J Microbiol Immunol Infect
2005;38:376-382

Community-acquired methicillin-resistant *Staphylococcus aureus* in Taiwan

Chih-Jung Chen, Yhu-Chering Huang

Division of Pediatric Infectious Diseases, Department of Pediatrics, Chang Gung Children's Hospital, Taoyuan, Taiwan

Received: September 28, 2005 Revised: September 30, 2005 Accepted: October 4, 2005

Staphylococcus aureus is a major cause of infections in both hospitals and communities, and is exhibiting increasing resistance to methicillin (methicillin-resistant *S. aureus*, MRSA) and related β-lactams. MRSA is usually considered a nosocomial pathogen, but increasingly it is acquired in the community. In Taiwan, MRSA was colonized in a substantial proportion of healthy children and accounted for 25% to 75% of childhood community-acquired (CA) *S. aureus* infections. From the preliminary data, the isolates of sequence type (ST) 59 by multilocus sequence typing method appeared to be the major clone of CA-MRSA in northern Taiwan. Compared with those reported from the US and other countries, CA-MRSA isolates in Taiwan did not always harbor type IV staphylococcal cassette chromosome (SCC*mec*) and were resistant to multiple non-β-lactam antibiotics, including clindamycin and macrolides. Molecular evidence suggested transmission of the community strain of MRSA into the hospital setting, and that the community strain had became a health care-associated pathogen. The treatment of putative CA *S. aureus* infection should be stratified according to the severity and the disease entity.

Key words: Community-acquired infections, methicillin resistance, review, *Staphylococcus aureus*, Taiwan

Emergence of Community-acquired Methicillin-resistant *Staphylococcus aureus*

Staphylococcus aureus is a major cause of infections in both hospitals and communities, causing diseases ranging from mild skin infections to fulminant septicemia, and has become increasingly resistant to methicillin (oxacillin). Methicillin-resistant *S. aureus* (MRSA) was first reported in the early 1960s and rapidly increased and spread in 1980s [1]. Nowadays, MRSA is endemic in most hospitals in the world and accounts for 40-60% of all nosocomial *S. aureus* infections [2]. In Taiwan, MRSA was first documented in the early 1980s and rapidly increased in the 1990s [3]. In 2000, methicillin resistance had been identified in 53-83% of all *S. aureus* isolates in 12 major hospitals of Taiwan [4].

Although MRSA infections in the community were not uncommon, they were traditionally confined to individuals with health care-associated risk factors such as residence in long-term care facility, recent hospitalization or surgery, indwelling catheter or hemodialysis [5,6]. The changing epidemiology of MRSA became evident in the 1990s when MRSA infections occurred in previously healthy children without established risk factors for MRSA acquisition [7-11]. These infections were acquired in the community and have been referred to as community-acquired or community-associated (CA) MRSA infections. CA-MRSA has been recognized as a novel pathogen genetically different from nosocomial MRSA [10,12, 13]. Community-acquired strains were characterized by limited antibiotic resistance (except to β-lactams), with cellulitis and abscess the major clinical manifestations. They have a common pulsed-gel electrophoresis (PFGE) pattern, which is distinct from the major pandemic clones of hospital-acquired (HA) isolates [14], possess different exotoxin gene profiles (e.g., Panton-Valentine leukocidin, PVL), and may represent a new acquisition of type IV staphylococcal cassette chromosome *mec* (SCC*mec*) DNA in a previously susceptible *S. aureus* strain [12,15-17]. SCC*mec* is the genetic element that carries the methicillin-resistant gene, *mec*A, and integrates in the *S. aureus* genome in a site-specific manner. There are at least 5 SCC*mec* types identified at present (Table 1) [18-20].

The CA-MRSA appeared to be an epidemiologically successful clone which had spread rapidly and

Corresponding author: Dr. Yhu-Chering Huang, Division of Pediatric Infectious Diseases, Department of Pediatrics, Chang Gung Children's Hospital, 5, Fu-Shin Street, Kweishan 333, Taoyuan, Taiwan.
E-mail: ychuang@adm.cgmh.org.tw

Table 1. Characteristics of staphylococcal cassette chromosome *mec* (SCC*mec*) types (data adapted from [18-20])

SCC*mec* type	Representative strain	Origin	SCC*mec* size of the representative strain (bp)	Major determinants in SCC*mec*		Antibiotic-resistant gene carried by SCC*mec*
				mec complex[a]	*ccr* complex[b]	
I	NCTC10442	HA	34,364	Class B	Type 1 (*ccr*A1, *ccr*B1)	*mecA*
II	N315	HA	53,017	Class A	Type 2 (*ccr*A2, *ccr*B2)	*mecA*, *aadD*[c], *ermA*[d]
III	85/2082	HA	66,896	Class A	Type 3 (*ccr*A3, *ccr*B3)	*mecA*, *aadD*, *tetK*[e]
IV	CA05 (JCSC1968)	CA	24,248	Class B	Type 2 (*ccr*A2 variant, *ccr*B2 variant)	*mecA*
V	WIS	CA	27,624	Class C	Type 5 (*ccr*C)	*mecA*

Abbreviations: *ccr* = cassette chromosome recombinase; HA = hospital-acquired; CA = community-acquired

[a]*mec* complex structure, Class A: *mecI-mecR1-mecA*-IS*431*, Class B: IS*1272-ΔmecR1-mecA*-IS*431*, Class C: IS*431-mecA-ΔmecR1*-IS*431.*

[b]The *ccrA* and *ccrB* genes encode putative site-specific recombinases of SCC*mec* which is responsible for the movement of SCC*mec.*

[c]*aadD* encodes resistance to tobramycin and kanamycin.

[d]*ermA* encodes resistance to macrolide-lincosamide-streptogramin antibiotics.

[e]*tetK* encodes tetracycline resistance.

predominated over methicillin-susceptible *S. aureus* (MSSA) in certain populations such as a rural mid-western American Indian community [21]. In the Texas Children's Hospital, 76.4% of CA *S. aureus* isolates were methicillin resistant in 2004 [22]. Recent studies further demonstrated a remarkable success of CA-MRSA strains in replacing other MRSA strains in some hospitals [23-25]. In addition, the virulence of CA-MRSA seemed to parallel its epidemiologic success. Although skin and soft tissue infections remained the most common clinical syndromes, invasive CA-MRSA infections and even death did occur increasingly in apparently healthy pediatric patients [26-28]. With the emergence of a virulent MRSA in the community, an understanding of the epidemiology of MRSA in the local community is crucial for physicians to appropriately manage their patients with putative CA *S. aureus* infections.

Epidemiology in Taiwan

In Taiwan, CA-MRSA infections have been increasingly reported in pediatric patients since 2000 [29-31]. The reported incidence of CA-MRSA infections in children was discrepant in different retrospective studies with similar designs between 1997 and 2001 [26,32,33]. Of 2 studies conducted in the urban hospitals of northern and central Taiwan, MRSA accounted for 74% and 28%, respectively, of all CA *S. aureus* clinical infections [32, 33]. The rate of MRSA was 47% in our previous study of hospitalized children with CA *S. aureus* infections in suburban Taiwan [26]. After pooling these data, the rate of MRSA was estimated to be 44% in pediatric cases of CA *S. aureus* infections. A substantial proportion (35-59%) of the pediatric patients with CA-MRSA infection had no identified risk, although the definition of health care-associated risks varied among different studies.

In addition to the hospital-based studies, several community-based studies [34-36] were conducted to estimate the extent of MRSA in the community. We surveyed the nasal carriage of *S. aureus* and MRSA among 262 school children attending child care centers, elementary schools or junior middle schools and 137 health care workers in a teaching hospital during 2001-2002 [34]. MRSA carriage rate was 1.9% among school children and 13% among health care workers. In a study conducted by Boyle-Vavra et al, 640 healthy children less than 12 years of age who either presented for a well-child health care visit or attended 1 of 3 kindergartens in Taipei near Tri-Service General Hospital (TSGH), were sampled in 2003 and the nasal carriage rate of MRSA in those without designated risk factors for MRSA was 5.3% [36]. We also investigated 66 contacts following a case of severe CA-MRSA disease, and MRSA carriage rate among the contacts was 13.6% [35]. Some contacts were colonized with an indistinguishable MRSA strain as the clinical isolates from the case patient, indicating that MRSA can spread in a school once MRSA emerges in a school child. Nevertheless, more than 50% of the contacts were colonized with MRSA strains of distinct clones, suggesting that not all MRSA isolates from the contacts were related to the case patient and indirectly implying that MRSA was circulating in the community in Taiwan.

In contrast to pediatric cases, CA-MRSA infections were uncommon in adults. In 2 island-wide surveys of representative isolates of *S. aureus* from medical centers and local hospitals in 1998 and 2000, respectively, the rate of MRSA was estimated to be 40% in outpatient

settings [37,38]. Exposures to the risk factors for MRSA acquisition were not mentioned in these cases. In 2 other studies of CA *S. aureus* bloodstream infections, the rates of MRSA were 26% and 33.7%, respectively [39,40]. Almost all of the patients had identified risk factors. These observations suggest that CA-MRSA in adults is still limited and most adult patients have traditional health care-associated risks.

Molecular epidemiology of CA-MRSA

Our preliminary data disclosed that there were 3 major pulsotypes (designated as PFGE type A, C, and D in our hospital) of MRSA strains simultaneously circulating in the hospitals and communities of Taiwan [26,41-43]. Type IV SCC*mec*, an epidemiologic marker for CA-MRSA, was identified in 25% and 40% of CA and HA isolates, respectively [26]. We therefore considered that the CA-MRSA isolates in Taiwan, distinct from those reported from US and other countries, were closely associated with the HA isolates. However, Wang et al collected and analyzed 17 consecutive CA-MRSA isolates from children hospitalized at TSGH for skin and soft tissue infections during the 5-year period from September 1997 to August 2002 and disclosed that these CA-MRSA isolates were of a single clone [44]. The pulsotype of these 17 CA-MRSA (similar to type D in our study) isolates was different from 4 nosocomial isolates and the genotype was ST (sequence type) 59 by multilocus sequencing typing (MLST). Only 2 of 16 isolates studied carried type IV SCC*mec* and 13 isolates carried a newly identified subtype of SCC*mec* V, called SCCmec V_T [36]. In order to clarify this issue, we recently had some MRSA strains of representative PFGE patterns in our studies genotyped by MLST. The results disclosed that the strains of PFGE type A in our studies were ST239, while the strains of both PFGE types C and D were ST59. ST239 was a Brazilian or Hungarian epidemic MRSA clone, which was among the 6 pandemic clones of HA isolates and has been shown to be the major clone of nosocomial MRSA in Taiwan [45,46]. The strain of ST59 was a clone less commonly reported but was recently identified as a major MSSA genotype causing CA abscess and soft tissue infections among intravenous drug users in the UK [47]. Our previous studies also disclosed that PFGE types C and D (ST59) accounted for 76% of 40 CA-MRSA isolates [26]. Thus, it appeared that the strain of ST59 was a prevalent clone of CA-MRSA in Taiwan. If this was the case, the additional findings in our previous study [26] that the isolates of PFGE types C and D (possibly ST59) accounted for 70% of childhood HA-MRSA isolates may imply that CA-MRSA strains did spread into the hospital and even successfully replaced the original hospital strains (PFGE type A), and became a dominant clone in our pediatric wards. Replacement of nosocomial MRSA strains by CA-MRSA strains had been reported previously in other countries [23,24]. However, these studies were retrospective and thus the interpretation may be misleading. We are now undergoing a comprehensive large-scale prospective study to delineate the molecular epidemiology of CA-MRSA in Taiwan.

Antibiotic resistance of CA-MRSA

The methicillin resistance of *S. aureus* is due to the acquisition of *mecA* gene encoding penicillin-binding protein, PBP2a. The *mecA* gene is carried by a mobile element (SCC*mec*). This PBP2a protein has low affinity for most β-lactam antibiotics and, therefore, mediates cross-resistance to all of these compounds. In our previous study, *mecA* gene was identified in all of the 40 CA-MRSA isolates. Wang et al examined the minimal inhibitory concentration (MIC) level of their 17 CA-MRSA isolates, and found that only 6 isolates (35%) had an oxacillin MIC of at least 8 μg/mL [44]. However, most of the colonized isolates in our previous studies had an oxacillin MIC of at least 24 μg/mL [34,35].

The antibiograms of CA-MRSA isolates in Taiwan disclosed a specific pattern which was different from that in the United States. Similar to both nosocomial MRSA isolates and CA-MRSA isolates from children with risk factors, the CA-MRSA isolates from children without risk factors were also resistant to multiple antibiotics, including clindamycin (93-100%), erythromycin (94-100%) and chloramphenicol (57-65%) [26,32,44]. Trimethoprim-sulfamethoxazole (SXT) was the only drug associated with different susceptibility between CA- and HA-MRSA strains, to which CA-MRSA isolates were significantly more susceptible than HA-MRSA isolates [26]. In the studies reported by Wang et al [44] and Fang et al [32], the CA-MRSA isolates were also less resistant to gentamicin (11-34%), ciprofloxacin (0%), fusidic acid (0%) and minocycline (7%) than nosocomial MRSA. Wang et al [32] further examined their 17 CA-MRSA isolates using the double disk diffusion method and polymeraase chain reaction for macrolide resistance gene detection, and indicated that all strains had the macrolide-lincosamide-streptogramin (MLS)-constitutive phenotype and the *ermB* gene.

Virulence of CA-MRSA

Recent studies regarding the natural history of CA-MRSA infection disclosed that subjects colonized with CA-MRSA were more likely to develop clinical disease than those colonized with CA-MSSA [48]. Patients with musculoskeletal infections caused by CA-MRSA required longer hospital stays and had more febrile days than did those affected by CA-MSSA [49]. CA-MRSA strains seemed to be more virulent than CA-MSSA strains. Molecular analysis of CA *S. aureus* strains has shown that CA-MRSA isolates harbor genes encoding superantigen toxins such as enterotoxins [12]. In 1999, 4 children died of fulminant CA-MRSA sepsis [27]. The MRSA isolates accounting for the 4 pediatric deaths were genetically related and the whole genome sequences of 1 isolate (MW2) disclosed a range of virulence genes that were distinct from those displayed on the chromosome of extant *S. aureus* strains [17]. These genes encoded for several superantigens and leukotoxins such as PVL. PVL had been shown to be associated with necrotizing hemorrhagic pneumonitis and skin abscess [50-53]. Furthermore, PVL gene was seen as a genetic marker of CA-MRSA, since it was infrequently found in HA-MRSA [54]. PVL gene was also identified in the CA-MRSA isolates in Taiwan and may also contribute to severe and even fatal infections in pediatric cases [44,55].

Clinical manifestations of CA-MRSA infections

Skin and soft tissue infections remained the most common manifestations of CA-MRSA infections. Invasive CA-MRSA infections and even death, however, were increasingly reported [30,35,55]. Among 54 episodes of CA-MRSA infections in our pediatric series, 28% were considered to be serious [26]. Some cases even developed sepsis with multiple focal infections, including pneumonia, pyomyositis, arthritis and/or osteomyelitis. Invasive diseases were also noted in 8% of 59 children with CA-MRSA infections in Fang et al's study [32]. Pulmonary septic embolism secondary to primary sites infection, often bones or joints, was a common and characteristic manifestation in severe pediatric cases [26,31,35].

Therapeutic strategy for CA-MRSA infections

Due to the high rate of multi-resistant MRSA in the community, increasing usage of glycopeptides or linezolid would be inevitably expected. However, the usage of glycopeptides in management of children with CA-MRSA infections did not increase markedly, since the most common manifestation of CA-MRSA infection was skin and soft tissue infections and most skin and superficial soft tissue infections resolved spontaneously or after incision and drainage with and without susceptible antibiotic treatment [26,32,44]. Auto-drainage of the infected site and host defenses may play important roles in these superficial soft tissue infections. Borderline methicillin resistance in some *S. aureus* isolates may be another consideration [44]. For severe cases, initial non-susceptible antibiotic therapy was not associated with unfavorable outcome in our previous study [26]. However, delayed use of effective antibiotics may have contributed to a fatal outcome in pediatric cases with fulminant CA-MRSA sepsis [55]. The management of CA *S. aureus* infections, therefore, should be stratified according to the severity and site of disease entity in an area where high prevalence of methicillin resistance was noted such as Taiwan. In Taiwan, we suggest that for skin and superficial soft tissue infections, oral form of SXT can be considered as the first-line regimen. For those with soft tissue infections and systemic symptoms and signs requiring hospitalization and considering the adverse effects of the intravenous form of SXT, we suggest that empiric therapy with intravenous forms of β-lactams such as oxacillin or a first-generation cephalosporin may be used in most cases. Incision and drainage should be attempted and done if possible. Oral SXT can be used as sequential therapy for these patients. If the infection is invasive or located in deep-seated structures, glycopeptides or linezolid should be used empirically and continued as definitive therapy if MRSA is identified subsequently. Clindamycin and macrolides are not suitable for treating children with putative CA *S. aureus* infections at present in Taiwan.

Conclusion

CA-MRSA with multiple drug resistance has established itself as a prevalent pathogen in the community of Taiwan. Skin and superficial soft tissue infections remain the most common manifestation of CA-MRSA infections and often resolve after auto- or incisional drainage in spite of initial inactive antibiotic treatment. Significant morbidity and even mortality associated with CA-MRSA infection are increasingly reported, especially in pediatric patients. Management of CA *S. aureus* infections should be stratified according to the site and severity of the disease entity and for severe cases glycopeptides or linezolid should be used

empirically. Further studies should be conducted to elucidate the epidemiology of CA-MRSA in Taiwan.

References

1. Chambers HF. The changing epidemiology of *Staphylococcus aureus*? Emerg Infect Dis 2001;7:178-82.
2. Fluit AC, Wielders CL, Verhoef J, Schmitz FJ. Epidemiology and susceptibility of 3,051 *Staphylococcus aureus* isolates from 25 university hospitals participating in the European SENTRY study. J Clin Microbiol 2001;39:3727-32.
3. Chen ML, Chang SC, Pan HJ, Hsueh PR, Yang LS, Ho SW, et al. Longitudinal analysis of methicillin-resistant *Staphylococcus aureus* isolates at a teaching hospital in Taiwan. J Formos Med Assoc 1999;98:426-32.
4. Hsueh PR, Liu CY, Luh KT. Current status of antimicrobial resistance in Taiwan. Emerg Infect Dis 2002;8:132-7.
5. Brumfitt W, Hamilton-Miller J. Methicillin-resistant *Staphylococcus aureus*. N Engl J Med 1989;320:1188-96.
6. Lowy FD. *Staphylococcus aureus* infections. N Engl J Med 1998;339:520-32.
7. Fergie JE, Purcell K. Community-acquired methicillin-resistant *Staphylococcus aureus* infections in south Texas children. Pediatr Infect Dis J 2001;20:860-3.
8. Frank AL, Marcinak JF, Mangat PD, Schreckenberger PC. Community-acquired and clindamycin-susceptible methicillin-resistant *Staphylococcus aureus* in children. Pediatr Infect Dis J 1999;18:993-1000.
9. 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.
10. Herold BC, Immergluck LC, Maranan MC, Lauderdale DS, Gaskin RE, Boyle-Vavra S, et al. Community-acquired methicillin-resistant *Staphylococcus aureus* in children with no identified predisposing risk. JAMA 1998;279:593-8.
11. Hussain FM, Boyle-Vavra S, Bethel CD, Daum RS. Current trends in community-acquired methicillin-resistant *Staphylococcus aureus* at a tertiary care pediatric facility. Pediatr Infect Dis J 2000;19:1163-6.
12. Fey PD, Said-Salim B, Rupp ME, Hinrichs SH, Boxrud DJ, Davis CC, et al. Comparative molecular analysis of community- or hospital-acquired methicillin-resistant *Staphylococcus aureus*. Antimicrob Agents Chemother 2003;47:196-203.
13. Daum RS, Ito T, Hiramatsu K, Hussain F, Mongkolrattanothai K, Jamklang M, et al. A novel methicillin-resistance cassette in community-acquired methicillin-resistant *Staphylococcus aureus* isolates of diverse genetic backgrounds. J Infect Dis 2002;186:1344-7.
14. 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;41:3806-15.
15. Naimi TS, LeDell KH, Boxrud DJ, Groom AV, Steward CD, Johnson SK, et al. Epidemiology and clonality of community-acquired methicillin-resistant *Staphylococcus aureus* in Minnesota, 1996-1998. Clin Infect Dis 2001;33:990-6.
16. Naimi TS, LeDell KH, Como-Sabetti K, Borchardt SM, Boxrud DJ, Etienne J, et al. Comparison of community- and health care-associated methicillin-resistant *Staphylococcus aureus* infection. JAMA 2003;290:2976-84.
17. Baba T, Takeuchi F, Kuroda M, Yuzawa H, Aoki K, Oguchi A, et al. Genome and virulence determinants of high virulence community-acquired MRSA. Lancet 2002;359:1819-27.
18. Ito T, Katayama Y, Asada K, Mori N, Tsutsumimoto K, Tiensasitorn C, 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;45:1323-36.
19. 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;48:2637-51.
20. Ma XX, Ito T, Tiensasitorn C, Jamklang M, Chongtrakool P, Boyle-Vavra S, et al. Novel type of staphylococcal cassette chromosome *mec* identified in community-acquired methicillin-resistant *Staphylococcus aureus* strains. Antimicrob Agents Chemother 2002;46:1147-52.
21. Groom AV, Wolsey DH, Naimi TS, Smith K, Johnson S, Boxrud D, et al. Community-acquired methicillin-resistant *Staphylococcus aureus* in a rural American Indian community. JAMA 2001;286:1201-5.
22. Kaplan SL, Hulten KG, Gonzalez BE, Hammerman WA, Lamberth L, Versalovic J, et al. Three-year surveillance of community-acquired *Staphylococcus aureus* infections in children. Clin Infect Dis 2005;40:1785-91.
23. 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;53:808-13.
24. Saiman L, O'Keefe M, Graham PL 3rd, Wu F, Said-Salim B, Kreiswirth B, et al. Hospital transmission of community-acquired methicillin-resistant *Staphylococcus aureus* among postpartum women. Clin Infect Dis 2003;37:1313-9.
25. 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; 37:2858-62.
26. Chen CJ, Huang YC, Chiu CH, Su LH, Lin TY. Clinical features and genotyping analysis of community-acquired methicillin-

resistant *Staphylococcus aureus* infections in Taiwanese children. Pediatr Infect Dis J 2005;24:40-5.
27. From the Centers for Disease Control and Prevention. Four pediatric deaths from community-acquired methicillin-resistant *Staphylococcus aureus*--Minnesota and North Dakota, 1997-1999. JAMA 1999;282:1123-5.
28. Gonzalez BE, Martinez-Aguilar G, Hulten KG, Hammerman WA, Coss-Bu J, Avalos-Mishaan A, et al. Severe staphylococcal sepsis in adolescents in the era of community-acquired methicillin-resistant *Staphylococcus aureus*. Pediatrics 2005; 115:642-8.
29. Lin JC, Wu JS, Chang FY. Community-acquired methicillin-resistant *Staphylococcus aureus* endocarditis with septic embolism of popliteal artery: a case report. J Microbiol Immunol Infect 2000;33:57-9.
30. Wang CM, Chuang CH, Chiu CH. Community-acquired disseminated methicillin-resistant *Staphylococcus aureus* infection: case report and clinical implications. Ann Trop Paediatr 2005;25:53-7.
31. Wong KS, Lin TY, Huang YC, Hsia SH, Yang PH, Chu SM. Clinical and radiographic spectrum of septic pulmonary embolism. Arch Dis Child 2002;87:312-5.
32. Fang YH, Hsueh PR, Hu JJ, Lee PI, Chen JM, Lee CY, et al. Community-acquired methicillin-resistant *Staphylococcus aureus* in children in northern Taiwan. J Microbiol Immunol Infect 2004;37:29-34.
33. Wu KC, Chiu HH, Wang JH, Lee NS, Lin HC, Hsieh CC, et al. Characteristics of community-acquired methicillin-resistant *Staphylococcus* aureus in infants and children without known risk factors. J Microbiol Immunol Infect 2002;35:53-6.
34. Huang YC, Su LH, Chen CJ, Lin TY. Nasal carriage of methicillin-resistant *Staphylococcus aureus* in school children without identifiable risk factors in northern Taiwan. Pediatr Infect Dis J 2005;24:276-8.
35. Huang YC, Su LH, Lin TY. Nasal carriage of methicillin-resistant *Staphylococcus aureus* in contacts of an adolescent with community-acquired disseminated disease. Pediatr Infect Dis J 2004;23:919-22.
36. Boyle-Vavra S, Ereshefsky B, Wang CC, Daum RS. Successful multiresistant community-associated methicillin-resistant *Staphylococcus aureus* lineage from Taipei, Taiwan, that carries either the novel Staphylococcal chromosome cassette *mec* (SCC*mec*) type V_T or SCC*mec* type IV. J Clin Microbiol 2005; 43:4719-30.
37. Ho M, McDonald LC, Lauderdale TL, Yeh LL, Chen PC, Shiau YR. Surveillance of antibiotic resistance in Taiwan, 1998. J Microbiol Immunol Infect 1999;32:239-49.
38. McDonald LC, Lauderdale TL, Shiau YR, Chen PC, Lai JF, Wang HY, et al. The status of antimicrobial resistance in Taiwan among Gram-positive pathogens: the Taiwan Surveillance of Antimicrobial Resistance (TSAR) programme, 2000. Int J Antimicrob Agents 2004;23:362-70.
39. Chi CY, Wong WW, Fung CP, Yu KW, Liu CY. Epidemiology of community-acquired *Staphylococcus aureus* bacteremia. J Microbiol Immunol Infect 2004;37:16-23.
40. Lin JC, Yeh KM, Peng MY, Chang FY. Community-acquired methicillin-resistant *Staphylococcus aureus* bacteremia in Taiwan: risk factors for acquisition, clinical features and outcome. J Microbiol Immunol Infect 2004;37:24-8.
41. Chuang YY, Huang YC, Lee CY, Lin TY, Lien R, Chou YH. Methicillin-resistant *Staphylococcus aureus* bacteraemia in neonatal intensive care units: an analysis of 90 episodes. Acta Paediatr 2004;93:786-90.
42. Huang YC, Su LH, Wu TL, Lin TY. Molecular surveillance of clinical methicillin-resistant *Staphylococcus aureus* isolates in neonatal intensive care units. Infect Control Hosp Epidemiol 2005;26:157-60.
43. Huang YC, Su LH, Wu TL, Liu CE, Young TG, Chen PY, et al. Molecular epidemiology of clinical isolates of methicillin-resistant *Staphylococcus aureus* in Taiwan. J Clin Microbiol 2004;42:307-10.
44. Wang CC, Lo WT, Chu ML, Siu LK. Epidemiological typing of community-acquired methicillin-resistant *Staphylococcus aureus* isolates from children in Taiwan. Clin Infect Dis 2004; 39:481-7.
45. Aires de Sousa M, Crisostomo MI, Sanches IS, Wu JS, Fuzhong J, Tomasz A, et al. Frequent recovery of a single clonal type of multidrug-resistant *Staphylococcus aureus* from patients in two hospitals in Taiwan and China. J Clin Microbiol 2003;41: 159-63.
46. Aires de Sousa, 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;41:3806-15.
47. Monk AB, Curtis S, Paul J, Enright MC. Genetic analysis of *Staphylococcus aureus* from intravenous drug user lesions. J Med Microbiol 2004;53:223-7.
48. 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;39:971-9.
49. Martinez-Aguilar G, Avalos-Mishaan A, Hulten K, Hammerman W, Mason EO Jr, Kaplan SL. Community-acquired, methicillin-resistant and methicillin-susceptible *Staphylococcus aureus* musculoskeletal infections in children. Pediatr Infect Dis J 2004;23:701-6.
50. Baggett HC, Hennessy TW, Rudolph K, Bruden D, Reasonover A, Parkinson A, et al. Community-onset methicillin-resistant *Staphylococcus aureus* associated with antibiotic use and the cytotoxin Panton-Valentine leukocidin during a furunculosis

outbreak in rural Alaska. J Infect Dis 2004;189:1565-73.
51. Boubaker K, Diebold P, Blanc DS, Vandenesch F, Praz G, Dupuis G, et al. Panton-valentine leukocidin and staphyloccoccal skin infections in schoolchildren. Emerg Infect Dis 2004;10:121-4.
52. Boussaud V, Parrot A, Mayaud C, Wislez M, Antoine M, Picard C, et al. Life-threatening hemoptysis in adults with community-acquired pneumonia due to Panton-Valentine leukocidin-secreting *Staphylococcus aureus*. Intensive Care Med 2003; 29:1840-3.
53. Gillet Y, Issartel B, Vanhems P, Fournet JC, Lina G, Bes M, et al. Association between *Staphylococcus aureus* strains carrying gene for Panton-Valentine leukocidin and highly lethal necrotising pneumonia in young immunocompetent patients. Lancet 2002;359:753-9.
54. Vandenesch F, Naimi T, Enright MC, Lina G, Nimmo GR, Heffernan H, et al. Community-acquired methicillin-resistant *Staphylococcus aureus* carrying Panton-Valentine leukocidin genes: worldwide emergence. Emerg Infect Dis 2003;9:978-84.
55. Tseng MH, Wei BH, Lin WJ, Lu JJ, Lee SY, Wang SR, et al. Fatal sepsis and necrotizing pneumonia in a child due to community-acquired methicillin-resistant *Staphylococcus aureus*: case report and literature review. Scand J Infect Dis 2005;37:504-7.