

Is methicillin-resistant *Staphylococcus aureus* replacing methicillin-susceptible *S. aureus*?

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Despite extensive research on the emergence of and treatments for methicillin-resistant *Staphylococcus aureus* (MRSA), prior studies have not rigorously evaluated the impact of methicillin resistance on the overall incidence of *S. aureus* infections. Yet, there are direct clinical and research implications of determining whether methicillin-susceptible *S. aureus* (MSSA) infection rates remain stable in the face of increasing MRSA prevalence or whether MSSA will be replaced over time. A synthesis of prior studies indicates that the emergence of health-care-associated MRSA (HA-MRSA) and community-associated MRSA (CA-MRSA) has led to an increase in the overall incidence of *S. aureus* infections, with MRSA principally adding to, rather than replacing, MSSA. However, colonization with CA-MRSA may at least partially replace colonization with MSSA. So far, evidence indicates that MSSA still accounts for many infections. Therefore, eradication of MRSA alone is not sufficient to address the public health burden of *S. aureus*.

Keywords: bacterial resistance, staphylococcal infections, healthcare-associated infections, community-associated infections

Introduction

Staphylococcus aureus is a ubiquitous member of the human microbiological flora, with up to 20%–30% of humans persistently asymptomatically colonized and 50%–60% intermittently colonized.^{1,2} It is the most commonly isolated human bacterial pathogen, and it is the cause of many skin and soft tissue infections (SSTIs) and invasive diseases, such as sepsis, endocarditis, pneumonia and osteomyelitis.³ The emergence of healthcare-associated methicillin-resistant *S. aureus* (HA-MRSA) has posed a major public health problem since the 1960s and the rapid rise of community-associated MRSA (CA-MRSA) in the late 1990s has further directed attention towards the burden of MRSA infections. To date, CA-MRSA and HA-MRSA have each been associated with a limited number of bacterial genetic backgrounds, combined with specific resistance elements; thus, MRSA as a group have remained less genetically diverse than the background methicillin-susceptible *S. aureus* (MSSA) lineages from which they are thought to be descended.^{4,5} Recent attention has focused on the increasing severity and frequency of infections caused by MRSA, especially with regard to its greater clinical and economic impact compared with MSSA.⁶ Since empirical regimens for sepsis are often not effective for MRSA infections, and vancomycin is generally considered to be a suboptimal anti-staphylococcal agent, drug development has focused on

identifying effective treatments for MRSA infections. However, MSSA strains continue to cause a considerable number of *S. aureus* infections.⁷

Despite extensive research on the emergence of MRSA, its clinical course and treatment, few studies have rigorously evaluated the impact of methicillin resistance on the overall incidence of *S. aureus* infections. The treatment of susceptible strains may have created an ecological niche for resistant bacteria that would otherwise not be available. Thus, one may expect that treatment with cloxacillin and other antistaphylococcal β -lactams may result in selective killing of the susceptible strains in the population and allow for replacement by resistant strains.⁸ As a result, increased MRSA rates over time should correlate with a compensatory decline in MSSA.⁹ This hypothesis is concordant with bacterial interference studies showing that colonization with one strain of *S. aureus* prevents subsequent colonization with other strains of *S. aureus*.¹⁰ Alternatively, it is plausible that MRSA and MSSA do not compete, and, thus, increasing MRSA incurs an additive burden of morbidity and mortality. Lastly, there may be both replacement and additive effects, with the magnitude of increased *S. aureus* infection depending on the colonization capacity and invasiveness of different strains (see Figure 1).

Because we reviewed observational studies, it is difficult to draw firm causal conclusions about the biological mechanisms

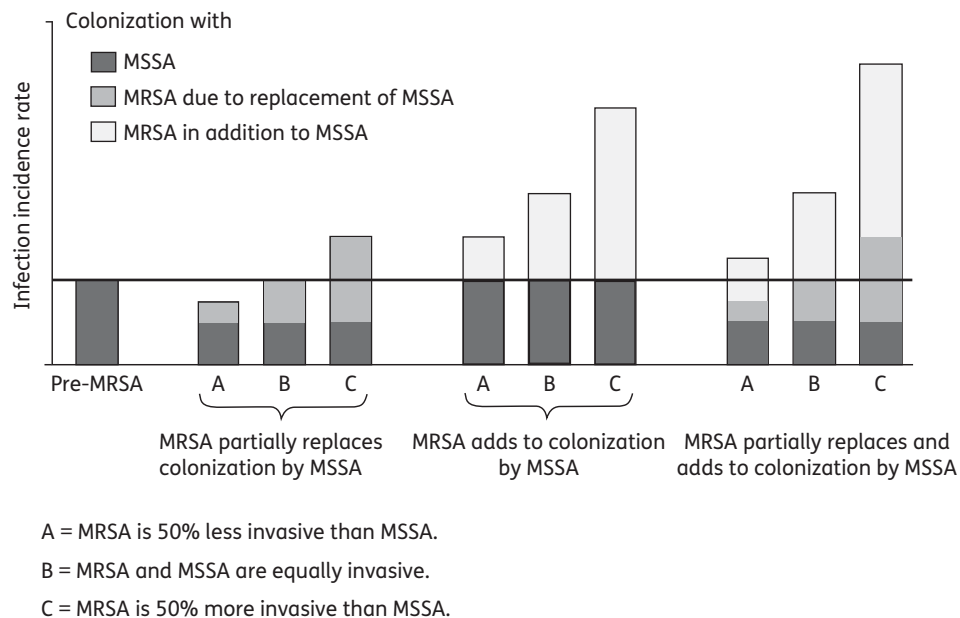


Figure 1. Schematic representing the impact of MRSA on the infection incidence rate for *S. aureus*, depending on both the colonization and infectiveness of MRSA and MSSA. The schematic shows that even if the infection incidence rate of total *S. aureus* is increasing, it may be due to replacement of MSSA, MRSA incidence in addition to MSSA or a combination of the two processes. Furthermore, the magnitude of the increased *S. aureus* infection rates depends on the colonization capacity and invasiveness of different strains. The greater the invasiveness of MRSA relative to MSSA, the greater the impact of MRSA on the total *S. aureus* burden. The horizontal line indicates the *S. aureus* infection incidence rate before the emergence of MRSA.

involved. Ideally, we would compare the incidence and prevalence of MSSA in the presence of MRSA to the same quantities for MSSA in the same population at the same time in the complete absence of MRSA. However, the latter scenario is counterfactual and not observed.¹¹ Therefore, if the studies show that both MRSA and MSSA are increasing, this is consistent with the hypothesis that the two strains do not compete. However, it is also consistent with the possibility that MRSA may partially replace MSSA, yet MSSA continues to increase due to other factors, such as lapses in infection control or an increase in the number of sicker patients vulnerable to infection. Similarly, if the studies show that increasing MRSA is associated with decreasing MSSA, this may suggest that the two strains compete for the same ecological niche. However, it may alternatively be due to a decline in MSSA resulting from improved infection control efforts that are more effective against MSSA than MRSA, combined with the selective emergence of MRSA. At present, we cannot conclusively address these causal questions, though observational studies can provide suggestive evidence. Throughout this review, we therefore emphasize the descriptive question of the absolute incidence of MSSA infections in the presence of MRSA, while commenting on possible causal mechanisms.

Notwithstanding the causal question, there are direct clinical implications of determining whether MSSA infection rates remain stable in the face of increasing MRSA prevalence or whether MSSA is declining in absolute incidence over time. Since MRSA is not susceptible to β -lactam antibiotics, vancomycin is widely used for the empirical treatment of suspected Gram-positive bloodstream infections (BSIs) in patients with MRSA risk

factors. However, vancomycin treatment of invasive MSSA infections is associated with higher microbiological and clinical failure rates, and increased toxicity relative to β -lactam antibiotics.^{12,13} Therefore, if MRSA is expected to replace most or all of MSSA infections, perhaps empirical treatment with vancomycin is correct and research efforts should focus on identifying more effective antimicrobials for MRSA. However, if MSSA is expected to remain prevalent, perhaps investigators should focus on developing rapid diagnostic tests that will distinguish between MRSA and MSSA, and thereby enable immediate therapy with the optimal anti-infective. Additionally, the potential finding that MSSA is expected to remain prevalent indicates that health services must concentrate efforts on preventing all kinds of *S. aureus* infections, and highlights the importance of understanding the factors that promote the coexistence of MRSA and MSSA, at the biological level and at the population level.^{9,14} Understanding the mechanisms underlying the potential coexistence of drug-susceptible and drug-resistant strains may provide insight into the population dynamics of pathogens with drug resistance, and help to identify the distinctive features of MSSA in this context. This review presents data from the relevant epidemiological studies on *S. aureus* to provide insight into the changing epidemiology of *S. aureus* and point to various limitations that should be addressed in future analyses.

Search strategy and selection criteria

Studies for this review were identified by searches of Medline and the references from relevant articles. The search terms were 'methicillin', 'MRSA', 'MSSA', 'resistance', 'trends', 'replacement',

‘addition’, ‘selective pressure’ and ‘competition’. Only English language papers were reviewed. All studies reporting changes in both MRSA and MSSA in human subjects are included in Table 1. The search was limited to publications in English up to 9 February 2011.

In this systematic review, we present details of observational studies on CA-MRSA, HA-MRSA and MSSA (see Table 1). Since these studies are based on different populations and settings, we did not conduct a meta-analysis of the findings. Only one study¹⁵ focused specifically on changes in colonization, so it is unclear whether MRSA is replacing or adding to the frequency of MSSA colonization, or whether colonization rates are similar but MRSA is associated with greater invasiveness, reduced susceptibility to host immune responses and more severe infections. Whether increased MRSA impacts total *S. aureus* levels via changes in colonization or infection or both, the objective of this review is to assess the ultimate impact on disease burden.

Impact of MRSA on MSSA in hospitals

Since MRSA was first identified in nosocomial isolates of *S. aureus* in 1961,¹⁶ it has become endemic in hospitals and intensive care units around the world.⁶ Reports from the National Nosocomial Infection Surveillance System indicate that in the USA, the proportion of methicillin resistance among nosocomial *S. aureus* isolates has increased from 2.4% in 1975¹⁷ to 29% in 1991¹⁸ and 64.4% in 2003.¹⁹ In the UK, the proportion of *S. aureus* due to MRSA increased from 2% in 1990 to >40% in the early 2000s.²⁰

Many anticipated that MRSA would ultimately replace MSSA in a process similar to what happened in the 1960s when penicillin-susceptible *S. aureus* was replaced by resistant strains.²¹ Two early studies lent support to this hypothesis. Between 1979 and 1980, the number of hospital-acquired *S. aureus* BSIs, pulmonary infections and post-operative wound infections at the University of Virginia Medical Center remained unchanged, but there was a statistically significant increase in the proportion of *S. aureus* BSIs (13% versus 40%) and post-operative wound infections (27% versus 49%) that were methicillin resistant.²² In a similar study,²³ there was a stable incidence of nosocomial *S. aureus* BSIs in 1977–80, ranging from 4.5 to 5.0 cases per 1000 admissions during the 4 years of the study, but as MRSA BSIs increased to 1.2 per 1000 admissions in 1979, MSSA BSIs decreased to 3.5 per 1000; when MRSA BSIs decreased in 1980, MSSA BSIs increased.

With few exceptions,^{24,25} later studies typically found that the incidence of MSSA infections did not decrease in the face of rising MRSA prevalence.^{26–36} For instance, Stamm *et al.*³⁰ found that in 1986–91, the total risk of *S. aureus* infection increased from 14 to 17 cases per 1000 admissions, including an increased risk of MRSA infections (from 0 to 3 per 1000 admissions) and MSSA infections (from 5 to 7 per 1000 admissions). Other studies^{37–39} showed that infection control efforts led to declines in MRSA with no reciprocal increase in MSSA infections. In recent years, additional studies have accumulated, demonstrating that HA-MRSA does not simply replace MSSA, but rather it has led to an increase in the total number of *S. aureus* infections.^{40–49}

Rather than indicating a causal mechanism of independent ecological niches instead of strain replacement, this may be due to a changing case mix, such as increases in length of

stay. In a study of two Oxfordshire hospitals, Wyllie *et al.*⁴¹ reported that between 1997 and 2003, there was an increase in the number of nosocomial BSIs among hospital admissions, including a constant proportion due to MSSA BSIs and an increase in the proportion due to MRSA. However, although the unadjusted incidence of MSSA BSIs remained constant over time, when factors related to increased risk, including aging of the hospital population and increases in length of stay, are accounted for in a multivariable analysis, the incidence of MSSA BSIs appears to have decreased as MRSA BSIs increased. This discrepancy highlights the distinction between questions regarding clinical implications and causal mechanisms; when considering the overall burden of MRSA and MSSA in the total population irrespective of age and other risk factors, the unadjusted measures are relevant. However, when attempting to understand the causal association between MRSA and MSSA, adjusted measures are used to remove differences in the composition of the populations at the different timepoints to allow for comparisons independent of these extraneous factors.

In summary, most observational studies suggest that the growing disease burden of HA-MRSA has not been temporally associated with a decline in the burden of MSSA. Although most of the studies reported frequencies or proportions and not rates, and some of the studies only included 1 year of observation^{22,31} or consisted of small sample sizes,^{27,30} this finding appears to be consistent across studies (see Figure 2).

Impact of MRSA on MSSA in the community

In the past, MRSA was solely a nosocomial pathogen. However, in the late 1990s, MRSA infections were reported in young otherwise healthy people, causing infections with worse clinical outcomes than are seen with infections caused by HA-MRSA strains. Some of the earliest cases of CA-MRSA infection occurred among Western Australian aborigines who lived in a remote community with no access to healthcare centres.⁵⁰ In the USA, the CDC reported that between 1997 and 1999, four previously healthy children from the upper midwestern USA with no previous contact with healthcare facilities rapidly died of MRSA infections.⁵¹ Soon thereafter, CA-MRSA infections were identified among men who have sex with men and among incarcerated people in other areas.⁵² Since these initial reports, CA-MRSA has become epidemic in the USA^{53,54} and other countries,^{55,56} causing diseases ranging from mild and severe skin infections to fatal necrotizing pneumonia.⁵⁷ According to a 2006 study, it is the leading identifiable cause of SSTIs in US emergency department (ED) patients.⁵⁸

Initially, investigators distinguished between HA-MRSA and CA-MRSA by their different genetic characteristics, which result in important phenotypic effects.^{59,60} HA-MRSA strains are usually multiresistant to non- β -lactam antibiotics and contain staphylococcal cassette chromosome *mec* (SCC*mec*) type I, II or III. In contrast, CA-MRSA strains were initially susceptible to most antistaphylococcal antimicrobials, they have low methicillin MICs, they usually carry the smaller genetic island SCC*mec* type IV or V element and they have distinct genetic determinants of virulence, including Pantone–Valentine leucocidin, a cytotoxin that causes leucocyte destruction and tissue necrosis. Although these characteristics initially distinguished HA-MRSA from

Table 1. Studies reporting the impact of HA-MRSA and CA-MRSA on the overall burden of *S. aureus* in hospitals and communities

Reference (first author, year)	Study period	Location	Setting	Case detection	Case definition	Measure ^a	Main findings
Impact of MRSA on MSSA in hospitals							
Thompson, 1982 ²²	1979–80	Virginia, USA	hospital-wide	microbiology results, surveillance of HR patients	SAB, post-operative wound infection, pneumonia	2, 4	no change in incidence of <i>S. aureus</i> infections (from 0.20 to 0.25 <i>S. aureus</i> infections per 100 admissions); ↑ in % <i>S. aureus</i> infections due to MRSA (SAB: from 13% to 40%; post-operative wound infections: from 27% to 49%; pneumonia: from 19% to 24%)
Linnemann, 1982 ²³	1977–80	Cincinnati, USA	burn and surgical ICU	microbiology results, surveillance of HR patients	SAB	2, 5 ^b	incidence of SAB constant (from ~4.5 to 5.0 cases per 1000 admissions); as MRSA ↑ to 1.2 per 1000 admissions in 1979, MSSA ↓ to 3.5 per 1000; when MRSA ↓ in 1980, MSSA ↑
Pavillard, 1982 ²⁶	1978–80	Melbourne, Australia	population-based	questionnaire administered to hospital directors	<i>S. aureus</i> colonization or infection	1, 4	MRSA ↑ from 2 patients in 1978 (<2% of <i>S. aureus</i>) to 46 patients in 1979 (30% of <i>S. aureus</i>); MSSA frequency varied with no systematic trend
Boyce, 1983 ²⁷	1979–83	Mississippi, USA	burn unit	microbiology results	SAB	2, 4 ^b	↑ in % infections due to <i>S. aureus</i> (from 11% to 15%) and % <i>S. aureus</i> infections due to MRSA (from 11% to 32%)
Mylotte, 1987 ²⁸	1977–85	New York, USA	hospital-wide	microbiology results	SAB	1, 2	↑ in SAB (16.1 per 10000 discharges to 28.5 per 10000 discharges; from <i>n</i> =20 to 41), including ↑ in MRSA (from <i>n</i> =0 to 12) and MSSA (from <i>n</i> =20 to 29)
Tam, 1988 ²⁹	1976–85	Hong Kong, China	neonatal unit	microbiology results	severe <i>S. aureus</i> infection	1, 5 ^b	in 1976–80 versus 1981–85, ↑ in # of MRSA (from 7 to 35) and 4.5-fold ↑ in MRSA per 1000 admissions (from 2.5 to 11.2), # of MSSA constant (~1 or 2 per year)
Law, 1988 ³⁷	1985–86	London, England	acute medical and surgical wards	microbiology results	SAB and urinary tract infections	1 ^b	in response to infection control efforts, MRSA infections ↓ while MSSA infections remained fairly constant
Stamm, 1993 ³⁰	1986–91	Alabama, USA	hospital-wide	microbiology results	SAB	2, 5	↑ in total <i>S. aureus</i> (from 1.4 to 1.7 infections per 100 admissions), including ↑ in MRSA (from 0 to 0.3 infections per 100 admissions) and MSSA (from 0.5 to 0.7 infections per 100 admissions)

Pujol, 1994 ³¹	1990–91	Barcelona, Spain	hospital-wide	microbiology results, screening of HR patients	<i>S. aureus</i> colonization or SAB	1 ^b	↑ in # of total <i>S. aureus</i> , including ↑ in both MRSA and MSSA
Jernigan, 1995 ³²	1986–93	Virginia, USA	hospital-wide	microbiology results, surveillance of HR patients	<i>S. aureus</i> colonization or infection	4, 5 ^b	% <i>S. aureus</i> due to MRSA was constant in 1986–89 (5.4%), but ↑ to 17.7% thereafter; no correlation between the # of MRSA and MSSA infections per 1000 admissions
Spindel, 1995 ²⁴	1987–91	Vancouver, Canada	nursing home	microbiology results	<i>S. aureus</i> infection	1, 2, 6	stable # and rate per 1000 resident-days of total <i>S. aureus</i> (~12 cases per year, from 0.29 to 0.33 per 1000 resident-days); ↑ in # and rate of MRSA (from 0 to 5 cases, from 0 to 0.14 per 1000 resident-days), ↓ in # and rate of MSSA (from 12 to 7 cases, from 0.29 to 0.19 per 1000 resident-days)
Speller, 1997 ³³	1989–95	England and Wales	population-based	microbiology results	SAB	1, 2, 4 ^b	↑ in # of total <i>S. aureus</i> (from 3526 to 5770), representing constant proportion of all isolates; ↑ in # of MRSA (from 56 to 762) and % <i>S. aureus</i> due to MRSA (from 1.6% to 13.2%), ↑ in # of MSSA (from 3470 to 5008), ↓ in % <i>S. aureus</i> due to MSSA (from 98.4% to 86.8%)
Morgan, 1999 ³⁴	1993–97	Wales	population-based	microbiology results	<i>S. aureus</i> colonization or infection ^c	1, 4	↑ in # of total <i>S. aureus</i> (from 323 to 770), ↑ in # of MRSA and % isolates due to MRSA (from 11/2059=0.5% to 292/3924=7.4%), ↑ in # of MSSA but ↓ in % isolates due to MSSA (from 252/2059=12.2% to 379/3924=9.7%)
Albertini, 2002 ²⁵	1996–2000	France	population-based	microbiology results	<i>S. aureus</i> colonization or infection	1, 4, 6	no change in # of total <i>S. aureus</i> (from 6834 to 6824); ↑ in # of MRSA (from 2433 to 2798), % <i>S. aureus</i> due to MRSA (from 35.6% to 41.0%) and rate of MRSA (from 0.71 to 0.96 per 1000 hospital-days); ↓ in # of MSSA (from 4401 to 4026) and % <i>S. aureus</i> due to MSSA (from 64.4% to 59.0%)

Continued

Table 1. Continued

Reference (first author, year)	Study period	Location	Setting	Case detection	Case definition	Measure ^a	Main findings
Assadian, 2003 ³⁵	1994–98	Austria	population-based	questionnaire administered to hospital directors	<i>S. aureus</i> colonization or infection ^c	1, 2, 4, 5	↑ in # of total <i>S. aureus</i> (from 3012 to 22179), including ↑ in # of MRSA (from 476 to 1825) and MSSA (from 2536 to 20354); ↑ in # per 1000 hospital admissions with any <i>S. aureus</i> (from 7.07 to 15.73), MRSA (from 0.85 to 1.29) and MSSA (from 6.22 to 14.44); ↓ in % <i>S. aureus</i> due to MRSA (from 15.8% to 8.2%) and ↑ in % <i>S. aureus</i> due to MSSA (from 84.2% to 91.8%)
Seal, 2003 ³⁶	1986–2000	Chicago, USA	hospital-wide	microbiology results	<i>S. aureus</i> clinical isolates ^d	1, 4 ^b	↑ in # of total <i>S. aureus</i> (from 874 to 1176), including ↑ in # of MRSA (from 114 to 329) and MSSA (from 760 to 847); ↑ in % <i>S. aureus</i> due to MRSA (from 13% to 28%) and ↓ in % <i>S. aureus</i> due to MSSA (from 87% to 72%)
Whyte, 2005 ⁴⁰	2002–04	Limerick, Ireland	population-based	microbiology results	SAB ^c	1, 4, 6	# of total <i>S. aureus</i> was 96, 70 and 79; % <i>S. aureus</i> due to MRSA was 44%, 56% and 48%; rate of MRSA per 1000 bed-days was 0.176, 0.159 and 0.152
Wyllie, 2006 ⁴¹	1997–2003	Oxford, England	medical, surgical and trauma specialties	microbiology results	SAB	2, 5 ^b	↑ in # of <i>S. aureus</i> per 100000 admissions and # of MRSA per 100000 admissions; # of MSSA per 100000 admissions did not alter; after adjustment for case mix, ↑ in # of <i>S. aureus</i> per 100000 admissions (1.06 per year), ↑ in # of MRSA per 100000 admissions (1.22 per year) and ↓ in # of MSSA per 100000 admissions (0.93 per year)
Anderson, 2007 ⁴²	2000–05	south-eastern USA	population-based	microbiology results, screening of surgical patients, clinical rounds, questionnaire to surgeons	severe SSI	1, 2, 5 ^b	↑ in # of <i>S. aureus</i> per 100 procedures (from 0.39 to 0.49), ↑ in # of MRSA (from 24 to 56) and ↑ in # of MRSA per 100 procedures (from 0.12 to 0.23); no change in MSSA

van der Mee-Marquet, 2007 ⁴³	2004–06	France	population-based	microbiology results	SAB ^c	1, 4, 6	↑ in # of <i>S. aureus</i> (from 122 to 157), including ↑ in # of MRSA (from 33 to 46) and MSSA (from 89 to 111), but corresponds to stable % <i>S. aureus</i> due to MRSA (from 33/122=27% to 46/157=29%) and MSSA (from 89/122=73% to 111/157=71%); ↑ in rate of total <i>S. aureus</i> (from 0.202 to 0.234 per 1000 patient-days), MRSA (from 0.055 to 0.068 per 1000 patient-days) and MSSA (from 0.147 to 0.165 per 1000 patient-days)
Allard, 2008 ⁴⁴	1991–2005	Quebec, Canada	hospital-wide	microbiology results	SAB ^d	3	in 1997–99 versus 2003–05, ↑ in MRSA (from 0 to 7.4 per 100000 inhabitants) and MSSA stable (from 24.1 to 25.0 per 100000 inhabitants)
Robicsek, 2008 ¹⁰¹	2003–07	Illinois, USA	hospital-wide	microbiology results, screening of all ICU admissions	SAB	6	in response to infection control efforts, ↓ in rate of total <i>S. aureus</i> (from 8.9 to 3.9 per 10000 patient-days), including ↓ in rate of MRSA (from 2.1 to 1.1 per 10000 patient-days) and ↓ in rate of MSSA (from 2.1 to 1.6 per 10000 patient-days)
Burton, 2009 ⁴⁵	1997–2007	USA	population-based: ICUs	National Nosocomial Infection Surveillance System	central line SAB	4, 6	25.8% ↑ in % <i>S. aureus</i> due to MRSA (from 47.9% to 64.5%), 49.6% ↓ in rate of MRSA (from 0.43 to 0.21 per 1000 central line-days) and 70.1% ↓ in rate of MSSA (from 0.31 to 0.09 per 1000 central line-days)
Hacek, 2009 ⁴⁶	2002–07	Illinois, USA	hospital-wide	screening of all patient admissions	<i>S. aureus</i> clinical isolates ^c	1	in response to infection control efforts, ↓ in # of total <i>S. aureus</i> (from 842 to 649) and # of MRSA (from 434 to 255); # of MSSA remained constant (~400 per year)
Pearson, 2009 ⁴⁷	2004–08	England	population-based	microbiology results	voluntary: clinically significant SAB mandatory: microbiology results ^c	1 ^b	voluntary: ↓ in # of total <i>S. aureus</i> , 53% ↓ in # of MRSA, # of MSSA stable in 2004–06, then 6% ↑ in 2007 mandatory: ↓ in # of total <i>S. aureus</i> , 56% ↓ in # of MRSA, ↓ in # of MSSA

Continued

Table 1. Continued

Reference (first author, year)	Study period	Location	Setting	Case detection	Case definition	Measure ^a	Main findings
Chuang, 2010 ⁶⁵	1981–2007	Taipei, Taiwan	hospital-wide	microbiology results	<i>S. aureus</i> infection and SAB ^c	5 ^b	↑ in <i>S. aureus</i> infections (from 0.199 to 0.404 per 100 discharges), ↑ in MRSA infections (from 0.028 to 0.272 per 100 discharges), ↓ in MSSA infections (from 0.164 to 0.132 per 100 discharges); ↑ in SAB (0.024 to 0.203 per 100 discharges), ↑ in MRSA SAB (from 0.000 to 0.138 per 100 discharges), ↑ in MSSA SAB (from 0.020 to 0.066 per 100 discharges)
Chen, 2010 ⁴⁸	1994–2008	Beijing, China	hospital-wide	microbiology results	<i>S. aureus</i> clinical isolates ^c	1	↑ in # of MRSA (from 33 to 60) and # of MSSA (from 17 to 40)
Rodríguez-Baño, 2010 ³⁹	1995–2008	Seville, Spain	hospital-wide, patients and healthcare workers	microbiology results	<i>S. aureus</i> colonization or infection	1, 4, 6	in response to infection control efforts, ↓ in # of MRSA colonization or infection (from 190 to 65), ↓ in rate of MRSA colonization (from 0.56 to 0.07 per 1000 patient-days) and ↓ in % <i>S. aureus</i> due to MRSA (from 47 to 11); stable rate of MSSA (0.12 per 1000 patient-days), though intervention aimed specifically at MRSA (decolonization of MRSA at admission)
Wilson, 2011 ⁴⁹	2004–08	England	population-based	microbiology results	SAB ^c	1	↓ in # of total <i>S. aureus</i> (from 10 609 to 8255), ↓ in # of MRSA (from 4216 to 1893), # of MSSA constant (from 6393 to 6362)
Impact of MRSA on MSSA in the community							
Wyllie, 2005 ⁶⁸	1997–2003	Oxford, England	medical, surgical and trauma specialties	microbiology results	SAB	1, 4	# of <i>S. aureus</i> infections fairly stable, but ↑ in % <i>S. aureus</i> due to MRSA from 14% (16/115) in 1997–98 to 24% (25/105) in 2003
Kaplan, 2005 ⁶⁹	2001–04	Texas, USA	children's hospital	microbiology results	SAB (95.6% SSTI)	1, 4 ^b	2.2-fold ↑ in # of CA-MRSA and 1.7-fold ↑ in # of CA-MSSA isolates; % <i>S. aureus</i> due to MRSA ↑ from 71.5% (551/771) to 76.4% (1193/1562)
McCaig, 2006 ⁷⁰	1992–2003	USA	population-based	National Ambulatory Medical Care Surveys and National Hospital Ambulatory Medical Care Surveys	physician office, outpatient and ED visits for SSTI	3 ^b	no difference in # of overall and physician office visits for SSTIs per 10 000 inhabitants in 1992–94 versus 2001–03, but 59% ↑ in # of outpatient SSTI visits per 10 000 inhabitants and 31% ↑ in # of ED SSTI visits per 10 000 inhabitants

Arnold, 2006 ⁷¹	2000–04	Tennessee, USA	children's hospital	microbiology results	acute osteomyelitis or septic arthritis	1, 5 ^b	↑ in % infections due to MRSA (from 4% to 40%), % infections due to MSSA remained constant (from 10% to 13%)
Fortunov, 2006 ⁷²	2001–05	Texas, USA	neonatal unit	microbiology results	SAB	1, 4 ^b	↑ in # of <i>S. aureus</i> infections and % <i>S. aureus</i> due to MRSA from 50% (10/20 infections) in 2002 to 83% (30/36 infections) in 2004; absolute # of MSSA isolates remained steady or ↓ slightly
Manzur, 2007 ⁷³	1991–2003	Barcelona, Spain	hospital-wide	microbiology results	SAB	5	the incidence of MRSA BSIs at hospital admission increased from 0.08 to 0.37 cases per 1000 admissions; the incidence of MSSA BSIs at hospital admission remained constant, with an average of 2.45 cases per 1000 admissions
Klein, 2007 ⁷	1999–2005	USA	population-based	National Hospital Discharge Survey	<i>S. aureus</i> -related hospitalizations ^d	1, 2, 5	↑ in # of <i>S. aureus</i> (from 294 570 to 477 927) and # of <i>S. aureus</i> per 1000 hospital admissions (from 9.17 to 13.79); ↑ in # of MRSA (from 127 036 to 278 203), % <i>S. aureus</i> due to MRSA (from 43% to 58%) and # of MRSA per 1000 hospital admissions (from 3.95 to 8.02); ↑ in # of MSSA (from 167 534 to 199 724), ↓ in % <i>S. aureus</i> due to MSSA (from 57% to 42%), ↑ in # of MSSA per 1000 hospital admissions (from 5.21 to 5.76)
Hota, 2007 ⁷⁴	2000–05	Chicago, USA	ED, clinics and inpatient wards	microbiology results	SSTI	1, 3, 4 ^b	↑ in # of CA-MRSA and CA-MSSA isolates, and in % <i>S. aureus</i> due to CA-MRSA; ↑ in CA-MRSA infections from 24.0 to 164.2 per 100 000 inhabitants; ↑ in CA-MSSA infections from 90.7 to 121.9 per 100 000 inhabitants
Hersh, 2008 ⁷⁵	1997–2005	USA	population-based	National Hospital Ambulatory Medical Care Survey	SSTI ED visits and hospitalizations	3 ^b	↑ in # of SSTIs per 1000 inhabitants (from 32.1 to 48.1); ↑ in # of abscess/cellulitis (from 17.3 to 32.5 per 1000 inhabitants)
Pallin, 2008 ⁷⁶	1993–2005	USA	population-based	National Hospital Ambulatory Medical Care Survey	ED visits for SSTI	1	↑ in # of SSTIs (from 1.2 million to 3.4 million, from 1.35% to 2.98% of ED visits); antibiotics against CA-MRSA rarely used in 1993–2001, but ↑ to 38% by 2005

Continued

Table 1. Continued

Reference (first author, year)	Study period	Location	Setting	Case detection	Case definition	Measure ^a	Main findings
Laupland, 2008 ⁷⁷	2000–06	Calgary, Canada	population-based	microbiology results	SAB	3 ^b	# of total SAB per 100 000 inhabitants with HA-MRSA and HA-MSSA were similar throughout the study, but CA-MRSA ↑ as CA-MSSA ↓
Gorwitz, 2008 ¹⁵	2001–04	USA	population-based	National Health & Nutrition Examination Survey	nasal colonization with <i>S. aureus</i>	1, 3	in 2001–02 versus 2003–04, MRSA ↑ from 0.8% (2.3 million people) to 1.5% (4.1 million people) of the US population and <i>S. aureus</i> ↓ from 32.4% (89.4 million people) to 28.6% (78.9 million people) of the US population
Dailiana, 2008 ⁷⁸	2003–06	Thessalia, Greece	orthopaedic surgery unit and outpatient clinics	microbiology results	ulcerative upper extremity infections	1	↓ in # of total <i>S. aureus</i> (from 66 to 34), ↑ in # of MRSA (from 13 to 20), ↓ in # of MSSA (from 53 to 14)
Price, 2008 ⁷⁹	2003–05	'urban hospital'	orthopaedic surgery unit	screening of pre-operative outpatients	nasal colonization with <i>S. aureus</i>	1, 2, 5	↑ in # of total <i>S. aureus</i> and % of patients with <i>S. aureus</i> (from 25/78=32% to 37/97=38%), ↑ in # of MRSA and % of patients with MRSA (from 0/78=0% to 4/97=4%), no change in # of MSSA and % of patients with MSSA (from 25/78=32% to 33/97=34%)
Tattevin, 2009 ⁸⁰	1997–2006	California, USA	hospital-wide	microbiology results	<i>S. aureus</i> clinical isolates	1, 5	↓ in # of total <i>S. aureus</i> , including ↑ in # of patients with MRSA (from 56/147=38.1% to 99/137=72.3%) and ↓ in # of patients with MSSA (from 91/147=61.9% to 38/137=27.7%)
Orscheln, 2009 ⁸¹	1999–2007	Missouri, USA	children's hospital	microbiology results	SSTI	1 ^b	50-fold ↑ in # of MRSA abscess cultures and 5-fold ↑ in # of MSSA abscess cultures

#, number; ↑, increase; ↓, decrease.

SAB, *S. aureus* bacteraemia (i.e. BSIs); SSI, surgical site infection; HR, high risk; ICU, intensive care unit.

^a1=number of *S. aureus* or MRSA or MSSA (frequency); 2=number of *S. aureus* among all isolates/infections/procedures/admissions (proportion); 3=number of *S. aureus* or MRSA or MSSA among all inhabitants (proportion); 4=number of MRSA or MSSA among all *S. aureus* isolates/infections/procedures/admissions (proportion); 5=number of MRSA or MSSA among all hospital admissions/procedures (proportion); 6=number of *S. aureus* or MRSA or MSSA per person-days (rate).

^bSome measures were presented in a figure, so point estimates cannot be reported here.

^cSome studies did not distinguish between isolates.

^dSome studies reported that both HA-MRSA and CA-MRSA isolates are included in the analysis.

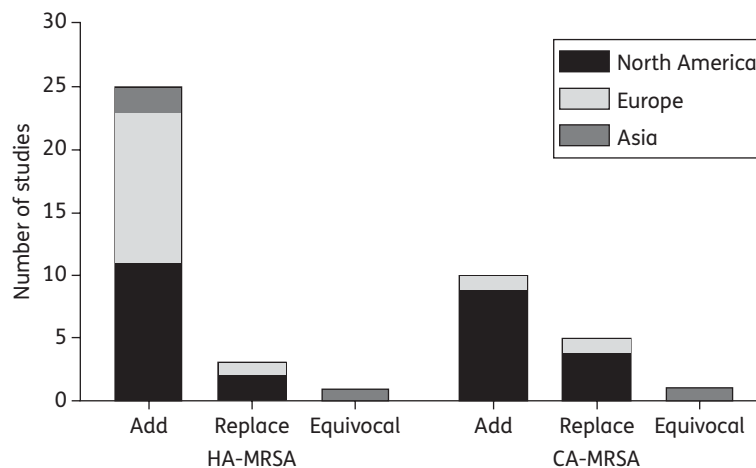


Figure 2. Number of studies identified from North America, Europe and Asia reporting evidence that MRSA is replacing MSSA, adding to MSSA or the study results are equivocal. The figure represents the conclusions from the 45 studies identified for this review. The figure does not account for differences in study quality or size, and it does not distinguish between colonization and infection.

CA-MRSA, there has been an increasing blurring of the two categories over time.^{61,62} Since asymptomatic colonization can persist for months to years,³⁸ the setting of organism acquisition may differ from that of disease onset. Thus, there are a few reports of community-onset HA-MRSA infections⁶³ and several reports of nosocomial CA-MRSA outbreaks.⁶⁴ Several of the studies identified for this review did not distinguish between HA-MRSA and CA-MRSA^{34,35,39,40,43,46–49,65} or stated that both types were included in their analysis.^{7,36,44}

Otter and French⁵⁶ note reasons why CA-MRSA colonization and infection may be underestimated. First, most carriers are not infected and therefore are likely to remain undetected. Second, although most patients with HA-MRSA infections have nasal colonization,² there have been reports of CA-MRSA colonization of non-nasal sites and infection without colonization at usual sites of colonization.^{66,67} Third, even when infections are present, patients are often treated in community or outpatient settings, where cultures for *S. aureus* might not be performed. Fourth, since community-associated strains are increasingly isolated in patients with healthcare contact and are gaining multi-drug resistance, they might be misclassified as HA-MRSA.⁶⁴ On the other hand, reports of increasing CA-MRSA over time may be due to increased reporting instead of a true increase in disease incidence. For instance, as public concern over MRSA increases, patients who may have treated infections at home or waited to see their physician may be more likely to visit the ED and physicians may be more likely to diagnose non-infectious conditions as SSTIs.

Despite these challenges, researchers have evaluated whether increased CA-MRSA is associated with a decline in MSSA in the community.^{7,15,68–81} In these studies, organisms were considered to be community acquired if the isolate was obtained from a patient with no underlying illnesses predisposing to frequent hospitalizations and if it was isolated either in an outpatient setting or in a hospital within 48 h of admission. In a study of CA-MRSA infection in children hospitalized in 2001–04,⁶⁹ the proportion of community-acquired *S. aureus* isolates that were methicillin resistant increased from 71.5% to 76.4%;

the number of CA-MRSA isolates increased 2.2-fold and the number of CA-MSSA isolates increased 1.7-fold. Similarly, Hota *et al.*⁷⁴ reported that from 2000 to 2005, the incidence of CA-MRSA SSTIs increased from 24.0 to 164.2 cases per 100 000 inhabitants and the incidence of CA-MSSA SSTIs increased from 90.7 to 121.9 cases per 100 000 inhabitants.

Some studies evaluated trends in outpatient visits for SSTIs as a proxy for changes in CA-MRSA.^{70,75,76} Pallin *et al.*⁷⁶ analysed data from the National Hospital Ambulatory Medical Care Survey for 1993–2005 to examine whether the frequency of ED visits for SSTIs increased contemporaneously with the emergence of CA-MRSA or whether this organism merely replaced others, with the underlying disease incidence remaining the same. Diagnoses of SSTIs increased from 1.2 million visits in 1993 (1.35% of all ED visits) to 3.4 million visits in 2005 (2.98% of all ED visits). Although data on the cause of the observed infections were not available, the results may suggest that ED utilization for SSTIs is increasing both in absolute terms and relative to all other conditions, and that CA-MRSA may be causing more disease, rather than displacing other organisms from pre-existing ecological niches.

In contrast to the studies suggesting that CA-MRSA adds to the total burden of *S. aureus*, three recent studies have reported that CA-MRSA replaces MSSA in the community.^{15,77,80} In a population-based study of *S. aureus* infections between 2000 and 2006,⁷⁷ the incidence of healthcare-associated and nosocomial MSSA BSIs was similar throughout the study. However, as the incidence of CA-MRSA BSIs increased, the incidence of community-acquired MSSA BSIs decreased. One study¹⁵ focused on colonization rather than infection, reporting that CA-MRSA has in fact started replacing MSSA to establish itself as commensal flora, just as penicillin-resistant *S. aureus* replaced its penicillin-susceptible predecessor in the 1940s. In a nationally representative survey of nasal *S. aureus* colonization between 2001 and 2004,¹⁵ the estimated proportion of the US population colonized with CA-MRSA increased from 0.8% (2.3 million people) to 1.5% (4.1 million people), but the proportion colonized with any *S. aureus* decreased from 32.4% (89.4 million people) in 2001–02 to 28.6% (78.9

million people) in 2003–04. The authors hypothesized that the decline in MSSA colonization is due to increased population-level exposure to antimicrobials that may suppress MSSA and promote colonization with MRSA. However, this study reports colonization rather than infection, so it is not necessarily comparable to other studies addressing the impact of MRSA on disease burden; whereas the estimated number of *S. aureus*-related hospitalizations increased 62% between 1999 and 2005,⁷ this study indicates that total *S. aureus* colonization is decreasing. The reason for such discrepant findings on the impact of CA-MRSA on total *S. aureus* is unclear. The results suggesting MSSA replacement, however, cannot be ignored, as both analyses involved large well-designed population-based cohorts. In summary, so far, the research suggests that CA-MRSA has most likely increased the total burden of *S. aureus* infections rather than simply displacing the problem of MSSA, though one colonization study suggests that colonization with CA-MRSA has coincided with reduced MSSA colonization.

Limitations of current research

There is an urgent need to clarify the prevalence and epidemiology of *S. aureus* infections and the relationship between susceptible and resistant strains. Since resistance development is an evolutionary process, continuing surveillance is essential to identify emerging pathogens at national and global levels, to create and refine strategies for controlling antimicrobial resistance and to guide clinical decisions regarding appropriate treatment. In order to improve the quality of these efforts, limitations of previous studies should be remedied in future analyses.

Many studies reported the proportion of isolates collected that are resistant to methicillin without reporting the total number of isolates or person-time used in the denominator. Though an increase in the proportion of isolates that are methicillin resistant inevitably results in a corresponding decreasing proportion due to MSSA, the absolute frequency of MSSA may decrease, remain stable or increase.⁸² Additionally, comparisons between proportions are vulnerable to the effects of chance variability, regression to the mean and low power to detect genuine underlying changes.⁸³ Therefore, it is preferable to report changes in the incidence rate of resistant and susceptible infections.^{40,84,85} Due to confusion in the terminology, many authors claimed to report rates of resistance, when in fact they had calculated proportions or vice versa. Several authors^{7,34} have provided examples showing why it is misleading to report trends using proportions without presenting absolute frequencies. Between 1999 and 2005, there was an increase in the number of MRSA-related hospitalizations, which represented an increase in the proportion of all *S. aureus*-related hospitalizations (127036/294570=43% to 278203/477927=58%). The number of MSSA-related hospitalizations increased, but this represented a decrease in the proportion of all *S. aureus*-related hospitalizations (167534/294570=57% to 199724/477927=42%).⁷ Similarly, Burton *et al.*⁴⁵ underscored the discrepancy between measures using data from US intensive care units in 1997–2007. While the overall proportion of *S. aureus* central line-associated BSIs due to MRSA increased by 25.8%, the rate of MRSA and MSSA BSIs per 1000 central line-days declined by 49.6% and 70.1%, respectively.

It is also difficult to compare results within and between studies when baseline rates differ, because these differences result in different levels of statistical power to detect these changes. When the MRSA or MSSA case count is low at baseline, a small incremental increase may represent a large proportional increase, but when case counts are higher, small incremental changes represent a smaller proportion of the sample. For instance, imagine a study that reports a baseline incidence of 1 MRSA case per 1000 admissions and 20 MSSA cases per 1000 admissions. At the end of the study, the incidence of MRSA has increased to 2 per 1000 admissions and the incidence of MSSA has decreased to 19 per 1000 admissions. Whereas a study may have the power to detect the 2-fold increase in MRSA, a similar one-unit change in MSSA represents a smaller proportional change and hence may not be detected in a statistical test.

Based on the published studies, it is unclear whether changes in the rates of MSSA and total *S. aureus* BSIs are causally related to changes in the rates of MRSA, or whether they are due to changes in screening and reporting protocols, population characteristics, healthcare practices, infection control efforts, geographical and temporal trends in microbial use, other sources of antimicrobial exposure in the community or a combination of factors.^{86,87} Trends in the number of MRSA infections may be due to changes in the number of total hospital admissions and in risk factors, such as co-morbidities and length of stay. Case definitions may vary between surveillance studies and over time, especially with the blurring of CA-MRSA and HA-MRSA. In response to increasing concerns about MRSA, clinicians may have obtained more specimens for culture, they may have attributed more non-infectious inflammatory conditions to MRSA or they may have been more likely to ask patients to return to the hospital for follow-up reassessments. Thus, ascertainment bias may have led to an inflated number of visits for resistant strains and under-reporting of infections caused by susceptible strains.

Many of the earlier studies constructed pre–post comparisons or tests for trend over several time periods. However, the statistical tests used in such studies assume that outcomes are independent, which is untenable in the setting of transmissible pathogens.⁸⁸ The use of time-series methods to study trends in *S. aureus* infections may improve the quality of these analyses, by accounting for the non-independence between cases. However, in attempting to assess causality from trends detected in this way, several difficulties arise. Proper statistical modelling of time-varying confounding factors can be challenging in time-series models. Furthermore, while accounting for changes in population risk factors may be possible by collecting demographic information and medical histories, it is far more challenging to prevent bias arising from changes in whether or not a patient seeks medical care, whether the treating physician obtains a bacteriological sample, and, if so, the method used to collect and process samples and the interpretation and reporting of the culture results. At the very least, guidelines for when cultures should be obtained and automated reporting of laboratory results may help minimize differences in the decision-making process, and help to standardize the process of collection and reporting between physicians and over time.

With the constant exchange of pathogens between community and nosocomial settings, surveillance systems that track

carriers through repeated transitions between healthcare and community settings⁸⁹ may be beneficial. Also, since resistant organisms may be more likely to be isolated multiple times,⁹⁰ it would be useful to conduct a longitudinal study following the same people over time, instead of cross-sectional estimates on different people at different timepoints. Pooling data from multiple surveillance programmes may help to identify reasons for discrepancies in infection rates and help elucidate potential interventions to mitigate or perhaps prevent further antimicrobial resistance.⁹¹ However, since hospitals may differ in their screening intensity and diagnostic practices, and they may include different case mixes due to variation in the care provided in each hospital and differences in referral practices, caution must be exercised when aggregating data from different populations.^{82,92} Additionally, most of the prior studies examined the increased burden of MRSA over MSSA in terms of in-hospital outcomes or cross-sectional surveillance of colonization levels and not long-term effects, which may indicate a different trend. For instance, despite an increase in the proportion of MRSA-related hospitalizations over time, the proportion of MRSA-related hospitalizations that resulted in death decreased over the study period.^{7,44,93} Therefore, use of mortality data and other measures of long-term outcomes deserve attention.

Combining efforts for epidemiological investigation with microbiological typing is essential for accurately documenting the evolving epidemiology of *S. aureus*, and may help focus infection control efforts and define reservoirs of transmission. The prevalence of methicillin resistance among *S. aureus* isolates varies widely between countries, regions, hospitals and different wards within the same hospital.⁹⁴ The rates of HA-MRSA vary within the USA, with more HA-MRSA infections seen in the south.⁹⁵ In Europe, the proportion of *S. aureus* isolates that are resistant to methicillin is only 0.5% in Iceland and <1% in Finland, but 10%–30% in Denmark and 44% in Greece.^{94,96} This variability may be due to different MRSA strains with different colonization and/or virulence characteristics, differences in infection control practices⁹⁷ or differences in population characteristics related to increased risk of MRSA infection.⁹⁸ The genotype distribution of CA-MRSA also varies by geographical region. In North America, USA300 (ST8; where ST stands for sequence type) and USA400 (ST1) are the predominant clones, whereas the most common strain in Europe is ST80, in Taiwan it is ST59 and in eastern Australia it is ST30.⁵⁴ The reason for this geographical variation remains a mystery. Molecular studies are therefore needed to further evaluate potential differences between regions and changes over time in virulence factors of *S. aureus*. Additionally, further studies are necessary to clarify the role of colonization in the pathogenesis of CA-MRSA and other *S. aureus* infections, and the role that non-nasal colonization plays as a reservoir for CA-MRSA transmission and re-infection.

Discussion

In summary, research suggests that MRSA need not replace MSSA. Rather, MRSA has in most cases added to the total burden of *S. aureus* infection in the population. It is not clear why MSSA remains prevalent in the presence of MRSA. Previous studies have shown that some MSSA lineages have a genetic

background that is not common to the endemic MRSA clones.⁴ These MSSA lineages may not provide a stable genomic environment for the integration of SCCmec and, hence, they are not replaced by MRSA. Alternatively, they may have a selective advantage in a subset of hosts (especially outside of hospitals) who are not exposed to much antimicrobial pressure and may be able to persist by circulating within this group. Yet, they probably possess characteristics that favour their persistence in the host as well as the transfer between hosts.⁹⁹ Thus, MSSA infection remains prevalent despite the increasing incidence of MRSA infection.

A mathematical model⁹ has suggested that improvements in infection control, with all else equal, may reduce drug-resistant infections while leaving drug-susceptible nosocomial infection incidence approximately unchanged; conversely, worsening infection control will disproportionately favour resistant strains. This counterintuitive result (counterintuitive because at the individual level, infection control can be effective against any infection, regardless of drug resistance) depends on a model assumption that patients admitted into the hospital are more likely to be already colonized with susceptible strains, while resistant strains tend to be more commonly acquired in the hospital. Thus, at the population level, resistant strains are more dependent on nosocomial transmission and, hence, are more sensitive to changes in infection control. A consequence of this finding is that (under the model's assumptions) it is possible that MRSA and MSSA compete to colonize hosts, but that increases in MRSA may occur without corresponding declines in MSSA.

Whether HA-MRSA and CA-MRSA partially replace MSSA infections or add to the total burden of *S. aureus*, perhaps the key conclusion from this review is that all studies reported that MSSA persisted, if not increased, in both hospitals and in the community. Therefore, since MSSA remains responsible for many *S. aureus* infections, efforts to reduce MSSA and not only MRSA deserve attention. Vancomycin is effective against MRSA, but β -lactams are more effective for MSSA infections. Consequently, since our review suggests that many *S. aureus* cases are attributable to MSSA, clinicians should be encouraged to obtain cultures from soft tissue infections before prescribing antimicrobial therapy. Instead of assuming that all cases are MRSA and, hence, should be treated with vancomycin, distinguishing between MRSA and MSSA infections would assure that patients receive optimal treatment. In order to meet this need, researchers should be encouraged to develop reliable and rapid techniques for the identification and characterization of clinical isolates of *S. aureus*.

As evidence continues to accumulate showing the massive clinical and economic burden of MRSA, research and health services efforts have largely focused on developing effective MRSA screening techniques, treatments and infection control programmes, and on preventing further resistant strains. While these objectives should remain a priority, the importance of preventing MSSA infections should not be dismissed. MSSA infections are usually not resistant to multiple drugs and basic infection control efforts have proven to be effective.¹⁰⁰ Therefore, as a modifiable public health problem with significant clinical and economic costs, efforts to prevent and effectively treat both MSSA and MRSA should be a high priority. Further research is necessary to develop more accurate and rapid diagnostics, to

gain a better understanding of the pathogenesis of staphylococcal colonization and infection, and to identify new antimicrobials and non-antimicrobial methods of *S. aureus* prevention and treatment. In the meantime, continued surveillance of emerging *S. aureus* strains and aggressive efforts to minimize excessive antimicrobial use and increase compliance with infection control programmes is necessary to reduce *S. aureus* infections due to both resistant and susceptible strains.

Acknowledgements

We thank Susan Huang for drawing our attention to the question posed in this manuscript, and we thank Murray A. Mittleman for critical review of this manuscript.

Funding

This work was supported by the Models of Infectious Disease Agents Study Program of the US NIH through cooperative agreements 5U01GM076497 and 1U54GM088558 to M. L. and T32 AI007535-12. M. L. has received honoraria and/or consulting fees from Pfizer, Novartis, i3 Innovus, AIR Worldwide and the Avian Pandemic Flu Registry (Outcome Sciences), funded by Roche. The funding sources had no involvement in the preparation of this paper or the decision to submit this paper for publication.

Transparency declarations

None to declare.

Disclaimer

The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute of General Medical Sciences or the NIH.

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