Invited Review

Control of healthcare- and community-associated MRSA: recent progress and persisting challenges

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Abstract

Background: Healthcare adapted meticillin-resistant Staphylococcus aureus (MRSA) has spread to hospitals around the world over 50 years. More recently, other strains of MRSA have emerged with the ability to spread in the community and infect otherwise healthy individuals. Morbidity and mortality associated with MRSA remains high and its control in both the healthcare and community setting has proven challenging.

Sources of data: Pubmed (Medline).

Areas of agreement: The use of targeted screening and decolonization, hand hygiene and antimicrobial stewardship is supported by the most robust studies, though many studies have implemented bundles for effective healthcare-associated (HA)-MRSA control.

Areas of contention: Universal screening, universal decolonization and contact precautions for HA-MRSA control are supported by less evidence. Some interventions may not be cost-effective. Contact precautions may be associated with potential for patient harm. Evidence for effective control community acquired (CA)-MRSA is largely lacking.

Growing points: Programmes that focus on implementing bundles of interventions aimed at targeting HA-MRSA are more likely to be effective, with an emphasis on hand hygiene as a key component. Control of CA-MRSA is
likely to be more difficult to achieve and relies on prevalence, risk factors and community healthcare interactions on a broader scale.

**Areas timely for developing research:** Further research in the area of CA-MRSA in particular is required. Antimicrobial stewardship for both CA and HA-MRSA is promising, as is the role of whole genome sequencing in characterizing transmission. However, further work is required to assess their long-term roles in controlling MRSA. With many institutions applying widespread use of chlorhexidine washes, monitoring for chlorhexidine resistance is paramount to sustaining efforts at controlling MRSA.

**Key words:** MRSA, control, prevention, risk factors, vaccine

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**Introduction**

The introduction in 1959 of the first penicillinase-stable anti-staphylococcal beta-lactam antibiotic, meticillin was followed closely by the first report of methicillin-resistant *Staphylococcus aureus* (MRSA) in a British hospital.\(^1\) This early MRSA belonged to a single clone that spread beyond Europe\(^2\) before being largely replaced by a limited number of other healthcare-associated (HA) clones, some with global reach.\(^3\) Meticillin-resistance in all of these clones was due to the same mechanism, with the responsible gene, *mecA*, being carried on variants of a chromosomally inserted gene cassette, SCC\(_{mec}\). Expression of *mecA* conferred resistance to all then available beta-lactam antibiotics, while resistance to non-beta-lactam antibiotics commonly accumulated in HA-MRSA due to a variety of mechanisms. High levels of antibiotic use in healthcare settings selected strongly for HA-MRSA which reached levels of over 50% of all *S. aureus* isolated in some countries.\(^4\) As vancomycin retained activity against HA-MRSA, it became the agent of choice for treatment, but was more toxic, more difficult to use and initially more expensive than agents used to treat meticillin-susceptible *S. aureus* (MSSA).\(^5\) HA-MRSA infections also were associated with higher mortality and prolonged lengths-of-stay compared with MSSA, thus making the case for control of HA-MRSA compelling.

The last decade of the 20th century saw the emergence of infections due to novel clones of MRSA in community settings unrelated to healthcare.\(^6\)\(^,\)\(^7\) These community-associated (CA) MRSA predominantly caused skin and soft-tissue infections of varying severity, but sometimes caused fatal CA pneumonia and severe bone and joint infections.\(^8\)\(^,\)\(^9\) CA-MRSA carried smaller SCC\(_{mec}\) variants and fewer, if any, other resistance determinants than HA-MRSA and this appeared to be associated with a reduced fitness cost and a competitive advantage over HA-MRSA even in healthcare settings.\(^10\) Mathematical models predicted the replacement of HA-MRSA by CA-MRSA\(^11\)\(^,\)\(^12\) and this trend is well advanced in some countries.\(^13\)\(^,\)\(^14\) Thus the distinction between HA- and CA-MRSA has become blurred. Here we will review efforts at their control but we will not consider the problem of livestock-associated MRSA which involves issues unique to commercial animal husbandry.

**Definitions**

Distinguishing between HA- and CA-MRSA has been problematic. Definitions based on epidemiological features have been used commonly. The CDC definition of CA-MRSA includes cases where MRSA is isolated <48 h after hospital admission and there is no history in the previous 12 months of hospitalization or surgery, permanent indwelling catheters or percutaneous medical devices, residence in a long-term care facility, dialysis or prior culture of MRSA.\(^15\) HA-MRSA cases are defined as those not meeting the CA-MRSA definition. However, as recurrences of CA-MRSA colonization and infection
are common\textsuperscript{16,17} there will be some misclassification of CA-MRSA as HA. Furthermore, it has been shown that HA infection due to clones usually associated with CA infection occurs earlier in the course of hospitalization than that due to long established HA-MRSA clones.\textsuperscript{18} This suggests that at least a proportion of infections classified as HA, but due to the more recently emerged CA clones, are endogenous rather than due to spread in hospital. It has been proposed that genotyping be included as part of the epidemiological evaluation of CA- and HA-MRSA.\textsuperscript{14} Early in the course of the CA-MRSA epidemic it was thought that the presence of some epidemiological markers such as Panton-Valentine leucocidin (PVL) or SCC\textsubscript{mec} type IV in the variable genome could be used to distinguish CA clones.\textsuperscript{7} However, the clonal diversity of CA-MRSA now far exceeds that of HA-MRSA with the uptake of diverse SCC\textsubscript{mec} elements into a great variety of genetic backgrounds. Thus, numerous PVL-negative CA-MRSA clones have been described and SCC\textsubscript{mec} type IV is not exclusive to CA-MRSA nor is it present on all clones.\textsuperscript{19,20} In practice, characterization of MRSA clones now requires comprehensive genomic techniques such as micro-array analysis or whole genome sequencing. A full understanding of the epidemiology of MRSA still requires ascertainment of details of acquisition and onset.\textsuperscript{14}

**Control of HA-MRSA**

Although many different strategies have been assessed for their impact in controlling HA-MRSA, significant controversy still exists as to which infection control practices are most effective. Often when studied or employed in healthcare settings, these practices make up part of a bundle of care, and therefore it is often difficult to assess for each strategy as a stand-alone intervention.\textsuperscript{21–23} An example of this, is the utility of contact precautions and isolation, which in the absence of effective hand hygiene, are unlikely to demonstrate a significant reduction in the transmission of HA-MRSA. In addition, some key components of the intervention bundle may have a greater impact in outbreaks as opposed to in areas of endemic transmission. Significant disagreement still remains over the importance of some interventions, in part due to large costs, potential for interference in patient care and an inability to eradicate endemic transmission in some cases. It should also be noted that the comparison of data within different settings may be difficult due to inconsistencies in case definitions, varied study populations and differences in baseline prevalence rates of MRSA. Despite national guidelines in many countries mandating prospective surveillance, the focus of this reporting is to guide institutions on benchmarking and monitoring of control strategies, not necessarily to demonstrate significant success from a single intervention employed amongst a bundle of healthcare activities. Thus, many studies are inadequately designed to address a clinical question of efficacy of a single intervention and many cases of reporting are subject to publication bias, whereby studies with negative results are less likely to be published.

As an example of an initiative designed successfully to reduce the incidence of MRSA infections, the National Health Service (NHS) in England developed a multi-faceted bundle based approach with a subsequent ~80% reduction in MRSA bloodstream infections (BSI).\textsuperscript{24} Rather than a single intervention, the initiatives targeted multiple aspects of healthcare services to reduce endemic MRSA BSIs to sporadic episodes. Therefore, although the following discussion focuses on interventions individually, the greatest reduction in MRSA acquisition and infection is likely to be achieved through a multi-faceted approach, with the key interventions chosen based upon the prevalence of MRSA within the hospital and region. Following a reduction in MRSA prevalence, the interventions can then be modified to ensure they remain cost effective, an example being risk based screening in areas of low prevalence compared to universal screening in outbreaks and high prevalence settings.

**Search and destroy**

The term ‘Search and Destroy’ was originally devised to describe a policy for controlling and
eradicating outbreaks of MRSA. Although costly and time consuming, this policy has been credited for successful control of a number of epidemics. Despite its success in areas with a low level baseline of MRSA prevalence, there is less evidence so far for its application in areas where high prevalence of HA-MRSA exists. As an example, in the largest outbreak of MRSA in the Netherlands to date, the baseline prevalence rate of MRSA rate was less than 1%. The use of enhanced screening of contacts (patients and staff), decolonization of colonized cases and electronic identifiers were used to control the outbreak in this example, with the full strategy described in the Dutch national guidelines (www.wip.nl). As the costs of search and destroy are significant, its use as a cost-effective measure is likely to be lost when prevalence cannot be returned to low baseline levels.

In some regions of the world where CA-MRSA rates are endemic, the practice of search and destroy can be more challenging. In Western Australia for example, the Western Australian Department of Health has taken the approach of differentiating carriers of HA-MRSA clones and CA-MRSA clones known to be virulent, transmissible or that are multi-drug resistant (Micro-Alert C) from other strains of CA-MRSA that rarely cause hospital outbreaks (Micro-Alert B). As a result, the two groups can be managed differently, with Micro-Alert C patients or healthcare workers recommended to be isolated and decolonized. Western Australian hospitals have comparatively reported much lower prevalence rates of HA-MRSA to other states in Australia, in part due to this strategy that was instituted as a state wide policy in 1982, as a result of the threatened spread of HA-MRSA to Western Australia from Eastern Australian states.

Screening

Persistent transmission of HA-MRSA within hospital settings relies upon a source to which new patients are exposed. In many cases, the environment plays a significant role through colonization of fomites. However, the presence of colonized patients, and less frequently hospital staff, also plays an important role in sustaining environmental reservoirs and direct transmission to patients. Because of this, many facilities will screen at risk patients either on admission or after admission to areas known to have high rates of MRSA transmission such as intensive care units. Once patients are detected as MRSA carriers a number of differing strategies have then been employed within healthcare settings. Furthermore, turn-around time (TAT) differs significantly between culture based methods and more rapid nucleic acid amplification tests (NAAT). Several studies have returned conflicting results with regard to the benefit of rapid NAAT compared to culture based detection. In a study by Roisin et al., NAAT screening led to a reduction in laboratory reporting (88–11 h) and time to isolation (96–25 h), but not in acquisition of MRSA, whereas a similarly designed study performed in surgical wards in a single institution reported 1.49 times higher MRSA acquisition on wards performing culture based methods when compared to PCR. The authors of another study concluded that rapid screening was not cost effective compared to standard culture based methods despite a reduction in TAT with NAAT and subsequent bed usage, with the conclusion based upon no significant reduction in MRSA acquisition in the comparator groups. In 2008, two well-designed studies reported conflicting results on the benefit of universal screening on acquisition of HA-MRSA in a hospital wide and surgical ward setting. Unfortunately, although several studies have subsequently been published, the results still remain divided with many institutions now moving towards screening according to risk stratification. Although this approach offers the ability to minimize costs whilst still screening high risk groups, institutions that implement this should be vigilant in their approach to monitoring for outbreaks and continuing to assess their risk stratification.

An additional factor to be considered with active surveillance of MRSA through screening is the significant costs associated with this approach. In a large before and after study comparing targeted risk-factor based screening to universal screening at a single institution in Canada, universal screening
was associated with an additional cost of $17.76 dollars per patient (overall representing an excess cost of $1.16 million per year).59 The same authors reported elsewhere that although MRSA detection rates increased from 9.8 to 26.2 cases per 1000 admissions, there was no significant difference in the rates of acquired MRSA in the two phases.40 Other studies have suggested that universal screening may provide a cost benefit when MRSA prevalence rates are high.41,42 Clancy et al. demonstrated a reduction in healthcare MRSA infections, and cost avoidance, by introducing universal screening upon admission to an intensive care unit when compared with no screening.43 Nevertheless, based upon the evidence at this point in time, it is not clear that active surveillance of HA-MRSA is cost effective. However, in spite of the current lack of clear supporting institutions utilizing this approach will need to consider the potential impact on their infection control programmes before discontinuing this practice.

Contact precautions

The high cost and potential detrimental effects of contact precautions on the interaction between healthcare professionals and patients have led many to question its overall benefit.44 Barrier precautions are well described in medical literature as playing a significant role in discouraging healthcare practitioner interaction with patients and may lead to adverse events without providing any benefit to the individual.45–48 Additionally, the activity of placing patients in single rooms as part of the contact precaution measure should be considered as an additional infection control practice on top of the use of gloves and gowns, and may itself account for much of the reported benefit described in some observational studies when part of a bundle approach. Therefore, in hospitals where the majority of patients are managed in single rooms, the addition of contact precautions with gloves and gowns may not add any significant benefit. In order to adequately assess the impact of gloves and gowns, a study design will need to take into account a suitable comparator arm in addition to a broad enough time scale to control for delayed effects or fluctuations in HA-MRSA acquisition related to other infection control interventions. To demonstrate the level of evidence that currently exists in the medical literature, two separate systematic reviews recently published were unable to identify any studies adequately designed that could be included to assess the impact of gloves, gowns and masks.49,50

In the REDUCE study by Huang et al., a cluster randomized trial of screening and contact precautions (including isolation) was compared with screening and targeted decolonization or universal decolonization (no screening and decolonization of all patients) within 74 intensive care units from 43 hospitals.51 Although not a direct comparator study, the effect of screening and contact precautions had minimal effect on reducing MRSA detected in clinical isolates when compared to a 12-month baseline period prior to introduction of the intervention (3.2 vs 3.4 per 1000 patient days).51 However, it should be noted that hospitals recruited to this study generally had single occupancy ICU rooms.51 Another recent cluster randomized study demonstrated a reduction in MRSA acquisition with universal glove and gown precautions in ICUs, yet this was the secondary outcome of the study, with the primary outcome, reduction in the acquisition of Gram positive multi-resistant organisms, not significant.52 A post-hoc analysis of the this study, performed with mathematical modelling to simulate transmission dynamics, suggested that universal glove and gown use accounted for 44% of the reductions in HA-MRSA acquisitions.53 Reassuringly, despite a reduction in healthcare interactions associated with universal contact precautions, there was no increase in adverse events associated with this.52 Despite its widespread and long-term acceptance as an infection control practice, the quality of evidence is low and potential for patient harm remains. The utility of contact isolation for MRSA in the era of epidemics with other multi-resistant organisms, such as carbapenemase producing enterobacteriaciae (CPE), is now being questioned in many institutions.44

Decolonization

Decolonization of patients with MRSA is often employed in order to reduce cross-infection by
eradicating or reducing the bacterial load on MRSA carriers. Whereas universal decolonization has been studied in a reasonable number of well-designed trials, targeted decolonization of MRSA carriers is predominantly performed for the benefit of the individual to reduce infection risk or, less commonly, in MRSA outbreaks where a known source (often a healthcare worker) is identified. A number of different decolonization strategies have been reported in studies to date, however the majority of them employ topical mupirocin (typically nasal) along with triclosan, chlorhexidine, provodine-iodine or systemic antibiotics.\(^{54-59}\) Two systematic reviews have provided strong summary evidence of the effect of decolonization in eradicating MRSA carriage, but without evidence that it prevents hospital transmission.\(^{60,61}\)

The evidence for universal decolonization as an infection control measure is supported by more robust data. In the REDUCE study, universal decolonization had a significant impact (2.1 vs 3.4 isolates per 1000 patient days) on MRSA acquisition when compared to a preceding 1-year period.\(^{51}\) However, it should be noted that this study did not report rates of hand hygiene, and other infection control practices, and therefore the individual effect of universal decolonization is difficult to estimate. In a study by Climo et al., a non-statistically significant trend was found in the rate of MRSA acquisition with daily chlorhexidine body wash compared to antimicrobial free washes, with the combined rates of MRSA and VRE significantly reduced, as were the hospital-acquired bloodstream infections.\(^{62}\) Lowe et al. reported lower rates of MRSA acquisition despite poor overall compliance with chlorhexidine body washes (58% compliance).\(^{63}\) In comparison, another two studies that randomized individual patients rather than units demonstrated no significant effect on MRO acquisition.\(^{64,65}\) A meta-analysis, published in 2016 and including many of these trials, demonstrated an overall reduction in MRSA acquisition with chlorhexidine bathing when compared to standard care, however, the greatest reduction in MRSA acquisition was associated with concomitant nasal mupirocin usage.\(^{66}\)

Although these studies provide a basis for supporting universal decolonization strategies, in particular with chlorhexidine and mupirocin, there remains considerable concern over the development of widespread resistance. Although evidence to date suggests that the appearance of chlorhexidine resistance is rare amongst MRSA strains with widespread chlorhexidine use, long-term prospective studies are still required. In a post-hoc analysis of the REDUCE trial, resistance to chlorhexidine was rare, and only 5/814 isolates tested carried qacA or qacB, which are plasmid based genes encoding for multi-drug efflux pumps responsible for chlorhexidine non-susceptibility.\(^{67}\) Nevertheless, the combination of non-susceptibility to chlorhexidine and mupirocin has been shown to lead to failure of decolonization in patients, and repeated mupirocin exposure has been associated with the emergence of mupirocin resistance.\(^{68,69}\)

### Hand hygiene

Hand hygiene is considered the most effective infection control intervention within acute care facilities for preventing transmission of MRSA. A number of studies have been published that have demonstrated a strong association in HA-MRSA acquisition rates and hand hygiene.\(^{70-74}\) However, although the intervention has been shown to reduce acquisition and provide a cost beneficial intervention, several questions remain, such as the temporal relationship between hand hygiene and MRO acquisition and the compliance target after which the effectiveness of the intervention tapers.\(^{75,76}\) A systematic review demonstrated a strong association between alcohol based hand rub usage and reduction in MRSA acquisition.\(^{77}\) Importantly, although there was a strong correlation in usage and MRSA rates, there was no significant correlation with compliance levels. It should also be noted that many of the hand hygiene interventions have implemented alcohol based hand rubs incorporating chlorhexidine.\(^{73,74}\) A recent study by Ho et al. demonstrated equivalent reductions in MRSA carriage on healthcare worker hands with alcohol alone and alcohol or chlorhexidine with the seven step WHO cleaning guidelines.\(^{78}\) Nevertheless, long-term studies are required to assess alcohol only based hand rubs in clinical practice (Table 1).
In areas of low endemicity of MRSA, the relationship between enhanced hand hygiene measures and MRSA acquisition may be less pronounced. In a multisite study by Lee et al. amongst 33 surgical wards, a combination of improved hand hygiene measures and universal screening with contact precautions and decolonization of MRSA carriers was found to reduce MRSA clinical isolates. However, neither intervention was associated with significant changes when implemented individually. A similar study, published in 2013 using publicly reported patient data in the province of Ontario, Canada, was also unable to demonstrate a change in MRSA rates despite overall improvements in hand hygiene compliance in an area of low MRSA prevalence.

Antimicrobial stewardship

In addition to colonization pressure from the environment or MRSA carriers, antibiotic usage has been identified as a key risk factor for acquiring MRSA. Although it is intuitive that reducing antimicrobial usage in institutions where it is associated with MRSA acquisition, limited studies to date have been reported on antimicrobial stewardship programmes that have successfully reduced MRSA acquisition. A retrospective ecological study with time series analysis in Scotland showed an association between the restriction of coamoxyclav, cephalosporins, clindamycin, fluoroquinolones and macrolides and a reduction in the acquisition of HA-MRSA in hospital and the community. However, it should be noted that the dominant MRSA clone at the time of the intervention was UK EMRSA-15 (ST22) which is invariably quinolone resistant and frequently resistant to macrolides. Therefore, the intervention could be expected to reduce specifically the selection pressure favouring ST22, but may not be generalizable to settings where clones with different resistance patterns are prevalent.

Whole genome sequencing

Several studies have reported the utility of whole genome sequencing in identifying transmission of MRSA in outbreak or endemic settings. However, further studies are required to determine its long-term impact on infection control programmes. In addition, real-time sequencing and analysis remains problematic for many institutions, despite significant reductions in costs. Further work is required in this area, though results to date are promising.

Control of CA-MRSA

Control of CA-MRSA is in its infancy compared to that of HA-MRSA and reports of interventional studies are almost completely lacking. Efforts at prevention and control require an understanding of the epidemiology and of risk factors that are amenable to modification. While those for HA-MRSA have been well established, those for CA-MRSA require consideration before we review initial efforts at intervention. It will be obvious that some risk factors apply generally while others apply to particular geographic and demographic conditions. For example, skin infections due to S. aureus in general and CA-MRSA in particular are well known to be influenced by climate, having higher incidence in warmer and more humid months in temperate regions but are generally more common in tropical climates.

Younger people have frequently been found to be at greater risk of CA-MRSA. The production of PVL by many CA-MRSA strains may play a part in this as predilection for youth is also found with meticillin-susceptible S. aureus strains producing PVL. Socio-economic deprivation and overcrowding also act as risk factors. It is therefore not surprising that indigenous populations have been found to be at particular at risk of CA-MRSA, as they frequently suffer from social deprivation and have a greater proportion of people in young age-groups. Other factors associated with social disadvantage have been implicated including higher levels of fomite and environmental contamination, obesity, smoking in the household, and skin infections in household contacts. Antibiotic use in the previous 12 months has been associated with increased risk in both the general population and in prison populations.
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<th>Study author</th>
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<td>Huang⁵⁰</td>
<td>2013</td>
<td>Screening and isolation vs decolonization (targeted or universal)</td>
<td>Cluster randomized trial comparing 12 month baseline period to 18 month intervention phase</td>
<td>ICU attributable, MRSA positive clinical cultures</td>
<td>Greatest reduction in MRSA clinical isolates from baseline vs intervention period with universal decolonization. Screening and isolation HR 0.92 (3.2 vs 3.4 isolates per 1000 patient days), targeted decolonization HR 0.75 (3.2 vs 4.3 isolates per 1000 patient days) and universal decolonization HR 0.63 (2.1 vs 3.4 per 1000 patient days)</td>
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<td>Harris⁵¹</td>
<td>2013</td>
<td>Universal glove and gown use compared to targeted use</td>
<td>Cluster randomized trial in 20 ICUs</td>
<td>Reduction in acquisition of MRSA and VRE</td>
<td>No statistical significant difference in combined acquisition rates of MRSA and VRE. Lower risk of MRSA acquisition alone (difference of 2.98 per 1000 patient days) as a secondary outcome</td>
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<td>Climo⁶¹</td>
<td>2013</td>
<td>2% CHG impregnated washcloths versus antimicrobial free washcloths</td>
<td>Cluster randomized crossover study in nine ICU and BMT units</td>
<td>Reduction in MRO acquisition and HA-BSIs</td>
<td>Non-significant reduction in MRSA acquisition rate with CHG washcloths (1.89 vs 2.32 cases per 1000 patient days, ( P = 0.29 ))</td>
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<td>Chen⁹⁰</td>
<td>2013</td>
<td>CHG body wash</td>
<td>Meta-analysis</td>
<td>Reduction in acquired colonization or infection with MRSA</td>
<td>Reduction in MRSA colonization ( IRR = 0.58 ) (95% CI 0.41–0.82) and infection ( IRR = 0.56 ) (95% CI 0.38–0.83)</td>
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<td>Lowe⁶²</td>
<td>2017</td>
<td>Universal CHG bathing</td>
<td>Prospective crossover study</td>
<td>Reduction in acquired MRSA colonization or infection rates</td>
<td>MRSA rates reduced by 55% (5.1 vs 11.4 per 10000 bed days, ( P = 0.04 )). Compliance with CHG body wash 58%</td>
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<tr>
<td>Kim⁶⁵</td>
<td>2016</td>
<td>Universal CHG bathing</td>
<td>Meta-analysis</td>
<td>Reduction in healthcare associated central line-associated infections and MRO acquisitions among critically ill patients</td>
<td>MRSA acquisition rate lower in CHG group compared to control (3.28 versus 4.97 per 1000 patient days). Concomitant use of mupirocin associated with lower MRSA incidence than with CHG alone (RR 0.81, ( P = 0.035 ))</td>
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<td>Stone⁷⁰</td>
<td>2012</td>
<td>Hand hygiene</td>
<td>Prospective, ecological, interrupted time series; July 2004–June 2008</td>
<td>Quarterly rates of alcohol hand rub and soap, MRSA BSI</td>
<td>Increased procurement of alcohol hand rub and soap associated with reductions in MRSA BSI in the final four quarters of the study</td>
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In the United States a high incidence of CA-MRSA in incarcerated populations has been associated with risk factors including previous skin infection, nasal colonization, lower educational level, less frequent showering, sharing soap and less healthcare contact. African Americans have been identified as more at risk than the general population. In Europe immigrant populations have been strongly associated with outbreaks although paradoxically both previous hospitalization and absence of healthcare contact have been identified as risk factors in different countries.

Staphylococcus aureus is carried as a commensal by approximately one-third of the population and so the prevalence of carriage of CA-MRSA will be a consideration in efforts to control its spread. Sites of carriage may also play a part. While the anterior nares, axillae and groin have long been accepted as important carriage sites, it has more recently become apparent that the oropharynx is also of major importance. Population-based studies have generally found very low levels of nasal carriage of MRSA including CA-MRSA. While studies in children in Argentina, Malaysia and Iraq found prevalence of MRSA carriage of 4.4%, 1.6% and 2.0%, respectively, others in the general populations in Germany, Ghana, Brazil and the United States, in children in Portugal and Turkey, and in adults in Australia showed prevalence of <1.0%. However, some specific population groups may be at greater risk. A study of 173 sexually transmitted disease patients found that 89 (51.4%) were colonized with S. aureus of which 14 (8.1%) were USAS300 CA-MRSA, with the most common site of carriage being the oropharynx.

The lack of widespread CA-MRSA carriage in the general community suggests that risk of acquisition may be due to local factors. Mathematical models derived from large data sets support this supposition. Spatial analysis of cross-sectional data from South London found CA-MRSA linked with household overcrowding, low income, homelessness and recent immigration. An agent-based model of Chicago CA-MRSA data indicated that contact with colonized individuals was probably

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<td>Derde 69</td>
<td>2014</td>
<td>Hand hygiene</td>
<td>Interrupted time series followed by cluster randomized controlled trial of universal CHG washing and hand hygiene improvement</td>
<td>Combined effect of CHG and hand hygiene associated with significant reduction in MRSA, particularly MRSA</td>
<td>Combined effect of CHG and hand hygiene associated with significant reduction in MRSA, particularly MRSA</td>
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Table 1 Continued

Abbreviations: HR, hazard ratio; CHG, chlorhexidine; EtOH, ethanol; BSI, bloodstream infection.
the major source of acquisition and that this was most likely to occur in households with school/day-care, hospital, sport and jails being of much less importance in descending order. A whole-genome sequencing study of household transmission of USA300 CA-MRSA in Los Angeles and Chicago demonstrated that single strains were transmitted within households and could persist for 2.5–8.5 years. Thus interrupting household transmission should be the main target for control of CA-MRSA.

Just as screening for and eradication of carriage of MRSA has been a mainstay of control in HA-MRSA, a similar approach has been attempted with CA-MRSA. Such an intervention was undertaken in Denmark following an outbreak involving 23 cases in 16 households with a total of 56 members all of whom were screened for carriage. A thorough programme of cleaning, linen changing, whole-body chlorhexidine washes and intranasal mupirocin was implemented while some throat carriers received oral antibiotics. Five days of eradication therapy was insufficient and three households required four cycles. There were no carriers after 1 year. However, a trial of 5-day eradication regime (twice-daily intranasal mupiricin, daily chlorhexidine body washes) in American paediatric patients with skin abscesses or colonization due to S. aureus including CA-MRSA with subjects randomized to receive either individual or household treatment produced less encouraging results: among subjects completing 12 months of follow-up, carriage was eradicated in 54% of the individual group and 66% of the household group. Therefore, it appears that the achievement of high eradication rates will require diligent follow-up and multiple cycles in a proportion of households.

A community-based educational intervention was undertaken in Northern Saskatchewan following a marked increase in the annual rate of CA-MRSA infection from 8.2 to 168.1 cases per 10,000 over a 5-year period. The intervention included the display of posters, radio broadcasts, community slide presentations, physician treatment algorithms, patient pamphlets, and school educational programmes. During the intervention, the rate decreased from 242.8 to 129.3 per 10,000 while the rate in adjacent non-intervention communities continued to increase. There was also significant improvement of community knowledge of appropriate hygiene and antibiotic usage.

Mathematical modelling based on monthly time series data on CA-MRSA skin and soft-tissue infection incidence in children under 20 years in Arizona has been used to evaluate the effect of some possible control interventions. The model predicted that strategies focused on infected individuals would not be capable of achieving disease control which is in keeping with other modelling data that predicts that most acquisition is from colonized individuals. The model did predict that strategies aimed at screening and decolonization in paediatric populations have the potential of achieving disease elimination. They suggest that decolonization of 30% of colonized individuals in the entire paediatric population could achieve elimination of transmission in about 5 years, whereas if only those aged 5–14 years were targeted elimination would require about 20 years. Such a strategy would be difficult to undertake and maintain. However, intervention in households was not modelled but the authors did identify it as an area of interest for further study.

Other possible interventions that could play a part in control of CA-MRSA include antibiotic restriction/stewardship and vaccination. The rationale for restriction/stewardship interventions seems sound in principle as resistance gives advantage in the face of antibiotic selection pressure and reduction in that pressure could be expected intuitively to negate that advantage and allow replacement of resistant clones. However, as indicated above only one ecological study has shown an association between antibiotic restriction and the decline of acquisition of one HA-MRSA clone. Furthermore, the generalizability of that finding to other HA-MRSA clones and indeed to CA-MRSA has yet to be established. While vaccination has proven successful in controlling a number of bacterial pathogens and could be of great benefit in the control of all invasive infection due to S. aureus, success with the formulation of candidate vaccines has proven elusive. As a human commensal adapted over a long-time scale to evade human immune
defences and as a sometimes invasive pathogen with a large array of virulence factors and evasive mechanisms, it is not surprising that efforts to provoke protective immunity specific to invasive staphylococcal infection have proven more difficult and complex than those for other pathogens. An effective vaccine is still awaited and issues related to achievement of that have been reviewed elsewhere.\textsuperscript{128,129}

**Conclusion**

Control of MRSA remains a major healthcare challenge. While it is clear that long term control of HA-MRSA can be achieved even in high prevalence settings, this is often done through the pragmatic use of bundles of interventions. The contributions of individual interventions to success are less well established and may never be confirmed with any rigour. Control of CA-MRSA presents a far greater challenge that is only beginning to be addressed. Current evidence suggests that well-resourced household interventions aimed at decolonization of infected cases and carriers may be successful in low prevalence settings. However, the prospects for population-based interventions in high prevalence settings are less clear, particularly for countries with limited resources. Removal of unnecessary antibiotic selective pressure by curtailing inappropriate use as mandated in objective 4 of the WHO Global Action Plan on Antimicrobial Resistance\textsuperscript{130} should be achievable, but the extent to which it will facilitate control is uncertain. Mathematical models suggest that case households and CA-MRSA carriage are major targets for intervention. Clearly more evidence is needed to delineate optimum control strategies.

**Conflict of interest statement**

The authors have no potential conflicts of interest.

**References**


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