Molecular epidemiology of community-associated meticillin-resistant *Staphylococcus aureus* in Europe

Jonathan A Otter, Gary L French

Over the past decade, community-associated meticillin-resistant *Staphylococcus aureus* (MRSA) has emerged in patients without health-care contact, especially in the USA. Although data are limited, the prevalence of community-associated MRSA in Europe seems to be low but is increasing. The organism has been reported in most European countries, including the Netherlands and Nordic countries, which have low rates of health-care-associated MRSA. In Greece, rates of community-associated MRSA in some centres approach those of the USA. By contrast with North America, where the USA300 clone (ST8-IV) predominates, community-associated MRSA in Europe is characterised by clonal heterogeneity. The most common European strain is the European clone (ST80-IV), although reports of USA300 are increasing. Several community-associated MRSA clones have arisen in Europe, most notably the ST398-V pig-associated MRSA clone in the Netherlands and Denmark. An understanding of the epidemiology of community-associated MRSA is essential to guide new control initiatives to prevent these organisms from becoming endemic in Europe.

**Introduction**

Meticillin-resistant *Staphylococcus aureus* (MRSA) is endemic in many hospitals worldwide. Previously, MRSA infections were nearly always associated with hospital or health-care contact, but new strains of MRSA have emerged that cause community infection in patients without previous health-care contact.

New MRSA clones emerge because of acquisition of meticillin resistance by previously susceptible *S aureus* strains. Clinically significant meticillin resistance is conferred by expression of the mecA gene, which encodes a modified penicillin-binding protein (PBP2a or PBP2`) that has low affinity for β-lactam antibiotics and facilitates cell-wall synthesis in the presence of meticillin and other β-lactams. The mecA gene is carried on a mobile genetic element, the staphylococcal cassette chromosome (SCCmec). SCCmec probably originated in coagulase-negative staphyloocci and integrates site-specifically into the *S aureus* genome. A range of SCCmec types, known as I to VII and their variants, have been described and new types continue to emerge.

Despite the global scale of the problems caused by health-care-associated MRSA, only a small number of major clones have been identified. These clones can be characterised by multilocus sequence typing (MLST) and SCCmec type. The five predominant health-care-associated MLST clonal complexes are listed in the panel.

The rate of meticillin resistance in blood isolates of *S aureus* (mostly health-care-associated MRSA) in European countries ranges from less than 1% in Norway, Sweden, and Denmark and less than 5% in the Netherlands, to more than 40% in Greece and the UK and more than 50% in Malta. The wide range of MRSA prevalence in Europe might be associated with the effectiveness of implementation of national antibiotic prescribing and infection control policies. Additionally, the dominance of just a few health-care-associated MRSA clones suggests that some strains have particular abilities to survive and transmit in hospital environments and, once they are established in a health system, are difficult to eradicate. The emergence of endemic health-care-associated MRSA in England since 1990, for example, has mainly been caused by the spread of EMRSA-15 (ST22-IV) and EMRSA-16 (ST36-II). However, the reasons why some clones are more successful than others have not been established.

MRSA colonisation can persist for months or years and, until recently, MRSA infections presenting in the community were usually caused by health-care-associated MRSA strains acquired directly or indirectly during previous hospital or health-care contact. In general, however, health-care-associated MRSA has not spread within the community. True community-acquired

<table>
<thead>
<tr>
<th>Panel: Five predominant health-care-associated MRSA MLST clonal complexes</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>The most frequent examples of clones within each complex are shown</td>
<td></td>
</tr>
</tbody>
</table>
| CC5 | ST5 SCCmec type II (New York/Japan)  
ST5-IV (paediatric)  
ST228-I (southern German) |
| CC8 | ST250-I (Archaic clone)  
ST8-IV (EMRSA -2,-6)  
ST8-II (Irish-1)  
ST239-III (Brazilian/Portuguese)  
ST247-I (Iberian) |
| CC22 | ST22-IV (EMRSA-15) |
| CC30 | ST36-II (EMRSA-16) |
| CC45 | ST45-IV (Berlin) |

ST = multilocus sequence type.
or associated MRSA infection, caused by strains distinct from health-care-associated MRSA, was first reported as an outbreak of skin and soft-tissue infection in drug users in Detroit, MI, USA, in the early 1980s. Community-associated MRSA infections in patients without previous health-care contact began to emerge in the early 1990s in western Australia and in US children, and in some European countries in the late 1990s. Community-associated MRSA infections have since been seen worldwide, with substantial increases in prevalence in the USA, where they were the predominant cause of S aureus skin and soft-tissue infections in patients presenting to emergency departments in 2004.

We review the molecular epidemiology of community-associated MRSA in Europe to identify priorities for future infection control policies.

**Characteristics**

Health-care-associated MRSA strains usually cause infection in hospitalised, compromised, elderly patients. Community-associated MRSA strains, common with meticillin-susceptible S aureus, can affect younger, healthy people and can spread readily in community settings. Community subsets that are at high risk of infection include injecting drug users, prisoners and those of low socioeconomic status, men who have sex with men, players of contact sports, and children. Risk factors for outbreaks of community-associated MRSA in these groups form the basis of the US Centers for Disease Control and Prevention’s (CDC) five Cs of transmission: contact, cleanliness, compromised skin integrity, contaminated objects, and crowded living conditions. Antimicrobial use is also a risk factor for community-associated MRSA and has been proposed as a sixth C: capsules. Risk factors not related to outbreaks are more difficult to identify, but include the presence of children at home, home contacts with community-associated MRSA skin and soft-tissue infections, recent travel to areas of high prevalence, injecting drug use, alcoholism, HIV, and crowded housing. However, infections are not restricted to the community; once introduced into hospitals by the admission of carriers, they can cause epidemic and endemic nosocomial infection.

An emerging feature of the epidemiology of community-associated MRSA is colonisation of non-nasal sites and infection without colonisation at sites of usual carriage. Although most patients with health-care-associated MRSA infection have nasal colonisation, Yang and colleagues reported that only 37% of 65 patients with community-associated MRSA infection had colonisation at any site, and only 25% had nasal colonisation. Another study suggested that exclusive throat carriage of MRSA is associated with community-based younger individuals. Some outbreaks of community-associated MRSA have involved infection in the absence of nasal colonisation or transmission by routes that might not involve nasal colonisation, such as homosexual and heterosexual contact and contamination of fomites.

Community-associated MRSA strains usually carry SCCmec types IV and V, which are smaller than the health-care-associated SCCmec types I to III, and seem to offer a fitness advantage in community settings. However, although SCCmec type IV is less common in health-care-associated MRSA strains, ST22 (EMRSA-15), one of the most common clones in the UK, carries SCCmec IV, as does the ST5 paediatric clone.

Community-associated MRSA is associated with production of Panton-Valentine leukocidin (PVL). PVL is a two-component cytotoxin that is produced by about 2% of meticillin-susceptible S aureus and is encoded by the lukS-PV and lukF-PV genes, which are carried on a bacteriophage. PVL is probably a direct virulence factor in staphylococcal necrotising pneumonia, but its role in skin and soft-tissue infections and other invasive disease is controversial. There is an epidemiological association between community-associated MRSA and PVL, particularly in the USA where the predominant community-associated MRSA clone, USA300, is PVL-positive. However, since several lineages are PVL-negative, the toxin is not a universal marker for community-associated MRSA.

By contrast with health-care-associated MRSA, community-associated strains are susceptible to most non-β-lactam antimicrobial drugs, with a faster growth rate and a low level of meticillin resistance, which is often expressed heterogeneously. However, multidrug-resistant community-associated MRSA strains have started to emerge.

**Molecular epidemiology**

The most useful molecular methods to differentiate community-associated from health-care-associated MRSA are MLST, SCCmec type, sequencing of the repeat regions of the S aureus protein A (spa) type, PVL status, and pulse-field gel electrophoresis (PFGE) profile. These methods can be combined to characterise community-associated MRSA clones internationally. As with health-care-associated MRSA, successful clones of community-associated MRSA are usually associated with specific geographical locations for reasons that are not well understood, but probably relate to socioeconomic factors, antimicrobial prescribing policies, and community and hospital outbreaks. There have been several descriptions of the introduction of specific community-associated MRSA clones into a new area by migrant carriers.

Community-associated MRSA is particularly well established in the USA. Although USA400 (PVL-positive ST1 SCCmec type IV [ST1-IV]) strains were responsible for initial cases, USA300 (PVL-positive ST8-IV) is now the predominant cause of North American infection and has begun to replace health-care-associated strains as the
most frequent cause of health-care-associated MRSA infection.46,47

By contrast, USA300 is uncommon in Europe, where community-associated MRSA is characterised by clonal diversity.48 USA300 and its variants have been reported in small numbers in Italy,49 Spain,50–52 Germany,53–55 Austria,56 and Denmark.57 and other common international clones such as ST1-IV (USA400), ST8-IV (USA300), ST30-IV (southwest Pacific), and ST59-V have also been reported in Europe44 (figure). The most common European community-associated MRSA isolate is PVL-positive ST80-IV, the so-called European clone, which has a characteristic antimicrobial susceptibility pattern of resistance to fusidic acid, tetracycline, and kanamycin and variable resistance to ciprofloxacin.54,64 The European clone has been reported in France and Switzerland,58 Austria,61 Bulgaria,59 Belgium,60 Germany,79,81 Greece,78 the Netherlands,78,82 Denmark,83 Finland,84 Norway,85 and Sweden.86 This clone might have emerged originally in the Mediterranean, Middle East, or north Africa because many of the first patients infected with this clone in Europe had travel histories to these regions.87,88 However, irrespective of where the clone originated, it is currently the most frequently reported community-associated MRSA clone in Europe; therefore, we refer to it as the European clone in this Review.

Several clones seem to have emerged in Europe, such as the ST398-V pig-associated clone (which was reported first in the Netherlands69–71 and Denmark,72–74), a PVL-positive ST152-V clone in the Balkan region,36,91 a Swedish ST150 clone with a novel SCCmec type,52 PVL-negative clones causing infections in injecting drug users in Switzerland (ST45)75 and the UK (ST1),76,77 and an ST377-V clone in Greece.77 Several of these clones, such as the European clone and, increasingly, the ST398-V pig-associated clone, have spread worldwide, whereas others remain localised within Europe.45,46 Similarly, the occurrence of successful clones from other parts of the world, most worryingly the USA300 clone from North America, is increasing in Europe.71,72

Despite the increasing global presence of community-associated infection, rates of MRSA carriage in the healthy population remain low in most parts of the world. Even in the USA where community-associated MRSA is widespread, the prevalence of nasal colonisation with MRSA in a large sample of healthy Americans was only 1·5% in 2003–04,96 although current national prevalence is unknown. Similarly, community nasal carriage seems to be low in most parts of Europe, mostly linked to health-care exposure.97–99 For example, none of 2691 patients attending general practices in Denmark (a country with a low prevalence of health-care-associated MRSA) were colonised with MRSA during 2002,98 and less than 1% of healthy elderly people in the UK (a country with a high prevalence of health-care-associated MRSA) were colonised with MRSA in a 2002 survey.99

Table 1 and 2 summarise the published information about the molecular epidemiology of community-associated MRSA in Europe.

**France, Belgium, and Italy**

The first European cases of MRSA infection in patients without recognised risk factors were reported in 2002 by the French staphylococcus reference laboratory99 (table 1). More recent reports from France have suggested that the prevalence of community-associated MRSA is increasing.85 In Belgium, community-associated MRSA is characterised by substantial heterogeneity, although the European clone is most frequently reported.86 Reports of community-associated MRSA from Italy have been sparse, but a recent Italian laboratory-based study showed that 12 (6%) of 188 *S aureus* isolates from outpatients were MRSA and nine of these were USA300 type.40

**Spain and Portugal**

Spain and Portugal have high rates of health-care-associated MRSA but low, albeit increasing, rates of community-associated MRSA. In two Spanish studies, ST8-IV (USA300) was the most frequent clone and these PVL-positive isolates were associated with immigrants from South America, mainly Ecuador and Bolivia.65,66 Portugal has a very high rate of meticillin resistance in hospital isolates of *S aureus*,1 but a very low incidence of community-associated MRSA.124,125

**Switzerland**

Initial reports of MRSA in patients without risk factors for health-care-associated MRSA occurred in the Geneva region in 2002 and seemed to have been caused by the same community-associated MRSA reported in France.100 More cases of community-associated infection have since been reported in Geneva and Zurich,101,102 but the overall prevalence remains low: only nine (0·06%) of 14253 patients admitted to the Geneva University
<table>
<thead>
<tr>
<th>Study period</th>
<th>Location, setting</th>
<th>Selection criteria</th>
<th>Number of isolates</th>
<th>PVL-positive isolates (%)</th>
<th>Clinical details</th>
<th>Molecular characterisation (%)</th>
<th>Antimicrobial resistance (%)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Worldwide studies</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tristan et al (2007)14</td>
<td>2006</td>
<td>17 countries, reference laboratory</td>
<td>Referred PVL+</td>
<td>469</td>
<td>469 (100%)</td>
<td>ST80 (76%); ST1 (7%); ST30 (4%)</td>
<td>–</td>
<td>Many patients had a history of international travel; MDR isolates detected in Singapore, China, and Algeria</td>
</tr>
<tr>
<td>Sousa et al (2003)15</td>
<td>2003</td>
<td>Three continents, reference laboratory</td>
<td>Referred PVL+</td>
<td>117</td>
<td>117 (100%)</td>
<td>ST80 (57%); ST1 (25%); ST30 (11%); ST59 (3%); ST93 (3%)</td>
<td>–</td>
<td>Isolates were tightly clustered geographically, with ST80 isolates from Europe, ST1 isolates from the USA, and ST30 isolates from Oceania</td>
</tr>
<tr>
<td>Linde et al (2006)16</td>
<td>2006</td>
<td>Germany, ten health-care facilities</td>
<td>Outbreak</td>
<td>75</td>
<td>75 (100%)</td>
<td>Among patients: colonised (73%), infected (27%)</td>
<td>ST22 (100%); Fus</td>
<td>Evidence of recent international travel in three of 16 patients with PVL+ isolates</td>
</tr>
<tr>
<td>Linde et al (2005)17</td>
<td>2005</td>
<td>Germany, neonatal unit</td>
<td>Outbreak</td>
<td>8</td>
<td>8 (100%)</td>
<td>Among patients: colonised (60%), infected (40%)</td>
<td>ST80 (100%); Fus</td>
<td>Nasal colonisation was identified in five of six cases; decolonisation treatment failed for one patient</td>
</tr>
<tr>
<td>Wagenlehner et al (2007)18</td>
<td>2007</td>
<td>Germany</td>
<td>Outbreak, long-term care facility</td>
<td>78</td>
<td>78 (100%)</td>
<td>Colonised (97%); SSTI (3%)</td>
<td>ST22 (100%); Fus</td>
<td>Evidence of recent international travel in three of 16 patients with PVL+ isolates</td>
</tr>
<tr>
<td>Aires de Sousa et al (2003)19</td>
<td>1998-2000</td>
<td>Greece, single hospital</td>
<td>Molecular definition</td>
<td>11</td>
<td>11 (100%)</td>
<td>ST80 (100%); Fus</td>
<td>Prevalence of the ST80 clone increased sharply in 2000; no risk factor analysis was reported</td>
<td></td>
</tr>
</tbody>
</table>

| Studies in central, southern, and eastern Europe |
| Ruppitsch et al (2007)20 | 2005-07 | Austria, reference laboratory | PVL+ | 9 | 9 (100%) | SSTI (89%); abscess (67%) | ST8 (100%); Ery, cip | PVL detected in 0.6% of 1500 isolates tested; seven isolates positive for ACME; all isolates positive for arcA |
| Kriwanek et al (2008)21 | 1996-2006 | Austria, reference laboratory | PVL+ | 64 | 64 (100%) | ST8 (34%); ST80 (16%); ST152 (13%); ST30 (11%); ST59 (7%); ST93 (3%); ST3 (1%) | Fus (22%) | PVL detected in 10% of 627 randomly selected isolates from 1439 isolates submitted to the reference laboratory |
| Bauer et al (2009)22 | 2009-2007 | Austria, single centre | Antibiotogram | 41 | 16 (39%) | ST80 (24%); ST80 (10%) | Fus | 3% of 2542 MRSA isolates obtained during the study period were defined as CA-MRSA |
| Grindoll et al (2009)23 | 2002-07 | Austria, several hospitals | Epidemiological | 70 | – | ST80 (40%); ST80 (10%); ST10 (10%); ST3 (1%) | Tet (34%); fus (14%); cip (14%) | 40% of 70 patients required admission to hospital |
| Denis et al (2005)24 | 2002-04 | Belgium, reference laboratory | Referred presumptive CA-MRSA isolates | 41 | 16 (40%) | SSTI (75%); SSTI (100%); SSTI (100%); SSTI (83%); ST80 (5%) | All cip susceptible | Evidence of recent international travel in three of 16 patients with PVL+ isolates |
| Nashev et al (2007)25 | 2005-07 | Bulgaria, reference laboratory | Antibiotogram | 6 | 6 (100%) | SSTI (100%); SSTI (83%); ST80 (10%) | – | Nasal colonisation was identified in five of six cases; decolonisation treatment failed for one patient |
| Dufour et al (2002)26 | 1999-2001 | France, reference laboratory | PVL+ isolates, defined epidemiologically | 14 | 14 (100%) | SSTI (79%); European clone (PFGE) | Fus, tet, kan | PVL detected in 0.6% of 1500 isolates tested; seven isolates positive for ACME; all isolates positive for arcA |
| Naas et al (2005)27 | 2001-03 | France, single hospital | Antibiotogram | 17 | 16 (100%) | SSTI (12%); European clone (PFGE) | Fus, kan | 16 of 17 isolates available for molecular analysis; three infections defined epidemiologically as health-care-associated infections |
| Del Guidice et al (2006)28 | 1999-2003 | France, dermatology | MRSA SSTI, epidemiologically defined | 6 | 6 (100%) | SSTI (100%); European clone (PFGE) | Kan, fus, tet | 11% of 197 S aureus isolates were MRSA; 11% of 22 MRSA patients had CA-MRSA, with the proportion increasing from 0 to 40% |
| Witte et al (2004)29 | 2002-03 | Germany, reference laboratory | PVL+ | 4 | 4 (100%) | SSTI (100%); ST80 | Fus, cip | All four patients had no previous hospital admission |
| Witte et al (2005)30 | 2002-04 | Germany, reference laboratory | PVL+ | 28 | 28 (100%) | SSTI (68%); abscess (42%) | ST80 (96%); Fus, cip | 0.5% of 6345 MRSA isolates were PVL+; nine isolates were obtained from sites associated with HA-MRSA |
| Witte et al (2007)31 | 2006-07 | Germany, reference laboratory | PVL+ | 117 | 117 (100%) | SSTI (90%); abscess (65%) | ST80 (68%); ST (20%); Fus | 2% of 4815 MRSA isolates were PVL+; many patients with PVL+ ST8 isolates had a personal or family history of travel to the USA |
| Linde et al (2005)32 | 2003-04 | Germany, ten health-care facilities | Outbreak | 75 | 75 (100%) | Among patients: colonised (73%), infected (27%) | ST22 (100%); Fus | 52 patients, 21 health-care workers (all colonised), and two others were affected |
| Linde et al (2005)33 | 2003-04 | Germany, neonatal unit | Outbreak | 8 | 8 (100%) | Among patients: colonised (60%), infected (40%) | ST80 (100%); Fus | Five patients and three health-care workers (all colonised) were affected |

(Continues on next page)
Hospitals with no previous hospital contact screened positive for MRSA carriage in 2003. Sax and colleagues recently reported an outbreak of a PVL-positive, ST5-IV strain of community-associated MRSA in a Swiss intensive care unit, highlighting the potential of community-associated MRSA to cause hospital outbreaks.

### Germany and Austria

The European clone was first reported in Germany in 2002. The most recent report from the German reference laboratory suggests an increase in prevalence of the European clone and also the emergence of a USA300-like strain of community-associated MRSA in Germany. However, other more recent reports suggest that ST80-IV might now be more common in some parts of the country.

**Greece**

Greece has one of the highest rates of health-care-associated MRSA in Europe. In 2007, 48% of cases of invasive S aureus were meticillin resistant. Information about community-associated MRSA in Greece is limited; the PVL-positive European clone (ST80-IV) seems to be the most common type, but the novel ST377-V clone has been reported recently in Patras in southwest Greece and Larissa in central Greece. During 2001–03, PVL-positive community-associated MRSA accounted for 55% of health-care-associated MRSA infections at hospitals in these regions. This rate of community-associated MRSA is nearly as high as that seen in the USA.

### UK and Ireland

Health-care-associated MRSA is common in the UK, but reports of community-associated infection are rare but...
### UK and Ireland

<table>
<thead>
<tr>
<th>Study period</th>
<th>Location, setting</th>
<th>Selection criteria</th>
<th>Number of isolates</th>
<th>PVL-positive isolates (%)</th>
<th>Clinical details (%)</th>
<th>Molecular characterisation (%)</th>
<th>Antimicrobial resistance</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Holmes et al (2005)</td>
<td>2002-05</td>
<td>UK, reference laboratory</td>
<td>PVL + MRSA in S aureus referrals</td>
<td>14</td>
<td>14 (100%)</td>
<td>ST80 (86%); ST30 (7%)</td>
<td>Tet, fus</td>
<td>3% of 515 S aureus isolates were PVL+ MRSA; clinical information was not available for several isolates</td>
</tr>
<tr>
<td>Otter et al (2008)</td>
<td>2000-06</td>
<td>UK, two hospitals</td>
<td>Antibiogram</td>
<td>194</td>
<td>49 (25%)</td>
<td>ST80 (6%)</td>
<td>-</td>
<td>6% of 746 MRSA isolates in the study period were ciprofloxacin susceptible. A PVL– ST8 clone associated with drug users predominated</td>
</tr>
<tr>
<td>Karden-Lilja (2007)</td>
<td>2005-07</td>
<td>UK, single hospital</td>
<td>Antibiogram</td>
<td>94</td>
<td>23 (24%)</td>
<td>ST8 (24%); ST80 (12%)</td>
<td>-</td>
<td>35 of the recovered isolates were classified as CA-MRSA on the basis of phenotypic and genotypic characteristics</td>
</tr>
<tr>
<td>Rossney et al (2007)</td>
<td>2003-04</td>
<td>Ireland, reference laboratory</td>
<td>PVL+ isolates</td>
<td>25</td>
<td>25 (100%)</td>
<td>ST30 (44%); ST8 (32%); ST80 (8%)</td>
<td>Fus (44%); ery (40%); cip (28%)</td>
<td>2% of 138 isolates in the study period were PVL+, 78% of epidemiologically defined CA-MRSA isolates were PVL+; nine of 25 patients with PVL+ MRSA were non-Irish and six of 25 cases were health-care-associated</td>
</tr>
</tbody>
</table>

### Nordic countries

<table>
<thead>
<tr>
<th>Study period</th>
<th>Location, setting</th>
<th>Selection criteria</th>
<th>Number of isolates</th>
<th>PVL-positive isolates (%)</th>
<th>Clinical details (%)</th>
<th>Molecular characterisation (%)</th>
<th>Antimicrobial resistance</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1997-99</td>
<td>Denmark, one county</td>
<td>Community cluster</td>
<td>46</td>
<td>46 (100%)</td>
<td>Abscess (76%)</td>
<td>ST80 (100%)</td>
<td>Tet, str, kan, fus</td>
<td>Cases often linked through schools, workplaces, and homes. A home-based decolonisation regimen was largely successful</td>
</tr>
<tr>
<td>2001</td>
<td>Denmark, reference laboratory</td>
<td>All national MRSA, epidemiologically defined</td>
<td>45</td>
<td>37 (82%)</td>
<td>ST80 (76%)</td>
<td>Tet, kan, fus</td>
<td>55% of 81 isolates were community onset and 46% of 81 isolates were defined epidemiologically as community acquired</td>
<td></td>
</tr>
<tr>
<td>1999-2005</td>
<td>Denmark, reference laboratory</td>
<td>CCR MRSA in all national MRSA</td>
<td>516</td>
<td>44 (9%)</td>
<td>ST80 (100%)</td>
<td>-</td>
<td>26% of 1986 reported isolates were CCB; epidemic year-on-year increase in the number of PVL+ ST8 (USA300) isolates from 2000</td>
<td></td>
</tr>
<tr>
<td>1999-2004</td>
<td>Denmark, reference laboratory</td>
<td>PVL+ ST80 MRSA in all national MRSA</td>
<td>294</td>
<td>294 (100%)</td>
<td>Abscess (82%); ST80 (100%)</td>
<td>Tet, str, kan, fus</td>
<td>5% of 37 143 reported isolates were ST80; prevalence remained fairly constant; 41% of patients had recent international travel experience</td>
<td></td>
</tr>
<tr>
<td>2003-04</td>
<td>Denmark, single hospital</td>
<td>Epidemiologically defined</td>
<td>65</td>
<td>53 (82%)</td>
<td>CCR (29%); CCBO (28%); CCJO (26%)</td>
<td>-</td>
<td>45% of 143 MRSA isolates during the study period were defined epidemiologically as CA-MRSA</td>
<td></td>
</tr>
<tr>
<td>2009 (Concluded)</td>
<td>Denmark, reference laboratory</td>
<td>All national MRSA from infection, defined epidemiologically</td>
<td>526</td>
<td>172 (70%)</td>
<td>ST8 (76%); CCBO (29%); CCJO (19%); CCJO (19%)</td>
<td>Tet, kan, fus</td>
<td>Incidence of CA-MRSA increased ten-fold over the study and exceeded that of HA-MRSA in 2006 (2.81 vs 1.34 per 100 000 inhabitants)</td>
<td></td>
</tr>
<tr>
<td>1997-99</td>
<td>Finland, reference laboratory</td>
<td>All national MRSA, defined epidemiologically</td>
<td>108</td>
<td>Infected (65%); colonised (35%)</td>
<td>ST80 (69%)</td>
<td>-</td>
<td>21% of 526 S aureus isolates were defined epidemiologically as CA-MRSA; a detailed history of health-care contact was available</td>
<td></td>
</tr>
<tr>
<td>1997-99</td>
<td>Finland, one county</td>
<td>Isolates from Salmenlinna et al (2002)</td>
<td>108</td>
<td>13 (12%)</td>
<td>ST80 (69%)</td>
<td>-</td>
<td>PVL was more common in CA-MRSA strains, but 1% of 406 HA-MRSA strains were PVL+</td>
<td></td>
</tr>
<tr>
<td>1997-2004</td>
<td>Finland, reference laboratory</td>
<td>All national MRSA</td>
<td>4091</td>
<td>ST80 (1%); ST80 (1%); ST8 (2%)</td>
<td>-</td>
<td>-</td>
<td>More than 50% of isolates were SCCmec type IV</td>
<td></td>
</tr>
<tr>
<td>1995-2003</td>
<td>Norway, northern Norway</td>
<td>All MRSA</td>
<td>67</td>
<td>ST80 (40%); ST80 (13%); Fus (48%); kan (37%); ery (33%)</td>
<td>-</td>
<td>75% of 67 patients had no health-care contact; 91% were SCCmec type IV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2003</td>
<td>Norway, southeastern Norway</td>
<td>All MRSA</td>
<td>100</td>
<td>-</td>
<td>ST80 (27%)</td>
<td>-</td>
<td>Sharp increase in the number of ST80 isolates in 2003</td>
<td></td>
</tr>
<tr>
<td>1997-2004</td>
<td>Sweden, one county</td>
<td>All MRSA, epidemiologically defined</td>
<td>36</td>
<td>-</td>
<td>ST8 (16%)</td>
<td>-</td>
<td>39% of 92 isolates reported in the study period defined epidemiologically as CA-MRSA; 38% of 92 isolates had an unknown SCCmec type; PVL detected in 54% of 92 isolates</td>
<td></td>
</tr>
<tr>
<td>2000-05</td>
<td>Sweden, single hospital</td>
<td>Epidemiologically defined</td>
<td>104</td>
<td>54 (52%)</td>
<td>ST80 (38%); ST8 (16%)</td>
<td>-</td>
<td>ST150 from a cluster of homeless individuals; ten cases were family contacts of other cases</td>
<td></td>
</tr>
</tbody>
</table>

(Continues on next page)
increasing (table 2). Unusual community strains of MRSA were first identified in injecting drug users in 2003. More recent reports suggest that an ST1, PVL-negative community-associated MRSA clone is circulating among injecting drug users and homeless people in the UK. In 2005, the national staphylococcus reference laboratory for England and Wales reported that only 100 diverse community-associated MRSA isolates had been referred in the previous 3 years, accounting for just 0.005% of all referred MRSA isolates. There have been several sporadic reports of community-associated MRSA from other UK laboratories, including two health-care-associated outbreaks in 2006, one caused by the PVL-negative ST1-IV clone and one by the PVL-positive ST30-IV clone.

Several studies suggest that the prevalence of community-associated MRSA in the UK might be increasing. A recent retrospective analysis of the UK General Practice Research Database reported that the incidence of epidemiologically defined presumptive community-associated MRSA increased by 46%, from 332 cases in 2000 to 484 cases in 2004. We did a retrospective study of presumptive community-associated MRSA in a London hospital during 2000–06 and identified increases in the proportion of MRSA isolates that were susceptible to ciprofloxacin and the proportion that were PVL positive.

There are few reports on community-associated MRSA in Ireland. However, these strains seem to account for less than 2% of all MRSA isolates in the country and are characterised by genetic diversity associated with international travel.

### The Netherlands and Nordic countries

The prevalence of health-care-associated MRSA in the Netherlands and Nordic countries is very low but community-associated MRSA infections have recently emerged despite strict national antimicrobial restriction and infection control policies. The Netherlands reported an increase in the incidence of PVL-positive MRSA, from 1% of 216 isolates during 1987–95 to 5% of 99 isolates in 2000, and 15% of 98 isolates in 2002. In 2002 the European clone of community-associated MRSA, and were associated with skin and soft-tissue infections in both community and hospitalised patients. A more recent study from the northern Netherlands identified the European clone as the most frequent isolate among 54 PVL-positive isolates, but only 37% of affected patients did not have health-care-associated risk factors. Notably, 16% of cases were in household contacts, which has been a feature of community-associated MRSA transmission in other studies.

An emerging feature of MRSA epidemiology in the Netherlands is the appearance of the ST398-V pig-associated clone. In 2003, MRSA colonisation was detected in pig farmers. The colonising strain was subsequently identified as ST398-V and unusually non-typable by PFGE with smal. It was found to colonise a high proportion of pigs and pig farmers and has the capacity to cause human infections. The ST398-V clone recently caused a health-care-associated outbreak in a Dutch hospital that affected nine individuals, including five staff,
Review

There has been a similar situation in Denmark, Sweden, Finland, and Norway. These countries have a low prevalence of health-care-associated MRSA and the appearance of unusual MRSA strains was first noted in the mid-to-late 1990s. ST80-IV is the most frequent community-associated MRSA type in these Nordic countries, although ST8-IV (USA300) has been reported.

A comprehensive study by the Danish reference laboratory of all MRSA infections from 1999 to 2006 found that CC80 is the most prevalent clone, accounting for 39% of isolates, but that CC8 now accounts for 19% of isolates. The incidence of community-associated MRSA increased by ten times over the study and exceeded the incidence of health-care-associated MRSA in 2006 (2.81 vs 1.34 per 100,000 inhabitants). Other Danish studies report that the prevalence of PVL-positive, ST8-IV (USA300) isolates has increased sharply in recent years. The ST398-V pig-associated MRSA clone has also been identified in Denmark, a major producer of pork: 12.5% of 272 pig farmers were colonised with this clone, which has been reported as a cause of human MRSA infection in Denmark.

In Finland, strains of MRSA without multidrug resistance were largely responsible for the increase in reports of MRSA from 120 in 1997 to 597 in 2002 (from 2.3 to 11.5 cases per 100,000 population). ST80-IV was the most frequent type recorded among epidemiologically defined community-associated MRSA, although a study of all national isolates of MRSA from 1997 to 2004 suggested that the prevalence of recognised types of community-associated bacteria was low.

Analysis of all reported MRSA in Norway from 1995 to 2003 identified that the predominant strain was a variant of health-care-associated MRSA ST8-IV, followed by ST80-IV, which accounted for 19% of MRSA isolates nationally.

There has been no report of all national MRSA isolates in Sweden. One local study showed that ST80-IV was the most frequent cause of epidemiologically defined community-associated infection but ST8 isolates accounted for 16% of cases. A novel ST150-V clone was responsible for a cluster of MRSA infections in homeless individuals. PVL-positive MRSA accounted for 17% of the 181 reported cases of MRSA infection from southern Stockholm in 2000–03; almost a third of these were thought to have been acquired abroad and almost all were associated with "mini-outbreaks" of less than ten epidemiologically related patients.

Other European countries

There have been few reports of community-associated MRSA in other European countries. For example, case reports or small case series have been reported from Russia, Latvia, Poland, and Croatia and nine cases of community-associated MRSA were identified by the Slovenian reference laboratory after an outbreak in a sports team. However, because of the scarcity of data, the common types and prevalence of community-associated MRSA in these countries are unclear.

Discussion

Accurate ascertainment of the prevalence of community-associated MRSA in Europe is difficult for several reasons. First, most carriers are not infected and therefore are likely to remain undetected. Second, community-associated MRSA colonisation of other body sites in the absence of nasal colonisation is common, so surveys of rates of nasal colonisation will underestimate true prevalence. Third, even when infections are present, patients are often treated in community or outpatient settings where cultures for Staphylococcus aureus might not be done or organisms not identified to strain level. Fourth, since community-associated strains are increasingly isolated in patients with health-care contact and are gaining multidrug resistance, they might be misclassified as health-care-associated MRSA. Finally, we only included English language papers in this Review, which might have underestimated the prevalence of community-associated MRSA in some countries.

Notwithstanding the limited surveillance data, some conclusions can be made. The prevalence of community-associated MRSA in Europe is low but increasing. Notably, community-associated MRSA has been reported in Nordic countries and the Netherlands, where health-care-associated MRSA rates remain very low; indeed, community-associated infections now seem to be more common than health-care-associated infections in these countries and this is threatening the countries' longstanding successes with MRSA control. Community-associated MRSA is especially common in Greece, where PVL-positive strains have emerged as a widespread cause of endemic health-care-associated infections in some hospitals. This situation has worrying parallels with that in the USA and shows the potential for the spread of community-associated MRSA in Europe. Hospital outbreaks of community-associated MRSA have also been reported in other European countries, although these have been sporadic and uncommon. As in the USA, there are clusters of community-associated MRSA infections in some high-risk groups such as injecting drug users, sports teams, and children, but in Europe such outbreaks are uncommon. In Denmark and the Nordic countries where community-associated MRSA has caused much concern, follow-up and investigation of family contacts has increased ascertainment and shown the occurrence of community spread.

By contrast with the predominance of USA300 in the USA, there are many different community-associated MRSA clones in circulation in Europe. These clones tend to vary geographically but the PVL-positive, ST80-IV European clone is widespread. USA300 does occur in Europe and has been reported in several countries, but it has not spread widely so far. Several reports have shown that USA300, the European clone, and other unusual types have been introduced into specific areas by...
immigrants or international travellers.7,75 In Denmark and the Netherlands, countries with large pig-farming industries, the pig-associated ST398-V clone is an increasing cause of human infections that has already been disseminated internationally.149 The reasons for the differences in the molecular epidemiology of community-associated MRSA between Europe and the USA are not well understood. Environmental factors and patient demographics (in particular ethnicity and associated host factors) and socioeconomic factors are probably involved but have not yet been properly investigated. International travel has clearly contributed to global spread, but its effects have been rather limited. In a similar way, the much more prevalent and established health-care-associated MRSA strains also remain largely localised. For example, two clones, ST22-IV (EMRSA-15) and ST36-II (EMRSA-16) dominate health-care-associated MRSA in the UK whereas ST5-II (USA100) predominates in the USA.146,147 We postulate, therefore, that community-associated MRSA has emerged spontaneously by the transfer of mecA to local meticillin-susceptible community strains of S aureus in many geographical areas. Those new community-associated strains that have the ability to spread do so locally and then begin to disseminate by international travel. Successful clones might then gradually disseminate widely over time, as USA300 has throughout the USA and, to a lesser extent, the European clone has done throughout Europe. The burgeoning international spread of these two clones and the pig-associated clone suggests that some strains could become disseminated globally in the future. However, as with health-care-associated MRSA, the reasons why some clones are more successful than others remain to be elucidated.

The emergence of community-associated MRSA has produced new challenges for infection control that need to be urgently addressed to prevent sporadic infections in Europe from becoming endemic, as in the USA. The control of pig-associated community-associated MRSA is a special issue that is being addressed by the Netherlands and Denmark.166 Otherwise, control measures are hampered by an incomplete understanding of the epidemiology of community-associated MRSA. For example, non-nasal sites of colonisation and uncertainty surrounding transmission routes makes identification of carriers and the development of community-based infection control strategies difficult.11 One recent study showed that community-based decolonisation can be effective in an area where colonisation was sporadic,13 but this method might not be feasible in areas of higher incidence. Indeed, the latest CDC guidelines for the control of community-associated MRSA in the USA do not recommend contract tracing or decolonisation with topical antimicrobial agents.169

Unlike health-care-associated MRSA, community-associated strains spread successfully in the community149,150,151,152,153 and transmission among household contacts or within community subsets such as injecting drug users has been a feature of several European reports.13,40,41,42 Community-associated strains cause nosocomial outbreaks,9 affecting younger and less compromised patients than do health-care-associated strains. Community-associated MRSA strains also often infect previously spared groups, such as children and health-care workers.

Conclusion

The main burden of MRSA disease in Europe continues to be health-care associated. However, infections by the transfer of mecA to local meticillin-susceptible community strains of S aureus have no conflicts of interest.

References


