Invasive Methicillin-Resistant *Staphylococcus aureus* Infections in the United States

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Context As the epidemiology of infections with methicillin-resistant *Staphylococcus aureus* (MRSA) changes, accurate information on the scope and magnitude of MRSA infections in the US population is needed.

Objectives To describe the incidence and distribution of invasive MRSA disease in 9 US communities and to estimate the burden of invasive MRSA infections in the United States in 2005.

Design and Setting Active, population-based surveillance for invasive MRSA in 9 sites participating in the Active Bacterial Core surveillance (ABCs)/Emerging Infections Program Network from July 2004 through December 2005. Reports of MRSA were investigated and classified as either health care–associated (either hospital-onset or community-onset) or community-associated (patients without established health care risk factors for MRSA).

Main Outcome Measures Incidence rates and estimated number of invasive MRSA infections and in-hospital deaths among patients with MRSA in the United States in 2005; interval estimates of incidence excluding 1 site that appeared to be an outlier with the highest incidence; molecular characterization of infecting strains.

Results There were 8987 observed cases of invasive MRSA reported during the surveillance period. Most MRSA infections were health care–associated: 5250 (58.4%) were community-onset infections, 2389 (26.6%) were hospital-onset infections; 1234 (13.7%) were community-associated infections, and 114 (1.3%) could not be classified. In 2005, the standardized incidence rate of invasive MRSA was 31.8 per 100 000 (interval estimate, 24.4-35.2). Incidence rates were highest among persons 65 years and older (127.7 per 100 000; interval estimate, 92.6-156.9), blacks (66.5 per 100 000; interval estimate, 43.5-63.1), and males (37.5 per 100 000; interval estimate, 26.8-39.5). There were 1598 in-hospital deaths among patients with MRSA infection during the surveillance period. In 2005, the standardized mortality rate was 6.3 per 100 000 (interval estimate, 3.3-7.5). Molecular testing identified strains historically associated with community-associated disease outbreaks recovered from cultures in both hospital-onset and community-onset health care–associated infections in all surveillance areas.

Conclusions Invasive MRSA infection affects certain populations disproportionately. It is a major public health problem primarily related to health care but no longer confined to intensive care units, acute care hospitals, or any health care institution.

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AFTER BEING INITIALLY REported among injecting drug users in Detroit in 1981[1] and then associated with the deaths of 4 children in Minnesota and North Dakota in 1997,[2] community-associated methicillin-resistant *Staphylococcus aureus* (MRSA) has become the most frequent cause of skin and soft tissue infections presenting to emergency departments in the United States.[3] Although community outbreaks of MRSA in diverse populations, including American Indian and Alaska Natives,[4] sports

See also p 1803 and Patient Page.

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teams,[5,6] prison inmates,[7] and child care attendees,[8] usually involved skin disease, MRSA also can cause severe, sometimes fatal invasive disease.[9-13]

Studies of the emergence of community-associated MRSA disease over the past decade determined that isolates causing community-associated and health care–associated MRSA infections were distinct.[10] Isolates from the community were susceptible to most non–β-lactam antimicrobial agents,[10] carried staphylococcal cassette chromosome type IV,[14] and frequently encoded the dermonecrotic cytotoxin known as Panton-Valentine leukocidin.[15] The strain most often isolated in community outbreaks was pulsed-field type USA300.[16] Other strains of community origin include USA400, USA1000, and USA1100.[17] In contrast, strains most frequently associated with MRSA infections in health care settings were USA100, USA200, and less often, USA500[18]; these traditionally have been multidrug-resistant and have carried staphylococcal cassette chromosome type II.[10]

In hospitalized patients, MRSA has been a problem since the 1960s[19]; approximately 20% of bloodstream infections in the hospital setting have been caused by *S aureus*.[20] The proportion of hospital-onset *S aureus* infections that were methicillin-resistant reached 64.4% in US intensive care units in 2003.[21] In the hospital, MRSA infections are associated with greater lengths of stay, higher mortality,[22] and increased costs.[23,24] Although more recently there has been increased surveillance activity for invasive MRSA infections in the community, surveillance for MRSA bloodstream infections in the United States traditionally has been limited to hospital-onset (ie, nosocomial) disease.[20,21]

As the epidemiology of MRSA disease changes, including both community- and health care–associated disease, accurate information on the scope and magnitude of the burden of MRSA disease in the US population is needed to set priorities for prevention and control. In this report we describe the incidence and distribution of invasive MRSA disease in 9 US communities and use these results to estimate the burden of invasive MRSA infections in the United States.

METHODS

Surveillance Methodology and Definitions

The Active Bacterial Core surveillance system (ABCs) is an ongoing, population-based, active laboratory surveillance system and is a component of the Emerging Infections Program (EIP) of the US Centers for Disease Control and Prevention (CDC). From July 2004 through December 2005, 9 EIP sites conducted surveillance for invasive MRSA infections. A site number was assigned in descending order of population size: site 1, the state of Connecticut (estimated population, 3.5 million); site 2, the Atlanta, Georgia, metropolitan area (8 counties; estimated population, 3.5 million); site 3, the San Francisco, California, Bay Area (3 counties; estimated population, 3.2 million); site 4, the Denver, Colorado, metropolitan area (5 counties; estimated population, 2.3 million); site 5, the Portland, Oregon, metropolitan area (3 counties; estimated population, 1.5 million); site 6, Monroe County, New York (estimated population, 733 000); site 7, Baltimore City, Maryland (estimated population, 636 000); site 8, Davidson County, Tennessee (estimated population, 575 000); and site 9, Ramsey County (St Paul area), Minnesota (estimated population, 495 000). The total population under surveillance in 2005 was an estimated 16.5 million, or approximately 5.6% of the US population. Surveillance sites were similar to the US population in the distribution by male sex (49.2% and 49.3%, respectively); however, surveillance sites had a lower frequency of whites (72.7% and 81.0%, respectively) and of persons 65 years and older (10.8% and 12.4%, respectively).

ABCs case finding was both active and laboratory-based. Clinical microbiology laboratories in acute care hospitals and all reference laboratories processing sterile site specimens for residents of the surveillance area were contacted regularly for case identification. In hospitals without computerized microbiology data, surveillance personnel telephoned designated microbiology laboratory contacts regularly to identify new cases and request isolate submission. Where microbiology data were computerized, electronic line listings of all MRSA isolated from normally sterile sites were received on a monthly basis by surveillance staff, which investigated each potential case to confirm residency status, presence of infection, demographic characteristics, and underlying illness. The burden of disease can be estimated by this surveillance method using census data and the surveillance site–specific incidence rates and age-, race-, and sex-adjusted incidence rates pooled across all surveillance sites. This infrastructure is the same as that used for estimated incidence and disease burden for bacterial meningitis[25] and invasive infections with *Streptococcus pneumoniae*.[26,27]

Case reporting and isolate collection were determined to be surveillance activities at the CDC; in addition, each of the 9 participating surveillance sites evaluated the protocol and either deemed it a surveillance activity (eg, that involving a reportable disease) or obtained institutional review board approval with a waiver of informed consent.

A case of invasive MRSA infection was defined by the isolation of MRSA from a normally sterile body site in a resident of the surveillance area, including residents institutionalized in long-term care facilities, prisons, etc. Normally sterile sites included blood, cerebrospinal fluid, pleural fluid, pericardial fluid, peritoneal fluid, joint/synovial fluid, bone, internal body site (lymph node, brain, heart, liver, spleen, vitreous fluid, kidney, pancreas, or ovary), or other normally sterile sites. Cultures designated as "fluid" were investigated as potentially sterile culture sites; cultures designated as "tissue" with no specification of original source were not investigated.

Personnel in each EIP site abstracted data from medical records from hospital and clinic visits using a standard case report form. Information on the following health care risk factors for MRSA was collected: culture obtained more than 48 hours after admission; presence of an invasive device (eg, vascular catheter, gastric feeding tube) at time of admission or evaluation; and a history of MRSA infection or colonization, surgery, hospitalization, dialysis, or residence in a long-term care facility in the 12 months preceding the culture. Cases could have more than 1 health care risk factor. For this analysis, we used health care risk factor information to classify cases into mutually exclusive groups (those with health care–associated and community-associated infections) justified previously[28] and consistent with other studies (TABLE 1).[29,30] Health care–associated infections, in turn, were classified as either community-onset (cases with a health care risk factor but with a culture obtained ≤48 hours after hospital admission) and hospital-onset (cases with culture obtained >48 hours after admission, regardless of whether they also had other health care risk factors). Community-associated cases were those without documented health care risk factors.

Surveillance personnel also collected demographic (including race), clinical, and outcome (hospital death or discharge) information on each case from the initial hospitalization. Mortality was collected from the patient record and represented crude, in-hospital deaths only. Race was collected from information available in the medical record. Cases were considered to have a diagnosis of bacteremia, pneumonia, cellulitis, osteomyelitis, endocarditis, septic shock, or other infection, if there was documentation of such a diagnosis in the medical record, regardless of the source of the isolate. Cases could have more than 1 clinical diagnosis. Bacteremias included those classified as primary, secondary, and not specified. Use of up to 4 antimicrobial agents was recorded, but all such agents reflected only initial empirical therapy and did not include dose, duration, therapeutic changes, or procedures (eg, draining, surgical therapy). Concordant empirical therapy was defined as receipt of any antimicrobial agent to which the isolate was susceptible by laboratory testing and that was documented in the medical record. Recurrent invasive MRSA was defined as a positive culture result obtained from the same case 30 days or more after the initial culture.

Table 1. Definitions Used for Epidemiologic Classification of Invasive Methicillin-Resistant *Staphylococcus aureus* (MRSA) Infections

Classification	Definition
Health care–associated	
Community-onset	Cases with at least 1 of the following health care risk factors: (1) presence of an invasive device at time of admission; (2) history of MRSA infection or colonization; (3) history of surgery, hospitalization, dialysis, or residence in a long-term care facility in previous 12 mo preceding culture date
Hospital-onset	Cases with positive culture result from a normally sterile site obtained >48 h after hospital admission. These cases might also have ≥1 of the community-onset risk factors.
Community-associated	Cases with no documented community-onset health care risk factor

Isolate Collection and Testing

Laboratories identified by the EIP site were asked to submit isolates from invasive MRSA infections. Of 123 laboratories serving residents of the surveillance areas, 48 (39%) contributed isolates. All isolates were sent to the CDC for identification, selected testing, and storage. In situations in which more than 1 isolate was available from a single case, the protocol selected 1 isolate, preferably from a nonblood sterile site. Isolates were prioritized for testing as follows: within each geographic site, all nonblood isolates and the subsequent submitted blood isolate were selected; then, among blood isolates, those from cases with a diagnosis other than uncomplicated bacteremia were selected. Testing included confirmation of *S aureus* identification using catalase and Staphaurex (Remel Europe Ltd, Dartford, United Kingdom) agglutination tests and tube coagulase if necessary, as well as description of morphology on nonselective blood agar, confirmation of oxacillin resistance by the broth microdilution method,[18] and pulsed-field gel electrophoresis (PFGE) using the restriction endonuclease *Sma*I. PFGE patterns were analyzed using BioNumerics version 4.01 (Applied Maths, Austin, Texas) and grouped into pulsed-field types using Dice coefficients and 80% relatedness, as previously described.[18] PFGE testing was conducted at the CDC and at the reference centers in Colorado, Connecticut, Georgia, Minnesota, and Oregon. All PFGE patterns were entered into a single database for analysis.

Statistical Analysis

We selected cases reported from July 2004 through December 2005 to describe epidemiologic, clinical, and microbiological characteristics. We included only cases reported from January through December 2005 for the annual 2005 incidence rate calculations. Recurrent cases were excluded from incidence calculations. We used US Census Bureau bridged-race vintage postcensus population estimates for 2005, provided by the National Center for Health Statistics for surveillance area and national denominator values.

Because the surveillance sites varied in the distribution by age and race, for national estimates of burden of disease we multiplied the aggregate age-, race-, and sex-specific rates of disease in the surveillance areas by the age, race, and sex distribution of the US population for 2005. Because 1 site (site 7, Baltimore City) reported an excessively high incidence of infection, we calculated interval estimates for the age-, race-, and sex-adjusted incidence rates and estimated burden as well. This was performed by creating a lower bound by pooling data from the 3 EIP sites

Table 2. Observed Incidence Rates of Invasive Methicillin-Resistant *Staphylococcus aureus* (MRSA) by Active Bacterial Core Surveillance Site and Epidemiologic Classification, United States, 2005[a]

		Incidence per 100 000			
			Health Care–Associated		
Surveillance Site No. (Location)[b]	No. of Cases	Community-Associated	Community-Onset	Hospital-Onset	Total
1 (Connecticut)	952	2.7	15.6	8.4	27.1
2 (Atlanta, GA, metropolitan area)	1165	5.1	16.7	10.3	33.0
3 (San Francisco, CA, Bay Area)	936	4.5	15.9	7.7	29.2
4 (Denver, CO, metropolitan area)	480	2.8	12.3	6.0	21.2
5 (Portland, OR, metropolitan area)	305	4.7	11.4	3.6	19.8
6 (Monroe County, NY)	307	2.7	22.2	16.8	41.9
7 (Baltimore City, MD)	742	29.7	62.9	19.7	116.7
8 (Davidson County, TN)	305	6.8	30.4	13.9	53.0
9 (Ramsey County, MN)	95	1.6	11.5	6.1	19.2

[a] Epidemiologic classification of disease consisted of health care–associated (either hospital-onset cases with a culture collected >48 h after hospital admission or community-onset cases with health care risk factors but a culture collected ≤48 h after hospital admission) and community-associated cases (no health care risk factors).
[b] Site numbers were assigned in descending order of population size.

Table 3. Estimated Incidence Rates of Invasive Methicillin-Resistant *Staphylococcus aureus* Infections by Race, Active Bacterial Core Surveillance, United States, 2005

		Incidence per 100 000		
Age, y	No. of Cases	White	Black	Other
<1	60	14.9	65.9	14.2
1	9	3.7	5.9	0
2-4	18	1.9	6.0	0
5-17	47	0.7	4.8	0.4
18-34	434	7.3	29.1	3.2
35-49	1082	16.1	84.9	6.3
50-64	1327	35.1	127.5	15.8
≥65	2308	118.0	253.8	67.0
Total (interval estimates)[a]	5287	27.7 (21.9-32.4)	66.5 (43.5-63.1)	10.4 (10.7-16.4)

[a] Interval estimates for the overall incidence by race were calculated for the lower bound by pooling data from the 3 surveillance sites reporting the lowest incidence rates; for the upper bound, by pooling data from the 3 sites reporting the highest rates, excluding data from site 7 (Baltimore City), which reported excessively high rates. These race-specific interval estimates are adjusted by age and sex.

with lowest overall incidence (sites 4, 5, and 9) and an upper bound by pooling data from the 3 EIP sites with highest overall incidence (sites 2, 6, and 8), excluding site 7. Because data from site 7 were excluded from the interval estimates, there are occasions when the intervals do not include the overall rate. Confidence intervals are based on the properties of a sampling distribution and cannot be calculated with our data because our surveillance areas captured all cases, not a sample. We tested differences in proportions of descriptive characteristics using χ^2. Analyses were performed using SAS version 9.1.3 (SAS Institute Inc, Cary, North Carolina).

RESULTS

Incidence of Invasive MRSA

There were 8987 observed cases of invasive MRSA reported from July 2004 through December 2005. Most were health care–associated, with 5250 (58.4%) community-onset infections, 2389 (26.6%) hospital-onset infections, 1234 (13.7%) community-associated infections, and 114 (1.3%) that could not be classified.

Unadjusted incidence rates of all types of invasive MRSA ranged between approximately 20 to 50 per 100 000 in most ABCs sites but were noticeably higher in 1 site (site 7, Baltimore City) (TABLE 2). The rate of invasive community-associated MRSA was less than 3 per 100 000 in 4 sites and approximately 5 per 100 000 in 3 sites. Incidence rates were consistently higher among blacks compared with whites in the various age groups (TABLE 3). Adjusting for age, race, and sex, the standardized incidence rate of invasive MRSA for calendar year 2005 was 31.8 per 100 000 persons (TABLE 4). The overall interval estimate after exclusion of the outlier site (site 7) was 24.4 to 35.2 per 100 000.

The rate of health care–associated, community-onset infections (17.6 per 100 000; interval estimate, 14.7-18.2) was greater than either health care–associated, hospital-onset infections (8.9 per 100 000; interval estimate, 6.1-11.8) or community-associated infections (4.6 per 100 000; interval estimate, 3.6-4.4). Standardized incidence rates overall were highest among persons 65 years and older (127.7 per 100 000; interval estimate, 92.6-156.9), blacks (66.5 per 100 000; interval estimate, 43.5-63.1), and males (37.5 per 100 000; interval estimate, 26.8-39.5) (Table 4). Rates were lowest among persons aged 5 to 17 years (1.4 per 100 000; interval estimate, 0.8-1.7).

The standardized mortality rate was 6.3 per 100 000 (interval estimate, 3.3-7.5) overall, and was higher among persons 65 years and older (35.3 per 100 000; interval estimate, 18.4-44.7), blacks (10.0 per 100 000; interval estimate, 5.7-9.9), and males (7.4

per 100 000; interval estimate, 3.7-8.9) (Table 4). Among persons with MRSA, mortality for health care–associated, community-onset infections was higher (3.2 per 100 000; interval estimate, 1.7-3.7) than for health care–associated, hospital-onset infections (2.5 per 100 000; interval estimate, 1.2-3.1) or for community-associated infections (0.5 per 100 000; interval estimate, 0.3-0.6).

There were 5287 infections reported in the surveillance areas during 2005; after adjusting for age, race, and sex to the US population, we estimated that 94 360 (interval estimate, 72 850-104 000) patients had an invasive MRSA infection. There were 988 reported deaths, which we estimated were 18 650 (interval estimate, 10 030-22 070) in-hospital deaths subsequent to invasive MRSA infections in the United States (Table 4).

Pooled among all sites, we looked at the frequency of reports over the 18-month period from July 2004 through December 2005. The number of cases reported per month ranged from 443 in August 2004 to 541 in September 2005. Among all cases reported in the 18-month period, the percentage with community-associated infections ranged from 4.2% in April 2005 to 6.6% in July, August, and October 2005. When limiting the evaluation to only the 172 community-associated pneumonia reports, there was no apparent clustering by season (data not shown).

Established MRSA Risk Factors and Spectrum of Disease

Apart from community-associated cases which, by definition, had no established health care risk factors for MRSA, 4105 of 5250 (78.2%) cases with health care–associated, community-onset infections and 1993 of 2389 (83.4%) cases with health care–associated, hospital-onset infections had more than 1 health care risk factor for MRSA documented in medical records. The most common health care risk factors among cases with community-onset infections and hospital-onset infections were a history of hospitalization (76.6% and 57.7%, respectively), history of surgery (37.0% and 37.6%), long-term–care residence (38.5% and 21.9%), and MRSA infection or colonization (30.3% and 17.4%).

Of the 8792 cases with complete information, the clinical syndrome associated with invasive MRSA disease included bacteremia (75.2%), pneumonia (13.3%), cellulitis (9.7%), osteomyelitis (7.5%), endocarditis (6.3%), and septic shock (4.3%). Almost all cases (8304 [92.4%]) were hospitalized, 1598 (17.8%) of all cases died during hospitalization, and 1162 (12.9%) developed recurrent invasive infections. Cases with endocarditis had a high frequency of recurrent infections (108 [19.3%]). Clinical outcome was recorded for 8849 cases (98%). Crude

Table 4. Numbers and Incidence Rates of Invasive Methicillin-Resistant *Staphylococcus aureus* (MRSA) Infections and Deaths, by Selected Demographic Characteristics and Epidemiologic Classifications, Active Bacterial Core Surveillance, United States, 2005[a]

	Invasive MRSA Infections						Invasive MRSA Deaths					
			Incidence per 100 000						Incidence per 100 000			
				Health Care–Associated						Health Care–Associated		
Demographic	Actual No.	Estimated No.	Community	Community-Onset	Hospital-Onset	Total	Actual No.	Estimated No.	Community	Community-Onset	Hospital-Onset	Total
Sex												
Male	3066	54 790	6.1	20.6	10.1	37.5	571	10 840	0.8	3.9	2.7	7.4
Female	2220	39 360	3.2	14.7	7.9	26.3	417	7820	0.3	2.6	2.2	5.2
Age, y												
<1	60	950	3.5	4.7	14.7	23.1	5	80	0	0.3	1.6	2.0
1	9	160	2.9	0.0	1.0	3.8	0	0	0	0	0	0
2-4	18	290	0.8	1.0	0.6	2.4	1	10	0	0	0.1	0.1
5-17	47	730	0.6	0.4	0.3	1.4	3	60	0	0	0.1	0.1
18-34	434	7050	3.2	4.2	2.4	10.1	31	460	0.1	0.2	0.3	0.7
35-49	1082	16 100	6.3	11.9	5.3	24.3	92	1400	0.4	0.8	0.9	2.1
50-64	1327	22 120	6.7	23.9	12.1	43.9	224	3640	0.9	3.2	2.9	7.2
≥65	2308	46 970	8.9	78.2	39.1	127.7	632	13 000	2.1	19.7	13.4	35.3
Race												
White	2716	66 590	3.8	15.3	8.1	27.7	596	14 270	0.4	3.1	2.4	5.9
Black	1794	25 980	10.9	37.2	16.6	66.5	263	3900	0.2	4.8	3.7	10.0
Other	139	1790	1.6	5.4	3.3	10.4	38	480	0.1	1.3	1.2	2.8
Total (interval estimates)	5287	94 360 (72 850-104 000)	4.6 (3.6-4.4)	17.6 (14.7-18.2)	8.9 (6.1-11.8)	31.8 (24.4-35.2)	988	18 650 (10 050-22 100)	0.5 (0.3-0.6)	3.2 (1.7-3.7)	2.5 (1.2-3.1)	6.3 (3.3-7.5)

[a] Epidemiologic classification of disease consisted of healthcare-associated (either hospital-onset cases with a culture collected >48 hours after hospital admission or community-onset cases with healthcare risk factors but a culture collected ≤48 hours after hospital admission) and community-associated cases (those with no healthcare risk factors). There were 638 cases and 91 deaths with unknown race.

mortality varied by MRSA-related diagnosis, with high rates observed among cases with septic shock (55.6%) and pneumonia (32.4%), low rates among those with cellulitis (6.1%), and moderate rates among those with bacteremia (10.2%) or endocarditis (19.3%). The proportion of cases presenting with each major clinical condition varied between epidemiologic classifications (TABLE 5). Compared with the distribution of syndromes among cases with community-associated infections, bacteremia was more common, and cellulitis and endocarditis were significantly less common, among each of the cases with health care–associated infections.

Empirical therapy was documented for 5730 of the 8987 cases (63.8%). Overall, 4720 cases (82.4%) received concordant empirical therapy. Differential outcomes based on discordant therapy were not evaluated, since required data such as dose, duration, therapy changes, and adjunctive therapy were not abstracted. Receipt of concordant therapy was slightly lower among cases with community-associated infections compared with those having health care–associated infections either of community onset (80.1% vs 82.9%, respectively; $P = .03$) or hospital onset (80.1% vs 86.0%, $P < .001$). Vancomycin was the antimicrobial agent most frequently used for empirical therapy (75%), followed by semisynthetic penicillins (28%) and fluoroquinolones (26%). Similar proportions of cases were prescribed monotherapy (31.3%), therapy with 2 antimicrobials (37.9%), or therapy with more than 2 antimicrobials (30.9%).

Table 5. Number and Percentage of Invasive Methicillin-Resistant *Staphylococcus aureus* Infections by Clinical Condition and Epidemiologic Classification, Active Bacterial Core Surveillance, United States, July 2004-December 2005[a]

Condition[b]	Community-Associated (n = 1226)	Health Care–Associated, No. (%)		Total, No. (N = 8792)[c]
		Community-Onset (n = 5191)	Hospital-Onset (n = 2375)	
Bacteremia	798 (65.1)	4019 (77.4)[e]	1794 (75.5)[e]	6611
Pneumonia	172 (14.0)	616 (11.9)[d]	383 (16.1)	1171
Cellulitis	278 (22.7)	456 (8.8)[e]	114 (4.8)[e]	848
Osteomyelitis	99 (8.1)	415 (8.0)	142 (6.0)[d]	656
Endocarditis	155 (12.6)	341 (6.6)[e]	60 (2.5)[d]	556
Septic shock	46 (3.8)	233 (4.5)	99 (4.2)	378

[a] Epidemiologic classification of disease consisted of health care–associated (either hospital-onset cases with a culture collected >48 h after hospital admission or community-onset cases with health care risk factors but a culture collected ≤48 h after hospital admission) and community-associated cases (those with no health care risk factors).
[b] Cases could have ≥1 clinical syndrome.
[c] Of 8987 observed cases with invasive methicillin-resistant *Staphylococcus aureus*, 114 (1.3%) could not be classified and 81 had missing condition.
[d] $P < .05$.
[e] $P < .01$; all comparisons use community-associated as the referent category.

Table 6. Number and Percentage of Pulsed-Field Types USA100 and USA300 of Methicillin-Resistant *Staphylococcus aureus* Isolates, Active Bacterial Core Surveillance Sites, United States, 2005[a]

Surveillance Site No. (Location)[b]	No. of Cases	Isolates at Each Site, No. (%)			
		Isolates	USA100	USA300	Other
1 (Connecticut)	1583	142 (9.0)	109 (76.8)	5 (3.5)	28 (19.7)
2 (Atlanta, GA, metropolitan area)	1995	134 (6.7)	36 (26.8)	64 (47.8)	34 (25.4)
3 (San Francisco, CA, Bay Area)	1604	141 (8.8)	66 (46.8)	53 (37.6)	22 (15.6)
4 (Denver, CO, metropolitan area)	805	85 (10.6)	68 (80.0)	14 (16.5)	3 (3.5)
5 (Portland, OR, metropolitan area)	562	175 (31.1)	83 (47.4)	77 (44.0)	15 (8.6)
6 (Monroe County, NY)	546	81 (14.8)	61 (75.3)	13 (16.3)	7 (8.6)
7 (Davidson County, TN)	423	40 (9.5)	23 (57.5)	15 (37.5)	2 (5.0)
9 (Ramsey County, MN)	130	66 (50.8)	54 (81.1)	11 (16.7)	1 (1.5)
Total	7648	864 (11.3)	500 (6.5)	252 (3.3)	112 (1.5)

[a] Isolates not available from site 7, so total does not include 1339 cases reported from that site.
[b] Site numbers were assigned in descending order of population size.

Pulsed-Field Typing

PFGE results were available for 864 of the 1201 (71.9%) isolates received from 8 of the 9 ABCs sites (isolates were not available from site 7); these results represent 11.3% of the 7648 cases reported from these 8 sites (TABLE 6). Of these results, 81.6% were from blood cultures, 4.7% from bone, 4.8% from synovial fluid, 1.9% from pleural fluid, 1.5% from peritoneal fluid, and the remaining 5.5% from other normally sterile sites; this culture site distribution is similar to the distribution of culture sites reported among all 8987 cases. Isolates tested were associated with all of the major clinical conditions previously described, including uncomplicated bacteremia (69.8%), pneumonia (19.3%), cellulitis (11.3%), osteomyelitis (10.4%), endocarditis (8.5%), and septic shock (5.0%).

USA300 was the strain type identified for 100 of 150 (66.6%) isolates from community-associated cases and also was found among 108 of 485 (22.2%) isolates from health care–associated, community-onset cases and among 34 of 216 (15.7%) health care–associated, hospital-onset cases (TABLE 7). Also, 35 of 150 (23.0%) isolates from community-associated cases were USA100. In contrast, other strains of community origin (USA400, USA1000) were rare, accounting for only 3 of 150 (2.0%) isolates from community-associated cases, perhaps reflecting that these isolates all come from normally sterile sites and not skin abscesses, where these strain types have often been reported. USA100 and USA300 were the predominant pulsed-field types in each surveillance site, with the exception of site 1 (state of Connecticut) (Table 6).

COMMENT

These data represent the first US nationwide estimates of the burden of invasive MRSA disease using population-based, active case finding. Based on 8987 observed cases of MRSA and 1598 in-hospital deaths among patients with MRSA, we estimate that 94 360 invasive MRSA infections occurred in the United States in 2005; these infections were associated with death in 18 650 cases. The standardized incidence rate of invasive MRSA for calendar year 2005 was 31.8 per 100 000 persons. The incidence of other important invasive pathogens in 2005, such as invasive infections with *S pneumoniae* or *Haemophilus influenzae*, ranged from 14.0 per 100 000 to less than 1 per 100 000, largely due to the availability and success of vaccination.[31-33]

The estimated 94 360 infections is larger than the estimate from a recent study using hospital discharge–coded data; in 2000, the CDC estimated that there were 31 440 hospitalizations for MRSA bacteremias (ie, septicemia) in the United States.[34] Some of the discrepancy may relate to a more inclusive definition of invasive disease in our study and to the limitations inherent in discharge coded data. Of the estimated 94 360 infections from this study, 75.2% were bacteremias, and 26.6% were of hospital onset; thus, our estimates would yield approximately 18 900 MRSA, hospital-onset bacteremias. In 2002, the CDC estimated that there were 248 678 hospital-acquired bacteremias in the United States,[35] of which approximately 20 390 (8.2%) could be expected to be MRSA[20]—a result consistent with our findings.

Regarding community-associated MRSA, noninvasive infections with MRSA greatly outnumber invasive MRSA infections. In fact, when 3 of the ABCs sites began surveillance in 2000 for all MRSA infections, only 7% represented invasive disease. However, findings described here further document that invasive MRSA disease does occur in persons without established health care risk factors,[28] is associated with strains of both community and health care origin,[36] and is associated with significant mortality. Molecular analysis of isolates in our study provides evidence supporting other studies[36] showing that strains of community origin do now cause some hospital-onset disease but also that, overall, most invasive MRSA disease is still caused by MRSA strains of health care origin.

Table 7. Pulsed-Field Gel Electrophoresis Type of Methicillin-Resistant *Staphylococcus aureus* Isolates Cultured From Invasive Sites, by Epidemiologic Case Classification, Active Bacterial Core Surveillance, July 2004-December 2005 (n = 864)[a]

	No. (%)				
		Community-Onset			
Pulsed-Field Type	Hospital-Onset	Health Care–Associated	Community-Associated	Unknown	Total
USA100	160 (74)	303 (62)	35 (23)	2 (15)	500 (58)
USA200	5 (2)	9 (2)	0	0	14 (2)
USA300	34 (16)	108 (22)	100 (67)	10 (77)	252 (29)
USA400	1 (<1)	4 (1)	1 (<1)	0	6 (<1)
USA500	9 (4)	30 (6)	4 (3)	0	43 (5)
USA600	1 (<1)	4 (1)	0	0	5 (<1)
USA700	0	0	1 (<1)	0	1 (<1)
USA800	0	6 (1)	1 (<1)	0	7 (1)
USA1000	0	3 (1)	2 (2)	0	5 (<1)
Iberian	4 (2)	6 (1)	3 (2)	1 (8)	14 (2)
Not typeable[b]	2 (1)	12 (2)	3 (2)	0	17 (2)
Total	216	485	150	13	864

[a] Epidemiologic classification of disease consisted of health care-associated (either hospital-onset cases with a culture collected >48 h after hospital admission or community-onset cases with health care risk factors but a culture collected ≤48 h after hospital admission) and community-associated cases (those with no health care risk factors).
[b] *Sma*I pulsed-field gel electrophoresis typing was successful in giving these isolates a pattern number, but numbers were outside of the 80% similarity range.

Compared with rates of invasive MRSA infections in 2 of our sites from 2001-2002, the incidence of invasive MRSA has increased in 2005 from 19.3 per 100 000 to 33.0 per 100 000 in Atlanta and from 40.4 per 100 000 to 116.7 per 100 000 in Baltimore.[13] These increases were in both community- and health care–associated disease. However, in the state of Connecticut, the rate of community-onset MRSA bacteremias has been relatively stable at 2.5 per 100 000 in 1998[29] and 2.8 per 100 000 in 2005.

We describe striking differences in rates of invasive MRSA infections by race among all age groups. Connecticut documented a disparity for community-onset *S aureus* bacteremias in 1998.[29] More recently, surveillance in Atlanta reported a significantly higher rate of community-associated MRSA among blacks compared with whites[13]; however, little progress has been made in understanding why. It is likely that the prevalence of underlying conditions,[37] at least some of which vary by race,[38] may play a role. The incidence of invasive pneumococcal disease varies widely by underlying chronic illness, but racial disparities persist for all conditions evaluated.[39] MRSA prevalence has been linked to socioeconomic status,[40] and this might confound the association between race and incidence of MRSA. Future analyses should focus on understanding reasons for differences in MRSA incidence rates.

The geographic variability in MRSA rates has been documented in other studies.[3,13] In this study we found that areas with lower incidence rates of invasive MRSA overall did not always have lower rates of community-associated MRSA. For example, site 6 (Monroe County, New York) had a relatively high rate of invasive MRSA overall (41.9 per 100 000) but a low rate of community-associated MRSA (2.7 per 100 000); site 5 (the Portland, Oregon, metro area) had a relatively low rate of invasive MRSA overall (19.8 per

100 000) but a high rate of community-associated MRSA (4.7 per 100 000). In addition to factors already mentioned such as socioeconomic status and underlying conditions, MRSA rates may be higher in urban areas.[29] As with differences in the incidence of invasive MRSA by race, geographic differences are probably multifactorial and complex. Improved understanding can help design and focus prevention messages as well as increase the timeliness of diagnosis and clinical management of invasive infections.

The majority of invasive MRSA cases occurred outside of the hospital (58%) but among persons with established risk factors for MRSA, such as a history of hospitalization in the past year. This observation was also made recently in a study from a single facility.[30] Patients with health care risk factors and community-onset disease likely acquired the pathogen from their health care contacts, such as those from a recent hospitalization or nursing home residence. Molecular analysis suggests that most of these infections were caused by MRSA strains of health care origin. If, in fact, these infections represent acquisition during transitions of care from acute care,[41] it follows that strategies to prevent and control MRSA among inpatients,[42,43] if properly applied, may have an impact on these infections as well as on the traditional hospital-onset infections. Since interventions for MRSA prevention are inconsistently implemented in US hospitals,[44] correlating the impact on either inpatient or outpatient disease will be challenging. Interventions used in the community to control outbreaks consist of improving hygiene and infection control along with enhanced surveillance, diagnosis, and appropriate treatment of infections[45-47]; however, studies of the effectiveness of community-based prevention and control interventions are lacking.

Our estimates have certain limitations. First, we may have underestimated the incidence of invasive MRSA disease if persons in the surveillance areas sought health care from facilities using laboratories outside the surveillance area. However, any underestimate is probably minor in light of the estimates derived from discharge data on MRSA hospitalizations.[34]

Second, we may have overestimated the incidence of community-associated MRSA if health care risk factors were not well documented in medical records. During surveillance conducted in 2000-2001, patient interviews were used to elicit undocumented health care risk factors; however, the effect on reclassification was small.[13]

Third, our surveillance sites were largely urban areas; thus, we might be overestimating the incidence of invasive MRSA.[29] Although our surveillance areas comprise a diverse set of regions and are likely representative of the United States, it is not known whether the incidence rates in the observed populations are actually representative of the distribution of incidence rates in other US cities. Since the methodology of population-based surveillance produces a single point estimate without confidence intervals (ie, all cases are identified), we calculated interval estimates excluding site 7 (Baltimore City) to allow the reader to interpret a range of estimates reflecting different metropolitan areas. Regarding the high observed incidence rates reported by site 7, we conducted an evaluation to determine whether these results were valid, including a review of case-finding methods, elimination of cases to include only those with zip codes represented in the denominator, contamination in any laboratory, and other potential causes for increased rates; however, none were in error.

Fourth, our measures of deaths represented crude, in-hospital deaths, rather than attributable mortality. It is possible that MRSA infection did not cause or contribute to some deaths.

Fifth, the evaluation of isolates in this study was meant to describe strain diversity and to shed light on the potential crossover of strains from a community origin into the hospital setting. The isolate collection was a convenience sample. Furthermore, we only had test results from isolates of 864 (11.3%) of the cases reported; extrapolation of the molecular characterization to the US population should be avoided.

In conclusion, invasive MRSA disease is a major public health problem and is primarily related to health care but no longer confined to acute care. Although in 2005 the majority of invasive disease was related to health care, this may change.

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Acquisition of data: Klevens, Morrison, Nadle, Petit, Ray, Harrison, Lynfield, Dumyati, Townes, Craig, Fosheim.
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