

# Comparison of Community- and Health Care–Associated Methicillin-Resistant *Staphylococcus aureus* Infection

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**M**ETHICILLIN-RESISTANT *Staphylococcus aureus* (MRSA) was identified as a nosocomial pathogen in the 1960s.<sup>1-4</sup> Established risk factors for MRSA infection include recent hospitalization or surgery, residence in a long-term care facility, dialysis, and indwelling percutaneous medical devices and catheters.<sup>5,6</sup> More recently, however, cases of MRSA have been documented among healthy community-dwelling persons without established risk factors for MRSA acquisition. These infections were apparently acquired in the community and have been referred to as either *community-acquired* or *community-associated* MRSA infections. Published reports of community-associated MRSA infections in North America include Minnesota and North Dakota,<sup>7-9</sup> Nebraska,<sup>10</sup> Alaska,<sup>11</sup> Chicago, Ill,<sup>12-14</sup> Dallas, Tex,<sup>15,16</sup> Winnipeg, Manitoba,<sup>17</sup>

**Context** Methicillin-resistant *Staphylococcus aureus* (MRSA) has traditionally been considered a health care–associated pathogen in patients with established risk factors. However, MRSA has emerged in patients without established risk factors (community-associated MRSA).

**Objective** To characterize epidemiological and microbiological characteristics of community-associated MRSA cases compared with health care–associated MRSA cases.

**Design, Setting, and Patients** Prospective cohort study of patients with MRSA infection identified at 12 Minnesota laboratory facilities from January 1 through December 31, 2000, comparing community-associated (median age, 23 years) with health care–associated (median age, 68 years) MRSA cases.

**Main Outcome Measures** Clinical infections associated with either community-associated or health care–associated MRSA, microbiological characteristics of the MRSA isolates including susceptibility testing, pulsed-field gel electrophoresis, and staphylococcal exotoxin gene testing.

**Results** Of 1100 MRSA infections, 131 (12%) were community-associated and 937 (85%) were health care–associated; 32 (3%) could not be classified due to lack of information. Skin and soft tissue infections were more common among community-associated cases (75%) than among health care–associated cases (37%) (odds ratio [OR], 4.25; 95% confidence interval [CI], 2.97-5.90). Although community-associated MRSA isolates were more likely to be susceptible to 4 antimicrobial classes (adjusted OR, 2.44; 95% CI, 1.35-3.86), most community-associated infections were initially treated with antimicrobials to which the isolate was nonsusceptible. Community-associated isolates were also more likely to belong to 1 of 2 pulsed-field gel electrophoresis clonal groups in both univariate and multivariate analysis. Community-associated isolates typically possessed different exotoxin gene profiles (eg, Panton Valentine leukocidin genes) compared with health care–associated isolates.

**Conclusions** Community-associated and health care–associated MRSA cases differ demographically and clinically, and their respective isolates are microbiologically distinct. This suggests that most community-associated MRSA strains did not originate in health care settings, and that their microbiological features may have contributed to their emergence in the community. Clinicians should be aware that therapy with  $\beta$ -lactam antimicrobials can no longer be relied on as the sole empiric therapy for severely ill outpatients whose infections may be staphylococcal in origin.

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The epidemiology of community-associated MRSA has not been fully described. Furthermore, there are limited data comparing community-associated with health care-associated MRSA cases, and no studies from multiple geographic locations. Finally, there has been no systematic comparison of the molecular characteristics (eg, exotoxin gene profiles) of community and health care isolates in the United States. Such genetic information could improve understanding of the pathogenesis of different MRSA strains, and could ultimately help shape strategies for the prevention and treatment of MRSA infections both in the hospital and in the community.

To better characterize MRSA in Minnesota, the Minnesota Department of Health established a sentinel surveillance network of 12 laboratory facilities in 1999. In 2000, the Minnesota Department of Health began a prospective study of all MRSA infections identified at these facilities. The objectives of this study were to characterize demographic and clinical features of patients with community-associated and health care-associated MRSA, and to characterize the microbiological and molecular features of community-associated and health care-associated MRSA isolates.

## METHODS

### Facility Enrollment

Twelve laboratory facilities were selected as MRSA surveillance sites. They were selected to be diverse in terms of their location, size, and facility type. Six of the 12 participating facilities were located in the 7-county Minneapolis-St Paul metropolitan area and 6 were located in nonmetropolitan Minnesota. All laboratories served both outpatient clinic networks and hospital inpatients. Ten facilities served both adult and pediatric patients and the remaining 2 served pediatric patients exclusively.

### Case Ascertainment and Case Definitions

In 2000, participating laboratory facilities identified all patients with MRSA

isolates from clinical cultures. Infection-control practitioners at those facilities obtained additional information about the patients and their infections via medical record review. For community-associated MRSA cases, clinical information about underlying chronic conditions was obtained (this information was not collected for health care-associated MRSA cases). A surrogate for median household income was estimated using US Census data. Community-associated and health care-associated MRSA cases were assigned median household incomes based on the 2000 US Census for their respective ZIP code of residence.

*Health care-associated MRSA* cases were defined as patients with (1) an MRSA infection identified after 48 hours of admission to a hospital; (2) a history of hospitalization, surgery, dialysis, or residence in a long-term care facility within 1 year of the MRSA culture date; (3) a permanent indwelling catheter or percutaneous medical device (eg, tracheostomy tube, gastrostomy tube, or Foley catheter) present at the time of culture; or (4) a known positive culture for MRSA prior to the study period. Cases that had none of the above features were classified as *community-associated*. Because the community-associated case definition depended on the absence of health care-related risk factors, patients who appeared to have community-associated infections on the basis of medical record review were also interviewed to ensure that they did not have any exclusion criteria that were not documented in their medical records. Overall, 13% of patients who appeared to have community-associated MRSA infections on the basis of medical record review were reclassified as health care-associated after being interviewed.

This study was approved by the institutional review boards of both the Minnesota Department of Health and the Centers for Disease Control and Prevention. Medical record reviews were conducted in accordance with Minnesota public health law, and informed consent was obtained for all those who were interviewed.

### Laboratory Methods

Sentinel facility laboratories sent all MRSA isolates identified from January 1, 2000, through December 31, 2000, to the Minnesota Department of Health laboratory. All available community-associated isolates and a sample of health care-associated isolates (every fourth isolate received per facility) were evaluated using antimicrobial susceptibility testing and pulsed-field gel electrophoresis (PFGE) subtyping. Laboratory staff were unaware of the epidemiological case classification of the isolates.

Identification of *S aureus* was confirmed with a tube coagulase test (Difco Laboratories, Detroit, Mich). Oxacillin (methicillin) resistance was confirmed using an oxacillin agar screen test (Becton Dickinson, Cockeysville, Md); susceptibility interpretations for other antimicrobials were made using broth microdilution (PML Microbiologicals, Wilsonville, Ore) according to break points established by the National Committee for Clinical Laboratory Standards.<sup>20,21</sup> Molecular typing of isolates was performed by PFGE using *Sma*I as a restriction endonuclease. The PFGE patterns were compared using the Dice coefficient (Bionumerics Software, Applied Maths, Kortrijk, Belgium). Patterns that had exact matches of all bands in the range of 70 to 700 kilobases were considered indistinguishable. Isolates of MRSA that differed from a reference strain (MR14, the most common community-associated strain) by 6 bands or fewer were characterized as belonging to a single clonal group.<sup>22</sup> Polymerase chain reaction testing was performed to confirm the presence of the *mecA* gene.<sup>23</sup>

Additionally, 26 community-associated MRSA and 26 health care-associated MRSA isolates were sent to the French Reference Centre for Staphylococci. These isolates were selected by alphabetizing the list of case isolates in each group, then choosing every fourth community-associated MRSA isolate and every ninth health care-associated MRSA isolate. The isolates sent for gene testing were representative of the larger group of isolates from which they

**Table 1.** Facility Characteristics and *Staphylococcus aureus* Infections by Case Status\*

Facility Description	Total <i>S aureus</i> Cases	No. (%) of Total MRSA Cases†	No. (%) of MRSA Cases‡	
			Community-Associated	Health Care-Associated
<b>Total</b>	<b>4612§</b>	<b>1100</b>	<b>131 (12)</b>	<b>937 (85)</b>
<b>Metropolitan  </b>				
Public				
Urban	NA	123 (NA)	9 (7)	109 (89)
Private				
Urban	470	144 (31)	6 (4)	138 (96)
Suburban	867	228 (26)	19 (8)	206 (90)
Suburban	NA	161 (NA)	8 (5)	137 (85)
Pediatric				
Urban	431	62 (14)	19 (31)	41 (66)
Urban	144	18 (13)	9 (50)	9 (50)
<b>Nonmetropolitan</b>				
Regional				
Community	907	104 (11)	9 (9)	93 (89)
Private	1044	103 (10)	26 (25)	74 (72)
Community				
Private	204	38 (19)	5 (13)	33 (87)
Private	192	24 (13)	3 (13)	21 (88)
Private	131	64 (49)	10 (16)	53 (83)
Private	222	31 (14)	8 (26)	23 (74)

Abbreviations: MRSA, methicillin-resistant *Staphylococcus aureus*; NA, not available.

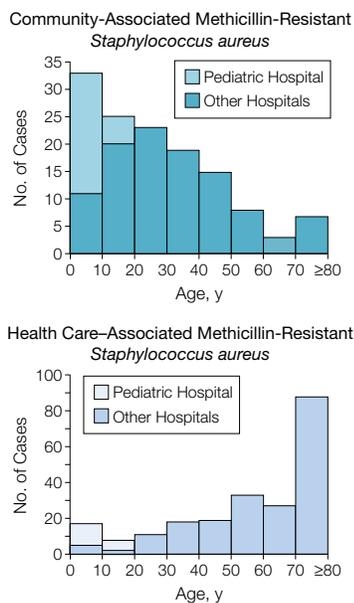
\*All numbers represent individual patients.

†Thirty-two (3%) of infections could not be classified due to lack of information. The percentage refers to the proportion of all *S aureus* that were MRSA.

‡In several places, the percentages of community-associated plus health care-associated do not total to 100%.

§Does not include *S aureus* cases from 2 hospitals in which the total number of cultures was not available.

||Refers to the 7-county Minneapolis-St Paul, Minn, area.

**Figure 1.** Age Distribution of Community-Associated and Health Care-Associated Methicillin-Resistant *Staphylococcus aureus* Cases

were selected (eg, there were no statistically significant differences in terms of case sex, age, race, or infection site). Investigators from the Reference Centre were blinded regarding the epidemiological case classification of the isolates. Sequences specific for a variety of staphylococcal enterotoxin genes, the toxic shock syndrome toxin gene, exfoliative toxin genes, Panton Valentine leukocidin genes, the leukocidin E-D gene, the leukocidin M gene,  $\beta$  and  $\gamma$  hemolysin genes, methicillin-resistance (*SCCmec*) gene alleles and accessory gene regulator alleles were detected by polymerase chain reaction as previously described.<sup>24-26</sup> Toxin results of a portion of the community-associated MRSA isolates have been previously characterized<sup>27</sup>; however, a direct comparison of community-associated MRSA and health care-associated MRSA isolates obtained from the 12 sentinel sites in 2000 has not been reported previously and is reported herein using similar laboratory methods.<sup>27</sup>

## Statistical Methods

Bivariate analysis of data was performed using Epi Info statistical software (Version 6.04c, Centers for Disease Control and Prevention, Atlanta, Ga). The Yates continuity-corrected  $\chi^2$  test was examined for comparison of categorical data and the *t* test was used for continuous data. Unconditional logistic regression models were used to predict case definition (community-associated vs health care-associated). An  $\alpha = .05$  significance level was required for predictors to remain in the model. Results were computed using SAS statistical software (Version 8.0, SAS Institute Inc, Cary, NC). Because of the high incidence (>10%) of outcome measures, odds ratios (ORs) and 95% confidence intervals (CIs) were corrected to approximate relative risk using methods previously described.<sup>28</sup>

## RESULTS

During 2000, 4612 unique patients with a *S aureus* isolate from a clinical culture were identified from 10 participating facilities (data on total *S aureus* infections were not available at 2 facilities) (TABLE 1). Approximately 25% of all *S aureus* infections were MRSA (range among sites, 10%-49%). Among MRSA infections, 12% (131) MRSA cases were classified as community-associated, 85% (937) were classified as health care-associated, and 3% (32) could not be classified due to lack of information. Among the sites, the proportion of MRSA cases that were community-associated ranged from 4% to 50%. Of the community-associated MRSA cases, 53% (70) were identified at Minneapolis-St Paul metropolitan sites and 47% (61) were identified at greater Minnesota sites. However, the ratio of community-associated MRSA cases to total MRSA cases was somewhat higher at greater Minnesota sites than at Minneapolis-St Paul metropolitan sites (61/358 [17%] vs 70/710 [10%]; OR, 1.66 [95% CI, 1.24-2.15]).

## Case Characteristics and Antimicrobial Treatment

Community-associated MRSA patients were younger than health care-

associated MRSA patients (median age, 23 years vs 68 years;  $P < .001$ ) (FIGURE 1 and TABLE 2). After excluding cases from the 2 pediatric hospitals, the median age of community-associated MRSA patients was still significantly younger than health care-associated MRSA patients (median age, 30 years vs 70 years;  $P < .001$ ). Race/ethnicity was documented for 72% of community-associated MRSA cases and 64% of health care-associated MRSA cases. Among those whose race/ethnicity was documented, community-associated MRSA patients were more likely than health care-associated MRSA patients to be nonwhite (OR, 3.13; 95% CI, 2.16-4.32). Median surrogate household income was less for patients with community-associated (\$25 395) and health care-associated (\$28 290) MRSA infection. The median household incomes for both types of cases were both considerably less than the median for state residents overall (\$47 111).

Among pediatric (age <18 years) community-associated MRSA cases, dermatological conditions (9% [5 patients]) were the most common underlying medical condition documented in the medical record (TABLE 3). Among adult community-associated MRSA cases (age  $\geq 18$  years), tobacco use (19% [15 patients]) and diabetes (17% [13 patients]) were the most common underlying conditions by medical record review, followed by dermatological conditions (13% [10 patients]).

The distribution of clinical infections differed between community-associated and health care-associated MRSA cases (TABLE 4). Compared with health care-associated cases, community-associated case infections were more likely to involve skin and soft tissue (OR, 4.25; 95% CI, 2.97-5.90) and less likely to be respiratory tract infections (OR, 0.22; 95% CI, 0.09-0.49) or urinary tract infections (OR, 0.04; 95% CI, 0-0.24) ( $P < .001$  for all comparisons). Bloodstream infections were more common among health care-associated cases (9% [83 patients] vs 4% [5 patients]), although this was not statistically significant. Of the 131 community-associated cases, 24% (31) were hospitalized due to

their MRSA infection and 5% (7) required intensive care treatment.

Among community-associated cases, oral or parenteral antimicro-

bial treatment was documented in 70% (92/131) of cases. Of these cases, 77% (71/92) were skin and soft tissue infection, similar to the

**Table 2.** Demographic Characteristics of Community-Associated and Health Care-Associated Methicillin-Resistant *Staphylococcus aureus* Cases

Characteristic	No. (%) of Methicillin-Resistant <i>S aureus</i> Cases		P Value*
	Community-Associated (n = 131)	Health Care-Associated (n = 937)	
Race/ethnicity†			
White	52 (40)	496 (53)	<.001
Unknown	37 (28)	340 (36)	.09
Nonwhite	42 (32)	101 (11)	<.001
Black	12 (9)	51 (5)	.26
American Indian	22 (17)	36 (4)	<.001
Asian	4 (3)	3 (0)	.008
Hispanic	4 (3)	6 (1)	.04
Other	0	5 (1)	NA
Age, median (range), y	23 (0-95)	68 (0-104)	<.001
Median income, \$‡	25 395	28 290	.02

Abbreviation: NA, not applicable.

\*Refers to the statistical probability that the characteristics among community-associated cases differed from the percentage among health care-associated cases ( $\alpha = .05$ ).

†Race/ethnicity calculated using the No. of cases with known race as the denominator.

‡Based on mean household income in each case's ZIP code (source: 2000 US Census data).

**Table 3.** Underlying Conditions of Community-Associated Methicillin-Resistant *Staphylococcus aureus* Cases, by Age

Condition	No. (%) of Patients	
	<18 y (n = 53)	$\geq 18$ y (n = 78)
Dermatological	5 (9)	10 (13)
Asthma	2 (4)	4 (5)
Alcohol abuse	1 (2)	4 (5)
Tobacco use	0	15 (19)
Diabetes	0	13 (17)
Chronic obstructive pulmonary disease	0	5 (6)
Hypertension	0	5 (6)
Coronary artery disease	0	3 (4)
None of the above	45 (85)	19 (24)

**Table 4.** Community-Associated and Health Care-Associated Methicillin-Resistant *Staphylococcus aureus* Cases, by Infection Type

Infection Type*	No. (%) of Methicillin-Resistant <i>S aureus</i> Cases		P Value†
	Community-Associated (n = 131)	Health Care-Associated (n = 937)	
Skin/soft tissue	98 (75)	343 (37)	<.001
Otitis media/externa	9 (7)	11 (1)	<.001
Respiratory tract‡	8 (6)	205 (22)	<.001
Bloodstream	5 (4)	83 (9)	.07
Urinary tract‡	1 (1)	185 (20)	<.001
Other§	10 (8)	110 (12)	.21

\*If patients had more than 1 type of infection, only 1 was selected for inclusion in this table. The hierarchy for choosing the type of infection for patients with multiple sources was: bacteremia, bone, pleural fluid, peritoneal fluid, joint, surgical specimen, postoperative wound, eye, ear, sputum, urine, and skin.

†Refers to the statistical probability that the type of infection among community-associated cases differed from the percentage among health care-associated cases ( $\alpha = .05$ ).

‡Among health care-associated isolates, some respiratory tract isolates were obtained from endotracheal tubes, and some urinary tract isolates were obtained from Foley catheters.

§Included bone, peritoneal fluid, joint, surgical specimen, and postoperative wound.

skin and soft tissue infection rate of 72% (28/39) for infections without documented antibiotics. Sixty-one percent (80) of community-associated MRSA infections were initially treated exclusively with  $\beta$ -lactam antimicrobials to which these isolates are

not susceptible. Other antimicrobial treatment included 13% who received quinolones; 7%, clindamycin; 5%, trimethoprim-sulfamethoxazole; 5%, tetracycline; 3%, vancomycin; 3%, aminoglycosides; and 2%, macrolides.

**Microbiological Characterization of MRSA Isolates**

Susceptibility and PFGE testing were performed on 106 community-associated isolates (25 isolates were unavailable from participating facilities) and a representative sample of 211 health care-associated isolates (see “Methods” section). Oxacillin resistance (a surrogate for methicillin resistance) was confirmed in all MRSA isolates. Community-associated MRSA isolates were generally susceptible to antimicrobials other than  $\beta$ -lactams and were more likely than health care-associated isolates to be susceptible to multiple agents (TABLE 5). Among community-associated isolates, susceptibilities did not differ between pediatric and adult isolates. Community-associated isolates from skin sites were more likely to be susceptible to ciprofloxacin (OR, 1.90; 95% CI, 1.44-2.11) and clindamycin (OR, 1.46; 95% CI, 1.04-1.68) compared with community-associated isolates from other sites. Community-associated MRSA isolates were also more likely than health care-associated MRSA isolates to be susceptible to all 4 of the following antimicrobial agents: ciprofloxacin, clindamycin, gentamicin, and trimethoprim-sulfamethoxazole (OR, 5.88; 95% CI, 4.86-6.64). In a logistic regression model adjusted for age, sex, surrogate income, laboratory location (Minneapolis-St Paul metropolitan vs greater Minnesota), and culture site (skin vs other), susceptibility to all 4 antimicrobials was an independent predictor of having a community-associated case definition (adjusted OR, 2.44; 95% CI, 1.35-3.86).

Overall, 119 distinct PFGE subtype patterns were identified. Five clonal groups containing 3 or more isolates were identified; these clonal groups accounted for 96% of all isolates. One PFGE clonal group, designated clonal group A, accounted for 62% (66) of community-associated isolates compared with 9% (18) health care-associated isolates (OR, 4.61; 95% CI, 3.82-5.16) (FIGURE 2 and FIGURE 3). Clonal group A isolates comprised the majority of the community-associated isolates from various age groups (31 [63%] of 49 isolates

**Table 5.** Antimicrobial Susceptibility Profiles of Community-Associated and Health Care-Associated Methicillin-Resistant *Staphylococcus aureus* Isolates

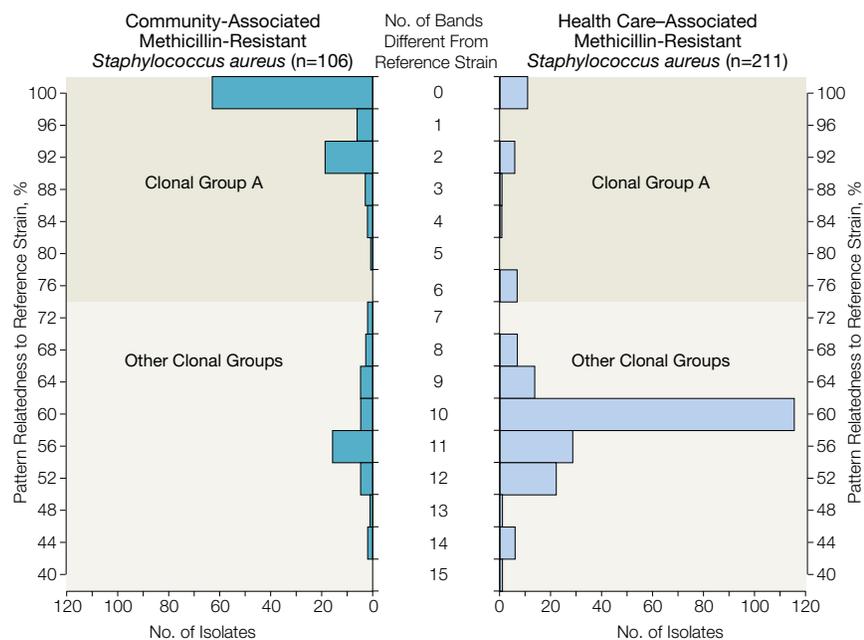
Type of Antibiotic	No. (%) Susceptible*		P Value†
	Community-Associated (n = 106)	Health Care-Associated (n = 211)	
Oxacillin (methicillin)	0	0	NA
Ciprofloxacin	84 (79)	33 (16)	<.001
Clindamycin	88 (83)	44 (21)	<.001
Erythromycin	47 (44)	18 (9)	<.001
Gentamicin	100 (94)	168 (80)	.001
Rifampin	102 (96)	199 (94)	.64
Tetracycline	98 (92)	194 (92)	.95
Trimethoprim-sulfamethoxazole	101 (95)	189 (90)	.13
Vancomycin	106 (100)	211 (100)	NA

Abbreviation: NA, not applicable.

\*Tested at the Minnesota Department of Public Health Laboratory by broth microdilution using National Committee for Clinical Laboratory Standards break points.

†Refers to the statistical probability that the percentage susceptible among community-associated isolates differed from the percentage susceptible among health care-associated isolates ( $\alpha = .05$ ).

**Figure 2.** Pulsed-Field Gel Electrophoresis Pattern Relatedness of Community-Associated and Health Care-Associated Methicillin-Resistant *Staphylococcus aureus* Isolates to a Reference Strain



The reference strain was MR14, which was the most commonly identified pattern among Minnesota methicillin-resistant *S aureus* isolates with a community-associated case definition.

from patients <18 years and 35 [61%] of 57 isolates from patients aged 18 years or older), racial groups (19 [95%] of 20 from American Indians, 8 [80%] of 10 from blacks, and 23 [52%] of 44 from whites), and geographic regions (31 [57%] of 54 from Minneapolis-St Paul metropolitan-area hospitals and 35 [67%] of 52 from greater Minnesota hospitals). Clonal group B also was associated with community-associated MRSA infection, with 15 (14%) of the community-associated MRSA isolates being in group B compared with 5 (2%) of the health care-associated isolates (OR, 2.43; 95% CI, 1.61-2.93). Compared with health care-associated MRSA isolates, community-associated MRSA isolates were more likely to belong to either clonal group A or clonal group B (81 [76%] of 106 vs 23 [11%] of 211; OR, 6.52; 95% CI, 5.41-7.31). A third clonal group, designated clonal group H, was strongly associated with health care-associated isolates. Of health care-associated isolates, 80% (168) were in clonal group H compared with 16% (17) of community-associated isolates (OR, 2.83; 95% CI, 2.60-2.97) (Figure 3). In another multivariate model adjusted for age, sex, surrogate income, laboratory facility (Minneapolis-St Paul metropolitan area vs greater Minnesota), and culture site (skin vs other), PFGE clonal groups A and B (adjusted OR, 2.75; 95% CI, 1.58-4.26) or clonal group A alone (adjusted OR, 2.37; 95% CI, 1.36-3.54) were independently associated with community-associated case status.

Both exotoxin genes (eg, Pantone Valentine leukocidin genes), and gene alleles (SCC*mec* alleles and accessory gene regulator alleles) were disproportionately distributed between community-associated and health care-associated isolates (TABLE 6). Of 25 genes tested, 8 genes were not identified in any isolates (listed in Table 6). Of the 16 exotoxin genes that were present in at least some MRSA isolates, 6 (Pantone Valentine leukocidins, staph enterotoxins A, C, and K, accessory gene regulator 3, and SCC*mec* IV) were significantly more likely to be found among community-associated iso-

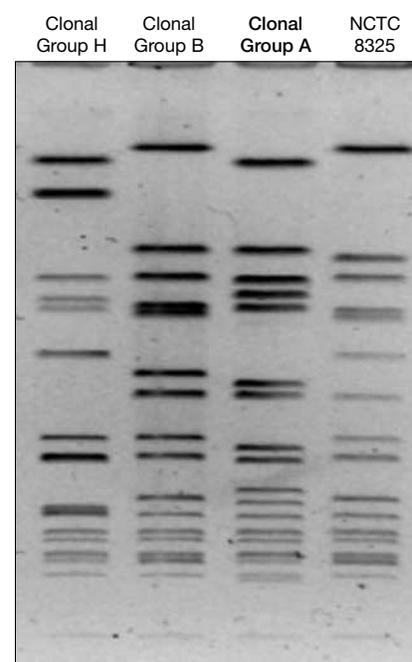
lates, and 7 were significantly more likely to be found among health care-associated isolates. Only 3 exotoxin genes were found in the majority of case isolates from both groups.

Pantone Valentine leukocidin genes were identified in 20 community-associated MRSA isolates tested (77%) compared with 1 health care-associated isolate (4%) (OR, 5.01; 95% CI, 3.49-5.25). Overall, 18 community-associated isolates with Pantone Valentine leukocidin genes (90%) were associated with skin or soft tissue infections. Even though the *mecA* gene, which confers methicillin resistance, and the accessory gene regulator alleles were present in all isolates, SCC*mec* IV allele and *agr* 3 allele were statistically more likely to be present in community-associated isolates than in health care-associated isolates. Conversely, SCC*mec* II and *agr* 2 were more commonly identified among health care-associated isolates.

### COMMENT

This is the first prospective comparison of community-associated and health care-associated MRSA cases in the United States, to our knowledge, and it is the first study performed at multiple sites. Overall, patients with community-associated MRSA (defined as MRSA infections identified in patients who lack established MRSA risk factors) were significantly younger and had different distributions of clinical infections compared with health care-associated MRSA patients. In fact, a previous study in Minnesota showed that there were actually strong similarities (eg, age distribution, infection characteristics) between community-associated methicillin-sensitive *S aureus* infections and community-associated MRSA patients.<sup>8</sup> Although the origin of community-associated MRSA strains remains speculative, these data suggest that their emergence may be due to the insertion of a *mecA* gene into methicillin-susceptible *S aureus* strains. This speculation is further strengthened by a recent report documenting this event in a clinical isolate, and by the fact that SCC*mec* IV is

**Figure 3.** Pulsed-Field Gel Electrophoresis Patterns of the Predominant Methicillin-Resistant *Staphylococcus aureus* Clonal Groups



Isolates from clonal group H were statistically associated with health care-associated case status. Isolates from clonal groups B and A were statistically associated with community-associated case status. NCTC 8325 represents a molecular weight standard.

probably more mobile than other SCC*mec* alleles.<sup>29,30</sup>

Another unique feature of our investigation was our attempt to collect MRSA isolates from all reported cases. Community-associated MRSA isolates were more likely to be susceptible to multiple antimicrobial classes and to have distinct molecular features (based on PFGE) compared with health care-associated isolates. These findings further support our contention that most community-associated MRSA infections in Minnesota are not due to casual health care exposures or to MRSA strains that originated in health care settings, although this remains controversial.<sup>31-33</sup>

The differences in exotoxin genes between community-associated and health care-associated isolates also suggest that the pathogenesis of these MRSA in-

fections may differ. Recent evidence indicates that Pantone Valentine leukocidins and the SCCmec IV allele, which are rarely found in health care–associated MRSA strains globally, are common among community-associated MRSA strains from 3 different continents, even though community-associated strains from these continents do not share a common genetic lineage.<sup>27</sup> The Pantone Valentine leukocidin genes code for the production of cytotoxins that cause tissue necrosis and leukocyte destruction by forming pores in cellular membranes. In Europe, Pantone Valentine leukocidin genes are associated with community-associated staphylococcal skin infections and necrotizing pneumonia.<sup>26,34,35</sup> Similarly, in our study, most community-associated MRSA isolates that had Pantone Valentine leukocidin genes were associated with skin and soft

tissue infections. Furthermore, the community-associated MRSA strains responsible for severe cases of necrotizing pneumonia in Minnesota and North Dakota<sup>7</sup> all had Pantone Valentine leukocidin genes.<sup>34</sup> However, it is important to emphasize that the association between Pantone Valentine leukocidin genes and particular clinical manifestations needs further work to demonstrate causation because other exotoxin genes (eg, *sea*, *sec* or *sek*; Table 6) or combinations of genes could also be important pathogenic factors.

Our study had several limitations. It is likely that some health care–associated MRSA cases were misclassified as community-associated MRSA cases, and vice versa. Misclassification, however, would only have minimized the observed differences between community-associated and

health care–associated MRSA patients and isolates. Because our study was not population-based, it is possible that MRSA cases identified through sentinel site surveillance were not representative of all cases that occurred throughout Minnesota. However, to date there have been no published population-based studies of MRSA patients and isolates. We also believe that our study is more representative than previous studies because we identified cases from multiple laboratory facilities in both urban and rural areas from different geographic locations statewide. Finally, because we have not studied MRSA colonization in Minnesota, we cannot determine the prevalence of MRSA among those colonized with *S aureus*, and therefore we do not know whether community-associated MRSA strains are more likely than other *S aureus* strains to cause disease.

Because there are epidemiological and microbiological differences between community-associated and health care–associated MRSA infections, strategies to prevent and treat these infections likely differ as well. To prevent clinical complications from community-associated MRSA infections, clinicians working in outpatient or emergency department settings should consider practice modifications in areas where such infections are known to be prevalent. These modifications could include (1) more frequent culturing and susceptibility testing of *S aureus* isolates of clinical infections, particularly among pediatric patients; (2) surgical drainage of infections when appropriate; and (3) careful selection of empirical antimicrobials when such treatment is indicated for suspected staphylococcal infections (ie, clinicians should be aware that MRSA organisms are nonsusceptible to  $\beta$ -lactam antimicrobials). Because most community-associated MRSA isolates were susceptible to several already-available antimicrobial agents, and because most patients had noninvasive infections, the treatment of community-associated MRSA infections should not routinely require the use of vancomy-

**Table 6.** Exotoxin Genes and Gene Alleles Among Community-Associated and Health Care–Associated Methicillin-Resistant *Staphylococcus aureus* Isolates

Gene Sequence	No. (%) of Cases With Gene Sequence		Odds Ratio (95% Confidence Interval)*
	Community-Associated (n = 26)	Health Care–Associated (n = 26)	
	<b>Exotoxin Gene†</b>		
$\beta$ Hemolysin	2 (8)	0	Undefined
$\gamma$ Hemolysin variant	25 (96)	26 (100)	0 (0-1.00)
Leukocidin E-D	24 (92)	26 (100)	0 (0-1.00)
PVL	20 (77)	1 (4)	5.01 (3.49-5.25)
<i>sea</i>	15 (58)	1 (4)	3.03 (2.03-3.22)
<i>seb</i>	6 (23)	1 (4)	3.35 (0.80-5.14)
<i>sec</i>	13 (50)	0	Undefined
<i>sed</i>	5 (19)	14 (54)	0.41 (0.13-0.93)
<i>seg</i>	5 (19)	25 (96)	0.17 (0-0.67)
<i>seh</i>	17 (65)	1 (4)	3.63 (2.47-3.84)
<i>sei</i>	5 (19)	25 (96)	0.17 (0-0.67)
<i>sej</i>	5 (19)	14 (54)	0.41 (0.13-0.93)
<i>sek</i>	16 (62)	0	Undefined
<i>sem</i>	5 (19)	25 (96)	0.17 (0-0.67)
<i>sen</i>	5 (19)	25 (96)	0.17 (0-0.67)
<i>seo</i>	5 (19)	25 (96)	0.17 (0-0.67)
	<b>Gene Allele‡</b>		
<i>agr</i> 2	4 (15)	25 (96)	0.20 (0-0.67)
<i>agr</i> 3	17 (65)	1 (4)	3.63 (2.47-3.84)
SCCmec II	3 (12)	21 (81)	0.14 (0-0.53)
SCCmec IV	22 (85)	3 (12)	5.87 (3.67-6.55)

Abbreviations: AGR, accessory gene regulator; PVL, Pantone Valentine leukocidins; SCC, Staphylococcal chromosomal cassette; se, Staphylococcal enterotoxin.

\*The corrected odds ratio of being associated with community-associated vs health care–associated case isolates. †Toxins not present in either community or health care–associated methicillin-resistant *S aureus* included *sea*, toxic shock syndrome toxin, leukocidin M, exfoliative toxins A, B, and D, epidermal inhibitor A, and  $\gamma$  hemolysin.

‡Although all isolates had SCCmec and *agr* alleles, the total percentage of isolates with the listed allele does not total to 100% because some isolates had alleles that were not shown.

cin. However, patients with MRSA infections should be evaluated and treated appropriately and receive follow-up evaluation to ensure resolution of their infection.

To improve prevention strategies, more work is needed to characterize specific risk factors for community-associated MRSA infections. However, at least one study has implicated prior exposure to antimicrobial agents as an independent risk factor for community-associated MRSA infection.<sup>36</sup> This suggests that the judicious use of antimicrobials, particularly in outpatient settings, could help control the emergence of community-associated MRSA strains and limit the acquisition of additional antimicrobial resistance genes in existing strains. Currently, there are no data to suggest that decolonization protocols for MRSA patients or their families are necessary or have long-term effectiveness. Resistance to antimicrobial agents used for decolonization has evolved rapidly in settings in which such strategies have been attempted.<sup>37</sup>

Because community-associated infection is frequently identified in children, questions have arisen regarding transmission in group settings.<sup>16,18,38</sup> Although it is common to exclude those with uncontained *S aureus* infections, there is no evidence that excluding MRSA-colonized children from normal activities such as group child care, school, or athletics is effective in limiting the spread of community-associated MRSA strains, and we do not recommend such steps. Future strategies such as vaccination to prevent *S aureus* infections in both community and health care settings hold greater promise. However, it is likely that antimicrobial-resistant strains of *S aureus* will continue to evolve and that *S aureus* will remain an important and adaptive human pathogen.<sup>2,39,40</sup>

**Author Contributions:** Dr Naimi had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analyses.

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**Acquisition of data:** Naimi, LeDell, Borchardt, Boxrud,

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**Drafting of the manuscript:** Naimi, LeDell, Borchardt, Etienne, Johnson.

**Critical revision of the manuscript for important intellectual content:** Naimi, LeDell, Boxrud, Como-Sabetti, Etienne, Vandenesch, Fridkin, O'Boyle, Danila, Lynfield.

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**Obtained funding:** Fridkin, Danila.

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**Study supervision:** Naimi, LeDell, Danila, Lynfield.

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... Nature's works are always worthy of our preservation and protection; and the further we become separated (and the face of the country) from that pristine wildness and beauty, the more pleasure does the mind of enlightened man feel in recurring to those scenes, when he can have them preserved for his eyes and his mind to dwell upon.

—George Catlin (1796-1872)