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High burden of antimicrobial drug resistance in Asia^{\star}

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ABSTRACT

The rapid development of antimicrobial resistance among micro-organisms is a serious public health concern. Moreover, the dissemination of antibiotic-resistant bacteria makes this issue a global problem, and Asia is no exception. For example, since New Delhi metallo- β -lactamase (NDM)-producing Enterobacteriaceae were identified in India, further spread of NDM has become a worldwide threat. However, the epidemiology of antibiotic-resistant bacteria in Asia may be different to other regions, and clinical condition may be worse than in western countries. Antibiotic-resistant bacteria, including community-acquired and hospital-acquired meticillin-resistant *Staphylococcus aureus* (MRSA), vanco-mycin-intermediate *S. aureus* (VISA), vancomycin-resistant enterococci, macrolide- and penicillin-resistant *Streptococcus pneumoniae*, extend-spectrum β -lactamase (ESBL)-producing *Escherichia coli* and *Klebsiella pneumoniae*, carbapenem-resistant Enterobacteriaceae, and multidrug-resistant *Steudomonas aeruginosa* and *Acinetobacter* spp., are becoming prevalent in many countries in Asia. Moreover, the prevalence of each antibiotic-resistant bacterium in each country is not identical. This review provides useful information regarding the critical condition of antibiotic resistance in Asia and emphasises the importance of continuous surveillance of resistance data.

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1. Introduction

Antibiotic resistance has become a global public health issue. The emergence and spread of antibiotic resistance can limit the choice of antibiotics used for treatment of infectious diseases and further poses a negative impact on patient outcome. Although this serious problem occurs worldwide, the pattern of antibiotic drug resistance varies geographically. Therefore, each site should establish relevant updated data through timely surveillance to guide the appropriate use of antibiotics in clinics.

In western countries, community-associated meticillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci (VRE), extended-spectrum β -lactamase (ESBL)-producing *Escherichia coli* and *Klebsiella pneumoniae*, and carbapenemresistant Enterobacteriaceae (CRE) [1–4] have become more prevalent than before. In addition, more and more antibioticresistant bacteria have been detected and spread worldwide. There is no exception for Asia. For example, since the first detection of a novel metallo- β -lactamase (MBL), named New Delhi metallo- β lactamase-1 (NDM-1), from *K. pneumoniae* isolates in India [5], in a short time it has disseminated in many areas, including North America, Europe and Africa [6–8]. Thus, this review presents an overview of the prevalence and emergence of antimicrobial resistance among several important clinical pathogens in Asia.

2. Status of antibiotic resistance among clinically important pathogens

2.1. Staphylococcus aureus

Hospital-associated (HA) MRSA is a serious problem worldwide, including in Asia. In an investigation regarding the spread of MRSA between the community and hospitals in Asian countries, MRSA accounted for 25.5% of community-associated (CA) S. aureus infections and 67.4% of HA infections [9]. The proportion of MRSA among HA S. aureus infections was low in India (22.6%) and The Philippines (38.1%) but was high in Sri Lanka (86.5%), South Korea (77.6%) and Vietnam (74.1%). The proportion of MRSA among CA S. aureus infections differed according to different sites: Sri Lanka, 38.8%; Taiwan, 34.8%; The Philippines, 30.1%; Vietnam, 30.1%; South Korea, 15.6%; Hong Kong, 8.5%; India, 4.3%; and Thailand, 2.5% (Fig. 1) [9]. Moreover, the study also found that the genotypic characteristics of MRSA varied in different settings and countries [9]. In China, the prevalence of MRSA among S. aureus isolates ranged from 43.1% to 62.3%, especially in some cities (Beijing, Shanghai, Guangzhou and Wuhan, where >60% of S. aureus belonged to MRSA) [10]. A recent national laboratory-based multicentre surveillance study in China [10] investigated a total 1141 MRSA isolates characterised by multilocus sequence typing (MLST), staphylococcal cassette chromosome mec (SCCmec) and spa typing. ST239 (MLST)-III(SCCmec)-t030(spa type), ST239-IIIt037 and ST5-II-t002 were the predominant HA-MRSA clones, with prevalences of 57.1%, 12.9% and 8.1%, respectively, in contrast to only 6.6% of isolates belonging to ST59, which had typical CA-MRSA features [10]. Between 2008 and 2009 in India, the Indian Network for Surveillance of Antimicrobial Resistance (INSAR) found that the overall prevalence of meticillin resistance was 41% among a total of 26 310 isolates. In addition, the rates of isolation of MRSA from outpatients, ward inpatients and intensive care unit patients were 28%, 42% and 43%, respectively in 2008, and 27%, 49% and 47%, respectively, in 2009 [11]. In Saudi Arabia in 2009–2010, MRSA accounted for 39.5% of *S. aureus* isolates, in particular HA-MRSA accounted for 52.6% of hospital *S. aureus* infections [12].

The secular trend of MRSA prevalence was also found to vary by study design and study sites. In China, the prevalence of MRSA remained stable between 2005 and 2010 [13]. In Taiwan, the incidence of MRSA nosocomial bloodstream infections (BSIs) significantly decreased with time between 2000 and 2010 [14]. In South Korea, the incidence of MRSA BSI significantly reduced from 2009 to 2011 [15]. Overall, these phenomena should be attributed to implementation of infection control measures.

Another critical issue with S. aureus is reduced susceptibility to vancomycin, such as vancomycin-intermediate S. aureus (VISA) and heterogeneous vancomycin-intermediate S. aureus (hVISA). From 1997 to 2001, a study of 1357 MRSA clinical isolates from 12 centres in 12 Asian countries showed that hVISA strains were found in Japan (19/231; 8.2%), India (5/80; 6.3%), South Korea (28/ 457; 6.1%), The Philippines (1/28; 3.6%), Vietnam (1/41; 2.4%), Singapore (2/87; 2.3%) and Thailand (2/96; 2.1%) [16]. In China, an investigation of 1012 MRSA isolates from 14 cities from 2005 to 2007 revealed that the prevalence of hVISA was 13–16% [17]. In Taiwan, 43 isolates of meticillin-resistant VISA were detected from 21 hospitalised patients and caused clonal spread in a hospital [18]. Another study in a medical centre in Taiwan showed that 5 (4.2%) of 118 S. aureus isolates causing bacteraemia were hVISA, and 3 of them belonged to ST239 [19]. In summary, although the prevalence of MRSA may be decreasing, the emergence of hVISA/VISA cannot be neglected.

2.2. Enterococci

Since VRE was first described in 1982 in South Korea, this pathogen has become a new threat, especially in the setting of healthcare-associated infections in Asia [20]. In China, the prevalence of VRE increased from 0% in 2005 to 4.9% in 2010, and the *vanA* gene was the most prevalent gene [13]. In Taiwan, the non-susceptible rate to vancomycin of enterococci isolates causing nosocomial bacteraemia significantly increased from 1.7% in 2000 to 25.1% in 2009 [21]. This is consistent with another study in Taiwan where the incidence rate increased from 0.01 episodes of VRE BSI/1000 patient-days in 2005 to 0.07 episodes of VRE BSI/1000 patient-days in 2010 [22]. In contrast, >98% of enterococci isolates remain susceptible in Hong Kong, The Philippines, Thailand, Saudi Arabia and India [21–25]. In addition, nosocomial

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