MAJOR ARTICLE

A Population-Based Study of the Incidence and Molecular Epidemiology of Methicillin-Resistant *Staphylococcus aureus* Disease in San Francisco, 2004–2005

Catherine Liu,[1,2,a] Christopher J. Graber,[1,2,a,b] Michael Karr,[1,2] Binh An Diep,[1,2] Li Basuino,[1,2] Brian S. Schwartz,[1,2] Mark C. Enright,[9] Simon J. O'Hanlon,[9] Jonathon C. Thomas,[9] Francoise Perdreau-Remington,[1,2] Shelley Gordon,[3] Helen Gunthorpe,[4] Richard Jacobs,[1,5] Peter Jensen,[1,6] Gifford Leoung,[7] James S. Rumack,[8] and Henry F. Chambers[1,2]

[1]University of California, San Francisco, [2]San Francisco General Hospital, [3]California Pacific Medical Center, [4]St. Mary's Medical Center, [5]Moffit-Long Hospital, [6]Department of Veterans Affairs Medical Center, and [7]St. Francis Memorial Hospital, San Francisco, and [8]Seton Medical Center, Daly City, California; and [9]Department of Infectious Disease Epidemiology, Imperial College, London, United Kingdom

Background. Methicillin-resistant *Staphylococcus aureus* (MRSA) infections have become a major public health problem in both the community and hospitals. Few studies have characterized the incidence and clonal composition of disease-causing strains in an entire population. Our objective was to perform a population-based survey of the clinical and molecular epidemiology of MRSA disease in San Francisco, California.

Methods. We prospectively collected 3985 MRSA isolates and associated clinical and demographic information over a 12-month period (2004–2005) at 9 San Francisco–area medical centers. A random sample of 801 isolates was selected for molecular analysis.

Results. The annual incidence of community-onset MRSA disease among San Francisco residents was 316 cases per 100,000 population, compared with 31 cases per 100,000 population for hospital-onset disease. Persons who were aged 35–44 years, were men, and were black had the highest incidence of community-onset disease. The USA300 MRSA clone accounted for 234 cases of community-onset disease and 15 cases of hospital-onset disease per 100,000 population, constituting an estimated 78.5% and 43.4% of all cases of MRSA disease, respectively. Patients with community-onset USA300 MRSA versus non-USA300 MRSA disease were more likely to be male, be of younger age, and have skin and soft-tissue infections. USA300 strains were generally more susceptible to multiple antibiotics, although decreased susceptibility to tetracycline was observed in both community-onset ($P = .008$) and hospital-onset ($P = .03$) USA300 compared to non-USA300 strains.

Conclusions. The annual incidence of community-onset MRSA disease in San Francisco is substantial, surpassing that of hospital-onset disease. USA300 is the predominant clone in both the community and hospitals. The dissemination of USA300 from the community into the hospital setting has blurred its distinction as a community-associated pathogen.

Since the late 1990s, methicillin-resistant *Staphylococcus aureus* (MRSA) has emerged as a significant pathogen in the community [1–6]. In particular, the USA300 MRSA clone has become a primary cause of community-associated disease [2, 7, 8] and an increasingly important source of health care–associated infection [9, 10]. The USA300 genome contains numerous elements that may affect its transmissibility and virulence—most notably, the gene encoding Panton-Valentine leukocidin (PVL) and the arginine catabolic mobile element (ACME), a novel genetic element [11].

Many studies characterizing community-associated MRSA and the USA300 strain have focused on outbreaks in particular groups [12–16] or among people presenting with skin and soft-tissue infection [7, 17]. The burden of disease has been examined at several medical centers [7, 8, 17–26] and is quite substantial

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[a] C.L. and C.J.G. contributed equally to this article.

[b] Present affiliation: Infectious Diseases Section, VA Greater Los Angeles Healthcare System, Los Angeles, California.

Reprints or correspondence: Dr. Catherine Liu, Div. of Infectious Diseases, University of California, San Francisco, 513 Parnassus Ave., S-380, Box 0654, San Francisco, CA 94143 (catherine.liu@ucsf.edu).

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for invasive MRSA [27]. Few studies have characterized both the clinical and molecular epidemiology of overall MRSA disease in an entire community [2, 8].

Since 2001, a dramatic increase in the number of MRSA infections has been observed in 1 San Francisco, California, medical center [20, 28]. To characterize the epidemiology of MRSA throughout the entire city, a consortium of physicians from 9 San Francisco medical centers was established to collect all unique MRSA isolates and associated demographic and clinical information over a consecutive 12-month period from 2004 to 2005. We characterized the clonal distribution and features associated with community-onset and hospital-onset MRSA infection in these medical centers and determined the annual incidence of community-onset and hospital-onset MRSA disease among San Francisco residents.

METHODS

Medical center participation. Eight of the 9 medical centers in San Francisco and 1 hospital in Daly City, just across the San Francisco county line, participated in this study. These are acute care facilities that operate a total of 4368 licensed hospital beds; the medical center that did not participate was a 59-bed hospital. One center has a 150-bed children's hospital, and 5 of the 9 hospitals have inpatient pediatric beds. These centers also include affiliated outpatient clinics and long-term care facilities. This study was approved by the institutional review board of each medical center.

Isolate collection and classification. The medical centers used passive surveillance to detect cases of MRSA infection; physicians submitted cultures to laboratories for identification of pathogens when patients presented with disease that, in the physician's opinion, required culture. Active surveillance for MRSA was not performed at any center during the study period. The participating medical centers initiated routine specimen collection from February through September of 2004 and collected clinical MRSA specimens from unique patients for 12 consecutive months. MRSA disease was defined as cases in which an isolate was obtained for suspected infection from a clinically relevant site; nasal isolates were excluded from analysis. A unique isolate was defined as a single isolate per patient during the study period. If a specimen was submitted from a patient for whom a sample was cultured earlier in the study period, only the first specimen was used. When isolates were collected from several sources from a single patient on the same day, our selection priority order was as follows: blood, respiratory, urine, and skin and soft-tissue samples. For patients who had samples cultured at multiple centers, only the first isolate collected in chronological time was included.

Isolates collected in the outpatient setting or within 24 h of admission were classified as "community-onset;" those collected over 100 h after admission were classified as "hospital-onset." To ensure a rigorous classification of cases as community-onset or hospital-onset, isolates collected >24 and <100 h from admission were not included in the analysis. All patients'

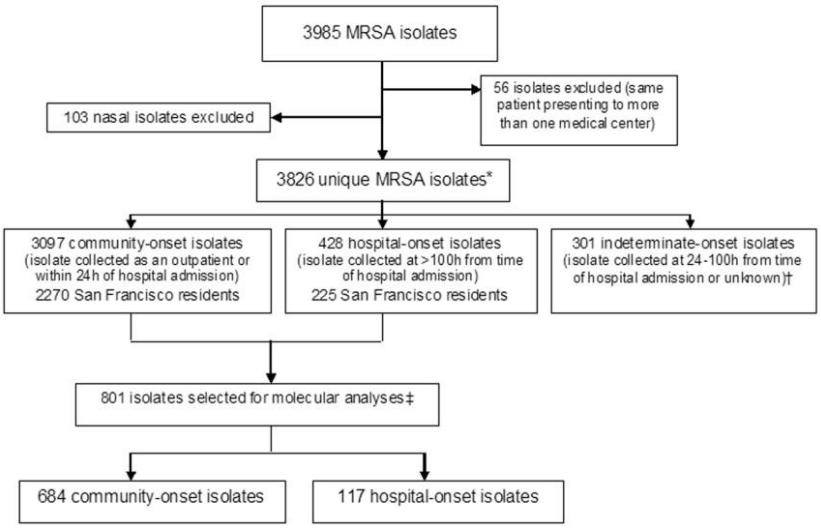

Figure 1. This diagram represents the consortium collection and sampling scheme. MRSA, methicillin resistant *Staphyloccus aureus.* *A unique isolate was defined as a single isolate per patient during the 12-month study period. If more than 1 isolate was available, the first and most clinically significant (the preferred order of isolate sources was blood followed by respiratory, urine, and skin and soft tissue) isolate was chosen. †One hundred fifteen isolates were collected at 24–48 h, 74 isolates were collected at 48–72 h, 60 isolates were collected at 72–100 h, and 52 isolates were not classified because of a lack of information. ‡Up to 8 isolates per month per medical center were randomly selected for molecular analysis from the collection of 3525 community-onset and hospital-onset isolates.

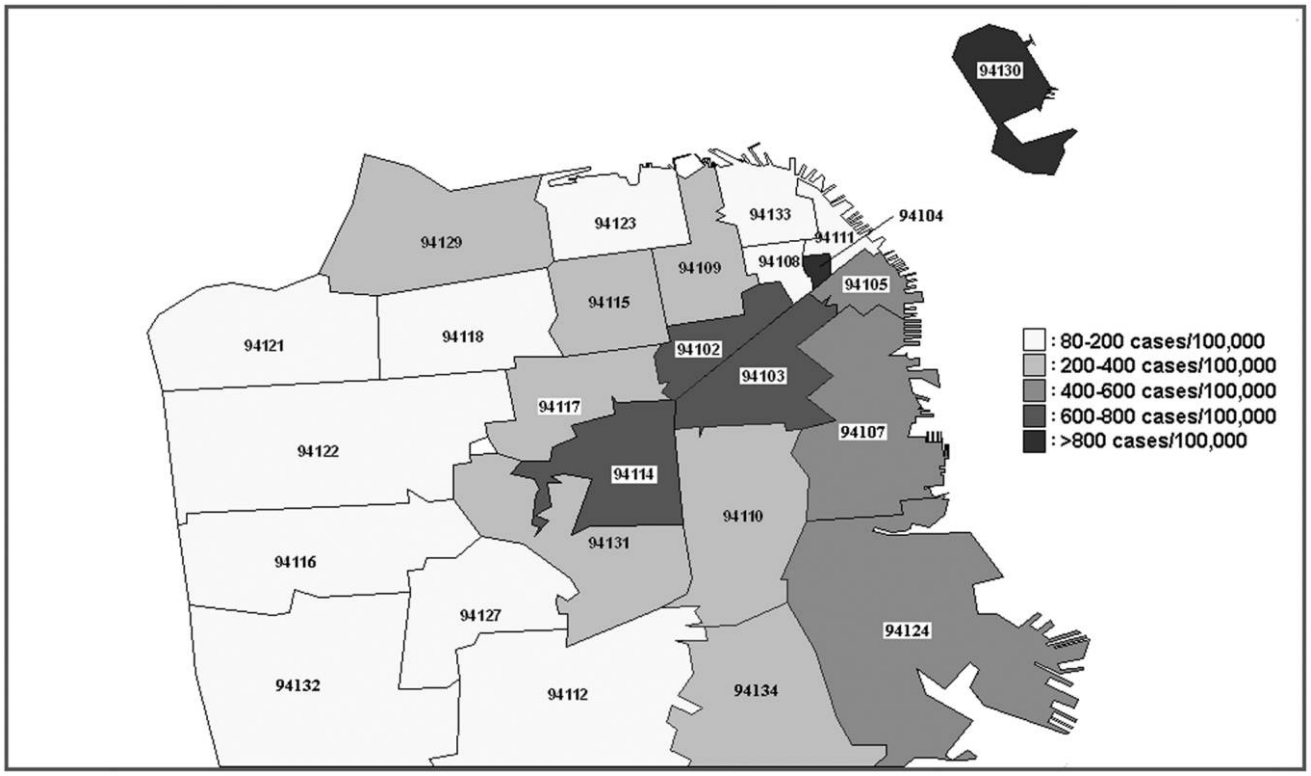

Figure 2. The annual incidence of community-onset methicillin-resistant *Staphylococcus aureus* (MRSA) infection in San Francisco, by zip code of patient residence, 2004–2005. The estimated annual incidence of community-onset MRSA infection in San Francisco is 316 cases per 100,000 population. Exclusion of those patients admitted to the hospital within 1 year results in an annual incidence of 243 cases per 100,000 population.

medical records were reviewed to obtain information on age, sex, race/ethnicity, zip code of residence, date of hospital admission, and history of acute-care hospitalization in the preceding year.

Laboratory methods. Up to 96 isolates from each medical center were randomly sampled among isolates classified as community-onset or hospital-onset for molecular analysis. Isolates from each center were listed in chronologic order by date of specimen collection, and up to 8 isolates were chosen from each 1-month block using a random number generator. If <96 isolates were available from a particular medical center, then molecular analysis was performed on all isolates from that center. A total of 801 isolates were selected for sequencing of the protein A gene polymorphic region (*spa* typing) [29] and PCR testing for ACME [11] and PVL genes [30]. Unique *spa* sequence types were further characterized by multilocus sequence typing (MLST) [31] and eBURST (http://saureus.mlst.net/) [32]. PCR confirmed the presence of the *mec*A gene in all isolates [33]. All PCR-based assays were performed in duplicate. An isolate was classified as USA300 if it had a *spa* sequence consistent with MLST type 8 and both ACME and PVL genes were detected using PCR [11, 34, 35]. PFGE was performed on a representative sample of 19 isolates. Fourteen (73.7%) were classified as USA300 by the molecular methods discussed above and were determined to be USA300 by PFGE. The remaining 5 isolates of the representative sample were not classified as USA300 by MLST, PCR testing for ACME and PVL genes, or PFGE.

We performed susceptibility testing on the sample of 801 isolates using broth microdilution according to breakpoints established by the Clinical and Laboratory Standards Institute. The D-zone test was performed on a selected subset of 83 isolates; only 1 isolate tested (non-USA300) carried the inducible clindamycin-resistant phenotype [36].

Statistical methods. Annual incidence of community-onset and hospital-onset MRSA disease was determined for San Francisco residents by dividing the total number of unique patient isolates obtained from patients residing in San Francisco zip codes by the total population of San Francisco. Population demographic data was obtained from the 2005 American Community Survey for San Francisco County (http://factfinder.census.gov). Zip code–specific incidence rates for community-onset MRSA disease were estimated using the most recent data from the 2000 US Census. We conducted an analysis to determine whether the differences in the start date for isolate collection among the medical centers significantly influenced

Table 1. Annual incidence of community-onset and hospital-onset methicillin-resistant *Staphylococcus aureus* disease in San Francisco residents by demographic characteristics and disease source.

Characteristic	2005 census data[a] (n = 719,077)	Community-onset disease		Hospital-onset disease	
		Patients (n = 2270)	Annual incidence[b]	Patients (n = 225)	Annual incidence[b]
Age, years					
Median	39.4	42	…	59	…
<5	39,718 (6)	90 (4)	227	5 (2)	13
5–14	52,911 (7)	53 (2)	100	1 (0.4)	2
15–24	64,680 (9)	184 (8)	284	3 (1)	5
25–34	133,331 (19)	368 (16)	276	11 (5)	8
35–44	140,775 (20)	605 (27)	430	21 (9)	15
45–54	105,896 (15)	453 (20)	428	39 (17)	37
55–64	76,590 (11)	230 (10)	300	46 (20)	60
65–74	50,928 (7)	110 (5)	216	41 (18)	81
75–84	38,735 (5)	111 (5)	287	37 (16)	96
⩾85	15,513 (2)	66 (3)	425	21 (9)	135
Sex					
Male	362,869 (50)	1614 (71)	445	142 (63)	39
Female	356,208 (50)	656 (29)	184	83 (37)	23
Race/ethnicity					
White	382,220 (53)	1028 (45)	269	98 (44)	26
Black	46,779 (7)	381 (17)	814	37 (16)	79
Hispanic[c]	98,891 (14)	134 (6)	136	15 (7)	15
Asian/Pacific Islander	240,859 (33)	92 (4)	38	30 (13)	12
Other/unknown[d]	49,219 (11)	635 (28)	ND	45 (20)	ND
Source					
Skin/soft tissue	NA	1987 (88)	276	94 (42)	13
Respiratory	NA	80 (4)	11	85 (38)	12
Blood	NA	102 (4)	14	24 (11)	3
Urine	NA	45 (2)	6	15 (7)	2
Other	NA	56 (2)	8	7 (3)	1

NOTE. Data are no. (%) of individuals, unless otherwise indicated. NA, not available; ND, not done.

[a] Data obtained from the 2005 American Community Survey, which excludes the population living in institutions, dormitories, and other group quarters.

[b] No. of events per 100,000 residents. Annual incidence, according to source of disease, was calculated using the total San Francisco population estimate (n = 719,077).

[c] Hispanic race was classified as a discrete race in our analysis, but in the 2005 American Community Survey, persons identified as Hispanic were distributed among white, black, and other races.

[d] Persons describing themselves as >1 race are included in this category.

the number of isolates obtained. The number of isolates obtained per month at each center was divided by the total number obtained over the 12 month study period at each center. These ratios were analyzed for a significant linear trend which was not observed ($P = .71$).

All calculations performed on molecular data were adjusted by weighting each isolate by the inverse probability of being included in the sample using the "svy" (survey) command in Stata version 9.1 (Statacorp). Annual incidence of community-onset and hospital-onset USA300 MRSA infection was determined using 2005 American Community Survey data. Comparisons of median age were made using the Wilcoxon rank-sum test. Relative risk was used to compare disease caused by USA300 versus non-USA300 strains across categorical variables, and a χ^2 test for trend was used to compare hospital day of culture among USA300 and non-USA300 isolates.

RESULTS

Results of isolate collection and the sampling strategy used are illustrated in figure 1. A total of 3985 isolates were collected. After excluding 56 isolates from patients with isolates obtained

Table 2. Distribution of USA300 among community-onset and hospital-onset methicillin-resistance *Staphylococcus aureus* disease cases, by medical center.

Medical center	Total isolates	Community-onset disease (n = 684)			Hospital-onset disease (n = 117)		
		Collected	Sampled	USA300	Collected	Sampled	USA300
1	1014	851	85	70 (82)	107	6	3 (50)
2	75	46	46	30 (65)	16	16	5 (31)
3	423	312	78	53 (68)	73	14	7 (50)
4	843	745	90	73 (81)	43	6	2 (33)
5	282	177	70	41 (59)	72	22	5 (23)
6	242	190	81	63 (78)	29	14	7 (50)
7	97	70	70	55 (79)	19	19	12 (63)
8	314	245	77	60 (78)	34	13	9 (69)
9	536	461	87	73 (84)	35	7	2 (29)
Total	3826	3097	684	518 (76)	428	117	52 (44)

NOTE. Data are no. or no. (%) of isolates. When each isolate is weighted by the inverse probability of being included in the sample, USA300 is estimated to account for 78.5% and 43.4% of community-onset and hospital-onset disease, respectively.

from multiple medical centers and 103 nasal isolates, there were 3826 unique isolates. Of these, 3097 (81%) were classified as community-onset and 428 (11%) were hospital-onset isolates. Three hundred one (8%) were obtained within 24–100 h after hospital admission or could not be classified because of a lack of information.

Annual incidence and demographic characteristics. Of 3826 unique MRSA infections, San Francisco residents accounted for 2270 and 225 cases of community-onset and hospital-onset disease, respectively. The annual incidence of community-onset MRSA disease among San Francisco residents was 316 cases per 100,000 population, compared with 31 cases per 100,000 population for hospital-onset infection. If patients hospitalized within the prior year were excluded, the annual incidence of community-onset disease was 243 cases per 100,000 population. Of the 26 San Francisco zip codes, 8 had annual incidence rates of >400 cases per 100,000 population (figure 2). According to year 2000 US Census data, the 3 zip codes with the highest incidence rates (94104, 94102, and 94103) of MRSA included families with the lowest median household

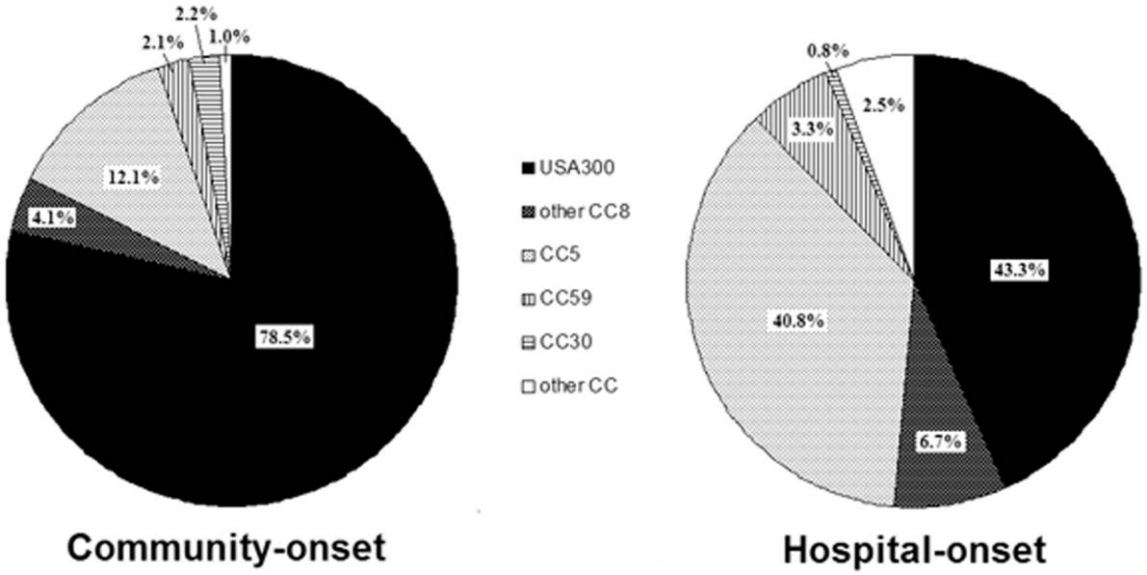

Figure 3. The estimated clonal distribution of methicillin-resistant *Staphylococcus aureus* among patients with community-onset and hospital-onset disease. CC, clonal complex.

Table 3. Demographic and clinical characteristics associated with USA300 among community-onset and hospital-onset methicillin-resistant *Staphylococcus aureus* disease cases.

Variable	Community-onset disease[a] (*n* = 684)				Hospital-onset disease[a] (*n* = 117)			
	USA300 (*n* = 518)	Non-USA300 (*n* = 166)	Relative risk[b] (95% CI)	*P*	USA300 (*n* = 52)	Non-USA300 (*n* = 65)	Relative risk[b,c] (95% CI)	*P*
San Francisco resident[d]								
Yes	378 (73)	97 (58)	1.1 (1.0–1.3)	.05	32 (63)	25 (38)	1.6 (1.0–2.5)	.04
No	140 (27)	69 (42)	Ref		20 (37)	40 (62)	Ref	
Sex								
Male	369 (71)	110 (66)	1.1 (0.98–1.2)	.12	34 (65)	37 (57)	1.5 (0.93–2.3)	.09
Female	149 (29)	56 (34)	Ref		18 (35)	28 (43)	Ref	
Age, years								
Median	41	62	…	<.001	61	70	…	.05
<5	17 (3)	3 (2)	1.0 (0.85–1.2)	.97	3 (6)	0 (0)	ND	
5–14	9 (2)	3 (2)	0.83 (0.58–1.2)	.18	0 (0)	1 (2)	ND	
15–24	45 (9)	10 (6)	0.94 (0.82–1.1)	.32	1 (2)	0 (0)	ND	
25–34	100 (19)	12 (7)	1.0 (0.94–1.1)	.64	5 (10)	2 (3)	ND	
35–44	129 (25)	16 (10)	Ref		5 (10)	4 (6)	ND	
45–54	100 (19)	26 (16)	0.91 (0.81–1.0)	.06	6 (11)	4 (6)	ND	
55–64	54 (10)	22 (13)	0.86 (0.74–1.0)	.02	8 (15)	14 (22)	Ref	
65–74	27 (5)	24 (14)	0.57 (0.41–0.79)	<.001	9 (17)	16 (25)	1.0 (0.54–2.0)	.91
75–84	27 (5)	26 (16)	0.60 (0.44–0.82)	<.001	11 (21)	15 (23)	0.90 (0.43–1.9)	.78
⩾85	10 (2)	24 (14)	0.33 (0.18–0.63)	<.001	4 (8)	9 (14)	0.61 (0.20–1.8)	.36
Race/ethnicity								
White	223 (43)	85 (51)	Ref		25 (46)	31 (48)	Ref	
Black	79 (15)	18 (11)	1.1 (1.0–1.2)	.04	4 (11)	6 (9)	ND	
Hispanic	35 (7)	3 (2)	1.2 (1.0–1.3)	.04	3 (6)	3 (5)	ND	
Asian/Pacific Islander	24 (5)	19 (11)	0.77 (0.56–1.0)	.03	8 (15)	12 (19)	0.41 (0.18–0.93)	0.01
Other/ unknown	157 (30)	41 (25)	ND		12 (22)	13 (20)	ND	
Source								
Skin/soft tissue	449 (87)	100 (60)	Ref		24 (46)	23 (35)	Ref	
Respiratory	23 (4)	28 (17)	0.63 (0.46–0.86)	<.001	18 (35)	25 (38)	0.87 (0.53–1.4)	.58
Blood	27 (5)	12 (7)	0.94 (0.79–1.1)	.42	2 (4)	7 (11)	ND	
Urine	5 (1)	12 (7)	0.13 (0.036–0.49)	<.001	3 (6)	3 (5)	ND	
Other	14 (3)	14 (8)	0.57 (0.36–0.89)	<.001	5 (10)	7 (11)	0.82 (0.37–1.8)	.60
Prior admission within past 1 year[e]								
Yes	122 (24)	68 (41)	0.80 (0.71–0.90)	<.001	17 (35)	36 (55)	0.53 (0.32–0.88)	.007
No	396 (76)	98 (59)	Ref		35 (65)	29 (45)	Ref	

NOTE. Data are no. (%) of individuals, unless otherwise indicated. ND, not done; Ref, reference.

[a] The community-onset disease category included 684 individuals, sampled from 3097. The hospital-onset disease category included 117 individuals, sampled from 428.

[b] Relative risk comparisons between categorical variables were adjusted for sampling to generate estimates for the entire strain collection.

[c] Relative risk was not calculated for any category where the combined number of isolates (USA300 and non-USA300) was ⩽10, as small sample size limits the reliability of the estimate obtained.

[d] San Francisco residency as determined by zip code.

[e] Admission within the 1 year prior to the date the isolate was obtained.

incomes in San Francisco ($19,904, $29,073, and $39,208, respectively). High incidence rates were also observed in zip code 94114, which corresponds to the Castro-Noe Valley district and includes a large community of men who have sex with men [37].

The annual incidence of community-onset MRSA was highest among those in the 35–44-year, 45–54-year, and ⩾85-year age groups (table 1). Annual incidence of hospital-onset MRSA infection increased with age, with the highest rate observed among those in the oldest age category. Men were 2.4 and 1.7 times more likely to have community-onset and hospital-onset MRSA than women, respectively. The annual incidence of both community-onset and hospital-onset MRSA was 3 times higher in persons who were black versus persons who were white.

Molecular analysis and patient characteristics. Of 801 isolates selected for molecular analysis, 684 (85%) and 117 (15%) represented community-onset and hospital-onset isolates, respectively. USA300 was the predominant clone, accounting for

59%–84% of community-onset MRSA isolates and 23%–69% of hospital-onset MRSA infection isolates (table 2).

The annual incidence of community-onset and hospital-onset USA300 MRSA disease among San Francisco residents was 234 cases per 100,000 population and 15 cases per 100,000 population, respectively. The USA300 clone accounted for 78.5% of community-onset and 43.4% of hospital-onset isolates (figure 3). Clonal complex 5 MRSA, a major epidemic hospital lineage, constituted 12.1% and 36.5% of the community-onset and hospital-onset isolates, respectively.

Compared with non–San Francisco residents, San Francisco residents with community-onset ($P = .05$) and hospital-onset disease ($P = .04$) were more likely to have USA300 versus non-USA300 MRSA disease (table 3). The median age of patients with USA300 versus those with non-USA300 MRSA disease was, respectively, 41 versus 62 years ($P < .001$) in the community and 61 versus 70 years in the hospital setting ($P = .05$). The relative risk of becoming infected with community-onset USA300 MRSA compared to non-USA300 MRSA progressively decreased as age increased above 35–44 years. Among those with community-onset disease, there was a slight association between black persons (relative risk, 1.1; 95% CI, 1.0–1.2, $P = .04$) and Hispanic persons (relative risk, 1.2; 95% CI, 1.0–1.3, $P = .04$) and the rate of USA300 MRSA infection (compared with white persons), whereas Asians/Pacific Islanders were less likely to be infected by USA300 MRSA than were white persons (relative risk, 0.77; 95% CI, 0.56–1.0; $P = .03$). Asians/Pacific Islanders with hospital-onset disease were less likely to be infected with USA300 MRSA than were white persons (relative risk, 0.41; 95% CI, 0.18–0.93; $P = .01$). USA300 was significantly less likely to be recovered from respiratory samples (relative risk, 0.63; 95% CI, 0.46–0.86), urine samples (relative risk, 0.13; 95% CI, 0.04–0.49), and other sites (relative risk, 0.57; 95% CI 0.36–0.89), compared with skin and soft-tissue samples among individuals with community-onset disease. There was no significant association between infection source and genotype for hospital-onset disease. Hospitalization in the year prior to sample collection was associated with a decreased likelihood of recovering USA300, compared with non-USA300 MRSA. In persons with hospital-onset disease, those isolates obtained early in hospitalization were more likely to be USA300, whereas those recovered later were more likely to be non-USA300 MRSA ($P < .001$, by the χ^2 test for trend) (figure 4).

Compared with the non-USA300 MRSA strains, USA300 strains were more susceptible to antimicrobial agents (table 4), although decreased susceptibility to tetracycline among USA300 strains was observed in both community-onset (78.9% vs. 88.7%; $P = .008$) and hospital-onset isolates (86.6% vs. 97.4%; $P = .03$). Susceptibility patterns among USA300 strains recovered from community-onset and hospital-onset settings were similar; however, a significantly higher proportion of USA300 strains isolated from the hospital setting was susceptible to clindamycin ($P = .03$).

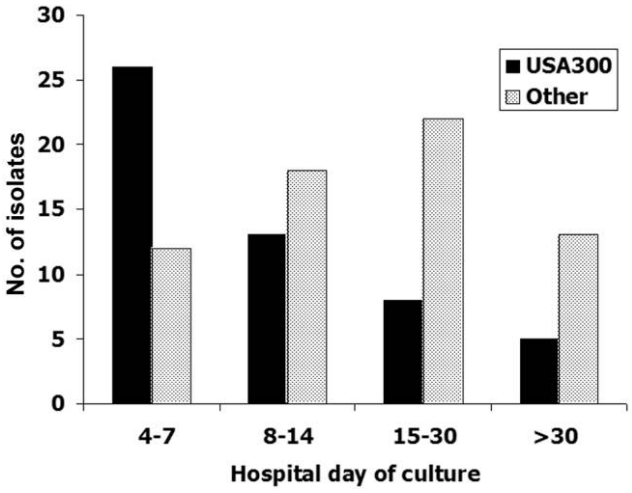

Figure 4. Genotypes of hospital-onset methicillin-resistant *Staphylococcus aureus* isolates, by hospital day of culture. $P < .001$, by the χ^2 test for trend.

DISCUSSION

MRSA has emerged as a major public health threat in the community. In 2004–2005, community-onset MRSA accounted for >80% of all MRSA infections. This study highlights the changing paradigm of MRSA—prevalence of disease in the community now surpasses that in the hospital. Our data indicate much higher numbers of community-onset MRSA disease cases than observed in other community-based studies [2, 8]. Only 12% of 1100 MRSA infections in 12 sentinel hospitals in Minnesota were community associated [2]. Population-based surveillance studies in Baltimore, Maryland, and Atlanta, Georgia, observed 18 cases of community-associated MRSA disease per 100,000 population and 25.7 cases per 100,000 population in the 2 cities, respectively [8]. These aforementioned studies collected data from 2000 through 2002, early in the community MRSA epidemic. Follow-up surveillance data in Baltimore and Atlanta indicated a rise in the incidence of invasive MRSA disease in 2005. Although information for sterile sites other than the bloodstream were not available, our incidence data on bloodstream infections (14 and 3 cases per 100,000 population for community-onset and hospital-onset disease, respectively) is consistent with findings regarding invasive disease from the Active Bacterial Core Surveillance group for the San Francisco Bay Area (20.4 community-onset and 7.7 hospital-onset cases per 100,000 population) [27].

Men comprised the vast majority of individuals infected with community-onset and hospital-onset USA300 and non-USA300 MRSA in this study. Consistent with findings from

Table 4. Antimicrobial susceptibility profiles among USA300 and non-USA300 strains in community-onset and hospital-onset disease cases.

	Community-onset disease (n = 684)			Hospital-onset disease (n = 116)		
Antibiotic	USA300 (n = 518)	Non-USA300 (n = 166)	P	USA300 (n = 52)	Non-USA300[a] (n = 64)†	P
Ciprofloxacin	43.4	38.5	.32	31.2	16.9	.07
Clindamycin	84.9	54.7	<.001	95.0	46.5	<.001
Erythromycin	4.0	15.9	<.001	5.1	12.5	.24
Gentamicin	100	95.9	<.001	100	91.6	.05
Rifampin	99.0	97.9	.27	98.9	89.6	.07
Tetracycline	78.9	88.7	.008	86.6	97.4	.03
Tobramycin	91.3	50.6	<.001	88.5	35.5	<.001
Trimethoprim-sulfamethoxazole	100	98.4	.007	100	99.6	1.0

NOTE. Data are percentage of susceptible isolates.

[a] Susceptibility tests could not be performed on 1 hospital-onset non-USA300 isolate.

other studies [2, 7, 17, 38], incidence of community-onset MRSA was the highest in a younger age group (35–44 years). Also notable was the high incidence of community-onset infections among those aged ⩾85 years. In this group, the majority (35 of 66) were hospitalized in the prior year, suggesting health care–associated disease, and most of the MRSA strains isolated from these individuals were of the clonal complex 5 hospital lineage. Zip code regions with the highest incidence of MRSA disease corresponded to neighborhoods of lower socioeconomic status and of a large community of men who have sex with men. These demographic characteristic correlates likely reflect the underlying predictors of transmission of this disease which include crowded living conditions, frequent close contact, and/or contact with an active case or carrier [17, 18, 38].

USA300 was the predominant MRSA clone, recovered in >75% of community-onset infections. USA300 was isolated in 43% of hospital-onset infections, replacing the clonal complex 5 lineage as the most common genotype to cause hospital-onset MRSA disease. Among patients with hospital-onset infection, USA300 was more likely to be recovered earlier than later during hospitalization. Because USA300 is a community strain, it is likely that infection in these patients arose from endogenous colonization with this clone acquired from the community rather than horizontal transmission. The high prevalence of USA300 in hospital-onset infection suggests that the community is an important and increasing reservoir for MRSA disease that occurs in hospitalized patients.

Although USA300 isolates were generally more susceptible to antibiotics than non-USA300 isolates, resistance will likely increase as a consequence of increasing antibiotic selection pressure in both community and hospital settings. Of note, USA300 had decreased susceptibility to tetracyclines, compared with non-USA300 strains; this result was perhaps related to the frequent use of doxycycline for the treatment of uncomplicated infections in our community. Lower rates of clindamycin susceptibility were observed among community-onset USA300 isolates than among hospital-onset USA300 isolates. Direct transmission of antibiotic-resistant clones in the community may be important, and the dissemination of a multidrug-resistant strain of USA300 among men who have sex with men has recently been observed in San Francisco and Boston, Massachusetts [36]. In addition, we have reported a case of intermediate vancomycin susceptibility in a methicillin-resistant USA300 strain [39]. These findings emphasize the need to obtain cultures and perform susceptibility testing as part of the treatment of patients with suspected MRSA disease.

Our study had several limitations. We only report data from individuals for whom cultures were obtained; because infections are not consistently cultured, it is probable that a number of cases were missed. In addition, this study did not include isolates that were submitted to private laboratories from patients who were treated in private offices. Because the 9 major medical centers in the area were included, it is likely that we collected the majority of MRSA isolates in San Francisco. Therefore, our estimate of the annual incidence of community-onset MRSA disease among San Francisco residents is conservative, with the actual incidence likely being higher. Finally, limited information regarding health care–associated risk factors was collected; thus, time of disease onset alone was used to distinguish between community-onset and hospital-onset infection. To address the limitations of these definitions, we chose a time of isolate collection of ⩽24 h as a more stringent criterion for community-onset infection and collected information on hospitalization in the prior year. With exclusion of those individuals who were hospitalized in the prior year, the adjusted annual incidence of community-onset MRSA disease was calculated to be 243 cases per 100,000 population, which is substantially higher than previous reports.

The impact of the USA300 strain on MRSA disease in San Francisco is dramatic and particularly remarkable, given that USA300 was first detected in San Francisco only 3 years before the initiation of the study [20]. The substantial incidence of disease observed may be because this study was conducted at a later time in the epidemic and because USA300 was more established in San Francisco than in other areas. However, given that this clone has demonstrated potential for spread throughout other communities and to other countries [40], San Francisco is a case study of the continued rising burden of MRSA disease in the community, which now exceeds disease that occurs in the hospital by 10-fold. This study has several important implications. First, the significant incidence of MRSA in the community and increasing antibiotic resistance raise further questions about optimal therapy for the empirical treatment of outpatient skin and soft-tissue infection. Second, the application of molecular epidemiologic tools allowed us to confirm the community as a significant reservoir of MRSA disease that occurs in hospitals. However, the extent to which hospital-onset infections are due to horizontal transmission versus infection from prior colonization is unclear, although the decaying incidence rate of USA300 infection in the hospital over time suggests the latter. The biology and pathogenesis of community-associated MRSA appear to differ from health care–associated MRSA as nonnasal sites of colonization may play an important role in infection [41]. For these reasons, traditional infection control strategies aimed solely at the prevention of MRSA transmission in hospitals may be ineffective or insufficient. New approaches, including public health measures that focus on the community as a source of MRSA, are needed to contain this epidemic. Additional research is essential to elucidate the reasons for the rapid spread and virulence of the highly successful USA300 MRSA clone.

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References

1. Gorak EJ, Yamada SM, Brown JD. Community-acquired methicillin-resistant *Staphylococcus aureus* in hospitalized adults and children without known risk factors. Clin Infect Dis **1999**; 29:797–800.
2. Naimi TS, LeDell KH, Como-Sabetti K, et al. Comparison of community- and health care-associated methicillin-resistant *Staphylococcus aureus* infection. JAMA **2003**; 290:2976–84.
3. Herold BC, Immergluck LC, Maranan MC, et al. Community-acquired methicillin-resistant *Staphylococcus aureus* in children with no identified predisposing risk. JAMA **1998**; 279:593–8.
4. Groom AV, Wolsey DH, Naimi TS, et al. Community-acquired methicillin-resistant *Staphylococcus aureus* in a rural American Indian community. JAMA **2001**; 286:1201–5
5. Weber JT. Community-associated methicillin-resistant *Staphylococcus aureus.* Clin Infect Dis **2005**; 41(Suppl 4):S269–72.
6. Zetola N, Francis JS, Nuermberger EL, Bishai WR. Community-acquired methicillin-resistant *Staphylococcus aureus:* an emerging threat. Lancet Infect Dis **2005**; 5:275–86.
7. King MD, Humphrey BJ, Wang YF, Kourbatova EV, Ray SM, Blumberg HM. Emergence of community-acquired methicillin-resistant *Staphylococcus aureus* USA 300 clone as the predominant cause of skin and soft-tissue infections. Ann Intern Med **2006**; 144:309–17.
8. Fridkin SK, Hageman JC, Morrison M, et al. Methicillin-resistant *Staphylococcus aureus* disease in three communities. N Engl J Med **2005**; 352:1436–44.
9. Seybold U, Kourbatova EV, Johnson JG, et al. Emergence of community-associated methicillin-resistant *Staphylococcus aureus* USA300 genotype as a major cause of health care-associated blood stream infections. Clin Infect Dis **2006**; 42:647–56.
10. Kourbatova EV, Halvosa JS, King MD, Ray SM, White N, Blumberg HM. Emergence of community-associated methicillin-resistant *Staphylococcus aureus* USA 300 clone as a cause of health care-associated infections among patients with prosthetic joint infections. Am J Infect Control **2005**; 33:385–91.
11. Diep BA, Gill SR, Chang RF, et al. Complete genome sequence of USA300, an epidemic clone of community-acquired meticillin-resistant *Staphylococcus aureus.* Lancet **2006**; 367:731–9.
12. Centers for Disease Control and Prevention. Methicillin-resistant *Staphylococcus aureus* infections among competitive sports participants—Colorado, Indiana, Pennsylvania, and Los Angeles County, 2000–2003. MMWR **2003**; 52:793–5.
13. Centers for Disease Control and Prevention. Methicillin-resistant *Staphylococcus aureus* skin or soft tissue infections in a state prison—Mississippi, 2000. MMWR **2001**; 50:919–22.
14. Centers for Disease Control and Prevention. Methicillin-resistant *Staphylococcus aureus* infections in correctional facilities—Georgia, California, and Texas, 2001–2003. MMWR **2003**; 52:992–6.
15. Centers for Disease Control and Prevention. Outbreaks of community-associated methicillin-resistant *Staphylococcus aureus* skin infections—Los Angeles County, California, 2002–2003. MMWR Morb Mortal Wkly Rep **2003**; 52:88.
16. Zinderman CE, Conner B, Malakooti MA, LaMar JE, Armstrong A, Bohnker BK. Community-acquired methicillin-resistant *Staphylococcus aureus* among military recruits. Emerg Infect Dis **2004**; 10:941–4.
17. Moran GJ, Krishnadasan A, Gorwitz RJ, et al. Methicillin-resistant *S. aureus* infections among patients in the emergency department. N Engl J Med **2006**; 355:666–74.
18. Bratu S, Landman D, Gupta J, Trehan M, Panwar M, Quale J. A population-based study examining the emergence of community-associated methicillin-resistant *Staphylococcus aureus* USA300 in New York City. Ann Clin Microbiol Antimicrob **2006**; 5:29.
19. Buck JM, Como-Sabetti K, Harriman KH, et al. Community-associated methicillin-resistant *Staphylococcus aureus*, Minnesota, 2000–2003. Emerg Infect Dis **2005**; 11:1532–8.
20. Carleton HA, Diep BA, Charlebois ED, Sensabaugh GF, Perdreau-Remington F. Community-adapted methicillin-resistant *Staphylococcus aureus* (MRSA): population dynamics of an expanding community reservoir of MRSA. J Infect Dis **2004**; 190:1730–8.
21. Chavez-Bueno S, Bozdogan B, Katz K, et al. Inducible clindamycin resistance and molecular epidemiologic trends of pediatric community-acquired methicillin-resistant *Staphylococcus aureus* in Dallas, Texas. Antimicrob Agents Chemother **2005**; 49:2283–8.
22. Crum NF, Lee RU, Thornton SA, et al. Fifteen-year study of the changing epidemiology of methicillin-resistant *Staphylococcus aureus.* Am J Med **2006**; 119:943–51.
23. Hasty MB, Klasner A, Kness S, et al. Cutaneous community-associated methicillin-resistant *Staphylococcus aureus* among all skin and soft-tissue infections in two geographically distant pediatric emergency departments. Acad Emerg Med **2007**; 14:35–40.
24. Huang H, Flynn NM, King JH, Monchaud C, Morita M, Cohen SH.

Comparisons of community-associated methicillin-resistant *Staphylococcus aureus* (MRSA) and hospital-associated MSRA infections in Sacramento, California. J Clin Microbiol **2006**; 44:2423–7.
25. Szumowski JD, Cohen DE, Kanaya F, Mayer KH. Treatment and outcomes of infections by methicillin-resistant *Staphylococcus aureus* at an ambulatory clinic. Antimicrob Agents Chemother **2007**; 51:423–8.
26. Frazee BW, Lynn J, Charlebois ED, Lambert L, Lowery D, Perdreau-Remington F. High prevalence of methicillin-resistant *Staphylococcus aureus* in emergency department skin and soft tissue infections. Ann Emerg Med **2005**; 45:311–20.
27. Klevens RM, Morrison MA, Fridkin SK, et al. Community-associated methicillin-resistant *Staphylococcus aureus* and healthcare risk factors. Emerg Infect Dis **2006**; 12:1991–3.
28. Diep BA, Carleton HA, Chang RF, Sensabaugh GF, Perdreau-Remington F. Roles of 34 virulence genes in the evolution of hospital- and community-associated strains of methicillin-resistant *Staphylococcus aureus*. J Infect Dis **2006**; 193:1495–503.
29. Shopsin B, Gomez M, Montgomery SO, et al. Evaluation of protein A gene polymorphic region DNA sequencing for typing of *Staphylococcus aureus* strains. J Clin Microbiol **1999**; 37:3556–63.
30. Lina G, Piemont Y, Godail-Gamot F, et al. Involvement of Panton-Valentine leukocidin–producing *Staphylococcus aureus* in primary skin infections and pneumonia. Clin Infect Dis **1999**; 29:1128–32.
31. Enright MC, Day NP, Davies CE, Peacock SJ, Spratt BG. Multilocus sequence typing for characterization of methicillin-resistant and methicillin-susceptible clones of *Staphylococcus aureus*. J Clin Microbiol **2000**; 38:1008–15.
32. Feil EJ, Enright MC. Analyses of clonality and the evolution of bacterial pathogens. Curr Opin Microbiol **2004**; 7:308–13.
33. Oliveira DC, de Lencastre H. Multiplex PCR strategy for rapid identification of structural types and variants of the mec element in methicillin-resistant *Staphylococcus aureus*. Antimicrob Agents Chemother **2002**; 46:2155–61.
34. Diep BA, Stone GG, Basuino L, et al. The ACME and SCCmec linkage: convergence of virulence and resistance in the USA300 clone of methicillin-resistant *Staphylococcus aureus*. J Infect Dis (in press).
35. Goering RV, McDougal LK, Fosheim GE, Bonnstetter KK, Wolter DJ, Tenover FC. Epidemiologic distribution of the arginine catabolic mobile element among selected methicillin-resistant and methicillin-susceptible *Staphylococcus aureus* isolates. J Clin Microbiol **2007**; 45: 1981–4.
36. Diep BA, Chambers HF, Graber CJ, et al. Emergence of multidrug-resistant, community-associated, methicillin-resistant *Staphylococcus aureus* clone USA300 in men who have sex with men. Ann Intern Med **2008**; 148:249–57.
37. Gates GJ, Ost J. Facts and findings. From: The gay and lesbian atlas. Washington DC: Urban Institute Press, **2004**. Available at: http://www.urban.org/UploadedPDF/900695_GL_FactSheet.pdf.
38. Hota B, Ellenbogen C, Hayden MK, Aroutcheva A, Rice TW, Weinstein RA. Community-associated methicillin-resistant *Staphylococcus aureus* skin and soft tissue infections at a public hospital: do public housing and incarceration amplify transmission? Arch Intern Med **2007**; 167: 1026–33.
39. Graber CJ, Wong MK, Carleton HA, Perdreau-Remington F, Haller BL, Chambers HF. Intermediate vancomycin susceptibility in a community-associated MRSA clone. Emerg Infect Dis **2007**; 13:491–3.
40. Larsen A, Stegger M, Goering R, Sorum M, Skov R. Emergence and dissemination of the methicillin resistant *Staphylococcus aureus* USA300 clone in Denmark (2000-2005). Euro Surveill **2007**; 12 [Epub ahead of print].
41. Miller LG, Diep BA. Clinical practice: colonization, fomites, and virulence: rethinking the pathogenesis of community-associated methicillin-resistant *Staphylococcus aureus* infection. Clin Infect Dis **2008**; 46:752–60.