

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*

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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 RRS 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

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