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Spread of methicillin-resistant *Staphylococcus aureus* between the community and the hospitals in Asian countries: an ANSORP study

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Objectives: Methicillin-resistant *Staphylococcus aureus* (MRSA) is highly prevalent in hospitals in many Asian countries. Recent emergence of community-associated (CA) MRSA worldwide has added another serious concern to the epidemiology of *S. aureus* infections. To understand the changing epidemiology of *S. aureus* infections in Asian countries, we performed a prospective, multinational surveillance study with molecular typing analysis.

Methods: We evaluated the prevalence of methicillin resistance in *S. aureus* isolates in CA and healthcare-associated (HA) infections, and performed molecular characterization and antimicrobial susceptibility tests of MRSA isolates.

Results: MRSA accounted for 25.5% of CA *S. aureus* infections and 67.4% of HA infections. Predominant clones of CA-MRSA isolates were ST59-MRSA-SCC*mec* type IV-*spa* type t437, ST30-MRSA-SCC*mec* type IV-*spa* type t019 and ST72-MRSA-SCC*mec* type IV-*spa* type t324. Previously established nosocomial MRSA strains including sequence type (ST) 239 and ST5 clones were found among CA-MRSA isolates from patients without any risk factors for HA-MRSA infection. CA-MRSA clones such as ST59, ST30 and ST72 were also isolated from patients with HA infections.

Conclusions: Our findings confirmed that MRSA infections in the community have been increasing in Asian countries. Data also suggest that various MRSA clones have spread between the community and hospitals as well as between countries.

Keywords: *S. aureus*, methicillin resistance, community-associated infections, genotypes

Introduction

Methicillin-resistant *Staphylococcus aureus* (MRSA) has been considered the most representative nosocomial pathogen since the pandemic waves of MRSA of SCC*mec* types I, II and III over the past decades.[1] MRSA infections in hospital have obviously imposed a high burden on healthcare resources as well as significant morbidity and mortality.[2] Particularly, some Asian countries have been reported to show the highest rates of MRSA among *S. aureus* isolates from hospitals. Prevalence rates of MRSA in hospitals in Korea, Japan, Taiwan and China were reported to be 70%–80%.[3–6] A high prevalence of MRSA in the Asian region might be partly due to the spread of a few epidemic clones. Previous data documented that two major MRSA clones were prevalent in Asian hospitals: ST239-SCC*mec* type III found in China and some south-east Asian countries; and ST5-SCC*mec* type II found only in Japan and Korea.[7] The epidemiology of *S. aureus* infections, however, has dramatically changed in the past 15 years due to the widespread emergence of community-associated (CA) MRSA infections caused by strains containing SCC*mec* type IV. Particularly, the USA300 clone was reported to be the most prominent strain in the USA.[8] Outbreaks of CA-MRSA infections have been reported worldwide, although the prevalence of CA-MRSA varies geographically.[2] Despite the widespread emergence of MRSA in hospitals in many Asian countries, very few studies have addressed the epidemiology of MRSA infection in the community in Asian countries.

To understand the changing epidemiology of *S. aureus* infections in Asian countries, we performed a prospective, multinational surveillance study of MRSA infections in the community and in hospitals in eight Asian countries and investigated the molecular characteristics of MRSA isolates and antimicrobial resistance profiles of the predominant MRSA clones.

Materials and methods

Study population

This is a prospective surveillance study conducted by ANSORP, the Asian Network for Surveillance of Resistant Pathogens, from September 2004 to August 2006. A total of 17 ANSORP hospitals in eight countries, namely, Korea (7), Taiwan (3), Hong Kong (1), Thailand (2), the Philippines (1), Vietnam (1), India (1) and Sri Lanka (1), participated in this study. All participating hospitals were tertiary- or secondary-care teaching hospitals with 300–3000 hospital beds located in urban areas. All consecutive cases of culture-proven *S. aureus* infection during the study period were enrolled in the study. Only the first episode of *S. aureus* infection was included for each patient. Based on clinical evaluation, colonization by *S. aureus* without any clinical evidence of infection was excluded from the study. The procedures were in accordance with the ethical standards of the hospitals.

Definitions

Using the epidemiological definition, CA-MRSA infection was defined as MRSA infection occurring in the community or <48 h after hospital admission in patients without healthcare-associated (HA) risk factors.[9] HA infections were defined according to the definitions proposed by the CDC as those in which patients had hospitalization, surgery, dialysis, residence in a long-term care facility or use of indwelling catheters in the previous 12 months.[9] If an *S. aureus* infection did not meet these criteria, it was considered a CA infection. Infections in patients with a history of MRSA infection or colonization (if documented) were also defined as HA infections by CDC definitions. HA risk factors were identified by history taking and review of the medical records.

Bacterial isolates and antimicrobial susceptibility testing

All *S. aureus* isolates from participating centres were transported to the central laboratory (Infectious Disease Research Institute, Asia Pacific Foundation for Infectious Diseases, Seoul, Korea) for further tests. Isolates were identified again by using a Staphaurex Plus Kit (Murex Diagnostics Ltd, Dartford, UK) at the central laboratory. Antimicrobial susceptibility testing was performed by a broth microdilution method in accordance with CLSI guidelines.[10] MICs of 12 antimicrobial agents were determined: oxacillin; penicillin; gentamicin; ciprofloxacin; clindamycin; erythromycin; rifampicin; tetracycline; trimethoprim/sulfamethoxazole; vancomycin; teicoplanin; and ceftobiprole. Detection of inducible clindamycin resistance was by the disc approximation D-zone test. The MIC_{90} of ceftobiprole was determined for MRSA isolates. Isolates were classified as multidrug-resistant (MDR) if they were resistant to three or more different classes of non-β-lactam antimicrobial based on susceptibility to gentamicin, erythromycin, clindamycin, ciprofloxacin, rifampicin, tetracycline and trimethoprim/sulfamethoxazole.[11] *S. aureus* ATCC 29213 was used as a control strain.

Molecular characterization of the strains

We randomly selected >500 MRSA isolates including both CA- and HA-MRSA isolates from all countries for *spa* typing and SCC*mec* typing. The *spa* typing was performed as previously described.[12,13] The *spa* types were determined by using Ridom SpaServer (http://spaserver2.ridom.de/spatypes.shtml). SCC*mec* types were determined by the multiplex PCR method.[14] SCC*mec* types that could not be determined by the above method were further tested using updated methods from Milheirico[15] and Zhang *et al.*[16] SCC*mec* types that could not be assigned to any known type finally were classified as non-typeable (NT). *S. aureus* TSGH17 was used as a control strain of SCC*mec* type VT. Multilocus sequence typing (MLST) was carried out by PCR amplification and sequencing of seven housekeeping genes (*arcC*, *aroE*, *glpF*, *gmk*, *pta*, *tpi* and *yqiL*) by using the primer pairs as described previously.[17] The allelic profiles and sequence types (STs) were assigned by the MLST web site (http://saureus.mlst.net/). For phylogenetic analysis of the strains, the eBURST algorithm, available at http://saureus.mlst.net/eburst/, was used. STs that shared at least five of seven identical alleles were grouped into a single clonal complex (CC). PFGE types were determined for selected CA-MRSA isolates of ST5 and ST239, and they were compared with those of HA-MRSA isolates of the same ST in each country. PFGE was performed as described previously.[18] The PFGE patterns were analysed using GelCompar II software (Applied Maths, Belgium).

Isolates were screened for the *lukF-PV* and *lukS-PV* genes encoding the components of the Panton–Valentine leucocidin (PVL) toxin by PCR amplification of a portion of both the *lukS-PV* and *lukF-PV* ORFs by using the primer pair luk-PV-1 and luk-PV-2 designed by Lina *et al.*[19]

Results

Prevalence of MRSA infections in the community and in hospitals

A total of 4117 isolates from patients with *S. aureus* infection were collected. Mean age of the patients was 47.6 years (range, 1 month to 104 years) and 42% were female. Among all cases, CA infections accounted for 1463 (35.5%). The number of MRSA isolates was 2162 (52.5%). MRSA accounted

Table 1. Distribution of MRSA isolates by country

	No. of MRSA/no. of total *S. aureus* isolates (%)	
	CA	HA
Korea	23/147 (15.6)	547/705 (77.6)
Taiwan	94/270 (34.8)	373/574 (65.0)
Hong Kong	7/82 (8.5)	196/345 (56.8)
The Philippines	28/93 (30.1)	37/97 (38.1)
Thailand	3/122 (2.5)	180/316 (57.0)
Vietnam	197/654 (30.1)	109/147 (74.1)
India	2/46 (4.3)	21/93 (22.6)
Sri Lanka	19/49 (38.8)	326/377 (86.5)
Total	373/1463 (25.5)	1789/2654 (67.4)

for 25.5% of total isolates of CA *S. aureus* infections, whereas 67.4% of HA infections were caused by MRSA (Table 1). HA-MRSA infections were further classified based on the onset of infection: 25.4% were community-onset HA *S. aureus* infections; and 74.6% were hospital-onset infections. The proportion of MRSA among HA *S. aureus* infections was relatively low in India (22.6%) and the Philippines (38.1%), whereas Sri Lanka (86.5%), Korea (77.6%) and Vietnam (74.1%) showed very high rates of MRSA. The proportion of MRSA in CA *S. aureus* infections also varied by country: Sri Lanka (38.8%); Taiwan (34.8%); the Philippines (30.1%); Vietnam (30.1%); Korea (15.6%); Hong Kong (8.5%); India (4.3%); and Thailand (2.5%). Pus (34.1%), sputum (26.3%) and blood (21.0%) were the main culture specimens in cases of HA-MRSA infection, while the most frequent culture specimen in CA-MRSA infections was pus (70.5%), followed by blood (9.1%), sputum (8.6%) and urine (4.3%).

Characterization of MRSA by SCCmec type and spa type

Distribution of SCC*mec* types of CA-MRSA and HA-MRSA isolates differed by country. Among CA-MRSA isolates, SCC*mec* type IV accounted for 78.6% and 43.5% in the Philippines and Korea, respectively (Table 2), where major *spa* types of these SCC*mec* type IV isolates were t019 and t324, respectively. In Taiwan, the most frequent SCC*mec* type of CA-MRSA isolates was type III followed by SCC*mec* type IV, in both of which *spa* type t437 was predominant. In Sri Lanka, the most common *spa* types were t002 (31.6%) and t425 (31.6%). In Hong Kong, CA-MRSA isolates of SCC*mec* type III were also most frequent (71.4%). In Korea and Taiwan, SCC*mec* type II of *spa* type t002 and SCC*mec* type III of *spa* type t037, which were predominant in HA-MRSA isolates, were also found in CA-MRSA isolates. SCC*mec* type III of *spa* type t037 was also found in CA-MRSA isolates from Vietnam.

Among the HA-MRSA isolates, SCC*mec* type III was the most frequent in Taiwan, Hong Kong, Thailand, Vietnam, India and Sri Lanka (Table 2). The most frequent *spa* type among these HA-MRSA isolates of SCC*mec* type III was t037 except in Sri Lanka where t425 was the most frequent *spa* type. In Korea, SCC*mec* type II of *spa* type t002 was the most frequent type in HA-MRSA isolates. MRSA isolates of SCC*mec* type IV, which represent a major genotype of CA-MRSA in Asian countries, were found among HA-MRSA infections in Taiwan, the Philippines and Korea.

Characterization of MRSA according to MLST and PFGE

One of the prevalent CCs in CA-MRSA isolates from Asian countries was CC59 including ST59, ST1241 and ST338, which were frequently found in Taiwan (Table 3). The latter two were single locus variants (SLVs) of ST59. ST59 was also found in HA-MRSA isolates from Taiwan. The most frequent *spa* type in the isolates of CC59 was t437 and they contained SCC*mec* type III or IV.

ST30 (CC30) with t019 was common among CA-MRSA isolates from the Philippines and Taiwan, and was also found in HA-MRSA isolates from the Philippines. These isolates contained SCC*mec* type IV. Other STs included ST72 (CC72) of SCC*mec* type IV, which was found only in Korea, ST1 and its SLV, ST772 (CC1).

The most frequent STs in HA-MRSA isolates were ST5 (CC5) and ST239 (CC8) (Table 3). Most isolates of ST5 (CC5) were found in Korea, and were *spa* type t002 or t601 and SCC*mec* type II. Isolates of ST5 of *spa* type t002 were also found in CA-MRSA isolates from Korea, Sri Lanka and Taiwan. ST239 (CC8) was found in HA-MRSA isolates from Thailand, Vietnam, Taiwan, Korea, India and Hong Kong. The most frequent *spa* type of ST239 isolates was t037 and common SCC*mec* types were III and II. MRSA isolates of ST368 (CC8), which is an SLV of ST239, were only found in Sri Lanka, and they contained SCC*mec* type III. ST239 and its SLVs were also found in CA-MRSA isolates from Taiwan, Korea, Vietnam, Thailand, Hong Kong and Sri Lanka. The PFGE patterns of selected CA-MRSA isolates of ST5 and ST239 were compared with those of HA-MRSA isolates of the same STs in each country (Figure 1). The 13 MRSA isolates of ST5 were clustered into three clonal groups with >70% similarity. Among these, a major group included CA- or HA-MRSA isolates from Korea, Taiwan and Sri Lanka. Of 13 MRSA isolates of ST239 and *spa* type t037, 10 were clustered into a major clonal group with >70% similarity (Figure 1). Within this group, two subgroups were further clustered with >80% similarity: the first subgroup included CA- and HA-MRSA isolates from Korea and Taiwan; and the second subgroup included those from Thailand and Hong Kong.

PVL production in MRSA isolates

The presence of *lukF-PV* and *lukS-PV* genes encoding the components of the PVL toxin was evaluated according to CA-MRSA versus HA-MRSA. The genes for PVL were present in 28 (14.3%) out of 196 CA-MRSA isolates compared with 13 (5.7%) of 227 HA-MRSA isolates ($P=0.003$). The presence of the genes for PVL differed according to SCC*mec* type, and they were positive in 10% (1/10), 0% (0/49), 7.7% (18/235), 16.3% (16/98) and 19.4% (6/31) of MRSA isolates of SCC*mec* types I, II, III, IV and NT, respectively ($P=0.006$). The genes for PVL were positive in 10 (29.4%) out of 34 MRSA isolates with *spa* type t019 and 13 (12.9%) of 101 MRSA isolates with *spa* type t437. All four MRSA isolates of *spa* type t324 were negative for *lukF-PV* and *lukS-PV* genes. PVL was positive in 6 (46.2%) out of 13 isolates of ST30, 2 (15.4%) of 13 isolates of ST59 and 2 (16.7%) of 12 isolates of ST1241. However, none of the tested isolates of ST239 (25 isolates) and ST72 (16 isolates) was positive for PVL.

Table 2. Distribution of MRSA isolates from Asian countries by SCC*mec* type and *spa* type

	CA ($n=207$)			HA ($n=319$)		
Country	SCC*mec* type	no. of SCC*mec* type (%)	*spa* type (no./tested)	SCC*mec*.type	no. of SCC*mec* type (%)	*spa* type (no./tested)
Korea (CA, $n=23$; HA, $n=101$)	I	0 (0)		I	0 (0)	
	II	6 (26.1)	t002 (3/4)	II	61 (60.4)	t002 (31/61), t601 (15/61), t2460 (6/61), t037 (2/61), t509 (1/61), t1452 (1/61), t5076 (1/61)
	III	5 (21.7)	t037 (4/5), t018 (1/5)	III	20 (19.8)	t037 (18/20), t324 (1/20)
	IV	10 (43.5)	t324 (6/10), t286 (2/10), t148 (1/10), t2431 (1/10)	IV	19 (18.8)	t324 (8/19), t148 (4/19), t901 (2/19), t286 (1/19), t937 (1/19), t2182 (1/19), t2460 (1/19)
	NT	2 (8.7)	t009 (1/2), t2575 (1/2)	NT	1 (1.0)	
Taiwan (CA, $n=94$; HA, $n=79$)	I	1 (1.1)	t437 (1/1)	I	1 (1.3)	t304 (1/1)
	II	3 (3.2)	t3520 (2/3), t002 (1/3)	II	10 (12.7)	t002 (8/10), t437 (2/10)
	III	60 (63.8)	t437 (48/60), t037 (4/60), t441 (4/60), t1950 (1/60), t3517 (1/60), t3523 (1/60)	III	48 (60.8)	t037 (14/36), t654 (12/36), t437 (10/36)
	IV	30 (31.9)	t437 (18/30), t1751 (4/30), t019 (2/30), t073 (1/30), t084 (1/30), t441 (1/30), t3485 (1/30)	IV	17 (21.5)	t437 (12/16), t015 (1/16), t441 (1/16), t3517 (1/16), t019 (1/16)
	NT	0 (0)		NT	3 (3.8)	t437 (1/3), t654 (1/3), t1751 (1/3)
Hong Kong (CA, $n=7$; HA, $n=19$)	I	1 (14.3)	t437 (1/1)	I	0 (0)	
	II	0 (0)		II	2 (10.5)	t002 (1/2), t494 (1/2)
	III	5 (71.4)	t437 (2/5), t011 (1/5), t037 (1/5), t1081 (1/5)	III	15 (79.0)	t037 (12/12)
	IV	1 (14.3)	t019 (1/1)	IV	0 (0)	
	NT	0 (0)		NT	2 (10.5)	t002 (1/1)
The Philippines (CA, $n=28$; HA, $n=18$)	I	0 (0)		I	0 (0)	
	II	0 (0)		II	2 (11.1)	t002 (1/2), t018 (1/2)
	III	0 (0)		III	5 (27.8)	t002 (2/5), t030 (1/5), t037 (1/5), t2670 (1/5)
	IV	22 (78.6)	t019 (16/22), t2670 (2/22), t267 (1/22), t1133 (1/22)	IV	9 (50.0)	t019 (6/8), t002 (1/8), t1081 (1/8)
	NT	6 (21.4)	t019 (6/6)	NT	2 (11.1)	t019 (2/2)
Thailand (CA, $n=3$; HA, $n=29$)	I	0 (0)		I	0 (0)	
	II	1 (33.3)	t2879 (1/1)	II	5 (17.2)	t037 (4/5)
	III	2 (66.7)	t037 (1/2), t654 (1/2)	III	24 (82.8)	t037 (19/24), t654 (4/24)
	IV	0 (0)		IV	0 (0)	
	NT	0 (0)		NT	0 (0)	
Vietnam (CA, $n=31$; HA, $n=21$)	I	4 (12.9)	t026 (1/2), t437 (1/2)	I	1 (4.8)	t437 (1/1)
	II	5 (16.1)	t037 (5/5)	II	7 (33.3)	t037 (7/7)
	III	16 (51.6)	t037 (11/14), t437 (2/14), t091 (1/14)	III	10 (47.6)	t037 (9/9)
	IV	1 (3.2)		IV	0 (0)	
	NT	5 (16.1)	t037 (3/5), t437 (1/5), t5231 (1/5)	NT	3 (14.3)	t037 (3/3)

Continued

Table 2. *Continued*

Country	CA (*n*=207) SCC*mec* type	no. of SCC*mec* type (%)	*spa* type (no./tested)	HA (*n*=319) SCC*mec*.type	no. of SCC*mec* type (%)	*spa* type (no./tested)
India (CA, *n*=2; HA, *n*=11)	I	0 (0)		I	1 (9.1)	
	II	0 (0)		II	0 (0)	
	III	0 (0)		III	9 (81.8)	t037 (7/9), t064 (1/9), t748 (1/9)
	IV	2 (100)	t657 (2/2)	IV	1 (9.1)	t2177 (1/1)
	NT	0 (0)		NT	0 (0)	
Sri Lanka (CA, *n*=19; HA, *n*=41)	I	1 (5.3)	t002 (1/1)	I	0 (0)	
	II	0 (0)		II	1 (2.4)	t021 (1/1)
	III	9 (47.4)	t425 (6/9), t002 (1/9), t127 (1/9)	III	33 (80.5)	t425 (26/33), t127 (2/33), t002 (1/33), t021 (1/33), t3184 (1/33)
	IV	5 (26.3)	t002 (1/5), t127 (1/5), t437 (1/5), t448 (1/5), t2601 (1/5)	IV	2 (4.9)	t1081 (1/1)
	NT	4 (21.1)	t002 (3/4), t084 (1/4)	NT	5 (12.2)	t425 (2/5), t002 (1/5), t3635 (1/5), t4188 (1/5)

Type of infection by MLST CC

Among CA-MRSA infections, the most common type was skin and soft tissue infection (SSTI) (66.7%), followed by respiratory tract infection (8.3%), urinary tract infection (8.3%) and primary bacteraemia (4.2%). In contrast, respiratory tract infection was the most common (33.3%) in HA-MRSA infections, and SSTI accounted for 26.9%, followed by bone and joint infection (7.7%), urinary tract infection (6.4%) and primary bacteraemia (12.8%).

SSTI was the most common type of CA-MRSA infection (41.2%) caused by CC59 followed by urinary tract infection (17.6%). All CA-MRSA infections by CC30 and 75% of CA-MRSA infections by CC72 were also SSTI. In contrast, the most common HA-MRSA infection caused by CC72 was respiratory tract infection (37.5%) followed by primary bacteraemia (25.0%), bone and joint infection (12.5%), intra-abdominal infection (12.5%) and urinary tract infection (12.5%). The most common types of HA-MRSA infection by CC5 were respiratory tract infection (33.3%), followed by SSTI (22.9%), primary bacteraemia (14.6%), urinary tract infection (8.3%), bone and joint infection (4.2%), intra-abdominal infection (4.2%) and catheter-related infection (4.2%). HA-MRSA infections by CC8 included SSTI (43.8%), respiratory tract infection (31.3%) and bone and joint infection (18.8%).

Antimicrobial resistance to non-β-lactam agents of MRSA

Antimicrobial resistance rates of 357 isolates of CA-MRSA and 313 HA-MRSA isolates were analysed (Table 4). Among CA-MRSA isolates, resistance rates to gentamicin, ciprofloxacin and trimethoprim/sulfamethoxazole were significantly lower than those of HA-MRSA isolates (61.2% versus 78.6%, $P<0.001$; 52.5% versus 77.6%, $P<0.001$; 31.3% versus 43.5%, $P=0.001$). Resistance rates to clindamycin, erythromycin and tetracycline were similarly high in both CA-MRSA and HA-MRSA (66.5% versus 64.2%, $P=0.038$; 84.1% versus 90.4%, $P=0.032$; 69.3% versus 72.2%, $P=0.036$). Rifampicin resistance rates were 5.3% and 9.9%, respectively ($P=0.072$). The MDR rate was 73.1% and 83.7% in CA-MRSA and HA-MRSA isolates, respectively ($P=0.001$).

Antimicrobial resistance rates of MRSA isolates were analysed according to *spa* type (Table 4). Isolates of *spa* types t019 and t324, representing ST30 and ST72, which were the predominant CA-MRSA strains in the Philippines and Korea, respectively, showed very low resistance rates to non-β-lactam agents. MDR rates were 4.0% and 0%, respectively. Isolates of *spa* type t437, representing ST59, showed higher resistance rates than those of *spa* types t019 and t324, and the MDR rate was 68.0%. Even HA-MRSA isolates of *spa* types t019 and t324 showed similar resistance profiles to CA-MRSA isolates of the same *spa* types, and MDR rates were 0% and 11.1%, respectively. In contrast, isolates of *spa* types t037 and t002, which represent ST239 and ST5 from CA infections, showed high MDR rates (100% and 60.0%).

Discussion

This first international surveillance study on the epidemiology of CA-MRSA in Asian countries revealed important findings with regard to the current epidemiology of MRSA infections in the community and hospitals in Asian countries. Our data suggest the spread of MRSA between the community and hospitals in Asian countries as well as the potential spread of clones between different continents based on the molecular characteristics of MRSA isolates. The first finding was that CA-MRSA isolates with various genotypic characteristics have spread from the community to hospitals in some Asian countries. Among various clones of CA-MRSA in Asian countries, the most

Table 3. Distribution of MRSA isolates from Asian countries by MLST ST and their genotypic characteristics

		CA (n=63)					HA (n=98)				
MLST	CC	no.	*spa* type (no.)	SCC*mec* type (no.)	PVL positive/ tested	countries (no.)	no.	*spa* type (no.)	SCC*mec* type (no.)	PVL positive/ tested	countries (no.)
ST1241	59	12	t437 (10) t1751 (1), t441 (1)	III (9), IV (2), I (1)	2/12	TW (10), HK (2)	0				
ST59	59	10	t437 (6), t1751 (2), t441 (1)	IV (5), IIIA var (4), I (1)	2/10	TW (8), HK (1), VT (1)	3	t437 (3)	IV (1), III (1)	0/3	TW (3)
ST338	59	3	t437 (1), t441 (1), t1950 (1)	III (3)	0/3	TW (3)	0				
ST30	30	8	t019 (6), t2670 (2)	IV (1), NT (1)	4/8	PH (5), TW (2), HK (1)	5	t019 (4), t2670 (1)	IV (3), III (1)	2/5	PH (4), TW (1)
ST1	1	1	t286 (1)	IV (1)		KO (1)	1	t286 (1)			KO (1)
ST772	1	2	t657 (2)	IV (2)	2/2	IN (2)	0				
ST72	72	7	t324 (6), t148 (1)	IV (7)	0/7	KO (7)	9	t324 (9)	IV (8)	0/9	KO (9)
ST1240	72	0					1	t037 (1)	III (1)		KO (1)
ST5	5	6	t002 (6)	II (4), I (1), III (1)	1/4	KO (3), SL (2), TW (1)	52	t002 (36), t601 (15), t494 (1)	II (49), III (1), IV (1)	0/10	KO (46), HK (2), PH (2), TW (1), SL (1)
ST239	8	10	t037 (9), t654 (1)	III (8), II (1), NT (1)	0/10	VT (3), KO (2), TW (2), TH (2)	17	t037 (12), t654 (2), t901 (1)	III (10), II (3), IV (1)	0/15	TH (5), VT (4), TW (3), KO (2), IN (2), HK (1)
ST368	8	2	t425 (2)	III (2)	0/2	SL (2)	4	t425 (3), t002 (1)	III (4)	1/4	SL (4)
ST900	8	2	t037 (2)	III (2)	0/2	TW (2)	1	t654 (1)		0/1	TW (1)
ST8	8	0					2	t064 (2)	I (1), III (1)	0/2	IN (2)
ST585	8	0					2	t037 (2)	III (2)		KO (2)
ST623	8	0					1	t037 (1)	IV (1)	0/1	HK (1)

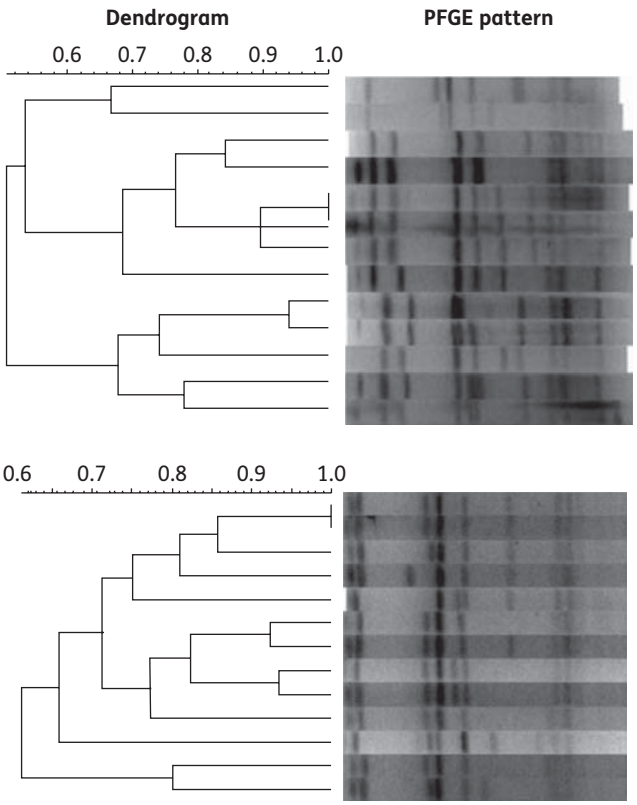
KO, Korea; TW, Taiwan; HK, Hong Kong; TH, Thailand; PH, the Philippines; IN, India; SL, Sri Lanka; VT, Vietnam.

Table 4. Comparison of antimicrobial resistance rates between CA- and HA-MRSA isolates

	No. (resistance rate, %)		
	CA (n=357)	HA (n=313)	P value
Gentamicin	218 (61.2)	246 (78.6)	<0.001
Ciprofloxacin	187 (52.5)	243 (77.6)	<0.001
Clindamycin	327 (91.6)	201 (64.2)	0.038
Erythromycin	300 (84.1)	283 (90.4)	0.032
Rifampicin	19 (5.3)	31 (9.9)	0.072
Tetracycline	247 (69.3)	226 (72.2)	0.036
Trimethoprim/sulfamethoxazole	112 (31.3)	136 (43.5)	0.001
Vancomycin	0 (0)	0 (0)	
Teicoplanin	0 (0)	0 (0)	
MDR	261 (73.1)	262 (83.7)	0.001

predominant clones in the region included ST59-MRSA-SCC*mec* type IV-*spa* type t437 in Taiwan, Hong Kong, Vietnam and Sri Lanka, ST30-MRSA-SCC*mec* type IV-*spa* type t019 in the Philippines and ST72-MRSA-SCC*mec* type IV-*spa* type t324 in Korea. Some of the HA-MRSA isolates from Taiwan, the Philippines and Korea showed the same genotypic characteristics as CA-MRSA isolates in these countries. Given that SCC*mec* type, *spa* type, antimicrobial susceptibility profile and ST of these MRSA isolates were typical for CA-MRSA isolates, this finding suggests that CA-MRSA clones have already spread into hospitals in these Asian countries.

The second important finding was a possible spread of HA-MRSA clones to the community in some countries including Korea, Taiwan, Thailand, Vietnam and Sri Lanka. Our study showed that major clonal lineages of HA-MRSA isolates were ST239-MRSA-SCC*mec* type III-*spa* type t037 in Thailand, Korea, Vietnam, Taiwan and India and ST5-MRSA-SCC*mec* type II-*spa* type t002 in Taiwan, the Philippines, Hong Kong, Sri Lanka and



Strain	Country	CA/HA	Specimen	ST	*spa*	SCC*mec*
SL01-017	Sri Lanka	CA	Pus	ST5	t002	I
K07-288	Korea	CA	Blood	ST5	t002	II
SL01-041	Sri Lanka	HA	Pus	ST5	t002	NT
K06-012	Korea	HA	Blood	ST5	t601	II
K10-013	Korea	CA	Pus	ST5	t002	II
TW01-095	Taiwan	HA	Others	ST5	t002	II
TW02-004	Taiwan	CA		ST5	t002	II
K06-038	Korea	HA	Blood	ST5	t601	II
K07-001	Korea	HA		ST5	t002	II
K10-007	Korea	HA		ST5	t002	II
K08-136	Korea	CA	Blood	ST5	t002	II
K01-173	Korea	HA	Pleural effusion	ST5	t601	II
SL01-040	Sri Lanka	CA	Pus	ST5	t002	III
K08-722	Korea	CA	Blood	ST239	t037	III
K01-304	Korea	HA	Sputum	ST239	t037	III
TW03-079	Taiwan	CA	Pus	ST239	t037	III
TW02-091	Taiwan	HA		ST239	t037	III
V01-006	Vietnam	CA	Pus	ST239	t037	III
TH01-059	Thailand	CA	Pus	ST239	t037	III
TH01-323	Thailand	HA	Pus	ST239	t037	III
HK01-053	Hong Kong	CA	Blood	ST239	t037	III
HK01-252	Hong Kong	HA	Pus	ST239	t037	III
TW02-044	Taiwan	CA		ST239	t037	III
K03-044	Korea	CA	Urine	ST239	t037	III
TW03-116	Taiwan	CA	Blood	ST239	t037	III
V01-234	Vietnam	HA	Pus	ST239	t037	III

Figure 1. Dendrogram of the PFGE profiles of selected CA-MRSA and HA-MRSA isolates of ST5 and ST239.

Korea. Previous studies also documented that ST5-MRSA-SCC*mec* type II-*spa* type t002 was a major clone of HA-MRSA isolates in Korea and Japan.[7,20] In our study, these MRSA clones in hospitals were found among CA-MRSA isolates from patients without any risk factors for HA-MRSA infection. Analysis of the PFGE patterns of selected MRSA isolates of ST5 and ST239 supported the possibility of the spread of MRSA hospital strains of ST5 and ST239 into the community. CA-MRSA isolates of ST5 from Korea and Taiwan and those of ST239 from Korea, Taiwan, Thailand and Hong Kong were closely related to HA-MRSA isolates of the same ST from the respective country. Thus, our data suggest that major HA-MRSA clones that are endemic in hospitals in some Asian countries have spread to the community. Given that penicillin-resistant *S. aureus* spread from hospitals to the community in the 1950s,[21] it is theoretically reasonable to anticipate the spread of HA-MRSA clones from hospitals to the community. However, there have been no reports documenting such a spread of HA-MRSA isolates to the community.

The third finding from this study was the potential spread of CA-MRSA clones to remote regions or countries. ST59-MRSA-SCC*mec* type IV-*spa* type t437, which was one of the most prevalent clones of CA-MRSA isolates in this study, was also recently reported as the predominant clone of CA-MRSA isolates in Chinese children.[22] The ST338 MRSA strain, which was found in CA-MRSA isolates from Taiwan in our study, was also found in the southern region of China.[22] These findings suggest the possible spread of CC59 CA-MRSA clones between Taiwan and China. Genetic analysis of CA-MRSA clones based on MLST also showed that the ST30-MRSA-SCC*mec* type IV-*spa* type t019 strain has spread from Oceania towards Asia, Europe and the Americas.[23,24] This clone was found mainly in the Philippines and also in Taiwan and Hong Kong in our study. This clone was also found among HA-MRSA isolates from the Philippines in our study, which suggested the spread of this clone from the community into hospitals in that country. Our data suggested that ST30 and ST59 are prevalent in Asian countries with possible spread between countries. However, ST8 (USA300), which is the most prevalent CA-MRSA clone in the USA or ST80 (European clone) have not been found in any Asian countries in our study. Although a very few cases of ST8 CA-MRSA infection have recently been reported from Japan[25] and Korea[26] or ST80 CA-MRSA infections reported from Singapore[27] and Malaysia,[28] the ST8 and ST80 MRSA clones are obviously rare in Asian countries. Distribution of major strains of CA-MRSA and HA-MRSA in Asian countries is summarized in a map based on our data and other reports (Figure S1, available as Supplementary data at *JAC* Online).[22,28–35]

In vitro antimicrobial susceptibility tests showed that the isolates of *spa* types t019 and t324, which represent ST30 and ST72, respectively, showed very low resistance rates to non-β-lactam agents. This is a typical characteristic of CA-MRSA isolates containing SCC*mec* type IV elements. Isolates of *spa* type t437, representing ST59, showed high resistance rates to erythromycin, clindamycin and tetracycline. Recently, MDR USA300 clones with resistance to doxycycline, gentamicin, trimethoprim/sulfamethoxazole and clindamycin were reported.[36,37] As there would be the increasing possibility of transfer of mobile genetic elements encoding antimicrobial resistance between CA-MRSA

and HA-MRSA isolates both in the community and in hospitals, multidrug resistance in CA-MRSA isolates will become more frequent in the future. Also, given the possible spread of HA-MRSA clones, which are typically resistant to multiple antibiotics, from the hospitals to the community, multidrug resistance in *S. aureus* infections in the community would be a more serious problem in Asian countries. If the MDR rate is increasing in community *S. aureus* infections, it makes antimicrobial selection more difficult in the community setting.

This study has some limitations. First, except for Korea and Taiwan, only one or two hospitals located in the urban areas from each country participated in this study. Therefore, data from this study are not representative of the current epidemiology of CA-MRSA in the whole country but could indicate the current situation in participating hospitals. Second, we used an epidemiological definition of CA-MRSA that was proposed by the CDC, which may preclude comprehensive assessment of possible risk factors for HA infection from the patients.

In conclusion, we found that MRSA has emerged as an important pathogen of community infections in many Asian countries. The predominant clones of CA-MRSA in Asian countries include ST59-MRSA-SCC*mec* type IV-*spa* type t437, ST30-MRSA-SCC*mec* type IV-*spa* type t019 and ST72-MRSA-SCC*mec* type IV-*spa* type t324. Molecular characteristics of CA- and HA-MRSA isolates suggest the spread of CA-MRSA clones into the hospitals, the spread of HA-MRSA clones to the community and the spread of CA-MRSA clones between Asian countries. Given the widespread endemicity of MRSA infections in hospitals in most Asian countries and the possible spread of HA-MRSA strains to the community, further emergence of MDR CA-MRSA strains is anticipated in the Asian region. Continuous efforts to understand the changing epidemiology of *S. aureus* infection are necessary for appropriate antimicrobial treatment and effective control of resistance problems.

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Transparency declarations

None to declare.

Supplementary data

Figure S1 is available as Supplementary data at *JAC* Online (http://jac.oxfordjournals.org/).

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