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# Community-Associated Methicillin-Resistant *Staphylococcus aureus*: Epidemiology and Clinical Consequences of an Emerging Epidemic

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## INTRODUCTION

*Staphylococcus aureus* is the most commonly isolated human bacterial pathogen and is an important cause of skin and soft-tissue infections (SSTIs), endovascular infections, pneumonia, septic arthritis, endocarditis, osteomyelitis, foreign-body infections, and sepsis (559). Methicillin-resistant *S. aureus* (MRSA) isolates are resistant to all available penicillins and other β-lactam antimicrobial drugs. They were once confined largely to hospitals, other health care environments, and patients frequenting these facilities. Since the mid-1990s, however, there has been an explosion in the number of MRSA infections reported for populations lacking risk factors for exposure to the health care system (4, 37, 105, 133, 140, 153, 158, 192, 237, 247, 259, 284, 300, 304, 306, 349, 383, 393, 456, 460, 654, 762, 802, 816, 972, 1020, 1029). This increase has been associated with the recognition of new MRSA strains, often called community-associated MRSA (CA-MRSA) strains, that have been responsible for a large proportion of the increased disease burden observed in the last decade. These CA-MRSA strains appear to have rapidly disseminated among the general population in most areas of the United States and affect patients with and without exposure to the health care environment.

The purpose of this review is to detail what is known about the epidemiology of CA-MRSA strains and the clinical spectrum of infectious syndromes associated with them, which ranges from a commensal state to severe, overwhelming infection. We will also discuss the therapy of these infections and strategies for their prevention.

CA-MRSA strains have been distinguished from their health care-associated MRSA (HA-MRSA) counterparts by molecular means. HA-MRSA strains carry a relatively large staphylococcal chromosomal cassette *mec* (SCC*mec*) belonging to type I, II, or III. These cassettes all contain the signature *mecA* gene, which is nearly universal among MRSA isolates. They are often resistant to many classes of non-β-lactam antimicrobials. HA-MRSA strains seldom carry the genes for the Panton-Valentine leukocidin (PVL). In contrast, CA-MRSA isolates carry smaller SCC*mec* elements, most commonly SCC*mec* type IV or type V. These smaller elements also carry the *mecA* gene and are presumably more mobile, although few explicit data support this notion (61). They are resistant to fewer non-β-lactam classes of antimicrobials and frequently carry PVL genes.

In addition to these genotypic characteristics, CA-MRSA strains affect a population distinct from those affected by HA-MRSA and cause distinct clinical syndromes. CA-MRSA infections tend to occur in previously healthy younger patients. They have been associated predominantly with SSTIs (105, 642, 654) but have also been linked to several severe clinical syndromes such as necrotizing pneumonia and severe sepsis. In contrast, HA-MRSA strains have been isolated largely from people who are exposed to the health care setting; the patients are older and have one or more comorbid conditions. HA-MRSA strains tend to cause pneumonia, bacteremia, and invasive infections.

CA-MRSA infections, far from being the clinical curiosity that they were in the mid-1990s, have become commonplace and have created a public health crisis in U.S. emergency departments (EDs) and other clinical settings. A population-based study of MRSA infections in San Francisco, CA, in 2004 to 2005 demonstrated that 90% of MRSA infections had onset in the community, with an incidence rate of 316 cases/100,000 population; excluding those with a history of hospitalization in the previous year, the incidence rate was 243 cases/100,000 population. There were many fewer hospital-onset infections, with an incidence of 31 cases/100,000 population (543). Furthermore, a U.S. Centers for Disease Control and Prevention (CDC) study estimated that in 2005, there were 31.8 culture-confirmed invasive MRSA infections in the United States per 100,000 population, amounting to 94,360 cases in that year. Because an estimated 7% of culture-confirmed CA-MRSA infections were invasive (481), it is likely that greater than 1,300,000 MRSA infections, in total, occurred in that year in the United States. Annual outpatient and ED visits for abscesses or cellulitis in the United States were estimated to have nearly doubled from 17.3 to 32.5 cases per 1,000 population between 1997 and 2005 (384), and CA-MRSA isolates are

believed to be largely responsible for this rise. In some regions, CA-MRSA isolates account for 75% of community-associated *S. aureus* infections in children (460).

Complicating the epidemiological framework, some community-onset MRSA (CO-MRSA) infections are caused by HA-MRSA strains, perhaps related to the increasingly common management of complex HA-MRSA infections at home. Thus, MRSA in the community has a complex epidemiology arising from the circulation of "escaped," or so-called feral, HA-MRSA strains in the general population (115, 117, 154, 437, 529, 852) and the newly recognized CA-MRSA strains (654).

The emergence of new CA-MRSA strains has important implications. Large reservoirs of MRSA isolates now exist outside health care facilities (188, 277, 385). Obviously, this implies that attempts in the United States to contain MRSA using currently accepted methods of infection control based in health care facilities are unlikely to succeed without a similar effort to control spread in the community (154, 186, 217, 543). Additionally, MRSA infections may be more expensive and difficult to treat than infections caused by methicillin-susceptible *S. aureus* (MSSA) (741). There are relatively few antibiotic agents available to treat MRSA infections (210). Moreover, the available agents have important limitations, and the development of new antibiotic classes has slowed (882, 994). *S. aureus* isolates that are resistant to each of the few antibacterial drug classes effective against MRSA have been reported (242, 562, 586, 599, 776), raising the theoretical possibility of untreatable multidrug-resistant (MDR) *S. aureus* infections.

With the antibiotic pressure exerted by the increasing use of vancomycin to treat MRSA infections, nine vancomycin-resistant *S. aureus* (VRSA) isolates have now been reported in the United States (142, 145, 146, 151, 286, 996). Vancomycin-intermediate *S. aureus* (VISA) strains, first reported in Japan in 1996 (389, 391), have been identified more commonly in many countries, including the United States (143, 542). The recognition of these strains represents an ominous threat (210). Perhaps a more important concern comes from the observed slow but steady increase in the level of resistance to vancomycin among unselected *S. aureus* strains that can occur with vancomycin therapy (327, 795, 892, 973). Therefore, clinical reliance on vancomycin—the centerpiece of our armamentarium against invasive MRSA infections—may no longer be possible (229).

## EMERGENCE AND HISTORY OF MRSA

In 1961, soon after the introduction of methicillin, the first β-lactamase-resistant penicillin, strains of *S. aureus* that were resistant to methicillin were identified in the United Kingdom (438). From the 1960s into the early 1970s, MRSA infections in Europe were limited largely to hospital outbreaks caused predominantly by *S. aureus* phage type 83A (subsequently identified to be sequence type 250 [ST250]); this so-called "archaic clone" gradually became infrequent and was replaced in the 1970s and 1980s by five prevalent clonal lineages (10, 267, 771), although many MRSA backgrounds existed between the 1960s and 2000 (999). In the United Kingdom, MRSA was rare until the early 1990s and has since gradually increased in frequency as a nosocomial pathogen (347). The first case of MRSA infection recorded in Australia was in Sydney in 1965. Thereafter, nosocomial MRSA infections occurred sporadically in Melbourne and Sydney (323) and later appeared in other cities. Most Australian nosocomial MRSA isolates had a distinctive antibiogram, with resistance to trimethoprim-sulfamethoxazole (TMP-SMX), erythromycin, clindamycin, tetracycline, and gentamicin (919). Western Australia remained relatively free of MRSA until the late 1980s, when a distinctive non-MDR (gentamicin-susceptible) MRSA strain appeared in a remote northern region and quickly spread to the rest of Western Australia (908). In Queensland, Eastern Australia, in 2000 to 2006, population-based surveillance of antibiotic resistance patterns of MRSA strains causing infections among inpatients demonstrated an increase from 71 to 315 cases/1 million accrued patient-days for non-MDR (i.e., resistant to at least one non-β-lactam antibiotic and susceptible to ciprofloxacin)-resistant strains. A similar large increase was documented among outpatients during this period, from 52 to 490 cases/1 million outpatient visits, suggesting a rapid dissemination of the non-MDR MRSA strains. At the same time, the rates of inpatient bloodstream infection and other sites of infection caused by any MRSA strain decreased by 35% and 26%, respectively, while among outpatients, the rates increased by 31% and 224%, respectively (671). In Japan, MRSA isolates have been prevalent in academic hospitals since the late 1980s and spread into community hospitals in the 1990s (465), and while community-associated MRSA infections have been reported (465, 723, 881), the first clinical isolate known to carry the PVL genes in the CA-MRSA era was reported in 2003 (429, 881).

In contrast, in Finland, Norway, Sweden, the Netherlands, and Denmark, MRSA infections have remained rare even in the health care setting, which has been attributed by many to strict surveillance programs that have been the norm for decades in each of these nations (18, 469, 843, 860, 899).

In 1968, the first hospital outbreak of MRSA in the United States was reported from Boston, MA (45). In the 1960s to the 1990s, MRSA gradually became entrenched as an endemic pathogen in large, urban, university hospitals in the United States, particularly in intensive care units (ICUs). Subsequently, the percentage of *S. aureus* isolates from hospitalized patients in the United States that were resistant to methicillin increased from 2.4% in 1975 to 29% in 1991 (704). A diagnosis of MRSA infection was made for approximately 125,969 hospitalizations per year in the United States in 1999 to 2000 (493). Between January 1998 and June 2003, the annual average percentage of *S. aureus* isolates that were MRSA increased further to 51.6% of ICU and 42% of inpatient non-ICU *S. aureus* isolates (240). Similar persistently high or increasing rates of MRSA among *S. aureus* isolates have also been observed for health care settings in many other regions of the world (11, 32, 181, 253, 278, 291, 394, 539, 579, 692, 899).

Prior to the mid-1990s, investigation into the epidemiology of MRSA was limited largely to the health care setting because it was rare that MRSA strains would infect otherwise healthy people. The recognized risk factors then identified for MRSA infection and colonization included recent hospitalization; other exposures to the health care system; residence in a long-term care facility (91, 95, 245, 246, 524, 637, 638, 649, 864, 867, 897) or an acute-rehabilitation unit (578); the presence of an indwelling line or catheter; surgical wounds; chronic liver, lung, or vascular disease; malignancy; recent exposure to antibiotics;

intravenous drug use (130); ICU admission; and exposure to a patient with any of these risk factors for MRSA (148, 383, 559, 914).

## WHAT IS COMMUNITY-ASSOCIATED MRSA?

The terms CA-MRSA and HA-MRSA have been used to call attention both to the genotypic differences of certain MRSA isolates as well as to the epidemiological and clinical features of the infections that they cause. This sometimes loose interchange of terms has created confusion (216, 606, 796, 878). An essential component of epidemiological studies has been to define the clinical burden of CA-MRSA and HA-MRSA isolates, both of which circulate in the community. Important concepts bearing on these definitions are (i) the setting in which the MRSA infection begins; (ii) current or prior patient exposure to health care settings; (iii) poorly defined CA-MRSA patient risk factors, including prior MRSA infection; (iv) genetic characteristics and antibiotic susceptibilities of the causative MRSA isolate; and (v) the clinical syndrome manifested by the patient.

In 2000, the CDC created a case definition for a CA-MRSA infection: any MRSA infection diagnosed for an outpatient or within 48 h of hospitalization if the patient lacks the following health care-associated MRSA risk factors: hemodialysis, surgery, residence in a long-term care facility or hospitalization during the previous year, the presence of an indwelling catheter or a percutaneous device at the time of culture, or previous isolation of MRSA from the patient (132, 635). All other MRSA infections were considered to be HA-MRSA. This case definition was initially used to demonstrate that MRSA infections were occurring among healthy people in the community without health care exposure (306, 654). The case definition has been modified for the purposes of the CDC's Active Bacterial Core Surveillance Program for invasive MRSA infections to exclude the previous isolation of MRSA as a criterion for HA-MRSA (481).

A simpler, temporal definition is often used to designate CA-MRSA. By this criterion, all infections occurring among outpatients or among inpatients with an MRSA isolate obtained earlier than 48 h after hospitalization would be considered CA-MRSA. Infections meeting either of these temporal criteria are sometimes referred to as "community-onset" MRSA (CO-MRSA) infections.

Other criteria used to define CA-MRSA infections relate to relevant isolate characteristics. CA-MRSA isolates have been pedigreed by their antimicrobial susceptibility profiles, their DNA fragment patterns upon pulsed-field gel electrophoresis (PFGE) (587, 595, 894), protein A (*spa*) gene typing (486, 866, 868), carriage of PVL genes (540), multilocus sequence typing (MLST) (266, 268), and the type of SCC*mec* element carried (427). Definitions based on one or more of these isolate characteristics have been used to quantify the MRSA disease burden inside and outside the health care setting, but each one actually provides a different perspective. Importantly, none of the genotypic isolate characteristics are helpful to a clinician caring for an acutely ill patient because assessing them requires molecular strain testing that is not routinely or rapidly available (216).

When the CDC case definition is used to define the burden of disease caused by CA-MRSA isolates, two interesting phenomena can be demonstrated. The application of the definition to cases of infection with MRSA with onset in the community accurately identifies patients with infections caused by CA-MRSA isolates. However, if one uses the case definition to identify patients with infection caused by CA-MRSA isolates, the burden of disease caused by CA-MRSA isolates will be greatly underestimated (216, 217), and this analysis yields a reciprocal overestimation of health care-associated MRSA disease.

TABLE 1. Characteristics associated with CA-MRSA among consecutive MRSA isolates obtained from patients at the University of Chicago Medical Center in 2004 to 2005[a]

| Strain characteristic | % of strains with indicated characteristic ($n$ = 616) |
|---|---|
| Panton-Valentine leukocidin gene carriage | 54.6 |
| SCC*mec* type IV or V carriage | 62.8 |
| MLST-8 or MLST-1 | 59.7 |
| Clindamycin susceptibility | 56.3 |
| Non-multidrug-resistant susceptibility pattern | 62.5 |

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If the CDC case definition of CA-MRSA were used in the acute-care setting to aid in the selection of empiric antibiotic therapy, many people who could be managed with clindamycin, for example, would be unnecessarily treated with intravenous antimicrobial drugs because they have an illness caused by a CA-MRSA isolate and not a multiply resistant HA-MRSA isolate (217). The CDC case definition applied to patients with an MRSA infection is not a reliable proxy for the genetic characteristics or phenotype of the MRSA strain causing the infection. For example, at the University of Chicago in 2004 to 2005, the CDC definition would have classified 65.6% (404/616) of MRSA patients as having an HA-MRSA infection. However, among these "HA-MRSA" patients, 47% of the isolates carried SCC*mec* type IV, 35.9% were PVL positive ($PVL^+$), and 40.1% were ST8 (Table 1) (216), traits attributed to CA-MRSA isolates. These data may have relevance to a large, recent study that estimated that only 8 to 20% of MRSA infections in three communities in the United States were CA-MRSA infections (306) when the CDC definition was applied. It is probable that many more than 8 to 20% of these infections were caused by novel CA-MRSA strains.

Since about 2003, the distinctions between CA-MRSA and HA-MRSA isolates have become increasingly blurred. As mentioned above, HA-MRSA isolates do circulate in the community, especially among adults. Additionally, many reports have demonstrated that MRSA clones bearing SCC*mec* type IV, and particularly USA300, the predominant U.S. CA-MRSA PFGE type, now cause nosocomial MRSA outbreaks and infections among patients with chronic illnesses (Table 2). For example, among bloodstream infections in Atlanta, GA, in 2004, 34% of nosocomially transmitted isolates belonged to the USA300 CA-MRSA genotype (820), and in a Detroit, MI, hospital in 2005 to 2007, USA300 accounted for 20% (9/45) of tested nosocomial bloodstream infections (171). A study of

TABLE 2. Reports of CA-MRSA strains likely acquired in the health care setting in 1995 to 2008

| Location | Setting/source | Yr | Description | Reference |
|---|---|---|---|---|
| North America | | | | |
| Los Angeles, CA | Hospital | 2004 | Breast milk transmission of MRSA in neonatal intensive care unit | 313 |
| Los Angeles, CA | Hospital | 1999–2004 | SCC*mec* type IV MRSA infections | 580 |
| Atlanta, GA | Hospital | 2003–2004 | 2 prosthetic joint infections caused by USA300 strains | 487 |
| Atlanta, GA | Hospital | 2004 | 34% of nosocomial MRSA bloodstream infections were USA300 | 820 |
| Iowa City, IA | Hospital | 2002–2006 | USA300 in burn trauma unit | 998 |
| Chicago, IL | Hospital | 2000–2006 | Non-MDR MRSA strains | 732 |
| Chicago, IL | Hospital | 2005–2007 | USA300 strains in kidney transplant recipients | 7; T. Stosor, personal communication |
| Denver, CO | Hospitals | 2003–2007 | USA300 bacteremia | 436 |
| Detroit, MI | Hospital | 2000–2005 | SCC*mec* type IV and $PVL^+$ MRSA in end-stage renal disease patients | 444 |
| Detroit, MI | Hospital | 2005–2007 | USA300 bloodstream infections | 171 |
| Detroit, MI | Hospital | 2006 | SCC*mec* type IV and $PVL^+$ MRSA in end-stage renal disease patients | 445 |
| Detroit, MI | Hospital | 2005–2006 | 36 USA300 infections with onset >48 h after hospital admission | 626 |
| New York City | Hospital | 2002 | USA400 infection in nursery | 93 |
| New York City | Hospital | 2002 | Non-multidrug-resistant MRSA-caused postpartum infections | 794 |
| Houston, TX | Veteran's hospital | 2003–2004 | USA300 bloodstream infections | 329 |
| San Antonio, TX | Hospital | Not stated | Pneumonia in neonate and colonization of other patients with USA300 strain | 590 |
| United States | Population-based national estimate | 2005–2006 | 12.1% of HA-MRSA (by CDC criteria) invasive infections caused by USA300 strains | 537 |
| Toronto, Ontario, Canada | Maternal-newborn unit, hospital | 2004 | Colonization or infection of 38 babies and 7 mothers by USA300 | 803 |
| 7 Canadian cities | Pathogens from ICU patients | 2005–2006 | 18/193 MRSA isolates were USA300 or USA400 reported from ICU surveillance project from 19 medical centers in Canada; all USA300 and USA400 strains were from 7 cities | 1026 |
| Asia | | | | |
| Taiwan | Hospital | 1999–2005 | SCC*mec* type IV MRSA | 414 |
| Taiwan | Hospital | 1995–2006 | ST59 $PVL^+$, SCC*mec* type IV or $V_T$ MRSA accounted for 18.7% of 257 MRSA bloodstream infections | 160 |
| Australia | | | | |
| Western Australia | Hospital | 1995–1996 | Outbreak of MRSA infections caused by a strain commonly isolated in the community | 681 |
| Europe | | | | |
| Paris, France | University hospital | 2001–2003 | $PVL^+$, SCC*mec* type IV MRSA infections | 650 |
| Centre Region, France | Hospitals | 2004–2006 | Non-MDR MRSA strains | 934 |
| Poland | Hemodialysis patient | 2004 | ST80 SCC*mec* type IV, $PVL^+$ colonizing strain | 80; A. Bogut, personal communication |
| Birmingham, United Kingdom | Hospital | 2004 | CA-MRSA in neonatal care unit | 214 |
| West Midlands, United Kingdom | Hospital | 2006 | $PVL^+$, likely ST30 strain caused fatal pneumonia, sepsis, and shock in a health care worker | 376 |
| South America | | | | |
| São Paulo, Brazil | Hospital | 2002–2003 | SCC*mec* type IV MRSA infection | 912; A. Levin, personal communication |
| Uruguay | Hospitals | 2003–2004 | USA1100 MRSA strains | 58 |

surgical skin site infections in Birmingham, AL, from 2004 to 2005 demonstrated that USA300 was a common nosocomial pathogen (716) that first appeared in this setting in 2004 (715). The appearance of CA-MRSA strains in hospitals in the United States is likely responsible for the decreasing non-β-lactam antimicrobial resistance rates noted for MRSA isolates in ICUs between 1992 and 2003 (479). The presence of USA300 increased among MRSA isolates from a 1,000-bed long-term care facility in San Francisco, CA, from 11.3% in 2002 to 64% in 2006 (889).

Given the complex epidemiology of CA-MRSA strains in health care settings and the circulation of HA-MRSA strains that occurs in the community, establishing a clear delineation between CA-MRSA and HA-MRSA strains has not been possible. CDC investigators have used a third category of MRSA infections, "health care-associated, community-onset" MRSA (HACO-MRSA) infection (480); this category includes cases that would be HA-MRSA infections by history of health care exposure but have onset in the community. This tripartite classification scheme, HA-, CA-, and HACO-MRSA, still has limitations because a history of exposure to a health care setting does not exclude the possibility of MRSA acquisition and infection in the community (217, 481).

The complex system of nomenclature now in use for MRSA infections in the United States is based on the historical limitation of MRSA infections to the health care system and among those with exposure to it. A revision of the nomenclature is warranted; to better reflect the contemporary epidemiology of MRSA, a paradigm shift is required.

### CA-MRSA: an Epidemic and Its Origins

Scattered case reports describing patients with none of the known health care-associated risk factors for MRSA that had MRSA colonization or a clinical infection were published in the 1980s and the mid-1990s (29, 64, 205, 339, 359, 530, 711, 748, 801), including several outbreaks caused by different MRSA strain types in remote regions in Western Australia and then in the Northern Territory of Australia (670). Subsequently, beginning in 1993, case series of MRSA infection and colonization of patients lacking health care-associated risk factors were reported from six continents, in diverse states, nations, and regions (Table 3).

In many countries, MRSA cases among patients without health care risk factors were reported for only small outbreaks or case series, while in the United States, Taiwan, Canada, and Australia, such MRSA infections in patients lacking health care exposure became common. CA-MRSA strains, often responsible for these infections, became endemic pathogens in certain population groups in each of these countries. Within the United States, the incidence of invasive CA-MRSA infections has not been geographically homogeneous (481), and the reasons for this are not understood. The highest prevalence of MRSA colonization recorded (with testing of several anatomical sites) was 42% (18/43 people tested) in a village in Western Australia (681). The impact of globalization has been felt in Scandinavia and other parts of Europe that have a low prevalence of MRSA, where many reported cases of CA-MRSA infection are suspected to have been imported from regions where the disease is endemic (40, 77, 147, 257, 262, 381, 459, 508, 509, 554, 828, 900, 956).

In other regions where the prevalence of CA-MRSA isolates has remained low, community-onset MRSA infections are still more likely to be caused by HA-MRSA strains. For example, HA-MRSA strains were responsible for community-onset bacteremia among military veterans in Taipei, Taiwan, in 1999 to 2002 (165); for community-onset MRSA infections in children in Birmingham, United Kingdom, in 2004 (5); and for SSTIs in outpatients in one region of the United Kingdom in 2005 (774). Few data that describe the epidemiology of MRSA in developing countries are available, but there is concern that CA-MRSA may have devastating consequences if it becomes epidemic in resource-poor regions (666).

An unanswered question is whether CA-MRSA strains are replacing other *S. aureus* strains causing colonization and infection or if they are instead adding to the burden of *S. aureus* infections and colonization in the United States and elsewhere. Evidence to support the latter contention is provided by several studies. For example, a study demonstrated that the number of SSTIs treated in U.S. ERs rose dramatically in 1997 to 2005; the increase was probably driven by CA-MRSA isolate infections (384), the predominant cause of SSTIs in ERs according to a recent study (628). At a children's hospital in St. Louis, MO, the number of abscesses with MSSA isolated in 1999 to 2007 increased 5-fold, while during the same period, the number of isolates with MRSA increased 250-fold. The increase in numbers of MSSA infections was not due to an increase in the number of cultures sent, and the USA300 PFGE pattern was found for six MSSA isolates tested (691). In a long-term care facility in San Francisco, CA, as USA300 became the predominant MRSA strain to cause infections, the incidence of MRSA infections doubled from 1997 to 2006 (889). In contrast, in other geographic locales, there is little evidence that the overall incidence of invasive *S. aureus* infections is increasing as rapidly; instead, it appears that as the number of invasive CA-MRSA infections rise, the number of invasive infections caused by HA-MRSA is decreasing. For example, in Chicago at Cook County Hospital, the incidence density, that is, the person-time incidence rate, of bloodstream infections caused by MRSA diagnosed >72 h after admission in January 2000 to June 2003 did not differ compared with that in July 2003 to December 2006. However, the proportion caused by CA-MRSA strains (defined by a specific antibiotic susceptibility pattern) doubled from 24% to 49% (732). In Denver, CO, at a city-owned hospital and its affiliated clinics, the number of community-acquired (i.e., a culture obtained from an ED or clinic or within 48 h after a hospital admission) *S. aureus* SSTIs did not increase overall, but the percentage caused by MRSA increased from 6% in the first quarter of 2002 to 45% in the second quarter of 2004 ($P < 0.001$) (173). Similarly, in the Calgary Health Region of Canada, as MRSA became a more common cause of *S. aureus* bacteremia in 2000 to 2006, the total incidence of *S. aureus* bacteremia did not rise (512).

A similar trend has been demonstrated for the prevalence of asymptomatic MRSA carriage. For example, there is evidence from population-based surveillance in the United States that as the prevalence of MRSA nasal colonization increased, the

TABLE 3. Cities, states, regions, and countries with reports of CA-MRSA infections and/or colonization in 1993 to 2009

| Location | Reference(s) |
|---|---|
| Africa | |
| Algeria | 56 |
| Egypt | 264 |
| Nigeria | 317 |
| Tunisia | 57 |
| Asia | |
| Cambodia | 164 |
| China | |
| Mainland | 1028 |
| Hong Kong | 395, 398 |
| India | 652 |
| Japan | 429, 465, 697, 723, 828, 881 |
| Kuwait | 920 |
| Malaysia | 799 |
| Saudi Arabia | 13, 16, 106, 107 |
| Singapore | 1001 |
| South Korea | 437, 474, 522, 563, 708, 710 |
| Taiwan | 90, 159, 160, 165, 166, 275, 410, 411, 412, 414, 415, 525, 547, 548, 879, 880, 915, 934, 971, 972, 974, 975, 977, 1012 |
| Australia/Oceania | |
| Australia | 178, 184, 185, 296, 337, 338, 340, 352, 572, 573, 594, 641, 643, 644, 645, 647, 670, 672, 680, 681, 761, 861, 919, 921 |
| New Zealand | 8, 354, 605 |
| Europe | |
| Austria | 348 |
| Belgium | 227 |
| Bulgaria | 657 |
| Denmark | 46, 77, 508, 509, 510, 923 |
| Finland | 459, 462, 469, 798, 924 |
| France | 225, 247, 312, 533, 555, 934, 955 |
| Germany | 199, 574, 1005 |
| Greece | 168, 461, 467, 571, 673, 814, 815, 909, 962 |
| Ireland | 778 |
| Italy | 40, 701, 728, 858, 901, 926, 956 |
| Latvia | 604 |
| Netherlands | 419, 856, 946, 1013, 1016 |
| Norway | 366, 379 |
| Russia | 42, 43 |
| Spain | 208, 579 |
| Sweden | 62, 274, 378, 847, 848 |
| Switzerland | 283, 289, 299, 534, 554, 865 |
| United Kingdom | 257, 262, 381, 439, 556, 693, 694 |
| North America | |
| Canada | 120, 144, 344, 395, 404, 443, 496, 541, 585, 586, 690, 794, 812, 813, 817, 832, 885, 960, 1027 |
| Mexico | 938 |
| United States | |
| Alaska | 36, 37, 125, 218, 504 |
| Alabama | 189, 373, 714 |
| Arkansas | 784 |
| California | |
| Loma Linda | 426 |
| Los Angeles | 140, 432, 607, 608, 609, 850 |
| Sacramento | 405, 406 |
| San Diego | 137, 193, 195, 589 |
| San Francisco | 153, 235, 303, 481, 543, 703, 744, 788, 888, 1020 |
| Colorado | 173, 436, 481 |
| Connecticut | 481, 695 |
| Georgia | 306, 385, 475, 481, 820, 821, 1000 |
| Hawaii | 85, 131, 270, 333 |
| Illinois | 19, 215, 216, 300, 301, 383, 403, 422, 423, 733 |
| Iowa | 846 |
| Kentucky | 446, 811 |
| Maryland | 158, 277, 306, 481 |
| Michigan | 1, 434, 445, 506, 626 |
| Midwestern rural Native American community | 349 |
| Minnesota | 104, 180, 481, 653, 654, 893 |
| Missouri | 308, 596, 691, 810 |
| Nebraska | 359 |
| New England | 235, 237, 279, 515, 541, 876 |
| New York | 94, 481, 743, 827, 891 |
| North Carolina | 100, 570, 824 |
| Ohio | 433 |
| Pennsylvania | 353, 476, 527, 690, 911, 1023 |
| South Dakota | 30 |
| Tennessee | 28, 72, 105, 188, 450, 473, 481, 655, 688, 883 |
| Texas | 12, 156, 175, 248, 261, 284, 293, 421, 442, 460, 499, 630, 739, 740, 791, 841, 842, 855, 898, 993 |
| Virginia | 1545, 863 |
| Washington and Oregon | 123, 223, 481 |
| West Virginia | 356 |
| Wisconsin | 833 |
| South America | |
| Argentina | 310, 852, 903 |
| Brazil | 292, 656, 757, 758, 813, 960 |
| Chile | 675 |
| Colombia | 17, 26 |
| Uruguay | 58, 564 |

overall prevalence of any *S. aureus* nasal colonization decreased (895).

The emergence of CA-MRSA isolates and associated increases in methicillin resistance among *S. aureus* isolates may be recapitulating the epidemiological pattern that marked the increase in the prevalence of penicillin resistance among *S. aureus* isolates circulating in the community that had occurred years earlier. Resistance to penicillin, mediated by the production of β-lactamase, was identified among strains of *S. aureus* almost immediately after the introduction of penicillin in 1944 (477). By the late 1970s more than 80% of these isolates were penicillin resistant, and rates of penicillin resistance have remained in this range since. If the emergence of MRSA is following this pattern (148), the percentage of community-associated *S. aureus* infections caused by MRSA strains may continue to rise in the coming decades and may approach 100%.

Abundant molecular evidence supports the hypothesis that CA-MRSA clones have arisen in the community by the horizontal transfer of SCC*mec* elements and PVL genes, molecular features commonly associated with CA-MRSA isolates as well as perhaps other virulence and resistance factors, to the genomes of MSSA strains (212, 252, 281, 285, 388, 392, 536, 621, 687). However, a comparative study of CA-MRSA isolates from sentinel surveillance health care facilities in Minnesota, North Dakota, and Nebraska showed that locally prevalent CA-MRSA and MSSA strains were related and that the identified CA-MRSA strains differed from HA-MRSA isolates collected at the same facilities (285). Some researchers have proposed that an ST30 MSSA strain first acquired the PVL genes

and then the SCC*mec* type IV element to become a $PVL^+$ MRSA strain now uncommon in the United States (234). However, in Wisconsin, an ST30 strain isolated in the 1980s carrying the SCC*mec* type IV element but lacking PVL genes was identified, possibly representing a precursor to a later $PVL^+$ CA-MRSA strain (92). These observations suggest that the currently prevalent CA-MRSA strains may have developed over several decades of complex evolution.

In Australia, it was hypothesized that new clones of CA-MRSA arose on several occasions in remote aboriginal communities after the introduction SCC*mec* type IV into already prevalent and virulent MSSA background strains (905). In a study of MRSA infections in 2004 to 2005 in the Northern Territory, clonal cluster 75 (CC75) strains (a clonal cluster not described for any other region) represented 25% of *S. aureus* isolates; MRSA and MSSA CC75 strains were both found among these isolates in a ratio of 2:1 (594), suggesting the local transmission of SCC*mec* to an MSSA CC75 clone with subsequent clonal expansion. In contrast, in other remote communities in Australia, such transfers did not occur in the most prevalent MSSA clones colonizing the population (680).

### Why Did CA-MRSA Strains Appear and Succeed?

Several hypotheses to explain the emergence and entrenchment of CA-MRSA isolates have been proposed. None of these hypotheses definitively explain the observed epidemiological data. They are reviewed briefly here.

Because the emergence of new CA-MRSA isolates occurred in the late 1990s in tandem with the increasing use of fluoroquinolones (FQs), some have suggested that the relationship between the phenomena might be more than a coincidence. However, there is no known mechanism to link these phenomena. If they are related, the mechanism must be complex because most CA-MRSA isolates in the United States and Australia have been susceptible to FQs. Circumstantial evidence for an FQ-MRSA association in the health care setting is limited. The increased use of FQ has been associated with the elimination of MSSA strains from the colonization of the nasal mucosa (517), which might predispose one to colonization by MRSA strains. Other ideas have been proposed to link FQ exposure to epidemic CA-MRSA disease. For example, in an *in vitro* study, CA-MRSA strains obtained from subjects with nasal colonization were exposed to a subinhibitory concentration of FQ. In a microarray analysis, this resulted in the increased expression of 53 open reading frames of the exposed CA-MRSA isolates, including *mecA*, suggesting that β-lactam resistance may be increased by FQ exposure (890). Moreover, the restriction of FQ use in the health care setting has been shown to decrease the rate of MRSA isolation (121, 152), and FQ use has been identified as a risk factor for MRSA infection of hospitalized patients (254). Patients with a nosocomial MRSA infection at one medical center in 1997 to 1999 were more likely than patients with a nosocomial MSSA infection to have been previously treated with the FQ levofloxacin (odds ratio [OR], 8.01; 95% confidence interval [CI], 3.13 to 20.3) (345). A study in Hong Kong demonstrated that when MRSA nasal carriers were treated with an FQ or a β-lactam, they had a significantly increased MRSA nasal bacterial burden demonstrated by quantitative nasal culture and an increased likelihood of MRSA contamination of fomites in their environment (163), suggesting that FQ exposure may be associated with the dissemination of MRSA strains. Further circumstantial evidence of a relationship between FQ use and MRSA infection comes from an administrative health database in the United Kingdom, where in 2000 to 2004, 1,981 adults with an MRSA infection and no known health care exposure had a higher risk (OR, 3.37; 95% CI, 2.80 to 4.09) of having an FQ prescribed within the year prior to their MRSA infection than did 19,779 matched controls (809).

Other researchers have noted that the introduction of a routine childhood conjugate pneumococcal vaccination (Prevnar) in the United States in February 2000 coincided with the increase in the CA-MRSA infection rate and suggested that there may be a causal, and not just a temporal, link between the two phenomena. The United States, which has uniquely experienced epidemic CA-MRSA infections, was the only country recommending the vaccine for routine use for several years. Moreover, the recommendation for the routine use of Prevnar in 2002 in Canada may have retrospectively correlated with a rise in CA-MRSA infections there. Conversely, CA-MRSA was already commonly reported from Australia in January 2005 at the time of the addition of Prevnar to the National Immunization Program Schedule for the routine vaccination of children younger than 2 years of age. Prevnar was introduced as a recommended routine childhood vaccine in September 2006 in the United Kingdom, where CA-MRSA has continued to be rare. Only occasional case reports of MRSA infection in the community in the United Kingdom have been published to date. By August 2008, Prevnar was introduced as a routine childhood vaccine in 26 nations, introduced in 18 nations since 2006 (139). If the use of Prevnar is related to CA-MRSA incidence, more countries may experience CA-MRSA epidemics, but it should be noted that the predominant CA-MRSA genetic background differs in much of the world from those in the United States and Canada, and this may affect the association.

Biological plausibility for this relationship has been suggested by the observation that Prevnar vaccinees have decreased asymptomatic carriage of the seven vaccine serotypes of *Streptococcus pneumoniae*. Some researchers have postulated that decreased pneumococcal colonization may provide a new ecological niche for colonization with CA-MRSA strains; this is supported by evidence that the cocarriage of *S. pneumoniae* and *S. aureus* was found rarely among 790 healthy children in Israel in 2002 (753), a country with few CA-MRSA infections. In the Netherlands, a negative correlation was found between colonization by the vaccine serotypes of *S. pneumoniae* and *S. aureus* in children who had recurrent otitis media; *S. aureus* became a more common cause of otitis media in children after Prevnar vaccination (78). One mechanistic hypothesis suggested that *S. aureus* is inhibited by $H_2O_2$ produced by *S. pneumoniae* strains, an effect demonstrated *in vitro* (752, 754), which theoretically may decrease the likelihood of cocolonization in the nasal mucosa or elsewhere. Hypothetically, if Prevnar vaccination opened an ecological niche and if CA-MRSA strains were prevalent in the community and more fit than other *S. aureus* strains, CA-MRSA strains would occupy the niche.

Brook and Gober demonstrated an increase in the recovery

of MRSA from acute otitis media with otorrhea. Among 50 children in suburban Washington, DC, in 1993 to 1998, prior to the licensure of Prevnar, 0/61 bacterial isolates recovered were MRSA isolates, compared with 5/63 (10%) MRSA isolates recovered in 2001 to 2006 ($P < 0.05$). During the second period, 92% of the patients had received Prevnar (97). Because otitis media is an infection of the middle ear caused by pharyngeal flora, this increase in MRSA otorrhea may reflect an increased pharyngeal colonization with MRSA with the elimination of vaccine serotypes of *S. pneumoniae*.

Controversy still surrounds the notion that Prevnar is associated with increasing MRSA colonization in a given population; some authors have not found evidence to support the contention that cocolonization with *S. aureus* and *S. pneumoniae* is uncommon (79, 597). One study showed no difference in the rates of *S. aureus* nasal carriage in children with otitis media who had received Prevnar and those who had not (176). Another study demonstrated no increase in the prevalence of *S. aureus* (neither MSSA nor MRSA) nasal colonization in a large group of children seen in Massachusetts primary care offices from November 2003 to April 2004, before the widespread use of Prevnar, compared with the prevalence from October 2006 to April 2007, after its introduction. However, that study was limited in that only children 3 months to 7 years of age were included, enrichment broth was not used to enhance the detection of *S. aureus*, and New England was among the last regions of the United States to report widespread CA-MRSA infections (518).

In a similar vein, group B *Streptococcus* and CA-MRSA isolates may compete for colonization in the vagina. In a study of vaginal colonization among pregnant women in New York City, NY, only 1/13 (7.7%) patients vaginally or rectally colonized with CA-MRSA (i.e., the isolates carried the SCC*mec* type IV or V element) were also colonized with group B *Streptococcus*; in contrast, 26/52 (50%) group B *Streptococcus*-colonized women had MSSA vaginal colonization, possibly suggesting increased competitive fitness among CA-MRSA strains relative to that of MSSA with respect to group B streptococcal colonization (161).

## SCC*mec* ELEMENTS AND CA-MRSA

Nearly all MRSA strains contain the SCC*mec* element, which is uniformly integrated into a specific *S. aureus* chromosomal site known as *orfx*. SCC*mec*, which was likely acquired from a coagulase-negative staphylococcus species (622, 1004), carries the *mecA* gene, which encodes penicillin binding protein 2a (PBP2a), a cell wall transpeptidase, which, in conjunction with native PBP2, allows continued cell wall synthesis in the presence of β-lactams (726). In addition, SCC*mec* elements variably carry the *mecR1* and *mecI* genes, which regulate the expression of *mecA*, with increased *mecA* translation induced by β-lactam antibiotic exposure. The *mecA* gene and its regulatory elements, taken together, comprise the *mec* complex (463). Different complex types have evolved, giving rise to MRSA strains with the class B *mec* complex, which express PBP2a constitutively, and strains with the class A *mec* complex, which express PBP2a only when induced by β-lactams. Two additional *mec* complexes, called classes C and D, have also been identified (390), although the class D complex has been found only in coagulase-negative *Staphylococcus* species.

### Main Types of SCC*mec* Elements

To date, nine types of SCC*mec* (types I to VIII and $V_T$) have been defined, which can be distinguished by the type of *ccr* gene complex that mediates the site-specific excision and insertion of the SCC*mec* cassette out of or into the bacterial genome and the class of *mec* complex that they bear (428, 430, 431) (Fig. 1). The large SCC*mec* types I to III are present in HA-MRSA strains and were likely transferred to *S. aureus* from a commensal staphylococcal species on a few occasions (565). Among U.S. HA-MRSA isolates, SCC*mec* type II elements are usually carried, whereas SCC*mec* type III elements are more commonly identified in HA-MRSA isolates in other countries. The smaller SCC*mec* types IV and V, however, are believed to have been transferred to methicillin-susceptible backgrounds frequently, with the resultant emergence of novel, fit MRSA strains bearing the type IV or V elements (61, 207, 357). One study suggested that the type IV SCC*mec* element has been transferred to an MSSA strain >20 times (771). Although it was initially thought that SCC*mec* type IV first integrated into pathogenic *S. aureus* backgrounds in the mid-1990s, it is now known that this integration first occurred much earlier. For example, in Taiwan, SCC*mec* type IV elements were identified in PVL-negative ST59 MRSA isolates from 1992 (978).

The type IV SCC*mec* element has been strongly associated with strains causing MRSA infections in patients with no HA-MRSA risk factors (212, 565) in the United States and elsewhere. The type II and III SCC*mec* elements include sites, called by some the junkyard regions, for the insertion of genes conferring non-β-lactam resistance phenotypes to *S. aureus* strains and, therefore, are more commonly associated with MDR phenotypes (392, 430). The presence of the SCC*mec* type IV element, which lacks genes conferring non-β-lactam antimicrobial resistance, may account for the decreased likelihood that CA-MRSA strains are MDR. Several subtypes of SCC*mec* type IV that vary depending on the typing system used have been described. An international committee of experts in 2009 formulated a consensus nomenclature for SCC*mec* types (427).

### SCC*mec* Types IV and V in CA-MRSA Isolates

Children may be at a higher risk of infection by SCC*mec* type IV-bearing isolates than adults. In a study of MRSA infections at the University of Chicago Hospitals in 2004 to 2005, children were more likely than adults to be infected by strains that carried SCC*mec* type IV and the PVL genes and by strains that were susceptible to many non-β-lactam antibiotics (216, 219). Although no clinical data were available to assess the rate of community-onset infections, surveillance at a South Korean hospital in 2003 to 2005 demonstrated that children were more likely to be infected by SCC*mec* type IV-bearing strains (68% ST72 strains bearing SCC*mec* type IV and 6.8% ST5 strains bearing SCC*mec* type II), while adults were more likely to be infected by SCC*mec* type II-bearing strains (12% ST72 and 58% ST5 strains). Pediatric strains were also more likely to be

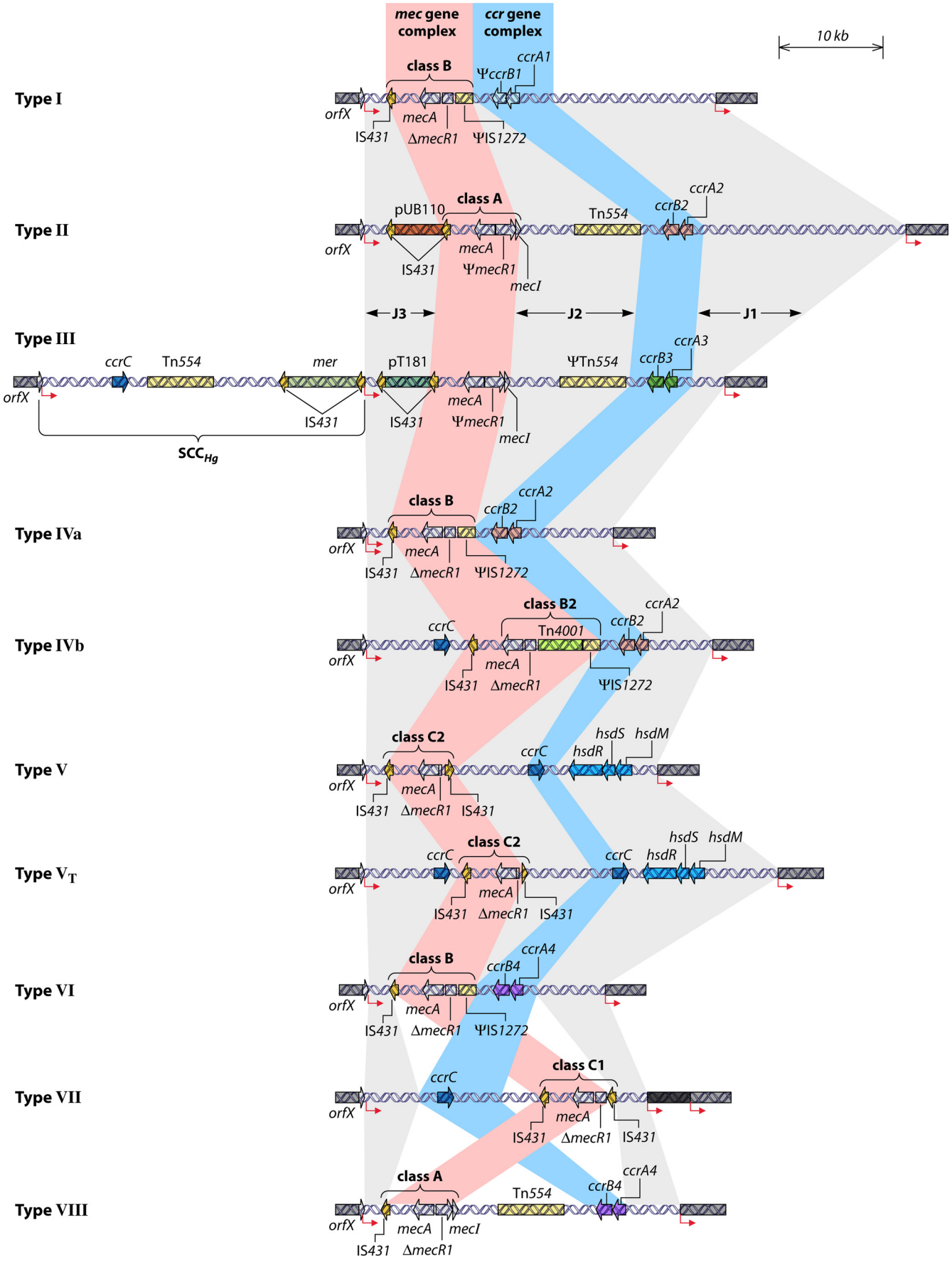


FIG. 1. Classification scheme for SCC*mec* type by *ccr* complex and *mec* complex type. (Adapted from reference 427.)

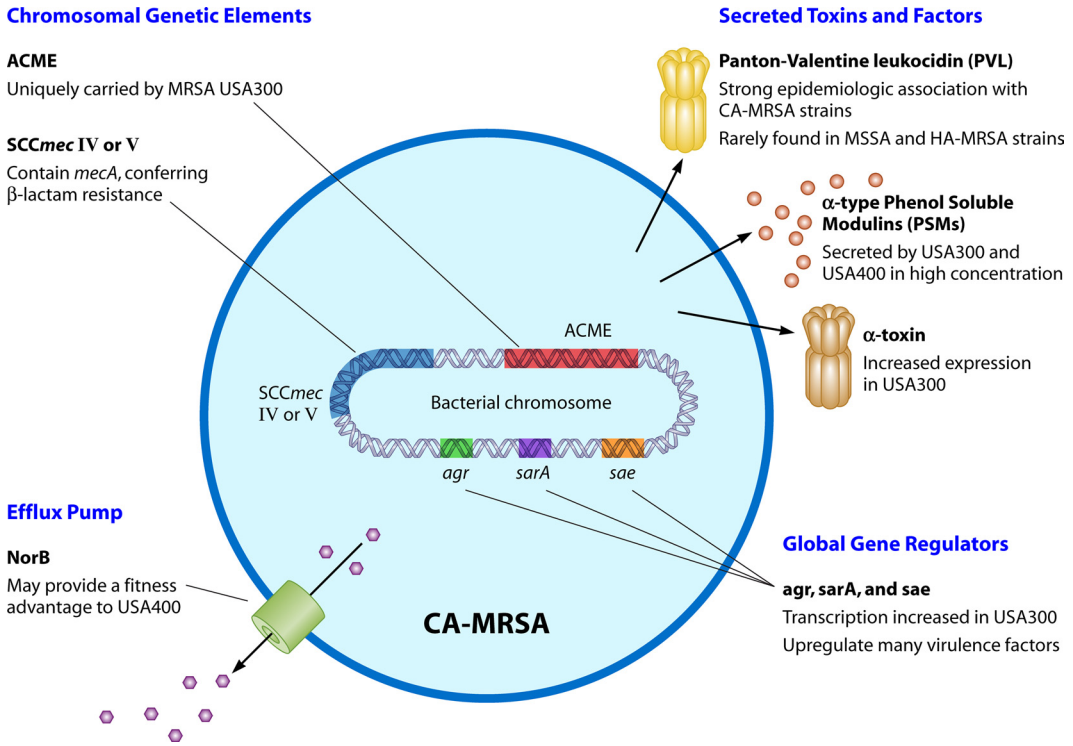


FIG. 2. Hypothetical virulence factors in USA300 and other CA-MRSA strains. For details, see the text.

susceptible to gentamicin, clindamycin, ciprofloxacin, and rifampin (709). These studies suggested that children are differentially exposed or differentially susceptible to SCC*mec* type IV-bearing strains or perhaps reflect more common exposure to the health care setting among adults. The reasons are not known, and this area requires further research.

SCC*mec* type V is similar to type IV in that it is small and presumably similarly mobile. It has been found in CA-MRSA isolates predominantly in Australia (670) and Taiwan (411, 414, 975). SCC*mec* type V is rare in Europe and the United States. However, in 2004 an ST377 strain of $PVL^+$ MRSA with SCC*mec* type V was reported from Greece (168, 316) and elsewhere (312). More research is needed to determine why SCC*mec* type IV is associated with prevalent CA-MRSA strains, including USA300, and why strains bearing SCC*mec* type V remain limited largely to Asia and are relatively uncommon.

Because SCC*mec* types IV and V appear to be highly mobile, the dissemination of MRSA in a community population has probably been accomplished most commonly by transfers of MRSA strains from carriers to other individuals and also by the transfer of the smaller SCC*mec* elements that can be passed from MRSA strains to MSSA strains or even from a coagulase-negative staphylococcal strain to an MSSA strain (269). All these processes are probably facilitated in the presence of antibiotic receipt (84, 831).

In the countries of northern Europe that have accurate population-based reporting of MRSA infections, there has been an increase in numbers of reports of polyclonal CA-MRSA colonization and infection by SCC*mec* type IV-bearing, $PVL^+$ MRSA strains. This presumably resulted from the easy and rapid transmissibility of the SCC*mec* type IV element from MRSA backgrounds to methicillin-susceptible *S. aureus* backgrounds. For example, in Denmark, the first ST80, $PVL^+$, SCC*mec* type IV isolate was identified in 1993, although by 2004, only 88 cases were recorded (510). Among the few known MRSA isolates from infections of outpatients in Denmark in 2004, 82% (28/34 isolates) carried SCC*mec* type IV, and 47% were $PVL^+$ (77). Another study from Copenhagen, Denmark, demonstrated the initial spread of $PVL^+$ SCC*mec* type IV and V strains and showed that many genetic background types bearing these SCC*mec* elements were present there in 2003 to 2004 (46). SCC*mec* type IV became the most common SCC*mec* type carried by MRSA strains isolated from inpatients at a hospital in Basel, Switzerland. SCC*mec* type IV carriage increased from 33.3% among MRSA strains isolated in 2000 to 57.9% in 2004. Most of the SCC*mec* type IV-bearing MRSA strains were MDR and were isolated from patients who had CA- or HA-MRSA infections by the CDC definition (865).

## VIRULENCE FACTORS IN CA-MRSA

A number of putative virulence factors have been identified by experimental and epidemiological studies of CA-MRSA strains, particularly in USA300 (Fig. 2). They are reviewed here.

### PVL and CA-MRSA

PVL is a two-component *S. aureus* pore-forming protein encoded by the *lukF-PV* and *lukS-PV* genes. It was first described in 1894 by Van de Velde (935) and was associated with

SSTIs in 1932 by Panton et al. (707). The genes encoding PVL, which can spread from strain to strain by bacteriophages, were previously believed to be present in fewer than 5% of unselected clinical *S. aureus* isolates (540, 707) before the advent of CA-MRSA strains in the mid-1990s, although the genes were transiently found in a circulating ST30 clone in Japan in 1979 to 1985 (566).

**PVL and CA-MRSA infections.** In the United States, after the mid-1990s, carriage of the PVL genes has been closely linked to infections caused by CA-MRSA strains in numerous epidemiological studies. Approximately 60 to 100% of CA-MRSA strains (by various definitions) have been shown to carry PVL genes. For example, in 2000, a large study from Minnesota found that 77% of patients with infections caused by CA-MRSA isolates (by the CDC case definition) were $PVL^+$, but only 4% of HA-MRSA isolates were $PVL^+$ (654). Among 812 military recruits in Texas in 2003, 66% of 45 MRSA strains colonizing the nares of recruits or causing infections among them were $PVL^+$ (259). PVL genes were found in 33.5% of 671 banked MRSA isolates obtained in 1997 to 2002 from four clinical sites in the San Francisco area. Among MRSA isolates from detainees in the San Francisco County Jail, more than 70% were $PVL^+$; of MRSA isolates from a clinic specializing in the treatment of SSTIs (all collected in 2000), 69% were $PVL^+$. All $PVL^+$ MRSA strains also carried the SCC*mec* type IV element (232).

While PVL has been strongly linked epidemiologically to prevalent CA-MRSA strains, it is not known with certainty how they contribute to their fitness and/or virulence or if they are merely a marker for other fitness or virulence determinants. $PVL^+$ strains carrying SCC*mec* type IV, V, or $V_T$ (90, 411) with varied background genotypes in many geographic settings have now been identified, although the chromosomal site of PVL gene integration lacks any known genetic linkage to the insertion site of SCC*mec* elements. Moreover, no other *S. aureus* toxin genes have been associated as strongly with CA-MRSA strains as PVL (234, 609, 933). PVL genes are rarely found in MRSA strains carrying SCC*mec* types I, II, and III.

PVL genes may be more common among *S. aureus* isolates causing clinically apparent infection than among isolates causing asymptomatic colonization, although there are conflicting data. For example, among 13 SCC*mec* type IV-bearing MRSA strains colonizing New York State Prison detainees in 2005, 8 (61.5%) were $PVL^+$. *S. aureus* strains causing infection, however, were more likely to be $PVL^+$ than those causing asymptomatic colonization (24/60 strains [40%] versus 32/124 strains [25.8%]; $P = 0.0498$) (560). In contrast, among clinical USA400 MRSA isolates (see below) in the Calgary Health Region in Canada in 2000 to 2005, $PVL^+$ and PVL-negative strains were as likely to cause mild or severe disease, and both were equally likely to asymptomatically colonize (1027).

In the United States, PVL genes have been almost universally detected among CA-MRSA strains causing SSTIs and *S. aureus* invasive diseases such as community-acquired necrotizing pneumonia (86, 190, 312, 321, 540, 618, 720, 917), severe sepsis, and other sometimes fatal infections (6, 33, 76, 133, 192, 584, 636, 719, 907, 917). Among patients with *S. aureus* pneumonia, higher mortality and an increased likelihood of sepsis, hemoptysis, and pleural effusion were documented for cases caused by a $PVL^+$ strain (321).

In Australia, the first reports of community-onset MRSA infections in 1993 were caused by strains that lacked PVL genes. Subsequently, however, a polyclonal surge of largely $PVL^+$ MRSA infections occurred among previously healthy, young adults and children; each newly described $PVL^+$ SCC*mec* type IV-bearing community strain identified in that country had a distinct geographic distribution (670). Furthermore, the clinical syndromes among SSTIs in Australia caused by $PVL^+$ MRSA strains differed from syndromes caused by PVL-negative strains. For example, in Queensland, Australia, in 2004 to 2005, 59% of SSTIs caused by $PVL^+$ *S. aureus* strains were designated "furunculosis," compared with only 10% of SSTIs caused by PVL-negative strains; the remainder of the SSTIs were described as "cellulitis" (34% versus 58%, respectively) or "surgical-wound infection" (7% versus 32%, respectively). Patients with $PVL^+$ strains were younger, less likely to have SSTIs as a complication of surgery, and more likely to have been hospitalized for the management of SSTIs (642).

Studies from many countries in Europe also documented the emergence of $PVL^+$ SCC*mec* type IV-bearing CA-MRSA strains in multiple *S. aureus* backgrounds, although CA-MRSA infections occur far less commonly there than in the United States (Table 4). For example, only 22.2% (12/54) of isolates from CA-MRSA patients (by the CDC case definition) submitted to an Irish reference laboratory from 1999 to 2005 were $PVL^+$ (778) (Table 4).

In Asia, the reported occurrence of MRSA infections that have onset in the community and the rate of PVL gene carriage have varied by country. In Taiwan, $PVL^+$ CA-MRSA strains of a single background type commonly cause infections. PVL genes were identified in all 17 isolates in one study of CA-MRSA infections in children, the majority of whom had SSTIs (972). Of 204 MRSA isolates colonizing the nares of healthy Taiwanese children in 2005 to 2006, 28% were $PVL^+$; all $PVL^+$ MRSA strains had one of two PFGE types, and all tested isolates were ST59 isolates or single-locus variants of ST59 (411).

In South Korea and China, $PVL^+$ strains remain rare among reported community-onset MRSA infections. Only 1 of 138 MRSA isolates from patients in South Korea with CA-MRSA infections (by CDC criteria) in 2004 to 2005 was $PVL^+$ (708). Among 3,096 healthy people in Seoul, South Korea, in 2003, the MRSA colonization prevalence was 0.97%; 30% of MRSA isolates carried SCC*mec* type IV. Of the 30 MRSA isolates identified, 70% (21) were $PVL^+$; these were polyclonal, representing four STs, ST1, ST5, ST72, and ST83 (437). In Wenzhou, China, of 195 *S. aureus* isolates from clinical specimens at a single medical center in 2005 to 2006, 25 (12.8%) were $PVL^+$; these belonged to six MLSTs. Of the 25 $PVL^+$ *S. aureus* isolates, 19 were MRSA isolates. Six of the 25 $PVL^+$ *S. aureus* isolates, including 2 of 19 MRSA isolates, were from "community-acquired" infections, although the criteria for this designation were not provided (1022). At pediatric hospitals in five Chinese cities in 2005 to 2006, 73 MRSA isolates were identified among 4,254 clinical *S. aureus* isolates. Of the 73 MRSA isolates, 30% (22/73) were $PVL^+$, and these included the ST1,

TABLE 4. Case series and surveillance studies of PVL$^+$ SCC*mec* type IV- or V-bearing community MRSA infections reported in Europe indicating the genetic backgrounds identified

| Country and/or city | Collection details | Yr | No. of MRSA isolates tested | No. (%) of PVL$^+$ isolates | Molecular typing results for PVL$^+$ isolates | Reference |
|---|---|---|---|---|---|---|
| Finland | CA-MRSA from national reporting system | 2004–2006 | 298 | 90 (30) | ST80-IV/t044, ST8-IV/t008, ST30-IV/t019, ST1-IV/t127, miscellaneous types | 459 |
| Ireland | MRSA from national reference collection | 1999–2005 | 1,389 | 25 (1.8)[a] | ST5, ST8, ST22, ST30, ST80, ST154 | 778 |
| Denmark | Sample of isolates from CA-MRSA patients[b] in Denmark collected by the Statens Serum Institut | 1999–2006 | 244 | 163 (66.8) | MLST clonal clusters CC1, CC5, CC8, CC22, CC30, CC59, CC80, CC88, CC152/377, CC398, miscellaneous CCs | 509 |
| Lyon, France | CA-MRSA and CA-MSSA infections; case series | 1999–2001 | 14 | 14 | 13 shared PFGE type; 1 differed by 1 band | 247 |
| Fréjus-Saint Raphaël, France | Community-onset MRSA disease at 1 hospital | 1999–2003 | 21[c] | 6[c] (28.6) | 5 same PFGE type as dominant strain in reference 247; 1 differed by 1 band; all *agr* type 3 | 225 |
| Geneva, Switzerland | SSTI patients with no health care exposure from private physicians' offices in city | 2002 | 10 | 7 (70) | 6 PFGE pulsotypes | 534 |
| Geneva, Switzerland | CA-MRSA isolates (i.e., from patients with no hospitalization in past 12 mo and nonstandard antibiogram) from 1 hospital | 2002–2005 | 151 | 60 (39.7) | ST1, ST5, ST8, ST30, ST59, ST80, ST152 | 299 |
| London, England | Ciprofloxacin-susceptible MRSA strains from 2 hospitals | 2000–2006 | 194 | 49 (25.3) | 24 *spa* types, ST1, ST8, ST59, ST80 | 694 |
| England and Wales | *S. aureus* isolates from clinical infections; reference collection | 2002–2003 | 470[d] | 23 (4.9); 12 were MRSA | 11 MRSA isolates, ST8 ($n = 1$), ST22 ($n = 1$), ST30 ($n = 1$), ST80 ($n = 10$) | 401 |
| England and Wales | Ciprofloxacin-susceptible strains isolated from boils, abscesses, and pneumonia from centers across England and Wales | 2005–2006 | 1,087 | 275 (25.3) | CC1 ($n = 13$), CC5 ($n = 10$), CC8 ($n = 70$), CC22 ($n = 33$), CC30 ($n = 49$), CC59 ($n = 4$), CC80 ($n = 88$), ST93 ($n = 1$) | 257 |
| Austria | Large reference collection | 2001–2006 | 1,150 | 94 (8.2) | ST5, ST8 (32%), ST22, ST30, ST80, ST152 (17%), ST777 | 490 |
| Vienna, Austria | MRSA isolates obtained at 1 hospital from patients with colonization or infection resistant only to β-lactams or β-lactams and fusidic acid | 1999–2007 | 41 | 16 (39) | 9 *spa* types (t021, t975, t3140, t3150, t044, t376, t3149, t3256, t1028) | 48 |
| Madrid, Spain | PVL$^+$ MRSA infections in an emergency department (9 SSTIs, 1 bacteremia, 2 asymptomatic colonization, and 1 otitis media) | 2004–2007 | 13 | 13 | ST5, ST8, ST80 | 147 |
| Dresden, Germany | SSTIs with PVL$^+$ strains | 2004–2005 | 3 | 3 | ST8, ST80 | 619; S. Monecke, personal communication |
| Örebro County, Sweden | Clinical PVL$^+$ isolates (4 SSTIs, 1 joint, 1 pleural effusion) | 2001–2005 | 6 | 6 | ST8, ST36, ST80, ST152, ST154, ST256 | 62 |

[a] All PVL$^+$ isolates were from 2002 to 2005.
[b] CA-MRSA infections had their onset in the community or were cultured <48 h after hospital admission, and the patients had no stay in a hospital or long-term care facility for 12 months.
[c] Six patients with SSTI and no health care exposure had infections with PVL$^+$ MRSA strains among 21 patients with community-onset MRSA infections.
[d] This is the number of *S. aureus* isolates; the authors did not report how many were MRSA isolates.

ST910, ST88, ST59, and ST338 genetic backgrounds. Among the 22 PVL$^+$ MRSA strains, 16 (73%) were CA-MRSA infections according to the CDC case definition (1028).

The prevalence of the PVL genes was less common among MSSA isolates than among MRSA isolates from infections and colonization in several studies. For example, in a case-control study in rural Alaska in 2000 following an outbreak of MRSA SSTIs, no MSSA isolates causing colonization ($n = 49$) or clinical infection ($n = 34$) carried PVL genes, compared with 92% (73/79) of MRSA isolates causing colonization or infection (36). Among *S. aureus* isolates causing musculoskeletal infections in 59 children in Houston, TX, in 2000 to 2002, causative MRSA isolates were more likely to carry PVL genes than were causative MSSA isolates (27/31 versus 6/24; $P = 0.00001$) (584). PVL$^+$ MSSA strains can cause serious infections (321, 765, 797, 851, 902), although such outbreaks appear to be relatively rare.

**Role of PVL in the pathogenesis of MRSA infections.** PVL is a leukocidin that can lyse the cell membrane of human neutrophils, although its importance in pathogenesis is controversial. Recent evidence suggests that PVL may also inactivate mitochondria (315) and culminate in apoptosis. In animal models, PVL has been shown to be dermonecrotic (190, 981), perhaps explaining the pathobiology of the characteristic skin lesions associated with CA-MRSA SSTIs. These lesions often resemble an injury produced by a spider bite (241, 954), although common house spiders were not found to be carriers of CA-MRSA (50), and a correlation between the geographic distribution of recluse spiders and these typical lesions associated with MRSA infection has been lacking.

Recently, the importance of PVL in the pathogenesis of SSTIs and necrotizing pneumonia has come into question. Voyich et al. found that the presence or absence of PVL genes in MRSA strains did not affect strain virulence in mouse models of sepsis and SSTI, and their presence did not decrease neutrophil survival in *in vitro* assays (963). Wardenburg et al. found that the presence or absence of PVL did not affect the mortality rate of *S. aureus* pneumonia in a mouse model. Also, the absence of the PVL gene locus in deletion mutants did not alter the cytotoxic effect of wild-type USA300 (LAC) and USA400 (MW2) strains *in vitro* in human alveolar epithelial cells (983). That same group also found no difference in pneumonia and skin abscess rodent models after inoculation with a USA300 strain or its isogenic PVL knockout (982). In contrast, Labandeira-Rey et al. demonstrated that both the purified PVL protein and an RN6390 derivative with the PVL genes overexpressed on an introduced phage caused necrotizing pneumonia in a mouse model (498). In a model of rat pneumonia, in contrast, USA400 and USA300 clones and their respective isogenic PVL knockout strains did not differ in virulence (624). Diep et al. compared wild-type and isogenic PVL knockout strains of two USA300 isolates and demonstrated no differences in the isogenic mutants in their proteomes or in their global gene expression patterns irrespective of the presence of PVL genes (230). That same group challenged rabbits intravenously with a 1:1 mixture of a wild-type USA300 strain and an isogenic PVL knockout mutant and demonstrated that 24 and 48 h, but not 72 h, later, the PVL-containing wild-type strain was present in a greater density in homogenized kidneys of sacrificed rabbits, suggesting that PVL may provide an early survival benefit to MRSA strains in this model (230). Tseng et al. found that PVL was responsible for increased tissue damage in a myositis model in young, but not older, mice by comparing an MRSA isolate obtained from a patient with necrotizing fasciitis with its isogenic PVL knockout mutant (916). Those authors hypothesized that the younger mice had a more robust neutrophil response to PVL, resulting in more severe injury to muscle (916).

Hongo et al. found that PVL toxin did not produce a lysis of neutrophils from BALB/c mice, but the lytic activities against human neutrophils of supernatants from USA300 and USA400 strains were abrogated in the presence of monoclonal anti-PVL antibodies (402). Löffler et al. found that PVL did not lyse neutrophils from monkeys or mice, but it did lyse rabbit and human neutrophils (553). These findings support the importance of PVL in the pathogenesis of CA-MRSA infections in humans, while mouse models may not be appropriate to assess the contribution of PVL.

The conflicting results for the role of PVL in the pathogenesis of CA-MRSA infections may relate to the amount of PVL produced by individual strains. For example, Varshney et al. demonstrated that in a variety of clinical MRSA and MSSA strains, PVL production varied. When used in a murine skin infection model, strains with more PVL production produced larger skin lesions and higher bacterial burdens in the lesions at 7 days (947).

The PVL gene DNA sequences have allelic variation that may help to explain the conflicting results seen in animal studies. Among 28 *S. aureus* strains that underwent PVL gene sequencing, 7 nucleotide polymorphisms were found, but only 1 resulted in an amino acid substitution. The strains included representatives of the CA-MRSA ST80, USA300, and USA400 clones as well as a phage type 80/81 strain (ST30). The PVL gene sequence in the phage type 80/81 strain was hypothesized to contain the progenitor of the PVL gene sequences carried by the other isolates in the collection (1007). The PVL *lukSF-PV* gene sequences found in an international collection of isolates had two predominant variants; the two variants differed by a single amino acid substitution. The R variant was found only in USA300 and USA400 MRSA isolates from the United States, while the H variant was common in MSSA strains obtained elsewhere (685). In a separate study of a different group of *S. aureus* isolates, the R variant was found in USA300 and USA400 strains and in a CC93 clinical isolate from Australia; in contrast, the H variant was present in MSSA and MRSA strains from around the world and nearly all PVL$^+$ CA-MRSA clones outside the United States (249). It is possible that the polymorphisms distinguishing the R and H variants may result in changes in the function of the PVL protein, potentially explaining the apparently contradictory results demonstrated in animal studies of the virulence of PVL$^+$ MRSA strains (498, 983). The importance of these polymorphisms, if any, requires further research (441).

### Other Virulence Factors in CA-MRSA Strains

Other candidate genes have been proposed to be important virulence factors driving the dominance of USA300 and other CA-MRSA clones in the community (679). It is estimated that 22% of the genome of *S. aureus* varies among strains, and these

variable regions may include structural genes and regulatory apparatus that may influence fitness, pathogenicity, and virulence (287). Several examples that have received recent attention are discussed in this section.

**ACME.** The arginine catabolic mobile element (ACME) is a 30.9-kb DNA element that contains 33 expressed reading frames and is present in many USA300 strains. It is integrated into *orfx*, the same site on the *S. aureus* chromosome into which SCC*mec* integrates, and it is frequently found in coagulase-negative staphylococcal species (236). It has been postulated that ACME may play a role in pathogenesis by conferring an enhanced ability of CA-MRSA strains to colonize the skin of healthy people and, thus, more easily disseminate in the community, although no experimental data exist to substantiate this hypothesis. ACME contains the structural gene *arcA*, encoding arginine deiminase, which in *Streptococcus pyogenes* inhibits the proliferation of peripheral blood monocytes and enhances bacterial survival at a low pH, such as that found on normal skin, in intracellular compartments of phagocytic cells (236), and in abscess cavities. In addition, arginine deiminase may deplete L-arginine, which is a substrate for nitric oxide production; nitric oxide is a toxic metabolite generated by human macrophages and other leukocytes to control microbial pathogens. While *arcA* is found in nearly all staphylococcal strains, the *arcA* gene contained in ACME has a distinctive nucleotide sequence. The consequences of carriage of the distinct *arcA* gene are unknown (236). Other open reading frames within ACME may also be relevant virulence factors; further research is necessary to investigate this possibility.

Of 214 *S. aureus* isolates from a reference collection, *arcA* was identified only in USA300 MRSA backgrounds containing SCC*mec* type IVa. It was not found in other successful CA-MRSA background types (e.g., USA400 or ST80 strains). Thus, like PVL, ACME is not necessary for the broad dissemination of an MRSA clone (326). Diep et al. found that all but 1 of 1,248 USA300 isolates tested from a reference collection carried the ACME element (233), although Montgomery et al. found that 8/90 (9%) tested USA300 isolates lacked *arcA*, a proxy marker for the ACME element (623). In an assay for competitive fitness, USA300 had superior fitness, as measured by the differential bacterial burden in tissues at autopsy compared with an isogenic mutant that had ACME and the SCC*mec* element deleted. Those authors concluded that the absence of the ACME element significantly decreased the *in vivo* fitness of USA300; ACME may therefore be central to the pathogenesis of USA300 infections (233). In contrast, Montgomery et al. found no difference between the virulence of USA300 strains and that of an isogenic ACME knockout in a rat model of necrotizing pneumonia or skin infection; furthermore, no difference was found in the expressions of global regulators of virulence determinants in these two strains (623).

**The α-type PSMs.** The α-type phenol-soluble modulins (PSMs) and β-type PSMs, two groups of cytolytic peptides that are produced in higher concentrations *in vitro* by two U.S. CA-MRSA clones, USA400 (MW2) and USA300 (LAC), than by HA-MRSA strains tested have recently received attention as candidate virulence factors. PSMs are also found in coagulase-negative staphylococcus species (980). Delta-toxin is produced by *S. aureus* and is similar in structure to α-type PSMs. Isogenic clones of USA400 MW2 and USA300 LAC were created, in which the genetic loci PSMα and PSMβ were deleted and the start codon of the gene encoding delta-toxin (*hld*) was altered, abolishing the production of PSMs and delta-toxin in the mutants. These two deletion mutants were less lethal in a mouse model of bacteremia and less likely to cause skin lesions in infected mice than the corresponding wild-type strains. *In vitro* studies demonstrated that synthetic PSM-activated human neutrophils and that certain PSMs, especially PSMα3, caused neutrophil lysis *in vitro*. The *in vitro* lytic activities of the MW2 and LAC strains were increased compared with those of the corresponding mutant strains. This activity was restored by complementation using a plasmid expressing all α-type PSMs and partially complemented by a plasmid expressing PSMα3 alone. Strains lacking delta-toxin did not demonstrate any change in their abilities to lyse human neutrophils. These experiments suggested that PSMs may be in part responsible for the virulence of successful CA-MRSA clones (231, 980). Hongo et al. demonstrated that PSMα3, while it did not lyse human neutrophils at low concentrations, may be a cofactor that enhances the ability of PVL to lyse human neutrophils (402).

**Protein A.** The species signature gene *spa* encodes protein A, which is expressed on the surface of nearly all *S. aureus* strains. Protein A contributes to the prevention of opsonization and subsequent phagocytosis by ineffectually binding the Fc region of IgG (295, 922). It also initiates a proinflammatory cascade in the airway by activating tumor necrosis factor receptor 1 (TNFR1) (328) and B cells in concert with other ligands (55). Protein A was also shown to enhance the activity of alpha-toxin in a murine model of skin infection (712). MRSA strains with certain *spa* types have a decreased ability to invade human cells *in vitro* (995), suggesting an association with certain *spa* types and virulence. This observation has not been confirmed by experiments using isogenic bacterial mutants with different *spa* types, and further research is needed to assess the importance of protein A as a virulence factor in CA-MRSA strains.

**Other candidate virulence factors and mechanisms.** It has been proposed that MRSA strains lacking the *pls* gene, coding for the surface protein Pls, which decreases adhesion to human cell ligands and invasiveness, have decreased pathogenicity (995), but further research is needed to determine if this effect has clinical importance.

One group demonstrated with a mouse abscess model that the efflux pump *norB*, responsible for resistance to fluoroquinolones and other antimicrobial compounds, may provide a fitness advantage to wild-type MW2 (USA400) strains (239).

Recently, Montgomery et al. demonstrated increased levels of transcription of the PVL and alpha-toxin (*hla*) genes and of the global regulators *agr*, *sarA*, and *saeRS* in three USA300 MRSA strains compared with two USA400 strains. *agr*, *sarA*, and *saeRS* regulate the increased expression of many toxin and other proteins associated with virulence (624). This increased transcription was correlated with increased virulence in several rodent models of CA-MRSA pneumonia. These observations suggested that a difference in the quantitative expression of key virulence genes rather than their presence alone might account for the increased virulence or fitness of USA300. In further support of this, in a global assessment of exoprotein abun-

dance, Burlak et al. found that 11 virulence factors, including Cna and Hla, had increased production in a USA300 (LAC) strain compared with a USA400 (MW2) strain. These virulence factors included proteases, molecules involved in adhesion to host cells, and toxins; the PVL protein was not detected in the supernatant from either strain (110).

## NON-β-LACTAM ANTIBIOTIC SUSCEPTIBILITY AND CA-MRSA

CA-MRSA isolates have typically been susceptible to most non-β-lactam antimicrobial drugs (383, 654), including several orally available agents. This enables clinicians to have a number of options when selecting empiric treatments of putative CA-MRSA infections. CA-MRSA isolates are usually susceptible to clindamycin in the United States (300, 301), gentamicin in Australia (672), and ciprofloxacin in England (262, 375, 694). Indeed, susceptibility to more than two non-β-lactam antimicrobials (642) has been used as a proxy defining criterion to identify CA-MRSA. The treatment of CA-MRSA infections is discussed below; here we focus on the generally broad susceptibility and trends for increasing resistance among CA-MRSA strains (235, 779).

### Mupirocin Resistance

Mupirocin, a topical antimicrobial, is often used as an intranasal agent in MRSA decolonization protocols and for the topical therapy of impetigo. It acts by binding bacterial isoleucyl tRNA synthetase, thereby inhibiting protein synthesis. Low-level mupirocin resistance results from point mutations in the *ileS* gene, while high-level resistance is associated with the presence of the *mupA* gene, which is carried on a plasmid and codes for a mutant isoleucyl tRNA synthetase that does not bind mupirocin (398).

Few centers routinely test MRSA isolates for susceptibility to mupirocin, but there is evidence that when it is used in decolonization regimens, resistance emerges rapidly (713). Among 14,840 patients admitted to a medical center in Chicago, 591 patients had a positive PCR assay and a positive culture for nasal MRSA. Of the 591 MRSA isolates, 17 (2.9%) had low-level mupirocin resistance, and 3 (0.5%) had high-level resistance (34), although the use of mupirocin at the center was not quantified. Similarly, among 4,980 MRSA isolates from 32 Canadian hospitals, high-level mupirocin resistance increased from 1.6% in 1995 to 1999 to 7.0% in 2000 to 2004. Mupirocin resistance mediated by the *mupA* gene was more common for isolates obtained from aboriginal populations than from others, from those with asymptomatic MRSA colonization than from those with a MRSA infection, and from those with CA-MRSA infection (as defined by a lack of risk factors for exposure to health care facilities) than from those with HA-MRSA infection (838); the use of mupirocin was not quantified for these hospitals.

In other centers, mupirocin use was quantified and correlated with increasing rates of resistance among MRSA isolates. In a study of MRSA nasal colonization among ICU patients in St. Louis in 2002 to 2004, where mupirocin was routinely administered to carriers for a mean of 6.08 days/1,000 patient-days, resistance was common: 13.2% of 302 isolates were resistant to mupirocin (MIC $\geq$ 8). Of these, 4.6% had low-level resistance and 8.6% had high-level resistance (449). At three hospitals in suburban Chicago, a mupirocin-based decolonization protocol was used routinely for 3 years for any patient found by active screening at admission to have nasal colonization with MRSA. In August 2005 to 2008, 4,934 MRSA isolates were obtained. Mupirocin resistance was detected for 4.1%, 5.5%, and 7.2% of the isolates during the first, second, and third years of the program, respectively (717).

In contrast, not all centers have noted frequent mupirocin resistance among MRSA isolates. Among 409 clinical MRSA isolates obtained in 2006 to 2007 at the Madigan Army Medical Center in Fort Lewis, WA, only 1.7% had high-level resistance to mupirocin (MIC $>$ 1,024 μg/ml) and 2.4% had intermediate resistance (MIC, 1 to 32 μg/ml) by Etest. Those authors found no trend toward an increased prevalence of resistance over time despite the extensive usage of mupirocin-based topical creams in the Western Regional Command (96,968 g prescribed between March 2006 and February 2007) (721). Further studies are necessary to define the impact of mupirocin use on the development of resistance.

### Clindamycin Resistance

Increasing non-β-lactam antimicrobial resistance among CA-MRSA clones, particularly to clindamycin, may complicate efforts to manage infections in the community. A study in Boston and San Francisco showed the emergence of a multidrug-resistant strain of MRSA carrying plasmid pUSA03, predominantly among isolates from men who have sex with men (MSM) in the community. This plasmid codes for resistance to clindamycin and mupirocin (235) and may be responsible for a high rate of failure in mupirocin decolonization attempts among MSM patients in New York City (343). At a health center in Boston serving a patient population in which >50% of the patients reported being MSM, among 123 first-patient MRSA isolates obtained in 2004 to 2005, 83% belonged to one of two subclones of USA300. Among the 102 isolates that had antimicrobial susceptibility testing, 98 (96%) were resistant to erythromycin, 87 (85%) were resistant to levofloxacin, 58 (57%) were resistant to clindamycin, and 31 (30%) were resistant to tetracycline. Twelve of the MDR isolates were tested, and all carried the *mupA* gene. All were susceptible to doxycycline and TMP-SMX (361). Similarly, in a study of CA-MRSA SSTIs among MSM patients in New York, only 37% were susceptible to clindamycin and 9% were susceptible to ciprofloxacin (825). Of 21 MRSA isolates obtained from the axillae or nares of otherwise healthy HIV-infected patients in New York City in 2005 to 2006, 8/21 (38%) carried the *mupA* gene, and 7/8 of these strains had constitutive resistance to clindamycin; all 8 isolates were USA300 strains. Ciprofloxacin resistance was found for 14/15 USA300 colonization isolates in the study (827).

### Reduced Susceptibility to Vancomycin and Daptomycin

Rare cases of resistance of USA300 strains to intravenous non-β-lactam antibiotics have been reported. For example, a USA300 MRSA isolate that had low-level resistance to vancomycin and reduced susceptibility to daptomycin was isolated

TABLE 5. $PVL^+$ strains of MRSA reported to cause infections among healthy populations in different regions of the world

| MLST | Predominant SCC*mec* type(s) | *spa* type(s) | Strain(s) | Regions where strain is common | References |
|---|---|---|---|---|---|
| ST1 | IV | t125, t127,t128, t175, t558, t1272, t1274 | USA400, CMRSA-7 | United States, Canada, Europe, Australia | 133, 184, 203, 218, 309, 509, 640, 913, 924, 956, 1017, 1027 |
| ST8 | IV | t008 | USA300, CMRSA-10, WA-MRSA-12 | United States, Canada, Europe | 171, 208, 216, 234, 309, 385, 403, 419, 443, 475, 481, 509, 543, 628, 702, 845, 875, 893, 895, 924 |
| ST30 | IV | t012, t018, t019, t021, t030, t043, t318 | SWP clone, WA MRSA, USA1100 | Australia, United States, Japan, Latin America, Turkey, Egypt, Middle East, Europe | 58, 92, 184, 252, 264, 276, 294, 352, 376, 429, 472, 509, 604, 644, 670, 682, 757, 778, 886, 905, 913, 920, 924 |
| ST59 | IV, V, $V_T$ | t216, t437 | USA1000 | Australia, Europe, Taiwan, United States | 68, 90, 92, 160, 184, 294, 411, 418, 509, 595, 694, 879, 913, 975, 977 |
| ST80 | IV | t042, t044, t070, t131, t237, t376, t455 | European clone | Australia, Europe, Kuwait, Algeria, Tunisia, Egypt, Malaysia | 56, 57, 184, 213, 264, 274, 299, 379, 490, 509, 510, 548, 555, 673, 693, 694, 814, 823, 913, 920, 924, 962 |
| ST93 | IV | t202 | Queensland clone | Australia, England | 184, 257, 258, 352, 641, 643, 670, 763, 913 |

from a patient in San Francisco who died of MRSA lumbar discitis (344).

## MOLECULAR EPIDEMIOLOGY OF CA-MRSA

### USA300 Strains

In the 1990s, several *S. aureus* genetic backgrounds were responsible for initiating the CA-MRSA epidemic, but by the first years of the 21st century (309, 888), one well-characterized genetic background, USA300, emerged as the most prevalent strain in the contiguous 48 states in the United States (403, 475, 543, 702, 893, 895). Elsewhere in the world, including rural southwestern Alaska (218), other $PVL^+$ genetic MRSA backgrounds have predominated (Table 5). USA300 has been isolated from patients on all continents except Antarctica, but its role as the dominant genetic background of CA-MRSA has not been duplicated outside the United States.

Relevant characteristics of USA300 include the carriage of SCC*mec* type IV, PVL genes, and, in most strains, the ACME element. USA300 is classified as ST8 by MLST and is usually classified as t008 by *spa* typing. It is frequently susceptible to many non-β-lactam antimicrobials. USA300 is not the sole ST8, *spa* type t008, and SCC*mec* type IV-bearing MRSA strain (213), but other genetic backgrounds have not been as widely distributed.

USA300 became the dominant CA-MRSA strains in the United States in a remarkably brief period of time. Its predominance has been documented in a number of disparate settings. For example, in a population-based study of MRSA infections in San Francisco in 2004 to 2005, 78.5% of community-onset MRSA infections were caused by USA300 clones (543). At the Baltimore, MD, Veterans Affairs Medical Center in 2001 to 2005, the incidence of MRSA infections increased among patients with no history of MRSA colonization or infection from 0.2 (6 infections) to 5.9 (180 infections) per 1,000 outpatient visits; USA300 caused no MRSA SSTIs in 2000 but caused 84% of MRSA SSTIs in 2005. In this 5-year period the proportion of SSTI cultures that yielded MRSA increased from 4% to 42%. This increase was accompanied by an increase in the number of visits for SSTIs from 20 to 61 per 1,000 outpatient visits, an increase that was accounted for by the rising number of USA300 MRSA infections (443). USA300 was responsible for an estimated 29% of invasive MRSA disease in the United States in 2005 (481) and for 31.4% in 2005 to 2006 (537). In EDs in 11 U.S. cities in August 2004, USA300 was identified among 97% of MRSA isolates obtained from SSTI cultures (628). In Chicago, ST8 strains, corresponding to USA300, made up 55.4% of MRSA strains from individual inpatients and outpatients in 2004 to 2005 at a large tertiary care medical center and 82.8% of all MRSA isolates obtained from patients seen in the ED but not admitted (216). USA300 caused 35% (74/210) of MRSA bloodstream infections at the Henry Ford Hospital in Detroit, MI, in July 2005 to February 2007; 88% (65/74) had onset in the community (171). Among 53 patients admitted to Grady Memorial Hospital in Atlanta, GA, in 2003 and found to be nasally colonized with MRSA, a population presumably having a great chance of health care exposure, 16 (30%) carried USA300 strains (385).

In addition to infection-causing strains, USA300 has become increasingly common as a cause of asymptomatic colonization in the general population. In a nationally representative study of the noninstitutionalized U.S. population, the percentage of MRSA isolates recovered from nasal colonization that were USA300 strains doubled from 8.0% in 2001 to 2002 to 17.2% in 2003 to 2004 ($P = 0.03$) (895).

USA300 strains have been isolated disproportionately from certain high-risk groups in the United States. For example, of MRSA strains obtained in an international study of therapy of endocarditis, all 23 patients with USA300 strains were from North America; these patients were younger, more likely to be black, more likely to be intravenous drug users (IVDUs), and more likely to have right-sided endocarditis than were the 65 patients with non-USA300 strains (500).

USA300 emerged later in Canada than in the United States;

limited evidence suggests that it may be following the same pattern of rapid dissemination in similar populations. USA300 was first reported by a large surveillance program in Canada in 2004, when it caused an outbreak of SSTIs in Alberta (170, 318). It was also isolated in 2004 to 2005 from SSTIs in MSM patients in Toronto (875) and from the nares of an Ontario schoolteacher in 2006 (363). First noted as a cause of bacteremia in the Calgary Health Region in 2004, USA300 quickly became the most common strain causing MRSA bacteremia, accounting for 26 of 88 (30%) reported cases in 2004 to 2006 (512). In 2005, 271 people in Calgary participating in a needle exchange program, a jail, a homeless shelter, or a substance abuse program were tested for colonization or infection with MRSA; 5.5% carried USA300 (319). USA300 was found to be the most common cause of skin infections in an emergency department in Vancouver, Canada, in 2003 to 2005 (14), although it was isolated only once (among 36 MRSA infections) among patients in the intensive care unit of a hospital in Edmonton, Alberta, in 1997 to 2005 (845).

USA300 has more recently been identified in Western Europe (40, 283, 299, 381, 419, 469, 508, 579, 786, 900), Japan (828), and Australia, where it has been called WA-MRSA-12 (184, 340, 620), but it remains an uncommon cause of SSTIs in the community in those regions.

The origin of USA300 has been uncertain, but O'Hara et al. analyzed the *lukSF-PV* DNA sequences encoding the PVL toxin in a sample of international clinical MRSA isolates and hypothesized that USA300 emerged after a CC8 MRSA strain acquired the PVL genes from a preexisting USA400 strain (685). If this is true, and if USA300, endowed with the PVL genes, became more fit than USA400, the acquisition of PVL might account for USA300 becoming the predominant MRSA genetic background circulating since 2001 (156, 309). As noted above, genes carried by the ACME element, specifically associated with USA300, may be virulence factors (233, 623). However, more research is needed to assess their importance. Particularly needed is an evaluation of the many open reading frames in the element that have not been adequately examined.

A prototype USA300 clone, USA300-0114, defined by the CDC by a PFGE pattern (595), has been sequenced (236), as has another USA300 clone isolated from Houston, TX. The two USA300 strains showed little difference in gene content, but they did have many polymorphisms in shared genes (386). Kennedy et al. sequenced the genomes of 10 USA300 patient isolates from diverse geographical locations in the United States to assess genetic variation. Those authors concluded from the relatively few single-nucleotide polymorphisms in the genomes that there has been a recent clonal diversification of a USA300 progenitor strain rather than an evolutionary convergence. Two of the 10 isolates, while genotypically closely related to the others, were associated with decreased virulence in a mouse sepsis model. These two isolates showed a decreased *in vitro* secretion of LukF-PV and the absence of alpha-hemolysin. One of these two isolates had a missense mutation in the *agrA* gene (a regulator of many secreted exoproteins) that may have been the critical reason for its decreased virulence, but the other isolate did not share this missense mutation (468).

USA300 may also be a common pulsotype among clinical MSSA isolates, suggesting that the genetic background, rather than the carriage of the SCC*mec* element, may underlie the fitness of USA300 (691). USA300 was the most common genotype among *S. aureus* strains causing nasal colonization among New York State Prison detainees in 2005 to 2006 and accounted for 16% (20/124) of *S. aureus* isolates. Seventy percent of the USA300 isolates were MSSA. In the same prison system, USA300 strains accounted for 48% (29/60) of *S. aureus* isolates from infections (560). Of invasive MSSA infections in children at a Houston, TX, hospital, 60% (77/128) were from patients with osteomyelitis; 14% (2/14) of invasive infections were caused by USA300 in 2001, and the percentage increased to 35% (11/31) in 2006. Of the 35 $PVL^+$ MSSA isolates in that study, 25 (71%) were USA300 strains. This suggests that USA300 MSSA may also be increasingly common as a cause of invasive infections in the community (593).

### Other Prominent CA-MRSA Genetic Backgrounds

Since the 1990s, MRSA strains with different genetic backgrounds carrying SCC*mec* type IV or V elements have been identified as etiological agents of infections among previously healthy people in different parts of the world (913, 933). These clones, like USA300, tend to be susceptible to most non-β-lactam antimicrobial drugs, tend to be $PVL^+$, and have been associated with distinctive SSTIs resembling spider bites and necrotizing pneumonia.

It is likely that few countries have experienced epidemic community MRSA disease or frequent asymptomatic MRSA colonization among the general population as described for the United States. Indeed, reported rates of asymptomatic MRSA colonization in the developing world, Turkey, and northern Europe suggest that rates are low. For example, in 2005 the prevalence of nasal colonization with MRSA was 0.2% among hospitalized patients in Mali (785) and was similarly low in Malaysia (169). In Brazil in 2000 to 2001 the prevalence of MRSA nasopharyngeal colonization in children younger than 5 years of age with respiratory tract infections or meningitis within 6 h of hospitalization was 1.02% (7/686). All seven MRSA isolates obtained carried SCC*mec* type III (502), typical of HA-MRSA strains. In Switzerland in 2006, only 1 of 1,337 pediatric patients admitted to a group of hospitals had MRSA colonization (380). In England, colonization with MRSA in the community is rare, despite an estimated 3-fold increase in the rate of hospitalizations for abscesses, carbuncles, furuncles, and cellulitis between 1989 to 1990 and 2003 to 2004 and a greater-than-5-fold increase in the rate staphylococcal pneumonia (374). Similarly, in Ankara, Turkey, 4,050 schoolchildren were assayed for nasal colonization with MRSA in 2007: 24.7% carried *S. aureus*, but only 0.07% (3 children) carried MRSA (472).

The principal background genotypes of CA-MRSA strains other than USA300 are as follows.

**ST1.** USA400 is the pulsotype of the strain of ST1 CA-MRSA that predominated among CA-MRSA clones in the United States when first recognized in the late 1990s. The genome of a prototype strain, MW2, has been sequenced (33). Curiously, there were scarcely any transposons or insertion sequence (IS) elements in the sequence, and many toxins were identified that were absent from other *S. aureus* genomic se-

quences, as were multiple superantigen genes. Moreover, the sequence was highly similar to that of MSSA476, also a cause of severe invasive disease in an immunocompetent child (399). MW2 was the CA-MRSA strain responsible for a fatal infection in a child from North Dakota in 1999 (133). USA400 was also identified in the community in 1999 to 2002 in Saskatchewan, Canada (640), and in 1995 to 2000 in Manitoba, Canada (1017). USA400 remained the predominant genotypic background of CA-MRSA strains in rural southwestern Alaska in 2004 to 2006 (218). Despite the ability of USA400 to cause severe, invasive disease, soon after 2000 it was replaced by USA300 as the predominant CA-MRSA strain in most regions of the United States (309) and later in parts of Canada (1027).

An ST1 strain carrying SCC*mec* type IV that has been usually susceptible to most non-β-lactam antimicrobial drugs and has been found most commonly to cause SSTIs has been described. This strain lacked PVL genes and circulates in the community in Australia, particularly in Western and South Australia (184, 352, 642), and England (693, 694); in Australia, it is designated WA-MRSA-1.

**ST80.** CA-MRSA infections have remained infrequent in Western Europe relative to the United States. In Europe, ST80 is likely the most common $PVL^+$, SCC*mec* type IV-bearing MRSA strain causing such infections. $PVL^+$ ST80 MRSA strains bearing SCC*mec* type IV have been reported by many Western European nations as an increasingly common cause of skin infections in the community (913) in Austria (490), Norway (379), Denmark (509, 510), Sweden (274), England (693, 694), Switzerland (299), and Greece (673, 814). ST80 was a rare cause of sporadic invasive infections in France in 2006 to 2007 and accounted for 3.6% of 111 MRSA isolates collected during a national survey of patients with invasive disease (213). It is not known why ST80 strains have not spread to North America or why USA300 strains have not spread widely to Western Europe.

Less commonly, ST80 MRSA strains have also been reported for other parts of the world. In a nationwide surveillance of MRSA isolates from outpatients in Australia in 2004 to 2006, 2/462 (0.43%) isolates were ST80 (184). SCC*mec* type IV-bearing, $PVL^+$, ST80 strains were also found to be the etiology of 10 CA-MRSA infections in Kuwait and comprised 39% of MRSA isolates collected by a reference laboratory from five hospitals in that country in 2001 to 2003. These ST80 isolates were isolated from inpatients and outpatients from skin, wounds, or groin (920). In Tunisia in 2003 to 2005, ST80 was the dominant genetic background identified among CA-MRSA isolates (i.e., isolated either from outpatients or from inpatients within 48 h of hospital admission) (57); ST80 was also obtained from CA-MRSA (CDC criteria) infections in Egypt (264). In Malaysia in late 2005, a person was identified with MRSA nasal colonization by a $PVL^+$, ST80 strain that carried SCC*mec* type IV (823; V. Neela, personal communication).

**ST30.** ST30 corresponds to phage type 80/81 strains of *S. aureus* that were virulent nosocomial pathogens in the United States during the 1950s and 1960s. These strains were MSSA strains and often carried the PVL genes (770). An ST30 MRSA clone, known as the Southwest Pacific (SWP) clone, is likely a direct descendant of the older 80/81 clones and has long been a common human pathogen in Australia (184, 352, 770, 905). Since the mid-1990s, MRSA ST30 clones with different pulsotypes and genetic characteristics have been reported from many parts of the world, including the United States, Japan, Latin America, Turkey, the Middle East, Egypt, and many countries in Western Europe (58, 264, 429, 472, 604, 670, 757, 778, 913, 920). ST30 isolates reported from many regions, including PFGE type USA1100 in the United States, carry the genetic determinants of PVL and the SCC*mec* type IV element (58), but these clones have many *spa* types, suggesting continued evolution (92, 252, 276, 294, 429, 682, 886). Such CA-MRSA-type ST30 MRSA strains have been reported more commonly than USA300 in certain countries, notably in Australia in 2004 to 2006 (184); it is not known why they persist as causes of community-associated infection in some regions and not in others.

**ST59.** ST59 isolates are prevalent in Taiwan. Strains that are $PVL^+$ have diverse *spa* types and several SCC*mec* types. $PVL^+$ ST59 isolates have also been recovered from patients in Australia, Taiwan, the Netherlands, Denmark, England, the United States (92, 160, 184, 294, 418, 509, 694, 913, 977), and elsewhere. In Taiwan, ST59 clones with a distinctive SCC*mec* DNA sequence, type $V_T$, and a multidrug-resistant phenotype are common (880). For example, $PVL^+$ ST59 isolates bearing SCC*mec* type $V_T$ accounted for 25% (53/212) of MRSA strains colonizing healthy children in 2005 to 2006 at medical centers in three Taiwanese cities. However, ST59 strains that were PVL negative and carried SCC*mec* type IV accounted for 59% (129/212) of MRSA strains from tested children (411). Among 3,098 adult workers in Taiwan attending mandatory health screening in 2007, 3.8% (119/3,098) had nasal MRSA carriage. Of 119 MRSA isolates, 100 were ST59. Among these, 65/100 (65%) carried SCC*mec* type IV, of which 10/65 (15%) were $PVL^+$; 35/100 (35%) carried SCC*mec* type V, of which 35/35 (100%) were $PVL^+$ (977). In Taiwan, $PVL^+$ ST59 strains tend to be resistant to more non-β-lactam antimicrobials than strains sharing this ST background in other parts of the world (879). In a study at the 2,500-bed National Taiwan University Hospital in Taipei in 2001 to 2006, 92% of the 30 available CA-MRSA isolates (by CDC criteria) from patients with bacteremia were ST59 strains (975). ST59 strains are currently rare in the United States, although an ST59 clone called USA1000 in the CDC classification has been identified sporadically (68, 595); the reasons for the high prevalence of ST59 in Taiwan, in contrast to its rarity in the United States, are not understood.

**ST93.** The ST93 Queensland MRSA strain was first identified in 2000 in Queensland and New South Wales, Australia. It spread rapidly to become the predominant $PVL^+$ MRSA clone isolated from infections in those regions. For example, in 2004 to 2005, in a national surveillance program in Australia, 87/462 (18.8%) MRSA isolates obtained from outpatients were ST93 strains, and all were $PVL^+$. Among $PVL^+$ MRSA isolates, 87/136 (63.9%) were ST93 strains, and they were isolated in all regions of the country (184). Despite the high prevalence of this strain in Australia (670), it has rarely been identified on other continents (258). It has been associated with severe infections, including necrotizing pneumonia (763), as well as SSTIs (352). A study of nasal colonization among healthy Queensland residents in 2005 to 2006 demonstrated a 0.7%

(5/699) MRSA carriage rate; 20% (1/5) of the MRSA isolates were ST93 strains (643). As with ST59 in Taiwan, ST80 in Western Europe, and USA300 in North America, the proclivity of ST93 strains to colonize and infect Australians from certain regions with limited spread elsewhere (258) is not understood.

## *STAPHYLOCOCCUS AUREUS* AS A COMMENSAL ORGANISM: ROLE OF ASYMPTOMATIC COLONIZATION

The epidemiology of CA-MRSA strains remains incompletely studied, but it must be considered in the context of what is known about asymptomatic colonization dynamics of other *S. aureus* strains. Most available information predates the emergence of CA-MRSA, and much of it is from Europe, where CA-MRSA infections remain relatively uncommon. Thus, the applicability of knowledge gained in that setting to the CA-MRSA strains epidemic in the United States is uncertain.

The asymptomatic carriage of *S. aureus* by humans is the primary natural reservoir, although domestic animals, livestock, and fomites may serve as adjunctive reservoirs. The anterior nasal mucosa has traditionally been thought to be the most frequent site for the detection of colonization of healthy carriers with *S. aureus* (91, 482, 773, 1002). The site sampled in the nasal mucosa may affect the demonstrable prevalence of colonization; for example, in one study, 22% of 412 patients carried *S. aureus* in the *cavitas nasi* but not in the more distal *vestibulum nasi* (325). Also, certain rapid PCR-based laboratory detection systems sometimes used in studies lack the sensitivity of culture and lack adequate sensitivity to detect small numbers of organisms (929).

A widely prevalent view was promulgated by Kluytmans et al., who distinguished three patterns of asymptomatic *S. aureus* carriage in the general population. Those authors estimated that 20% are persistent carriers, 60% are intermittent carriers, and 20% are noncarriers who rarely harbor the bacterium (482). It is not known if CA-MRSA strains colonize people in this fashion.

Recent studies have suggested that other anatomical sites may be asymptomatically colonized with *S. aureus* in the absence of nasal colonization. For example, among patients, health care workers, and blood donors in Basel, Switzerland, in 2000 to 2005, *S. aureus* carriage was underestimated by 25.7% when nasal cultures were not accompanied by throat cultures (600). In a study of 3,464 people in Switzerland in 2000 to 2006, including inpatients, health care workers, healthy blood donors, and dental patients, throat carriage of *S. aureus* with no concomitant carriage in the nares was found for 428 subjects (12.4%). This was associated with an age of <30 years (OR, 1.66; $P < 0.001$) and a lack of exposure to the health care setting (OR, 0.67; $P = 0.001$) (601). *S. aureus* colonization was found in the throat among orthopedic inpatients and staff more commonly than was colonization of the anterior nares (668). Among 89 tested health care workers at a hospital in Singapore, 18 (20%) carried MRSA in the throat, in the nares, or in both. Two (11%) were carriers in the throat and not the nose (150).

Similarly, for MRSA colonization among European inpatients, assessments of nasal carriage may not be adequate to test for asymptomatic carriage. At an English hospital that practiced routine MRSA screening at multiple body sites in 2008, MRSA colonization was identified slightly more often in the throat (72/635; 11.3%) than in the nose (59/635; 9.3%) or perineum (55/635; 8.7%); importantly, 23/72 (32%) patients with positive throat swabs did not have an isolate from another body site (71). Although these findings were not supported by a study of 150 adult ICU patients in Switzerland in 2005 where throat culture uniquely identified only 1 of 13 MRSA-colonized patients (368), the preponderance of evidence suggests that the human oropharynx may be an important reservoir for MRSA colonization. The same may be true for CA-MRSA strains in Europe or the United States, but data are lacking.

In a study of SSTI patients in Los Angeles, CA, 37% of 65 CA-MRSA patients (CDC criteria) were colonized with MRSA in at least one of four tested anatomical sites: 25% were colonized in the nares, 6% were colonized in the axilla, 11% were colonized in the inguinal region, and 13% were colonized in the rectum. Nonnasal colonization was identified for 25% of the patients, and 96% of colonized patients would have been identified by testing of nasal and inguinal swabs. In contrast to CA-MRSA, nonnasal *S. aureus* colonization was rare among CA-MSSA, HA-MSSA, and HA-MRSA patients (1018).

The asymptomatic carriage of *S. aureus* can be dynamic. For example, in 2001 to 2003 at an Australian hospital, half of 224 patients found to be colonized with MRSA carried more than one strain, and only 15.3% of colonized patients had persistent colonization at the same anatomical sites (535). Evidence from studies prior to the emergence of MRSA in the health care setting suggested that an individual with persistent nasal carriage of *S. aureus* is generally protected against the acquisition of new *S. aureus* strains. Intermittent *S. aureus* carriers, in contrast, may be at risk of acquiring MRSA colonization (482, 674), although persistence and strain variability of *S. aureus* carriage have not been well studied in the CA-MRSA era.

The reported duration of asymptomatic carriage of *S. aureus* has varied. In one study the half-life of MRSA nasal carriage was 40 months (800), and in another, nasal carriage of CA-MRSA isolates could be demonstrated for 2 years or longer (907). In a Swiss hospital, even in the setting of a study of routinely attempted decolonization of MRSA carriers, the median time to clearance was 226 days, and the maximum was 3.3 years. Risk factors for a longer duration of carriage were antibiotic use, the presence of an SSTI, the presence of an indwelling device, receipt of immunosuppressive therapy, and hemodialysis (582). At three suburban Chicago hospitals, hospitalized patients were routinely screened for nasal colonization with MRSA. From these data and chart records of any history of MRSA infection or previous MRSA colonization, it was estimated that 48.8% of patients (95% CI, 45.8% to 51.7%) continued to have MRSA carriage after 1 year and that 21.2% (95% CI, 13.1% to 31.4%) continued to have MRSA carriage after 4 years (769).

MRSA colonization of the nares is believed to be a risk factor for a clinically apparent infection with MRSA (191, 413, 561, 637), although the magnitude of the risk is not known. Ellis et al. demonstrated that 24 of 812 (3%) U.S. soldiers tested at a Texas Army base carried MRSA in the nares, and

9 of the 24 soldiers (38%) developed an SSTI in the course of 10 weeks, while only 8/229 (3%) soldiers carrying an MSSA strain developed an SSTI in the same period (259). Among 1,195 pediatric patients presenting for an outpatient physician's office visit in St. Louis tested for *S. aureus* nasal colonization, an SSTI was self-reported for 31.8% of those colonized with MRSA, 9.9% of those colonized with MSSA, and 8.9% of those with no *S. aureus* colonization during a 1-year follow-up. For all three groups combined, SSTI in the child during follow-up was associated with a history of SSTI in the child during the year prior to initial enrollment and also with an SSTI in a household member during the year of follow-up (307).

CA-MRSA infections often occur in people lacking simultaneous nasal MRSA carriage (466, 760). Among 64 pediatric patients with MRSA SSTIs at a Baltimore medical center, only 20 (31%) had MRSA nasal carriage, and only 23/39 (59%) patients with *S. aureus* recovered from an SSTI and a nasal swab culture had a concordance of both *S. aureus* PFGE type and susceptibility to methicillin in the two isolates (157).

Most data relating MRSA colonization risk to risk for subsequent disease are derived from settings where HA-MRSA is endemic and may not apply to CA-MRSA strains. For example, MRSA nasal carriage among adult ICU patients (220) and nasal or stool carriage among patients with cirrhosis (121) were a risk factor for subsequent infection.

Evidence that *S. aureus* nasal carriage predisposes one to infection with the same strain, which may or may not be applicable to CA-MRSA strains, comes from a study in Germany. Among 219 patients with *S. aureus* bacteremia, 180 (82.2%) had *S. aureus* in the nares of an identical PFGE type. Moreover, among 14 patients with *S. aureus* bacteremia, 12 had previous nasal carriage of the same strain as assessed by PFGE (959).

It is believed that hand carriage of MRSA is the major means of nosocomial MRSA transmission, but its role in the transmission of CA-MRSA backgrounds like USA300 and USA400 outside the health care setting has not been defined. Hand carriage of *S. aureus* was more likely for nurses with irritated skin (511). Furthermore, MRSA in the health care setting can be isolated from skin surfaces, such as the hands, even in the absence of nasal carriage (800), and transient hand carriage has been repeatedly demonstrated among health care workers (183, 592, 885) and may be more common among those wearing rings (910). Several studies from outside the United States have demonstrated the same phenomenon of MRSA transmission from health care workers to patients in the household setting. For example, a French study demonstrated that prior nursing home care was independently associated with infection by prevalent HA-MRSA strains when controlled for prior hospitalization, age of >65 years, and transfer from another institution (529), suggesting transmission from health care workers to patients in their homes. A Brazilian study demonstrated the transmission of MRSA from patients to their home-visiting health care workers (780). These data may not be applicable to an understanding of the transmission of CA-MRSA strains in households; if CA-MRSA is similarly transmitted from person to person by hand carriage, specific hand washing interventions may be appropriate to prevent its spread.

TABLE 6. Groups presumed to be at risk for CA-MRSA infections in the United States

| At-risk group |
|---|
| Neonates |
| Children beyond the neonatal period |
| Athletes |
| Household contacts of MRSA SSTI patients |
| Emergency department patients |
| Urban undeserved communities |
| Indigenous populations |
| Detainees in jail or prison |
| Cystic fibrosis patients |
| Military personnel |
| Men who have sex with men |
| HIV patients |
| Veterinarians, livestock handlers, and pet owners |

## RISK FACTORS AND HIGH-RISK GROUPS FOR CA-MRSA CARRIAGE OR INFECTION IN THE UNITED STATES

Prior to the late 1990s, MRSA infections were confined largely to patients and others who had known exposures to the health care setting, but the epidemic of CA-MRSA infections in the United States has required a redefinition of the risk factors for MRSA disease. CA-MRSA infections have been reported for diverse populations, including adults and children, residents of inner city neighborhoods, Native American (NA) and Pacific Islander populations, incarcerated and military populations, and athletes, who lack risk factors for exposure to the health care setting. Low socioeconomic status may be one common link among many of the identified high-risk groups, although many patients with CA-MRSA infections have no apparent risk factor (596). Environmental, behavioral, or other as-yet-unidentified social risk factors for CA-MRSA colonization await systematic study.

New MRSA risk factors for infection or colonization with MRSA in the community have been identified since 1998. Groups thought to be at high risk for MRSA infection based on anecdotal occurrences are listed in Table 6. Each will be discussed in detail in this section; people in close contact with individuals in these groups may also be at an increased risk. Further research is needed to assess how these risk groups interact and what risk factors or exposure they may have in common.

In addition to the putative high-risk groups for CA-MRSA infection listed in Table 6, there has been evidence of CA-MRSA strain transmission among children in day care centers (4, 822) and outbreaks of MRSA SSTIs within families (193, 237, 271, 272, 350, 381, 395, 533, 967), among children on a camping trip (180), among IVDUs (406), and in individuals exposed to another person with an SSTI by skin-to-skin contact during sexual activity (767). Inhalation drug use has also been shown to be a means of *S. aureus* transmission (742) and may play a role in CA-MRSA transmission, although this has not been well studied. Recent use of antibiotics has been associated with MRSA colonization (385) and infection (215, 841), but it is not known if this is an independent risk factor for MRSA or an association that may have confounding variables. Patients with atopic der-

matitis have long been known to be predisposed to *S. aureus* and, by extension, MRSA infections and colonization; of 54 children with atopic dermatitis in Philadelphia, PA, in 2004, 80% (43/54) had skin or nare colonization with *S. aureus*, and 13% (7/54) carried MRSA (872).

While many studies have demonstrated that the prevalence of CA-MRSA infections has increased rapidly among certain populations in the United States, the prevalence of nasal colonization in the general population has increased less rapidly and remains relatively low (188, 385). For example, among 100 healthy students and faculty members at a community college in Hawaii, an area with a high rate of MRSA infection, 3% were colonized with MRSA (632), similar to the rate among 200 health care workers at Johns Hopkins University Hospital in 2004 to 2005, in the midst of epidemic CA-MRSA invasive infections in Baltimore (481), where only 2% were colonized with MRSA (447). In the National Health and Nutrition Survey (NHANES), which is administered to a demographically and geographically representative sample of the noninstitutionalized U.S. population, an estimated 2.3 million Americans carried MRSA in the nares in 2001 to 2002, or 0.8% of the population (346, 492). In 2003 to 2004 the prevalence of MRSA nasal colonization nearly doubled to 1.5% of the population despite an overall decrease in the percentage of the population colonized with any *S. aureus* strain between 2001 to 2002 and 2003 to 2004 (32.4% versus 28.6%; $P < 0.05$) (336, 895). The relatively low rates of colonization determined from the NHANES survey and other studies may reflect, in part, geographic variability, a characteristic of the CA-MRSA epidemic to date, or an anatomical site of MRSA carriage other than the nose.

The epidemiology of CA-MRSA is complex, and several studies suggested that there is no obvious boundary dividing the populations at risk for MSSA and MRSA infections in the community, even in high-risk settings such as a jail (215). A study in Los Angeles demonstrated that adult patients with community-onset MRSA could not be distinguished from adult patients with community-onset MSSA infections by characteristics such as age, race, comorbidities, site of infection, antibiotic use, duration of symptoms, bathing habits, level of education, level of crowding at home, substance use, history of homelessness, sexual behavior, or use of a public shower, spa, pool, or gym (608). Thus, it is difficult to determine which patients with suspected *S. aureus* infections require specific therapy for MRSA.

### Neonatal MRSA Infections and Maternal Colonization and Infection

*S. aureus*, whether susceptible or resistant to methicillin, has long been known to be a cause of epidemic and endemic disease and a cause of infection in the first days of life among newborns in neonatal intensive care units (NICUs) and other settings. Since 2000, there has been an increasing number of reported outbreaks and cases caused by CA-MRSA strains. Several neonatal MRSA outbreaks have been linked to CA-MRSA strains (377, 435, 629), including USA300 (590, 591, 664, 777, 803) and USA400 (93) strains, and have been associated with visiting fathers (15), maternal mastitis (750, 807), expressed breast milk (313), peripartum maternal MRSA infection (255), and health care workers colonized or infected with MRSA, implying a community source (65, 214, 598, 803).

Case reports and case series have described a variety of clinical syndromes and means of introduction of MRSA into neonatal units. In 2001 to 2006 in Texas, neonatal MRSA infection in healthy term and near-term newborns was associated with a history of maternal MRSA skin infection (293). Among 23 MRSA SSTIs in mothers and newborn infants at a Toronto, Canada, hospital in 2004, the source was linked to a health care worker with eczema. The majority of the isolates were USA300 MRSA strains but were resistant to clindamycin and ciprofloxacin (803). Cases of severe, fatal neonatal MRSA pneumonia caused by USA300 have also been reported among neonates (590, 1019), as has necrotizing fasciitis (224).

What is the source of neonatal *S. aureus* acquisition? Vertical transmission undoubtedly plays a role. There is evidence that vaginal colonization with *S. aureus* is common (949), but vaginal MRSA colonization is unusual and has rarely been linked to neonatal infection. Neonatal dacrocystitis, lung abscess, and empyema were believed to result from vertical transmission from the mother of a 12-day-old infant in Los Angeles in 2007 (788; T. Ruter, personal communication). However, among 5,732 pregnant women in Alabama in 2003 to 2006, 3.5% were vaginally colonized with MRSA, but no neonatal MRSA infection was documented. Women with MRSA vaginal colonization in that study were more likely to be black, unmarried, and intravenous drug abusers and to have a lower level of education (21). A study in Cleveland, OH, demonstrated a 2.1% prevalence of nasal or vaginal colonization with MRSA among 96 women admitted to a labor and delivery unit; one woman had MRSA colonization at both sites. There was no association between neonatal infection and maternal colonization with *S. aureus* (54).

In New York City in 2005, 0.47% (14) of 2,963 pregnant women undergoing culture for group B streptococcal vaginal colonization had vaginal MRSA colonization (162). In a case-control study of that same population, women with any *S. aureus* vaginal colonization (8/65) were more likely than those without *S. aureus* colonization (1/52) to have a postpartum fever (161), suggesting that *S. aureus* vaginal colonization may be a risk factor for infection. In another study from New York City, 34/304 (11.2%) women in labor at term had nasal or vaginal colonization with MSSA, and 9/304 (3.0%) had MRSA. Infants born to these women underwent skin and nasal cultures after birth and again at 48 h; 16/252 (6.4%) infants were colonized with MSSA, and 9/252 (3.6%) infants were colonized with MRSA. A total of 5/252 (2.0%) infant-maternal pairs both carried MSSA, and 1/252 (0.4%) pairs both carried MRSA (i.e., the maternal vaginal colonization and the infant 48-h cultures were positive for MRSA). The infant and maternal MRSA strains in the concordant pair were identical by PFGE. At a 4-week follow-up, the single infant colonized at 48 h with MRSA and four infants not colonized with any *S. aureus* at birth or at 48 h developed *S. aureus* infections. That study suggested that MRSA colonization of neonates was not common and that most *S. aureus* infections of newborns were not due to vertical transmission (727).

Colonization in the hospital by means other than vertical

transmission likely plays a major role in neonatal colonization. For example, in a hospital in Florida, 288 mother-neonatal pairs were assessed for MRSA colonization by nasal swabs of mothers and neonates, umbilicus cultures of the newborns within 24 h after birth, and a vaginal culture of the mother within 24 h prior to delivery. Only vaginal births were included. Six (2.1%) mothers and two (0.7%) newborns were colonized with MRSA; no mother-infant pair shared the same SCC*mec* type. Colonization of mothers was associated with black race, antibiotic use during pregnancy or intrapartum, and attendance by another child of the mother at a day care or an after-school program (756).

Outside the United States, MRSA vaginal colonization has been studied less well. In Japan, oropharyngeal MRSA colonization in the first week of life in extremely low-birth weight infants in an intensive care unit in 1997 to 2003 was associated with an increased risk of MRSA sepsis and with MRSA colonization during week 6 of life. Those authors hypothesized that colonization of the oropharynx in the first week of life with other, nonpathogenic bacteria may protect against colonization with MRSA (829). This suggests that colonization of the maternal vagina may not be implicated in neonatal MRSA infections.

In an Israeli NICU in 1993 to 2003, among 43 cases of MRSA bacteremia, 11 were caused by SCC*mec* type IV-bearing, PVL-negative strains susceptible to all non-β-lactam antimicrobial drugs tested, suggesting a CA-MRSA strain. Infants with infections caused by CA-MRSA strains did not differ in risk factors or outcomes compared to MSSA infections or MDR MRSA infections (494). Those authors concluded that it was difficult to judge the likelihood of MRSA infection in a hospitalized neonate with a suspected *S. aureus* infection; they recommended in such cases that initial treatment include an agent effective against MRSA (guided by the local *S. aureus* antibiogram).

Thus, it appears that neonates in both the United States and some foreign hospitals face the risk of early MRSA infections that may be related to vertical transmission but that neonates frequently acquire MRSA from other sources as well. More research is necessary to enact effective measures to curtail potentially fatal MRSA infections among neonates.

### Children beyond the Neonatal Period

CA-MRSA in the United States was first identified in the 1990s among children in the Midwest (383). Since that time many areas in the United States have experienced a steep rise in the prevalence of colonization and the incidence of infection with MRSA among healthy children. In contrast, few other countries have experienced a comparable burden of pediatric CA-MRSA infections.

**Early reports.** The emergence of community-based MRSA disease in the United States was heralded by the observation that children with MRSA SSTIs and no known exposure to health care environments presented with increasing frequency to the University of Chicago Hospitals between 1988 to 1989 and 1993 to 1995 (383). A follow-up study in 1998 to 1999 demonstrated a continued high rate of hospitalization for CA-MRSA disease at that institution (423). Those same investigators demonstrated asymptomatic carriage of MRSA in otherwise healthy children in the community in Chicago (422, 871). At the nearby University of Illinois at Chicago, a similar phenomenon was documented during the late 1990s through the surveillance of infections of children caused by MRSA strains susceptible to clindamycin (300, 301, 302). The early CA-MRSA isolates from the University of Illinois and those from the University of Chicago were genotypically similar (2); they were subsequently shown to be predominantly USA400 strains (309). In addition, in 1999, cases of fatal severe sepsis from MRSA were reported among previously healthy children in Chicago and elsewhere in the Midwest (133, 621), also caused by MRSA USA400.

**MRSA colonization prevalence in U.S. children is increasing.** Nationally representative data showed that the prevalence of nasal carriage of MRSA in noninstitutionalized children aged 1 to 19 years more than doubled from 0.6% in 2001 to 2002 to 1.3% in 2002 to 2004 (336). However, studies from several cities in the United States have demonstrated an even more rapid rise in the prevalence of asymptomatic MRSA colonization of children. In Nashville, TN, in 2004, 9.2% of children attending two clinics for health maintenance visits were colonized by MRSA (188), an increase of more than 10-fold from 2001, when a similar study showed that 0.8% of children were colonized (655). Among 1,300 children presenting to 11 pediatric practices in St. Louis, MO, in 2005 to 2006, 2.4% had nasal colonization with MRSA. Risk factors for colonization included pet ownership, participation in sports, and fingernail biting. Of the MRSA isolates obtained, 66% carried SCC*mec* type IV and were therefore considered CA-MRSA strains (7/21 USA300, 3/21 USA800, and 3/21 USA1000 strains); black race and Medicaid enrollment were disproportionally represented among carriers of CA-MRSA compared with HA-MRSA genotypes (308). Within 48 h of admission to a children's hospital in Corpus Christi, TX, in 2005, a convenience sample of 76/350 (22%) pediatric patients had MRSA nasal colonization, one of the highest prevalence rates reported for any U.S. population (12).

**Increasing burden of CA-MRSA infections among U.S. children.** Many medical centers in the United States have documented an increasing burden of CA-MRSA infections in children as a percentage of *S. aureus* infections, an absolute increase, or both (120, 353, 1023). Children in Texas cities experienced CA-MRSA earlier than in many parts of the United States. For example, in a children's hospital in Corpus Christi, 147 MRSA infections were identified in outpatients and inpatients in 1990 to 2000. Among these patients, 60 (47%) had CA-MRSA infections (by the 1988 CDC criteria for nosocomial infections [311]), and in 88% of patients (53/60), no HA-MRSA risk factors (i.e., no chronic disease; no day care attendance; no household contact with a known risk factor; no hospitalization, antibiotic use, or surgery in the previous 6 months; no indwelling catheter; and no history of intravenous drug use) were identified. A rapid rise in the number of cases in each subsequent year was noted: 35 of the 60 (58%) cases occurred in 2000, the final year of the study (284). In follow-up studies examining trends from 1990 to 2004 at the same hospital, it was reported that the number of CA-MRSA infections increased rapidly, from 0 to 9 per year in 1990 to 1999 to 459 per year in 2003 (739) and to 589 per year in 2004 (741).

In a prospective study in 2000 at Texas Children's Hospital in Houston, 44% of 144 community-acquired *S. aureus* infec-

tions were CA-MRSA (i.e., children lacked risk factors for health care exposure). There was a high monthly proportion of CA-MRSA among community-onset *S. aureus* disease isolates that increased from 60% in August 2001 to 67% in January 2002 (802) and to 76.4% in 2004 (460). At another hospital in Houston, among children hospitalized in 2000 to 2003, CA-MRSA (i.e., isolates from lesions cultured <72 h after hospitalization) accounted for 67% of community-associated *S. aureus* infections (683).

At a pediatric hospital in Memphis, TN, in 2000 to 2002, 52% of patients with MRSA isolates from clinical infections were CA-MRSA (by CDC criteria). This percentage of MRSA isolates that were from CA-MRSA infections increased from 38% in the first 18 months of the study to 67% in the last 12 months. Fifteen of the 16 CA-MRSA isolates tested shared the USA300 pulsotype (105). Children who presented in 2002 to 2003 to Johns Hopkins University Hospital with a skin infection caused by *S. aureus* were more likely to have an MRSA infection if they were African American or if they lived in a zip code near the hospital, an area with a high rate of poverty (158). Of *S. aureus* SSTIs in children at the Johns Hopkins ED in 2003 to 2005, 73% (217/296) were caused by MRSA; 81% were CA-MRSA infections (by the CDC criteria) in 2003, and this percentage increased to 85% in the second year (874).

**CA-MRSA pediatric infections outside the United States.** Asymptomatic CA-MRSA colonization has not been reported for children in other countries, with a few exceptions. In Asia, reports that identified isolates that were predominantly ST59 and $PVL^+$ and carried SCC*mec* type V or $V_T$ have come from Taiwan, South Korea, and Japan. A single colonizing MRSA genotype was identified among several schoolchildren in one class in Taiwan (415). In Taiwan in 2004, 9 of 69 (13.2%) kindergarteners in Taipei had nasal MRSA colonization (547; W. T. Lo, personal communication). In 2004 to 2006, 8.1% of 1,615 children <14 years of age in kindergartens or presenting to a physician for a health maintenance visit in Taipei, Taiwan, had MRSA nasal colonization, and 1.5% (25) were colonized by $PVL^+$ strains. Of the $PVL^+$ strains, 92% were resistant to clindamycin, and 68% carried SCC*mec* type $V_T$ (548). In a separate study, 6.7% of 3,046 children in Taiwan attending well-child visits had MRSA nasal colonization in 2005 to 2006 (411), an increase compared with 1.9% (5/262) of schoolchildren in 2001 to 2002 (412). In Seoul, South Korea, at an outpatient clinic at a tertiary care hospital, 6.1% (18/296) of children presenting for care had MRSA nasal colonization in 2005 to 2006; of these, 14/18 isolates were CA-MRSA (by the CDC definition), and 7/14 CA-MRSA isolates belonged to ST72 bearing SCC*mec* type IVa (484). In Niigata, Japan, in 2006 to 2007, 3/426 (0.7%) children attending outpatient physician's office visits had MRSA nasal carriage; in 2007 to 2008, 5/136 (3.7%) healthy children living with their families in eight prefectures had MRSA nasal carriage. None of the children in that study had been hospitalized in the previous year, and the MRSA isolates had a variety of genetic backgrounds, with none carrying the genes for PVL (697). In Narketpally, Andra Pradesh, India, in 2006, 12/392 (3.1%) children aged 5 to 15 years had nasal carriage of MRSA, but genotyping studies were not conducted (745; K. V. Ramana, personal communication).

MRSA infections have also been reported for children in a few regions of Asia. At a hospital in Taiwan, 210 MRSA isolates were obtained from clinical infections of 173 children in 2004 to 2005. Of the 210 isolates, 56% (102) were CA-MRSA by the CDC case definition; of these, 69% were ST59, 79% were $PVL^+$, 70% carried SCC*mec* type $V_T$, and 21% carried SCC*mec* type IV. In contrast, among isolates from health care-associated MRSA infections, only 20% were ST59 and carried the PVL genes, 21% carried SCC*mec* type $V_T$, and 28% carried type IV (410). MRSA infections in nine children in Vietnam, including one fatal case of severe sepsis, were believed to result from exposure to a community vaccinator who was colonized with an ST59 strain bearing SCC*mec* type V (887). In Cambodia, 17 children in 2006 to 2007 had CA-MRSA infections by CDC criteria identified by surveillance at a clinical microbiology laboratory at a single children's hospital. The causative strains were ST834 with SCC*mec* type IV and were PVL negative or ST121 with SCC*mec* type V and were $PVL^+$ (164). At pediatric hospitals in five Chinese cities, 29 CA-MRSA (by CDC criteria) infections in 2005 to 2006 were reviewed retrospectively. Several MLSTs were represented, including ST59, ST910, ST1, and ST88 (1028).

In Latin America, Europe, and Australia, case series have documented the presence of CA-MRSA in children. In 2002 to 2003, 22/2,345 (0.93%) children attending day care centers in 14 Mexican cities had nasal carriage of MRSA; however, only 10.1% of the children were identified as being *S. aureus* carriers, a rate lower than that found by most studies (950). In Buenos Aires, Argentina, in 2005, five SSTIs in children without exposure to the health care system were caused by $PVL^+$ MRSA strains carrying SCC*mec* type IV (903). At a clinic in Athens, Greece, 88 CA-MRSA infections (by CDC criteria) among children younger than 14 years old were recorded in 2003 to 2005; 68% (28/41) of the strains belonged to one PFGE clonotype (similar to the PFGE type of ST80 strains) that was $PVL^+$ and SCC*mec* type IV. Twenty of the 28 strains (71%) belonging to this clonotype were isolated from patients with SSTIs (673). In New South Wales, Australia, a retrospective review of gentamicin-susceptible MRSA infections in 2001 to 2002 at a children's hospital showed that 87 of 100 MRSA infections were caused by CA-MRSA (i.e., no health care exposure in the previous 12 months and a culture obtained <48 h after admission). Of the 87 infections, 67% caused SSTIs, and the majority were ST30 strains carrying SCC*mec* type IV (352).

Thus, CA-MRSA infections and colonization of children have been reported outside the United States; as it was in the United States, pediatric infections may be a harbinger of an epidemic to come in the general population of these countries.

### Athletes

MRSA infections have been reported for members of athletic teams in a variety of sports and related activities such as dance (83), at levels from high school to professional in a variety of sports (Table 7). The frequency of these reports has suggested that athletes constitute a population at risk for MRSA infections and that athletic facilities constitute a new environment for the transmission of MRSA outside the health care system.

Causative isolates obtained from athletes have usually shared characteristics with CA-MRSA strains, and USA300

TABLE 7. Athletic activities in which participants were reported to have MRSA infections

| Sport | Yr | Location | Level of competition | Reference(s) |
|---|---|---|---|---|
| Football | 2002–2003 | California | College | 135, 665 |
| | 2000 | Pennsylvania | College | 135 |
| | 2004 | Illinois | High school | 83 |
| | 2007 | New York | High school | 134 |
| | 2006 | West Virginia | College | 356 |
| | Not stated | California | College | 792 |
| | 2006 | Pennsylvania | College | 87 |
| | 2005 | Florida | College | 25 |
| | 2003–2004 | Texas | High school | 44 |
| | 2002–2004 | Texas | College | 174 |
| | 2003 | Connecticut | College | 53 |
| | 2003 | Missouri | Professional | 466 |
| Badminton | 2006 | Vladivostok, Russia | Unknown | 43 |
| Basketball | Not stated | Virginia | College | 863 |
| | 2002–2004 | Texas | College | 174 |
| Cross-country running | 2003–2004 | Texas | High school | 44 |
| Fencing | 2002–2003 | Colorado | Unknown | 135 |
| Rugby | 1996 | United Kingdom | Unknown | 854 |
| Saturation diving | Unknown | Texas | Unknown | 976 |
| Soccer | 2005–2006 | Netherlands | Unknown | 416 |
| | 2004 | Slovenia | Unknown | 639 |
| Volleyball | 2002–2004 | Texas | College | 174 |
| | 2003–2004 | Texas | High school | 44 |
| Weight lifting | 2002–2004 | Texas | College | 174 |
| Wrestling | 1993–1994 | Vermont | High school | 541 |
| | 2003 | Indiana | High school | 135 |
| | 2003–2004 | Texas | High school | 44 |

has been identified as a frequent cause (665). Risk factors identified among athletes have included sharing personal items, such as soap, towels (134), razors, athletic training equipment, and clothing, in addition to poor hygiene habits (356, 665). In one case-control investigation of a USA300 SSTI outbreak on a high school football team, higher body mass index was a risk factor for MRSA infection (134). Data from Texas and Nebraska suggest that MRSA infections among high school athletes are very common and increasing in incidence. Among 186 athletic trainers at Texas high schools responding to a survey, 60 (32.3%) reported that they were aware of at least one case of MRSA infection in their athletic department in 2003 to 2004 (44). Among 271 Nebraska high schools surveyed, 4.4% reported having at least one athlete with an MRSA infection in 2006 to 2007, while 14.4% reported at least one infection in 2007 to 2008 (114).

While MRSA SSTIs have afflicted participants in many sports, football teams have been most frequently implicated. An outbreak in a college football team resulted in MRSA SSTIs in 1.8% (2/107) of players in 2002 and 15.8% (17/107) of players in 2003. The rate decreased to 1.0% (1/104) of players in 2004 with the introduction of an educational campaign, hexachlorophene-containing soap, disposable towels, showering before use of the athletic training room, improved decontamination of athletic training and weight room equipment, and increased availability of hand sanitizers (775). Unfortunately, it is not known which of these interventions, if any, contributed to the decreased rate of infection. A case-control study after an SSTI outbreak in 2005 in a Florida college football team identified previous skin abscess as the only independent risk factor for an MRSA SSTI among 13 patients (25). An outbreak of 6 confirmed and 19 suspected (cellulitis during the outbreak period with two or more of the following: swelling, fever, heat, or purulence) cases occurred in a college football team in August to September 2006; the three MRSA isolates tested belonged to USA300 or USA800, and risk factors for infection included the use of hydrocollator packs and other athletic training equipment as well as being a lineman or a tight end (356). In a meta-analysis of four previously published studies (53, 135, 665, 775) of players from three division I college football teams in 2003 to 2006, MRSA infections occurred in 6.7% (33/491) players, primarily on the extremities, with no relationship to position played (87).

### Household Contacts of MRSA Patients

Transmission of *S. aureus* in the household setting was documented prior to the CA-MRSA epidemic (706), but new

attention has been focused on the issue, with anecdotal suggestions that such transmission may be common. Reports of household contact transmission of CA-MRSA have been documented among health care workers (613) and, more recently, among non-health care workers in the community (193, 237, 272, 350, 400) in the United States, but the subject has not been studied rigorously. The role of fomites in household transmission is not known (see below).

Household transmission of CA-MRSA strains in the United States, Europe, and elsewhere (3, 271, 376, 378, 381, 395, 522, 533, 672, 697, 967, 977) has been reported. For example, among MRSA infections of families of military personnel in San Diego, CA, 10% of the 632 isolates in 2004 were from patients who had a family member who also had an MRSA infection in the same year (193). In Europe, where contact tracing of index MRSA cases is commonly performed, several case reports demonstrated household transmission (847). In Greece in 2003 to 2005, among 88 CA-MRSA infections of children, 15.9% had suspected transmission of MRSA from family members (673). In Lund, Sweden, in 2000 to 2005, household contacts were tested routinely for MRSA colonization when a hospitalized patient was identified with an MRSA infection. In 22 of 51 cases with contact tracing, 42 colonized household contacts were identified. In the 22 households with colonized contacts, 70% of the contacts were colonized with MRSA in the anterior nares, throat, or perineum or at the site of a skin lesion. With a single exception, all MRSA isolates from household contacts shared the *spa* type of the isolate from the corresponding index patient (440).

Sexual activity or other skin-to-skin contact may be a means of household CA-MRSA transmission (766), as was suggested by the apparent heterosexual transmission of USA300 among members of three households in New York City in 2004 to 2006 (182). More research is needed to assess the role of MRSA transmission within households and by sexual contact.

### Emergency Department Patients

U.S. ED visits for SSTIs increased from an estimated 1.2 million in 1993 to 3.4 million in 2005, an increase from 1.35% to 2.98% of all ED visits (699), likely reflecting the impact of CA-MRSA. EDs serve as a safety net that provides health care for uninsured populations in the United States, and thus, the number of SSTIs treated may reflect the prevalence of these infections in communities with a low socioeconomic status (SES). The higher SES of patients in private physicians' offices, in contrast, may explain why a similar study of U.S. physicians' offices in 1993 to 2005, using data from the National Ambulatory Medical Care Survey, did not show an increase in the percentage of all office visits due to dermatitis or SSTI during this period (700).

Several studies of EDs support the finding that there is an increase in MRSA disease among ED patients. In August 2004, among 11 university-affiliated EDs in U.S. cities, MRSA accounted for 59% of 320 *S. aureus* SSTIs; 97% of the MRSA isolates were USA300 strains (628). Cultured skin lesions among adults presenting to an ED in Cincinnati, OH, with an SSTI in 3 months during 2005 yielded MRSA at a rate of 58%. Risk factors for MRSA infection included in a best-fit multivariable regression model were young age, sexual contact in the past month, the presence of an abscess cavity, and residence in a group home (433). In a Nashville, TN, ED, MRSA was isolated from 67.6% (255/367) of adult and 79.7% (145/182) of pediatric SSTI cultures in 2004 to 2005 (883). Of a convenience sample of 68 children who presented to an urban North Carolina emergency department with abscesses in 2005 to 2006 and underwent drainage, 88% (60/68) of isolates grew *S. aureus*; 85% (51/60) were MRSA (570). Among 195 children with SSTIs presenting to a suburban New Jersey ED in 2003 to 2007, 27% of isolates grew MRSA (453). In Philadelphia in 2007, 47/85 (55%) community-associated (by CDC criteria), culture-proven hand infections of adults presenting to an ED were caused by MRSA; MRSA was associated with intravenous nonmedical drug use and a high white blood cell (WBC) count of >8,700 cells/ml (690). In a Chicago, IL, ED, surveillance in 2004 to 2005 demonstrated that among 128 MRSA isolates recovered from ambulatory patients, 84.4% were susceptible to clindamycin, 94.5% carried SCC*mec* type IV, 89.1% were $PVL^+$, 82.8% were ST8, and 91.4% were SSTIs, all characteristics of CA-MRSA strains and the SSTIs that they cause (216). At two military hospitals in Texas in 2004 to 2005, 68% of 220 abscesses cultured yielded MRSA (248). MRSA was the most common etiology of septic arthritis identified among 109 synovial fluid cultures sent from two EDs in California in 2006 to 2007; 6/12 (50%) cases diagnosed as septic arthritis were caused by MRSA, and 4/12 (33%) were caused by MSSA (303).

There are fewer studies from EDs outside the United States. At a French ED in 2004 to 2005, patients with MSSA and MRSA were compared. Of 93 MRSA patients, 9 were younger than 40 years of age and had no known health care exposure (955), documenting the existence CA-MRSA patients served by an ED in France. In a surveillance study of EDs in 2006 to 2007 in Hong Kong, MRSA was responsible for a minority, 19/298, of SSTI cultures and 19/126 *S. aureus* SSTI cultures. CA-MRSA (CDC criteria) accounted for 13/241 abscess cultures, 12 of which were $PVL^+$; all carried SCC*mec* type IV or V. Six were ST30 strains and were susceptible to all non-β-lactams tested. Five were ST59 strains with variable susceptibility to tetracycline, clindamycin, and erythromycin. Of the 12 CA-MRSA SSTIs, 4 were infections of foreign workers from the Philippines (397). In an ED in Madrid, Spain, in 2007, seven CA-MRSA (by CDC criteria) SSTIs were diagnosed in children: 6/7 isolates obtained were ST8 isolates bearing SCC*mec* type IV, and 5/6 of these were $PVL^+$ (208).

CA-MRSA infections are often treated in EDs, which provide care to an underserved and underinsured population in the United States; more research is needed to determine why they are a focus of the CA-MRSA epidemic.

### Urban Underserved Communities

Studies of medically underserved communities in U.S. cities have revealed foci of CA-MRSA SSTIs and frequent asymptomatic MRSA nasal colonization. In San Francisco, CA-MRSA has been well documented to have targeted certain adult populations. For example, in 1999 to 2000, 2.7% of 833 homeless or poor adults harbored MRSA (153), a rate higher than that found in 2001 to 2002 in the general U.S. population (492). Among IVDUs in that city in 1999, 6.1% carried MRSA.

Of the 35 MRSA isolates genotyped, 28 carried SCC*mec* type IV (154). Of isolates from adult patients at a clinic opened to treat SSTIs in an underserved community in 2000 to 2003, 91% were *S. aureus*, and 59% of the *S. aureus* isolates were MRSA isolates. Many of these patients were IVDUs (1020). At an urban public hospital in that same city, among 137 patients from a population skewed to the homeless and IVDUs in 2003 to 2004, 51% of cultures from SSTIs grew MRSA. Of cultures obtained from the nose or an SSTI in this population, 75% were MRSA isolates; 99% carried SCC*mec* type IV, and 94.1% were $PVL^+$ (304). Among homeless and runaway youths (12 to 24 years old) in San Francisco in 2002, 6.2% of 308 subjects had nasal MRSA colonization. Of the 19 MRSA isolates identified, 84% were strains of USA300 or USA1000 (702), well-known CA-MRSA clones. Among 215 homeless men and women in Cleveland, OH, 25.6% (55/215) had nasal carriage of MRSA; MRSA carriage was associated with antibiotic use in the previous 30 days ($P < 0.04$), a history of alcoholism ($P < 0.08$), current smoking ($P < 0.06$), and a lower frequency of staying with a friend for at least 1 night in the previous 30 days ($P < 0.03$) than non-MRSA carriers. All of these associations remained significant upon multivariate analysis except cigarette smoking (dates of the study were not provided) (505).

It is likely that USA300 is more widespread in populations affected by poverty. MRSA isolates causing community-onset SSTIs in 2000 to 2002 from Stanford University Hospital (SUH), located in a suburban area that serves a population largely covered by private insurance, were compared with those from San Francisco General Hospital (SFGH), a hospital serving an inner-city community. At SUH, MRSA isolates were less likely to carry SCC*mec* type IV (29% versus 90%) and less likely to be $PVL^+$ (16% versus 55%). Furthermore, 69% of SSTIs at SUH had their onset in the community, compared with 93% at SFGH. USA300 was the dominant clone causing SSTIs at SFGH in 2002 but was not at SUH. Being nonwhite and younger than 60 years of age were associated with infection caused by SCC*mec* type IV-bearing and $PVL^+$ strains of MRSA (68).

Similarly, in Chicago, contrasting the experiences of a large public hospital and a large private hospital demonstrated different epidemiological patterns. At Cook County Hospital and its associated clinics, an increase in the incidence of CA-MRSA SSTIs from 24 cases/100,000 population in 2000 to 164.2 cases/100,000 population in 2005 was documented. In January 2000 to August 2005, 971 CA-MRSA SSTIs were recorded (using criteria similar to the CDC case definition). Risk factors for CA-MRSA infection, compared with CA-MSSA infection, included recent incarceration, African American race, and residence in a public housing complex (403, 731). In contrast, among adults hospitalized in 1998 to 1999 at Northwestern Memorial Hospital in Chicago, located near the more-affluent Loop region, only 1.9% ($n = 20$) of MRSA isolates cultured from 1,071 patients within 72 h of hospital admission were clindamycin susceptible (a frequently used proxy for CA-MRSA isolates) (873), suggesting that CA-MRSA disease had remained infrequent during that period in that population.

In other cities, including Dallas and Atlanta, racial and socioeconomic disparities predisposing one to MRSA infection risk were similarly documented. For example, during 5 months in 2003 at a Dallas hospital, among inpatient adults with *S. aureus* infections with isolates cultured within 72 h of admission, 63% had MRSA infections. The patients with MRSA were more likely than patients with MSSA to have a history of homelessness, to be African American, to have an SSTI, and/or to have used antibiotics in the previous 6 months (841). In Atlanta in 2003 at a large public hospital serving the inner city, 7.3% of 726 hospitalized patients had nasal colonization with MRSA at admission. Risk factors included HIV infection, SSTI, recent use of antibiotics, or admission to the hospital in the previous 12 months (385). A study in Atlanta in 2003 at a 1,000-bed public hospital and its affiliated clinics found that the USA300 strain was the predominant cause of *S. aureus* SSTIs diagnosed in outpatients or within 72 h of hospital admission and that African American race, female sex, and hospitalization within the previous 12 months were independently associated with infection by a CA-MRSA strain (475).

By 2007, most major urban centers in the United States had reported CA-MRSA case series. However, geographic variation continued. For example, CA-MRSA was recognized later on the East Coast than in the Midwest, Texas, Tennessee, and California. In 1999 to 2000, among 500 patients enrolled in a methadone program in New York City who were not current i.v. heroin users, only 10 (2% of all tested) had nasal colonization with MRSA. These MRSA isolates were genetically distinct from locally prevalent HA-MRSA strains; 9 of the 10 MRSA colonization isolates carried SCC*mec* type IV (611), suggesting a community origin. Since 2000, however, USA300 has become more common in New York City, and infections with USA300 have been associated with a higher incidence in neighborhoods with lower SES. In a study from Brooklyn, NY, in 2005 to 2006, hospitals in areas with a low SES (by several measures) were reported to have a higher rate of USA300 infections than hospitals in areas with a higher SES (94).

Outside the United States, few studies have documented similar associations between CA-MRSA and low SES. An exception was in Alberta, Canada, where CA-MRSA infection was associated with homelessness (318).

### Indigenous Populations

Multiple indigenous populations, including Native American (NA), First Nation (Manitoba and Nunavut, Canada), Australian Aboriginal, Pacific Islander, and Alaska Native ethnicities, have been associated with a high risk of infection with CA-MRSA strains (Table 8). Many of these groups are disadvantaged in their societies, and their association with lower SES may be responsible for the increased risk of CA-MRSA infection (905). In Australia, CA-MRSA was first noted for aboriginal communities, a socially disadvantaged group with crowded living conditions and frequent use of antimicrobial drugs (905). In a small indigenous community in Australia, 15% of tested children had either infections or colonization by MRSA (958). In the United States, at hospitals administered by the Indian Health Service, MRSA-associated hospitalizations increased from 4.6 per 100,000 American Indians/Alaska Natives in 1996 to 1998 to 50.6 per 100,000 in 2003 to 2005. Among these patients, 59% had a diagnosis of SSTI (116).

Pacific Islanders in many regions have been found to be a

TABLE 8. Indigenous populations and CA-MRSA[a]

| Ethnicity | Yr | Study summary | Setting | Reference(s) |
|---|---|---|---|---|
| Native Americans (United States) | 1997 | 74% (46/62) of isolates identified in a review of MRSA infections at an Indian Health Service facility were CA-MRSA (i.e., obtained from an outpatient or <48 h after admission from an inpatient, no history of hospitalization, renal dialysis, or residence in an LTCF in the previous yr, and no documentation of i.v. drug use); the percentage of *S. aureus* isolates that were MRSA in this community increased from 4% in 1989 to 10% in 1993, 25% in 1994, and 57% in 1997 | Rural Midwestern Native American community | 349 |
| | 2001 | 1.9% (9/468) of patients had asymptomatic carriage of MRSA; 56% (5/9) were CA-MRSA (i.e., taken from a patient without inpatient health care exposure, hemodialysis, or occupation in a health care facility in the previous year); 5 of the 9 (56%) MRSA isolates were closely related by PFGE typing; 8/9 (89%) isolates were susceptible to all non-β-lactam antibiotics tested with the exception of erythromycin (3/9 were resistant to erythromycin) | Predominantly Native American community, Washington State | 526 |
| Native Alaskans (United States) | 1996, 2000 | Outbreaks of MRSA SSTIs; causative isolates were predominantly ST1, ST30, or ST59, all were $PVL^+$, and all carried SCC*mec* type IV | Remote Native Alaskan villages, southwestern Alaska | 36, 37, 504 |
| Australian Aboriginal people and PIs | 2004 | MRSA colonization in 14 of 92 (15%) children in nose, throat, or skin wounds; 6/14 (43%) carried $PVL^+$ ST93 strains, and 2/14 (14%) carried $PVL^+$ ST30 strains; 5/14 (36%) carried PVL-negative ST5 strains; 14/15 (93%) were susceptible to all tested non-β-lactam antibiotics | Indigenous community, schoolchildren in grades 1-7, Queensland, Australia | 958 |
| | 2000–2003 | 8 cases (4 pediatric and 4 adults) of severe invasive infections with either ST93 or ST30 $PVL^+$ MRSA isolates obtained <48 h after admission, with no health care exposure or antibiotics in previous 12 months; 5/8 (63%) patients were PIs or of Aboriginal ethnicity | 3 large hospitals, Southeast Queensland, Australia | 720 |
| | 1991–1995 | Community-acquired WA-MRSA (i.e., Western Australian strain, defined by antibiotic susceptibilities) infections were more likely to occur in Aboriginals than in non-Aboriginals (RR, 25.9; 95% CI, 12.51-53.47) | Royal Darwin Hospital, Northern Territory, Australia | 573 |
| | 1997–1998 | 35 gentamicin-susceptible MRSA isolates from infections; 23 were community acquired; 17/23 (74%) patients had no health care exposure; 10/17 (59%) were PIs, and 1/17 (6%) was Aboriginal; all 11 isolates from PIs or Australian Aboriginal people were of the same pulsotypes | Clinical microbiology laboratory, 4 hospitals, Brisbane metropolitan area, Queensland, Australia | 672 |
| | 1998–2001 | Of 15 episodes of community-onset MRSA bacteremia (i.e., patients with isolates cultured <48 h after admission, with no indwelling catheter, and with no history of hospitalization or stay in an LTCF in previous 90 days) in 14 patients, 12/14 (86%) patients self-identified as being Aboriginal, while 25% of the population served by the hospital was Aborginal; 10 isolates carried SCC*mec* type IV | Royal Darwin Hospital, Northern Territory, Australia | 647 |
| | 2004–2005 | Case-cohort study of 100 non-MDR MRSA (i.e., resistant to ≤2 tested non-β-lactam antibiotics) infections compared with matched MSSA-infected patients (2:1) and MDR MRSA-infected patients (1:1); Aboriginal or Torres Strait Islanders had an odds ratio of non-MDR MRSA infection compared with MDR MRSA infection of 3.9 (95% CI, 1.16-16.92) upon univariate analysis; this was not significant upon multinomial logistic regression | 8 hospitals, southeast Queensland, Australia | 642 |
| | 2001–2002 | 100 gentamicin-susceptible MRSA infections of 98 patients; 20 patients were PIs (60% had ST30 SCC*mec* type IV isolates), and 10 were Aboriginal (80% had ST93 $PVL^+$, SCC*mec* type IV isolates); all 3 episodes of bacteremia were in Aboriginal children with an ST93 strain; PIs and Aboriginals each accounted for <2% of the population of New South Wales | Pediatric teaching hospital, New South Wales, Australia | 352 |

*Continued on following page*

TABLE 8—*Continued*

| Ethnicity | Yr | Study summary | Setting | Reference(s) |
|---|---|---|---|---|
| | 2005–2006 | 89% (98/104) of infections caused by non-MDR MRSA isolates (i.e., isolates resistant to <3 non-β-lactam antibiotics tested) were of Aboriginal people | Alice Springs Hospital, Alice Springs, Northern Territory, Australia | 861 |
| Canadian FN | 1990–1992 | 259 MRSA infections of 135 inpatients in 36 mo; 85 patients had MRSA cultured <72 h after admission (community acquired); CA-MRSA patients were younger, more likely to have a rural residence, and more likely to be of FN ethnicity than HA-MRSA patients; 62% of CA-MRSA infections were in FN, and 14% of HA-MRSA infections were in FN ($P < 0.001$) | Five tertiary care hospitals in Winnipeg, Manitoba, Saskatoon, Saskatchewan, Calgary, Alberta, and Edmonton, Alberta, Canada | 263 |
| | 2006–2007 | Outbreak of 43 CA-MRSA infections; 95% of isolates were USA400; for 5- to 9- and 20- to 29-yr-old populations, the cumulative incidence was 26/1,000; the outbreak accounted for 80% of reported MRSA cases in the province | Remote Inuit community with population of 2,000 in Nunavut, Canada | 203 |
| | 2003–2006 | Rising rates of MRSA cases reported from clinics serving FN communities, reaching an incidence of 8 to 16/10,000 in areas of 2 regional health authorities | Northern Manitoba, Canada | 507 |
| | 1995–2002 | 279 FN patients with MRSA infection or colonization; their isolates were more likely to be susceptible to erythromycin, clindamycin, TMP-SMX, and ciprofloxacin, more likely to be resistant to mupirocin, and more likely to have a pulsotype similar to USA300 (CMRSA-5) than MRSA isolates from non-FN patients; 61% of FN inpatients vs 33% of non-FN patients had a clinical MRSA infection; FN patients were 6-fold-more likely to have a CA-MRSA infection than non-FN patients | 38 hospitals, inpatients, Canada | 684 |
| PIs | 2001–2003 | 51% of 346 CA-MRSA infections (CDC criteria) were of PIs, while only 24% of the state population was PIs in 2001; 92% of the infections studied were SSTIs | 4 health care facilities, Hawaii | 131, 270 |
| | 1996–2000 | 80% of samples from Samoan or PI patients (4/5) vs 12% of non-Samoan/non-PI patients (4/34) with *S. aureus* SSTIs were MRSA | Surveillance, family practice clinic, Anchorage, AK | 125 |
| | 1997–1998 | Case series of 74 CA-MRSA infections (i.e., no previous contact with hospital or nursing home); disproportionate no. of cases in people from the South Pacific (e.g., Tonga and Western Samoa) | Hospitals in Brisbane, Canberra, Melbourne, and Sydney, Australia | 178 |
| | 1993–2004 | Review of 58 pediatric *S. aureus* sepsis cases; isolates from all 7 MRSA (12%) cases were cultured <48 h after admission, and all 7 patients were PIs or Maori | Hospital pediatric ICU in Auckland, New Zealand | 605 |
| | 1992–1996 | Case series of 10 MRSA infections in inpatients with onset in the community (excluding nursing home residents, those hospitalized in the previous 6 mo, or those with isolates cultured >48 h after admission); 2/10 (20%) patients were from American Samoa | Tripler Army Medical Center, Hawaii | 333 |
| | 1998 | Chart review of all 9 non-MDR MRSA isolates (susceptible to erythromycin, tetracycline, ciprofloxacin, gentamicin, rifampin, fusidic acid, and vancomycin) obtained in 2 months; all patients were Polynesians, and all had severe SSTIs | Clinical microbiology laboratory serving public hospitals, South Western Sydney Area Health Service, Australia | 337 |
| | 1998–1999 | 26 non-MDR MRSA infections; 29% (7/24) of non-MDR MRSA vs 0% (0/9) of MDR MRSA infections were in people born in Samoa, Tonga, or New Zealand; 44% of non-MDR MRSA vs 0% of MDR MRSA infections were CA-MRSA (i.e., no hospitalization, surgery, or residential care in previous 12 mo and no chronic disease) | Patients at emergency or dermatology departments at hospitals, South Western Sydney Area Health Service, Australia | 338 |
| | 2000–2001 | 39% (17/44) of infections with non-MDR MRSA occurred in patients from the Southwest Pacific Islands, while 3% of the general population was from these islands; 16/17 (94%) infections in PIs were community acquired (i.e., cultured <48 h after admission and in patients with no health care contact in the previous 12 mo and no chronic illness); 7 isolates were the "Pacific Island strain" by PFGE | Ipswich Hospital, Queensland, Australia | 645 |

[a] Abbreviations: FN, First Nations; LTCF, long-term care facility; PI, Pacific Islander.

high-risk group for MRSA infection. Higher rates of all *S. aureus* infections have also been noted for Pacific Islanders by investigators in New Zealand and Australia (196, 387). The reasons for this association are not known. In Hawaii, a prospective study of all MRSA infections diagnosed at four health care facilities from July 2001 to June 2003 found that among 1,389 patients with MRSA infection, 28% were infected by CA-MRSA. These infections were disproportionately more common among self-described Pacific Islanders than among Asians. Those investigators did not collect markers for SES in this cohort. However, they did note that Pacific Islanders had a higher poverty rating, larger families, and a lower proportion of college graduates than did Asians (131).

More study is needed to determine why certain ethnic populations face a disproportionate risk of MRSA infection or asymptomatic colonization.

### Incarcerated Populations

Incarcerated populations in the United States are at a high risk of MRSA infections. Many outbreaks have been reported in jails and prisons (136, 138, 918), and in many urban jails, MRSA has become an endemic pathogen and the predominant etiology of cultured SSTIs (39, 215, 703, 888). There have also been many case reports of detainees and recently released prisoners with MRSA infections (241, 299, 789, 832, 835, 941, 1021). Molecular evidence has linked the MRSA isolates from correctional facilities to local CA-MRSA strains (140, 215, 703, 918). In the only large-scale study of its kind, in 1999 to 2001, the Texas Department of Criminal Justice found that 12 MRSA infections occurred per 1,000 prisoner-years, a very high rate; among the risk factors identified were female gender, white race, jail (as opposed to prison) incarceration, and young age (39). The higher risk demonstrated for younger inmates suggests an epidemiological pattern consistent with CA-MRSA (136) in other populations.

Many detainees in urban jails are held for only brief periods of time and are often recidivists; this revolving door is potentially an amplifier of epidemic MRSA colonization in communities with a high prevalence of recently jailed individuals and their contacts. In the United States, the incarcerated population increased from 325,400 in 1970 (51) to 2,245,189 in June 2006 (793). Approximately 11.5 million inmates were released from incarceration facilities in 1998, most from local jails (660). In 2006, 1 in every 133 U.S. residents was incarcerated, but more than 1 in 9 (11.7%) African American men aged 25 to 29 years were detained (793). If jails are a common site of MRSA colonization, as they appear to be, this population and their contacts may face a high risk of MRSA colonization and infection.

MRSA has been shown to be the predominant pathogen causing SSTIs among detainees in jails in many U.S. cities. A study of MRSA isolates causing infections in five county jails near San Francisco demonstrated a dramatic rise in the percentage of *S. aureus* SSTIs caused by MRSA, from 29% in 1997 to 74% in 2002. There were two predominant MRSA clones, suggesting the spread of these clones in the jail or a common source of colonization among detainees (703). Among 502 MRSA isolates obtained in 2001 to 2007 from infections of detainees in the San Francisco County Jail, USA300 first appeared in 2001 and rapidly became the predominant strain after 2005. The number of MRSA infections rose each year, from 25 in 2000 to 60 in 2007, although there was little change in the numbers of MSSA infections each year. The majority of the strains were isolated from patients with SSTIs. Clindamycin resistance was found for 9.3% of MRSA isolates and did not significantly change over time (888). In an 18-month period in 2004 to 2005 in the Cook County Jail in Chicago, IL, the largest single-site pretrial detention facility in the United States, MRSA was identified as the etiology of 63.5% (240/378) of all cultured skin lesions and 85% (240/283) of all *S. aureus* skin infections (215). At Stroger Hospital of Cook County and its clinics in Chicago in 2000 to 2005, incarceration during the previous year was an independent risk factor for an MRSA SSTI (403). At the Whatcom County Jail in Washington, 50/74 (68%) SSTIs in 2005 were caused by MRSA (223).

In 2001 to 2002, an outbreak of MRSA SSTIs was recognized at the Los Angeles County Jail (LACJ), the largest county jail system in the United States. From January 2002 to June 2003, there were 1,697 MRSA skin infections reported; 79% were reviewed. The predominant isolates from the jail had CA-MRSA PFGE pulsotypes (140). The early diagnosis of some lesions (9% in 2002 and 14% in 2003 were diagnosed within 5 days of booking) (136, 140) may have reflected a high incidence of MRSA colonization in the community or, alternatively, rapid transmission in the jail setting. Further supporting the former position, a mathematical model of MRSA in the LACJ demonstrated that although >8,000 CA-MRSA SSTIs were recognized in 2002 to 2005, the inflow of infected detainees from the community may have fueled the epidemic (454).

The importance of fomite contamination with MRSA in jails is not known, but in a Texas jail, investigators in 2005 found that 8/132 (6.1%) fomites had recoverable MRSA; 4/6 tested MRSA isolates were USA300 isolates by PFGE (282).

There have been few studies of nasal MRSA colonization in a prison or jail. In 2000, 4.9% (86/1757) of inmates at a Mississippi prison were colonized with MRSA. There was a disproportionately high colonization rate for females (5.9%) compared with males (2.5%). The major risk factor identified for MRSA nasal colonization was residence in the prison for ≥60 days. Longer-term detainees had a 5.4% MRSA colonization rate, versus 0.7% for those incarcerated for a shorter time. Of 41 isolates cultured from infected detainees, the vast majority were susceptible to non-β-lactam antibiotics, and PFGE demonstrated three predominant clonotypes, suggesting a local focus of dissemination of MRSA among the detainees (138). In a study of detainees admitted to a correctional ward of a hospital in Maryland in 2003 to 2004, 13% had either a clinical MRSA infection or colonization; female detainees were more likely to be colonized (relative risk [RR], 2.46). Detainees from the Baltimore City Jail were more likely to be MRSA carriers than were detainees from other correctional institutions, with a very high carriage prevalence of 17%. The USA300 genotype constituted 36% of the 56 MRSA isolates tested and was the most common genotype recovered (1010). At the Baltimore City Jail in 2006, 15.8% (95/602) of newly arriving detainees had MRSA nasal colonization; 80% of the recovered strains were USA300 or related types. Surprisingly, only 13.1% (3/23) of SSTIs identified in this population were caused by MRSA (277).

Outbreaks in prisons have been studied less often, but they have provided insight into possible risk factors and means of MRSA transmission among incarcerated populations. For example, a CDC-sponsored case-control study after an outbreak of 59 cases of MRSA SSTI in a Mississippi prison in 1999 to 2000 demonstrated that 78% of the patients were female, while only 40% of the prison detainees were female. Detainee patients with an SSTI caused by MRSA were more likely than controls to have helped an inmate or to have been helped by another inmate with dressing changes of wounds, to have lanced their own or other detainees' boils, or to have shared personal items with other detainees (138). Poor personal hygiene, measured by using a composite hygiene score, was blamed for an outbreak of MRSA SSTIs in 2002 to 2003 in a prison in Missouri (918).

In 2001 to 2003, the CDC investigated MRSA outbreaks in Georgia prisons. A case-control study was performed for a 200-bed short-stay detention center, where 11 cases of MRSA SSTIs occurred in 2001. Risk factors for infection included incarceration for more than 36 days and outdoor work duty. Despite improvements to hygiene, after a 5-month hiatus with no infections, 19 more MRSA cases were detected in 2002 to 2003 (136). A second Georgia prison housed 1,500 inmates and had 11 cases of MRSA infection in 2002. A case-control study revealed the following risk factors: previous antibiotic use, self-draining of boils, skin laceration, washing clothes by hand, and arrival to the prison after 2001. Further surveillance revealed 73 additional infections in April 2002 to February 2003. Despite the isolation of inmates with MRSA infections and the provision of a 5-day supply of chlorhexidine-based soap for all inmates, 29 additional cases occurred in March to May 2003 (136). These studies demonstrate that while some risk factors are understood, the control of MRSA in places of incarceration may be a difficult task.

In 2005 to 2006, information on *S. aureus* infections and colonization was collected from the New York State prison system. In two prisons, MRSA nasal colonization was found for 0.8% (2/251) of men and 4.7% (11/236) of women; all 13 MRSA isolates carried SCC*mec* type IV, and 6/13 (46%) isolates were USA300 strains. Among 60 *S. aureus* isolates from infections of detainees occurring in January to June 2006, 48.3% (29/60) were MRSA isolates; of the 29 MRSA infection isolates, 48.2% (14/29) were $PVL^+$, and 93.1% (27/29) carried SCC*mec* type IV, findings consistent with CA-MRSA strains. Associations between an increased length of stay and the likelihood of a PVL-positive MRSA infection were found for maximum-security prisoners. Among medium-security prisoners with *S. aureus* infections, both older age and longer length of stay were associated with a decreased likelihood of having an MRSA infection (560).

Most reports of incarceration-related MRSA disease have been from the United States. However, in Alberta, Canada, an outbreak of USA300 MRSA infections in 2004 demonstrated that a history of recent incarceration was a significant risk factor for infection (318). Two five-person outbreaks of MRSA SSTIs were recorded for a 500-person correctional facility in Hamilton, Ontario, in 2002 and 2004. All SSTIs were caused by USA300 strains that were $PVL^+$, and there was proven contact among only some of the detainees, at least two of whom had shared a cell with a detainee who lanced the boils of others and one of whom had AIDS (575). A large outbreak of skin infections caused by CA-MRSA strains was reported for a prison in Uruguay, which was associated with a scabies infestation (564).

Overall, poor hygiene is likely a major contributor to the problem of MRSA infections in places of incarceration, but there may be other risk factors for incarcerated populations that put them at a specific risk for exposure to MRSA outside jails and prisons. Furthermore, if detainees are likely to become asymptomatic carriers of MRSA while incarcerated, with jail and prisons serving as a reservoir, released detainees may also spread MRSA to their families and other contacts.

### Cystic Fibrosis

Cystic fibrosis (CF) is a chronic disease resulting from one of many mapped mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene, which usually leads to progressive dysfunction in many organ systems, particularly the lung and respiratory tract. Patients with CF suffer from recurrent infections, bronchiectasis, and frequent respiratory tract colonization with antimicrobial-resistant bacterial pathogens, particularly *Pseudomonas aeruginosa* and *S. aureus*. MRSA respiratory carriage and infection are becoming increasingly common among CF patients according to data from the Cystic Fibrosis Foundation. In 1995, only 0.1% of CF patients had MRSA recovered from their respiratory tract; the prevalence increased to 7.3% in 2001 and 17.2% in 2005 (200, 201, 202). Some researchers have suggested that MRSA colonization is a poor prognostic sign in CF. During 2001, in an epidemiological study of 1,834 children from North America with CF and *S. aureus* in their respiratory tract cultures, CF patients with MRSA had a lower mean forced expiratory volume in 1 s ($FEV_1$), were more likely to be treated with an antimicrobial drug, and were more likely to be hospitalized than those with MSSA infections. These children were likely colonized predominantly by HA-MRSA strains (755). A study from the Cystic Fibrosis Foundation registry from 1996 to 2005 including 17,357 CF patients aged 8 to 21 years, controlling for severity of disease at baseline, common coinfections, and common comorbidities, found that the $FEV_1$ decline was 43% more rapid among the 1,732 patients who developed new and persistent MRSA infection than among the noncolonized patients with CF (206). Other researchers, using data for 5,090 patients in 2001 to 2003 from the Epidemiologic Study of CF, suggested that this association is not significant if one accounts for $FEV_1$ prior to MRSA colonization (806). A prospective study is needed to definitively determine if there is a true association (805).

Several studies have examined the relative burden of CA- and HA-MRSA strain types among strains isolated from screening cultures and infections of CF patients to assess the impact of the CA-MRSA epidemic in this population. CF patients at Emory University in 2004 to 2005 were more likely to harbor an MRSA strain with inducible clindamycin resistance (68/143; 48%) than were non-CF patients (43/560; 8%) ($P < 0.01$) (627). At Washington University in St. Louis, 15% of children with CF newly colonized with MRSA in 2001 to 2004 had $PVL^+$ MRSA strains. These children were more

likely to have an active pulmonary infection than children colonized with PVL-negative strains (256). In Chapel Hill, NC, in 2005 to 2007, 19/707 (2.7%) CF patients were colonized by $PVL^+$ MRSA strains that carried SCC*mec* type IV, while overall, 140/707 (19.8%) patients had at least one respiratory culture that grew MRSA in this period (332).

A study from Dallas and Chicago compared MRSA isolates obtained from 34 children with CF and 331 children without CF in 2004 to 2005. Of the CF patient isolates, 64.7% belonged to MLST clonal cluster 5 (CC5) and carried SCC*mec* type II, both markers for HA-MRSA strains, and 26.5% belonged to CC8 and carried SCC*mec* type IV, both markers for CA-MRSA strains. In contrast, among MRSA isolates from non-CF patients, 88.8% belonged to CC8 and carried SCC*mec* type IV, and only 4% had HA-MRSA markers. Isolates from CF patients were more likely to be resistant to clindamycin and ciprofloxacin. Isolates from screening cultures compared with isolates from active infections did not differ in the likelihood of carriage of PVL genes, suggesting that $PVL^+$ isolates may not be more likely to cause disease in CF patients (324).

Although there are few data, MRSA colonization overall and $PVL^+$ MRSA colonization in particular may be less common among CF patients in Europe than among CF patients in the United States. In Italy, 181/2,362 (7.6%) CF patients at nine centers were colonized with MRSA in 2004 to 2006. Of the 181 MRSA-colonized patients, 36% had isolates carrying SCC*mec* type IV. MRSA strains of a single, unstated PFGE type colonized 31 patients; 24 of these carried SCC*mec* type IV, and none of the 24 isolates carried PVL (119; S. Campana, personal communication). At nine centers in Belgium in 2001, 5% of 627 CF patients carried MRSA strains, and 67% were genotypically related by PFGE to "epidemic clones that are disseminated in Belgian hospitals" (952). In Madrid, 93 MRSA isolates from 18 CF patients were obtained in 1994 to 2006; all the isolates were MDR and polyclonal, but 44 of them were ST228 isolates bearing SCC*mec* type I and lacked the PVL genes (617). All CF patients in Northern Ireland are tested every 3 months for MRSA colonization; 17/250 were found to carry MRSA at some time during 1999 to 2004. By using a three-step protocol requiring 1 or 2 courses of oral fusidic acid and rifampin followed, if necessary, by intravenous teicoplanin, investigators were able to decolonize 16 of the 17 CF patients; they all remained free of MRSA sputum colonization 1 year later (567).

In summary, it appears that CF patients may be colonized with MRSA strains and that the rate is increasing. Some are CA-MRSA strains, but the patients remain at as great a risk or are at a greater risk for colonization and infection by the HA-MRSA strains that predominate in their geographical region. The importance of asymptomatic CA-MRSA colonization as a predictor of disease in this population remains unclear.

### Military Populations

Healthy military populations and their families are another group who may be at risk for CA-MRSA infection and colonization (501). For example, among 812 new military recruits reporting for training in Texas in 2003, 24 (3%) carried MRSA in their nares; most had at least one risk factor for HA-MRSA. After 8 to 10 weeks of training, 9 of these 24 soldiers (35%) developed SSTIs, although 16 (66%) were no longer colonized with MRSA. Four recruits became newly colonized with MRSA while in training (259). This suggests that many recruits were transiently colonized and that colonization predisposes one to disease. In a follow-up study of 3,447 U.S. soldiers in Texas in 2005, 134 (3.9%) were colonized with MRSA (260). Of isolates from these soldiers, 53% were USA300 strains. Among the 3,066 soldiers who completed the study, 39 had an SSTI caused by MRSA, 97% of which were caused by USA300 strains (261). Among active military service members deployed to Iraq in March to July 2008, 66 were diagnosed with a carbuncle, furuncle, boil, or abscess, as determined by a retrospective review of administrative records. Of isolates from the 66 service members, 26 (39%) underwent culture; 22/26 (85%) grew *S. aureus*, and of these isolates, 15/22 (68%) grew MRSA (768).

Many other case series from various locations in the United States demonstrate how widespread CA-MRSA infections are among military populations. After a large outbreak of MRSA SSTIs in 2000 to 2002 among military recruits at a training facility in Virginia, of 874 healthy workers who had direct contact with the recruits, 2.7% (24/874) carried MRSA in their nares (1029). At a military facility in Washington State in 1994 to 1997, of 67 adult patients presenting with MRSA infections or carriage, 13% (9) were CA-MRSA infections (i.e., from patients presenting as outpatients or cultured $<72$ h after admission and with no hospitalization, surgery, or use of antibiotics in the previous 12 months and no cystic fibrosis, i.v. drug use, HIV infection, diabetes mellitus, cirrhosis, or hemodialysis) (49). Among patients hospitalized with MRSA infections on a military base in Honolulu, HI, in 1992 to 1996, 41% had a CA-MRSA infection (by the CDC case definition) (333). MRSA was the leading cause of cultured skin abscesses at EDs at two military hospitals in Texas in 2004 to 2005 (248).

The burden of CA-MRSA disease may be increasing among active-duty and retired military personnel and their dependents. At the Naval Medical Center in San Diego, in a retrospective analysis of MRSA disease isolates obtained in 1994 to 1997, the incidence of CA-MRSA (i.e., patients with no hospitalizations in the previous 6 months and if MRSA was cultured from an isolate from an outpatient or within 24 h of hospital admission) infections rose quickly, from 14% of all MRSA infections in 1994 to 1995 to 29% in 1996 to 1997 (456).

Military recruits, active-duty personnel, and their contacts may be exposed to a common reservoir of CA-MRSA (259). The risk factors for CA-MRSA colonization may be analogous to those in local jails, including crowded living conditions and suboptimal personal hygiene at times of intensive training.

In a review from a Veterans Affairs hospital in Houston in 2000 to 2001, investigators studied cultures from all SSTIs, which by patient self-report were related to "spider bites" and required surgical intervention. All 38 cultures meeting these two criteria grew *S. aureus*, and 87% (33/38) of the *S. aureus* isolates were MRSA isolates (273).

Outside the United States, few studies of MRSA colonization among military personnel have been published. Among 959 Greek Air Force employees in 2004 to 2005, 9 (0.94%) had nasal colonization with MRSA, and 2 of the 9 had no previous known exposure to the health care system (461).

### HIV Infection/AIDS

HIV infection has been determined to be an independent risk factor for CA-MRSA infection and colonization in some settings, particularly after 2001 (109, 589, 911). For example, 41/44 (93%) isolates from SSTIs cultured at an HIV clinic in Dallas County, TX, in 2003 to 2004 grew MRSA (842). In 2002 to 2004, at a clinic in Houston serving 3,500 HIV-infected patients, 74% of 93 consecutive cultures of isolates from SSTIs with a recoverable organism grew MRSA (489; G. W. Krucke, personal communication). Of 146 HIV patients at a clinic in Dallas in 2005, 15 (10.3%) had MRSA nasal colonization, 8 of whom carried USA300 or USA400 strains. Independent risk factors for MRSA carriage were prior infection with MSSA or MRSA (OR, 32.4 and 9.71, respectively), no current or recent antimicrobial drug therapy (OR, 0.026), and a low mean CD4 cell count (374 versus 252 cells/mm$^3$; OR, 0.996). Interestingly, none of the patients taking TMP-SMX prophylaxis for *Pneumocystis jirovecii* pneumonia were colonized with MRSA (128). In 2000 to 2003 at the Naval Medical Center in San Diego, 31/458 (6.8%) HIV-infected patients had an SSTI caused by CA-MRSA (by CDC criteria), and patients with a CA-MRSA SSTI did not differ significantly in age, gender, or race from the overall cohort of HIV-infected patients. CA-MRSA patients did not have advanced HIV disease. They had a mean CD4$^+$ cell count of 445 cells/mm$^3$, and the HIV viral load was <1,000 copies/ml in 48% of the patients; 71% of the patients were receiving antiretroviral therapy at the time of their infections (195). A study performed in 2000 to 2003 demonstrated a steady rise in the incidence of MRSA infections among patients at an adult HIV clinic in San Diego from 2 to 5 per 100 patients in a 6-month period (589). At a clinic in Maryland, the incidence of CA-MRSA infections among HIV patients was 40.3 cases per 1,000 person-years in 2005. MRSA infection was associated with a low CD4$^+$ count, a high HIV viral load, recent use of systemic antibiotics, and a history of syphilis. As in Texas, no CA-MRSA infections occurred among the patients taking TMP-SMX prophylaxis (194). HIV infection was a risk factor for MRSA colonization among *S. aureus*-colonized individuals admitted to a hospital in Atlanta, GA, in 2003 (385). In 2004 to 2006 at a clinic in Philadelphia, 43 CA-MRSA SSTIs (by the CDC definition except that a previous isolation of MRSA was not considered to be an HA-MRSA infection) were identified among HIV-infected patients, with the number increasing from 5 in 2004 to 22 in 2006; 58.5% had a CD4 cell count of >200 cells/mm$^3$, and 17% had an HIV viral load of >100,000 copies/ml (911). At the Cook County Hospital and its associated clinics in Chicago, CA-MRSA and CA-MSSA (criteria for community-associated infections were not provided) SSTIs were retrospectively reviewed for 2000 to 2007, and population-based incidence estimates were calculated. HIV-infected patients were more likely to have CA-MRSA SSTIs than were non-HIV-infected patients (incidence of 952 versus 156/100,000 population; RR, 6.1; $P < 0.001$) (733).

HIV-infected patients are at an increased risk not just for MRSA colonization but also for any *S. aureus* colonization; the reasons for this association are not known. Among 282 recreational drug users in New York City in 1999 to 2000, 46% of HIV-infected subjects and 29% of uninfected subjects were colonized with *S. aureus*. When isolates from subjects were cultured at 6-month intervals, the likelihood of new *S. aureus* nasal colonization was twice as great among HIV-infected subjects as that among non-HIV-infected subjects (hazard ratio, 2.2; 95% CI, 1.1 to 4.6). Furthermore, among the nine subjects with MRSA colonization in the first 18 months, seven were HIV infected (610).

Further research is needed to determine which HIV-infected patients are at the greatest risk for CA-MRSA colonization and infection. In New York City in 2005 to 2006, 107 HIV-infected patients and 52 matched non-HIV-infected patients (including close contacts of the HIV-infected subjects) with no hospitalization in the previous year were tested for nasal or axillary MRSA carriage during at least one of three monthly assessments and prospectively monitored. HIV-infected patients who had a mean CD4$^+$ cells count of 559 cells per mm$^3$ were more likely than controls to have MRSA carriage (16.8% versus 5.8%; $P = 0.04$) and were more likely to develop an MRSA infection (10 versus 0). HIV-infected patients were more likely than controls to have any *S. aureus* colonization (58.9% versus 34.6%; $P = 0.004$). MRSA infections were associated with previous antibiotic use ($P = 0.04$) (827).

The association of CA-MRSA and HIV may be greater in certain regions of the United States than in parts of the world where CA-MRSA colonization is less common. For example, among HIV patients in Rome, Italy, the risk for a severe MRSA infection was independently associated with exposure to the health care system; among 27 HIV-infected patients with a severe MRSA infection in 2002 to 2005, only 1 infection was caused by CA-MRSA (by the CDC definition) (244). In Omaha, NE, 2/100 tested HIV-infected patients at a single clinic had nasal or perigenital MRSA colonization; these cultures were processed without enrichment broth, and this may have decreased the sensitivity of the cultures (569). The finding of predominantly HA-MRSA infections among HIV-infected patients in Italy and in Nebraska contrasts with data from studies in many parts of the United States. This difference may indicate variable susceptibility to MRSA or, more likely, the geographic variation in CA-MRSA infections and colonization.

### Men Who Have Sex with Men

Some researchers have suggested that MSM in the United States and Canada face an increased risk of MRSA colonization and infections (361, 521, 825, 840, 875). For example, among the MRSA isolates obtained from patients with infections in San Francisco in 2004 to 2006, infection caused by a USA300 strain carrying resistance plasmid pUSA03 (see discussion above) was most common among patients residing in eight zip code regions with a high proportion of same-sex male couples. Among patients who had an MRSA infection, self-identification as a man who has sex with men was associated with an MDR USA300 infection. The authors of that study speculated that the MDR USA300 strain may be sexually transmitted (235). At a clinic in Boston where approximately 70% of patients were MSM by self-report, 3.8% (30/795) of patients in 2005 to 2007 had MRSA recovered from the nares, the perianal region, or a skin infection, and 73% (22/30) of the isolates were USA300 strains. Among enrollees, 3.7% (29/795)

had an SSTI at enrollment, and 9.2% (73/795) of patients had an SSTI during a 16-month period in 2005 to 2007. Any SSTI, whether caused by MRSA or not, was strongly associated with previous perianal carriage of MRSA (OR, 10.34; 95% CI, 2.84 to 37.60), prior skin infection (OR, 4.08; 95% CI, 2.31 to 7.22), and crystal methamphetamine use (OR, 4.98; 95% CI, 2.60 to 9.55). The authors of that study suggested that skin-to-skin contact and multiple sexual partners may predispose one to SSTIs caused by MRSA (877).

Outside the United States, studies have not shown an elevated rate of MRSA carriage in MSM. In Toronto, for example, only 1.6% (8/500) of MSM had asymptomatic carriage of MRSA in the nares or rectum in 2007 (23). No enrichment broth culture was utilized in the processing of culture swabs, which may have decreased their sensitivity compared with that of studies of many other populations. Furthermore, the MRSA epidemic may not have been as widespread in Canada in 2007. More research is needed to assess the reasons for the spread of CA-MRSA in the MSM population.

### Veterinarians, Livestock Handlers, and Pet Owners

Domestic pets, livestock, wild birds, and other animals have recently been identified as carriers of MRSA in several countries and settings (Tables 9 and 10). The role of animals as vectors for human MRSA infection and colonization has not yet been fully characterized. It has been suggested that MRSA in animals may be a "humanosis"; this implies that MRSA generally originates from people and puts animals at risk for carriage and infection. Further research is necessary to assess this hypothesis. MRSA isolates obtained from domestic animals often belong to common human MRSA clonotypes (759); in contrast, MRSA isolates obtained from livestock are often genetically distinct.

**Livestock as a reservoir for human MRSA colonization and infection and the ST398 sequence type.** Mounting evidence suggests that livestock, particularly pigs, may represent an important reservoir for CA-MRSA strains that can colonize and infect humans in close contact with them (222, 528, 625, 968, 1013) (Table 9). ST398 is the most commonly reported MRSA sequence type among large livestock in Europe. ST398 MRSA strains often carry genes coding for non-β-lactam antimicrobial resistance, including a plasmid-borne trimethoprim resistance gene, *dfrK*, identified in an isolate from a pig in Germany (452). These ST398 isolates are often referred to as nontypeable by PFGE because their genome is resistant to SmaI digestion (59). The isolates carry SCC*mec* type IV or V and typically lack PVL genes; several common *spa* types have been associated with these isolates.

Studies of asymptomatic MRSA colonization of a variety of farm animals have suggested that carriage rates vary widely. Among 300 healthy horses in Slovenia in 2005, no MRSA carriage was identified (951); a similar finding was obtained for 497 horses on 50 farms in 2006 in the maritime provinces of Canada (112) and for 87 military horses in Austria (year of collection not indicated) (853). In contrast, among 110 horses attending a clinic in Belgium in 2007, 10.9% (12 horses) had nasal colonization with MRSA ST398 strains of two *spa* types (932). ST398 was also isolated from poultry in Belgium in 2006 (663). In the Netherlands in 2006, MRSA colonization of pigs was identified in 7/31 (23%) tested farms. The ST398 MRSA strains from this study also had a variety of *spa* types (940).

Several studies have suggested high rates of asymptomatic colonization by ST398 MRSA backgrounds among swine and their handlers, suggesting that frequent transmission occurs, although secondary human-to-human spread to close contacts appears to be rare (199). Moreover, clinical infections among exposed swine farm workers have been reported infrequently. In Iowa, 49% (147/299) of swine and 45% (9/20) of farm workers in 2007 to 2008 carried ST398 MRSA in the nares; no other MRSA genetic backgrounds were identified. Younger swine were more likely to be carriers (846; T. Smith, personal communication). In Austria in March 2008, 13/162 (8%) pig farmers who attended a conference had MRSA nasal carriage, and all eight isolates examined had *spa* type t034, a type associated with ST398 strains (853). Among 127 farm workers and their contacts on 50 pig farms in Belgium in 2007, 37.8% (48/127) had nasal or skin lesion colonization with MRSA. MRSA carriage was associated with close contact with pigs, dogs, and horses and, paradoxically, with the use of protective clothing. The 48 MRSA isolates belonged to three *spa* types (t011, t034, and t567), but 94% ($n = 45$) were t011 isolates. Representative isolates of each *spa* type were found to share the ST398 genotype (228). In the Netherlands in 2004, >20% of pig farmers were colonized with ST398 MRSA, as were 39% of pigs destined for slaughterhouses; seven *spa* types were represented, and four predominated (226, 1013). In Austria, 21 of the 1,098 MRSA isolates from humans submitted to a reference laboratory in January 2006 to May 2008 were ST398 isolates. Among these isolates, 5 were obtained from clinical infections, 15 were obtained from cultures to assess colonization status, and the source of 1 was unknown. Of the 19 isolates from patients with information regarding animal exposure, 10 were from pig farmers or their relatives, 6 were from farmers with other animal exposures, and 3 were from people who had no known animal contact. The percentage of ST398 isolates increased in each year of the study and peaked at 2.5% of submitted isolates in January to May 2008 (491).

Invasive infection caused by ST398 occurs but rarely. In Italy, a pig farm worker developed pyomyositis caused by an MRSA ST398 strain. A subsequent investigation of the farm employing the patient revealed colonization by ST398 strains among 1 of 11 other swine workers and family members; ST398 strains were isolated from seven dust samples from farrowing areas on the farm, suggesting a porcine origin of the strains (701).

Although PVL genes have been generally absent from ST398 strains, one report from Sweden described them for isolates from two SSTIs occurring in previously healthy patients in 2006 and 2007. The strains had the t034 *spa* type, which has been widely reported among PVL-negative ST398 strains (992). Another $PVL^+$ ST398 MRSA isolate (*spa* type t034 and SCC*mec* type V) was submitted to the national reference collection of the Netherlands in 2007 (420).

ST398 MSSA strains were also identified by colonization studies of pigs and pig farmers in France but not in a sample of non-pig farmers (27), suggesting that MSSA ST398 strains, like MRSA ST398 strains, are also most closely associated with pigs and pig farm workers. Similarly, MSSA ST398 isolates colo-

TABLE 9. Studies of MRSA carriage and infection in livestock animals and human contacts, 1993 to 2008

| Animals | Yr of study | Location(s) | Major finding(s) | Genotype(s) identified[a] | Reference(s) |
|---|---|---|---|---|---|
| Chickens | 2006 | Belgium | Chickens on farms with cloacal or nasal MRSA colonization | ST398-IVa or -V or nontypeable SCC*mec*/t011, ST398-III/t567 | 663 |
| | 2007 | Belgium | MRSA isolated from cloaca or nasal cavity of broiler chicken | *spa* type t1456, ST398 | 722 |
| Cows | 2002–2004 | Hungary | Milk samples from cows with subclinical mastitis and tonsillar swab culture of milk industry worker grew MRSA identical by PFGE | ST1-IVa/t127, PVL negative | 451 |
| Horses | 1993–1994 | Michigan | Horses with MRSA wound infections after procedures; 3 health care workers had nasal colonization with MRSA strains related by PFGE | Not stated | 817 |
| | 2000–2002 | Ontario, Canada | At a veterinary college and on 10 horse farms, MRSA isolates were obtained from screening cultures of the nares of horses and personnel as well as from sites of clinical infection; this yielded MRSA isolates from 79 horses and 27 personnel; a horse farm worker had the sole human infection; he had an MRSA SSTI complicating a tattoo wound; CMRSA-5 was isolated from him, and MRSA isolates identical by PFGE were recovered from 2 horses under his care | CMRSA-5 by PFGE (related to USA500, carrying SCC*mec* type IV, *spa* type t007, PVL negative) accounted for 26/27 (93%) isolates from people and 76/79 (96%) of isolates from horses | 991 |
| | 2004 | Ontario, Canada | A foal with MRSA arthritis and omphalophlebitis and its dam with MRSA nasal colonization were admitted to a veterinary hospital; health care workers who cared for the foal developed MRSA SSTIs, and 10/103 (9.7%) personnel had either nasal or groin colonization with MRSA | PVL negative and identical by PFGE, CMRSA-5 (related to USA500) | 988 |
| | 2004 | Liverpool, United Kingdom | 11/67 (16%) horses at a hospital had MRSA nasal or skin carriage; 3 others had clinical MRSA infections | 12 isolates from 7 horses had 5 PFGE types, all were PVL negative | 41 |
| | 2008 | Hertfordshire, United Kingdom | 2 MRSA infections in horses at a veterinary college hospital | ST398-IVa/t011, PVL negative | 552; A. Loeffler, personal communication |
| | 2003–2004 | Ireland | Horses at 7 veterinary clinics and a hospital with MRSA wound infections or "abdominal granuloma"; horse strains related to those recovered from the nares of attendant veterinary personnel | Unrelated to known clinical isolates held by a large Irish reference laboratory, all with identical or closely related PFGE types | 689 |
| | 2002–2003 | Ontario, Canada, and New York | Farm in Ontario with MRSA colonization in 9/53 (17%) horses and 1/10 (10%) personnel; farm in New York with MRSA colonization of 29/67 (43%) horses and 3/18 (17%) personnel | No information | 986 |
| | Not stated | Vienna, Austria | 2 horses with MRSA wound infections | ST398-IVa/t011 | 1006 |
| | Not stated | Lower Saxony, Germany | Foal with MRSA sinusitis | ST398-V/t1197 | 1006 |
| | 2002–2005 | Ontario, Canada | 69/3,372 (2.0%) horses upon admission to a teaching hospital had nasal MRSA colonization | No information | 987 |
| | 2007 | Belgium | 12/110 (10.9%) horses from Belgium, the Netherlands, France, and Luxemburg seen at a clinic had MRSA nasal colonization | ST398-IVa/t011 ($n = 10$), ST398-V/t011 ($n = 2$), and ST398-IVa/t1451 ($n = 1$) | 932 |

| | | | | | |
|---|---|---|---|---|---|
| | 2006–2007 | Vienna, Austria | MRSA infections among 25 horses at a university veterinary hospital; 18/131 (13.7%) personnel had MRSA colonization | Horse strains were ST1-IVa/t127 ($n$ = 3), ST254-IVd/t036 ($n$ = 15), and ST398-IVa/t011 ($n$ = 7), and all were PVL negative; personnel strains were ST1-IVa/t127 ($n$ = 2), ST254-IVd/t036 ($n$ = 13), ST398-IVa/t011 ($n$ = 2), and ST8-IVh/t008, and all were PVL negative | 198 |
| | 2003–2004 | United Kingdom | 9 MRSA isolates from clinical infections of horses | *spa*-CC8 ($n$ = 8) or related to EMRSA-15 ($n$ = 1); *spa* types included t020, t036, t064, and t451 | 625 |
| Pigs | Not stated | France | 5/112 (4.5%) pig farmers carried MRSA in the nasopharynx; none of 27 nonfarmer controls matched by age, sex, and county of residence carried MRSA | ST8 ($n$ = 2), ST5 ($n$ = 1), ST438 ($n$ = 1), and ST398 ($n$ = 1) | 27, 31 |
| | 2008 | China | MRSA isolated from dust samples on 5/9 (56%) pig farms in Sichuan Province | ST9/t899 or ST1376/t899, all PVL negative | 965 |
| | 2008 | China | MRSA isolated from nares of 58/509 (11.4%) pigs and 2/13 (15%) pig farm workers in 4 Chinese provinces; none of 276 cattle, 47 cattle workers, or 107 slaughterhouse workers had nasal MRSA carriage | ST9/t899 ($n$ = 46), ST912/t899 ($n$ = 13), and ST1297/t899 ($n$ = 1), all PVL negative | 197 |
| | 2004–2005 | Netherlands | 3 family members on a pig farm (farm A) colonized with identical MRSA strains; at a university medical center, another farmer, a veterinarian, his son, and his son's nurse carried the same strain as above-described family; 1/30 (3.3%) pigs on farm A had perineal carriage of the same MRSA strain; at a meeting of regional pig farmers, 6/26 (23%) were colonized with MRSA in the throat and/or nose | None typeable by PFGE; *spa* type t108, t567, or t943 | 961 |
| | 2005 | Netherlands | A woman with MRSA mastitis and her daughter had MRSA nasal colonization; 3 family members and 3 coworkers on her pig farm had MRSA throat or nasal colonization, and 8/10 (80%) pigs on the farm had throat, nasal, or perineal colonization | All isolates were ST398-V/*spa* t108, *agr* type 1, and PVL and TSST negative | 417 |
| | Not stated | Lower Saxony, Germany | MRSA colonization in 1 pig from a veterinary medical school | ST398-V/t034 | 1006 |
| | 2005–2006 | Netherlands | 209/540 (39%) pigs in 9 slaughterhouses had MRSA nasal colonization; transmission of MRSA both prior to arrival and at slaughterhouses was likely | ST398 with SCC*mec* type III ($n$ = 4), IVa ($n$ = 41), or V ($n$ = 59); *spa* types included t011, t108, t1254, t1255, t567, t034, and t943 | 226 |
| | 2005 | Singapore | 1/64 (1.5%) pigs used in exptl research, 1/50 (2%) pigs in a slaughterhouse, and 1/32 (3%) staff workers at an academic hospital's research facilities had MRSA nasal colonization | 2 isolates from pigs were ST398-V; 1 from a pig and 1 from a scientist were ST22-IV | 819 |
| | 2006 | Netherlands | 35/310 (11%) pigs on 7/31 (23%) farms had MRSA nasal colonization; 11 MRSA-colonized personnel had strains with the same genotype as those of pigs on their respective farms | ST398-IV or -V/t011, t108, t567, t899, and t1939, all PVL negative | 940 |
| | 2005 | Denmark | *S. aureus* nasal carriage in 10/100 (10%) pigs; 1/10 (10%) were MRSA, and 9/10 (90%) were MSSA | All nontypeable by PFGE; *spa* type t034 ($n$ = 9) or related t1793 ($n$ = 1) | 35, 351 |
| | 2004–2007 | Denmark | Pigs tested after a person working or living on the farm presented with CC398 MRSA (i.e., *spa* type t034, t108, or t1793) infection or carriage; 23/50 (46%) pigs had nasal carriage of CC398 MRSA | Pigs carried CC398, *spa* type t034 | 532 |

*Continued on following page*

TABLE 9—*Continued*

| Animals | Yr of study | Location(s) | Major finding(s) | Genotype(s) identified[a] | Reference(s) |
|---|---|---|---|---|---|
| | 2007 | Netherlands | On 50 farms, 33/232 (14%) pig farmers and their families had nasal colonization with MRSA, and either pigs had nasal carriage or fomites near pigs were contaminated with MRSA on 28/50 (56%) farms; on 15 farms with nasal colonization in people, animals and people had the same *spa* type | No information | 931 |
| | 2007–2008 | Iowa and Illinois | In 2 farm systems, 49% (147/299) of swine and 45% (9/20) of farm workers had MRSA nasal carriage | 15 MRSA isolates from animals and workers were all ST398-V, PVL negative | 846; T. Smith, personal communication |
| | Not stated | Ontario, Canada | 71/285 (24.9%) pigs on 20 farms had MRSA nasal or rectal colonization; 5/25 (20%) pig farmers had MRSA nasal carriage; on 5 farms with human colonization, concordant strain types were found in farmers and pigs | 59.2% of pig and human isolates had *spa* type t034 and could not be typed by PFGE; 10% of pig and 20% of human isolates were USA100 | 471 |
| | 2006 | Netherlands | MRSA SSTIs in 4 piglets on a breeding farm and 20 pigs on a supplier farm; MRSA nasal colonization in 2 farm workers | ST398-IV/t011 | 937 |
| | 2008 | Portugal | 4 pigs and 1 veterinarian from a pig farm had MRSA nasal carriage, and at a second farm, 3 pigs had MRSA nasal carriage | First farm had ST398-V/t011, PVL negative; second farm had ST30-V/t021, PVL negative | 730 |
| Rabbits | 2002–2003 | Pennsylvania | 1 rabbit with an ear infection | $PVL^+$ | 747 |
| | 2003 | Ireland | At a clinic, MRSA wound culture from rabbit and MRSA nasal carriage in veterinary worker | Both isolates had the same PFGE type | 689 |
| | 2003–2004 | Berlin, Germany | Wound infection in a rabbit at a hospital | ST22-IV, PVL negative | 969 |
| Rats | 2008 | Belgium and Netherlands | 5/40 (12.5%) black rats (*Rattus rattus*) trapped at pig farms had MRSA throat colonization | ST398/t011 ($n = 4$) and ST97/t1236 ($n = 1$), all PVL negative | 930 |

[a] MRSA composite strain genotypes are presented in the following format: MLST type-SCC*mec* type/*spa* type. For example, ST398-IVa/t011 indicates a MRSA strain that was ST398 by MLST, carried the SCC*mec* type IVa element, and was type t011 by *spa* typing.

TABLE 10. Studies of MRSA carriage and infection in domesticated and wild animals and human contacts, 1993 to 2008[a]

| Animals | Yr of study | Location(s) | Major finding(s) | Isolate characteristic(s)[b] | Reference(s) |
|---|---|---|---|---|---|
| Birds | 2002–2003 | Pennsylvania | Parrot with chronic MRSA sinusitis | $PVL^+$ | 747 |
| | 2003–2004 | Berlin, Germany | Parrot with MRSA osteomyelitis | ST22-IV, PVL negative | 969 |
| Cats | 2003 | Ireland | Cat with MRSA UTI | No information | 689 |
| | 2003–2004 | Germany | At a school of veterinary medicine, 2 cats with UTIs and 1 cat with an ear swab that grew MRSA | ST22-IV/t032, PVL negative | 869 |
| | 2002–2003 | Pennsylvania | Cat with an MRSA tooth abscess | $PVL^+$ isolate | 747 |
| | 2000–2004 | Washington State and Quebec, Canada | 2 kittens at a rescue center with rhinitis and an employee there had MRSA nasal colonization; a cat had MRSA UTI, and the genotypically same strain colonized the owner's nose | CMRSA-2 by PFGE, SCC*mec* type II, PVL negative | 989 |
| | 2003–2004 | Berlin, Germany | 4 cats at a hospital, 1 with MRSA otitis and 3 with MRSA wound infections | ST22-IV, PVL negative ($n = 3$); Barnim strain by PFGE, SCC*mec* type IV, PVL negative ($n = 1$) | 969 |
| | 2002–2005 | Pennsylvania | Clinical syndromes did not differ when 33 MSSA and 13 MRSA isolates from cats (among 11,149 cats treated) at a veterinary medical center were compared | 15 tested isolates had related PFGE types; all carried SCC*mec* type II | 633 |
| | Not stated | Germany | Pet cat with pharyngeal MRSA colonization; genotypically identical strain caused recurrent SSTIs in its owner | ST80-IV/*spa* t131 | 839 |
| | 2003–2004 | Ireland and United Kingdom | 6 cats with MRSA infections | EMRSA-15 strain by PFGE; *spa* types included t022, t032, t379, and t628 | 625 |
| Dogs | Not stated | United Kingdom, various locations | 210 dogs and cats with MRSA isolated from them | 29/31 isolates tested were EMRSA-15 ($n = 25$) or EMRSA-16 ($n = 4$), common pulsotypes in human infections | 759 |
| | 1998 | South Korea | MRSA isolates obtained from 12 dogs at a veterinary hospital, with 3 from catheters, 6 from nares, 1 from conjunctiva, 1 from recurrent pyoderma, and 1 from a surgical wound infection | All isolates were MDR; none were susceptible to quinolones, gentamicin, or tobramycin | 698 |
| | 2003–2004 | Pennsylvania | Among 20,366 dogs and 8,026 cats admitted to a university veterinary hospital, 137 animals had *S. aureus* isolated from them; 39/137 were MRSA isolates obtained from 28 dogs, 8 cats, and 3 unknown animals; isolates were from the skin ($n = 11$), ear canal ($n = 2$), genitourinary tract ($n = 5$), respiratory tract ($n = 4$), or another site ($n = 17$) | Minority of isolates susceptible to clindamycin (28%), erythromycin (15%), or fluoroquinolones (10%) | 634 |
| | 2004 | Liverpool, United Kingdom | 3 dogs with MRSA infections, including joint infection, wound infection, and pleuropneumonia; 1 of the 3 had MRSA nasal and fecal carriage; a veterinary student who cared for 1 dog also carried MRSA | All isolates were EMRSA-15 by PFGE and PVL negative | 41 |
| | 2003–2004 | Ireland | 14 dogs at 25 veterinary clinics or a hospital with MRSA isolation, wound ($n = 13$) and nares ($n = 1$); veterinary personnel were also tested for nasal colonization | PFGE types of isolates from animals and personnel were common in an Irish reference collection of isolates from human infections | 689 |
| | 2004 | London, United Kingdom | 4/45 (9%) dogs at a veterinary hospital had nostril ($n = 2$) or buccal mucosa ($n = 3$) MRSA colonization; 13/78 personnel had MRSA colonization when tested at the same anatomical sites | 4 animal isolates and 7/18 human isolates were EMRSA-15 by PFGE | 551; A. Loeffler, personal communication |
| | 2003–2004 | Germany | 13 dogs with MRSA isolated from them at a school of veterinary medicine; sources were fistula ($n = 1$), urine ($n = 2$), implant ($n = 1$), wound swab ($n = 5$), joint puncture ($n = 2$), and skin swab ($n = 2$) | All isolates were ST22-IV/t032, PVL negative | 869 |
| | 2001 | Missouri | A pet dog carried a strain identical by PFGE to that found in recurrent surgical wound infections of a man and cellulitis in a woman, his owners; the dog was likely a reservoir after colonization from his owners | No further information | 577 |
| | 2003 | Netherlands | A dog and its owner, a health care worker, carried MRSA with a PFGE type identical to that of isolates from a nursing home MRSA outbreak and identified in a dog | No further information | 939 |
| | 1993–2002 | Utrecht, Netherlands | 2 dogs with MRSA infections, wound infection ($n = 1$) and flank fistula ($n = 1$) | 2 PFGE pulsotypes | 936 |

*Continued on following page*

TABLE 10—*Continued*

| Animals | Yr of study | Location(s) | Major finding(s) | Isolate characteristic(s)[b] | Reference(s) |
|---|---|---|---|---|---|
| | 2002–2003 | Pennsylvania | 8 dogs with MRSA infections | 5 different PFGE types, all PVL$^+$ | 869 |
| | Not stated | United Kingdom | Pet therapy dog with MRSA colonization in pooled culture of nose, scalp, and interdigital folds of paws; likely acquired colonization during visit to human health care facility; 2 other therapy dogs were not colonized | Related to EMRSA-15, a common PFGE type among hospitalized patients in the United Kingdom | 265 |
| | 2000–2004 | Pennsylvania, New York State, and Ontario, Canada | Reports of a dog with a postoperative MRSA SSTI, and 4/37 (11%) personnel were colonized with the same strain; a dog had an MRSA surgical wound infection, another dog was colonized in the same facility, and 2/22 (9%) clinic personnel carried the same strain; a dog had MRSA infection after ocular surgery and was colonized with the same strain as his owner; and a dog with an MRSA UTI had an owner who was colonized with same strain | All isolates were CMRSA-2, SCC*mec* type II, and PVL negative | 989 |
| | Not stated | Geesthacht, Germany | A dog with an MRSA SSTI | ST398-V/*spa* t034 | 1006 |
| | Not stated | Hong Kong, China | 0.72% (6/815) of dogs tested had MRSA nasal colonization | SCC*mec* type IV ($n = 1$), type IV new variant ($n = 2$), and type IIIB ($n = 3$), all PVL negative | 81, 82 |
| | 2003–2004 | Berlin, Germany | 18 dogs at a hospital with MRSA isolated from them; anatomical sites were wounds ($n = 15$), dermatitis ($n = 1$), otitis ($n = 1$), and cystitis ($n = 1$) | ST22-IV ($n = 15$), ST239 ($n = 2$) with "untypeable" SCC*mec* and "related to the Barnim clone" with SCC*mec* type IV ($n = 1$); all 18 isolates were PVL negative | 969 |
| | 2003–2004 | Adelaide, South Australia | MRSA was obtained from cultures of 2/141 skin lesions in dogs at a 2 veterinary clinics; 0/51 healthy dogs had skin colonization with MRSA | No information | 576; M. Barton, personal communication |
| | 2003–2004 | Ireland and United Kingdom | 27 MRSA isolates from clinical cultures taken from dogs | 96% identical or closely related to EMRSA-15 by PFGE; *spa* types included t020, t022, t025, t032, t749, t883, t1021, t1041, and t1042 (the t1042 isolates were ST72 by MLST) | 625, 689 |
| Other | 2003 | Ireland | A seal with an MRSA culture from a lymph node | No information | 689 |
| | 2008 | United States | A premature elephant calf with MRSA SSTI; 20/55 previously healthy caretakers in contact with the calf had probable or confirmed MRSA SSTIs | Isolates from the calf ($n = 3$) and from caretakers ($n = 5$) were USA300 | 137 |
| | 2003–2004 | Berlin, Germany | A turtle and a guinea pig with MRSA dermatitis at a hospital | Both isolates were ST22-IV, PVL negative | 969 |

[a] UTI, urinary tract infection.
[b] MRSA composite strain genotypes are presented in the following format: MLST type-SCC*mec* type/*spa* type. For example, ST398-IVa/t011 indicates a MRSA strain that was ST398 by MLST, carried the SCC*mec* type IVa element, and was type t011 by *spa* typing.

nized two pig farmers in Holland and were also isolated from the blood of three elderly hospitalized patients, suggesting again that it may be a virulent clone in humans (928), at least occasionally.

MRSA genetic backgrounds other than ST398 have likely also been transmitted between farm animal handlers and livestock (Table 9). For example, at meat markets and livestock farms in Taiwan in 2004 to 2005, 3 MRSA isolates were isolated from fomites and 27 were isolated from the nares of workers; the most common strain types were ST59, ST338, and a single-locus variant of ST338 (404).

Transmission among swine and swine farm workers of ST398 MRSA strains and the isolation of ST398 strains among MRSA disease isolates from other patients have been studied most carefully in the Netherlands. At a hospital in a region of the country with 7,000 pig farms, screening of health care workers and high-risk individuals who were hospitalized was routinely performed in 2002 to 2006. Seventy-three colonized individuals were identified, 31.5% of whom (23 individuals) carried "nontypeable" MRSA presumed to be ST398 (226, 1013); all of the nontypeable strains were identified in 2004 to 2006. In July to December 2006, a period when a history of direct exposure to pigs or veal calves triggered a screening nasal culture, 19 patients with PFGE-nontypeable MRSA carriage were identified, 87% of whom had previous exposure to pigs or calves. Among MRSA carriers with PFGE-nontypeable strains, clinical infection was less common (13%) than among carriers of PFGE-typeable strains (42%), again suggesting that ST398 may not be as virulent as other genetic backgrounds (945). Among 1,721 health care workers in the Netherlands, MRSA colonization was 10-fold higher (1.7%) among those reporting contact with pigs and veal calves than among those without such contact (0.15%), although this difference was not significant (the time when the study was performed was not stated) (1015). At a Dutch hospital in 2000 to 2006, 26% of 95 patients and health care workers from whom MRSA was isolated likely acquired their isolate from animals. Individuals

with animal contact were responsible for the >3-fold annual increase in the rate of MRSA isolation during this period (946). In the 6 months after the introduction of more intensive surveillance programs in July 2006, >21% of all MRSA strains obtained by the national reference center for MRSA in the Netherlands were nontypeable and presumably ST398 strains (943). In 2007, the percentage of MRSA strains that were nontypeable increased to 30.3% (793/2619), with 80% of these isolates having *spa* type t011 or t108 (420).

In addition to the risk posed to farmers and others working with animals, the general population may be at risk for exposure to MRSA carried by livestock from poor hygienic practices at petting zoos (990). This suggestion requires further investigation.

**Veterinary practice as a risk factor for the transmission of MRSA between animals and humans.** Reported rates of asymptomatic MRSA colonization have varied among animals tested at veterinary facilities (Tables 9 and 10). Among 3,372 horses admitted to a veterinary teaching hospital in Ontario, Canada, in 2002 to 2005, 69 (2%) were colonized with MRSA; risk factors for colonization included antimicrobial use in the previous 30 days, previous MRSA colonization or infection, known MRSA colonization or infection in the past on the farm of origin, admission to the hospital's surgery service, or being in a neonatal intensive care unit (987). Among dogs admitted to a Canadian veterinary teaching hospital in 2004, 1/193 (0.5%) carried MRSA recovered from the nares, axilla, and rectum (365).

Several studies suggested that MRSA strains may be transmitted between humans and animals in the veterinary setting (27, 817, 969, 988) (Table 9). The human and animal strains share common genetic backgrounds and were closely related; few differences were identified when comparing the DNA sequences of selected genes of MRSA isolates sharing genetic backgrounds from humans and horses (970). More data are needed to determine if there are genetic differences in MRSA isolates that may be responsible for specific adaptation for the colonization of animals or humans.

Veterinarians, particularly those caring for large animals, have been identified as a high-risk group for asymptomatic MRSA carriage, likely because of their close animal contact. Among 152 Dutch veterinary doctors and students with a history of contact with livestock, a high prevalence (4.6%) of MRSA colonization was documented (the time when the study was performed was not stated) (1014). At a veterinary conference in 2005 in Baltimore, MD, 6.5% (27/417) of tested attendees carried MRSA in the nares, including 15.6% (15/96) of personnel caring for large animals (364). At an international equine veterinary conference in 2006 in San Antonio, TX, 10.1% (26/257) of attendees tested carried one of three pulsotypes of MRSA (USA300, USA100, or USA500). Risk factors for MRSA carriage included a history of caring for a horse with an MRSA infection in the previous year, the attendee having had an MRSA infection in the past year, and self-reported failure to wash hands between farms or between handling of infected animals (20). At an international conference of veterinarians in Denmark in 2006, 12.5% (34/272) carried MRSA in the nares or the throat; 31 of the 34 recovered MRSA isolates were likely ST398 isolates. MRSA carriers came from nine countries (1016; M. Wulf, personal communication). This trend was not observed for the Czech Republic, where, at a veterinary conference in 2008, only 0.7% (2/280) of screened attendees carried MRSA (1024). Similarly, at a university small-animal veterinary clinic in Scotland, 2/64 (3.1%) personnel had nasal carriage of MRSA; both isolates were EMRSA-15 by PFGE analysis, a common strain among human nosocomial infections (382).

**MRSA and meat or milk sold for human consumption.** In studies from three continents, MRSA has been isolated from retail meat products (676), from milk and meat samples (478, 497, 519, 538), and from meat industry workers. In the Netherlands, MRSA was isolated from 2 of 79 raw beef and pork samples from retail meat stores in 2006. One isolate was a USA300 strain, and the other was nontypeable by PFGE using SmaI digestion. This isolate may have been an ST398 strain, although sequence typing was not performed (942). In 2007 to 2008, 264/2,217 (11.9%) raw retail meat samples in the Netherlands had recoverable MRSA. Analysis of *spa* types suggested that 85% of the recovered isolates were ST398 isolates (221). In Austria, 1/82 raw meat products tested carried MRSA with *spa* type t011 (likely ST398) (the time when the study was performed was not stated) (853). The testing of 120 retail meat samples from grocery stores in Baton Rouge, LA, in 2008 revealed *S. aureus* on 45.6% of pork and 20% of beef samples. MRSA was isolated from 5% (6/120) of the meat samples. The MRSA strains belonged to the USA300 or USA100 pulsotype (738). There is no current indication that consumers face a risk of MRSA colonization or infection from this source, although studies have not been undertaken to assess this specifically. Further research is warranted to determine if contamination arises from the colonization of animals or of meat handlers.

**Household pets.** Although some researchers have suggested that household pets may be an important reservoir for MRSA in the community, there have been few explicit data (Table 10). The transmission of HA-MRSA strains among pets and owners did occur in the pre-CA-MRSA era (126), and after 2000, CA-MRSA strain transmission (790, 938), including USA300 (957) and ST398 (667) strains, has been reported. Among 70 *S. aureus* isolates from 46 cats treated at a clinic in Philadelphia in 2002 to 2005, all 15 MRSA strains tested carried SCC*mec* type II, a molecular characteristic of HA-MRSA strains from people (633). This finding suggests that cats may serve as a reservoir of MRSA in humans. In Hong Kong, only 17 of 736 tested dog owners both were colonized with *S. aureus* and owned a colonized dog. MRSA strains were isolated from 8.2% of the dogs and from 2.3% of the dog owners, but only one dog-owner pair was concordant in MRSA colonization status. Furthermore, only 6/17 of the dog-owner *S. aureus* isolate pairs shared PFGE types (81), implying that the transmission of *S. aureus* between dogs and their owners was relatively infrequent despite the high MRSA carriage rate. Some studies have not found any colonization among surveyed pets, for example, among 200 healthy dogs in Europe (951).

Despite this, pets have been anecdotally implicated as a source of human infection caused by MRSA. One outbreak of MRSA in a family was linked to a pet cat. The clearance of ST80 MRSA colonization in a family member with furunculo-

sis did not occur until systemic antimicrobial drug therapy was administered to the cat, which was colonized with the same strain (839).

More research is needed to assess the importance of pets as a reservoir of MRSA in the home and to what degree *S. aureus* is a zoonosis (853). Few data on the use of antimicrobial drugs among pets in the United States have been collected (544); the overuse of these drugs may increase the risk of MRSA carriage in pets.

## CLINICAL MANIFESTATIONS OF CA-MRSA

### Patients with SSTIs

Purulent SSTIs caused by CA-MRSA strains are the most common clinical manifestations of CA-MRSA (104, 216, 654). An uncomplicated CA-MRSA SSTI typically presents as an abscess that may resemble a spider bite filled with purulent material (241). Among adults with an abscess and surrounding erythema, the presence of a central black eschar had a positive predictive value of 94% and a negative predictive value of 45% for an MRSA isolate (113). CA-MRSA abscesses can be found in diverse anatomical locations, including the breast (615, 855, 1003), vulva (898), hand after clenched-fist injury (63), and neck (353, 426). However, SSTIs can vary in appearance and can also present as folliculitis, paronychia, furuncle, felon, cellulitis with drainage (628), or lymphadenitis (353). Except for the distinctive appearance noted above, MRSA SSTIs cannot be distinguished from SSTIs caused by other agents, including MSSA (215, 608), on clinical grounds.

Small studies have suggested that the recurrence of CA-MRSA SSTIs is common after treatment. In Dallas, a recurrent CA-MRSA SSTI was documented at a distinct anatomical site within 2 years of the index CA-MRSA infection in 11/41 (27%) HIV-infected patients (842). A recurrence of 1 to 3 CA-MRSA (i.e., onset outside the health care setting) SSTIs at a distinct anatomical site occurred among 5 of 11 adult HIV-infected patients in Chicago in 2003 to 2004; the intervals between index lesions and recurrences were not stated (19). Among 87 MSM in New York City who presented with a CA-MRSA (i.e., onset in the community) SSTI, 31% had a recurrence within 6 months after the resolution of the initial infection. Recurrence rates among those receiving MRSA-appropriate and MRSA-inappropriate initial antibiotic therapy (21/63 versus 6/20) were similar (825, 840). Among 61 patients with a CA-MRSA SSTI presenting to a New York City clinic in 2004 to 2006, 41% had one recurrence and 18% had more than one recurrence within 25 months; the median time to recurrence was 1 month. The likelihood of recurrence was not significantly different among HIV-infected patients, recipients of TMP-SMX prophylaxis, individuals with MRSA nasal colonization, or recipients of mupirocin for nasal decolonization (743). At a Boston clinic at which approximately 70% of patients self-identified as being MSM, in a 16-month period in 2005 to 2007, 9.2% (73/795) of patients developed an SSTI: 31/73 (43%) of the SSTIs were cellulitis, and 26/73 (36%) were furuncles. Of the SSTIs, 56% (41/73) were cultured, and 22/41 (54%) grew MRSA. Of those with an SSTI, 20% (16/73) developed a recurrence; culture data from recurrent lesions were not reported, so the proportion of recurrent lesions caused by MRSA was unknown. The authors of that study did not report whether antibiotics chosen for the treatment of the initial SSTIs were known to be active against the isolates obtained from the initial SSTIs (877).

SSTIs caused by MSSA also recur but less frequently than those caused by MRSA. Among detainees at the Cook County Jail in Chicago in 2004 to 2005, 14% of patients with an MRSA SSTI and 8.8% of patients with an MSSA SSTI had a recurrence within 6 months (215). Among 31 HIV-infected patients with a CA-MRSA (CDC criteria) SSTI in 2000 to 2007 at an HIV clinic in San Diego, 14 (41%) had a recurrent SSTI at a distinct anatomical location a median of 4 months after the index lesion. Culture results were available for only some recurrent lesions; of 14 patients with a CA-MRSA index SSTI and a recurrence, 7 (50%) had a culture-confirmed CA-MRSA SSTI recurrence. Recurrence was associated with an HIV viral load of >1,000 copies/ml (OR, 0.14; $P = 0.03$ for patients with a viral load of <1,000 copies/ml), and there was a trend for an increased risk of recurrence if an incision-and-drainage procedure was not performed for the index CA-MRSA SSTI (OR, 0.19; $P = 0.07$) (195).

Why recurrent CA-MRSA SSTIs are common is not known. Immunity after an initial MRSA SSTI would seem to be absent in patients with a recurrence. The mechanism by which recurrence occurs is unclear. Possibilities include reinfection from persistent asymptomatic CA-MRSA carriage or reinfection after acquisition from environmental MRSA contamination or after new MRSA acquisition from close human or animal contact.

### Invasive Infections and Necrotizing Pneumonia

Severe, invasive CA-MRSA disease in previously healthy patients has been reported from many centers. "New" staphylococcal syndromes have been recognized in association with CA-MRSA isolates, suggesting that CA-MRSA genetic backgrounds and, possibly, the corresponding MSSA genetic background may carry novel virulence genes, a combination of virulence factors absent in many MSSA strains, or an upregulation of widely prevalent virulence factors (204) (Table 11).

Necrotizing fasciitis, necrotizing pneumonia, severe sepsis, and septic thrombophlebitis of large veins such as the iliac or femoral veins caused by *S. aureus* were rarely reported for healthy individuals prior to the emergence of CA-MRSA. However, there are now many reports of such infections (Table 11). For example, Miller et al. described 14 adults with necrotizing fasciitis caused by MRSA at the University of California at Los Angeles (UCLA) in 2003 to 2004, 4 of whom had no preexisting medical comorbidity. The five available isolates were USA300 and $PVL^+$ and carried SCC*mec* type IV (609).

Severe, invasive CA-MRSA infections have a high mortality rate, even when optimal therapeutic regimens are used. For example, the mortality rate for eight children with CA-MRSA sepsis at Vanderbilt University Medical Center in Tennessee was 50% (124). While many invasive syndromes have been described (Table 11), this discussion will focus on necrotizing pneumonia.

CA-MRSA necrotizing pneumonia is a distinct syndrome of hemoptysis, leucopenia, high fever, and cavitary lung lesions upon radiography, often requiring mechanical ventilation.

TABLE 11. Reported invasive CA-MRSA infections in 1998 to 2009

| Type of infection or syndrome | Reference(s) |
|---|---|
| Brain abscess | 470, 546, 835 |
| Cavernous sinus thrombosis | 641, 651, 789 |
| Diarrhea and shock | 9 |
| Endocarditis | 38, 292, 367, 522, 728 |
| Epidural abscess | 103 |
| Fournier's gangrene | 111, 457 |
| Iliopsoas abscess, postpartum or otherwise | 850, 993 |
| Lemierre's syndrome | 60, 72 |
| Mediastinitis, mediastinal abscess | 118, 1009 |
| Meningitis | 641, 808, 960, 971 |
| Orbital cellulitis | 789, 948 |
| Acute osteomyelitis | 159, 379, 439, 467, 513, 584, 677, 791, 815, 821, 971 |
| Necrotizing conjunctivitis | 100 |
| Necrotizing fasciitis | 7, 17, 87, 159, 224, 379, 523, 525, 609, 911, 1021 |
| Necrotizing pneumonia | 3, 86, 96, 99, 102, 124, 141, 159, 189, 190, 247, 305, 312, 320, 321, 322, 331, 355, 372, 396, 429, 540, 564, 583, 590, 602, 614, 618, 669, 677, 719, 720, 763, 781, 804, 848, 858, 870, 906, 907, 917, 925, 926, 1028 |
| Prostatic abscess | 724 |
| Purpura fulminans | 488 |
| Pyomyositis | 7, 296, 354, 415, 467, 527, 545, 584, 701, 705, 826, 971 |
| Retropharyngeal abscess | 288 |
| Septic arthritis | 415, 564, 584, 720, 736, 857 |
| Septic thrombophlebitis or so-called "pelvic syndrome" | 330, 467, 677, 870 |
| Sepsis, severe sepsis | 6, 30, 124, 133, 159, 179, 192, 262, 360, 571, 603, 621, 720, 857, 887, 917, 1011 |

While infrequent, there is some evidence that the incidence of this condition may be increasing. Among inpatients at 59 U.S. hospitals in 2002 to 2003, MRSA was the etiology of 15.9% of pneumonias and 8.9% of community-acquired pneumonias; a case of pneumonia was defined by the presence of a billing code for pneumonia in administrative data and a concomitant positive respiratory bacterial culture (485). Cases of necrotizing MRSA pneumonia have often been linked to antecedent respiratory viral infection, particularly influenza (3, 96, 729, 906). The clinical presentation of CA-MRSA necrotizing pneumonia is reminiscent of rapidly progressive influenza cases during the 1918 influenza pandemic caused by *S. aureus* superinfection (167). Indeed, recent studies have suggested that most deaths related to the 1918 influenza pandemic were due to complicating bacterial pneumonia (101, 631). In 2009, in the first two waves of the worldwide pandemic of H1N1 2009 influenza A virus, several published series included cases of MRSA pneumonia complicating influenza in previously healthy people in the United States (129, 144, 320) and Australia (646). More data are needed to define the interaction of influenza virus and *S. aureus* in the human respiratory tract.

Necrotizing pneumonia often has a rapidly progressive, fatal course and occurs most often in children and young adult patients. Gillet et al. reported 16 cases of community-acquired *S. aureus* pneumonia caused by $PVL^+$ strains in France in 1986 to 1998 with a mortality rate of 63% (321). In a statewide surveillance of severe CA-MRSA (CDC criteria, except that health care exposures were "not recent") infections in 2005 to 2007 in Georgia, 101/1,670 (6.1%) patients had MRSA pneumonia, 29/101 (29%) of whom died. Controlling for age, patients with MRSA pneumonia had an odds ratio of dying of 11.34 (95% CI, 5.59 to 22.98; $P < 0.001$) (1000) relative to other patients with severe CA-MRSA infections. Among 50 cases of necrotizing community-acquired pneumonia caused by $PVL^+$ *S. aureus* strains in 1986 to 2005, the mortality rate was 56%, and the median age was 14.5 years. Death was independently associated with "airway bleeding," erythroderma, and leucopenia. A focal staphylococcal infection elsewhere, prior to the onset of pneumonia, was associated with decreased mortality (322). Anecdotal reports and series such as this report suggest that CA-MRSA lung infections resulting from hematogenous spread may have a lower case fatality rate than primary MRSA pneumonia.

During the 2003–2004 influenza season, 248 cases of secondary bacterial infection were reported among 13,560 laboratory-confirmed cases of influenza in the United States. *S. aureus* was the most commonly identified pathogen in these cases (44/248 [17.7%] *S. aureus* versus 32/248 [12.9%] *S. pneumoniae* isolates), and the majority of the *S. aureus* isolates were MRSA for both adults (24/31) and children (7/13) (729). Among children, 40 state health departments reported 153 deaths from influenza in 2003 to 2004. Among the 102 cases with adequate data, 24 (24%) had a coinfecting bacterium; nearly half (11 cases; 46%) were *S. aureus*. Six of the 10 *S. aureus* isolates for which data were available were methicillin resistant (67). In the largest series to date, 51 cases of *S. aureus* pneumonia were reported to a U.S. Emerging Infections Network survey in 2006 to 2007. Of the 47 isolates with known susceptibility, 37 (78%) were MRSA isolates, and the median patient age was 16 years. Thirty-three percent of those tested had concomitant influenza virus infection, and 51% (24/47) of the patients died a median of 4 days after the onset of symptoms. Leucopenia was independently associated with death. Of the 17 MRSA isolates available, 16 were USA300, and 1 was a PVL-negative USA100 isolate (455). In Atlanta in 2006 to 2007, 7/65 (11%) children admitted to hospitals with influenza had a simultaneous *S.*

*aureus* infection, most of which were MRSA (5/7) and most of which were pneumonia (5/7). An additional seven children had simultaneous respiratory syncytial virus (RSV) and *S. aureus* infections (751).

The pathogenesis of these severe CA-MRSA infections, such as pneumonia, sepsis, and septic thrombophlebitis, requires further research to define high-risk populations, to identify host genetic characteristics that increase susceptibility to infection, to assess the importance of antecedent colonization with MRSA as a risk factor, and to devise methods to prevent these devastating clinical syndromes.

## TREATMENT OF CA-MRSA INFECTIONS

### Uncomplicated SSTIs

Reviews and guidelines of therapy for CA-MRSA SSTIs abound (209, 335, 341, 516, 616, 735), although there have been few controlled studies. The choice of empiric therapy for CA-MRSA SSTIs requires the clinician to distinguish between uncomplicated SSTIs and severe or complicated SSTIs (209). Uncomplicated SSTIs are not accompanied by systemic signs that indicate a potential for rapidly progressive clinical decline and a lack clinical features of complicated SSTIs, including a large or rapidly growing lesion or a lesion with deep tissue penetration. A systemic inflammatory response syndrome and leucopenia are absent. Host characteristics such as immunocompromise, age younger than 6 months, lack of a reliable site for outpatient follow-up care, or poorly controlled comorbid conditions may dictate the need for hospitalization (209).

In a region or a population with a high prevalence of CA-MRSA, e.g., where >10% of clinical *S. aureus* isolates are MRSA isolates, β-lactam antibiotics are no longer reliable for empiric therapy. For small, uncomplicated CA-MRSA skin abscesses (i.e., those <5 cm in diameter), when reliable follow-up is available, incision and drainage may be adequate without antimicrobial drug therapy (362). This contention is supported by studies in which patients received MRSA-inappropriate antimicrobials for MRSA SSTIs and, nevertheless, did well. In 2002 to 2003 in Dallas, 58/62 (94%) children with SSTIs treated with an MRSA-inappropriate antimicrobial (i.e., antimicrobial drugs to which the cultured isolate was not susceptible *in vitro*) had improvement at a 1- to 6-day follow-up: 37/62 (60%) patients continued on the original drug regimen, while 21/62 (34%) patients were changed to an MRSA-appropriate agent; no difference in outcome was observed (520). Similar results were found by uncontrolled studies conducted with adults treated with MRSA-inappropriate antimicrobials in 11 geographically diverse U.S. emergency departments in 2004 (628) and among patients treated at a clinic for SSTIs in San Francisco in both 2000 to 2001 (718) and 2004 to 2005 (744). In 2004 to 2005, a subset of 166 outpatients attending a San Francisco wound clinic were randomized after incision, drainage, and packing of a skin abscess >2 cm in diameter to receive cephalexin or placebo. Although 87.8% of isolates from the study subjects were MRSA isolates, high cure rates did not differ significantly at 7 days for those treated with cephalexin (84.1%) and those treated with placebo (90.5%) (744).

MRSA-appropriate antimicrobial therapy appears to be important, however, for the treatment of at least some SSTIs caused by CA-MRSA strains, as suggested by a retrospective study of two hospitals in Arkansas. Treatment failure occurred for 5% of 312 patients with a CA-MRSA SSTI in 2003 to 2006 when MRSA-appropriate therapy was used within 48 h of presentation but occurred for 13% of 219 patients with SSTIs when MRSA-inappropriate therapy was used ($P = 0.001$). Incision and drainage were performed for 80% of the patients at the index visit. The difference in the rate of treatment failure was significant even when included in a logistic regression model with many other potential predictors. It is not clear if patients received therapy with a single antimicrobial or multiple agents (784).

Although some researchers have reported worse outcomes for CA-MRSA than for CA-MSSA infections, SSTIs caused by MRSA with onset in the community did not have worse outcomes than those caused by MSSA in Los Angeles in 2004 (607).

There is no consensus as to which patients can be treated with incision and drainage alone and which patients require adjunctive antimicrobial therapy (334). Readers of the *New England Journal of Medicine* demonstrated that U.S. providers polled to recommend treatment for a college athlete with a 5-by 3-cm buttock SSTI differed in their preferred initial management: among the 11,205 respondents, 41% advocated drainage and an antimicrobial agent active against MRSA, 31% advocated drainage alone, and 28% advocated drainage and an agent active against MSSA (149, 358).

Initial empiric antimicrobial therapy, when given, must be chosen in accordance with local institutional antibiotic susceptibility data. In geographic regions with a high prevalence of CA-MRSA, a sample of the purulent material should be sent for culture and susceptibility testing. Antimicrobials such as clindamycin, doxycycline, minocycline, and trimethoprim-sulfamethoxazole (TMP-SMX) are often recommended for empiric treatment, although randomized clinical trials have not been conducted to evaluate or compare these therapies for CA-MRSA; such trials were, however, initiated in 2009 under the sponsorship of the NIH. As always, therapy should be adjusted to target the culture and antimicrobial susceptibility results when available.

Clindamycin remains a mainstay of therapy for uncomplicated CA-MRSA SSTIs in much of the United States, although some researchers have suggested that resistance may be increasing among CA-MRSA strains (235, 361). Despite heavy use, however, the rate of clindamycin resistance changed little at a Baltimore pediatric ED: 96% of 217 MRSA isolates in 2003 to 2005 were susceptible to clindamycin, similar to the percent found in 2002 to 2003 (874). A group from Baylor University in 2000 to 2002 found in an uncontrolled study that clindamycin was effective for invasive community-onset MRSA infections of children (585). Although it is often associated with a successful outcome in therapy for SSTIs, concern has also been raised about the risk of *Clostridium difficile*-associated diarrhea (696) with clindamycin therapy. When an *S. aureus* isolate is susceptible to clindamycin but resistant to erythromycin, inducible resistance to clindamycin should be assessed by the D test, as recommended by the Clinical and Laboratory Standards Institute (661).

TMP-SMX is also favored by many experts for the treatment

of CA-MRSA SSTIs. However, it may be ineffective against cellulitis or other SSTIs caused by group A streptococci, and therefore, treatment failure may occur in this situation, although few explicit data are available. Allergy to sulfa drugs or renal failure can preclude its use. Furthermore, there is a theoretical risk of treatment failure of antifolate drugs in the presence of pus because the presence of large amounts of released thymidine from tissue damage may abrogate the effect of these agents (737). A randomized, placebo-controlled study of pediatric patients with an SSTI in an ED in St. Louis, MO, in 2006 to 2008 demonstrated that incision and drainage with subsequent oral placebo (4/76; 5.26%) were noninferior to incision and drainage with a 10-day course of TMP-SMX (3/73; 4.11%). Eighty percent of the lesions grew MRSA, and 100% of the isolates were susceptible to TMP-SMX (251). Investigators at Fenway Clinic in Boston reported that TMP-SMX was used to treat more than 76% of MRSA SSTIs in 2005. In a retrospective study, in 1998 to 2005, they found that therapy using an agent to which causative MRSA strains were susceptible (commonly TMP-SMX) was associated with a higher odds of clinical resolution of MRSA SSTIs in a multivariate logistic regression model (876). A retrospective study of children admitted to Texas Children's Hospital in Houston in 2004 to 2005 for CA-MRSA SSTIs (no hospitalization in the previous year, no indwelling catheters or percutaneous devices, and no chronic medical conditions that predispose one "to hospitalization or frequent medical visits") compared outcomes among those who received oral TMP-SMX and those who received clindamycin therapy prescribed at discharge. Patients with concurrent, invasive MRSA infection were excluded. Among 215 and 200 children receiving TMP-SMX and clindamycin, respectively, there was no difference in the percentages of patients returning to the hospital for a worsening of the index lesions. However, more patients treated with clindamycin had undergone surgical drainage prior to discharge (93.5% versus 86%; $P = 0.0003$), potentially biasing the outcome in favor of clindamycin treatment (424).

Limited data are available to document the efficacy of doxycycline or minocycline in the treatment of an MRSA SSTI after incision and drainage (783); like TMP-SMX, these agents are unlikely to be useful when there is a high suspicion for group A streptococcal infection. In an underpowered, small, open-label study of outpatients in 2005 to 2006 at an ED in Dallas, TX, 34 patients with an SSTI (23 with MRSA, 4 with MSSA, 2 culture negative, and the remaining 5 with coagulase-negative staphylococcus, *Corynebacterium* species, *Streptococcus milleri*, or "gastrointestinal flora") were randomized to receive TMP-SMX or doxycycline. Fourteen patients with an SSTI (8 of whom had MRSA) were randomized to receive TMP-SMX, and 20 patients (15 of whom had MRSA) were randomized to receive doxycycline; one patient in the TMP-SMX group was lost to follow-up. In an intention-to-treat analysis, no significant difference in the failure rate was found (3/14 [21%] in the doxycycline group and 0/19 [0%] in the TMP-SMX group; reported as a *P* value of 0.28) (127).

Oral therapy with linezolid, a bacteriostatic oxazolidinone, is effective in treating patients with an SSTI; resistance to linezolid among MRSA isolates has been reported with prolonged use (66) but is rare with short-term use. The use of linezolid is limited by high cost, limited availability of the suspension, the occurrence of thrombocytopenia with prolonged use, and the availability of less-expensive, effective oral antimicrobial drugs.

Certain antimicrobial drugs should be avoided as therapy for MRSA SSTIs despite susceptibility documented by laboratory testing. FQs are an important example. Resistance to FQs is common (628), and the rate of resistance of *S. aureus* increases rapidly with exposure. Resistance emerging during FQ therapy was related to the duration of therapy and dosing in an *in vitro* model (884). Rifampin should also not be used as a sole agent in the therapy of CA-MRSA infections because of the high rate of emergence of resistance (335).

### Severe Infections

Invasive CA-MRSA infections, such as bacteremia, pneumonia, and osteomyelitis, when suspected, usually require hospitalization and therapy with intravenous antibiotics (209). Although guidelines and reviews have been reported (47, 341, 658, 677), evidence to guide therapy remains scarce. Appropriate cultures are essential and should be obtained prior to the initiation of empiric antibiotic therapy. Antimicrobial therapy for such severe CA-MRSA infections is generally the same as that for invasive HA-MRSA infections (781). Vancomycin is still the primary agent used for suspected invasive CA-MRSA infections; it is generally well tolerated and has few adverse effects. Concerns have been raised about its poor penetration into lung tissue, underdosing, reported treatment failure in cases of necrotizing pneumonia caused by $PVL^+$ CA-MRSA strains (984), increasing low-level (intermediate) resistance (389, 542), and "MIC creep" (549, 795, 892). It is not known if alternative initial antibiotic choices would improve the often fatal outcome of severe, invasive CA-MRSA infections with their rapid, progressive clinical tempo (209, 298).

The efficacy of parenteral TMP-SMX for the therapy of invasive CA-MRSA infections has received little study. Among 100 IVDUs with severe *S. aureus* infections randomized to receive intravenous vancomycin or TMP-SMX, the cure rates, 57/58 (98%) for vancomycin and 37/43 (86%) for TMP-SMX, differed insignificantly; 47% of the patients had MRSA infections (581). That study was performed before the CA-MRSA infection era. Also, the study may have lacked adequate power to demonstrate a difference, as the authors themselves admitted, but the data suggest that intravenous TMP-SMX deserves additional evaluation.

The adjunctive use of an antimicrobial agent interfering with bacterial protein synthesis, such as clindamycin or linezolid, is sometimes advocated for a CA-MRSA infection in which toxin-mediated pathogenesis is suspected, although there is limited evidence to support this approach (250, 602). Such adjunctive therapy may be particularly valuable for intravascular infections when viable organisms are expected for several days despite therapy. The theoretical basis for this approach rests on the hypothesis that ribosomally active antibiotics decrease toxin production more rapidly than other antibiotics. The *in vitro* exposure of MRSA isolates to a subinhibitory concentration of β-lactam antibiotics increased the expression of toxin genes, including those for PVL, alpha-toxin, and toxic shock syndrome toxin 1 (TSST-1). In contrast, the use of clindamycin or linezolid decreased the production of these toxins (862).

Several newer antistaphylococcal agents are available for parenteral therapy, including daptomycin, linezolid, tigecycline, and quinupristin-dalfopristin. Daptomycin, which is bactericidal and can be administered once daily to patients with normal renal function, has been shown to be effective against MRSA SSTIs (24) and has been used in adults with bacteremic infections. In a randomized, controlled trial with adults, daptomycin was noninferior to vancomycin for the therapy of right-sided *S. aureus* endocarditis, although treatment failures occurred due to the emergence of daptomycin resistance during therapy (297). Daptomycin is not useful for pneumonia because it is inactivated by pulmonary surfactant (836). Although it is generally well tolerated, patients require weekly creatinine kinase testing to monitor for rhabdomyolysis, a rare but potentially serious adverse reaction (122). Safety and efficacy data are lacking for pediatric patients.

Tigecycline, a glycylcycline antibiotic chemically related to minocycline, has been approved for use in patients with intra-abdominal infections and MRSA SSTIs (776, 859) and is safe and effective for the therapy of complicated MRSA SSTIs in hospitalized patients, with a cure rate similar to that of vancomycin (78.6% versus 87.0% in a microbiologically modified intention-to-treat analysis) (290). This static agent is dosed twice daily intravenously; common adverse reactions include nausea, vomiting, and abdominal pain (290, 859). Tigecycline is not appropriate for children younger than 8 years of age.

Linezolid is well suited for the therapy of MRSA respiratory infection because of its excellent penetration into the lung, and it may be an appropriate choice especially in cases in which the MIC of vancomycin is high (844). Reports of linezolid resistance with prolonged use have occurred (599).

The use of the streptogramin antibiotic combination quinupristin-dalfopristin is sometimes limited by severe, reversible arthralgias as well as nausea, diarrhea, vomiting, conjugated bilirubinemia, and rash that occurs with prolonged use (782). Resistance of *S. aureus* has been reported (242, 562).

Two newly developed cephalosporins, ceftobiprole and ceftaroline, which differ from other β-lactam antimicrobials in their high affinity for PBP2a, show promise as agents effective against MRSA (172, 725, 1025). They have not been licensed for use in the United States. The novel glycopeptides dalbavancin (772), telavancin (155), and oritavancin (734) inhibit cell wall synthesis like vancomycin. Telavancin, which was approved by the U.S. Food and Drug Administration (FDA) in September 2009, also causes a depolarization of the bacterial cell membrane, theoretically enhancing its bactericidal effect (155). The main advantages of dalbavancin and oritavancin over vancomycin may be their long half-lives, which allow for infrequent dosing (927). No data for efficacy or safety in children are available for these novel agents.

One case report (360) and one *in vitro* study (314) suggested that intravenous immunoglobulin (IVIG) may be an effective adjunctive therapy for sepsis caused by $PVL^+$ CA-MRSA, but further study is needed to validate this observation (658). Infectious foci should be drained, and necrotic tissue should be debrided when feasible (7, 87, 159, 224, 379, 523, 525, 609, 1021).

## PREVENTION OF CA-MRSA INFECTIONS

Infection control practice in the health care setting relies on guidelines from professional and governmental bodies (177, 341, 834). The standard hospital guidelines regarding MRSA prevention stress that "antibiotic-resistant pathogens are sensitive to routinely used hospital disinfectants, but it is essential that correct and meticulous cleaning and use of disinfectants be performed" (648). With few exceptions (408), however, most specific interventions, including the isolation or cohorting of colonized individuals, active identification of MRSA carriage by surveillance cultures of high-risk populations, decolonization of MRSA carriers, environmental disinfection by chemical means or even light (568), or some combination of the above-described interventions, have failed to reliably limit transmission or spread (557). Even with this uncertainty, in community and other institutional settings, there is far less evidence to support the use of these approaches, and as the CA-MRSA epidemic continues, the need for effective interventions has become more acute.

### MRSA Recovery from Fomites

Many researchers have found MRSA in the environment outside the health care setting, but the relevance of its presence on fomites to human colonization and infection is not clear. A variety of MRSA genotypes has been isolated from seawater at recreational beaches in Hawaii (818) and beaches in California and Washington State (849); it has been recovered from coins in the presence of pus and blood, although MRSA could not be recovered from clean coins within 4 h of initial contamination (904). In Boston, *S. aureus* was recovered from fomites in 34/35 homes of healthy individuals with a child in diapers and a cat or dog in the home; MRSA was recovered from fomites in 9/35 homes. MRSA was recovered from sinks, countertops, faucet handles, dish sponges, pet food dishes, infant high-chair trays, and others (812). Efforts to eradicate the colonization of health care workers in Germany in 1995 to 2001 succeeded only when household contacts and heavily contaminated fomites in the homes of the health care workers were disinfected (483), suggesting that fomites may constitute important environmental reservoirs. Specific fomite materials have not been tested extensively for the survival of MRSA. Evidence from one study suggests that MRSA survives poorly on copper surfaces compared with stainless steel (678), but there are no studies available on the replacement of metal surfaces with copper in the community.

It is clear that MRSA environmental contamination is common, at least in the hospital (370) and, from case reports, in the community as well. MRSA can spread from person to person via direct casual contact or from the contamination of inanimate objects (88, 588). However, the importance of environmental contamination in MRSA transmission remains uncertain. Spread between patients and environmental surfaces may occur rapidly. Environmental contamination with MRSA occurred within 24 h of admission of two ICU patients with an MRSA infection in a hospital in England; the rooms had been cleaned with a hydrogen peroxide aerosol prior to the admissions (371). MRSA can survive on objects such as dry mops for up to 4 weeks (686); paper and foil wrappings of sterile hos-

pital goods for more than 38 weeks (238); plastic charts, a laminated table, and polyester cloth curtains for more than 1 week (407); and mattresses for months (662). MRSA can also be recovered from hospital ventilation systems (187, 495), chiropractic adjusting tables (70), computer keyboards, pagers (52), and faucet handles (108). In a Japanese hospital, MRSA was isolated from sinks, floors, bed sheets, and the air in a surgery ward. The number of CFU of MRSA detected from air samples increased more than 50 times during the changing of bed linens, although the significance of airborne MRSA in transmission is not known (830).

Even reportedly rigorous cleaning may not be effective in eradicating MRSA contamination of fomites. At a hospital in the United Kingdom, in 46% of rooms formerly housing MRSA-infected patients, cultures of mattresses, pillows, chairs, lockers, bed wheels, commodes, bed frames, nurse call buttons, a television set, floors, window sills, or door handles still grew MRSA despite "terminal" cleaning (75).

Limited evidence from studies in the health care setting indicates that environmental contamination can lead to human colonization and disease with MRSA (370), although much of the data are only suggestive. At a Baltimore, MD, outpatient infectious disease clinic in 2004, two health care workers developed MRSA SSTIs. Seven of 36 environmental cultures tested grew MRSA. All seven isolates carried the SCC*mec* type IV element and the genes for the PVL toxin (448). After a pediatric ICU MRSA outbreak in Taiwan, investigation revealed that 26.2% of health care workers were colonized with MRSA. Some of the health care workers carried the same MRSA clone that was isolated from patient infections and from a fomite; other health care workers carried different MRSA clones (539). In a dermatology ward, it was deemed likely that the contamination of hospital equipment with MRSA and borderline methicillin-resistant *S. aureus* led to 13 infections (514). Dutch investigators isolated a strain of MRSA from a physician's office floor that may have been the source of his nasal recolonization (966). A hospital outbreak of MRSA in a general surgical ward in the United Kingdom was contained only after an aggressive environmental cleaning program was instituted. This included the formation of a new infection control team that met monthly, sequential closure of each part of the ward for thorough cleaning, dust traps being removed from around radiators, ventilation ducts being cleaned, the hours of weekly person-cleaning time being increased from 66.5 to 123.5 h, curtains being laundered every 6 months at a minimum, and several other interventions. Of 673 environmental cultures obtained from hospital rooms before and after an intervention, 10.7% grew MRSA. Among MRSA isolates from male patients housed in these rooms, 55 had an identical PFGE type, the same type shared by all but 1 of 58 environmental isolates tested (746). A study of an ICU showed that the attributable risk for the acquisition of MRSA infections from occupying a bed previously occupied by a patient who was colonized by or infected with MRSA accounted for only 5.1% of MRSA cases in the ICU (409).

MRSA SSTIs and MRSA gastrointestinal colonization (89) in the health care setting may be more likely to produce environmental contamination than either other MRSA infections or colonization. In a study from a Rhode Island hospital, 36% of tested surfaces (including patient gowns, nurses uniforms, beds, blood pressure cuffs, over-bed tables, floors, linens, and door handles) were contaminated in rooms of patients with skin or urine infections with MRSA, whereas only 6% of surfaces were contaminated in rooms of patients with MRSA infections at other sites (88). A study of a nursing home showed rare environmental contamination by MRSA, despite a high prevalence of nasal colonization among its patients and despite the fact that 10% of patients newly acquired MRSA asymptomatic colonization while at the nursing home (91). This finding suggests that when active infections are rare, even in the presence of a high prevalence of asymptomatic colonization, environmental contamination may be uncommon.

### Chlorhexidine Gluconate and MRSA Decolonization

Chlorhexidine gluconate (CHG) is a skin antiseptic in use in the health care setting since the 1950s with many potential applications for infection control, as discussed in a recent review (612). CHG is bactericidal for several pathogenic bacteria (787), including MRSA (74, 458, 503). However, bacteria, particularly Gram-negative bacteria, can develop resistance to CHG (98) that may increase with increased CHG use (979). It has not been used widely or studied rigorously in community settings, although it is often recommended by decolonization protocols for patients with recurrent MRSA infections. It is also commonly used for preoperative bathing for surgical procedures, although a systematic review of randomized trials in the literature in 2006 showed no decrease in surgical-site infections in the hospital after preoperative antiseptic bathing; all six trials compared CHG with no intervention or bar soap (985).

In the health care arena, CHG is safe (464) and provides a "residual effect" that continues to kill pathogens for up to 48 h after application to the skin (558). CHG has been used successfully to limit the spread of vancomycin-resistant enterococci (VRE) in an medical intensive care unit (953), to prevent catheter infections (73, 531), and for hand disinfection (964). Universal CHG baths as part of a multifaceted intervention, including the screening of all admitted patients for nasal colonization, isolation of colonized patients, and rotating universal use of three intranasal antimicrobial ointments, was successful in decreasing MRSA infections in one ICU in the United Kingdom; the independent effect of CHG is not known (342). In one hospital study, the use of CHG baths alone was associated with a loss of MRSA colonization in 9 of 50 patients (369). An aggressive decolonization regimen applied to 87 patients in a randomized trial of CHG washes, mupirocin nasal ointment, and oral rifampin and doxycycline for 7 days yielded 74% decolonization 3 months later, compared with 32% among 25 untreated patients. At 8 months, 54% of the treated group remained free of MRSA colonization; again, however, the independent effect of CHG is not known (837).

It is not certain that evidence derived from the health care setting can be applied to CA-MRSA isolates in other arenas. One study of chlorhexidine skin cleaning in a large cohort of soldiers did not show an effect on decreasing the incidence of SSTIs (997).

### Mupirocin

Inside and outside the health care setting, mupirocin has long been used for the attempted decolonization of patients colonized by *S. aureus*, but the efficacy data are conflicting (713, 749) A 2008 review of four randomized, controlled trials showed a significant decrease in rates of postsurgical infections among *S. aureus*-colonized patients receiving mupirocin compared with either placebo or no treatment (3.6% versus 6.7%; RR, 0.55; CI, 0.34 to 0.89) (944). Another review in 2003 found no evidence to support the general practice of using topical or systemic antimicrobial therapy to decolonize people with MRSA in the nose or elsewhere on the body (550).

Few systematic studies of mupirocin to decolonize MRSA carriers have been attempted in the community. At a Texas Army base in 2005, 3,447 soldiers attending classes were randomized into two groups. All were screened for MRSA colonization. Those colonized with MRSA received mupirocin or placebo. A cotton-tipped applicator was used to apply 2% mupirocin ointment or placebo twice daily into the nasal vestibule for 5 days. Although mupirocin was effective at decolonizing 58 of 66 (87.9%) colonized soldiers compared with 42 of 65 (64.6%) colonized soldiers receiving placebo in a 16-week follow-up period, the incidence rates of MRSA skin infections were similar for the two groups (19 versus 20 confirmed MRSA skin abscesses). Also, the incidence of new CA-MRSA colonization in the group of soldiers decolonized with mupirocin (23/1,607; 1.4%) did not differ significantly from new colonization in the placebo-treated group (24/1,459; 1.6%) (260). In another community-based trial, mupirocin failed to produce lasting decolonization among MRSA carriers (343). Thus, there is no evidence that mupirocin or any other intranasal antimicrobial agent should be used in any community setting for MRSA decolonization.

### Retapamulin

Retapamulin is a topical antibiotic, the first in a class known as the pleuromutilins to be approved by the U.S. FDA for the treatment of impetigo. In part because cross-resistance to other antimicrobials is thought to be unlikely and because it is effective against tested MRSA strains, this drug may be useful in decolonization regimens for MRSA. The drug acts by inhibiting the 50S subunit of the ribosome. Clinical trials are needed to assess the value of retapamulin for this indication (211, 764).

### Specific Populations

**Athletes.** Among athletes, there are several published guidelines for the prevention of MRSA transmission, although few provide evidence. For example, a general guideline for the control of MRSA in the community, prepared in 2004 and updated in December 2007, has been released by the Washington State Department of Health in collaboration with other government bodies in the state. Guidelines for the control of MRSA in the athletic setting (425) were included. The National Collegiate Athletic Association (NCAA) has published guidelines specifically for wrestlers, recommending that wrestlers with an SSTI be excluded from play until 72 h after the initiation of therapy if there is marked clinical improvement and no new lesions appearing for 48 h. An intact occlusive dressing must be in place before and during competition or practice (659).

**Jails and prisons.** Although there are few relevant published data, the U.S. Federal Bureau of Prisons has released guidelines for the prevention and treatment of MRSA infections among incarcerated populations. These guidelines do not recommend routine attempts to decolonize detainees. Decolonization is recommended in the case of "recurrent MRSA infections or in the context of a MRSA outbreak" with intranasal mupirocin applied twice daily for 5 days. The guidelines call for detainee education that stresses the importance of regular hand washing, exclusion of infected detainees with draining wounds from certain activities, special procedures for the transfer of inmates, and early intervention for skin infections. Enhanced surveillance is recommended after a single case of MRSA is diagnosed. Detainees with infections are placed in individual cells only if they have uncontained drainage, whereas those with small skin infections that can be "easily contained by [a] simple dressing" can remain among the general population. In an outbreak setting, the cohorting of infected inmates, increased attention to hand hygiene, the use of antimicrobial soaps, more stringent infection control measures in clinics, and targeted examination of close contacts of infected inmates are recommended (280). Such a comprehensive program may not be practical in all jails and prisons, and more research is needed to evaluate the contribution of the individual interventions.

The Texas Department of State Health Services has prepared similar guidelines for MRSA prevention among incarcerated individuals (896).

Some researchers have advocated improved hygiene with better access to soap, showers, and clean clothing; educational campaigns; round-the-clock urgent care; and dedicated wound clinics as potential interventions to prevent the spread of MRSA in incarceration settings (69). For example, after an outbreak of MRSA SSTIs in a Georgia prison facility housing 197 detainees, administrators implemented several interventions, including skin examinations upon arrival, liquid soap near all bathroom sinks, CHG body washes for 5 days for all detainees at the start of the intervention, an educational program on skin hygiene, and waiving of the sick visit fee for skin complaints; all detainees were urged to visit the clinic if they had skin lesions. For detainees with MRSA skin lesions, a standardized antimicrobial regimen was prescribed, intranasal mupirocin and/or oral rifampin was given for decolonization, and careful attention was paid to dressing changes. With these interventions, the incidence of MRSA SSTIs decreased from 11.6 to 0 per 10,000 detainee-days (1008). The introduction of such a multiplicity of interventions, while apparently effective at curtailing an outbreak, may not be universally practical in jails and prisons. In other settings, alcohol-based hand sanitizers have been used to improve hand hygiene, but as demonstrated by a case of severe intoxication of a prison inmate who ingested hand sanitizer (243) and given their flammability, these agents are not typically allowed in places of incarceration.

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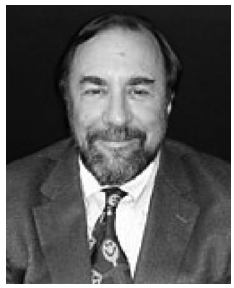

**Robert S. Daum**, MD, CM (McGill University), Professor of Pediatrics, heads the University of Chicago MRSA Research Center. His projects include a Household Contacts Study to prospectively define colonization and infection rates among household contacts of index patients with CA-MRSA infection and the rates of environmental contamination in these households, a Treatment Study to determine the optimal management of uncomplicated skin and soft-tissue infections, and a Jail Study to determine the frequency of environmental contamination in the Dallas County Jail and the effectiveness of bathing with chlorhexidine wipes in decreasing the prevalence of MRSA. He also studies staphylococcal signal transduction mechanisms to gain insight into antibiotic resistance mechanisms among MRSA strains. His laboratory focuses on molecular pathophysiology to investigate the reasons for the dominance of the USA300 CA-MRSA clone. A newly initiated immunological study is an attempt to understand why people are differentially susceptible to CA-MRSA infections.