MRSA:
We Don't Want It, But Can We Eradicate It?

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Objectives:

1) Briefly characterize the problem of methicillin-resistant *Staphyloccoccus aureus* (MRSA) colonization and infection
2) Outline methods of prevention and treatment modalities for MRSA
3) Describe the evidence for "search and destroy" strategy to controlling nosocomial MRSA infections

In this review, the author seeks to answer the question, "Should we eradicate MRSA in patients?" with the focus on the Dutch model of eradication. In order to fully answer this complex question, several questions need to be answered in advance, including: Is MRSA a worthy target of intervention? Is the distinction between community-associated and hospital-associated MRSA significant? Should eradication be a goal for all patients or limited to specific populations? What are the potential tools of eradication? The evidence for eradication methods is then reviewed.

MRSA: (Now No Longer Just a) Nosocomial Infection

Prevalence and cost of infection

MRSA was first identified in 1961[1] (in the United States in 1968[2]) as a hospital-acquired infection shortly after penicillinase-stable β-lactams and semisynthetic penicillins became available in the late 1950s.[3] Within several decades, an increasing prevalence of colonization and infection was recognized.[4-6] In one retrospective review of MRSA isolates from the CDC-administered National Nosocomial Infections Surveillance (NNIS), the percentage of MRSA isolates among *S. aureus* isolates rose from 2.4% in 1975 to 29% in 1991, with the greatest increase seen in hospitals with more than 500 beds (38.3%) [see Figure 1, from Panlilio et al].[7] This same reporting system (NNIS) reported a continued and alarming rise in MRSA infections during a more recent time period; there was an 11% increase in MRSA infections in ICU patients in 2003 compared with 1998 through 2002, with resistance rates of 59.5% among 4100 isolates.[8] MRSA was found to be prevalent in all healthcare settings: median rates of MRSA isolates among *S. aureus* isolates among 157 intensive care units, 56 non-intensive care inpatient units, and 49 outpatient areas were 48.1%, 44.9%, and 24.6%, respectively.[8] In a single-site, 15 year longitudinal study of MRSA isolates at U.S. military clinics and tertiary care hospital in San Diego, a marked increase in MRSA isolates—particularly community-acquired—was noted in the time period 1994 to 2004, particularly after 2002 [see figure 2, from Crum et al].[10]

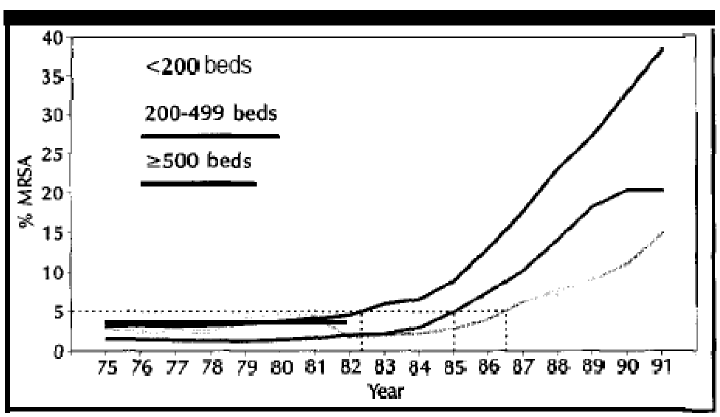
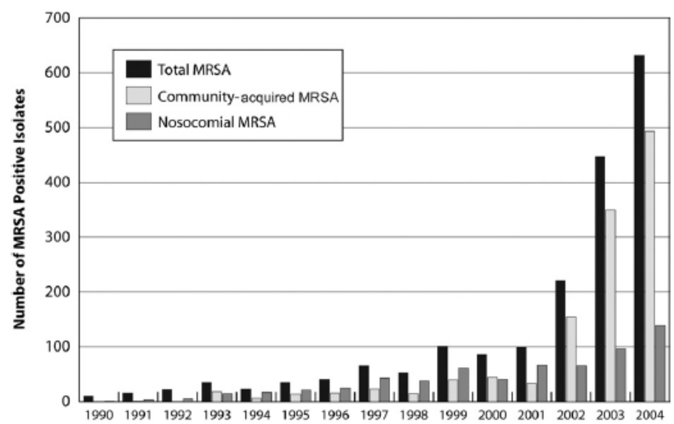


FIGURE 1. Temporal trends in percent of *S aureus* resistant to methicillin, oxacillin, or nafcillin by hospital bed size.



Highlighting the nationwide prevalence, a study conducted in August 2004 among 320 patients with purulent skin and soft tissue infections presenting to the emergency departments of 11 university-affiliated hospitals demonstrated MRSA from 59% of patients (78% of *S. aureus* isolates), with a range of 15 to 74%.[10] MRSA was the most common identifiable cause of skin and soft tissue infection in 10 of the 11 emergency departments.[10] The national scope of this problem is demonstrated by laboratory-based surveillance data from the 300 microbiology laboratories included in The Surveillance Network-USA (TSN); not only did this data from outpatient and inpatient isolates demonstrate a rise in percent of MRSA isolates from 1998 to 2005, but demonstrated high outpatient and inpatient rates in every region of the country [see Figures 3 and 4, from Styers et al; in figure 3, square line, all patients; diamond line, ICU patients; circle line, inpatients; triangle line, outpatients].[11]

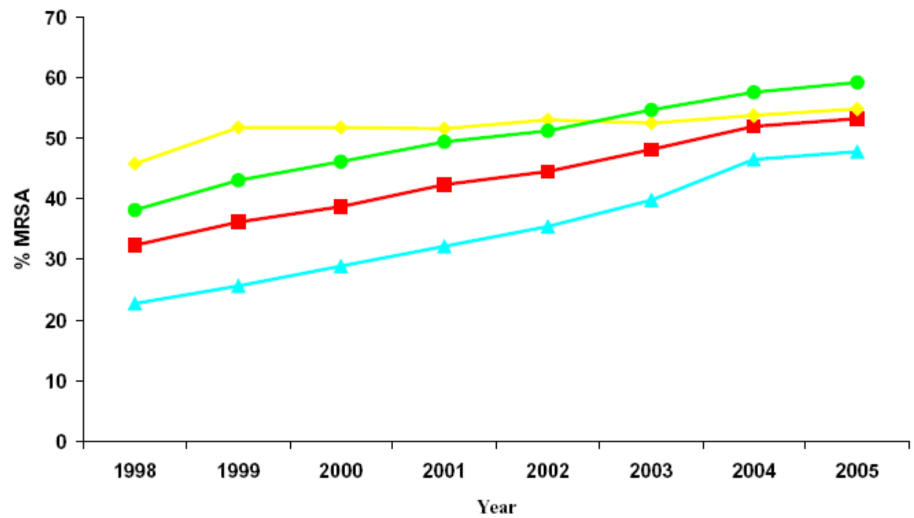


Figure 3
MRSA trends (1998 – YTD 2005) according to patient location. Data is cumulative data: 1998 – March 2005. Red line, all patients; yellow line, ICU patients; green line, inpatients; blue line, outpatients.

The significance of high prevalence is not limited to the United States. In a survey of bloodstream isolates from over 15000 patients in the United States, Canada, Latin America, Europe and the western Pacific during the period 1997 to 1999, MRSA prevalence ranged from 5.7% (Canada) to 46% (western Pacific region).[12] Prevalence for specific countries ranged from less than 2% in the Netherlands and Switzerland to more than 70% in Japan and Hong Kong. Similar to studies described above,[6,9] rates of both community-acquired

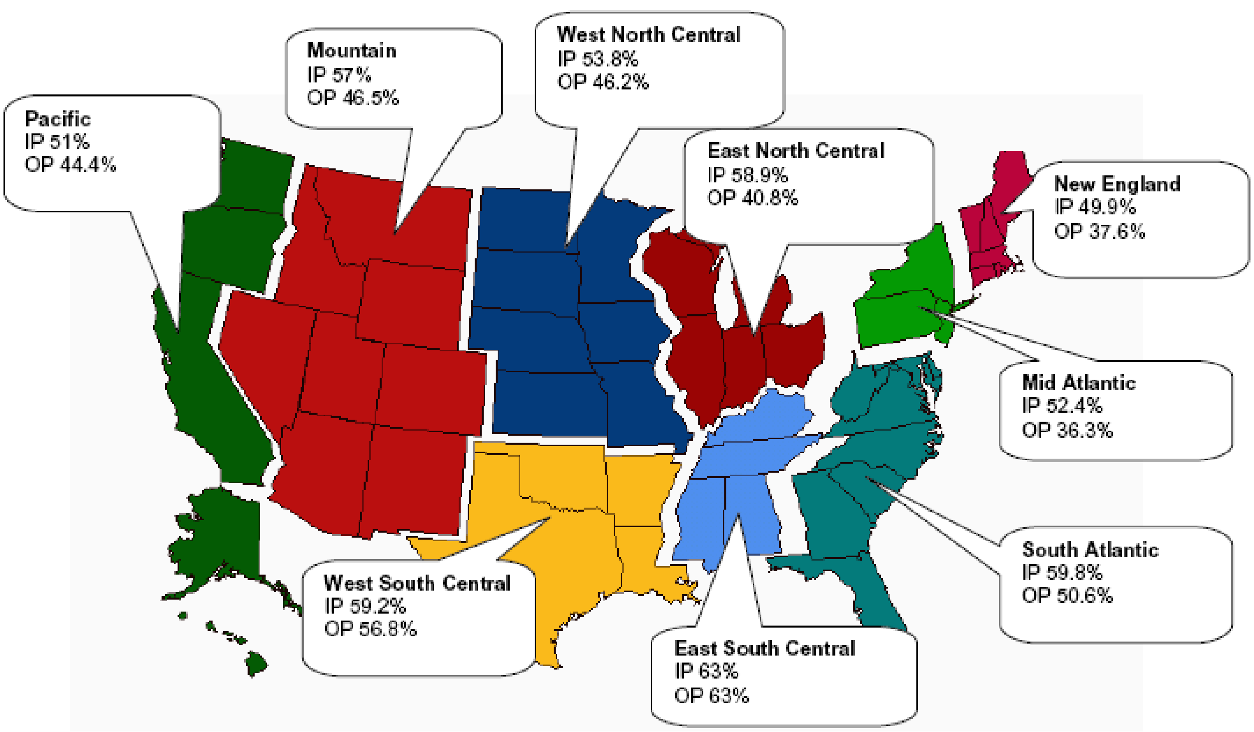


Figure 4
Inpatient (IP) and outpatient (OP) MRSA rates according to US Census Bureau Regions. Data is cumulative data: 1998 – March 2005.

and nosocomial MRSA increased over the time period 1997-1999.[12]

The cost of MRSA-associated morbidity and mortality has likely not been fully estimated, although the difficulty and complexity of estimating the significance of antimicrobial resistance has been described.[13] However, it appears clear from available data that—whether due to confounding factors, strain differences, or treatment differences—MRSA takes a higher morbidity and mortality toll than methicillin-sensitive *S. aureus* (MSSA), is a burden to the healthcare system in addition to (and not in replacement of) MSSA, and presents a patient and financial cost burden for many disease states beyond bacteremia.[14] Recently, the breadth and potential severity of invasive MRSA infections received widespread public attention[15] after a published study demonstrated a notably high incidence rate of 31.8 invasive infections per 100000 persons.[16] Among 8987 observed cases from the geographically- and demographically-varied nationwide Active Bacterial Core surveillance/Emerging Infections Program Network, collected from July 2004 through December 2005, 58.4% were community-onset health care associated, 26.6% were hospital-onset heath care-associated, and 13.7% were community-associated. Most significantly, the 988 deaths among 5287 hospitalized patients with MRSA infection reported in the study extrapolates to a nationwide death rate due to MRSA exceeding many other significant infectious causes.[16]

Escape from the institution?

Although MRSA had been identified in the community as early as the 1980s, these cases were strongly associated with populations such as intravenous drug abusers and long-term care facilities who are frequently hospitalized.[17] More substantial trends in community-associated MRSA (CA-MRSA) were reported by the mid- to late-1990s throughout the United States[18] and elsewhere,[19,20] and began to include case reports in the absence of predisposing risk factors.[21,22] An early series of four pediatric deaths highlighted the gravity and indiscriminate potential of CA-MRSA-associated infections.[17] CA-MRSA is defined by the characteristics in Table 1.

Initially thought to arise from hospital-associated clones (HA-MRSA), current evidence suggests that CA-MRSA acquired resistance independently of HA-MRSA.[3] Distinctions between HA-MRSA and CA-MRSA lie in the distinct spectrum of disease; resistance characteristics, and toxins expressed by each.[22-26] CA-MRSA strains are currently classified by pulsed-field electrophoretic patterns (described as strains USA100 through USA1200), and currently USA300 is the major circulating strain.

TABLE 1: CLINICAL CHARACTERISTICS OF COMMUNITY-ASSOCIATED MRSA INFECTION
Develops within **48 hours** of hospitalization
No history of MRSA colonization or infection
No indwelling medical device (including intravenous catheter) present at the time of isolation
No history of hospitalization, surgery or hemodialysis within **one** year

Spectrum of disease. As mentioned above and detailed in the section below on risk factors, the evolution of CA-MRSA infections include the emergence of MRSA infections in the absence of significant risk factors. Although it is generally thought that MRSA in patients without risk factors is more likely to be CA-MRSA and more invasive in nature[3,27]—with descriptions of necrotizing skin infections with abscess formation in particular—comprehensive studies of this difference are limited but growing.[22,23,28]

Resistance characteristics. CA-MRSA are pauciresistant and more likely to be polyclonal whereas hospital isolates tend to be resistant to multiple antibiotic classes and are clonal in nature.[3] Both carry a gene conferring resistance, the Staphylococcal cassette chromosome (SCC) *mec*A gene, which encodes for penicillin-binding protein 2a (PBP 2a), which has a low affinity for β-lactam antibiotics but allows for cell-wall synthesis even in the presence of β-lactam antibiotics. However the SCC*mec* identified in many CA-MRSA cases (SCC*mec* IV) is unique in both size and origin, and have been found to be small and easily transferable.[24,29,30] This gene is suspected to have arisen from methicillin-susceptible strains of S. aureus (MSSA)[23], evidenced in part by a report of the transfer from MSSA to MRSA in vivo[31] and whole-genome sequences of CA-MRSA compared with HA-MRSA strains.[32]

Toxins. *S. aureus* secretes several virulence factors, including enzymes that serve to transform the local tissue environment into one supporting bacterial growth: hemolysins (alpha, beta, gamma, delta), nucleases, proteases, lipases, hyaluronidase, collagenase.[33] Some strains also produce superantigentoxins (Sags) which include TSS toxin 1 (TSST-1), staphylococcal enterotoxin (SE) serotypes A to Q (SEA to SEQ) excluding F, exfoliative toxins (ETA, ETB), and leukocidin. These toxins mediate cytokine release from macrophages and T-cells and likely inhibit host immune responses.[24,33] They have been identified in CA-MRSA isolates as well as—and possibly more commonly than—HA-MRSA isolates. An apparently unique toxin, Panton Valentin Leukocidin (PVL), appears to be more commonly produced by CA-MRSA than HA-MRSA. It is an exotoxin that has been associated with necrosis of the skin, severe necrotizing pneumonia and abscess formation, although its role in the virulence of CA-MRSA is controversial.[34-36]

In one prospective cohort study from 12 regionally-varied laboratories in Minnesota in 2000[23], 1100 MRSA isolates were identified as either CA-MRSA (131, 12%) or HA-MRSA (937, 85%) and compared for type of clinical infection, microbiological characteristics and exotoxin production; 3% could not be classified as either CA-MRSA or HA-MRSA. In this population, 25% (range from individual sites, 10-49%) of *S. aureus* isolates were methicillin-resistant. CA-MRSA patients were younger (median age 23 years vs. 68 years, 30 years vs. 70 years if pediatric hospitals were excluded), more likely to involve skin and soft tissue infections (75% vs. 37%), and were less likely to have respiratory or urinary tract infections than HA-MRSA patients. Among a representative sample, CA-MRSA isolates were generally susceptible to antimicrobials other than β-lactams and were more likely to be susceptible to multiple agents. Antibiotics for which CA-MRSA was more likely to be susceptible to than HA-MRSA at a statistically significant rate were: ciprofloxacin (79% vs. 16%), clindamycin (83% vs. 21%), erythromycin (44% vs. 9%), and gentamicin (94% vs. 80%). Compared to HA-MRSA, CA-MRSA isolates were more likely to have distinct molecular features based on pulsed-field gel electrophoresis (clonality) and had a higher prevalence of PVL genes (77% vs 4%). Although all isolates carried the *mecA* gene conferring methicillin resistance, SCC*mec* IV allele and *agr* 3 allele were more associated with CA-MRSA whereas SCC*mec* II and *agr* 2 were more commonly associated with HA-MRSA.[23]

A similar study among 283 isolates in a California teaching hospital performed from December 2003 through May 2004 demonstrated concordant results: CA-MRSA most commonly caused skin and soft tissue infections (86% of CA-MRSA isolates, compared with 42% of HA-MRSA isolates), CA-MRSA isolates were less likely than HA-MRSA isolates to cause urinary or respiratory infections; CA-MRSA isolates were more likely to be susceptible to ciprofloxacin and clindamycin (although neither CA-MRSA nor HA-MRSA were likely to be susceptible to erythromycin, and both were highly susceptible to gentamicin).[22] This study is also notable for documenting high rates of USA300 clone (87% of CA-MRSA isolates, 33% of HA-MRSA isolates), a clone that is rapidly becoming ubiquitous.

Very similar trends regarding spectrum of disease, microbiological characteristics, and increasing prevalence rates have also been found in pediatric populations.[28]

An Ounce of Prevention is Worth a Pound of Cure

Carriage: colonization vs. infection

Staphylococci are normal skin flora and MRSA, like MSSA, primarily colonizes and is most readily cultured from the nares but may also colonize adjacent structures, such as the perineum, wounds, burns, respiratory secretions (including among intubated patients), urine and feces.[37] MRSA forms biofilms, which may enhance its ability to colonize certain surfaces and may contribute to its ability to cause nearly every type of nosocomial infection.[5]

Carriers of *S. aureus* are classified as: 1) persistent carriers, 2) intermittent carriers, or 3) noncarriers.[3,38,39] Approximately 10 to 35% of healthy people are persistent carriers, 20 to 75% are intermittent carriers and 5 to 50% are non-carriers; persistent carriers are less likely to have variation in *S. aureus* strains than intermittent carriers.[3,38,39] While cross sectional studies demonstrate an approximately 35% carriage rate in the general hospitalized population, populations described below have increased rates of carriage particularly those undergoing hemodialysis or CAPD, those with insulin-dependent diabetes mellitus, those with HIV infection, and patients receiving repeat injections for allergies.[38,39]

The prevalence of MRSA carriage in the general community has been harder to estimate, and is likely much lower than that among hospitalized populations. A meta-analysis of 10 studies performing surveillance cultures (among a total of 8350 persons) demonstrated a pooled prevalence of MRSA colonization of 1.3%; 9 studies (n = 4825) included populations in which 47.5% of colonized individuals had at least 1 risk factor and the pooled prevalence of CA-MRSA was 2.1%, while the one study (n = 3525) performing cultures in community members without risk factors demonstrated a prevalence of CA-MRSA of only 0.2%.[40] Furthermore, the same authors describe 4 studies that investigated colonization status of household contacts of MRSA patient discharged from a hospitalized setting (n = 191), with 17.8% of household contacts having the same MRSA strain as the index patient.[40] Finally, they identified 4 studies that investigated colonization status of team members or day care contacts of MRSA-colonized individuals (n = 517) and found that 5.4% had the same MRSA strain

TABLE 2: DESCRIBED SITES OF INFECTION FOR MRSA*
Skin and soft tissue
Cellulitis, impetigo, furunculosis, folliculitis
Abscess
Necrotizing fasciitis
Myositis
Surgical wound infections
Indwelling catheter
Urinary
Intravenous
Central nervous system shunt
Bone/joint, including prosthetic
Pulmonary
Necrotizing pneumonia/abscess
Empyema
Ventilator-associated pneumonia
Endocarditis, pericarditis
Central nervous system (meningitis, abscess)
Intra-abdominal or renal abscess
Septic thrombophlebitis with pulmonary embolism
Severe sepsis with purpura fulminans and Waterhouse-Friderichsen syndrome

* Adapted from Moellering JR, Daum RS, Cunha BA.[2,8,22]

as the index patient.[40] More recently, one study demonstrated a 1.0% prevalence of MRSA colonization in a random sample of 295 healthy subjects in 4 non-healthcare locations.[41] In a larger study of 9622 persons as part of the National Health and Nutrition Examination Survey (2001—2002), *S. aureus* was identified in 32.4% of persons, and MRSA colonization among 0.8% of persons.[42]

Although the majority of studies investigate MSSA/MRSA colonization by investigating nasal carriage, there is evidence that solely sampling the nares may inadequately capture all carriers. In one study among 5041 hospitalized patients, healthcare workers and blood donors, 37.1% had nasal carriage of *S. aureus* (with or without throat carriage), and 12.8% had throat colonization alone (representing 25.7% of all *S. aureus* carriers).[43] Although few other recent data is available investigating this issue, it is suggestive that a strategy of culturing areas other than the nares (forehead, axilla, groin, rectum) might be more sensitive for detection of MRSA carriers.[44-47]

S. aureus nasal carriage has been strongly associated with increased risk of developing a surgical site infection.[38,39] However, although it is thought that relatively few individuals colonized with MRSA develop infections, this relationship has mainly been studied in a clinical population (not a general asymptomatic one) and many questions remain regarding the relationship between colonization and infection.[48-50] There is some data to suggest that colonization with MRSA on admission or during hospital admission increases the risk of MRSA infection.[51]

MRSA causes a very broad range of infections, although the vast majority is skin and soft tissue infections. Described sites of infection for MRSA are listed in Table 2.[24,27,37]

Prevention of acquisition

In theory, the prevention of acquisition of MRSA should be straightforward: identify risk factors for acquisition of MRSA, identify MRSA as either colonized or infected in the population of interest, and limit transmission from identified carriers to contacts. Best evidence practices, however, for models of prevention remain to be established.[25] While risk factors for acquisition of colonization and infection are being clarified (see below), efforts to limit the spread of MRSA have been best studied in an outbreak setting.

The Centers for Disease Control and Prevention (CDC) has established recommendations to limit the spread of MRSA in the community.[50] A summary of the recommendations is detailed in Table 3.[50]

TABLE 3: CDC RECOMMENDATIONS TO LIMIT COMMUNITY SPREAD OF MRSA*
Keep wounds that are draining covered with clean, dry, bandages.
Clean hands regularly with soap and water or alcohol-based hand gel. Always clean hands immediately after touching infected skin or any item that has come in direct contact with a draining wound.
Maintain good general hygiene with regular bathing.
Do not share items that may become contaminated with wound drainage, such as towels, clothing, bedding, bar soap, razors, and athletic equipment that touches the skin
Launder clothing that has come in contact with wound drainage after each use and dry thoroughly.
If you are not able to keep your wound covered with a clean, dry bandage at all times, do not participate in activities where you have skin to skin contact with other persons (such as athletic activities) until your wound is healed.
Clean equipment and other environmental surfaces with which multiple individuals have bare skin contact with an over the counter detergent/disinfectant that specifies *Staphylococcus aureus* on the product label and is suitable for the type of surface being cleaned1.

* From Gorwitz et al.[50]

In the nosocomial setting, isolation or cohorting of patients identified as MRSA carriers or MRSA-infected and the use of contact precautions—disposable gown and gloves—is increasingly used to limit the spread of MRSA. The CDC recommend contact precautions for healthcare workers caring for hospitalized patients with MRSA.[52] Several studies have demonstrated the efficacy of isolation procedures and contact precautions in reducing rates of antibiotic-resistant organisms among hospitalized patients during outbreak investigations,[53-58] but the mechanisms for this benefit are not well understood. The role of healthcare worker as MRSA carrier and subsequently source of a MRSA outbreak among patients appears limited.[59] Furthermore, the role of fomites and animals in transmitting infection has been only partially described.[60,61]

Risk factors for acquisition

Early risk factors for colonization or infection in the hospital setting included antibiotic exposure, admission to an intensive care unit, surgery, and exposure to an MRSA-colonized patient.[4,62] Separate early reviews cite recent hospitalization or surgery, residence in a long-term care facility, hemodialysis and indwelling percutaneous medical devices as risk factors for MRSA acquisition.[63,64] Intravenous drug use has long been identified as a risk factor for MRSA carriage and infection.[65-67]

A more recent trend developing through the 1990s to present is the acquisition of MRSA (particularly CA-MRSA) in settings of close contacts and in populations with few to absent risk factors,[26,34] although there is some data to suggest that the prevalence of MRSA among people who are truly without risk factors may be low.[40] Notable cases include transmission documented among a professional American football team[68] demonstrating the role of close contact and hygiene, and more recently, the emergence of a multi-drug resistant USA300 strain among men who have sex with men.[69] This latter case is of particular concern as CA-MRSA has traditionally had a more limited range of antibiotic resistance characteristics than HA-MRSA.

Table 4 summarizes representative studies of recognized at-risk populations for the acquisition of MRSA.[25,27,34]

TABLE 4: POPULATIONS AT RISK FOR ACQUISITION OF MRSA	
Military	Observational study: 5-month outbreak from baseline incidence rate of < 1 MRSA infection/1000 recruits to a peak of 11.0 infections/1000 recruits[70] Observational study: demonstrated incidence rate of 9.5 MRSA skin infections per 1000 person-weeks during a 12-week outbreak; estimated baseline 3 episodes of cellulitis per 1000 person-weeks. Factors associated with infection include having a roommate with prior infection or a contact who worked in health care setting.[71]
Incarcerated persons	Case reports and case-control: among prisons in Georgia, Texas, California. Risk factors identified included barriers to routine hygiene, limited access to proper medical care, frequent medical staff turnover and therefore poor continuity of education on infection-control procedures, and misidentification of MRSA as cause of skin infections.[72]
Athletes	Retrospective cohort study: 8 CA-MRSA infections among 5 of 58 professional football players; player position, skin abrasions among affected players, lack of regular access to standard hygiene practice and absent nasal carriage was noted[68] Retrospective cohort study: 10 USA300 infections among 100 college football players; risk factors identified included player position, "turf burns", whirlpool use and body shaving[73] Case series, retrospective cohort study: 6 of 32 members of a high school wrestling team had documented MRSA infections, and 1 of 32 demonstrated nasal colonization; all isolates had identical PFGE isolates.[74]
Men who have sex with men	Population-based survey and cross-sectional study: among 9 hospitals and 2 outpatient clinics of San Francisco and Boston, highest rates of multidrug-resistant USA 300 MRSA infections were among those engaging in male-male sex, independent of past MRSA infection, HIV, or clindamycin use.[69] Case-control study: among 35 cases and 76 controls (all HIV-positive men who have sex with men), significant risk factors included public hot tub/sauna use, methamphetamine use, professional hands-on contact with customers and work, and sex partners with skin infections; protective exposures included condom use and trimethoprim-sulfamethoxazole use for prophylaxis against opportunistic infections.[75]
Intravenous drug abusers	Retrospective cohort: among 188 randomly-selected charts from patients admitted with skin and soft tissue infections, 70% documented intravenous drug use in the preceding 12 months; 29% had no history of intravenous drug use (63% had documented etiology)[43]
Homeless	Population-based observational study: of 833 homeless persons tested, 22.8% had nasal colonization with *S. aureus*, 12% of these (overall, 2.8%) with MRSA. Intravenous drug use, prior endocarditis, and recent hospitalization was associated with MRSA carriage.[76]
Tattoos	Case reports: 6 clusters totaling 34 primary cases and 10 secondary cases of CA-MRSA skin and soft tissue infections associated with 13 tattoo-parlors in 4 states; investigations identified the use of nonsterile equipment and poor infection-control practices as potential causes.[77]
Native Americans, Pacific Islanders	Retrospective cohort study: among 112 patients with *S. aureus* infections (55% MRSA), a marked increase in percentage of MRSA among all isolates from 1989 through 1997 was noted, with authors describing 74% of MRSA isolates as community-acquired.[78] Retrospective cohort study: documents a marked rise in MRSA infections among Alaskan natives in a rural community from Jan 1998 through July 2000; among 232 *S. aureus* infections during a 4-month period, 74% were MRSA, 83% of which causes skin and soft tissue infections.[79] Retrospective cohort study: among all patients among 4 diverse clinical settings over a 2 year period, there were 1389 MRSA isolates. 389 (28%) were classified as CA-MRSA infections. Pacific Islanders accounted for 51% of CA-MRSA patients, compared with 24% of the total population of Hawaii. [80]

Treatment modalities for MRSA

The treatment for MRSA infections is dependent on the clinical condition, and may involve no antibiotics, topical antibiotics, enteral antibiotics, parenteral antibiotics, or a combination of these. It should be mentioned that some lesions—specifically small abscesses in low-morbidity areas of the body in the absence of systemic signs of infection—may not require antibiotics and may be treated successfully with incision and drainage alone.[81] A recent randomized trial comparing placebo versus cephalexin in the adjunctive treatment of skin and soft tissue infections that have been incised and drained demonstrated that among 166 outpatients, there was an observed 7-day cure rate of 90.5% among 84 placebo-recipients and 84.1% among 82 cephalexin-recipients; 87.8% of the isolates tested were MRSA.[82] This demonstrates that in the setting of high-rates of MRSA-associated abscesses, incision and drainage is a essential principle (along with removing indwelling or foreign objects, and treating concomitant immunosuppressive conditions) in the treatment of bacterial infections.

Topical agents. Few infections (perhaps impetigo, although there is a lack of comparative trial data[34]) warrant treatment with topical antibiotics alone; topical agents, therefore, are likely to be reserved to aid in eradication. Four topical agents are available: Bacitracin, Mupirocin, Retapamulin, and Chlorhexidine; the first three are used as ointments, and the fourth as a body wash. Bacitracin may be used with or without both polymyxin and neomycin; in vitro susceptibility factors that predict outcome, however, are undefined.[34] Mupirocin is the more commonly evaluated topical agent and current standard topical agent used in decolonization; resistance has been described, and high-level resistance isolates predict clinical failure but are uncommon and usually follow prolonged use.[3,34] Beneficial characteristics include the absence of structural similarities with systemic antibiotics (limiting development of cross-resistance) and minimal toxicity.[83] Studies in healthy subjects demonstrate good efficacy in eliminating nasal carriage; several surgical and non-surgical (particularly dialysis) randomized controlled trials have demonstrated efficacy for clearance of *S. aureus* colonization, and with trends toward reduction in bacteremia and infection.[38,39] Retapamulin is a pleuromutilin compound with recent FDA approval for impetigo and secondarily infected traumatic lesions and dermatoses.[84] There is very limited data on its clinical use with MRSA, and resistant mutants can be selected in vitro.[34] In general—and in the case of chlorhexidine in specific—regimens including topical agents have been studied in the context of multi-faceted control interventions and is therefore difficult to independently evaluate.[50]

Oral and parenteral agents. The oral and parenteral agents with efficacy against MRSA are described in tables 5, 6 and 7. Tables 5 and 6 summarize dosage, cost and FDA-approved indications. Table 7 describes adverse effects, advantages, and disadvantages of each antibiotic. Fluoroquinolones and macrolides are not recommended for the treatment of *S. aureus* infections due to the high likelihood and rapid development of resistance. This recommendation comes despite the fact that ciprofloxacin and levofloxacin are FDA-approved for the treatment of complicated skin infections in adults, and moxifloxacin is FDA-approved for the treatment of uncomplicated skin infections due to *S. aureus*. Similarly, all macrolides/azalides are FDA-approved for the treatment of uncomplicated skin infections caused by *S. aureus*, but MRSA isolates are frequently resistant.[50]

Eradication regimens

To date, studies supporting the use of agents to eradicate *S. aureus* colonization are limited, particularly in the community setting,[50] and most experts feel an ideal regimen has not been found and may even be a fruitless search.[86] The CDC recommends considering eradication only after standard prevention measures* fail in the setting of 1) a patient who has multiple MRSA infections or 2) ongoing transmission in a closed or semi-closed setting (e.g., a household).[50] However, recent guidelines published by an American epidemiology society suggest potential efficacy of surveillance and eradication consistent with a Dutch-style "search and destroy" policy.[87] Historical regimens for MRSA eradication/decolonization have used topical agents (particularly mupirocin) or oral antibiotics plus rifampin.[83]

In one of the very few prospective randomized controlled trials performed independently of an outbreak setting, Simor et al evaluated the efficacy of chlorhexidine, mupirocin, rifampin and doxycycline versus no treatment for the eradication of MRSA.[88] Among 146 patients from 8 hospitals identified as colonized (on admission or as part of an outbreak investigation) but not infected, 111 were randomized to study treatment and 35 were randomized to no treatment; at the primary outcome of 3-month follow-up, 87 patients and 25 patients could be evaluated in each group, respectively. Cultures were obtained from the nares, perineum, skin lesions, and catheter or medical device exit sites at study onset, weekly for 4 weeks, and monthly for an additional 7 months. Patients randomized to treatment received a 7-day regimen of 2% chlorhexidine gluconate washing daily, 2% mupirocin ointment to both nares three times daily, rifampin 300mg twice daily and doxycycline 100mg twice daily. At 3-month follow-up 74% (64 of 87) of those treated and 32% (8 of 25) of untreated patients remained culture-negative for MRSA (relative risk 1.55, 95%CI 1.17-2.04). At the end of the 7-day decolonization regimen, 92% of patients cleared MRSA from all sites; at eight months, 54% of 48 patients available for follow-up remained negative for MRSA. After multivariate logistic regression analysis, mupirocin-resistant MRSA at baseline was independently associated with recolonization with MRSA at 3 months, while functional status, presence of skin lesions, presence of a medical device and

* Standard prevention measures defined as: hand hygiene (washing with soap and water or alcohol-based gel), particularly after touching body fluids or contaminated surfaces and after patient care; wearing gowns and gloves for all patient contact; wearing gloves, gowns, and eye protection for appropriate wound care and procedures; use of dedicated patient-care equipment when possible; cleaning of exam/patient room surfaces with appropriate detergent/disinfectant.

MRSA recovered from more than one body site were not associated with recolonization.[88]

Prior to the Simor study, a Cochrane review of antimicrobial drugs for treating MRSA colonization summarized the 6 randomized controlled trials (384 non-healthcare worker participants) performed to date, and found "insufficient evidence to support use of topical or systemic antimicrobial therapy for eradicating MRSA".[89] The 6 trials investigated: fusidic acid vs. no therapy; mupirocin twice daily for 5 days vs. placebo ointment; rifampin 600mg orally twice daily vs. minocycline 100mg orally twice daily vs. minocycline and rifampin (all for 5 days); mupirocin three times daily vs. fusidic acid three times daily vs. oral trimethoprim-sulfamethoxazole (TMP-SMX, DS) daily; ciprofloxacin 750mg orally twice daily and rifampin 300mg orally twice daily vs. oral TMP-SMX (DS) twice daily (both for 14 days); novobiocin 500mg orally twice daily and rifampin 300mg orally twice daily vs. oral TMP-SMX (DS) twice daily and rifampin 300mg orally twice daily (both regimens for 7 days). Outcomes of MRSA colonization (and in one case, infection) were reported at time points ranging from 12 to 180 days (typically 14). None of the trial endpoints demonstrated significant efficacy of any trial agents.[89]

If randomized trials as described in the Cochrane review do not demonstrate efficacy of eradication, where does support for eradication regimens arise? It may be possible that interventions described are—intentionally or otherwise—performed in addition to non-pharmacological interventions, such as hand cleansing, infection control protective clothing, environmental decontamination and/or patient cohorting or isolation. A significant number of studies, including case reports and case-control studies, and among topical and oral regimens, have demonstrated adequate or complete eradication rates, but lack experimental rigor both in design and follow-up.[83,89]

A Spectre is Haunting Europe

At this point, we have established that MRSA is a growing and costly health care threat, that there are changing epidemiologies as well as clinical and microbiological variations between HA-MRSA and CA-MRSA, and that while there is CA-MRSA at low rates among all populations, certain populations are at higher risk for acquisition and subsequent infection with MRSA. Any model of eradication should take into consideration these factors, and before evaluating the Dutch model of MRSA eradication, it is worth commenting on the distinguishing features of the Dutch and American settings.

Dutch health care setting

The Netherlands is a Northern European country of just over 16 million inhabitants, with a high population density. Healthcare is subsidized by the government and there is universal access to healthcare. There are approximately 100 to 150 hospitals, with a hospital size ranging from 300 to 1200 beds, and approximately 4 beds per 1000 inhabitants.[90,91]

Over the last 30-40 years, The Netherlands has developed a health care infrastructure supportive of nosocomial infection awareness. The Dutch Health Council released reports in 1966, 1976, and 1990, analyzing the control and protection of infectious disease, also creating infection control committees to give advice to healthcare workers and establishing the role of the infection control nurse (now termed infection control professional or practitioner).[82,83] Infection control practitioners—including medical microbiologists and infectious disease specialists—play a role in every Dutch hospital, as the control and prevention of hospital-associated infections is a legal requirement of all hospitals.[91] The Dutch Working Party on Infection Control (Werkgroep Infectie Preventie, a.k.a. Infection Prevention Working Party, WIP) was established in 1981; it is constituted by 4 Dutch medical/microbiological societies and functions to establish guidelines, form a document center for literature on infection control, and facilitate discussion on infection control issues. The work is strongly endorsed by the Chief Medical Officer of the The Netherlands.[90,91] Lastly, the Working Group of Hospital Epidemiologists (ZIEN) was founded in 1994 and includes representatives from 7 of the 8 Dutch university hospitals; it serves to sponsor research, discussion and training in infection control.[90,91]

Prevalence rates for MRSA colonization and infection in The Netherlands are among the very lowest in the world. In a study conducted in 1999-2000 at four Dutch hospitals (bed size ranging from 500 to 1300 beds), all admissions to non-surgical beds were screened for nasal carriage of MRSA.[92] Twenty-four percent of the nearly 10000 patients screened were positive for *S. aureus*, and only three patients (0.03%) were MRSA carriers; these three patients had no risk factors other than prior hospitalization and carried genetically unique MRSA strains.[92] Data from a broad, Europe-wide surveillance network demonstrated the prevalence of invasive MRSA isolates (among *S. aureus* isolates) in The Netherlands to be less than 1%, as it was in Iceland and Finland, while the prevalence in the neighboring countries of France, Belgium and

Germany were 27%, 31%, and 21%, respectively.[93] Among the 30 countries reporting through the EARSS (European Antimicrobial Resistance Surveillance System), 7 had rates less than 3%, 8 had rates over 40%, and although two countries had decreasing rates over the preceding 5 years (2000-2005), a broader trend is toward increasing rates. Figure 5 (EARSS) graphically presents prevalence rates for 2005.[93]

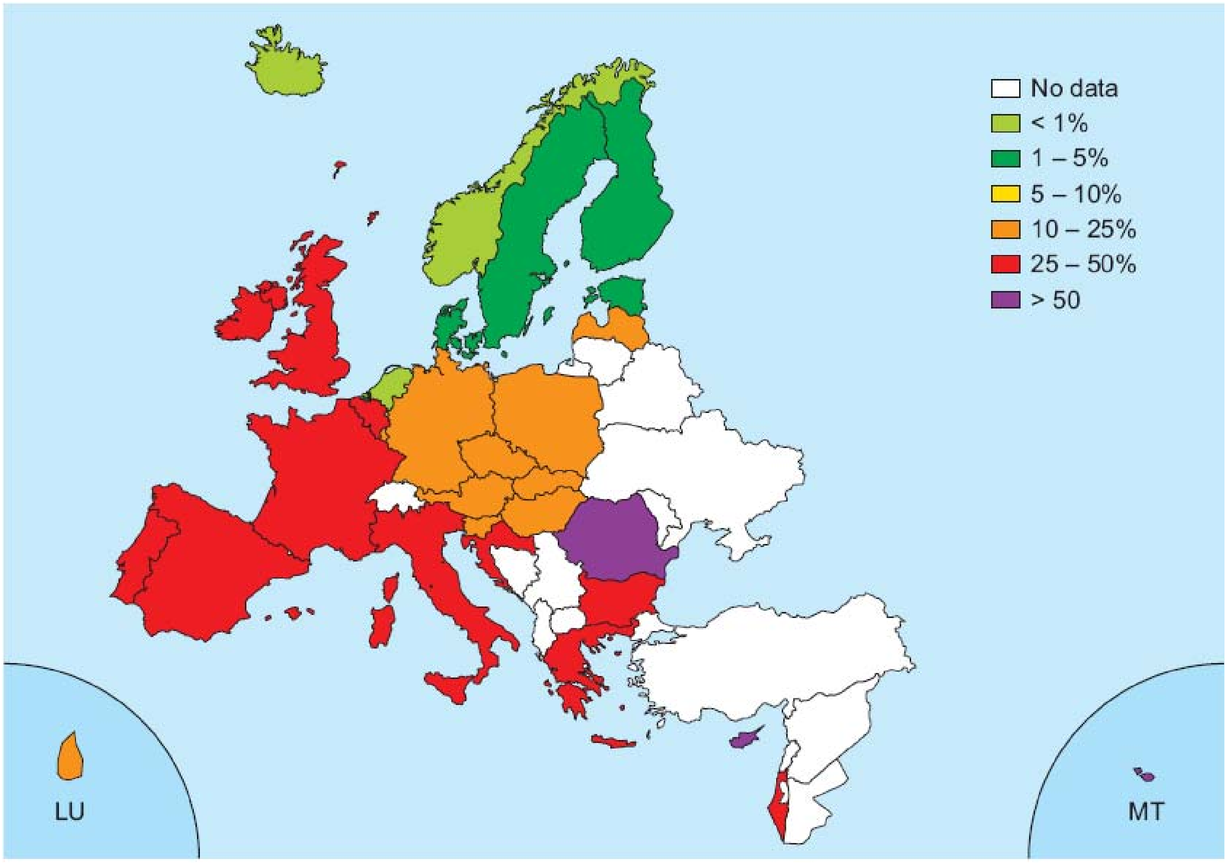


Figure 4.7. *Staphylococcus aureus*: proportion of invasive isolates resistant to oxacillin (MRSA) in 2005.

Given the low prevalence of carriage and infection in the Netherlands, recent studies investigating risk factors for acquisition in the Netherlands are lacking. Furthermore, while the risk factors studied in the United States exist in The Netherlands, whether or not they are risk factors acquisition of MRSA is not known. However, risk factors for continued transmission and recurrent colonization/infection in The Netherlands has been investigated.

Many authors cite the high rate of MRSA isolates in Dutch hospitals originating from outside The Netherlands—perhaps as many as 60-80% of isolates—as a significant risk factor for MRSA.[90,91] In a prospective study from 1998 to 2001, the prevalence rate of MRSA carriage among 1167 Dutch patients repatriated from foreign hospitals (49.7% to a Dutch hospital, 50.3% directly to their homes) was found to be 2.7% (95%CI 1.7-3.6).[94] Twenty-seven of the 31 MRSA-positive repatriated patients were repatriated to Dutch hospitals and 4 were repatriated directly home. Length of stay in the foreign hospital, mechanical ventilation and antimicrobial treatment were significant risk factors for MRSA carriage (odds ratio 5.4, 8.5, and 3.4, respectively).[94]

Prior MRSA carriage and associated factors have also been defined as risk factors for subsequent carriage. In a study of 56 patients identified as MRSA-carriers either during an epidemic outbreak (initial isolation 1986-1989, follow-up 1990-1991) or on admission to the study institution (initial isolation 1990-1995, follow-up 1996), 5 were found to be persistent MRSA carriers, identified as the identical strain by phage typing and antibiotic sensitivities. Of these 5, 1 had received antibiotics since discharge, 2 had re-admissions to study institution, 4 had continued skin lesions and 4 had persistence of their underlying disease (the latter two with p-value < 0.05 when compared to MRSA-negative study patients).[95] In a follow-up study involving 137 MRSA-positive patients at 8 hospitals (2.5 months to > 9 years after discharge), 11 patients were found to have MRSA colonization (all same strains by phage type and PFGE).[96] While persistent skin lesions were found to be a significant risk factor for prolonged carriage (p-value = 0.006, 8 patients), presence of persistent underlying disease, antibiotic use and re-admission were not significantly associated with persistent MRSA carriage.[96]

The Dutch policy for a "search and destroy" method of minimizing MRSA infections has evolved from early outbreaks of MRSA, nationwide surveillance, and professional group guidelines. Outbreaks during the 1980s were an influential factor in controlling MRSA, as described for Utrecht University Hospital by Verhoef et al and summarized in Table 8.[97]

Two nationwide surveillance programs have assisted in monitoring. In 1989 the National Institute of Public Health and Environmental Protection (RIVM) began surveillance by analyzing between 150 and 200 MRSA isolates from 30-50 different hospitals, and characterizing their microbial and genetic characteristics.[90,91] In 1996, the PREZIES project (Dutch acronym for prevention of hospital infection by surveillance) began evaluating data on surgical infections, subsequently infections in the intensive care unit and currently vascular device-related infections; approximately 80% of Dutch hospitals have participated in the project.[90]

The Dutch method

The basis for "search and destroy" is routine surveillance, strict isolation for MRSA-carriage patients and treatment/decolonization, for both patients and staff. Generally used measures for control of MRSA come from WIP guidelines, first published in 1988 and with a current revision published January 2007.[98] They classify patients and providers into four risk categories with associated recommended measures as summarized in Table 9.[98]

Table 8: Outbreaks of MRSA at Utrecht University Hospital, 1986-1998*

Year	No. of index patients	Patients colonized with MRSA during outbreak	Healthcare workers colonized with MRSA
1986	1	11	10
1987	1	19	9
1988-1989	1	32	39
1989	4	1	0
1990	2	1	0
1990-1991	1	5	0
1991	5	1	0
1992	6	1	1
1993	3	0	0
1994	3	0	6
1995	9	3	4
1996	8	0	0
1996-1997	2	22	14
1997	5	2	0
1997-1998	1	2	1
1998	6	1	4
Total	58	101	88

* Adapted from Verhoef et al.[97]

TABLE 9: INFECTION WORKING PARTY GROUP RECOMMENDATIONS FOR CONTROL OF MRSA*	
Categories of Patient and Caretaker Carriage	
1: proven MRSA carrier	Current cultures with MRSA
2: high risk of being a carrier	Patients receiving care in a foreign hospital (for more than 24hrs, less than 2 months before admission) Foreign patients receiving dialysis Patients from a facility with ongoing MRSA epidemic Patients with contact of unexpected MRSA carrier Patients who are category 1, with treatment for carriage without proven negative cultures Children who are adopted People who have contact with pigs
	Staff who have unprotected contact with MRSA carriers
3: moderately elevated risk of being a carrier	Patients in their first year following MRSA eradication (with negative cultures) Dutch patients receiving hemodialysis abroad Patients cared for in a foreign hospital with persistent risk factors (skin lesions, chronic respiratory or urinary tract infection) People who come in close contact with live veal calves (at veal calf farms)
	Staff who have had protected contact with MRSA carriers Staff who have worked in a foreign hospital (for more than 24hrs, less than 2 months prior) Staff who regularly work at a foreign hospital, or who escort patients across Dutch borders Staff who have been carriers (with current negative cultures) within one year of present
4. no elevated risk of being a carrier	Patients who have been cared for in a foreign hospital more than 2 months ago (without persistent lesions)
	Staff who have been successfully eradicated more than a year prior Staff who have had negative cultures after unprotected contact with MRSA carriers
Measures Taken to Limit Spread of MRSA, Based on Patient Category	
Category 1 Category 2	Care provided in strict isolation Providers must wear surgical mask, cap, coat with long sleeves and cuffs Care provided by fewest number of providers Staff with skin disorders (eczema or psoriasis) excluded from contact with patients A list of staff who have contact with the patient is kept
Category 3	Screening cultures on admission "Restraint should be exercised with regard to transfer, examination and treatment of the patient until results of the cultures are known." Patient with cultures positive for MRSA are assigned to category 1 Patient with cultures negative for MRSA are assigned to category 4
Category 4	No additional measures

* Adapted from Infection Prevention Working Party[98]

If a patient is unexpectedly found to be colonized with MRSA, they are placed in isolation and screening cultures are taken from all patients in the department (and all staff who have been in contact with people in the department). If another patient or staff member has positive cultures, then it is defined as an epidemic. If patients are found to be MRSA-positive not previously on isolation, the department is closed to new admissions. Isolation is continued until patients are treated for eradication, when control cultures (at least 3 sets at 7-day intervals) are negative and if the following three risk factors are *all* resolved: 1) antibiotic use, 2) skin disorders, including wounds, eczema, psoriasis, and 3) drains, catheters, intravascular lines.[98]

Screening cultures from patients are taken from: nose, throat, rectum or perineum, sputum (if expectorated), urine (if a catheter is present) and skin lesions and wounds (including catheter insertion sites); either one or two sets of cultures are collected depending on laboratory methodology. A separate protocol is observed for patients treated in the outpatient setting, although generally Category 1 and 2 patients are treated in strict isolation.[98]

A strict protocol of measures is undertaken for providers as well. Screening cultures are taken from the nose, throat, and significant skin lesions; control cultures are taken from those list and the perineum. Cultures must be taken by a separate provider, and preferably at the beginning of a shift. The extensiveness of the investigation depends on the circumstances of each case. In general, Category 1 and 2 healthcare workers are excluded from work until cultures are negative or treatment has been completed. Cultures for these providers are taken on the day MRSA is discovered, and subsequently on days 5 (in some cases), 10, 15 and 20. Initial treatment is with mupirocin ointment,[98] or mupirocin ointment in combination with either 4% chlorhexidine liquid soap or 7.5% polividone-iodine shampoo as whole-body wash.[92] Healthcare workers may be excluded from healthcare employment if MRSA cannot be eradicated.[97]

There is some variance in these protocols depending on the hospital. At Utrecht University Hospital, for example, a stricter policy is used, including more frequent and numerous cultures for foreign patients, a more aggressive ward/ICU closure policy, closer attention paid to airborne transmission (based on anecdotal evidence), and routine screening among patients and healthcare workers.[97] Only a few non-teaching hospitals perform routine prospective hospital-wide surveillance, while most make decisions on surveillance based upon daily review of microbiological data, concurrent changes in risk factors, or ward surveys for various reasons (e.g., study trial for new medical equipment).[91]

"Search and destroy"

Ultimately, the only true trial (albeit uncontrolled) to date as evidence for the "search and destroy" approach to MRSA has been the efficacy demonstrated in The Netherlands and other European countries who adhere to the policy. A recent outbreak of a single clone (Berlin epidemic MRSA), whether due to the acquisition of a unique *mecA* element among MSSA or due to the importation of a previously known MRSA clone from an Eastern European country, achieved control from a peak of over 300 patients and healthcare workers affected in 2002, with control thought attributable to a "search and destroy" strategy.[99,100] As described earlier in this article, the major shortcomings of studies investigating MRSA eradication include their uncontrolled nature and evaluation of only a part of the comprehensive strategy of MRSA control.

One systematic review of studies evaluating isolation measures and the incidence of MRSA colonization and infection was published in 2004.[101] The authors reviewed 46 studies, including 18 among isolation wards, 9 with nurse cohorting, and 19 involving other policies such as single bedded rooms, cohorting of patients, and barrier precautions. Shortcomings of the studies abound, including absent randomization (39 studies), significant differences in care for patients (e.g., differences in antibiotic use, lengths of stay; 31 and 29 studies, respectively), and lack of follow-up after discharge from hospital to re-evaluate colonization or infection (all studies).[101] Fourteen studies lack data warranting conclusions. In the 6 strongest studies, four demonstrated interventions (single room isolation, nurse cohorting, isolation ward) demonstrated control of major outbreaks, one demonstrated failure to control the epidemic, and one demonstrated initial success with eventual failure. Of the remaining studies, most demonstrated evidence of control, with some descriptions of failure.[101]

Conclusions

The recent surge in MRSA-associated infections may represent one of the most significant epidemics of modern times. Although the degree of virulence, the cost of associated infections, and the significance of genetic and microbiologic characteristics continue to be debated, there is little debate that MRSA is having an impact on our hospitals and communities, and will continue to for the foreseeable future. While the prevalence of MRSA colonization in low-risk American populations is likely to be quite low, the prevalence in a growing number of at-risk groups—including groups that have difficult access to health care and frequent interactions with various levels of the healthcare system—is rising dramatically, with new at-risk populations surfacing regularly. It is likely that focusing efforts on basic components of infection control (basic hygiene, hand washing, appropriate treatment of infection) will reduce the incidence of MRSA infections in high risk populations. However, in an increasingly mobile world, eradication with these methods alone is improbable. And while treatment options are available, eradication regimens have neither been fully evaluated nor entirely proven. The United States system of healthcare includes complexities not present in the Dutch system that would inhibit the efficacy of a "search and destroy" strategy; access to health care is not universal, is not localized at the patient or population level to a relatively closed and small geographic area, and is without a unified system of isolate monitoring, health care provision, and government oversight. Unless a stringent and universal policy or MRSA control is implemented, MRSA is unlikely to be eradicated from any area of the United States, and we would do better to focus on provider-level interactions to minimize its spread and impact.

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TABLE 5: ORAL AGENTS USED FOR THE TREATMENT OF MRSA			
Antimicrobial Agent	Adult Dosage	Cost ($, 10 day)	FDA Approval
Trimethoprim-sulfamethoxazole	1-**2 DS** tabs q12h (*also available IV*)	9.40 (generic), 39.40 (Bactrim DS)	Off label
Doxycycline	100mg q12h (*also available IV*)	22.00 (generic), 100.00 (Vibramycin)	Approved for treatment of *S. aureus* (not specifically MRSA) skin infections
Minocycline	100mg-200mg q12h (*also available IV*)	50.80 (generic); 77.00 (Minocin)	Off label
Rifampin	20mg/kg/day divided daily or bid; max dose 600mg/d	38.00 (generic)	Off label
Clindamycin	300-600mg q6-8hr	95.10 (generic)	Approved for serious infections due to *S. aureus*
Linezolid	600mg q12h	1286.80 (generic)	Approved for uncomplicated and complicated SSTI and hospital-acquired pneumonia due to MRSA

* Adapted from Moellering RC, Daum RS, Gorwitz RJ, and Cunha BS.[27,34,50,85]

TABLE 6: PARENTERAL AGENTS USED FOR THE TREATMENT OF MRSA			
Antimicrobial Agent	Adult Dosage	Cost ($, 10 day)	FDA Approval
Clindamycin	300mg q8h		Approved for treatment of *S. aureus* (not specifically MRSA) skin infections
Vancomycin	1g q12h; 2-4g/day in 2-4 divided doses	182.80 (generic)	Approved for S. aureus bacteremia
Daptomycin	4mg/kg q24h SSTI, 6mg/kg q24 bacteremia	1660.80 (Cubicin)	Approved for S. aureus bacteremia, including right-sided endocarditis
Linezolid	600mg q12h (*also available PO*)	1560.00 (Zyvox)	Approved for complicated SSTI and hospital-acquired pneumonia due to MRSA
Tigecycline	100mg then 50mg q12h	1362.00 (Tygacil)	Approved for complicated SSTI infections
Quinupristin and dalfopristin	7.5mg/kg q8-12hr	Approx 85-107 for 500mg vial (Synercid)	Approved for complicated SSTI infections (MSSA and *S. pyogenes* only)

* Adapted from Moellering RC, Daum RS, Gorwitz RJ, and Cunha BS.[27,34,50,85]

TABLE 7: AGENTS USED FOR THE TREATMENT OF MRSA			
Antimicrobial Agent	Important Adverse Effects	Advantages	Disadvantages
Trimethoprim-sulfamethoxazole	Nausea/vomiting, rash, photosensitivity, hematologic suppression (low platelets in particular), Stevens-Johnson syndrome	Several case reports and one case series suggested efficacy.	Common group A streptococcus resistance; add β-lactam. No adequate controlled trials to prove efficacy; one randomized-controlled trial compared to vancomycin suggested inferiority. Avoid in women in third trimester.
Doxycycline	Nausea, photosensitivity, deposition in teeth and bones	Good in vitro activity against staphylococci and streptococci Recent resistance among CA-MRSA in Calif and Boston	Data of efficacy limited to a small case series; insufficient data for invasive infections. Not for children < 9 yr
Minocycline	Same as doxycycline + vestibular toxicity.	PO formulation w/ excellent bioavailability Excellent CNS penetration (50%) Inexpensive	Same as for doxycycline
Rifampin	Discoloration of body fluids, liver transaminitis	High concentrations on mucosal surfaces.	Drug-drug interactions Cannot be used alone for risk of rapid resistance No clinical evidence of benefit; may add to TMP-SMX or tetracycline
Clindamycin	*C difficile*-associated diarrhea (rare; no direct comparative data from prospective trials)	Small reports of successful use in treating CA-MRSA infections	Possibility of resistance – assess for inducible resistance (D-zone test) Poor taste of suspension
Linezolid	Dose- and duration-dependent myelosupression (thrombocytopenia more than anemia or leukopenia); monitor CBC in patients receiving for more than 2 weeks Case reports: peripheral and optic neuropathy, lactic acidosis in prolonged use	PO formulation with excellent bioavailablity Good lung and CNS penetration Good for VISA/VRSA Efficacy demonstrated in controlled trials for SSTI May be superior to vancomycin for MRSA	Cytochrome P450 Serotonin syndrome Expensive Not recommended for catheter-related S. aureus Rare resistance described
Vancomycin	Neutropenia "Red Man" syndrome	Proven effectiveness	Increased MICs/resistance (VISA/VRSA) No PO formulation for MRSA Slow resolution of infection Therapeutic failures Poor CNS penetration (15%)
Daptomycin	None	Most effective/rapid bactericidal Good for VISA/VRSA; equivalent to vancomycin in controlled trials for SSTI Daily dosing	No PO formulation Cytochrome P450
Tigecycline	None	Non-inferior to vancomycin in controlled trials for SSTI	No PO formulation Limited data on MRSA
Quinupristin and dalfopristin	Painful myalgias (rare)	Proven effectiveness	No PO formulation, Q8 hour dosing Poor CNS penetration (<10%)

* Adapted from Daum RS, Gorwitz RJ, and Cunha BS.[34,50,85]