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## Review

# Emergence and resurgence of meticillin-resistant *Staphylococcus aureus* as a public-health threat

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## Summary

*Staphylococcus aureus* is a gram-positive bacterium that colonises the skin and is present in the anterior nares in about 25–30% of healthy people.<sup>1</sup> Dependent on its intrinsic virulence or the ability of the host to contain its opportunistic behaviour, *S aureus* can cause a range of diseases in man. The bacterium readily acquires resistance against all classes of antibiotics by one of two distinct mechanisms: mutation of an existing bacterial gene or horizontal transfer of a resistance gene from another bacterium. Several mobile genetic elements carrying exogenous antibiotic resistance genes might mediate resistance acquisition.<sup>2</sup> Of all the resistance traits *S aureus* has acquired since the introduction of antimicrobial chemotherapy in the 1930s, meticillin resistance is clinically the most important, since a single genetic element confers resistance to the most commonly prescribed class of antimicrobials—the  $\beta$ -lactam antibiotics, which include penicillins, cephalosporins, and carbapenems.

## History

In the 1950s, years before meticillin-resistant *Staphylococcus aureus* (MRSA) was reported for the first time, three independent developments led to appreciation of the potential public-health implications that *S aureus* might have in store. The first was the slow but persistent rise in penicillin resistance, which was noted soon after its first clinical trials.<sup>3</sup> By the end of the 1940s, hospitals in the UK and the USA reported that 50% of *S aureus* was resistant to penicillin.<sup>4 and 5</sup> The second was the development of an effective typing system based on a strain-specific lysis by a set of bacteriophages,<sup>6 and 7</sup> which provided the technical means to identify

possible sources for acquisition and infection. The third development was the emergence of an especially invasive, transmissible, and penicillin-resistant clone of *S aureus*, first in Australia<sup>8</sup> but rapidly appearing in different continents with a speed and virulence reminiscent of an influenza pandemic.<sup>9</sup> This strain was termed the 80/81 strain, according to its bacteriophage susceptibility pattern. By 1957, 80/81, or the hospital staphylococcus as it became known,<sup>10</sup> was responsible for nearly all the epidemics in maternity units in the USA and half of all hospital outbreaks in the UK.<sup>9</sup> A third of hospital patients who were nasal carriers of this strain, went on to develop septicaemia compared with only 2.5% who were colonised with other strains.<sup>11</sup> There was concern not only because of the high death rate in these patients<sup>12</sup> but also because outbreaks were not confined to patients and often caused invasive skin infections in health-care workers.<sup>9</sup> The 80/81 strain began to decline in the 1960s<sup>13</sup> when meticillin, the first semisynthetic penicillinase-fast penicillin was introduced.

### **Emergence of MRSA**

6 months after meticillin was marketed in October, 1960, three meticillin-resistant isolates were reported after the screening of 5000 clinical isolates.<sup>14</sup> All three had the same phenotype and were from the same hospital in southern England. But since meticillin resistance remained rare and was expressed only by the resistant organisms in conditions that seemed to be very different from those prevailing at the site of infections (such as at low temperatures and high salt concentrations), microbiologists remained confident about the long-term effectiveness of meticillin and its congeners as successful antistaphylococcal agents. By 1967, the situation started to change and multidrug-resistant MRSA was reported from Switzerland, France, Denmark, England, Australia, and India.<sup>15, 16, 17, 18, 19 and 20</sup> From 1967 to 1971, about 15% of all Danish *S aureus* isolates were meticillin resistant with combined resistance to penicillin, streptomycin, tetracycline, and occasionally to erythromycin. Most isolates belonged to the same phage type 83A complex. After the rapid dissemination of this clone, MRSA began to fall in Europe in the 1970s and early 1980s. In Zurich, the isolation rate dropped from 20% in 1971 to 3% in 1975<sup>21</sup> and the frequency of MRSA in Denmark fell to 0.2% in 1984 and has remained less than 2% ever since. The cause of this decline is not clear, but changes in prescribing of streptomycin and tetracycline and introduction of rigorous infection-control policies might have had a synergistic effect.<sup>22 and 23</sup>

There were renewed concerns in the early 1980s, when a rise in the frequency of gentamicin-resistant MRSA was reported from several countries, including the USA, Ireland, and the UK.<sup>24, 25 and 26</sup> In Australia, an epidemic multidrug-resistant MRSA strain was noted in the state of Victoria, which, after 1982, started to cause outbreaks in patients in London, UK, hospitals and was believed to have been imported by an Australian health-care worker.<sup>27 and 28</sup> When a second MRSA strain became prevalent in hospitals, a numerical prefix for epidemic MRSA was introduced by the staphylococcal reference laboratory of the UK Public Health Laboratory Service.<sup>29</sup> On the basis of this definition, 16 epidemic types of MRSA were identified in England and Wales until 1995. However, only UK EMRSA-3, UK EMRSA-15, and UK EMRSA-16 were still reported in the 1990s and UK EMRSA-15 and UK EMRSA-16 showed the most dynamic behaviour.<sup>30</sup> At the same time, six epidemic strains were identified with increasing frequency in central Europe<sup>31</sup> and some MRSA clones had spread between continents.<sup>32 and 33</sup>

## Community acquired MRSA

Most documented MRSA infections were acquired nosocomially with community acquired MRSA restricted to patients with frequent contact with health facilities, such as residents of long-term care facilities and intravenous-drug users.<sup>34 and 35</sup> In 1993, novel MRSA strains were reported from Western Australia. The strains had been isolated from Indigenous Australian patients who had not been previously exposed to the health-care system.<sup>36</sup> Publication of this information heralded the worldwide recognition of the striking evolution of genuine community acquired MRSA strains, which were transmitted in the community and differed from conventional endemic nosocomially acquired MRSA strains in several ways. First, they were more susceptible to antibiotic classes other than  $\beta$ -lactam antibiotics;<sup>37</sup> second, their genotypes were not the same as isolates from local hospitals;<sup>38</sup> third, they mainly harboured different meticillin-resistance cassettes;<sup>38, 39 and 40</sup> and finally, community isolates were more likely to encode a putative virulence factor called Panton-Valentine leukocidin.<sup>41</sup> Ever since this recognition, community acquired MRSA has been isolated from children and adults with skin and soft tissue infections, septic arthritis, bacteraemia, toxic shock syndrome,<sup>42 and 43</sup> necrotising fasciitis,<sup>44</sup> and necrotising pneumonia.<sup>43 and 45</sup> Community acquired MRSA has been reported most often from indigenous populations,<sup>46</sup> homeless people,<sup>47</sup> men who have sex with men,<sup>48</sup> jailed inmates,<sup>49</sup> military recruits,<sup>50</sup> children in day care centres,<sup>51</sup> and competitive athletes.<sup>52</sup> Common to all these groups is high intensity physical contact which might help with transmission. A publication from Texas, USA, showed that more than 70% of community-acquired *S aureus* infections in clinical settings were MRSA.<sup>53</sup> Not unexpectedly, community acquired MRSA has also found its way into hospitals where outbreaks have been reported.<sup>54, 55 and 56</sup>

## Vancomycin resistance

Clinical isolates of hospital MRSA with reduced susceptibility to third-line glycopeptide treatment were first described in 1997.<sup>57</sup> Reduced susceptibility was often heterogeneously expressed and associated with thickening of bacteria cell-walls.<sup>58</sup> Finally, in 2002, nature repeated what had been achieved only under experimental conditions 10 years previously;<sup>59</sup> MRSA with vancomycin resistance (VRSA) was isolated from two independent patients who were coinfecting with vancomycin-resistant enterococci.<sup>60 and 61</sup> In 2004, a third case was reported in New York, USA.<sup>62</sup> All of these isolates had acquired resistance by conjugative transposition of *vanA*-containing elements from vancomycin-resistant enterococci<sup>60</sup> and showed variable vancomycin resistance with minimum inhibitory concentrations ranging from 16 mg/L to 1024 mg/L. Reports also provided evidence of failure by frequently used automated antimicrobial-susceptibility testing to detect VRSA.<sup>62</sup> The shortcomings of routine laboratory procedures to identify reduced susceptibility to vancomycin and the poor effectiveness of vancomycin in eliminating even vancomycin-susceptible MRSA from deep-seated infections, hampers a thorough appraisal of the importance of vancomycin resistance in clinical practice. Although few publications have addressed this issue, heterogeneously expressed vancomycin resistance has proved to be associated with treatment failure, which is defined as persistent bacteraemia and fever for longer than 7 days.<sup>63</sup> However, successful treatment with alternative agents (eg, linezolid) has been documented after vancomycin treatment had failed.<sup>64</sup>

## Worldwide burden of MRSA

By contrast with the assumptions that predicted little or no in vivo relevance of the methicillin-resistant phenotype in the 1960s, MRSA is at present the most commonly identified antibiotic-resistant pathogen in many parts of the world, including Europe, the Americas, north Africa, the middle east, and east Asia. Moreover, MRSA rates have been swiftly increasing worldwide over the past decades, as data from continuing surveillance initiatives such as the National Nosocomial Infection Surveillance System and European Antimicrobial Resistance Surveillance System show.<sup>65, 66 and 67</sup> Even in Scandinavian countries and the Netherlands, where MRSA rates have been low and fairly stable for many years, the frequency is beginning to rise,<sup>66</sup> and this trend should be taken seriously since the threshold for losing control might be low and is not well defined. Because most MRSA infections are of nosocomial origin and manifest themselves as complications of health-care procedures or underlying disorders rather than representing defined nosological entities, mortality, morbidity, and loss of productivity caused by MRSA cannot be easily defined. Still, there is evidence that hospital-acquired MRSA infection increases morbidity, the risk of mortality, and costs.<sup>68, 69 and 70</sup> These infections also cause suffering and harm patients psychologically and financially.<sup>71</sup> The societal costs accrue either directly—as expenses caused by extension of hospital stay, additional diagnostic or therapeutic procedures, and additional antibiotic use—or indirectly through the loss of productivity, long-term disability, and excess mortality.<sup>72</sup> Other financial repercussions include the costs for containment of outbreaks, and the deliberate or unwitting changes of empirical antibiotic prescribing habits.

Although there are few routine surveillance systems for MRSA, prevalence data exist for many countries (see search strategy and selection criteria). The value of this information is, however, constrained by different study designs, different inclusion criteria for health-care institutions, the selection of clinical and surveillance specimens, and different antimicrobial testing and reporting routines, which makes international comparisons difficult.<sup>73</sup> Despite these drawbacks and the scarcity of data for many countries, especially for developing ones, an impression of the present MRSA pandemic begins to emerge (figure 1). Of the expected 2 billion individuals carrying *S aureus* worldwide, conservative estimates based on either Dutch or US prevalence figures would predict that between 2 million and 53 million carry MRSA.<sup>87 and 88</sup>

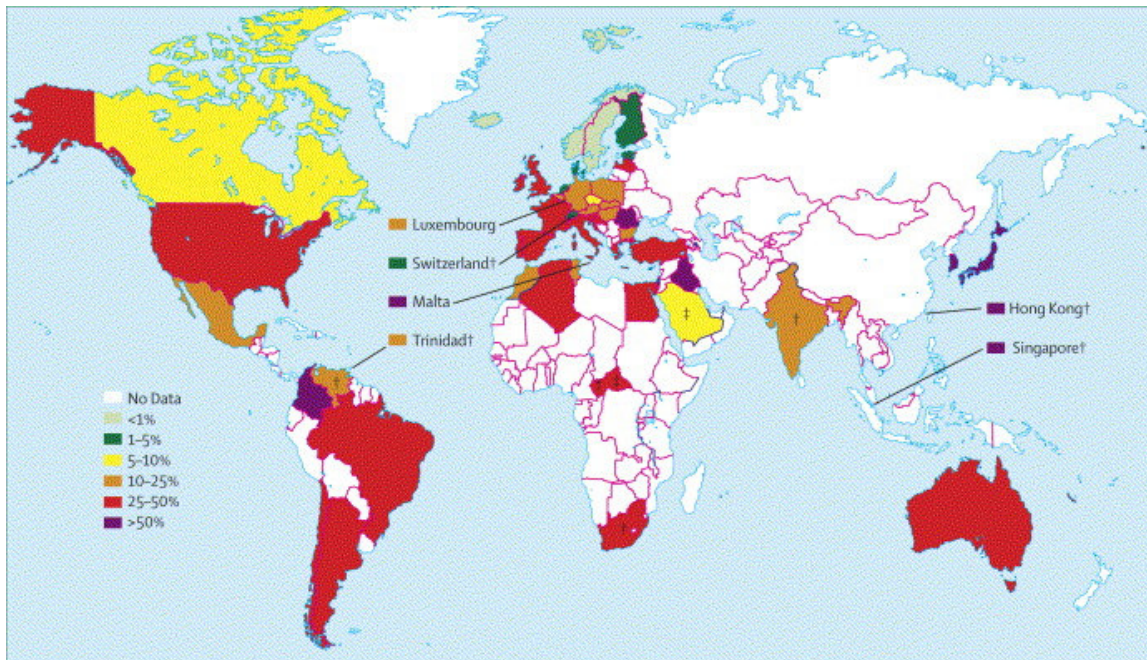


Figure 1. Worldwide prevalence of MRSA displayed by country\*

\*All presented MRSA proportions are from peer-reviewed studies undertaken since 1998.<sup>32, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84 and 85</sup> Prevalence estimates for Morocco, Algeria, Tunisia, Egypt, Jordan, Lebanon, and Turkey are from the antimicrobial resistance in the Mediterranean region website<sup>86</sup> at [www.slh.gov.mt/armed/earss.asp](http://www.slh.gov.mt/armed/earss.asp). Studies providing most recent estimate of the MRSA proportion taken into account. If more than one study reported over same period, study including different types of clinical isolates was preferred over studies including only one specific type of specimen. †=Prevalence estimates are based on a study that included only one hospital. ‡=Prevalence estimates are based on studies between 1993 and 1997.

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## Evolutionary biology and resistance determinants

The understanding of the evolution of MRSA has benefited from the development of molecular methods that provide characterisation of both the strain phylogeny (evolutionary history) and the meticillin-resistance determinant. Strain phylogenies can be resolved by multilocus sequence typing, which unambiguously identifies a strain on the basis of its sequence at seven housekeeping genes.<sup>89</sup> Consistent molecular epidemiological evidence supports the view that the evolution of MRSA and of *S aureus* as a species is predominantly clonal.<sup>90, 91 and 92</sup> Nevertheless, horizontal transfer of DNA from other strains or species occurs and plays an important part in resistance acquisition in *S aureus* and is brought about mainly by insertion of insertion sequences (IS), transposons, prophages, and incompletely understood events.<sup>2 and 92</sup>

### Staphylococcal cassette chromosome *mec*

MRSA originates from the introduction of a large mobile genetic element called staphylococcal cassette chromosome *mec* (SCC*mec*) into a methicillin-susceptible *S aureus* strain. The methicillin-resistance determinant *mecA*, which encodes an additional penicillin-binding protein (PBP2A) with reduced affinity for  $\beta$ -lactam antibiotics,<sup>93</sup> is carried on the SCC*mec* element. PBP2A is a transpeptidase that, assisted by the transglycosylase domain of the native PBP2 of *S aureus*, takes over the function of biosynthesis of cell-walls, which is otherwise blocked in the presence of  $\beta$ -lactam antibiotics.<sup>94</sup> SCC*mec* is inserted into the chromosome at a specific site (*attB<sub>SCC</sub>*) at the 3 prime end of an open reading frame of unknown function (*orfX*) located near the origin of replication of *S aureus*<sup>95</sup> and therefore will be replicated at an earlier stage, which might have strategic importance for immediate transcription of imported antibiotic resistance genes. For its mobilisation—ie, excision and integration into the host chromosome—SCC*mec* carries specific genes designated cassette chromosome recombinases (*ccrA/ccrB*<sup>96</sup> or *ccrC*<sup>40</sup>).

Up to now, five types of SCC*mec* (SCC*mec* I to V)<sup>40, 97 and 98</sup> and several variants<sup>2, 99 and 100</sup> have been described according to the combination of the *mec* and *ccr* gene complexes they contain (figure 2). Besides the difference in these two essential components, the various SCC*mec* elements differ from each other in the antibiotic resistance genes against the non- $\beta$ -lactam antibiotics they carry. By contrast with SCC*mec* types I, IV, and V that do not contain any antibiotic resistance genes other than *mecA* (with the exception of variants IA, IVA and IVc), SCC*mec* types II and III contain many antibiotic and heavy metal resistance genes in integrated plasmids or transposons.<sup>101</sup>

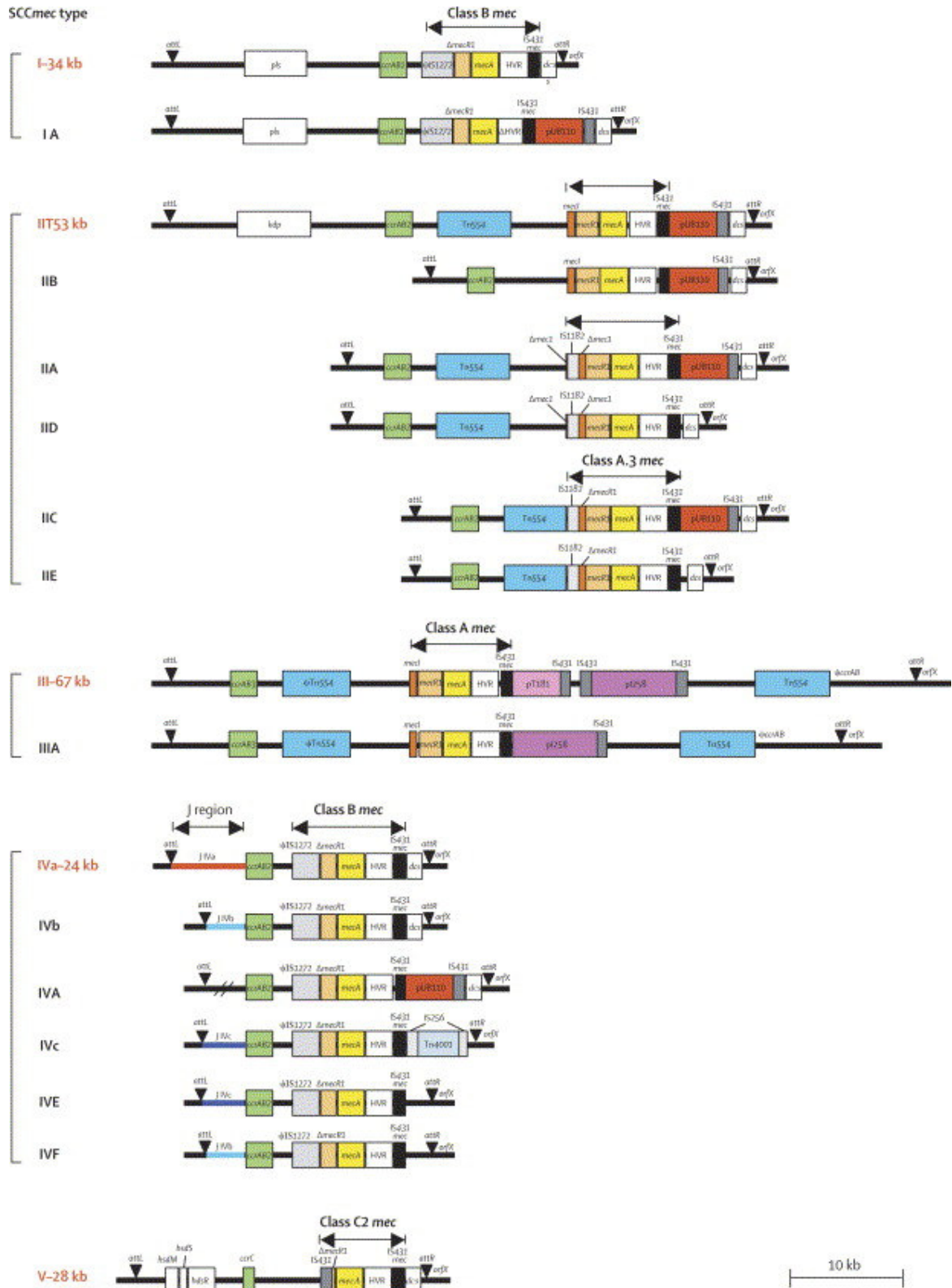


Figure 2. Schematic diagram showing the genomic organisation of SCCmec types I-V and variants



The illustrations of SCCmec types I, IA, II, III, IIIA, and IVA are based on Oliveira and colleagues,<sup>101</sup> those of SCCmec type IVa and IVb are based on studies by Okuma and colleagues,<sup>39</sup> those of SCCmec type V on Ito and colleagues,<sup>40</sup> and those of SCCmec types IIA, IIB, IIC, IID, IIE, IVc, IVE, and IVF on Shore and colleagues.<sup>100</sup>

### Origins and reservoirs of SCCmec

The origins and mechanism of transfer of SCCmec are still unclear and so far no bacterial isolates of any other genera have been reported to carry this element. A *mecA* homologue (88% of similarity) ubiquitous in the antibiotic-susceptible animal species *S sciuri* was a possible evolutionary precursor of the *mecA* of the MRSA strains.<sup>103, 104 and 105</sup> One theory is that *ccr* and *mec* genes could have been brought together in coagulase-negative staphylococci, where deletion in the *mec* regulatory genes took place before transfer to *S aureus* to generate MRSA isolates.<sup>105, 106 and 107</sup>

Several lines of evidence lend support to the hypothesis that SCCmec is transferred from coagulase-negative staphylococci to *S aureus*. First, IS1272 seems to be intact and exists in multiple copies in the genome of *S haemolyticus*, whereas it usually contains deletions in *S aureus* and *S epidermidis*, suggesting that *S haemolyticus* was one of the definitive hosts for the element but was only secondarily acquired by *S epidermidis* and *S aureus*.<sup>108 and 109</sup> Second, Wielders and colleagues<sup>110</sup> reported an MRSA in-vivo formation by horizontal transfer of *mecA* during antibiotic treatment between *S epidermidis* and *S aureus*. Third, recombination seemed to have taken place in coagulase-negative staphylococci between SCCmec type I and additional sequences generating SCCmec type IV that was subsequently transferred to *S aureus*.<sup>111</sup> Fourth, meticillin resistance is highly prevalent in *S epidermidis* isolates (over 70%) and less common in *S aureus*, suggesting that *S epidermidis* is the reservoir for SCCmec. Finally, SCCmec type IV proved prevalent in *S epidermidis* isolates in the early 1970s<sup>112</sup> and only in 1981 was it detected in *S aureus*.<sup>97</sup>

### Distribution of SCCmec types and frequency of transfer

Health-care associated and community-acquired MRSA strains have been proved genetically distinct with respect to the SCCmec type they contain. Although some epidemic nosocomial MRSA clones contain SCCmec type IV, most health-care associated MRSA strains carry one of three types of SCCmec (type I, II, or III),<sup>90 and 97</sup> whereas most community-acquired MRSA strains carry SCCmec type IV.<sup>38 and 39</sup> Type V has also been identified in a community-acquired MRSA isolate.<sup>38</sup> The extreme heterogeneity of the genetic backgrounds in community-acquired MRSA strains and the small size of SCCmec types IV and V suggest that these SCCmec allotypes are more readily transmissible between staphylococci than the larger SCCmec types and, once introduced, do not compromise the fitness of the pathogen.<sup>40 and 98</sup>

The detection of divergent MRSA lineages by different molecular typing techniques, including multilocus sequence typing and SCCmec typing, suggests that MRSA have arisen by the introduction of SCCmec into distinct successful meticillin-susceptible *S aureus* lineages.<sup>112 and 113</sup> Conversely, there is evidence that resistance has been transferred to *S aureus* on more than 20 occasions, since some lineages have acquired different structural types of the element.<sup>90 and 112</sup>



## **Control of MRSA**

### **Screening of patients**

Colonised and infected patients represent the most important reservoir of MRSA in health-care facilities.<sup>115</sup> However, 35–84% of patients colonised with MRSA are not detected by cultures that are ordered by doctors for clinical reasons.<sup>115, 116, 117, 118 and 119</sup> Screening of patients by culture of samples from body sites such as the anterior nares alone will identify 80%, and screening from additional body sites will increase the sensitivity to over 92%.<sup>115, 117 and 120</sup> These patients—who do not have clinically evident infection, but are carriers of MRSA—can serve as reservoirs from which the organism is transmitted to other patients.<sup>121</sup>

In the Netherlands and in parts of Scandinavia, where the prevalence of health-care-associated MRSA is less than 1–3%, screening of patients and exposed health-care workers is an integral part of the aggressive search and destroy strategy that most hospitals use.<sup>122 and 123</sup> Although such screening is widely accepted as useful and cost effective in low-prevalence areas, its value in areas where MRSA is highly endemic is controversial. Despite the increasing frequency of hospital acquired MRSA in the USA, a recent survey of specialists in infectious diseases showed that only 50% of 463 respondents favoured the use of screening cultures to detect multidrug-resistant pathogens, and only 30% worked in facilities where screening cultures were done routinely.<sup>124</sup> Those who do not favour routine use of surveillance cultures to detect MRSA often cite the reasons that such cultures; first, need additional laboratory resources and are costly; second, create increased demand for isolation rooms; third, could cause logistic difficulties when newly identified patients are moved from one room to another; and fourth, could delay placement of some patients into extended-care facilities.<sup>124 and 125</sup> Additionally, the effectiveness of screening cultures to reduce transmission of MRSA has not been established in randomised trials.<sup>126 and 127</sup>

Despite the concerns outlined here, there is substantial evidence that screening of high-risk patients, when combined with other measures such as contact precautions, appropriate hand hygiene, and education of personnel, can reduce transmission of MRSA, even in facilities where it is highly endemic.<sup>117, 118, 121, 128, 129, 130 and 131</sup> On the basis of the evidence available, several published guidelines have recommended screening of inpatients at high risk of carrying MRSA.<sup>132, 133, 134, 135, 136 and 137</sup> Commonly used strategies are screening of patients admitted to intensive-care units,<sup>116, 118, 127, 132, 138, 139 and 140</sup> those admitted to selected non-intensive-care wards,<sup>119, 129, 141, 142 and 143</sup> those thought to be at high risk of MRSA at the time of admission,<sup>117 and 144</sup> roommates of MRSA patients,<sup>129</sup> and elderly patients.<sup>120</sup>

Virtually all published analyses that have compared the costs of screening of patients on admission and using contact precautions with colonised patients with the cost savings made by preventing health-care associated MRSA infections have concluded that the combination of surveillance cultures and barrier precautions results in cost savings for hospitals.<sup>118, 144, 145, 146, 147 and 148</sup> The costs of caring for patients who become infected with MRSA are much greater than the costs of screening programmes.

### **Screening of staff**

Health-care workers who are nasal carriers can serve as sources of MRSA transmission, although they are not nearly as important a reservoir as are colonised or infected patients.<sup>149, 150, 151, 152 and 153</sup> Because nasal colonisation of

health-care workers can be transient, recovery of an outbreak or endemic strain from a health-care worker on one occasion does not provide convincing proof that they have transmitted the organism to patients.<sup>115 and 154</sup> In countries that use aggressive search and destroy strategies to control MRSA, health-care workers exposed to patients with MRSA are routinely screened. In other countries, screening of health-care workers is often reserved for situations in which no apparent index case is identified in patients and in which transmission continues despite the use of isolation and barrier precautions.<sup>150 and 155</sup> Failure to identify health-care workers who are persistently colonised or infected can lead to continuing transmission despite implementation of barrier precautions and hand hygiene.

### **Isolation and barrier nursing**

Patients colonised or infected with MRSA should, whenever possible be placed in a private room, or housed with other patients who have MRSA.<sup>30, 132, 133, 134, 135, 136, 137 and 156</sup> The effectiveness of this widely accepted policy has not been proven in randomised trials. Nonetheless, in a systematic review, Cooper and co-workers<sup>157</sup> concluded that patient isolation, when combined with other control measures could reduce the spread of MRSA. One prospective study compared the frequency of MRSA acquisition in two intensive-care units, in which one unit placed patients with MRSA in private rooms or housed them with other infected patients and the other did not.<sup>128</sup> The investigators showed that moving MRSA-positive patients into single rooms or dedicated bays did not reduce MRSA transmission. However, several factors such as nurse-to-patient ratios and low hand-hygiene-compliance rates could have made detection of a difference in transmission rates difficult during the trial periods.<sup>158 and 159</sup> Guidelines recommend that health-care workers wear gloves when caring for MRSA-positive patients and that gowns be worn when substantial contact with patients or their environment will occur.<sup>132, 133, 134, 135, 136, 137 and 156</sup> Effectiveness of the use of gloves and gowns to care for patients with MRSA has not been established in randomised trials, although epidemiological studies support their use.<sup>160, 161, 162 and 163</sup>

There is no consensus on the indications for wearing a mask when caring for patients colonised or infected with MRSA. Guidelines from the Netherlands and the Society for Healthcare Epidemiology of America recommend wearing a mask when entering the room of patients with MRSA.<sup>133 and 136</sup> Other guidelines recommend the use of masks only if the health-care worker were to be exposed to large droplets or aerosolised secretions of patients with MRSA in lower respiratory secretions.<sup>132, 134 and 135</sup> In one study, investigators cultured specimens from the nose, throat, and hands of nursing and physiotherapy staff before and after shifts for 2 months when masks were not worn when caring for MRSA patients, and showed that 48% of staff were colonised on one or more occasions. By contrast, only 26% were colonised during 2 months when masks were worn.<sup>164</sup>

No randomised trials have established the effectiveness of contact precautions in interrupting transmission of MRSA. However, an outbreak investigation that included surveillance cultures of patients and staff, molecular typing of isolates, and decolonisation of some patients revealed that the rate of MRSA transmission from patients not cared for in contact isolation was 15.6 times greater than that from patients who were cared for with contact precautions.<sup>122</sup> More recently, a two-stage longitudinal intervention trial showed that when surveillance cultures plus contact precautions were used, acquisitions of MRSA were significantly less common than when surveillance cultures were used alone.<sup>130</sup>

## **Hand hygiene**

Transient contamination of health-care workers' hands has been documented on many occasions,<sup>115, 154, 164, 165 and 166</sup> and is widely believed to be the predominant method by which MRSA is transmitted to patients. People with dermatitis or other lesions on hands that are colonised with MRSA are especially likely to be sources of transmission to patients.<sup>167, 168, 169 and 170</sup> Several studies have shown that improvement in hand-hygiene practices, when coupled with surveillance cultures and contact precautions, have greatly reduced transmission of MRSA.<sup>131 and 171</sup> The level of compliance with hand-hygiene needed to stop MRSA transmission is unknown, but one study of intensive-care units in which compliance was 59%, predicted that a 12% increase in compliance might have been sufficient to prevent transmission.<sup>166</sup> Guidelines have uniformly recommended that health-care workers clean their hands, preferably with an alcohol-based hand rub or an antimicrobial soap and water, after caring for patients with MRSA.<sup>132, 134, 135, 136 and 156</sup> Because health-care workers' hands can become contaminated even when gloves are worn,<sup>166</sup> hand hygiene is recommended after glove removal.<sup>172</sup>

## **Environmental cleaning**

How important are contaminated environmental surfaces as a reservoir for MRSA? The reported frequency of contaminated environmental surfaces has varied from a few percent in most studies to as high as 64–74% in others.<sup>162 and 173</sup> The US Centers for Disease Control and Prevention isolation guidelines recommend that hospitals have adequate procedures for routine care, cleaning, and disinfection of environmental surfaces, beds, bedrails, bedside equipment, and other frequently touched surfaces.<sup>156</sup> For patients in contact precautions, non-critical equipment (eg, stethoscopes and blood-pressure cuffs) should be dedicated to one patient whenever possible. Further studies are needed to find out if thorough decontamination of rooms occupied by patients with MRSA will affect MRSA transmission rates.

## **Decolonisation therapy**

In the Netherlands, hospitals routinely give decolonisation therapy to patients and health-care workers who are colonised.<sup>30 and 123</sup> However, in other countries, there is no consensus about the indications for administration of topical intranasal therapy, or systemic antibiotics to patients and staff who are colonised.<sup>134, 135 and 174</sup> Giving intranasal mupirocin to patients who are colonised at many body sites (especially chronic wounds) often fails to eradicate carriage.<sup>175</sup> Widespread use in a hospital or long-term use of mupirocin in patients should be avoided since these practices have been associated with emergence of mupirocin-resistant strains of MRSA.<sup>176</sup>

## **Multi-faceted MRSA control programmes**

No one measure to control the spread of MRSA has proved effective. However, comprehensive MRSA-control programmes that have included screening cultures to detect patients (and in many instances staff) colonised with MRSA, use of contact precautions, appropriate hand hygiene, automatic alerts of readmission of colonised patients, with or without decolonisation of colonised individuals, have reported success in controlling or reducing transmission of MRSA nationally, regionally, and institutionally.<sup>123, 129, 145, 177, 178, 179, 180 and 181</sup> Similar measures have also reduced acquisition of MRSA in high-risk units in hospitals.<sup>116, 131 and 132</sup> So far, there is no conclusive evidence that restriction of the use of antibiotics could control the spread of MRSA in hospitals or beyond. In one study, judged to be of

sufficient quality by the most recent systematic review,<sup>182</sup> an antibiotic-control strategy had no effect on the spread of MRSA during 7 years.<sup>182</sup> Nevertheless, curtailing the use of fluoroquinolones could be beneficial, since increasing epidemiological, pharmacological, and biological evidence incriminates this antibiotic class as an important risk factor for the acquisition and dissemination of MRSA.<sup>183, 184 and 185</sup>

MRSA can also be acquired outside hospitals, and recommendations to prevent its acquisition and spread centre around personal hygiene such as frequent hand washing, covering of wounds with dry bandages, and seeking advice from doctors when skin infection occurs. Sharing of personal items such as razors, towels, non-laundered clothing, uniforms, or equipment that has come into contact with wounds should be avoided. Showering after intimate or close body contacts and after sharing equipment in health clubs is also advisable.<sup>186</sup>

### Future perspectives

In the long evolutionary history of *S aureus*, strains with special epidemic properties have probably appeared from time to time. The present success of the few pandemic hospital-acquired-MRSA clones has been accounted for by the acquisition of additional fitness traits by already widespread and successful colonising strains, with the view that gaining  $\beta$ -lactam resistance yields a decisive advantage over competitors in hospitals.<sup>90</sup> There are also indications that epidemic hospital acquired MRSA differs from sporadic MRSA clones in biofilm production, improved adhesiveness, and epithelial invasiveness.<sup>187</sup> When taking the present increase in community-acquired MRSA into consideration, there is a new worry that some clones that have emerged in the community, and which combine resistance with transmissibility and virulence, will become established in hospitals and might even replace the endemic health-care-associated strains that are so prevalent today. Reports of outbreaks of community-acquired MRSA in hospitals<sup>54, 55 and 56</sup> and early indications of changes in the strain structure of MRSA in hospitals serving populations with high rates of community-acquired MRSA<sup>188 and 189</sup> could herald this uncomfortable trend. Because of the higher pathogenicity of community strains, MRSA could also change its predominantly opportunistic behaviour and cause infections in patients who are not seriously ill or even in health-care workers. This disquieting prospect is lent support by findings that the notorious 80/81 strain is closely related to an extant clone known as the southwest Pacific clone.<sup>190</sup> Both share the same ancestor (ST30), are equipped with the Pantone-Valentine leukocidin virulence genes (*lukS* and *lukF*), and were first identified in the same geographic region. However, only the southwest Pacific clone has acquired an SCCmec IV element to become methicillin-resistant and reportedly causes community-onset infections not only in Australia, Oceania, and Asia, but also in various European countries.<sup>38, 191, 192, 193, 194 and 195</sup> Outbreaks reminiscent of those in the late 1950s have so far, however, not been reported. Complete genome sequencing will identify any residual differences between the historic 80/81 and the strains circulating now.

The recently published genome sequence of another very successful clone of community-acquired MRSA, USA300, lends further support to the theory that successive genomic alterations led to the evolution of fitter clones that combine antimicrobial resistance with transmissibility and virulence.<sup>196</sup> In addition to its inherent virulence properties, community-acquired MRSA poses another threat. Mathematical models suggest that the present dynamics of the worldwide increase in hospital-acquired-MRSA clones can be best accounted for by repetitive introduction (by long-term carriers) and transmission in hospitals.<sup>197 and 198</sup> Central to this notion is the assumption that transmission outside the hospital is rare and

will by itself not maintain MRSA in the population. If the new community-acquired MRSA clones are, however, sufficiently fit to sustain endemic levels by transmission in the community, the MRSA situation in hospitals, which still remains out of control in many countries, could potentially become explosive. The onus is therefore on health-care authorities to develop not only surveillance systems that are able to monitor the clonal dynamics of MRSA over wide geographical areas but also to provide the resources for early recognition of MRSA carriers through rapid screening. Hospital staff have a responsibility to implement, maintain, and adhere to strict contact precautions, should hospitals remain places where citizens can aspire to positive health-care outcomes with confidence.

### **Search strategy and selection criteria**

We selected MEDLINE and PubMed hits generated by searches using the search terms: "Staphylococcus" or "Staphylococci" occurring in combination with one of the words "antimicrobial", "antibiotic", "susceptibility" or "resistance". We used available monographies and Index Medicus for historical articles. For the present estimates on worldwide prevalence of MRSA we included search terms such as "surveillance", "prevalence", "incidence", or "trend" occurring together with one or more of the above.

### **Conflict of interest statement**

We declare that we have no conflict of interest.

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