REVIEW 10.1111/1469-0691.12705

New epidemiology of *Staphylococcus aureus* infection in Asia

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Abstract

Not only is Asia the most populous region in the world, but inappropriate therapy, including self-medication with over-the-counter antimicrobial agents, is a common response to infectious diseases. The high antibiotic selective pressure among the overcrowded inhabitants creates an environment that is suitable for the rapid development and efficient spread of numerous multidrug-resistant pathogens. Indeed, Asia is among the regions with the highest prevalence rates of healthcare-associated methicillin-resistant *Staphylococcus aureus* (HA-MRSA) and community-associated methicillin-resistant *S. aureus* (CA-MRSA) in the world. Most hospitals in Asia are endemic for multidrug-resistant methicillin-resistant *S. aureus* (MRSA), with an estimated proportion from 28% (in Hong Kong and Indonesia) to >70% (in Korea) among all clinical *S. aureus* isolates in the early 2010s. Isolates with reduced susceptibility or a high level of resistance to glycopeptides have also been increasingly identified in the past few years. In contrast, the proportion of MRSA among community-associated *S. aureus* infections in Asian countries varies markedly, from <5% to >35%. Two pandemic HA-MRSA clones, namely multilocus sequence type (ST) 239 and ST5, are disseminated internationally in Asia, whereas the molecular epidemiology of CA-MRSA in Asia is characterized by clonal heterogeneity, similar to that in Europe. In this review, the epidemiology of *S. aureus* in both healthcare facilities and communities in Asia is addressed, with an emphasis on the prevalence, clonal structure and antibiotic resistant profiles of the MRSA strains. The novel MRSA strains from livestock animals have been considered to constitute a public health threat in western countries. The emerging livestock-associated MRSA strains in Asia are also included in this review.

Keywords: Asia, community-associated, healthcare-associated, heterogeneous VISA, livestock-associated, methicillin-resistant *Staphylococcus aureus*, molecular epidemiology, vancomycin-intermediate *S. aureus*, vancomycin-resistant *S. aureus*
Article published online: 2 June 2014
Clin Microbiol Infect 2014; **20**: 605–623

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Introduction

Staphylococcus aureus is a major cause of numerous infections in both communities and healthcare facilities, and is increasingly showing resistance to multiple antimicrobial agents [1,2]. The development of resistance to multiple drugs, including glycopeptides, has caused substantial difficulty in the management of staphylococcal infections, and has been long been a healthcare concern worldwide [3,4]. Asia is among the regions with the highest incidence of methicillin-resistant *S. aureus* (MRSA) in the world [5–7]. Vancomycin-intermediate *S. aureus* (VISA) strains and vancomycin-resistant *S. aureus* (VRSA) strains are also being increasingly identified in certain countries in this region [8–11]. Furthermore, similar to the reports in Europe, a novel MRSA strain that had spread in livestock animals was recently identified as a potential human pathogen in Asia [12]. Given the changing epidemiology, timely updated information on epidemic *S. aureus* strains in local and neighbouring countries is essential for the prevention and control of this pathogen. This information is also important for clinicians dealing with staphylococcal diseases. In this article, we comprehensively review the currently available data from Asian countries, and present the epidemiology, including the prevalence, molecular features, and antimicrobial resistance

profiles, of healthcare-associated MRSA (HA-MRSA), community-associated MRSA (CA-MRSA) and livestock-associated MRSA (LA-MRSA) in Asian countries.

HA-MRSA in Asia

MRSA is prevalent in nearly all healthcare facilities, and constitutes a huge infectious disease burden in Asia. The incidence varies significantly between different countries, and has changed over time [13–17]. Molecular epidemiology studies have demonstrated that the majority of HA-MRSA strains from different countries are of the same genotype, suggesting international dissemination of a few healthcare-associated clones in this region. However, most reports have been from certain relatively high-income countries, including Taiwan, Japan, Korea, Hong-Kong SAR, and Singapore. The information is either fragmentary or completely unavailable for the majority of the resource-limited countries in Southeast Asia and South Asia, and this has substantially limited our understanding of the epidemiology of staphylococcal diseases in this region [18]. In this section, we highlight the incidence, antibiotic resistance profiles and molecular features of HA-MRSA in Asian countries. Selected reports regarding the incidence of HA-MRSA in Asian countries are shown in Table 1.

East Asia

Taiwan, Korea, and Japan. Although increasing numbers of MRSA outbreaks were reported in Europe and the USA in the 1960s after the emergence of the first MRSA strain in the UK, MRSA was rarely documented before 1980 in East Asia. Japan was an exception; *S. aureus* with low-level resistance to methicillin was first identified in the early 1960s, but with a very low incidence (<3%) [19,20]. In Taiwan and Korea, MRSA had never been reported until 1981 and 1986, respectively [21,22]. *S. aureus* isolates collected during 1976–1978 in a university-affiliated teaching hospital in northern Taiwan showed 100% susceptibility to oxacillin [23]. The occurrence of nosocomial MRSA diseases remained at a low rate, and 0.2–0.9 episodes were identified per 1000 discharges in a hospital in the early 1980s [24].

The rate of MRSA increased remarkably in the next 20 years, from 1980 to 2000, in East Asia. In Taiwan, the proportion of MRSA among all nosocomial *S. aureus* isolates increased from 20.2% in 1981–1986 to 64.8% in 1993–1998, and further increased to 69.3% in 1999 [15,25]. Two subsequent multicentre studies consistently showed average MRSA rates of *c.* 60% for all *S. aureus* isolates and 50% for blood isolates in this island in 1998–2000 [7,26]. In Japan, a nationwide study including 43 hospitals showed that 58.6% of clinical *S. aureus* isolates were MRSA in 1990 [27]. The rate appeared to be continuously increasing, as shown by the SENTRY study, in which the rate of MRSA, obtained from three major hospitals in Japan, was 67–71.6% in 1998–2001 [7,28,29]. Nationwide surveillance in Korea also showed a mean MRSA rate of 72% for all clinical *S. aureus* isolates from 25 hospitals in 1998 [30]. The MRSA rate in East Asian countries appeared to reach its highest level at the end of the last millennium.

After the year 2000, the rate of HA-MRSA had still not significantly changed, and was still extremely high in Korea. The ANSORP study, including seven hospitals in Korea, showed an average MRSA rate of 77.6% for nosocomial *S. aureus* isolates during 2004–2006. The most recent report of the Regional Resistance Surveillance (RRS) programme showed that 73% of the clinical *S. aureus* isolates from two hospitals in Korea were MRSA in 2011 [31]. Korea has the highest MRSA rate among the 12 surveillance countries in the RSS programme. The epidemiology of HA-MRSA changed after 2000 in Taiwan and in Japan, where a declining trend of MRSA incidence was observed [31,32]. From 2000 to 2010, the proportion of MRSA among all *S. aureus* isolates obtained from patients with nosocomial bloodstream infections (BSIs) decreased from 68.8% in 2000 to 55.9% in 2010 in Taiwan (p 0.01) [33]. The incidence also significantly decreased, from 27.9 to 12.3 per 100 000 patient-days, with an annual decline of 8.5% over the 10-year study period in a hospital in Taiwan ($p < 0.001$) [33]. The RRS programme reported an MRSA rate of 41% in Japan in 2011, which was significantly lower than the values reported in SENTRY studies during 1998–2001 [7,28,29]. A reduction in the number of HA-MRSA infections was also seen in western countries during the same period [34–36]. Hand hygiene, antibiotic stewardship and surveillance programmes were considered to be possible explanations for the decline in HA-MRSA infections [37–40]. The change in MRSA strains, owing to the entry of CA-MRSA strains into hospitals, has also been proposed as a possible explanation [34].

Hong Kong and China. Epidemiological information on MRSA was largely lacking in China before 1998. The incidence remained at a relatively low level in the early 2000s, as shown by the SENTRY studies, in which MRSA accounted for 13–27.8% of clinical *S. aureus* isolates from three hospitals in 1998–2001 [7,29]. The rates increased dramatically to 50–62% in 2004–2005 in two multicentre studies [41,42]. A recent nationwide surveillance study in 2011, including 12 medical centres across China, showed a mean MRSA rate of 45.8% among all clinical *S. aureus* isolates. The epidemiology in Hong

TABLE 1. Prevalence of methicillin-resistant *Staphylococcus aureus* in Asian countries

Region/Years	Source of isolates	No of study site(s)/department	% Oxacillin resistance	Reference
East Asia				
China				
1998–1999	Clinical	Multiple (n = 3)	27.8	SENTRY study [7]
	Blood	Multiple (n = 3)	26.9	SENTRY study [7]
1999–2001	Clinical	Multiple (n = 3)	13	SENTRY study [29]
2004–2005	Clinical	Multiple (n = 17)	62.9	[41]
2005	Clinical	Multiple (n = 16)	50.5	[42]
2011	Clinical	Single	68.1	[194]
2011	Clinical	Multiple (n = 12)	45.8	[195]
Hong Kong SAR				
1984–1986	Nosocomial	Single	46	[43]
	Blood			
1998–1999	Clinical	Single	69.8	SENTRY study [7]
1998–1999	Blood	Single	58.2	SENTRY study [7]
1998–1999	Clinical	Single	73.8	SENTRY study [28]
1999–2001	Clinical	Single	55	SENTRY study [29]
2004–2006	Nosocomial	Single	56.8	ANSORP study [44]
2011	Clinical	Single	28	[31]
Japan				
1985	Clinical	Single	5.6	[196]
1988	Clinical	Single	50.0	[196]
1990	Clinical	Multiple (n = 43)	58.6	[27]
1998–1999	Clinical	Multiple (n = 3)	69.5, 71.6	SENTRY study [7,28]
1998–1999	Blood	Multiple (n = 3)	66.8	SENTRY study [7]
1999–2001	Clinical	Multiple (n = 3)	67	SENTRY study [29]
2011	Clinical	Multiple (n = 4)	41	[31]
Korea				
1986–1988	Blood	Single	21.6	[22]
1989–1996	Blood	Single	60.4	[22]
1998	Clinical	Multiple (n = 25)	72	[30]
1999–2001	Clinical	Multiple (n = 8)	64	[197]
2004–2006	Nosocomial	Multiple (n = 7)	77.6	ANSORP study [44]
2011	Clinical	Multiple (n = 2)	73	RRS programme [31]
Taiwan				
1976–1978	Nosocomial	Single	0	[23]
1981–1986	Nosocomial	Single	20.2	[15]
	Nosocomial	Single/ICU	27.8	[15]
1987–1992	Nosocomial	Single	31.4	[15]
	Nosocomial	Single/ICU	58.5	[15]
1993–1998	Nosocomial	Single	64.8	[15]
	Nosocomial	Single/ICU	86.9	[15]
1999	Nosocomial	Single	69.3	[15]
	Nosocomial	Single/ICU	87.4	[15]
1998–1999	Clinical	Multiple (n = 3)	59.6, 61.1	SENTRY study [7,28]
	Blood	Multiple (n = 3)	46.7	SENTRY study [7]
1999–2001	Clinical	Multiple (n = 3)	60	SENTRY study [29]
2000	Clinical	Multiple (n = 12)	53–83	[198]
2000	Clinical	Multiple (n = 21)	60.0	TSAR study [26]
2000	Nosocomial	Single	74	[198]
2000	Blood	Single	68.8	[33]
2004–2006	Nosocomial	Multiple (n = 3)	65.0	ANSORP study [44]
2010	Blood	Single	55.9	[33]
Southeast Asia				
Indonesia				
2011	Clinical	Single	28	[31]
Malaysia				
1996	Clinical	Multiple (n = 3)	39.7	[199]
2011	Clinical	Single	32	[31]
Philippines				
1999–2001	Clinical	Single	8	SENTRY study [29]
2004–2006	Nosocomial	Single	38.1	ANSORP study [44]
2011	Clinical	Single	59	[31]
Singapore				
1989–1991	Clinical	Single	39	[200]
1998–1999	Clinical	Single	62.3	SENTRY study [7,28]
1998–1999	Blood	Single	60.6	SENTRY study [7]
1999–2001	Clinical	Multiple (n = 2)	52	SENTRY study [29]
2006	Clinical	Multiple (n = 6)	35.3	[45]
2006	Clinical	Multiple/ICU (n = 6)	46.7	[45]
2006	Blood	Multiple (n = 6)	39.8	[45]
2011	Clinical	Single	52	[31]
Thailand				
2000–2005	Clinical	Multiple (n = ?)	24–27	NARST programme [201]
2004–2006	Nosocomial	Single	57.0	ANSORP study [44]
2011	Clinical	Multiple (n = 2)	53	[31]
Vietnam				
2004–2006	Nosocomial	Single	74.1	ANSORP study [44]
South Asia				
India				
1993–1994	Clinical	Single	24	[202]
1999	Clinical	Single	80.8	[46]
2000–2002	Clinical	Multiple (n = ?)	31.1	[203]
2003[a]	Clinical	Single	54.9	[204]
2004–2006	Nosocomial	Single	22.6	ANSORP study [44]

Table 1 (*Continued*)

Region/Years	Source of isolates	No of study site(s)/department	% Oxacillin resistance	Reference
2008–2009	Clinical	Multiple (n = 15)	41	[47]
2011	Clinical	Multiple (n = 5)	45	[31]
Pakistan				
2006–2008	Clinical	Multiple (n = 4)	41.9	[48]
Sri Lanka				
2004–2006	Nosocomial	Single	86.5	ANSORP study [44]

ICU, intensive-care unit; RRS, Regional Resistance Surveillance.
[a]Published year; study year not reported.

Kong appeared to be distinct from that in China. MRSA emerged early in the 1980s in Hong Kong, and a survey in the Prince of Wales Hospital in 1984–1986 showed MRSA rates of 25–30% and 46% among nosocomial isolates and blood isolates of *S. aureus*, respectively [43]. The MRSA rate increased to a high level of 73.8% in 1998–1999 in SENTRY studies, but appeared to decline thereafter [7,28,29]. The rate was 56.8% in 2004–2005 in the ANSORP study [44]. The latest survey of the RRS programme demonstrated an even lower MRSA rate of 28% in 2011 [31].

Southeast Asia

Most of the epidemiological data on MRSA in Southeast Asia were obtained from multinational surveillance programmes (i.e. RSS, ANSORP, and SENTRY), in which only limited numbers of hospitals and *S. aureus* strains were obtained from each participating country [7,29,31,44]. Nevertheless, the surveillance data suggested that MRSA was not uncommon in this region, and accounted for a substantial proportion of nosocomial infections. For instance, the ANSORP study showed MRSA rates of 38.1% for the Philippines, 57% for Thailand and 74.1% for Vietnam in 2004–2006 [44]. The data from the most recent multinational study of the RSS programme in 2011 revealed that the proportion of MRSA among clinical *S. aureus* isolates ranged from 28% in Indonesia to 59% in the Philippines [31]. A multicentre study sampling six hospitals in Singapore further showed average MRSA rates of 35.3% among all clinical *S. aureus* isolates and 46.7% among *S. aureus* isolates from patients in intensive-care units [45].

South Asia

The proportion of MRSA among *S. aureus* clinical isolates was strikingly high in South Asia, and a rate of 80.8% was reported in an Indian hospital in 1999. The 2004–2006 ANSOPR study showed a rate of 86.5% among nosocomial *S. aureus* isolates in Sri Lanka [44,46]. However, the MRSA rate appeared to vary significantly between distinct hospitals and different time periods. Two multicentre studies in India showed MRSA rates of 41% and 45%, respectively, in 2008–2009 and 2011 [31,47]. Another multicentre study of four hospitals in Pakistan showed a similar rate, of 41.9%, in 2006–2008 [48].

Molecular epidemiology of HA-MRSA in Asia

Taiwan. The majority of nosocomial MRSA isolates in the 1990s in Taiwan belonged to strains of sequence type (ST) 254 with SCC*mec* IV and clonal complex (CC) 239 (mainly ST239 or ST241) with SCC*mec* III [25]. The ST254-SCC*mec* IV strains prevailing in the early 1990s did not possess Panton–Valentine leukocidin (PVL) genes, and gradually lost their predominance to CC239 in the late 1990s. In 2000, 73% of 597 clinical MRSA isolates collected from six major hospitals in Taiwan belonged to CC239 [49]. It was estimated that 95% of MRSA strains from another institute in northern Taiwan also belonged to ST239 or ST241 with SCC*mec* III or SCC*mec* IIIA [50]. The CC239 clone predominated among nosocomial MRSA strains, and had island-wide dissemination in the late 1990s and early 2000s. However, with time, we found a continuous change in the molecular epidemiology, and another pandemic clone, ST5-SCC*mec* II, and the dominant Asian CA-MRSA clone, ST59, emerged as significant causes of nosocomial BSIs attributable to MRSA [51]. A recent study characterizing MRSA bloodstream isolates from six major hospitals collected in 2010 further indicated the waning dominance of CC239, the increasing rates of ST5 and ST59, and the emergence of few minor genotypes (CJ Chen, unpublished data) (Fig. 1).

Korea. ST5 and ST239 have been the two predominant MRSA clones in Korean hospitals since 1996 [52–55]. The majority of the ST5 strains carried SCC*mec* II elements, whereas most of the ST239 strains carried SCC*mec* III or SCC*mec* IIIA [52–54]. The ST5-SCC*mec* II clone was among the pandemic MRSA clones, known as New York/Japan clones, that were widely distributed in North America and Europe [56]. This clone prevailed in Korean and Japanese hospitals in the 1990s, and gradually spread to other Asian countries, including Taiwan,

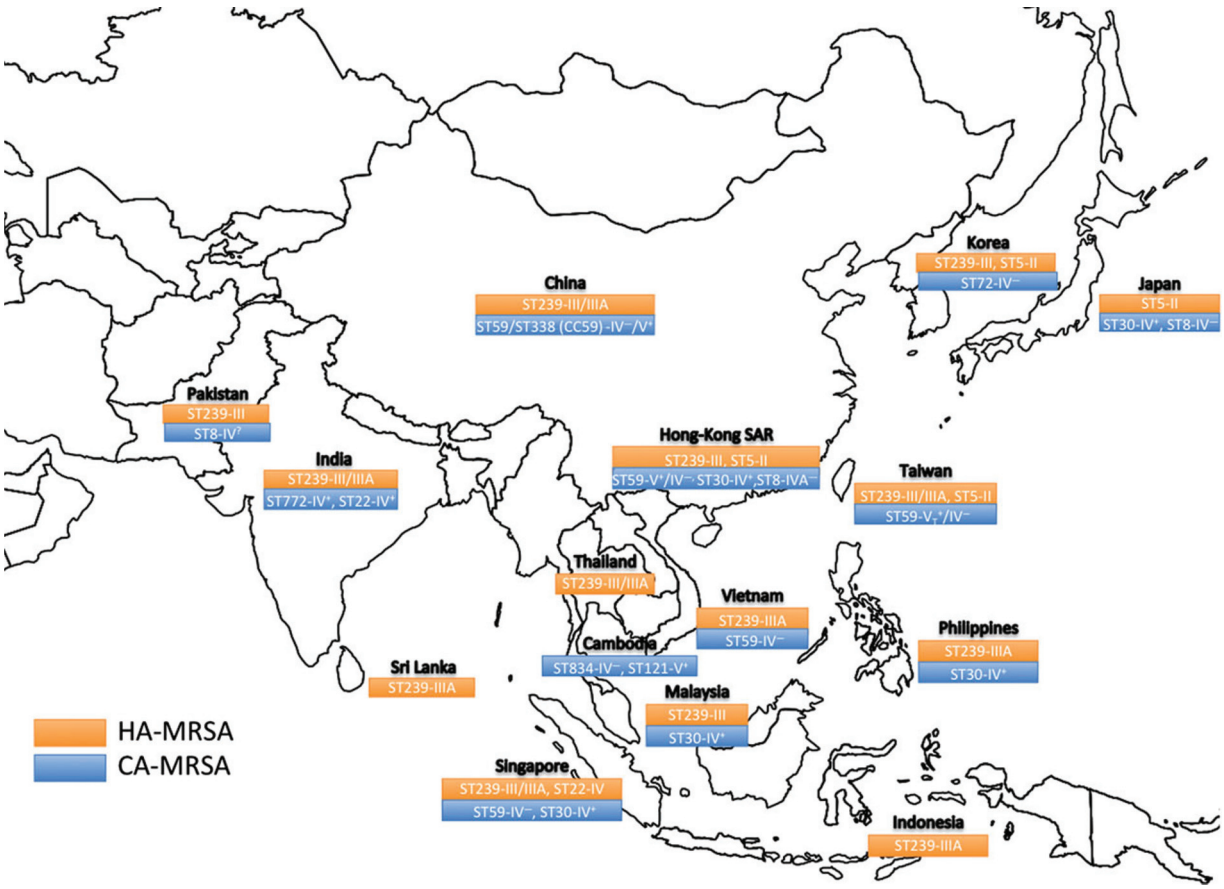

FIG. 1. Current clonal distributions of dominant healthcare-associated methicillin-resistant *Staphylococcus aureus* (HA-MRSA) and community-associated methicillin-resistant *Staphylococcus aureus* (CA-MRSA) strains in East, Southeast and South Asia. The prevalent clone(s) are indicated as multilocus sequence types (STs) followed by the SCC*mec* type. For CA-MRSA strains, the superscript '+' indicates the presence of Panton–Valentine leukocidin (PVL) genes. The superscript '−' indicates the absence of PVL genes.

Hong Kong SAR, and China, in the 2000s [51,57–59]. The ST239 MRSA strains had extremely high rates of resistance (>95%) to trimethoprim–sulphamethoxazole, ciprofloxacin, tobramycin, gentamicin, erythromycin, and tetracycline. The ST5 strains had lower frequencies of drug resistance, and were susceptible to trimethoprim–sulphamethoxazole [54,60]. With the increasing incidence of CA-MRSA strains, the strains of the dominant community genotype, ST72-SCC*mec* IV/IVA, also emerged as a significant cause of HA-MRSA infections in Korean hospitals [55,61].

Japan. A molecular epidemiology study covering 1979–1999 demonstrated that the majority of MRSA strains before 1985 in Japan were ST30, possessed SCC*mec* IV or SCC*mec* I, produced type 4 coagulase, and carried PVL genes at a high frequency [57]. A substantial proportion of the isolates were from outpatients, suggesting that the PVL-positive ST30-SCC*mec* IV strains might have spread in both the community and in hospitals in Japan before 1985. The predominance of ST30 strains waned in the 1990s, and ST5-SCC*mec* II became the most dominant MRSA clone, accounting for >95% of clinical MRSA strains in Japanese hospitals [57]. Most of the MRSA strains isolated after 1990 were highly resistant to tetracycline, levofloxacin, and imipenem, to which the majority of MRSA strains before 1985 were susceptible [57].

Hong Kong SAR and China. The MRSA isolates collected in 1988–2000 in the Prince of Wales Hospital in Hong Kong were clustered into two major phage types and five pulsotypes. The strains of two dominant pulsotypes (types A and B) belonged to the ST239-SCC*mec* III lineage [62,63]. Another multicentre study showed that a major clone (ST239-SCC*mec* III, 50%) and two minor clones (ST5-SCC*mec* II, 18%; ST45, 13%) predominated among MRSA bloodstream isolates from four hospitals in Hong Kong during 2000–2001 [58]. ST239-SCC*mec* III/IIIA

has also been the most dominant nosocomial MRSA clone in China since the late 1990s [50,64]. A nationwide study, including 18 hospitals in 14 cities in 2005–2006, showed that 77.1% of the MRSA clinical isolates belonged to the ST239-SCC*mec* III lineage, and that 15.5% belonged to the ST5-SCC*mec* II lineage [59]. Most of the ST239 strains were resistant to tetracycline, erythromycin, clindamycin, gentamicin, tobramycin, and ciprofloxacin [58,59]. ST5 strains were also multiresistant to the above antibiotics, except for clindamycin. Most of the ST45 strains in Hong Kong were susceptible to multiple non-β-lactams (except for clindamycin) and carried SCC*mec* IV, and they were considered to constitute the major CA-MRSA clone in Hong Kong. ST45 strains were also increasingly identified among MRSA bloodstream isolates during 1995–2005 in a multicentre study in Hong Kong [65].

Southeast Asia. Molecular typing of MRSA strains collected during 1998–2003 from Indonesia, the Philippines, Singapore, Thailand and Vietnam indicated that the majority of the strains belonged to the ST239 or ST241 lineage with SCC*mec* III/IIIA [64]. ST239-SCC*mec* III was also the dominant clone among MRSA clinical isolates in Singapore during 2006–2010. Similarly to the situation in East Asia, the molecular epidemiology was changing, and the ST239 clone among HA-MRSA was also gradually replaced by the strains of community genotypes, namely ST22-SCC*mec* IV and ST45-SCC*mec* IV [66].

South Asia. ST239-SCC*mec* III was the dominant genotype among hospital-onset MRSA isolates in Pakistan in 2006–2007. The molecular features of HA-MRSA strains were not comprehensively evaluated in India. A single-institute study, including 50 MRSA isolates causing skin and soft tissue infections (SSTIs) in southern India in 2011, showed that ST239-SCC*mec* III strains accounted for 32% of all isolates, and were multiresistant to mupirocin, amikacin, co-trimoxazole, erythromycin, rifampin and tetracycline with high frequencies.

VISA, heterogeneous VISA (hVISA) and VRSA in Asia

VISA

S. aureus strains with reduced susceptibility to vancomycin were first identified in 1996, when a strain (Mu 50) with a vancomycin MIC of 8 mg/L was isolated from the surgical wound of an infant in Japan [67]. Given the high incidence of MRSA and the common use of glycopeptides in this region, the emergence of vancomycin-non-susceptible strains was not surprising. Fortunately, it appeared that the VISA strains (vancomycin MIC of 4–8 mg/L according to CLSI criteria after 2006) had not disseminated widely in Asian countries, but were identified only sporadically from patients who had previously been exposed to glycopeptides or were on long-term glycopeptide therapy for persistent staphylococcal infections [68–71]. In 2003, a nationwide study screening 1000 clinical MRSA isolates from ten hospitals in Taiwan showed only two VISA isolates (0.2%) [72]. A multinational study screening 1357 clinical MRSA isolates from 12 Asian countries in 2004 identified no VISA strain [73]. Molecular typing of the reported VISA strains indicated that the strains belonged to distinct clones that had been endemic in hospitals or communities [68,74,75]. The data supported the limited spread of VISA internationally. Nevertheless, dissemination of the VISA strains in a single institute might have occurred, and should not be overlooked. A report from Taiwan characterizing 43 VISA strains in a medical centre demonstrated that all of the isolates shared the same *agr* and SCC*mec* types, and had at least 80% similarity of band patterns in pulsotyping, suggesting clonal spread of the VISA strains in this hospital [71]. Although transmission between facilities or countries was seldom documented, strict control measure should be applied to affected patients to prevent further dissemination of the VISA strains.

hVISA

hVISA strains are susceptible to vancomycin when tested with routine methods (≤2 mg/L) but contain subpopulations with MICs in the vancomycin-intermediate range (4–8 mg/L). The hVISA phenotype has been considered to be an essential step during the conversion of vancomycin-susceptible *S. aureus* and VISA phenotypes, and is associated with poor clinical outcome in patients with invasive staphylococcal infections. A national surveillance study in Japan in 1996–1997 demonstrated that 9.3% and 1.3% of clinical MRSA isolates, respectively, from university hospitals and non-university hospitals/clinics showed heterogeneous resistance to vancomycin (hVISA phenotype) [76]. However, with the same screening method, another nationwide study in Japan failed to identify any hVISA strain after screening 6625 clinical MRSA isolates [77]. The reason for this discrepancy remains unknown. Following the reports in Japan, hVISA and VISA strains were identified in several Asian countries/regions, including Korea, Thailand, Taiwan, Singapore, China, India, and Hong Kong [11,52,68,69,74,78–83]. Because there is no standard method for screening for hVISA, the reported incidence of hVISA strains may not be directly comparable between different regions. A multinational study that screened 1357 MRSA isolates from 12 Asian countries in 1997–2000, using brain–heart infusion agar plates

containing 4 mg of vancomycin per litre, showed that hVISA accounted for 4.3% of the MRSA isolates, ranging from 2.1% in Thailand to 8.2% in Japan. hVISA strains were also found among isolates from the Philippines and Vietnam in this study.

VRSA

Isolates with high-level resistance to vancomycin (VRSA strains; vancomycin MIC of ≥16 mg/L as defined by the CLSI) have remained very rare in upper-middle income and high--income countries in Asia. However, the condition is worrying in resource-limited countries, especially in South Asia, from which most VRSA strains were reported [10,11]. During 2002 and 2005, four isolates with vancomycin MICs of 16–64 mg/L were identified in northern India by screening 783 clinical *S. aureus* isolates with the agar dilution method [11]. None of the VRSA isolates carried *vanA* or *vanB*. Another clinical VRSA isolate (vancomycin MIC of 64 mg/L), identified in Kolkata in 2005, harboured *vanA* [10]. The *vanA* gene integrated into a plasmid has been shown to originate from vancomycin-resistant *Enterococcus faecalis* strains, and is associated with high-level vancomycin resistance in VRSA strains [84–87]. As most of the reported VISA and VRSA isolates were clinical isolates, it was noteworthy that two nasal VISA isolates (vancomycin MIC of 8 mg/L) carrying *vanA* were identified during a routine nasal carriage survey of VISA/VRSA strains in an intensive-care unit in northern India [9]. Asymptomatic colonization by *vanA*-positive *S. aureus* raised concerns about the spread of VRSA strains in local hospitals and to neighbouring countries. Given the high incidence of MRSA, uncontrolled access to antibiotics, and the emergence of strains with high-level resistance to vancomycin, an active surveillance system to closely monitor the real-time condition of *S. aureus* in this region is needed.

CA-MRSA in Asia

CA-MRSA has become widespread in many developed countries during the past decade [88,89]. CA-MRSA infection is defined as any MRSA infection diagnosed in an outpatient or within 48 h of hospitalization if the patient lacks the following HA-MRSA risk factors: haemodialysis, surgery, residence in a long-term-care facility or hospitalization during the previous year, the presence of an indwelling catheter or percutaneous device at the time of culture, or previous isolation of MRSA from the patient [90]. However, various MRSA clones have spread between the community and hospitals, particularly CA-MRSA transmitted in hospital settings, making the distinction between CA-MRSA and HA-MRSA difficult [44,91].

In addition to epidemiological features, CA-MRSA strains differ from HA-MRSA strains in their molecular characteristics [88,89]. CA-MRSA isolates usually carry SCC*mec* IV or SCC*mec* V, lack multiple antibiotic resistance, except to β-lactams, and frequently have different exotoxin gene profiles, e.g. PVL genes [88,89,92,93]. The major clinical manifestations are SSTIs, but severe life-threatening infections such as necrotizing fasciitis, necrotizing pneumonia and severe sepsis have been reported [88,89,94,95].

There have been no or few reports describing the epidemiology, particularly molecular epidemiology, of CA-MRSA in most Asian developing countries [6,44]. According to the published reports, the incidence of CA-MRSA in Asia varies markedly among countries. However, different study designs make comparisons among countries difficult, or even impossible. In a recent ANSORP study conducted in 17 hospitals in eight countries, namely Korea (seven hospitals), Taiwan (three), Hong Kong (one), Thailand (two), the Philippines (one), Vietnam (one), India (one), and Sri Lanka (one) [44], the rate of MRSA among community-associated *S. aureus* infections ranged from 2.5% to 39%, and the rates were >30% for the Philippines (28/93), Vietnam (197/654), Taiwan (94/270), and Sri Lanka (19/49), and <10% for India (2/46), Hong Kong (7/82), and Thailand (3/122). Except for Korea, Taiwan, and Hong Kong, this study is the only report of local epidemiological data regarding CA-MRSA available for the five developing countries.

The selective reports regarding the epidemiology of CA-MRSA clinical isolates and the nasal carriage rate of MRSA among populations from Asian countries are summarized in Tables 2 and 3, respectively.

East Asia: Taiwan, China, Japan, and Korea

. After it was first reported in 2002, the rate of MRSA among childhood community-associated *S. aureus* infections increased significantly from 9.8% (17/173) in 1999–2000 to 56% (102/183) in 2004–2005 in Taiwan [96,97]. CA-MRSA infections were relatively uncommonly reported in adults in Taiwan. In a hospital-based retrospective/prospective study conducted from 2001 to 2006, the rate of methicillin resistance among community-associated *S. aureus* BSIs in adults was 14% (30/215) [98]. The nasal MRSA carriage rate among children presenting for well-child healthcare visits and/or schoolchildren also increased significantly in Taiwan, from 1.9% (5/262) in 2001 to 7.8% (473/6057) in 2005–2008 [99,100]. In contrast, only 3.8% of 3098 adults presenting for health examination in 2007 had nasal MRSA colonization [101]. Carriage in healthy children and adults may accelerate the spread of MRSA in the community in Taiwan [96].

In China, Zhang *et al.* [102] analysed 4254 *S. aureus* strains collected from the five largest paediatric hospitals during

TABLE 2. Selected epidemiological reports on community-associated methicillin-resistant *Staphylococcus aureus* (CA-MRSA) infections in Asian countries

Authors (publication year)	Study period	Location, setting	Selection criteria	No. of cases	CA-MRSA, no. (%)	Remarks
Multinational studies						
Song *et al.* (2011) [44]	2004–2006	South Korea	Epidemiological definition, CA *S. aureus* infection, all ages	147	23 (15.6)	
		Taiwan		270	94 (34.8)	
		Hong Kong		82	7 (8.5)	
		Philippines		93	28 (30.1)	
		Thailand		122	3 (2.5)	
		Vietnam		654	197 (30.1)	
		India		46	2 (4.3)	
		Sri Lanka		49	19 (38.8)	
Regional studies						
Northeast Asia						
Zhang *et al.* (2009) [102]	2005–2006	China, five largest paediatric hospitals	Laboratory-based, 4254 *S. aureus* clinical isolates	73 MRSA	38	
Geng *et al.* (2010) [205]	2007–2008	China, five children's hospitals	<16 years with SSTIs, epidemiological criteria		47 cases	ST59-IV-t437 most prevalent (47%)
Wu *et al.* (2010) [103]	2008–2009	China, Beijing Children's Hospital, surgery OPD	0–14 years with SSTIs caused by CA *S. aureus*	351	14 (4.0)	
Kikuta *et al.* (2011) [206]	2009–2010	Hokkaido Japan, paediatric outpatients	Paediatric outpatient with impetigo caused by *S. aureus*	136	14 (10)	PVL-negative CC89-SCC*mec* II was the predominant strain among children with impetigo
Kawaguchiya *et al.* (2011) [207]	2009	Hokkaido Japan, outpatients	1015 *S. aureus* clinical isolates from outpatients, SCC*mec* IV or SSC*mec* V as CA-MRSA	189 (18.6) MRSA	19 (10)	
Mine *et al.* (2013) [107]	2008–2010	Okinawa, Japan, hospital	Outpatients with SSTIs caused by *S. aureus*	274	99 (36)	Twelve CA-MRSA isolates PVL-positive
Yanagihara *et al.* (2012) [106]	2008–2009	Japan, 16 medical centres	MRSA clinical isolates, SCC*mec* IV as CA-MRSA	857	171 (20)	Four CA-MRSA isolates PVL-positive; the number of SCC*mec* IV isolates was significantly higher in outpatients than in inpatients
Kim *et al.* (2007) [111]	2005	South Korea, four community-based and three tertiary hospitals	Laboratory-based survey, 3251 *S. aureus* isolates	1900 MRSA	112 (5.9)	ST72-IVa (35%)
Park *et al.* (2007) [208]	2004–2005	Four regions of South Korea, a tertiary-care hospital and five community hospitals	Invasive infections, SCC*mec* IV as CA-MRSA	138	81 (53)	ST72-IVa (39.5%), CC1-IVa (26%)
Bae *et al.* (2010) [209]	2004–2006	Gyeoongsang province, South Korea, tertiary-care hospital	MRSA clinical isolates	3389	33 (1.0)	ST72-IVa-t664 and ST72-IVa-t324 (81%)
Wu *et al.* (2002) [210]	1999–2000	Central Taiwan, tertiary-care hospital	Children aged <15 years, CA *S. aureus* infection	173	17 (9.8)	SSTIs (76), SSTI with rash (12)
Wang *et al.* (2008) [98]	2001–2006	Northern Taiwan, tertiary-care hospital	Adults aged >16 years, CA *S. aureus* bacteraemia	215	30 (14)	
Huang *et al.* (2008) [97]	2004–2005	Northern Taiwan, tertiary-care hospital	Children aged <18 years, CA *S. aureus* infection	183	102 (56)	SSTI (86%) ST59/SCC*mec* V_T/PVL-positive (69%) ST59/SCC*mec* IV/PVL-negative (9%)
Southeast Asia						
Chheng *et al.* (2009) [211]	2006–2007	Cambodia, Angkor Hospital for Children	Laboratory-based surveillance, children aged <15 years, identified by epidemiological criteria		17	SSTI (65%), invasive disease (35%) ST834-IV (88%) ST121-V (12%)
Ahmad *et al.* (2009) [126]	2006–2008	Malaysia, nine hospitals	Laboratory-based, MRSA clinical isolates, molecular criteria (SCC*mec* IV)	628	20 (3.2)	Nine (1.4%) isolates fulfilled epidemiological criteria of CA-MRSA ST30/PVL-positive (8/9) ST80/PVL-negative (1/9)
Lim *et al.* (2013) [127]	2008	Kuala Lumpur, Malaysia, tertiary-care hospital	Laboratory-based, MRSA clinical isolates, molecular criteria (SCC*mec* IV)	110	15 (13.6)	ST22-SCC*mec* IV most common
Rashid *et al.* (2013) [212]	2009	Kuala Lumpur, Malaysia, tertiary-care hospital	Laboratory-based, pauci-resistant MRSA		5	
Hsu *et al.* (2006) [148]	2004–2005	Singapore, public hospitals	MRSA with reduced antibiotic resistance	37	36	SSTI (81%) ST30-IVc (70%)
Ho *et al.* (2007) [120]	2004–2005	Hong Kong, five public and six private hospital laboratories, six stand-alone community laboratories	Laboratory-based surveillance, clinical isolates, epidemiological criteria		25 cases	SSTIs (96%) ST30-SCC*mec* IV (62%) ST59-SCC*mec* V (17%) ST8-SCC*mec* IVA (17%)

Table 2 (*Continued*)

Authors (publication year)	Study period	Location, setting	Selection criteria	No. of cases	CA-MRSA, no. (%)	Remarks
Ho *et al.* (2008) [119]	2006–2007	Hong Kong, six regional hospitals	Purulent SSTI caused by *S. aureus* after visiting emergency department <7 days	126	13 (10.4)	CA-MRSA infection or carriage was found in six (13%) of 46 household contacts Filipino ethnicity was a significant factor associated with CA-MRSA infection
South Asia						
Nagaraju *et al.* (2004) [135]	2000–2001	India, outreach camp	Community-acquired pyoderma caused by *S. aureus*	202	22 (10.9)	
D'Souza *et al.* (2010) [136]	2006–2009	India, tertiary hospital	Laboratory-based, MRSA clinical isolates, molecular criteria (SCC*mec* IV or SCC*mec* V)	395	298 (75)	214 (54%) isolates fulfilled epidemiological criteria of CA-MRSA ST22-IV (69%) ST772-V (31%)
Kini *et al.* (2013) [213]	2004–2008	India, tertiary hospital	Children aged <18 years, community-onset *S. aureus* bone and joint infection	74	41 (55)	
Alvarez-Uria (2012) [138]	2011–2012	Rural area of Andhra Pradesh, India, private district hospital	Patients with CA *S. aureus* infection, all ages	119	77 (65)	Mostly SSTIs
Phakade *et al.* (2012) [137]	2007–2008	Mumbai, India, tertiary hospital	Patients with *S. aureus* SSTIs, all ages	452	0	

CA, community-associated; CC, clonal complex; MRSA, methicillin-resistant *Staphylococcus aureus*; OPD, outpatient department; PVL, Panton–Valentine leukocidin; ST, sequence type; SSTI, skin and soft tissue infections.

2005–2006, and found that 73 (1.7%) isolates were MRSA and 38 (0.9%) were CA-MRSA. At Beijing Children's Hospital, in 1104 children with SSTIs during 2008–2009, 14 (4%) of 351 community-associated *S. aureus* infections were caused by MRSA [103]. The rate of nasal MRSA carriage among healthy persons from a Chinese medical college campus was 3%, but the nasal MRSA isolates showed considerable molecular heterogeneity [104]. In a recent countrywide study, 6.6% of 1141 HA-MRSA isolates collected from 69 hospitals during a 6-month period in 2011 had typical CA-MRSA features, suggesting penetration of CA-MRSA into the hospitals [105].

In Japan, *c.* 17–20% of *S. aureus* isolates from bullous impetigo obtained during the early 2000s were CA-MRSA. In a recent nationwide survey conducted in 2008–2009, although 94% of 857 clinical isolates were categorized as HA-MRSA, the proportion of SCC*mec* IV was 20.0% [106]. In a recent study in Okinawa, conducted in 2008–2010, in 36% of 274 outpatients with SSTIs caused by *S. aureus*, the strains were MRSA, and 12 of 17 PVL-positive strains were MRSA. Nine MRSA isolates were ST8/SCC*mec* IV, identical to USA300 [107]. The nasal MRSA colonization rate ranged from 0.7% for 426 paediatric outpatients, to 3.7% for 136 healthy children, to 4.3% of 818 children attending day-care centres/kindergartens in Japan [108]. Specifically, in Tokyo and Niigata, of the 349 trains sampled, 2.3% were positive for MRSA. Public transport could have contributed to the spread of CA-MRSA [109].

In Korea, the emergence of CA-MRSA infections was initially reported in Kyungnam Province in 2004–2005, and ST72 accounted for 11 of 23 CA-MRSA isolates [110]. In 2005, a hospital laboratory-based survey was conducted in seven major hospitals. CA-MRSA accounted for 5.9% of 1900 MRSA isolates [111]. The nasal MRSA carriage rate in children increased from 6.1% (18/296 outpatients) in 2005–2006 to 9.3% (40/428 healthy children attending day-care centres) in 2008 [112,113]. In addition, several studies showed that the community strain ST72-SCC*mec* IV/PVL-negative accounted for a substantial proportion of healthcare-associated infections in the hospitals [61,114,115], suggesting that CA-MRSA strains are emerging as major causes of healthcare-associated infections in Korea [116,117].

Southeast Asia

Since it was first reported in 2004, the incidence of CA-MRSA has been rapidly increasing in the Hong Kong community [118]. During a 4-month period from November 2006 to February 2007, in 42% of 298 patients with purulent SSTIs at the emergency departments in six regional hospitals, the infections were caused by *S. aureus*, and 10.4% of the 126 *S. aureus* isolates were PVL-positive CA-MRSA [119]. CA-MRSA infection or carriage was found in six (13%) of 46

TABLE 3. Reported prevalence rate and molecular characteristics of nasal methicillin-resistant *Staphylococcus aureus* (MRSA) carriage among population in Asian countries

Authors (publication year)	Study period	Country	Setting	Age	No. of subjects	No. (%) of *S. aureus*	No. (%) of MRSA	Remarks
Northeast Asia								
Du *et al.* (2011) [104]	?	China	Medical college campus	Healthy adult volunteers	935	144 (15.4)	28 (3)	ST59 (14.3%) ST338 (3.6%) Molecular heterogeneity
Hisata *et al.* (2005) [214]	2001–2002	Japan	Day-care centres/kindergartens	Healthy children	818	231 (28)	35 (4.3)	CC5/SCC*mec* IIA (25%) CC78 or CC91/IIb or IV (75%) CC5/IIa strains were indistinguishable from HA-MRSA strains in Japan
Ozaki *et al.* (2009) [108]	?	Japan	Paediatric OPD/community	Healthy children aged <18 years	426/136	–	3 (0.7)/5 (3.7)	
Ko *et al.* (2008) [112]	2005–2006	South Korea	Outpatients	1–11 years	296	95 (32)	18 (6)	ST72-IVA/PVL-negative (50%)
Lee *et al.* (2011) [113]	2008	Seoul, Korea	Healthy children attending day-care centres	12 months to 6.8 years	428	164 (38)	40 (9.3)	ST72-IV-(57.5%) ST72-II-(15%) ST1765-IV (10%) ST1765-II (5%)
Wang *et al.* (2009) [101]	2007	Northern Taiwan	Adults from health examinations at three medical centres	>18 years	3098	686 (22)	119 (3.8)	ST59-IV (55%) ST59-V (29%) Risk for MRSA colonization—household members aged <7 years, use of antibiotic within the past year
Lo *et al.* (2010) [215]	2004–2009	Taipei, Taiwan, tertiary hospital	Children from healthcare visits and in day-care centres	<14 years	3200	824 (26)	371 (11.6)	ST59 (86%) ST338, single-locus variant of ST59, (4.3%) Prevalence of MRSA colonization increased from 8% to 15% from 2004 to 2009
Chen *et al.* (2011) [100]	2005–2008	Taiwan, three tertiary hospitals	Children from healthcare visits	2–60 months	6057	1404 (23)	473 (7.8)	ST59-IV/PVL-negative (59.2%) ST59-V_T/PVL-positive (23%) MRSA colonization was associated with number of children in the family, and day-care centre attendance
Southeast Asia								
Nickerson *et al.* (2011) [133]	2008	Cambodia, hospital	Outpatients/inpatients	9 months to 8 years	2485/145	–	87 (3.5)/6 (4.1)	ST834 (91%) ST121 (3%) 32%, no history of recent healthcare contact
Ho *et al.* (2012) [121]	2009–2010	Hong Kong	Children attending 79 day-care centres and 113 kindergartens	2–5 years	2211	610 (27.6)	28 (1.3)	
Severin *et al.* (2008) [124]	2001–2002	Semarang/Surabaya, Indonesia	Healthy individuals	Children/adults	3995	329 (8.2)	1 (0.03)	
Choi *et al.* (2006) [128]	?	Malaysia	University	Adults	346	81 (23.4)	1 (0.3)	
Syafinaz *et al.* (2012) [216]	2011	Malaysia	Medical students	Adults	209	21 (10)	0	
Treesirichod *et al.* (2013) [131]	?	Thailand	Medical students	Adults	128	38 (30)	0	
Kitti *et al.* (2011) [130]	2009–2010	Thailand	University students	Adults	200	30 (15)	2 (1)	
Central Asia								
Pathak *et al.* (2010) [139]	2007–2009	Ujjain, India	Two hospitals, healthy preschool children (outpatients)	1 month to 5 years	1562	98 (6.3)	16 (1.0)	
Chatterjee *et al.* (2009) [141]	2005	India	Community medicine department, healthy children	5–15 years	489	256 (52.3) By PCR	19 (3.9)	The rate of CA-MRSA nasal carriage was 3.16% in children without prior exposure to healthcare settings
Chande *et al.* (2009) [142]	?	India	Nagpur urban community	6–10 years	1300	96 (7.38)	4 (0.31)	
Dey *et al.* (2013) [143]	2008–2010	Ujjain city, India	Children attending 100 anganwaries	Preschool children aged 1–6 years	1002	351 (35)	102 (10)	
Nadig *et al.* (2010) [217]	2006–2007/ 2007–2008	Saragur/Bengaluru, India	Rural tribe/outpatients visiting Victoria hospital	All ages	1500/400	Rural tribe 45 (3)	12 (0.8)/52 (13)	
Fomda *et al.* (2014) [218]	?	India	10% of general population in two villages in two districts	All ages	820	229 (28)	15 (1.8)	Tremendously high level of genetic diversity among CA-MRSA strains

CC, clonal complex; HA-MRSA, healthcare-associated methicillin-resistant *Staphylococcus aureus*; OPD, outpatient department; PVL, Panton–Valentine leukocidin; ST, sequence type.

household contacts [120]. In a study conducted in 2009–2010, Ho *et al.* [121] found that the nasal/nasopharyngeal MRSA carriage rate was 1.3% for 2211 children aged 2–5 years attending 79 day-care centres and 113 kindergartens in Hong Kong.

In Singapore, sporadic CA-MRSA isolates were found from the microbiology archives of the Singapore General Hospital from January 2001 to April 2004, yielding eight possible CA-MRSA cases, which were completely unrelated to each other genetically and epidemiologically [122]. Since then, however, non-systematic data collection has revealed that the number of infections has increased progressively [123], with the emergence of a predominant ST30-IVc clone, suggesting local transmission.

S. aureus reservoirs were defined in the community and hospitals from 329 nasal carriage isolates obtained from 3995 healthy individuals in Java, Indonesia. Only one isolate (0.3%) was identified as MRSA [124].

In Malaysia, a retrospective study conducted in 2002–2005 and a prospective study conducted in 2006–2007 identified multidrug-susceptible MRSA in 13 patients: two (0.5%) in 2003, two (0.6%) in 2006, and nine (3.1%) in 2007. These isolates carried SCC*mec* IV, and predominantly caused SSTIs. There was considerable clonal diversity [125]. During 2006–2008, 20 (3.2%) of 628 MRSA isolates collected from nine hospitals in Malaysia carried SCC*mec* IV. Eleven STs were found. Nine of 20 isolates were CA-MRSA, and eight were ST30/PVL-positive, and not multiresistant [126]. Among 110 MRSA isolates collected from a tertiary-care hospital in 2008, 13.6% carried SCC*mec* IV, and most belonged to ST22, a clone endemic in India [127]. In a nasal carriage survey, one of 346 healthy adults carried an MRSA strain, which was different from the hospital strain [128].

In Thailand, at Siriraj Hospital in 2005, 186 (41.5%) of 669 *S. aureus* isolates from 448 patients were MRSA. Three isolates (0.9% of total MRSA) from two patients (1.1% of MRSA-infected patients) were CA-MRSA. The prevalence of CA-MRSA infections in hospitalized patients was low [129]. The rate of MRSA nasal carriage was 1% (two of 200) among healthy young Thai adults. Both carriers had healthcare risk factors, and both MRSA isolates carried SCC*mec* II but were multidrug-susceptible [130]. However, none of 128 medical students had nasal MRSA carriage in a later study [131].

In Cambodia, CA-MRSA from three different north-western Cambodian provinces was identified in 2006–2007 at Angkor Hospital for children [132]. Paediatric MRSA carriage was found in 87 (3.5%) of 2485 children from the outpatient department and in six (4%) of 145 inpatients. Five genotypes were identified, with ST834 being the most common (91%) [133].

In Vietnam, an outbreak of MRSA infection associated with vaccination was reported in 2007. A genetically indistinguishable MRSA strain was isolated from injection site abscesses from four children, and from nasal and throat swabs from their vaccinator. All isolates carried PVL genes and SCC*mec* V, and belonged to ST59, the endemic CA-MRSA clone in Taiwan [134].

South Asia

In India, during 2000–2001, MRSA was responsible for 22 (10.9%) of 202 cases of community-associated pyoderma caused by *S. aureus* [135]. Between 2006 and 2009, 412 MRSA isolates from Mumbai were evaluated, and it was found that 34% of the isolates carried SCC*mec* IV and 41% carried SCC*mec* V. Of the patients with SCC*mec* IV and SCC*mec* V isolates, 72% had no risk factors for MRSA acquisition, demonstrating the emergence of CA-MRSA in Mumbai. ST22-SCC*mec* IV and ST772-SCC*mec* V were identified [136]. However, the proportion of MRSA among community-onset *S. aureus* SSTIs varied markedly between different cities, from 0% (0/452) in Mumbai [137] to 65% (77/119) in Andhra Pradesh [138]. The nasal MRSA carriage rate was 1.02% among healthy children aged 1 month to 5 years visiting the outpatient clinics of two hospitals in Ujjain, India [139], the rate for schoolchildren ranged from 0.31% (4/1300) to 3.9% (19/489) during the 2000s [140–142], and the rate reached 10% for 1002 preschool children aged 1–6 years in 100 anganwaries (preschools) in 2008–2010, indicating that MRSA is prevalent in the paediatric population in the community in India [143].

Major CA-MRSA clones in Asia

The distribution of dominant CA-MRSA clones in Asian countries and areas is shown in Fig. 1. PVL-positive ST30-SCC*mec* IV strains, known as the Southwest Pacific clone [144], appear to be highly adaptable and transmissible. ST30 MRSA was the most prevalent type in Singapore, involving individuals of different ethnic groups [123]; it was also prevalent in Hong Kong [119] and in The Philippines [44], and was recently reported in Korea [145]. In Japan, PVL-positive ST30 MRSA persisted for >30 years (since the 1980s), but it was not the same clone throughout, and after 2002 the prevalent *spa*19 clone was CA-MRSA [146]. ST30 MRSA has also been found in the USA and Europe, and can now be considered to be worldwide clone [147,148] (Fig. 1).

In addition to Taiwan, ST59 MRSA was shown to be prevalent in Hong Kong, and China, and was also identified in Vietnam, Japan, and Australia [103,118,134,149,150]. In the USA, ST59/SCC*mec* IV CA-MRSA was prevalent in selected populations, including human immunodeficiency virus carriers,

intravenous drug users and homeless persons in San Francisco [151]. However, ST59 prevailing in these countries is not a single clone, but a CC, including a single-locus variant (ST338). For the strains of ST59, at least two different SCC*mec* types (IV and V), two different pulsed-field gel electrophoresis (PFGE) patterns, the presence or absence of PVL genes and different antibiograms have been found. The Taiwan CA-MRSA clone, ST59/SCC*mec* V_T/PVL-positive, was distinguished from the Asia-Pacific clone, ST59/SCC*mec* IV/PVL-negative, by enhanced virulence in both humans and an animal infection model. The evolutionary acquisition of PVL, the higher expression of α-toxin and, possibly, the loss of a large portion of the β-haemolysin-converting prophage probably contribute to its higher pathogenic potential [152].

The major CA-MRSA clone in South Korea, ST72-SCC*mec* IVa/PVL-negative, is different from those that have spread in Asia or internationally. These isolates were also less multidrug-resistant [110]. The entire genome sequence of ST72 CA-MRSA was reported recently, and analysed with a focus on virulence factors; this showed that this strain does not have considerable differences in virulence factor content from other CA-MRSA strains (USA300 and USA400) [75]. ST22 and ST772 were the epidemic clones associated with both community-associated and healthcare-associated infections in India, and seemed to progressively replace the ST239 clone in hospitals [136]. ST772 MRSA was also reported in Bangladesh [153] and Malaysia [154], and was recently exported to Ireland [155]. ST22-SCC*mec* IV MRSA strains (CC22) corresponded with the epidemic UK EMRSA-15 strain [155,156], and were also reported in Japan [157] and Malaysia [127]. The success of ST22 CA-MRSA as both a colonizer and a pathogen could result from the combination of its strong biofilm formation and other virulence factors [157].

All of these Asian CA-MRSA clones were recently identified in several European countries, such as Denmark, Ireland, the UK, and Norway [158], through travel or immigration of Asian workers. In contrast, USA300 CA-MRSA-infected cases have been reported from Japan [159,160], South Korea [161,162], Taiwan (unpublished), and Singapore [163], and have even resulted in outbreaks, implying that this clone has penetrated into Asian countries. Further surveillance studies should be conducted to determine whether this clone has spread to other Asian countries.

The true incidence of CA-MRSA is difficult to ascertain, and has probably been underestimated, because most data were obtained from hospital-based surveys, not population-based studies. In the resource-restricted countries in Asia, many patients are treated as outpatients without any cultures being performed for *S. aureus* or identification of organisms to the strain level. Nasal colonization surveys may underestimate the true incidence of *S. aureus* disease, because MRSA colonization of other body sites is common [164].

Factors that are linked to CA-MRSA infections, such as high antimicrobial consumption, overcrowding, lack of water, resulting in poor hygiene, insect bites and scabies are prevalent throughout the developing world. Interventions for the control and prevention of CA-MRSA infections include general hygiene and cleaning measures to prevent transmission, antibiotic stewardship programmes, screening and decolonization in selected conditions, and, in the future, vaccination [165,166]. Educating patients and clinicians is mandatory to control CA-MRSA.

LA-MRSA in Asia

In addition to being a human pathogen, *S. aureus* causes an array of infections in economically important livestock animals, particularly pigs [167–169]. A specific MRSA ST (ST398) has been found to be associated with various animals and humans across European countries and North America [170–174]. ST398 has the capacity to colonize multiple host species, including pigs, cows, sheep, and poultry, may facilitate colonization in animal workers and in people with animal contact, and can cause severe infections in humans. Several cases of ST398 infection in humans have been reported in European countries, Hong Kong, and China [58,172,175–178].

The incidence of MRSA among pigs in Asian countries was lower than that for western countries. The rates reported from Asian countries were 16–21.3% for Hong Kong [179,180], 4–42.5% for Taiwan [181–183], 11.4% (58/509) for China [184], 3.2% (21/657) for Korea [185], 1.4% for Malaysia [186], and 0.9% for Japan [187]. Fang *et al.* [183] indicated that the nasal MRSA carriage rate among pigs was affected by the sampling location (pig farms or auction markets), the size of pig farms, and the age of the pigs sampled.

Rather than ST398, CC9 (ST9 and single-locus variants) is the most prevalent LA-MRSA clone in most Asian countries, such as China, Hong Kong, Taiwan, Thailand, and Malaysia, but not in Japan and Korea. In Japan, the main strain was found to be ST221 [187], whereas ST398/t034 and ST541/t034 were predominant in Korea [185]. Although the LA-MRSA isolates in most Asian countries shared a common ST, namely ST9, the molecular characterizations of these LA-MRSA isolates were not the same: they had different SCC*mec* types and *spa* types [12,179–184,186,188].

The nasal MRSA colonization rate among pig farmers and related personnel in Asian countries was lower than that in European countries (20–45%), and the rates reported from Asian countries were 5.5% (5/90) for Malaysia [154], 1.7% (2/

120) for China [184], and 13% (13/100) for Taiwan [183]. According to the report from Taiwan [183], ten of 13 MRSA isolates from humans belonged to ST9, and the PFGE pattern of these human MRSA isolates was indistinguishable from that of MRSA isolates from pigs. These findings suggest that ST9 probably spread via human contact rather than animal contact, a scenario demonstrated for ST398 MRSA transmission in Europe [189,190].

Human infections with ST398 LA-MRSA have been reported in Europe since it was first identified in pigs [169,176,177,191–193], but, despite the prevalence of ST9 MRSA among pigs in Asia, infections caused by this clone in animals and humans were not addressed in the literature. However, Wan *et al.* [12] found that, among the isolates collected from the Taiwan Surveillance of Antimicrobial Resistance, a biennial national surveillance programme, five human clinical isolates of ST9-t899/PVL-negative were identified and were isolated in 1998, 2004, 2006 (two isolates), and 2010; three were from outpatients and two were from inpatients. A highly homogeneous virulence genotype and homogeneous genomic profiles were identified among the ST9 MRSA isolates of human and pig origin. However, the PFGE patterns were different (personal communication, Tsai-Ling Lauderdale, National Health Research Institute, Taiwan). To better understand the epidemiology and transmission of LA-MRSA in Asia, further studies are needed.

Conclusions

S. aureus with resistance to multiple antibiotics continues to be an important medical organism and to be associated with a huge disease burden in Asia. The incidence of MRSA in healthcare facilities in Asia reached its peak in the late 1990s, and stayed at a plateau level during the 2000s. The emergence of CA-MRSA after 2000 also occurred in the majority of Asian countries, with strikingly high incidence rates of >50% in some regions. The high rates of MRSA in hospitals and communities have inevitably led to the increased use of glycopeptides and other anti-MRSA agents, and have promoted the development of glycopeptide-non-susceptible strains. Given the high transmissibility of *S. aureus* strains and the crowded living conditions in Asia, the VISA and VRSA strains, although only sporadically reported at present, constitute a substantial public health threat, especially in resource-poor countries, where diagnostic facilities are largely lacking and appropriate therapy is frequently unaffordable. Implementation of surveillance systems at the international level is urgently needed to gain insights into the current epidemiology of *S. aureus* in the resource-limited Asian countries. In middle-income to high-income countries with a high incidence of MRSA, effective infection control strategies, diagnostic culture and the judicious use of antimicrobial agents remain the best methods to prevent the transmission of MRSA and ease the associated disease burden.

Transparency Declaration

The authors declared no conflict of interest.

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