FRI FOOD SAFETY REVIEWS

White Paper on Sources of Methicillin-Resistant *Staphylococcus aureus* (MRSA) and Other Methicillin-Resistant Staphylococci: Implications for Our Food Supply?

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Abbreviations:
MRSA, Methicillin-resistant *Staphyloccus aureus*; CA-MRSA, Community-associated MRSA; HA-MRSA, Hospital-associated MRSA; LA-MRSA, Livestock-associated MRSA; MRSIG, Methicillin-resistant *S. intermedius*; MRSP, Methicillin-resistant *S. pseudintermedius;* MSSA, Methicillin-susceptible *S. aureus.*

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BACKGROUND ON PATHOGENIC STAPHYLOCOCCI

Staphylococcus aureus

Human foodborne intoxication

Staphylococcus aureus is a well-known foodborne pathogen that produces heat-stable enterotoxins during growth on a variety of foods, including meat and poultry products, eggs, cream-filled pastries, potatoes, and some salads. Vegetables are less commonly cited as vehicles for *S. aureus*. However, two outbreaks in restaurants in the U.S. in 2003 and 2005 were traced to carrots, green peppers, and leeks. In addition, a survey of minimally processed vegetables and sprouts in Korea found that about 11% were contaminated with *S. aureus* (*200*).

Numerous staphylococcal enterotoxins have been described and it is ingestion of these enterotoxins, and not of *S. aureus* cells, that causes a rapid onset of nausea and vomiting within 1–6 hours. Less than 200 ng toxin is sufficient to cause symptoms (*59*). Generally, *S. aureus* concentrations of 100,000 cells/g food are necessary. Although symptoms may be severe, they usually resolve within a day and serious complications, hospitalization, and death are rare, afflicting primarily the very young, the elderly, the chronically ill and those who have consumed a large amount of contaminated food.

In some circumstances, ingestion of staphylococci can cause enteritis. Staphylococcal enterocolitis occurs occasionally in infants, immunocompromised adults and others receiving large doses of antibiotics. When normal human intestinal flora is depleted or absent, *S. aureus* cells may grow in the intestines and produce enterotoxins that cause profuse diarrhea (*133*).

S. aureus has been a food safety concern for meat producers and food processors for decades because it is widespread in the environment and often detected in air, dust, water, raw milk, other foods, and on environmental surfaces. It survives desiccation and tolerates high levels of salt. *S. aureus* cells are destroyed by heat but if they have already produced enterotoxins in a food, the toxins will survive approved doses of irradiation and some thermal processes, including pasteurization (*69;179*).

S. aureus has also been a problem for caterers and others involved in food preparation. According to several studies, *S. aureus* is present in nasal passages or skin of about 50% of people and in intestines of about 20% of people in the general population (*4;66*). Thus, asymptomatic food handlers may harbor *S. aureus* and can contaminate food during preparation (*211*). If contaminated foods, for example salads or some desserts at a picnic, are left out at ambient temperature for extended periods, *S. aureus* may multiply and produce enterotoxins.

Staphylococcal food poisoning is believed to be greatly underreported (by about 25-fold) and underdiagnosed (by about 29-fold). The short duration of illness and infrequent complications seldom bring it to the attention of health care professionals. Staphylococcal enterotoxins cause foodborne illness in about 241,000 persons in the U.S. annually (*191*). Twenty-one outbreaks in the U.S. in 2007 (and 14 in 2008) (http://www.cdc.gov/foodborneoutbreaks/documents/2007/bacterial.pdf) and 291 outbreaks in Europe in 2008 (*56*) were attributed to staphylococcal enterotoxin poisoning. Data from Centers for Disease Control and Prevention (CDC) indicate that nearly half of the 542 outbreaks occurring in 1998–2008 were associated with some type of meat **(Table 1).** Seafood, potatoes/rice/noodles, vegetables/salads, combination foods, and dairy products were also cited as food vehicles. Reported annual outbreaks during this 10-year period peaked in 2002 and then declined **(Figure 1)**. Approximately 53% of reported outbreaks affected only 2 to 4 people, whereas only 6.7% of outbreaks involved more than 50 cases. **Table 2** lists some large outbreaks occurring during this period in the U.S., Argentina, Brazil, India, Japan, and Europe.

Table 1. Reported food vehicles for 542 outbreaks of staphylococcal food poisoning reported by CDC for 1998–2007. (http://wwwn.cdc.gov/foodborneoutbreaks/)

Food vehicle	# of outbreaks*
Meat (total)	254 (46.8%)
Beef	53 (9.8%)
Chicken	77 (14.2%)
Ham	36 (6.6%)
Pork	44 (8.1%)
Turkey	17 (3.1%)
Meat, cured, except ham	10 (1.8%)
Meat, other (alligator, rabbit, deli meat, unspecified)	18 (3.3%)
Seafood	35 (6.5%)
Vegetables/salad	30 (5.5%)
Potatoes	29 (5.4%)
Rice/noodles	24 (4.4%)
Dairy products	11 (2.0%)
Sauces/dressings	6 (1.1%)
Eggs	6 (1.1%)
Combination foods	38 (7.0%)
Multiple foods	8 (1.5%)
Unknown	102 (18.8%)

*Total of outbreak numbers is > 542 (and total of percentages is >100) because more than one food was implicated in some outbreaks.

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Figure 1. Outbreaks of staphylococcal food poisoning reported by CDC in the U.S. (1998–2007). (http://wwwn.cdc.gov/foodborneoutbreaks/)

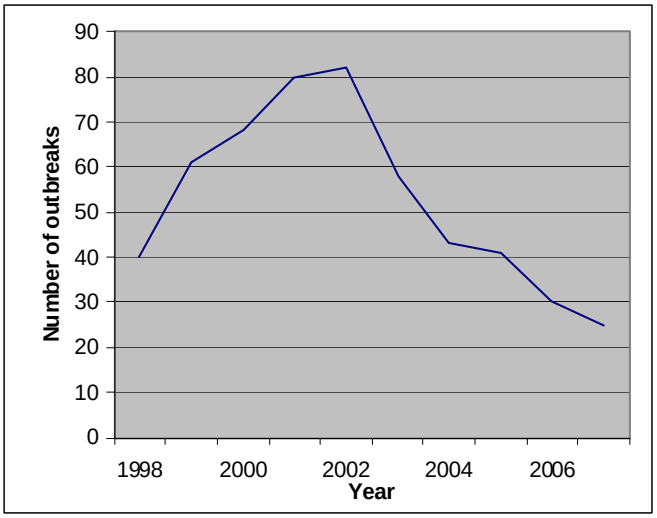

Table 2. Large outbreaks of staphylococcal food intoxication (1998–2008).

# Cases	Year	Location	Food vehicle * (*Reference*)
>13,000	2000	Community (Japan)	Low fat milk (*8*)
~4000	1998	Ordination dinner (Brazil)	Multiple foods, food handlers (*47*)
>600	2005	Military base (Greece)	Cheese, grated (*93*)
225	1998	Multiple locations (Texas, U.S.)	Ham salad
218	1998	Multiple locations (Texas, U.S.)	Turkey salad
180	1998	Brazil	Salad, chicken, food handlers (*31*)
166	2007	Schools (Austria)	Milk, pasteurized (*193*)
147	2006	Festival (Argentina)	Cake (*142*)
145	1998	Restaurant, home (Hawaii, U.S.)	Bento sandwiches
142	2008	Restaurant (Kentucky, U.S.)	Gravy
138	2005	Workplace (Kansas, U.S.)	Sausage
132	2004	Restaurant, home (Ohio, U.S.)	Ice cream
126	1999	Camp (West Virginia, U.S.)	Multiple foods
125	2000	Fair (Georgia, U.S.)	Pork BBQ
113	2006	Boarding school (Austria)	Boiled rice, food handler (*194*)
112	2001	Picnic, fair (Ohio, U.S.)	Pork, roasted; ham
101	1998	(Indiana, U.S.)	Macaroni salad
>100	2005	Fair (India)	Potato balls, fried (*159*)
100	1999	School (Georgia, U.S.)	Pork, BBQ
100	2000	School (Tennessee, U.S.)	Turkey, stuffing
100	2006	Wedding reception (Virginia, U.S.)	Chicken BBQ; ham; potato salad
95	2000	Nursing home (South Dakota, U.S.)	Chicken salad, potato salad
92	2001	Community (Arkansas, U.S.)	Ham, potato salad
89	2000	School (Georgia, U.S.)	Pork BBQ

* U.S. outbreak information from CDC: http://wwwn.cdc.gov/foodborneoutbreaks/

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Non-foodborne human illness

Nearly all *S. aureus* isolates are coagulase positive, i.e. they produce an enzyme that causes clotting of blood plasma. In addition, *S. aureus* produces many other virulence factors (besides enterotoxins) such as exfoliative toxins, toxic shock syndrome toxin, and leukocidins and is responsible for a variety of mild to severe skin and soft tissue infections and numerous serious infections, including endocarditis, endophthalmitis, osteomyelitis, meningitis, bacteremia, pneumonia, and toxic shock syndrome (*125*). Approximately 50% of healthy adults carry *S. aureus* in their nasal passages or on skin; about half of those persons are persistent carriers and the remainder are intermittent carriers (*66*). Some data indicate that host genetic factors (*181*) and competing microflora (*66*) may affect persistence of colonization by *S. aureus*. A review of published data revealed that, overall, nasal, inguinal or axillary colonization with *S. aureus* was associated with a four-fold increase in serious infections (*185*). Asymptomatic carriage or colonization of individuals with *S. aureus* may be a risk factor for person-to-person transmission of these bacteria and for contamination of food.

Animal infections

Infections due to *S. aureus* have been reported in many mammal species as well as for wild and domestic birds and in some reptiles. Some animals are asymptomatic while others suffer respiratory, gastrointestinal, or skin and soft tissue infections. *S. aureus* is a significant cause of mastitis in cows and small ruminants (*230*). Whether animals can be persistent carriers of *S. aureus* in a manner similar to humans has yet to be determined. However, animals can intermittently harbor *S. aureus*. A recent study found that 10% of healthy dogs visiting a clinic for regular vaccinations harbored *S. aureus* (*180*). Molecular analyses of isolates from different animals have revealed that there are some strains that appear to be host-adapted to a particular animal species (horses, cattle, pigs, sheep, chickens, or humans) and other strains can colonize multiple species of animals (*37*). *S. aureus* can be transferred between humans and animals, and frequently infections in companion animals can be traced back to their human caretakers (*184*).

Other pathogenic staphylococci

Coagulase-positive staphylococci, other than *S. aureus*, can cause infections in humans and animals. Some veterinary isolates of coagulase-positive staphylococci are classified in the *S. intermedius* group (SIG). *S. intermedius* was originally described in 1976 and appeared to be part of the normal microflora of the skin and mucosal membranes of dogs and cats. It has also been detected in a variety of other animals, including horses, mink, goats, foxes, raccoons, and pigeons but is not commonly present in humans. Recent molecular analyses demonstrated that isolates of *S. intermedius* detected in a large number of different animals and geographic locations have some significant differences and the species can best be reclassified into three clusters: *S intermedius, S. pseudintermedius*, and *S. delphini* A and B. These three species constitute the *S. intermedius* group (SIG) (*190*).

S. pseudintermedius is the most frequently encountered pathogen in the SIG and was first identified as a novel species in 2005 by examination of rRNA gene sequences in clinical staphylococcal isolates from several animals (*45*). The majority of isolates from dogs are now classified as *S. pseudintermedius* although earlier research papers identified them as *S. intermedius*. *S. delphini* was originally isolated from a dolphin but some isolates from horses, pigeons and mink, previously identified as *S. intermedius*, are now classified as *S. delphini* (*202*).

S. pseudintermedius has been isolated from pet owners and veterinarians (*154*) and occasionally causes infections in humans exposed to dogs carrying these bacteria (*29;206*). Invasive infections have occurred in persons bitten by dogs (*65*) and two recent articles reported *S. intermedius* as the cause of skin abscesses in an injecting drug user (*106*) and meningitis in an infant (*48*).

S. intermedius group pathogens produce a number of virulence factors (coagulase, hemolysins, exfoliative toxin and others) similar to those associated with *S. aureus* (*65;91*). When animals are injured, sick, or otherwise weakened, these bacteria may cause skin, ear, and wound infections (*240*). Some SIG isolates also produce enterotoxins and could potentially cause foodborne intoxication (*14*). One foodborne outbreak in southwestern U.S. in 1991 affecting over 265 people was traced to *S. intermedius* producing type A enterotoxin in a butter blend (*110*).

Compared to coagulase-positive staphylococci, coagulase-negative staphylococci are rarely pathogenic and are often considered to be opportunistic pathogens, such as *S. epidermidis* is for humans (*27*). However, occasionally coagulase-negative staphylococci produce enterotoxins and have been associated with foodborne outbreaks (*232*).

Certain coagulase-negative staphylococci are important components of meat starter cultures (*60*). Recent investigations found that genes coding for staphylococcal virulence factors were rare in coagulase-negative staphylococci isolated from sausage and cheese. Of 129 strains tested, only one contained a gene coding for an enterotoxin and none were capable of producing toxic shock syndrome toxin. Some strains

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did have genetic information coding for hemolysins and some were capable of producing biogenic amines. Of somewhat greater potential concern was the presence of antibiotic resistance genes in 71% of isolates, with nearly half the strains resistant to more than one antibiotic (*58*).

METHICILLIN RESISTANCE IN STAPHYLOCOCCI

Staphylococci are notorious for rapidly evolving resistance to many antibiotics. Penicillins and other β-lactam antibiotics kill bacterial cells by interfering with cell wall synthesis. Not long after penicillin was first used to treat human infections, *S. aureus* strains producing penicillinase (an enzyme that degrades penicillin) were detected and it is estimated that now >80% of *S. aureus* produce penicillinase. Methicillin (meticillin), a β-lactam antibiotic that is not inactivated by penicillinase, was introduced in the late 1950s. But by 1961, there were reports of methicillin-resistant staphylococci in a hospital in the United Kingdom (*94*). Although epidemiology of MRSA (methicillin-resistant *S. aureus*) is currently being intensely studied, it should be noted that in most hospitals and geographic areas MSSA (methicillin-susceptible *S. aureus*) are responsible for a greater number of infections and are often also resistant to multiple classes of antibiotics.

MRSA: Methicillin-resistant *Staphylococcus aureus*

Methicillin-resistant *S. aureus* (MRSA) are resistant to all currently available β-lactam antibiotics, including penicillins, cephalosporins, carbapenems, and their derivatives. Resistance to methicillin is mediated by the *mec*A gene which encodes an altered penicillin-binding protein, located in the cell wall, that has a low affinity for β-lactam antibiotics. Since β-lactam antibiotics interfere with bacterial cell wall synthesis, this decreased binding of β-lactams renders them ineffective against MRSA. The *mec*A gene resides on a large heterogeneous mobile genetic element called the staphylococcal cassette chromosome (SCC*mec*) (*90;105*).

To date, nine SCC*mec* variations have been described but types I–V are the most common. SCC*mec* types I–III are relatively large and are typically found in strains associated with hospitals and other healthcare facilities. SCC*mec* types IV and V are smaller in size and are usually found in MRSA associated with community-associated infections. Molecular analyses of numerous MRSA strains indicate that resistance genes have been transferred to various methicillin-susceptible *S. aureus* (MSSA) strains on multiple occasions (*177*). These resistance genes have also been transferred to other staphylococcal species. Many MRSA are also resistant to other classes of antibiotics, which makes it a challenge to treat serious infections. **Table 3** lists important events in the emergence of methicillin-resistant staphylococci that infect humans.

Table 3. Significant events in emergence of methicillin-resistant staphylococci infecting humans.

Year(s)	Event	Reference
1961	1st methicillin-resistant *S. aureus* identified in UK hospital	(*94*)
1965	1st MRSA cases recorded in Australia	(*39*)
1968	1st hospital outbreak of MRSA in U.S.	(*11*)
1981	CA-MRSA in injecting drug users	(*188*)
1988	CA-MRSA in hospitalized children, Chicago	(*83*)
1991–1992	1st CA-MRSA detected in Australia	(*217*)
1992–1993	Foodborne outbreak of HA-MRSA	(*118*)
1997	CA-MRSA in otherwise healthy children in Minnesota and North Dakota	(*89*)
1999–2000	Highly virulent USA300 strain first reported in football players (Pennsylvania) and prisoners (Missouri)	(*209*)
2000	Outbreak caused by USA300; prison, Mississippi	(*36*)
2001	Foodborne outbreak of CA-MRSA	(*98*)
2003	LA-MRSA strain ST398 from pigs in Netherlands detected in humans	(*42;233*)
2008	Emergence of CA-MRSA strain USA300 in Japan	(*85*)
2008–2009	Multi-drug-resistant, dog-related strains of methicillin-resistant *S. intermedius*/*pseudintermedius* (ST71) detected in humans in U.S., Switzerland	(*108;206*)

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MRSA have spread worldwide and are now the most commonly identified antibiotic-resistant bacteria in hospitals in Europe, the Americas, North Africa, and the Middle- and Far-East (*53*). Approximately 478,000 hospitalizations in the U.S. in 2005 were associated with *S. aureus* infections and 58% of those (278,000) were caused by MRSA (*114*). MRSA is estimated to cause illness in more than 150,000 persons annually in healthcare facilities in the European Union (*124*).

Terms used to designate different MRSA strains are sometimes inconsistent or confusing. Many isolates and clones were originally named according to the geographical areas where they were first described, for example USA100 (an isolate from U.S. hospitals) and the New York/Japan clone. In 2002, a proposal was made to identify isolates according to sequence type (ST), antibiotic resistance, and SCC*mec* type. ST is determined by multilocus sequence typing (MLST) of 7 housekeeping genes in an isolate and comparing these to known sequences published on the MLST website (http://saureus.mlst.net). As of February 2011, this site contained data on 3665 isolates, representing 1861 STs. Antibiotic resistance is designated as MRSA or MSSA and the SCC*mec* type as I to V. For example the New York/Japan clone is ST5-MRSA-II and USA300 is ST8-MRSA-IV. However, many publications continue to refer to well known strains by their old names. Sequence types that differ in only a few of the genetic loci tested are grouped into clonal complexes (CCs) using BURST (based upon related sequence types) analysis. The number of the ST that is considered closest to the ancestral type is used as the CC number. Five major clonal complexes originated in hospitals (*177*). Other CCs developed from *S. aureus* strains circulating in the community, outside of healthcare facilities (*39*). CC398 is a clonal complex that originated in swine (*37;129*).

MRSA carriage and infection in humans

According to several studies, approximately 50% of people in the general population are carriers of *S. aureus* (*4;66*). However, CDC estimates that only about 1.5% of the population are carriers of MRSA. Screening of 8,446 patients entering a hospital in England for elective day-surgery indicated that, overall, 0.76% were carriers of MRSA. However, the incidence was 4 times greater for persons >60 years of age than for those < 60 years old (*51*). A much higher prevalence of 7.5% was reported for >29,000 patients admitted to acute care hospitals in Scotland. Data showed that rates were much greater for patients >65 years of age and for those admitted from other healthcare facilities (*174*). Nasal carriage of a livestock-associated strain of MRSA was 5.6% among employees of a Dutch pig slaughterhouse (*220*). Several studies have demonstrated that carriers of MRSA are at greater risk for developing serious infections compared to people who are not carriers.

MRSA, like methicillin-susceptible *S. aureus*, can cause a range of infections from relatively mild skin infections to life threatening invasive bloodstream infections, pneumonia, central nervous system infections, and pericarditis. MRSA has been a chronic problem in hospitals and long-term care facilities for over 40 years, causing severe infections, particularly in patients in surgical wards and intensive care units. Infections acquired in the community typically affect skin and soft tissues, causing mild to severe symptoms. These infections often occur in healthy younger people without the usual risk factors for healthcare-aquired MRSA, and infections often recur after treatment. Severe, invasive community-associated MRSA infections, including pneumonia, also occur. There is evidence that these more severe infections are increasing as the virulent USA300 strain spreads (*39*).

Another troubling aspect of MRSA infections and colonizations is the fact that they often persist for extended periods. Persistence of MRSA was monitored in 403 patients admitted to a German hospital more than once during a three-year period. Overall half-life of persistence was 549 days, with duration of persistence dependent on the site(s) colonized or infected (*145*).

Hospital-associated MRSA (HA-MRSA)

MRSA was first detected in a UK hospital in 1961, and was detected a few years later in U.S. hospitals and other healthcare facilities where the widespread use of antibiotics selected for bacteria carrying resistance genes. Until the 1990s, MRSA was almost exclusively an issue in hospitals and long-term care facilities, affecting surgical patients, other aged or ill residents, and some healthcare workers. Some MRSA infections occurred in non-hospitalized persons but these were traced to close contacts with persons who had been hospitalized. MRSA infections were classified by CDC as HA if they were detected in patients 48 hours after admission to a hospital or were detected in patients with a recent history of hospitalization, surgery, dialysis, or an indwelling catheter. Due to the high rate of antibiotic usage in healthcare facilities, HA-MRSA are often resistant to many classes of antibiotics (tetracyclines, sulfa-drugs, gentamicin, tobramycin, etc.) in addition to the β-lactams. Five major lineages or clonal complexes (CC5, CC8, CC22, CC30, CC45) originated in hospitals and have spread globally. Most possess one of the larger SCC*mec* types I–III, which also carry genes for resistance to other antibiotics. Type II is most common in U.S. HA-MRSA, while type III is found more often in other countries (*39;146*).

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Recently, evidence has shown that a substantial minority of HA-MRSA infections are the result of transmission outside of healthcare facilities and are caused by so-called "feral" strains that "escaped" from the hospital environment. It has been suggested that the source of these feral HA-MRSA strains may be persons who acquired the strains years ago when they received healthcare and who then became long-term carriers in the community. These strains may also have been disseminated by healthcare personnel that provide in-home care (*152*).

Community-associated MRSA (CA-MRSA)

Cases of MRSA that genuinely originated in the community were originally reported from a sparsely populated region in western Australia in the early 1990s. MRSA isolates from these cases were not resistant to multiple antibiotics, and genetic analyses revealed that they were different from other MRSA in Australia (*32;217*). More frequent reports of CA-MRSA emerged in the late 1990s. Patients often suffered skin and soft tissue infections and were otherwise healthy with no history of recent antibiotic use or residence in healthcare facilities. Examination of these CA-MRSA isolates revealed that they were susceptible to more classes of antibiotics than HA-MRSA and they generally carried smaller, more mobile SCC*mec* elements, usually types IV or V (*39*). Many CA-MRSA strains produce a toxin that attacks white blood cells called PVL (Panton-Valentine leukocidin) that is not commonly present in HA-MRSA. Although some studies suggest that PVL is an important virulence factor, others have shown that strains that do not produce PVL cause lesions just as severe as those produced by PVL-positive strains (*130*).

Several CA-MRSA clones originated in Europe (ST80), North America (ST1 and ST8), and Australia (ST30) and subsequently spread worldwide, with reported cases in countries as diverse as the Republic of South Africa, Nepal, Argentina, Saudi Arabia, Japan, and Malaysia as well as most countries in Europe (*214*). A particularly virulent clone, USA300 (ST8), first reported as cause of a prison outbreak in 2000 *(36*), now causes nearly all CA-MRSA cases in the U.S. Over a 5-year period at a Baltimore Veterans' Hospital, skin and soft tissue infections (SSTIs) caused by USA300 went from 0 in 2001 to 84% of cases in 2005. This was accompanied by a tripling of the number of hospital visits for SSTIs (*95*). Cases of USA300 (Canadian name: CMRSA10) infection have also been increasing rapidly in Canada. Annual incidence of all MRSA infections in Alberta doubled from 2005 to 2008, primarily due to the rise of CMRSA10 (*112*). USA300 is among the most virulent clones and appears to be more capable of colonizing human epithelial surfaces and causing skin and soft tissue infections than other CA-MRSA clones. USA300 contains SCC*mec* type IV and genes encoding PVL.

Originally USA300 was resistant only to β-lactam antibiotics and erythromycin. However, in the past 5 years, USA300 has acquired a number of additional antibiotic resistance genes, apparently from USA100, a common HA-MRSA strain (*147*). It has also been increasingly identified in more serious invasive infections. This strain has spread to Europe, Asia, Australia, and South America, and was the most commonly detected clone in U.S. military hospitals in Iraq (*39;87;109;209*).

CA-MRSA have been reported to cause an increasing proportion of MRSA infections, including invasive infections, in hospitalized patients (*144;219;222;244*) and in patients with end-stage renal disease (*96*) and cystic fibrosis (*208*). An analysis of discharge data on 616,375 pediatric cases of skin and soft tissue infections occurring in the U.S. during a ten-year period revealed that hospitalizations for infections caused by CA-MRSA increased dramatically from <1 case/100,000 in 1996 to 25.5 cases/100,000 in 2006. Rates of CA-MRSA were highest in the South among white children without health insurance (*67*). The emergence of CA-MRSA in healthcare settings and the appearance of HA-MRSA in the community, along with changes in virulence and the scope of antibiotic resistance, have blurred the distinctions between HA-MRSA and CA-MRSA.

More extensive information on the evolution, virulence, and epidemiology of CA-MRSA can be found in two recent comprehensive review articles (*39;164*)

MRSA carriage and infection in animals

MRSA infects a variety of animals, including livestock, companion animals, and some wild animals. **Table 4** lists some important events in the emergence of methicillin-resistant staphylococci in animals. The earliest published report of MRSA in farm animals described the detection of MRSA, in 1972, in Belgian dairy cows with mastitis (*44*). Although current methods for typing MRSA strains were not available then, it is believed that these cases resulted from human to animal transmission of HA-MRSA. Later reports documented cases and outbreaks in horses, dogs, and other animals at veterinary clinics and hospitals (*79;198*). Some later reports described animals (dogs, horses and cats) at veterinary hospitals with CA-MRSA infections (*151*).

Table 4. Significant events in emergence of methicillin-resistant staphylococci infecting animals.

Year(s)	Event	Reference(s)
1972	MRSA identified in dairy cows with mastitis	(*46*)
1972	MRSA detected in dogs in Nigeria	(*136*)
1988	MRSA identified in the ward cat of a geriatric unit in England	(*197*)
1993–1994	MRSA outbreak among horses at veterinary hospital	(*198*)
1996	Methicillin-resistant *S. intermedius* from European animals first described	(*169*)
1997	MRSA isolated from leg wound in horse in U.S.	(*79*)
1999	MRSA detected in 11 dogs with wounds, pyoderma, or surgical procedures (U.S.)	(*213*)
1999–2001	Methicillin-resistant *S. intermedius* and *S. schleiferi* detected in dogs (U.S.)	(*71;97;104*)
2001–2003	MRSA detected in chickens in Korea	(*126*)
2003	LA-MRSA strain, ST398, described in pigs and humans in Netherlands	(*233*)
2004	MRSA identified in ovine cases of mastitis in Spain	(*72*)
2004–2005	MRSA detected in rabbit and seal in Ireland, and rabbit and avian and rodent companion animals in England	(*161;176*)
2005	Horse-adapted MRSA strain described from Canadian horses	(*238*)
2006–2007	MRSA strain ST398 detected in healthy poultry in Belgium	(*160;168*)
2005–2006	Multi-drug-resistant strain of methicillin-resistant *S. pseudintermedius*/*intermedius* (ST71) reported in animals (dogs, cats, horses) in Europe and Japan	(*102;135;182;189)*
2007	MRSA strain ST398 reported in a dog in Germany	(*242*)
2007	MRSA strain ST398 reported in veal calves and workers in Netherlands	(*73*)
2009	MRSA strain ST398 detected in swine and workers in U.S.	(*203*)
2009	MRSA strain ST398 reported in horses in the UK	(*134*)

A new MRSA strain, ST398, was first detected in 2003 in swine and swine farmers in the Netherlands (*226;233*). ST398 has also been detected in pigs and pig farmers in other countries, including the U.S. (*203*), Canada (*70;111*), Portugal (*170*), Belgium (*43*), and Germany (*123*). In the past three years, ST398 has been isolated from humans, horses, chickens, and other animals, including rats living on pig farms (*37;80;221*). A different swine-associated MRSA strain is circulating among pigs and pig farmers in China (*35*).

Most livestock-associated MRSA (LA-MRSA) isolates are resistant to tetracyclines, and over 70% of 54 strains tested were resistant to three or more classes of antibiotics, leading some to suspect that the use of antibiotics in pig farming may have played a role in the evolution of this strain. All of the strains tested were PVL negative and only four strains had genes coding for enterotoxins (*101*). Pigs, veal calves, and broilers appear to be the main reservoirs for ST398 (*50*).

Several studies reported that exposure to horses is a risk factor for human infection with certain horse-adapted MRSA strains *(26*). A majority of horse isolates in Canada belong to a subtype of the Canadian epidemic strain, MRSA-5, which has a type IV SCC*mec*. This strain is also present in horses in other countries and has been reported in numerous people working with horses (*26;238*). Horses can also be infected with ST398, and an outbreak of ST398 affecting 13 horses at a veterinary hospital in Finland resulted in one infected employee (*187*).

Swine. Of all livestock, swine appear to most commonly harbor MRSA. In most cases, MRSA does not appear to seriously affect the health of pigs but there have been reports of MRSA in pathological lesions in pigs (*149*). In 2005, a high prevalence of a new livestock-associated MRSA, ST398, was reported in pigs at Dutch slaughterhouses. This strain was apparently derived from a methicillin-sensitive *S. aureus* known to be associated with pigs and was designated livestock-associated or LA-MRSA (*42*). Data from the EU on MRSA in 4,597 swine holdings (breeding and production) in 26 countries revealed that overall 14% of breeding and 27% of production herds tested positive for MRSA. However, in some countries, no herds tested positive while in others, up to 51% of holdings contained MRSA. Highest prevalence of MRSA was recorded in Spain, Germany, Belgium, and Italy. LA-MRSA (ST398) accounted for 92.5% of isolates tested (*54*).

Other recent surveys report:

- 45% of farms and 25% of pigs in Canada carried MRSA; 59% of isolates identified as ST398 (*111*)
- 70% of German pig farms tested positive for MRSA; all were ST398 (*123*)

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- 45% of Italian farms tested positive for MRSA; ST398 was most common strain but several other types were identified (*13*)
- One U.S. study reported that MRSA was present on 70% of pigs sampled at one production facility and none of the pigs at another facility. Isolates were ST398 (*203*). Another study indicated that MRSA prevalence in pigs at 5 U.S. farms ranged from 0 to 33% (*153*). Data are currently available only for a few swine holdings in the U.S.
- A survey of swine in Japan found a low prevalence of MRSA (0.9%) in nasal samples and did not detect ST398 (*10*)

Factors positively associated with prevalence of MRSA in swine include larger herd sizes and greater numbers of imported pigs (*55*). "Open" versus "closed" farms also have more colonized pigs, perhaps because of importation of pigs by open farms from MRSA-containing herds (*57*). In a German study, conventionally raised pigs were found to have a higher frequency of MRSA colonization than organically raised pigs (*148*). Hygiene practices on farms also appear to affect prevalence rates (*157*).

Cattle. *S. aureus* is a significant cause of mastitis in cows and small ruminants (*230*). However, the prevalence of methicillin-resistant strains in European cows appears to be low, although there is intercountry variation (*6;82*). MRSA (probably of human origin) was first detected in Belgian cows in 1972 (*44*). Recent studies have demonstrated that ST398 is present in German cows (*64*), Dutch veal calves (*73*), and Belgian cows (*229*). CA-, HA-, and LA-MRSA were all recently detected in bulk tank milk from cows in Minnesota (*78*). Human-associated MRSA strains have also been detected in mastitic cows in Hungary (*100*) and Turkey (*215*).

Poultry. Little information is available on the occurrence of MRSA in chickens, and no reports were found on MRSA in turkeys. Methicillin resistance was first observed in *S. aureus* isolates from chickens in Korea in 2001–2003 (*126*). MRSA was later detected in broiler chickens in Belgium (*160;168*) and in broilers but not in breeder chickens in the Netherlands (*156*). These isolates were identified as the livestock-associated strain, ST398.

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Horses. MRSA was first reported in a horse with a surgical wound in 1996 (*79*). Eleven horses were infected with MRSA at another veterinary hospital with a strain that appeared to be identical to those isolated from staff members (*198*). Surveys of horses on farms during the past five years usually report a low prevalence of MRSA of 0–4.7%. A higher prevalence (up to 12%) has been observed in horses admitted to veterinary hospitals (*212;236;240*). Transmission of MRSA from humans appeared to cause the early infections in horses. The most common MRSA strain now identified in horses, Canadian CMRSA-5 or USA500, is a member of the ST8 or CC8 clone. Although this clone appears to be of human origin, it seldom causes illness in humans and now appears to be horse-adapted. It is the most prevalent MRSA strain detected in horses globally. Unlike other farm animals that are primarily transported only for slaughter, horses are transported internationally for breeding, racing and show-jumping, and these movements have contributed to the spread of this clone *(2*). Recently there have been reports of the livestock-associated strain ST398 in horses (*136;223*), including a veterinary hospital outbreak affecting 13 horses in Finland (*187*).

Dogs and cats. MRSA was first detected in companion animals in Nigeria in 1972. This strain was similar to human isolates (*136*). In 1988, a ward cat in a geriatric rehabilitation unit in England apparently became colonized after contact with a resident and then served

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as a reservoir spreading MRSA to other human residents (*197*). MRSA was later detected in dogs with surgical wounds or skin infections in 1998 (*71;213*). Surveys generally indicate that prevalence of MRSA in companion animals is low (<2%) (*1;129*) and MRSA in companion animals are primarily HA-MRSA. Epidemiology of MRSA in companion animals was recently reviewed (*136*).

Cases of MRSA infection in dogs and cats usually involve lesions in the skin or ears but invasive infections sometimes occur. Healthy dogs and cats can also carry MRSA asymptomatically. However, it is suspected that carriage is only transient or intermittent and that carriage is lost with time and the lack of selective pressure (*237*). The use of veterinary drugs and IV catheters were identified as risk factors for MRSA infections in dogs (*63;143*). Many early reports of companion animals infected with MRSA implicated HA-MRSA originating from humans but both CA-MRSA (*224*) and LA-MRSA (*242*) have caused infections in dogs.

Pets can acquire MRSA from humans and also be a potential reservoir for human MRSA infection. Similar MRSA strains have been detected in dogs and their owners, but surveys of dogs or humans colonized with MRSA have demonstrated that only a small number of human-dog pairs are infected with the same MRSA strain (*17;62*). HA-MRSA strains have been detected in therapy dogs and cats visiting human long-term care facilities (*33;128*). MRSA does not appear to spread easily from dog to dog (*137*).

Other animals. In addition to the companion animals and livestock described above, MRSA has been detected in avian pets, including a parrot (*176;178*), goats (*6*), sheep (*72*), farmed fish (*9*), wild rats living on a farm (*221*), a zoo elephant (*92*), seals, dolphins and walrus from marine parks/sanctuaries (*61;161*), and guinea pig, rabbit, bat, and turtle in a veterinary hospital (*234*). Origins of the MRSA were unknown in some cases but appeared to be from human caretakers for the birds, seal, and elephant calf and from pigs for the farm rats.

MRSA in foods

MRSA hase been detected in a variety of foods from countries in North America, Europe and Asia. Foods may be contaminated by human strains of MRSA present in meat processors and other food handlers. Meat may also be contaminated by MRSA carried in animals as demonstrated by a study following pigs from lairage through slaughter to commercial pork products (*153*). Another study investigating MRSA on German pigs at slaughter and at several steps during processing found that 65% of pigs were positive at stunning. However, only 6% of carcasses on the slaughter line, 4.2% of meat samples during processing, and 3% of finished meat products tested positive (*16*).

Some studies detected primarily HA-MRSA strains in foods, indicating that humans were the probable source (*81;171;216;239*) and others detected primarily LA-MRSA (*15;40;229*). An Australian study found that *S. aureus* isolates (not MRSA) on beef carcasses at an abattoir were indistinguishable from strains on workers' hands. It appeared that the workers contaminated the carcasses during evisceration and processing (*231*). However, in the Netherlands, a more recent study reported that meat handlers were not colonized with MRSA and that the MRSA detected on meat were LA-MRSA (*41*).

Table 5 summarizes results from surveys in several countries for MRSA in raw meats. There are also reports of low levels of MRSA in chicken meat in Japan and Jordan *(113;172*). Most of this research was aimed at detecting the presence of MRSA, and contamination levels were not quantified. A recent Canadian study found that most positive meat samples contained <100 cfu/g (*239*), and a recent Dutch study reported that MPN (most probable numbers) of MRSA in meat ranged from 0.06 (veal) to >10 (pork) bacteria/g (*41*). It should be noted that sampling and culture methods differed among the studies so that results are not strictly comparable. Within most studies, incidence of MRSA was less common in poultry than in beef and pork (*132;139;239*).

Since *S. aureus* is a known cause of mastitis in ruminants, several studies analyzed milk from cows with mastitis and detected MRSA (Table 5). Some of these strains also produced enterotoxins. Pasteurization kills *S. aureus* so this would be a potential problem only for raw milk and raw milk products.

MRSA has also been detected in other foods not included in Table 5, for example, goat milk (*49*), lamb and mutton (*40;172*), rabbit and wild boar meat (*139*), minimally processed vegetables (*200*), and fresh fish (*175*).

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Table 5. Reported incidence (% positive) of MRSA in beef, pork, chicken (c), turkey (t), and raw milk.

Location	Beef	Pork	Poultry	Ref.
U.S.	3.3	5.6		(*171*)
Canada	5.6	9.6	1.2	(*239*)
Netherlands	10.6 (beef) 15.2 (veal)	10.7	16.0 (c) 35.3 (t)	(*40*)
Netherlands	0	3.1		(*227*)
Germany	33.3	10.5	20.5 (c) 31.6 (t)	(*119*)
Germany	9.6 (beef and pork)			(*192*)
Spain	2.2 (veal)	1.8	0.7 (c) 0 (t)	(*139*)
Poland	0	3.9	0 (t)	(*23*)
Taiwan		4.3–11.3	0.3–7.8 (c)	(*132*)
Korea	1	0.3	0.3 (c)	(*131*)
Korea	5	0	0	(*175*)

Location	Raw milk	Ref.
Belgium	9.3	(*229*)
Italy	12.9	(*15*)
India	1.2	(*121*)
Japan	1.1	(*81*)
Turkey	17.2	(*216*)
Poland	1.1	(*23*)
U.S. (Minnesota)	5.3	(*78*)

Methicillin resistance in other species of *Staphylococcus*

Methicillin resistance in canine *S. intermedius* isolates was first reported in the mid-late 1990s (*71;169*). For several years, these strains appeared to constitute a small proportion of *S. intermedius* isolates from animals, and although they exhibited some resistance to other drugs there were other antibiotics effective against these bacteria. Early reports of methicillin-resistant *S. intermedius* from companion animals were probably isolates of methicillin-resistant *S. pseudintermedius* based on the recent changes to *Staphylococcus intermedius* group taxonomy (*190*).

Starting in 2006, there were more frequent reports of methicillin-resistant *S. pseudintermedius* (MRSP) and methicillin-resistant *S. intermedius* group (MRSIG) strains that were resistant to multiple classes of antibiotics, in addition to the β-lactam group (*102;135;183;189*). *S. pseudintermedius* ST71 became established as the most common multidrug-resistant strain in Europe during this time (*182*). Increasing prevalence of multidrug-resistant strains was also documented in an examination of clinical samples from dogs in Tennessee during the period from 2001 to 2005. Methicillin-resistance frequencies in *S. intermedius* and *S. schleiferi* isolates in 2005 were 15.6% and 46.6%, respectively (*97*).

Published reports generally indicate a low prevalence of MRSP in dogs and cats (*240*). However, a survey of healthy dogs in Hong Kong indicated a 17% prevalence of methicillin-resistant *S. intermedius* (*52*), and a study at a veterinary hospital reported that 30% of *S. pseudintermedius* isolates were methicillin resistant (*189*). A recent study of 103 canine methicillin-resistant *S. pseudintermedius* isolates from Europe and North America revealed that there were two major clonal lineages: ST71 in Europe and ST68 in North America. Nearly all strains were resistant to nine classes of important veterinary antimicrobials. Over 70% of these isolates contained the SCC*mec* element II-III. Types III, IV, V, and VII were present in other strains (*167*).

Methicillin resistance has been detected in other staphylococci, including *S. schleiferi* and *S. epidermidis* from dogs (*104*), a human clinical isolate of coagulase-negative *S. lugdunensis* (*116*), and several staphylococcal species on freshwater fish in Greece (*3*).

MRSP/MRSIG strains are seldom isolated from human food but there is one report of MRSIG in camel meat in Jordan (*5*). Methicillin-susceptible *S. intermedius* in a butter blend caused a foodborne outbreak in 1991 (*110*), indicating that MRSIG is a potential cause of foodborne staphylococcal intoxication.

EPIDEMIOLOGY OF MRSA AND MRSP / MRSIG IN HUMANS

Infections acquired in healthcare facilities

Methicillin-resistant staphylococci first emerged in 1961 in response to the use of methicillin in hospitals.

For most of the next 30 years, many strains of HA-MRSA evolved in healthcare facilities, and certain strains became increasingly prevalent endemic pathogens in hospitals in Europe and North America as infected or colonized patients shed MRSA into the surrounding environment and the bacteria then were spread by contaminated equipment and the hands of healthcare workers. MRSA continued to evolve in, and spread to, healthcare facilities around the world. By 1991, MRSA accounted for 29% of all clinical bacterial isolates in U.S. hospitals (*166*). In the U.S., about 2% of *S. aureus* infections in intensive care units were MRSA in 1974. This increased to 22% in 1995 and to 64% in 2004 (*117*). Data collected by CDC from 463 hospitals in the U.S. in 2006–2007 revealed that *S. aureus* caused 15% of healthcare-associated infections, particularly surgical site infections and ventilator-associated pneumonia. Methicillin-resistance was detected in 56.2% of the *S. aureus* strains responsible for these infections (*84*). Recently, concentrated efforts to prevent nosocomial transmission of MRSA in some hospitals appear to be reducing the proportion of *S. aureus* infections caused by MRSA; for example, from 52% to 39% over 4 years in one hospital system (*75*). Incidence of serious MRSA infections is also decreasing in U.S. hospitals (*19;103*).

MRSA can be transmitted in hospitals by person-to-person contact or, in one outbreak, by food. But MRSA infections acquired in hospitals are often invasive with serious effects because the bacteria bypass protective layers of skin and are introduced directly into the body through needles, tubes, or surgical procedures. Surgical site infections (SSIs) are estimated by CDC to complicate about 5% of surgeries performed in the U.S. each year, costing the healthcare system approximately $10 billion. MRSA is increasingly identified as the cause of SSIs; one study demonstrated that each SSI caused by MRSA results in an average of 23 additional days in the hospital and costs as much as $60,000 (*7;241*). Other studies of neonates in intensive care units (*204*) and patients with nosocomial pneumonia (*162*) demonstrated that MRSA infections increase mortality as well as causing longer hospital stays and much higher costs for care.

Some countries, other than the U.S., conduct nationwide surveys of hospitals to determine prevalence of MRSA. Results from the 2008 Canadian Ward Surveillance study (CANWARD) demonstrated that about 27% of *S. aureus* strains tested were MRSA and 68.8% of the MRSA isolates were HA-MRSA (*244*). A national hospital survey in 2007 in Australia reported that nearly 33% of *S. aureus* infections were due to MRSA and, of these, 76% were HA-MRSA strains and 24% were CA-MRSA strains (http://www.agargroup.org/surveys). National data are not available for many other countries, and information from individual hospitals demonstrates a range in the prevalence of MRSA; for example, a 69% prevalence rate in a tertiary hospital in Nepal (*210*) and a 45.5% prevalence rate in a community hospital in Japan (*122*). It should be noted that data from individual hospitals and different countries are not always comparable because in some cases all *S. aureus* infections in all patients are reported while other studies are restricted to reports on patients in intensive care or surgical wards.

Some European countries, including Denmark, Finland, the Netherlands, Norway, and Sweden, now have a very low prevalence of MRSA infections and fewer than 3% of clinical *S. aureus* isolates are MRSA. These countries have implemented intensive national "search and destroy" programs that reduce the incidence and transmission of MRSA in hospitals (*24;228*). According to data from 28 European countries compiled by EARS-NET (European Antimicrobial Resistance Surveillance Network), the proportion of MRSA among total *S. aureus* isolates has stabilized or declined in most countries. However the proportion of MRSA remains >25% in 10 countries (*53*).

Although efforts to control MRSA in healthcare settings appear to be achieving success, some countries with a low prevalence of MRSA, including Iceland and Denmark, have seen recent increases in numbers of MRSA infections as the epidemiology of MRSA changes (*86;201*). Newer LA- and CA-MRSA strains that originally evolved in human or livestock outside of healthcare institutions are increasingly being identified as the cause of infections acquired in hospitals (*115;123*). The CANWARD surveillance studies showed that the proportions of CA-MRSA among all MRSA isolated in Canadian hospitals increased from 9.1% in 2005–06 to 19.5% in 2007 and 27.6% in 2008 (*244*).

Infections acquired in the community

Prior to the 1990s, most cases of MRSA that were acquired outside of healthcare institutions could be traced to long-term treatment with antibiotics or contact with someone who had been in a healthcare facility. Strains causing these infections were typical HA-MRSA strains resistant to multiple classes of antibiotics. With the evolution of CA-MRSA strains and animal-associated MRSA strains, infections acquired outside of healthcare institutions, in the community, were caused by a more diverse array of strains of MRSA. A recent comprehensive review of CA-MRSA describes the emergence of CA-MRSA strains and their virulence, epidemiology, treatment, and prevention (*39*). Only a brief summary of the important aspects of MRSA epidemiology will be presented here.

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Community acquired infections often occur in young, healthy people and cause skin and soft tissue infections (SSTIs) or pneumonia rather than invasive disease. Data from the 2008 Australian survey noted that the median age of people infected with community-associated strains of MRSA was 35, while the median age for hospital-associated cases was 74. Similar age associations were reported for MRSA infections in Alberta, Canada (*112*). Groups of people living in close quarters, such as children at day care centers, military trainees, family members, prisoners, and athletes, and also persons at a low socio-economic status, such as inner city residents, Native Americans and other indigenous populations, are at higher risk for acquiring MRSA infections in the community.

There are no national surveillance programs for collecting data on MRSA infections and colonization in the general population but CDC estimates that although nearly 50% of people carry *S. aureus* in their nasal passages, a much smaller number, approximately 1.5% of the general population, are asymptomatic carriers of MRSA. Nasal colonization with MRSA has been shown to increase risk for infections by four-fold (*185*).

Examples of clusters and outbreaks of MRSA acquired in the community include the following:

- Over a 5-year period, 3,531 cases of MRSA occurred in service members and recruits (without recent surgery or hospitalization) at a large army training installation. Over 80% of infections were caused by CA-MRSA strains (*155*).
- An outbreak of MRSA occurred among players on a high school football team who were living in a school gymnasium during a training camp. Sharing towels, skin injuries, and higher BMI (body mass index) levels were identified as risk factors (*107*).
- Food is not a common vehicle of infection for MRSA. Only one foodborne community outbreak has been described, in Tennessee in 2000. Food involved was contaminated by a colonized food handler (*98*).

In the U.S., CA-MRSA strain USA300 causes the great majority of community-associated infections while CA-MRSA strains in Europe and Australia are more diverse with multiple important clones described. Rates of CA-MRSA are also much lower in Europe as compared to the U.S. (*163*). USA300 appears to be spreading to other countries in Asia, Europe, and South America and to Australia, and there is concern that this virulent strain may greatly expand its range and increase the burden of community-associated MRSA infections worldwide.

Community-associated MRSA infections have been increasing in developed countries but they are not as commonly reported in less developed countries, which may be a result of fewer laboratories with the capability of typing MRSA strains. A recent investigation of skin and soft tissue infections in Cambodian children identified numerous CA-MRSA infections (*28*). In Beijing, China, CA-MRSA was found to cause about 4% of SSTIs (*243*).

Infections acquired in the community can also come from animals. Animals may be a reservoir for human infection by MRSA since many different species can carry or have infections due to MRSA. Recently recognized at-risk human groups include veterinarians, livestock handlers and pet owners (*39*). For example, due to the increased prevalence of MRSA in some horse populations, horses may serve as a reservoir for acquisition of MRSA by people (*238*). Typing of isolates of MRSA from veterinary personnel and animals in Ireland detected a horse-adapted CC8 strain in 23 horses and 12 humans, including 7 people who worked closely with MRSA-positive horses (*2*). In addition, persons in contact with pigs are more susceptible to acquiring infections due to LA-MRSA. A high prevalence of nasal carriage of LA-MRSA strain, CC398, was detected in pig slaughterhouse workers in the Netherlands. Working with live pigs was the most important risk factor but exact transmission routes from animals to humans have yet to be determined (*220*). MRSA can also be transmitted between cows and humans (*100*).

There are also reports of MRSP infections in humans believed to be the result of contact with pets that were carrying or infected with MRSP (*240*). It may be possible for commensal methicillin-resistant staphylococci in dogs to serve as a reservoir for transmission of antimicrobial resistance determinants to susceptible strains of staphylococci in people (*240*).

Routes of infection

Staphylococci are spread among humans and animals and between species either by direct physical contact or indirectly through clothing, towels, equipment, food, air, or surfaces contaminated by infected or colonized persons or animals.

Person–person

Hospital outbreaks of MRSA have been traced to lax hygiene practices among healthcare workers, and MRSA outbreaks in the community often occur in groups of people living in close quarters where they may transmit MRSA through direct physical contact. MRSA transmission in a UK hospital was audited by swabbing patients' skin and their environment and also the hands of healthcare workers. MRSA was transmitted from a source, most commonly a patient's

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skin, to other patient skin areas, furniture, or note pads by the hands of healthcare workers in 22 of 24 cases. In one case a doctor entering an intensive care unit with MRSA on his/her hands contaminated a notes trolley near a patient (*140*). Another study found that the frequency of transfer of MRSA from the skin of a colonized patient to a gloved hand was 40% (*207*).

A cluster of CA-MRSA cases (strain USA300) in the Netherlands occurred in a beautician, her customers, family members, and contacts. Skin treatments (waxing) performed by the beautician were identified as the likely mode of transmission (*88*).

Airborne transmission

MRSA is present in the nose and on the skin and is shed into the environment by infected or colonized people and animals, indicating that airborne transmission is a possible route for infection. MRSA strains, identical to clinical isolates from patients, were detected in the air of hospital rooms (*68*). MRSA was detected in all of 57 samples taken of the air in pig fattening facilities. MRSA constituted about 0.1% of mesophilic bacteria detected in the air samples (*195*).

Animal contact

LA-MRSA ST398 was first described in pigs in the Netherlands in 2003 (*42;233*). Subsequent studies reported detection of this strain among farmers, and a survey indicated that human carriers of ST398 were 12.2–19.7 times more likely to be pig or cattle farmers than to work at other jobs (*226*). Whereas the overall number of MRSA infections in the Netherlands appears to have stabilized, an increasing percentage of MRSA infections in the country are caused by this livestock-associated strain, even among people without known exposure to pigs or veal calves. Total MRSA isolates submitted to the national laboratory in the Netherlands in 2008 numbered 2693. Of these, 42% were identified as the LA-MRSA ST398 strain as compared to 30% in 2007 and 14% in 2006. Only 29% of people surveyed indicated contact with live pigs or veal calves (*76*). A recent study in Germany found that 86% of farmers and 45% of veterinarians exposed to pigs with ST398 also carried this strain. However, it was not readily transmitted from the workers to others as only 4–9% of family members and other close contacts tested positive for ST398 (*38*).

Horses may be colonized or infected with an uncommon horse-adapted MRSA strain, CMRSA-5, and several studies have reported this strain in horse farmers and veterinarians (*2;238*).

Companion animals may also be carriers of MRSA. MRSA was first detected in a companion animal in a ward cat in a geriatric rehabilitation unit in England. The cat was apparently infected by a resident and then served as a reservoir spreading the infection to other human residents (*197*). HA-MRSA strains have been detected in therapy dogs and cats visiting human long-term care facilities and may be a souce of infection to residents (*33;128*).

Similar MRSA strains have been detected in dogs and their owners, but surveys of dogs or humans colonized with MRSA have demonstrated that only a small number of human–dog pairs are infected with the same MRSA strain (*17;62*). Evidence indicates that pets can acquire MRSA from humans and that the reverse is also true.

Contaminated equipment and surfaces

Surfaces in both homes (*196*) and healthcare facilities may harbor MRSA. For example, MRSA was detected on surfaces in 7 of 25 ambulances tested (*199*). Transmission of MRSA in healthcare facilities can occur by touching contaminated surfaces. Experiments have shown that gloved hands can pick up MRSA from bedrails, call buttons, tables, and phones at a frequency of 45% (*207*). Community-associated MRSA strains on contaminated needles have been transmitted among illicit drug users. A recent study of persons with MRSA in veterans' hospitals revealed that illicit drug users were more likely to be infected with USA300 (CA-MRSA) than non-drug users (*120*). Non-sterile equipment was cited as the cause of CA-MRSA infections in tattoo recipients in several states (*138*).

Numerous reports have also detailed outbreaks in high school and collegiate athletes where MRSA was detected on equipment and surfaces in athletic facilities as well as on towels and clothing (*18;21;34;173*).

Patients with end-stage renal disease (ESRD) are particularly vulnerable to invasive *S. aureus* infections because their blood must be treated using dialysis machines at least three times per week to remove toxins. These patients are frequently hospitalized, receive long courses of antibiotic treatment, and 14% die annually as a result of infections. Incidence of invasive MRSA was estimated at 45.2 cases/1000 population among dialysis patients, the highest for any patient population and about 100 times greater than incidence in the general population (*30*). An increasing proportion of MRSA infections in ESRD patients is due to community-associated MRSA strains (*96*).

Contaminated food

MRSA strains have been detected in meat and may also be present in a variety of other foods. The origin of these contaminants has been traced to infected / colonized food handlers in some outbreaks (*98;118*). Studies have demonstrated that meat can also become contaminated during slaughter and processing of animals carrying MRSA (*16;153*). In some surveys, MRSA detected on meat was identified as the livestock-associated strain, ST398 (*41*).

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Significance of MRSA contamination of foods remains uncertain. If meat and other foods are cooked properly, MRSA cells will be killed. However, as with enterotoxigenic MSSA strains, under conditions of temperature abuse MRSA cells could grow in foods, produce heat-stable enterotoxins, and cause foodborne intoxication. In some individuals whose normal flora has been depleted by antibiotic treatment, MRSA cells on ready-to-eat foods, including processed meats, cheeses, and fresh produce, could cause staphylococcal enterocolitis. Finally, MRSA present on foods could potentially cause skin infections in food handlers. The difficulty in treating infections caused by pathogens resistant to multiple antibiotics should motivate efforts to prevent contamination of food with MRSA.

To date, there have been only two reported outbreaks associated with MRSA-contaminated food. A community outbreak of foodborne illness caused by CA-MRSA occurred in Tennessee in 2000 (*98*). Identical MRSA isolates were recovered from 3 ill persons, the coleslaw they purchased from a convenience store deli, and the nose of a food handler at the convenience store. This strain produced enterotoxin C. The second reported outbreak of MRSA occurred in a Dutch hospital and affected 27 patients and 14 healthcare workers from 1992 to 1993, resulting in five deaths. Epidemiological investigations indicated that a colonized food handler apparently contaminated food (a peeled banana tested positive for MRSA) served to hospital patients, and some nurses may have inadvertently spread the bacteria to different wards (*118*).

MRSA does not appear to be transferred readily from meat to meat handlers. It was not detected on hands or in noses of 89 persons working in cold meat processing facilities or institutional kitchens in the Netherlands even though 14% of samples of meat (veal, pork, chicken) that they worked with did contain MRSA. Most of the MRSA isolates were identified as ST398, livestock-associated MRSA (*41*).

Other methicillin-resistant staphylococci could potentially cause foodborne intoxication but no cases have been reported yet. One outbreak in southwestern U.S. in 1991 was traced to methicillin-susceptible *S. intermedius* producing type A enterotoxin in a butter blend (*110*). Methicillin-resistant *S. intermedius* was detected in camel meat in Jordan (*5*). MRSIG strains have been detected in horses but are not usually present in livestock (*240*).

The advent of antibiotic-resistant staphylococci poses additional potential food safety and occupational health concerns. MRSA and MRSIG have been detected in livestock, companion animals, and wild animals and pose a potential risk to people working with animals. In addition, the presence of MRSA in food-producing animals and the detection of MRSA in a small percentage of retail meat samples raises concerns about the potential food-borne transmission of MRSA.

CONTROL AND PREVENTION

Prevention of staphylococcal infections/intoxication requires strategies to interrupt various modes of transmission. Essentially these control programs include improvements in personal hygiene practices among healthcare workers and food handlers, decontamination of equipment, surfaces, and clothing, judicious use of antibiotics, proper cooking and storage of foods, and screening programs.

Hospital and healthcare programs

Increased morbidity and mortality among hospital patients infected with MRSA has led to development of some effective control procedures, and strict enforcement of MRSA control policies has been found to decrease rates of MRSA infection in hospitals in 10 European countries (*77*). An important feature of these MRSA-control programs is screening of patients at admission to ascertain which patients are carriers of MRSA so they can be isolated and treated to prevent transmission to other patients.

For example, incidence of MRSA in the Netherlands is extremely low (0.7% in 2008) and this is attributed to effective implementation of the national MRSA guidelines in every healthcare setting for more than 20 years. These guidelines recommend prudent and restrictive use of antibiotics and an infection prevention program called "search and destroy." All patients and healthcare workers are screened for MRSA and if tests are positive they are isolated and treated to eliminate MRSA. Policies for cleaning and disinfection are also strictly followed (*225*). A cost–benefit analysis in a Dutch hospital concluded that this program prevented 36 cases of bacteremia annually and 10 deaths and saved >200,000 euros/yr (*228*).

Similar programs have been implemented in other European countries with similar success in preventing hospital-associated infections. However, there has been discussion recently regarding the merits of adopting such a strict control program. The "search and destroy" programs require a lot of resources in testing all patients, keeping them in isolation until test results come back, and continuing to isolate them if tests are positive (*22*). Patients infected with or carrying MRSA must then be treated to eliminate MRSA. Some have questioned the cost effectiveness of testing all incoming patients and instead recommend testing only certain patient populations, such as those entering intensive care units or those scheduled for surgery. Others recommend strengthening general infection

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control procedures throughout healthcare facilities to reduce all nosocomial infections. Still others point out that because increasing numbers of MRSA infections are acquired outside of healthcare settings, an effective MRSA control program will need to address prevention of infections arising in the community as well methods to control infections in hospitals.

Another strategy to reduce MRSA in healthcare facilities is the reduction of antibiotic use to lower selection pressure for MRSA. This may be a useful procedure as a decrease in antibiotic use in a Taiwanese hospital from 2004 to 2009 was significantly correlated with fewer MRSA infections in patients (*127*).

Sanitizers and surface treatments

Several sanitizers can be used to control methicillin-resistant staphylococci. Use of alcohol hand rubs has been significantly correlated with decreasing rates of MRSA infections (*186;205*). Chlorhexidine is also an effective antiseptic but some strains of MRSA have developed resistance to it (*12*). Mist application of a mixture of chlorine dioxide and a quaternary ammonium compound was found to inactivate MRSA on several environmental surfaces (*25*). Nonthermal plasmas were shown to be effective in inactivating both planktonic and biofilm-associated MRSA (*20;99*). Swimming pools containing chlorinated water, biguanide-treated water, or salt water did not permit survival of MRSA (*74*).

Certain chemicals added to surface materials exert toxic effects on bacteria. Copper is a known bacteriocide, and copper-based biocide solutions (*141*) and copper incorporated into surfaces (*235*) both effectively killed MRSA. Silver is also bactericidal and a TiO_2-Ag composite completely inactivated MRSA within 24 hours (*158*). Data comparing bactericidal effects of Cu- and Ag-containing materials, under different conditions of temperature and humididity, indicate that Cu may be more effective in indoor environments (*150*). A nanocomposite film incorporating a cell wall degrading enzyme has been developed and found to be effective in killing MRSA. This may prove useful in hospitals and other areas where infection control is critical (*165*).

Prevention of foodborne intoxication

Preventing staphylococcal intoxication by MRSA strains requires the same precautions as for MSSA strains. Efforts should be made to prevent contamination throughout the food production, processing and preparation chain. Workers have been implicated in many outbreaks of foodborne disease. They may shed bacteria and viruses, even when asymptomatic and several weeks after they have recovered from an illness. Improved hygiene precautions, consistently practiced by persons in food preparation and processing, would significantly improve safety of foods (*211*). Foods also must be cooked properly and refrigerated or kept hot until consumption. A recent analysis of growth requirements noted that *S. aureus* can grow at a water activity of 0.867 and at temperatures as low as 8°C (*218*).

DATA GAPS AND RESEARCH NEEDED

- Characteristics of different methicillin-resistant staphylococci should be compared to common methicillin-sensitive strains to determine any differences in growth in different foods and sensitivity to heat, sanitizers and other control methods and why/how certain strains are adapted for colonization of particular animal species.
- More data are needed on prevalence and concentration of MRSA in meats and the MRSA strains present to determine sources of contamination—human or livestock. Because the ecology of MRSA is changing, MRSA levels in foods should be monitored over time.
- Studies should determine whether food handlers can acquire MRSA from preparing meat and other foods containing MRSA.
- Risk factors associated with MRSA and MRSIG infections in animals need to be better characterized so that animal infections and potential transmission to humans can be better controlled.
- Animal husbandry practices and slaughtering methods vary in different countries. Research should determine whether some methods result in greater contamination of meat.
- Some studies in the U.S. and other countries reported that there is a relatively high prevalence of MRSA on some farms and a low prevalence or absence of MRSA on other farms. The reasons for this should be investigated.
- Important transmission pathways are not completely understood, including from animals to humans, among people in the community, and potential aerosolization and airborne spread.
- Genetic studies of the different SCC and MLST types would provide more information on important virulence and resistance factors.
- Potential for horizontal transfer of SCCmec among staphylococci is not well understood but may be an important factor in increasing prevalence of antibiotic resistance.

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SUMMARY AND PERSPECTIVE

S. aureus is commonly found in humans, with approximately 50% of the population colonized in the nasal passages or on the skin. A much smaller percentage, about 1.5% of people, are colonized with MRSA. While many people harboring *S. aureus* are asymptomatic, they may pass these bacteria to others directly or contaminate food, clothing, towels, and other surfaces. Carriage of MRSA increases risk for serious infections that are difficult and more expensive to treat. Methicillin resistance also occurs in other staphylococci, including *S. intermedius* and *S. pseudintermedius* that colonize and infect pets and other animals.

Enterotoxigenic staphylococci (including MRSA) that grow in foods can cause foodborne intoxication. Occasionally these staphylococci, when ingested, produce enterotoxins in the intestines, causing enterocolitis in people whose normal flora has been depleted. In hospitals, *S. aureus*, including MRSA, cause a large proportion of invasive infections when they enter the body through surgical wounds, catheters, or other medical devices or procedures. In the community, staphylococci primarily cause pneumonia and skin and soft tissue infections. Some MRSA strains are highly virulent, and MRSA infections cause significant morbidity and mortality.

Methicillin resistance was originally reported in hospitals, and HA-MRSA strains are usually resistant to many other antimicrobials besides penicillin-related compounds. CA-MRSA strains evolved outside of healthcare facilities and are usually sensitive to most other antibiotics. Many of these strains have spread globally. Methicillin resistance has also emerged in other environments where antibiotics are used, including veterinary hospitals (MRSP and MRSIG) and livestock operations (LA-MRSA). Methicillin resistance genes are carried on a mobile genetic element that can be transferred to other staphylococcal species.

Sources of methicillin-resistant staphylococci for human infections include colonized or infected people, companion animals, and livestock and objects and surfaces contaminated by them. Staphylococci have been detected in the air, indicating that aerosolization of staphylococci occurs and is potentially a transmission pathway in healthcare facilities and farms with large numbers of colonized animals. Since MRSA has been detected in retail foods and on animal carcasses at slaughter, food may also be a source of infection to food handlers or of foodborne intoxication to consumers. Surveys to date indicate that the prevalence of MRSA in meat is low and the concentration of bacteria in food samples is also low. In some cases MRSA contamination of foods appears to result from MRSA present in dairy cows or in animals before slaughter, and in other cases from human food handlers.

Although MRSA and MRSIG contamination of foods is not currently a significant problem, these bacteria continue to evolve and spread in the environment. MRSA was originally isolated in a UK hospital in 1961, community-associated MRSA strains appeared in the early 1990s as did methicillin-resistant *S. intermedius* (*pseudintermedius*) in companion animals, and livestock-associated MRSA strains were first described in 2003. Ongoing monitoring of methicillin-resistant staphylococci in foods and the environment would be prudent.

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