REVIEW

Community-acquired methicillin-resistant *Staphylococcus aureus*: current perspectives

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ABSTRACT

Methicillin-resistant *Staphylococcus aureus* (MRSA) has become a worldwide problem, although its prevalence varies considerably among countries. The epidemiology of MRSA is now changing; infections are no longer confined to the hospital setting, but also appear in healthy community-dwelling individuals without established risk factors for the acquisition of MRSA. Reported prevalence rates of community-acquired MRSA (CA-MRSA) vary widely among studies—largely because of the different definitions employed and different settings in which the studies have been performed. At present, molecular epidemiological definitions, based on staphylococcal cassette chromosome *mec* (SCC*mec*) typing and phylogenetic analyses of the MRSA isolates, are considered the most reliable means by which to distinguish between hospital-acquired MRSA (HA-MRSA) and CA-MRSA. CA-MRSA has been isolated predominantly from skin and soft tissue infections, such as abscesses, cellulitis, folliculitis and impetigo. Although CA-MRSA infections are usually mild, they may also be severe, and can result in hospitalisation and even death. CA-MRSA strains differ from the major pandemic clones of MRSA that account for the majority of epidemic HA-MRSA strains. Differences are found in SCC*mec* types, bacterial growth rate, and the distribution of antibiotic resistance genes and toxin genes. Mathematical models have shown that CA-MRSA has a high potential to become endemic in the community, and this will impact significantly on the control of MRSA in the hospital setting. Well-designed, community-based studies with adequate risk factor analysis are required to further elucidate the epidemiology of CA-MRSA and to improve strategies to control MRSA in both the community and hospital settings.

Keywords Community-acquired methicillin-resistant *Staphylococcus aureus*, epidemiology, hospital-acquired methicillin-resistant *Staphylococcus aureus*, infection control, methicillin-resistant *Staphylococcus aureus*, review

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INTRODUCTION

Methicillin-resistant *Staphylococcus aureus* (MRSA) has traditionally been considered a healthcare-associated pathogen in patients with established risk factors [1–3]. More recently, however, MRSA infections have been described in community-dwelling patients without established risk factors for the acquisition of MRSA [4–15]. The emergence of this community-acquired MRSA (CA-MRSA) as a clinically significant pathogen necessitates reconsideration of current empirical treatment with β-lactam antibiotics for community-acquired *S. aureus* infections and current control strategies for MRSA in hospitals. The objective of this article is to summarise the current knowledge concerning CA-MRSA that is relevant to the development of future infection control strategies.

MECHANISM OF RESISTANCE

MRSA strains harbour the *mecA* gene, which encodes the low-affinity penicillin-binding protein 2a (PBP2a). The production of PBP2a confers resistance to otherwise inhibitory concentrations of all β-lactam antibiotics. The *mecA* gene is carried on a mobile genetic element, the staphylococcal cassette chromosome *mec* (SCC*mec*), which is integrated in the chromosome of *S. aureus*.

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Phylogenetic analyses of international collections of MRSA and methicillin-susceptible *S. aureus* isolates have revealed that methicillin resistance has emerged in five phylogenetically distinct lineages, and on multiple occasions within a given phylogenetic lineage [16]. Up to now, five types of SCC*mec* have been identified, which differ in size and genetic composition. Notably, SCC*mec* type IV has been found in twice as many clones as any other SCC*mec* type, and it is this SCC*mec* type that is most commonly found in clones from patients with CA-MRSA infections [16].

DEFINITIONS

Several definitions for CA-MRSA infections have been proposed [17]. Epidemiological definitions have commonly been based on the timing of isolation of MRSA in relation to the time of admission to the hospital (that is, MRSA isolates were classified as community-acquired if they were cultured within the first 48–72 h of hospitalisation or in a community setting) [17,18]. However, colonisation with *S. aureus* (both methicillin-susceptible *S. aureus* and MRSA) can persist for months to years [19,20], and is asymptomatic in the majority of individuals. Consequently, clinical infections may develop in a setting different from that in which the organism was initially acquired [21]. A meta-analysis of studies reporting the prevalence of CA-MRSA indicated that at least 85% of hospitalised patients who met the time-based definition for CA-MRSA infection, and 47.5% of healthy community members found to be colonised with MRSA, had at least one healthcare-associated risk factor for acquisition [17]. This suggests that at least some of the isolates were healthcare-acquired, and that the use of time-based definitions may lead to overestimation of the true prevalence of MRSA originating in the community. Therefore, others have classified MRSA infections as community-acquired only if no healthcare-associated risk factors were identified [7,12,22,23]. Healthcare-associated risk factors include recent hospitalisation or surgery, dialysis, residence in a long-term care facility, and the presence of a permanent indwelling catheter or percutaneous medical device at the time of culture [6,14].

However, discounting the possible community origin of MRSA infections in patients with healthcare-associated risk factors may lead to an underestimation of the true prevalence of CA-MRSA, as patients with prior healthcare exposure may be at increased risk of colonisation and infection by a true community-dwelling pathogen (e.g., due to outpatient antibiotic use, immunosuppression, or long-term intravenous access) [24]. Moreover, CA-MRSA isolates have recently been reported to have spread into hospitals, causing nosocomial infections [21,24,25]. Definitions based on epidemiological information are therefore insufficient to distinguish between CA-MRSA and hospital-acquired MRSA (HA-MRSA). The use of antibiotic resistance profiles in discriminating between CA-MRSA and HA-MRSA can also be questioned; although antibiotic resistance in CA-MRSA isolates is often limited to β-lactam antibiotics, multidrug resistance has been reported [26].

At present, molecular epidemiological definitions, based on SCC*mec* typing and phylogenetic analyses, are considered the most reliable. According to these definitions, an MRSA strain is classified as community-acquired if the SCC*mec* type IV (or V) is present and if it is phylogenetically unrelated to previously known HA-MRSA clonal lineages [16].

EPIDEMIOLOGY

MRSA has become a worldwide problem, although its prevalence varies considerably among countries. Consistently high prevalence rates are found in the USA, South America, Japan and southern Europe, whereas prevalence rates are low in Scandinavia, The Netherlands and Switzerland [27–29]. Several investigators have suggested that the epidemiology of MRSA is changing, as infections are increasingly reported in healthy community-dwelling individuals without healthcare-associated risk factors for the acquisition of MRSA [4,7,17,24,30]. Clusters and outbreaks of these so-called CA-MRSA infections have been described in more-or-less 'closed populations', such as native Americans [5], men who have sex with men [10], prison inmates [10,31,32], children attending child-care centres [9], military recruits [33], and competitive sports participants [10,11,34]. Moreover, CA-MRSA has now been introduced from its site of origin in the community into the hospital setting [24,25,35,36]. At some hospitals, CA-MRSA strains are even displacing classic hospital-acquired strains of MRSA [21].

Reported prevalence rates of CA-MRSA vary widely among studies, in part because of the use of different definitions to distinguish between CA-MRSA and HA-MRSA, but also because of the different settings in which studies have been performed. It should be noted that relatively few studies have been conducted among randomly selected healthy members of the community. Most studies have been based on hospitalised patients, or patients upon admission to the hospital, which has probably resulted in an overestimation of the 'true' prevalence of CA-MRSA.

A meta-analysis of studies reporting prevalence rates of CA-MRSA has recently been conducted [17]. The pooled prevalence of CA-MRSA among MRSA isolates from hospitalised patients was 30.2% in 27 retrospective studies and 37.3% in five prospective studies. Among community members without healthcare contacts, the pooled MRSA colonisation rate was 0.2%. European data are limited: the prevalence of MRSA nasal carriage was found to be 0.7% in a Portuguese surveillance study among young and healthy individuals from the community [37]; the prevalence of CA-MRSA upon admission to the hospital has been reported to be 0.1% in Switzerland [38], and 0.03% in The Netherlands [39].

Data concerning potential risk factors for the acquisition of CA-MRSA are limited. CA-MRSA-infected patients have been found to be younger than patients with HA-MRSA infections [12,13]. However, this finding may well reflect the fact that hospitalised patients represent a selected group of older individuals. Previous exposure to antimicrobial agents has been associated with an increased risk for CA-MRSA infections in some studies [15,40], but not in others [38].

CLINICAL SPECTRUM OF DISEASE

The spectrum of clinical infections caused by CA-MRSA is similar to that caused by methicillin-susceptible *S. aureus* [5,7], but clearly distinct from that caused by HA-MRSA. Whereas HA-MRSA commonly causes bloodstream infections and infections of the urinary and respiratory tracts, CA-MRSA has predominantly been isolated from skin and soft tissue infections, such as abscesses, cellulitis, folliculitis and impetigo [5,6,10–12,14]. Although CA-MRSA infections are commonly mild, they may also be severe, and can result in hospitalisation and/or death [4]. For example, necrotising fasciitis caused by CA-MRSA has recently been reported as an emerging clinical entity [41]. In addition to skin and soft tissue infections, severe necrotising pneumonia due to CA-MRSA has occasionally been described in young patients without known healthcare-associated risk factors for the acquisition of MRSA [14]. The observed clinical spectrum of infections caused by CA-MRSA has been associated with the presence of Panton–Valentine leukocidin genes, which code for the production of cytotoxins that cause tissue necrosis and leukocyte destruction [13,42–44]. However, other exotoxin genes or combinations of genes could also be important pathogenic factors [13].

GENOTYPIC AND PHENOTYPIC CHARACTERISTICS

CA-MRSA strains differ from the major pandemic clones of MRSA that account for the majority of epidemic HA-MRSA strains [22,45,46]. Differences are found in SCC*mec* types, the presence of additional antibiotic resistance genes, bacterial growth rate and the distribution of toxin genes (Table 1).

Recent studies have indicated that well-defined CA-MRSA strains carry SCC*mec* type IV or V [22,45,47], whereas the majority of HA-MRSA strains carry SCC*mec* type I, II or III [48,49]. SCC*mec* types IV and V are relatively small in size; for SCC*mec* type IV, this appears to have resulted in its increased mobility and therefore greater potential for horizontal spread to diverse *S. aureus* genetic backgrounds, compared with other SCC*mec* types [16,22,45,50–53].

In contrast to the multidrug resistance that is usually seen in HA-MRSA strains, antibiotic resistance in CA-MRSA strains is often limited to β-lactam antibiotics [5,14,54]. This is consistent with the absence of antibiotic resistance genes other than *mecA* in SCC*mec* types IV and V, as compared to the accumulation of multiple additional antibiotic resistance genes in SCC*mec* types II and III [22,45,47,48].

CA-MRSA strains carrying SCC*mec* type IV have been reported to have a higher growth rate than HA-MRSA strains [22], which may have enhanced the ecologic fitness of CA-MRSA.

Several studies have indicated that the presence of Panton–Valentine leukocidin genes is common among CA-MRSA strains from different genetic

Table 1. Characteristics of staphylococcal cassette chromosome *mec* (SCC*mec*) types I–V [13,22,45–48]

SCC*mec*		*Staphylococcus aureus* carrying specified SCC*mec* type			
Type	**Size (kb)**	**Presence of other antibiotic resistance genes**	**Origin of isolates**	**Mean doubling time (min)**	**Presence of PVL genes**
I	34	No	Hospital	36	Infrequent
II	53	Yes	Hospital	32	Infrequent
III	67	Yes	Hospital	42	Infrequent
IV	21–24	No	Community	28	Frequent
V	28	No	Community	Unknown	Unknown

PVL, Panton–Valentine leukocidin.

backgrounds, whereas these genes are rare among HA-MRSA strains [13,43,46].

THREATS AND PREVENTION

The future impact of the emergence of CA-MRSA on the occurrence of MRSA infections in both the community and hospital settings is of great interest. Some authors predict that MRSA will become the most prevalent type of *S. aureus* in the near future, and that this will mirror the emergence of penicillin resistance in *S. aureus* in the 1950s and 1960s (Fig. 1) [30]. Dissemination of penicillin-resistant strains from the hospital setting into the community occurred at a time when the rate of penicillin resistance among hospital patients with staphylococcal disease approached 50%. This is comparable to the current rate of methicillin resistance among hospitalised patients with staphylococcal infections in US hospitals [29]. However, contrary to the view that the majority of CA-MRSA isolates result from the spread of hospital-acquired strains into the community, it appears that community-based strains are migrating into the hospital setting [21,24,25,35,36], and that MRSA in the community is independent of a hospital reservoir.

Mathematical models have been used to predict the future epidemiology of MRSA and to determine effective control strategies. With the use of such models, it has been shown that the presence of a community reservoir has a major impact on the control of MRSA in the hospital [55–57]. In open communities, it will take years or even

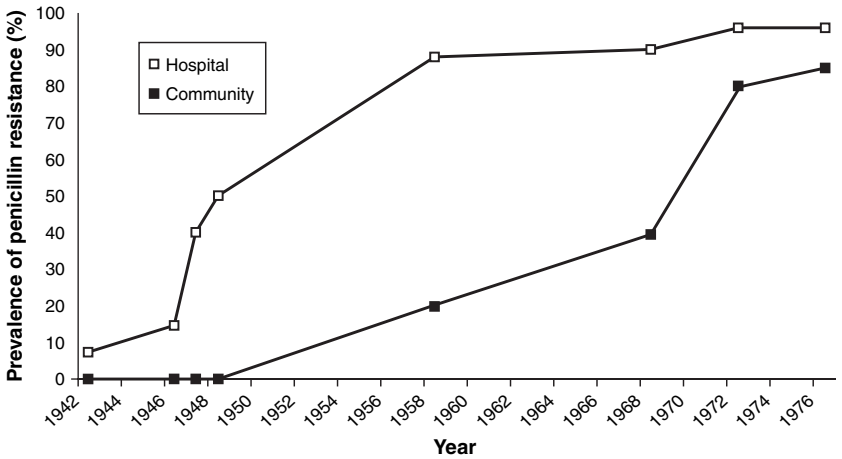

Fig. 1. Prevalence of penicillin resistance among *Staphylococcus aureus* in hospitals and in the community, 1940–1974. The prevalence of *S. aureus* strains resistant to penicillin within hospitals rose dramatically in the 1940s and 1950s. However, penicillin-resistant community-acquired strains of *S. aureus* were not reported until 1949, when the rate of penicillin resistance in hospitals approached 50%. The prevalence of penicillin-resistant *S. aureus* in communities continued to increase throughout the ensuing 20 years, finally approaching the resistance rates seen among hospital strains. Adapted from Chambers [30] and Salgado [17].

decades to see substantial reductions in the frequency of antibiotic resistance solely as a result of more prudent (reduced) use of antibiotics [57]. Furthermore, isolation of infected patients and contact tracing will be hardly effective within the community setting, because of the high frequency of transmission by asymptomatic colonised individuals [56]. Therefore, CA-MRSA has a high potential to become endemic in the community unless additional control measures are introduced, e.g., screening of asymptomatic individuals. Conversely, in the hospital setting, the frequency of resistance may be reduced substantially by restricting the input of resistant bacteria through the implementation of appropriate infection control and other measures [57].

CONCLUSION

Although our understanding of CA-MRSA is increasing, well-designed community-based studies with adequate risk factor analysis are required to further elucidate the epidemiology of CA-MRSA and to improve strategies to control MRSA in both the community and hospital setting.

REFERENCES

1. Thompson RL, Cabezudo I, Wenzel RP. Epidemiology of nosocomial infections caused by methicillin-resistant *Staphylococcus aureus*. *Ann Intern Med* 1982; **97:** 309–317.
2. Jorgensen JH. Laboratory and epidemiologic experience with methicillin-resistant *Staphylococcus aureus* in the USA. *Eur J Clin Microbiol* 1986; **5:** 693–696.
3. Brumfitt W, Hamilton-Miller J. Methicillin-resistant *Staphylococcus aureus*. *N Engl J Med* 1989; **320:** 1188–1196.
4. Centers for Disease Control and Prevention. Four pediatric deaths from community-acquired methicillin-resistant *Staphylococcus aureus*—Minnesota and North Dakota, 1997–1999. *JAMA* 1999; **282:** 1123–1125.
5. Groom AV, Wolsey DH, Naimi TS *et al.* Community-acquired methicillin-resistant *Staphylococcus aureus* in a rural American Indian community. *JAMA* 2001; **286:** 1201–1205.
6. Naimi TS, LeDell KH, Boxrud DJ *et al.* Epidemiology and clonality of community-acquired methicillin-resistant *Staphylococcus aureus* in Minnesota, 1996–1998. *Clin Infect Dis* 2001; **33:** 990–996.
7. Herold BC, Immergluck LC, Maranan MC *et al.* Community-acquired methicillin-resistant *Staphylococcus aureus* in children with no identified predisposing risk. *JAMA* 1998; **279:** 593–598.
8. Suggs AH, Maranan MC, Boyle-Vavra S, Daum RS. Methicillin-resistant and borderline methicillin-resistant asymptomatic *Staphylococcus aureus* colonization in children without identifiable risk factors. *Pediatr Infect Dis J* 1999; **18:** 410–414.
9. Adcock PM, Pastor P, Medley F, Patterson JE, Murphy TV. Methicillin-resistant *Staphylococcus aureus* in two child care centers. *J Infect Dis* 1998; **178:** 577–580.
10. Centers for Disease Control and Prevention. Outbreaks of community-associated methicillin-resistant *Staphylococcus aureus* skin infections—Los Angeles County, California, 2002–2003. *MMWR* 2003; **52:** 88.
11. Centers for Disease Control and Prevention. Methicillin-resistant *Staphylococcus aureus* infections among competitive sports participants—Colorado, Indiana, Pennsylvania, and Los Angeles County, 2000–2003. *MMWR* 2003; **52:** 793–795.
12. Fridkin SK, Hageman JC, Morrison M *et al.* Methicillin-resistant *Staphylococcus aureus* disease in three communities. *N Engl J Med* 2005; **352:** 1436–1444.
13. Naimi TS, LeDell KH, Como-Sabetti K *et al.* Comparison of community- and health care-associated methicillin-resistant *Staphylococcus aureus* infection. *JAMA* 2003; **290:** 2976–2984.
14. Gorak EJ, Yamada SM, Brown JD. Community-acquired methicillin-resistant *Staphylococcus aureus* in hospitalized adults and children without known risk factors. *Clin Infect Dis* 1999; **29:** 797–800.
15. Baggett HC, Hennessy TW, Leman R *et al.* An outbreak of community-onset methicillin-resistant *Staphylococcus aureus* skin infections in southwestern Alaska. *Infect Control Hosp Epidemiol* 2003; **24:** 397–402.
16. Robinson DA, Enright MC. Evolutionary models of the emergence of methicillin-resistant *Staphylococcus aureus*. *Antimicrob Agents Chemother* 2003; **47:** 3926–3934.
17. Salgado CD, Farr BM, Calfee DP. Community-acquired methicillin-resistant *Staphylococcus aureus*: a meta-analysis of prevalence and risk factors. *Clin Infect Dis* 2003; **36:** 131–139.
18. Garner JS, Jarvis WR, Emori TG, Horan TC, Hughes JM. CDC definitions for nosocomial infections, 1988. *Am J Infect Control* 1988; **16:** 128–140.
19. Sanford MD, Widmer AF, Bale MJ, Jones RN, Wenzel RP. Efficient detection and long-term persistence of the carriage of methicillin-resistant *Staphylococcus aureus*. *Clin Infect Dis* 1994; **19:** 1123–1128.
20. VandenBergh MF, Yzerman EP, van Belkum A, Boelens HA, Sijmons M, Verbrugh HA. Follow-up of *Staphylococcus aureus* nasal carriage after 8 years: redefining the persistent carrier state. *J Clin Microbiol* 1999; **37:** 3133–3140.
21. Turnidge JD, Bell JM. Methicillin-resistant *Staphylococcal aureus* evolution in Australia over 35 years. *Microb Drug Resist* 2000; **6:** 223–229.
22. Okuma K, Iwakawa K, Turnidge JD *et al.* Dissemination of new methicillin-resistant *Staphylococcus aureus* clones in the community. *J Clin Microbiol* 2002; **40:** 4289–4294.
23. Folden DV, Machayya JA, Sahmoun AE *et al.* Estimating the proportion of community-associated methicillin-resistant *Staphylococcus aureus*: two definitions used in the USA yield dramatically different estimates. *J Hosp Infect* 2005; **60:** 329–332.
24. Carleton HA, Diep BA, Charlebois ED, Sensabaugh GF, Perdreau-Remington F. Community-adapted methicillin-resistant *Staphylococcus aureus* (MRSA): population dynamics of an expanding community reservoir of MRSA. *J Infect Dis* 2004; **190:** 1730–1738.

25. Donnio PY, Preney L, Gautier-Lerestif AL, Avril JL, Lafforgue N. Changes in staphylococcal cassette chromosome type and antibiotic resistance profile in methicillin-resistant *Staphylococcus aureus* isolates from a French hospital over an 11 year period. *J Antimicrob Chemother* 2004; **53:** 808–813.
26. Deresinski S. Methicillin-resistant *Staphylococcus aureus*: an evolutionary, epidemiologic, and therapeutic odyssey. *Clin Infect Dis* 2005; **40:** 562–573.
27. Diekema DJ, Pfaller MA, Schmitz FJ *et al.* Survey of infections due to *Staphylococcus* species: frequency of occurrence and antimicrobial susceptibility of isolates collected in the United States, Canada, Latin America, Europe, and the Western Pacific region for the SENTRY Antimicrobial Surveillance Program, 1997–1999. *Clin Infect Dis* 2001; **32**(suppl 2)**:** S114–S132.
28. Tiemersma EW, Bronzwaer SL, Lyytikäinen O *et al.* Methicillin-resistant *Staphylococcus aureus* in Europe, 1999–2002. *Emerg Infect Dis* 2004; **10:** 1627–1634.
29. NNIS. National Nosocomial Infections Surveillance (NNIS) System Report, data summary from January 1992 through June 2004, issued October 2004. *Am J Infect Control* 2004; **32:** 470–485.
30. Chambers HF. The changing epidemiology of *Staphylococcus aureus*? *Emerg Infect Dis* 2001; **7:** 178–182.
31. Centers for Disease Control and Prevention. Methicillin-resistant *Staphylococcus aureus* infections in correctional facilities—Georgia, California, and Texas, 2001–2003. *MMWR* 2003; **52:** 992–996.
32. Pan ES, Diep BA, Carleton HA *et al.* Increasing prevalence of methicillin-resistant *Staphylococcus aureus* infection in California jails. *Clin Infect Dis* 2003; **37:** 1384–1388.
33. Zinderman CE, Conner B, Malakooti MA, LaMar JE, Armstrong A, Bohnker BK. Community-acquired methicillin-resistant *Staphylococcus aureus* among military recruits. *Emerg Infect Dis* 2004; **10:** 941–944.
34. Nguyen DM, Mascola L, Brancoft E. Recurring methicillin-resistant *Staphylococcus aureus* infections in a football team. *Emerg Infect Dis* 2005; **11:** 526–532.
35. Saiman L, O'Keefe M, Graham PL *et al.* Hospital transmission of community-acquired methicillin-resistant *Staphylococcus aureus* among postpartum women. *Clin Infect Dis* 2003; **37:** 1313–1319.
36. O'Brien FG, Pearman JW, Gracey M, Riley TV, Grubb WB. Community strain of methicillin-resistant *Staphylococcus aureus* involved in a hospital outbreak. *J Clin Microbiol* 1999; **37:** 2858–2862.
37. Sá-Leão R, Sanches IS, Couto I, Alves CR, de Lencastre H. Low prevalence of methicillin-resistant strains among *Staphylococcus aureus* colonizing young and healthy members of the community in Portugal. *Microb Drug Resist* 2001; **7:** 237–245.
38. Harbarth S, Francois P, Schrenzel J *et al.* Community-associated methicillin-resistant *Staphylococcus aureus*, Switzerland. *Emerg Infect Dis* 2005; **11:** 962–965.
39. Wertheim HF, Vos MC, Boelens HA *et al.* Low prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA) at hospital admission in the Netherlands: the value of search and destroy and restrictive antibiotic use. *J Hosp Infect* 2004; **56:** 321–325.
40. Ellis MW, Hospenthal DR, Dooley DP, Gray PJ, Murray CK. Natural history of community-acquired methicillin-resistant *Staphylococcus aureus* colonization and infection in soldiers. *Clin Infect Dis* 2004; **39:** 971–979.
41. Miller LG, Perdreau-Remington F, Rieg G *et al.* Necrotizing fasciitis caused by community-associated methicillin-resistant *Staphylococcus aureus* in Los Angeles. *N Engl J Med* 2005; **352:** 1445–1453.
42. Lina G, Piémont Y, Godail-Gamot F *et al.* Involvement of Panton–Valentine leukocidin-producing *Staphylococcus aureus* in primary skin infections and pneumonia. *Clin Infect Dis* 1999; **29:** 1128–1132.
43. Dufour P, Gillet Y, Bes M *et al.* Community-acquired methicillin-resistant *Staphylococcus aureus* infections in France: emergence of a single clone that produces Panton–Valentine leukocidin. *Clin Infect Dis* 2002; **35:** 819–824.
44. Gillet Y, Issartel B, Vanhems P *et al.* Association between *Staphylococcus aureus* strains carrying gene for Panton–Valentine leukocidin and highly lethal necrotising pneumonia in young immunocompetent patients. *Lancet* 2002; **359:** 753–759.
45. Ma XX, Ito T, Tiensasitorn C *et al.* Novel type of staphylococcal cassette chromosome *mec* identified in community-acquired methicillin-resistant *Staphylococcus aureus* strains. *Antimicrob Agents Chemother* 2002; **46:** 1147–1152.
46. Vandenesch F, Naimi T, Enright MC *et al.* Community-acquired methicillin-resistant *Staphylococcus aureus* carrying Panton–Valentine leukocidin genes: worldwide emergence. *Emerg Infect Dis* 2003; **9:** 978–984.
47. Ito T, Ma XX, Takeuchi F, Okuma K, Yuzawa H, Hiramatsu K. Novel type V staphylococcal cassette chromosome *mec* driven by a novel cassette chromosome recombinase, *ccrC*. *Antimicrob Agents Chemother* 2004; **48:** 2637–2651.
48. Ito T, Katayama Y, Asada K *et al.* Structural comparison of three types of staphylococcal cassette chromosome *mec* integrated in the chromosome in methicillin-resistant *Staphylococcus aureus*. *Antimicrob Agents Chemother* 2001; **45:** 1323–1336.
49. Oliveira DC, de Lencastre H. Multiplex PCR strategy for rapid identification of structural types and variants of the *mec* element in methicillin-resistant *Staphylococcus aureus*. *Antimicrob Agents Chemother* 2002; **46:** 2155–2161.
50. Aires de Sousa M, de Lencastre H. Evolution of sporadic isolates of methicillin-resistant *Staphylococcus aureus* (MRSA) in hospitals and their similarities to isolates of community-acquired MRSA. *J Clin Microbiol* 2003; **41:** 3806–3815.
51. Robinson DA, Enright MC. Multilocus sequence typing and the evolution of methicillin-resistant *Staphylococcus aureus*. *Clin Microbiol Infect* 2004; **10:** 92–97.
52. Hanssen AM, Fossum A, Mikalsen J, Halvorsen DS, Bukholm G, Ericson Sollid JU. Dissemination of community-acquired methicillin-resistant *Staphylococcus aureus* clones in northern Norway: sequence types 8 and 80 predominate. *J Clin Microbiol* 2005; **43:** 2118–2124.
53. Oliveira DC, Tomasz A, de Lencastre H. Secrets of success of a human pathogen: molecular evolution of pandemic clones of methicillin-resistant *Staphylococcus aureus*. *Lancet Infect Dis* 2002; **2:** 180–189.
54. Fey PD, Said-Salim B, Rupp ME *et al.* Comparative molecular analysis of community- or hospital-acquired

methicillin-resistant *Staphylococcus aureus*. *Antimicrob Agents Chemother* 2003; **47:** 196–203.
55. Cooper BS, Medley GF, Stone SP *et al*. Methicillin-resistant *Staphylococcus aureus* in hospitals and the community: stealth dynamics and control catastrophes. *Proc Natl Acad Sci USA* 2004; **101:** 10223–10228.
56. Fraser C, Riley S, Anderson RM, Ferguson NM. Factors that make an infectious disease outbreak controllable. *Proc Natl Acad Sci USA* 2004; **101:** 6146–6151.
57. Levin BR. Minimizing potential resistance: a population dynamics view. *Clin Infect Dis* 2001; **33**(suppl 3)**:** S161–S169.