittent carrier state could account for the similar rates of new CA-MRSA-colonized participants in both study groups, as these too might have been intermittent carriers. The remark-
ably similar rates of new CA-MRSA colonization in each study group (1.6% versus 1.4%) suggests a consistent epidemiological dynamic which we were unable to assess with only two samplings.

Although known to compete for the same ecological niche (11, 47), new CA-MRSA colonization detected at the second sampling was not prevented by MSSA colonization at the initial anterior nares culture. Those who had been colonized with MSSA at the outset of the study developed CA-MRSA colonization at a rate that was not different from those who had had no S. aureus recovered on the initial culture.

This investigation benefited from several strengths. First, because we used a selective culture medium, we were able to rapidly identify CA-MRSA-colonized participants and begin eradication therapy within 2 days of the soldiers arriving for their training. This minimized the time available for noncolonized participants to become colonized. Second, our study population is comprised of healthy soldiers drawn from all over the country and who are also free of the confounder of prior health care exposure. Third, the level of compliance and the number of participants who were available to be followed rivals that of an inpatient interventional study. We were able to directly administer the study medication to these participants in an outpatient setting achieving a greater than 99% compliance with therapy. A full 89% of the study participants were monitored throughout the study period. Those who did not complete follow-up were physically unavailable, and they did not differ from those who completed the study; it is unlikely that these participants altered the study outcomes. Last, all of the study participants received care from a single medical institution, Brooke Army Medical Center, to include outpatient clinic, urgent care, emergency room, and inpatient encounters, thereby maximizing the capture of all pertinent clinical and microbiological data.

Our study has other limitations. First, additional anterior nares cultures would have helped to better describe the persistent colonization state and the epidemiological dynamic of CA-MRSA within our study population, but this was not possible for the reasons indicated above. Second, we were unable to assess carriage at extranasal sites. Such sites, especially the hands, pharynx, and perineum, can harbor S. aureus, and intranasal mupirocin has been shown to have sometimes failed in decolonizing these anatomic sites (47, 48). Intranasal colonization may sometimes be absent, even in outbreak settings (26). Last, we did not determine the colonization status of the training cadre who interact daily with the participants, and we did not determine whether these cadre developed infections. These people outside of our study may have served as a reservoir for new CA-MRSA colonization and somehow impacted our results.

We detected no mupirocin resistance in any colonizing or clinical CA-MRSA isolate. This finding is consistent with those of other short-term mupirocin intervention trials, suggesting that limited application does not select for resistance (42, 50).

In conclusion, this study showed no benefit of targeted, mupirocin-based CA-MRSA eradication in colonized participants or in their larger group. Despite intranasal eradication in CA-MRSA-colonized participants, there was no decrease in infections in the mupirocin-treated individuals or in their study group. CA-MRSA eradication did not prevent new colonization within the study group. Our data suggest that effective prevention strategies against CA-MRSA in at-risk populations may require broader and more elaborate interventions than simple 5-day intranasal mupirocin.

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