The Global Spread of Healthcare-Associated Multidrug-Resistant Bacteria: A Perspective From Asia

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Since antibiotics were first used, each new introduced class has been followed by a global wave of emergent resistance, largely originating in Europe and North America where they were first used. Methicillin-resistant Staphylococcus aureus spread from the United Kingdom and North America across Europe and then Asia over more than a decade. Vancomycin-resistant enterococci and Klebsiella pneumoniae carbapenemase–producing K. pneumoniae followed a similar path some 20 years later. Recently however, metallo-β-lactamases have originated in Asia. New Delhi metallo-β-lactamase–1 was found in almost every continent within a year of its emergence in India. Metallo-β-lactamase enzymes are encoded on highly transmissible plasmids that spread rapidly between bacteria, rather than relying on clonal proliferation. Global air travel may have helped facilitate rapid dissemination. As the antibiotic pipeline offers little in the short term, our most important tools against the spread of antibiotic resistant organisms are intensified infection control, surveillance, and antimicrobial stewardship.

Keywords. bacterial drug resistance; methicillin-resistant Staphylococcus aureus; vancomycin-resistant Enterococcus; extended-spectrum beta-lactamase; carbapenem-resistant Enterobacteriaceae.

In addition to being detected in wild animals and remote human communities with little or no antibiotic exposure, antimicrobial resistance genes have been identified in bacterial DNA frozen in Arctic permafrost for 30,000 years, and in bacteria in a subterranean cave isolated from the surface for >4 million years [1]. But whereas antimicrobial resistance clearly predates modern antibiotics, the advent and mass production of antibiotics since the 1940s resulted in unprecedented selection pressure. Alexander Fleming was aware of the potential consequences as early as 1945, warning of the risk of emergent resistance in his Nobel prize lecture [2]. Just 3 years after Fleming’s speech, one London hospital reported Staphylococcus aureus penicillin resistance rates of 38% [3]. Each successive antibiotic introduction has been followed by global emergence of resistance, frequently starting in hospital settings (Figure 1). Asia faces a greater burden of gram-negative resistance compared to the West [4]. The potential for global spread is illustrated by the dissemination of New Delhi metallo-β-lactamase 1 (NDM-1) rapidly from India to the West, and the slower spread of Klebsiella pneumoniae carbapenemase (KPC) from West to East.

This review describes the global epidemiology of the major antibiotic-resistant bacteria over the past few decades, focusing on Singapore’s epidemiology and response. In much of Asia, surveillance of antimicrobial resistance is hampered by political and financial constraints. Singapore has a developed economy with a large migrant population and significant health...
tourism. Its strategic international location allows it to serve as a sentinel site for monitoring the emergence and spread of resistant organisms.

**Methicillin-Resistant Staphylococcus aureus**

Methicillin-resistant *Staphylococcus aureus* (MRSA) was first identified in the United Kingdom in 1961, only 2 years after the introduction of methicillin [5]. Over the next few decades MRSA became established in hospitals throughout North America and Europe, and subsequently Northeast, then Southeast, Asia (Figure 2). In North America and Europe in the 1970s and 1980s, healthcare-associated MRSA (HA-MRSA) strains traditionally carried staphylococcal cassette chromosome (SCC) type II, for example, USA100 (ST5) and USA200 (ST36). However, with the exception of USA100 in Japan, these strains have never become established in Asia. In Singaporean hospitals the SCCmec type III strain ST239 was endemic during this period [6]. All these strains are typically susceptible only to vancomycin, fusidic acid, and rifampicin.

The early 2000s saw the emergence of community-associated MRSA (CA-MRSA) clones, which previously had mainly been confined to isolated primarily rural communities (Figure 2). The nonmultiresistant USA 300, (CC8-ST8, SCCmec IV, Panton-Valentine leukocidin positive) strain emerged in the community in the United States, causing severe skin and soft-tissue infections and necrotizing pneumonia. This clone is typically susceptible to non-β-lactam antibiotics. It has never become established in Asia, for reasons that remain unclear. However, other SCCmec type IV CA-MRSA clones have become prevalent in the community in some Asian countries [7]. In many parts of Asia the major HA-MRSA clones that were endemic in hospitals, including ST239, have spread to the community, and CA-MRSA clones have become established in hospitals [8]. The terms “healthcare-associated” and “community-associated” are now therefore becoming largely historical.

In the United States and some European countries, including the United Kingdom, MRSA rates are actually falling [7]. This is likely due in part to the introduction of a care-bundle approach of improved infection control, screening, and decolonization, as well as restriction of some antibiotic classes. Alternatively, it may reflect biological factors rather than human effort [9]. Many Asian countries still have increasing rates, but in Singapore stabilization over the past 5 years is evident. Over the past decade, Singapore’s hospital-adapted ST239 strain has to some extent been replaced by UK-EMRSA-15 (ST22, SCCmec type IV) [6]. EMRSA-15 is a healthcare-associated strain that emerged in the United Kingdom in 1991, which, along with EMRSA-16, replaced the majority of the United Kingdom’s HA-MRSA strains by the late 1990s [10]. EMRSA-15 is usually resistant to erythromycin.
and ciprofloxacin but susceptible to other non-β-lactam antibiotics such as trimethoprim-sulfamethoxazole.

Reducing MRSA colonization and infection rates are becoming a priority for hospital administrations, given the excess risk of death in patients with MRSA clinical infection (odds ratio, 5.5) [11]. In Singapore hospitals, MRSA is endemic. At the National University Hospital, approximately 25% of all inpatient beds are dedicated to cohorting patients with MRSA infection or colonization and 8% of all inpatients are found to test positive via active surveillance on admission. Since the introduction of enhanced infection control measures (described later), MRSA colonization acquisition rates as determined by a single swab on discharge have dropped from >10% five years ago, to <2% in intensive care units and <4% in the general wards today (D. Fisher and colleagues, unpublished data).

Vancomycin-resistant intermediate \textit{S. aureus} (VISA) was first identified in Japan in 1996 (Figure 2) [12]. Seven cases of hetero-VISA were identified in Singapore in 2001 [13] and a study in 2005–2006 identified 7 cases of VISA and 3 hetero-VISA [14]. However, at 0.2%, rates of reduced susceptibility to vancomycin are still well below those seen in some North American centers. Until recently, reports of vancomycin-resistant \textit{S. aureus} (VRSA) in Asia were limited to Japan, but in 2011 a number of \textit{vanA}-positive and also \textit{vanA}-negative VRSA isolates were identified in Hyderabad, India [15]. VRSA has never been identified in Singapore. However in 2010, 6 cases of daptomycin-nonsusceptible \textit{S. aureus} bacteremia were reported, all in patients previously treated with vancomycin [16]. Despite the emergence of linezolid-resistant \textit{S. aureus} in Spain and Japan, no Singaporean cases have been reported to date [17, 18].

**Vancomycin-Resistant Enterococci**

Vancomycin had been used since the 1950s, but the emergence of resistance in \textit{Enterococcus} species was not reported until 1988, in the United Kingdom and France [19]. Incremental vancomycin usage for MRSA infection may explain the timing. Over the next decade, vancomycin-resistant \textit{Enterococcus} (VRE) spread throughout Europe and North America (Figure 3). Vancomycin resistance is predominantly mediated by \textit{vanA} or \textit{vanB} genes, both most likely having emerged in Europe. \textit{VanB} differs phenotypically in that it retains susceptibility to teicoplanin. Most VRE cases in Europe, the United States, and Korea are now due to \textit{vanA}, whereas the epidemic in Singapore and Australia has predominantly been \textit{vanB}, although Singapore has recently seen a

![Figure 2. Global dissemination of methicillin-resistant \textit{Staphylococcus aureus} (MRSA). This map indicates the countries in each continent providing the earliest reports of healthcare-associated MRSA, community-associated MRSA, and vancomycin-intermediate \textit{Staphylococcus aureus}. The white arrows indicate the early movements of healthcare-associated MRSA around the world. Poor surveillance is highlighted by the lack of data for some regions. Abbreviations: MRSA, methicillin-resistant \textit{Staphylococcus aureus}; UK, United Kingdom.](cid:1312-CID-2013-56-1-May)
number of \textit{vanA} cases. In the United Kingdom, \textit{vanA} is now seen in 15\%–25\% of \textit{Enterococcus faecium} and 2\%–3\% of \textit{Enterococcus faecalis}, rates it reached in the early 1990s [9]. Rates of vancomycin resistance in US hospitals reached much higher levels. By 2002, 60\% of \textit{E. faecium} and 2\% of \textit{E. faecalis} were resistant to vancomycin [20], climbing further to 80\% in \textit{E. faecium} and 7\% in \textit{E. faecalis} by 2007 [21]. As with MRSA, rates have started to decline in some parts of the West.

VRE was first reported in Singapore in 1994 [22]. Over the next decade, while the West was seeing a steady rise, only sporadic cases occurred in Singapore [23], until a single hospital outbreak in 2004 [24]. The following year, >5000 patients were screened, including 84\% of one hospital’s inpatients on a single day. A total of 147 carriers and 4 clinical cases were detected [25]. Pulsed-field typing revealed 1 major clone and several minor clones of \textit{vanB E. faecium}. All belonged to clonal complex 17, a distinct genetic lineage of \textit{E. faecium} implicated in hospital outbreaks worldwide [26]. It is likely that these strains were imported. The first case isolated in 2004 was in a patient from Indonesia, and the first case isolated in 2005 was in a Singaporean who had been hospitalized in India. Interestingly, a similar outbreak of \textit{vanB} VRE had occurred in Western Australia in 2001 [27]. Control measures for the next 5 years (see the section “Control of Antimicrobial Resistance”) resulted in VRE rates that were lower than those in many other developed nations. Outbreak strains, however, had become established, and maintained a low level of endemicity interspersed with occasional outbreaks [28]. Over the past 2 years, unlike in most Western countries, VRE rates in Singapore’s tertiary hospitals appear to have been trending upward, particularly among renal and hematology patients. This mirrors the pattern seen in countries outside Asia a decade ago. The reasons for this delay are unclear.

\textbf{Enterobacteriaceae}

\textbf{Extended-Spectrum and AmpC \(\beta\)-Lactamas}
es

The extended-spectrum cephalosporins ceftriaxone and ceftazidime were introduced in the early 1980s. By 1985, reports came out of Europe describing an extended-spectrum \(\beta\)-lactamase (ESBL) in \textit{Klebsiella pneumoniae} and \textit{Escherichia coli} [29]. During the 1980s and 1990s, TEM- and SHV-type ESBLs carrying \textit{Klebsiella} species spread, globally causing predominantly nosocomial infections. CTX-M type ESBLs have proliferated since 2000, initially in community \textit{E. coli} and nosocomial \textit{Klebsiella} species strains [29]. In the late 1980s, the AmpC cephalosporinase was discovered on plasmids in \textit{K. pneumoniae} and \textit{E. coli} [30]. Unlike ESBL, AmpC producers are usually susceptible to cefepime. Together ESBL and AmpC now make up the majority of the third-generation cephalosporin resistance seen worldwide. The distribution varies
dramatically by region, however. Nosocomial rates in North America have stabilized at around 10% for *E. coli* and *K. pneumoniae*, and a little higher in European hospitals. In contrast, in Asia, ESBL rates are >80% in India and >60% in China [9].

In Singapore, >30% of *Klebsiella* species—positive blood culture isolates were resistant to third-generation cephalosporins by 1990. Rates have not changed significantly since then, despite rising rates of third-generation cephalosporin use [31]. In fact, there is a recent trend toward decreasing resistance in *Klebsiella* species, which is unexplained [32]. The first AmpC-producing *E. coli* in Singapore was documented in 2003 [31]. Between 2006 and 2007, clinical samples collected across 7 hospitals in Singapore again revealed approximately 30% third-generation cephalosporin resistance in Enterobacteriaceae, of which ESBL rates were 19.6% in *E. coli* and 30.3% in *K. pneumoniae*, and AmpC rates were 8.5% in *E. coli* and 5.6% in *K. pneumoniae* (based on phenotypic data) [33]. One molecular study found that of 54 ceftriaxone-resistant *E. coli* isolates, 69% were positive for *bla_{CTX-M}* genes (group 1 and, to a lesser extent, group 9), and 33% screened positive for AmpC enzymes, of which 28% carried *bla_{AMP C}* genes [34]. Current inpatient bacteremia rates of ceftriaxone or ceftazidime resistance are 47% for *E. coli* and 67% in *K. pneumoniae* in Singapore, but these aggregate both community and hospital onset. In contrast, in India, the resistance rates in community *E. coli* are as high as the hospital rates, possibly because of the unregulated use of antibiotics in the community, including in agriculture, and lower sanitary standards [35].

**Carbapenemases**

Carbapenem-resistant Enterobacteriaceae (CRE) are a significant and growing problem in Asia. Low-level resistance can occur when high levels of AmpC or ESBL are combined with porin deficiencies. High-level resistance is primarily mediated by carbapenemases. The serine carbapenemase KPC was first identified in North Carolina in 1996, and soon afterward caused an outbreak in New York [36]. This enzyme inactivates all β-lactams. KPC-producing *K. pneumoniae* followed the movements of colonized patients to cause outbreaks in other countries, including Israel in 2004 and Greece in 2007 (Figure 4). Spread is predominantly via clonal dissemination. In Asia, KPC was initially detected in China in 2004, and subsequently South Korea and Taiwan [37]. In 2012, the first 4 cases of KPC were reported in Singapore [37, 38]. These *bla_{KPC-2}* plasmid-containing *K. pneumoniae* isolates were clonal, belonging to strain type 11 (ST11), and closely related to the Chinese strain. They were identified from epidemiologically unrelated patients from 2 different hospitals. Two of the patients were non-Chinese, with no recent travel, suggesting dissemination of KPC in the community.

Metallo-β-lactamases (MBLs) are a class of carbapenemases that remain susceptible to aztreonam (but are frequently accompanied by aztreonam hydrolyzing ESBLs). The first known plasmid-borne MBL was IMP-1, originally identified from *Pseudomonas aeruginosa* in Japan in 1988 [39]. The first case outside Japan was identified in *K. pneumoniae* in Singapore in 1996 [40]. While now endemic in Japan, this mechanism accounts for only a small percentage of carbapenem resistance in Enterobacteriaceae in Singapore today. Verona integron-encoded MBL (VIM), was first identified in Italy in 1997 but has never reached significance in Asia [29]. Of more concern is the recently identified NDM-1. NDM-1 plasmid-carrying organisms frequently possess multiple resistance mechanisms to other classes of antibiotics, typically rendering the bacteria resistant to all antibiotics except polymyxin and occasionally tigecycline [41]. NDM-1 was first reported from an Indian patient managed in 2008 in Sweden who had been transferred from a New Delhi hospital [42]. The following year, NDM-1 was identified in 29 patients in the United Kingdom and 143 patients from multiple sites in the Indian subcontinent [43]. NDM-1 has now spread by plasmid transfer into a wide range of bacteria (both environmental organisms and potential human pathogens), and been identified in sewage and tap water in India and Vietnam [44, 45]. Many other countries around the world, including the United States, have now reported sporadic cases in individuals returning from the Indian subcontinent (Figure 4) [46].

Singapore has a multicultural population with significant movement of people to and from the Indian subcontinent. It is therefore not surprising that in 2011 12 NDM-1–positive isolates were identified in Singapore, which represented 23% of all CRE [47]. The multilocus sequence typing strains were diverse, indicating that the clones were genetically unrelated. Most patients were of non-Indian ethnicity, and none had traveled overseas in the previous 2 years [48]. It is possible that in addition to KPC, NDM-1–positive Enterobacteriaceae are also now endemic in Singapore.

The most recent introduction to Singapore was OXA-181, a class D β-lactamase (oxacillinase). OXA-48 has caused a number of outbreaks in Europe and the Mediterranean countries [49], but is not endemic in the Americas yet. In the last year, OXA-181, an OXA-48 variant recently identified in India [50], has been reported in Singapore in *K. pneumoniae* bloodstream isolates from 2 Bangladeshi patients [51]. Further unpublished data suggest that it is now well established in Singapore.

Overall, <1% of hospital-associated Enterobacteriaceae infections in Singapore are carbapenem resistant, but numbers are increasing. By comparison, India’s rates are 5%–8% [52]. In Singapore, clinical isolates that screen positive for carbapenem resistance are referred to a reference laboratory for
carbapenemase detection by polymerase chain reaction. These surveillance data reveal that of carbapenem-resistant isolates, approximately 40% test positive for a carbapenemase, of which approximately two-thirds are NDM-1, 20% are OXA-181, and 5%–10% are KPC. Sporadic detection of VIM and IMP continues. There are plans to introduce targeted admission screening for CRE in all public hospitals in the coming year.

Nonfermenters

In tropical regions including Southeast Asia, nosocomial *Acinetobacter baumannii* infections are more frequent than in Europe and the United States. In addition, community-acquired infections can also occur [53]. Singapore has witnessed the stepwise loss of antibiotic classes for treating *A. baumannii* infection including carbapenems. Resistance to 3 or more classes (multidrug-resistant *A. baumannii*) represented 44% of isolates in Singapore between 2004 and 2007, as compared to the overall proportion across 9 Asia-Pacific countries of 34.2% [54]. Now 55% of Singapore’s isolates are multidrug resistant and infection rates are increasing both in intensive care units and general wards. Of concern is a small number of isolates that are truly panresistant, including to polymyxins. It is hoped that enhanced isolation and environmental cleaning processes will control the spread of multidrug-resistant *A. baumannii*.

Recently in Thailand, the enhanced cleaning that was necessitated by widespread flooding of hospitals and intensive care units resulted in the elimination of previously prevalent multidrug-resistant *A. baumannii* [55].

Although rates of resistance of *Pseudomonas aeruginosa* to the most commonly used antibiotic classes are typically high in Southeast Asia [29], rates in Singapore remain significantly lower than those of *A. baumannii*.

Control of Antimicrobial Resistance

The reduction in rates of nosocomial MRSA, and until recently VRE, was achieved with a coordinated interhospital infection control response. A care-bundle approach was introduced, which includes a checklist for routine hand hygiene and aseptic technique during line care or invasive procedures (which had not been optimally practiced in Singapore for many years [56]). With this approach, Singapore now seems to be following global trends in reducing central line–associated bloodstream infections, although there are no peer-reviewed data published. Enhanced environmental cleaning and active surveillance of high-risk patients with electronic tagging of colonized patients’ medical records were introduced [25], with isolation and cohorting of identified patients [25]. Now all new patients are screened for MRSA and cohorted appropriately.

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**Figure 4.** Global dissemination of *Klebsiella pneumoniae* carbapenemase–producing *K. pneumoniae* and New Delhi metallo-β-lactamase–producing Enterobacteriaceae. The earliest reported cases in each continent are shown. Arrows indicate the significant international movements of these organisms. Abbreviations: KPC, *Klebsiella pneumoniae* carbapenemase; NDM-1, New Delhi metallo-β-lactamase–1; UK, United Kingdom.
without contact precautions except for specific indications. Targeted patients undergo decolonization. However, the background rate of MRSA is high, so unlike some parts of Europe, widespread decolonization and eradication of MRSA from the hospitals is not yet an achievable goal. Isolation of patients with multidrug-resistant gram-negative organisms aims to curtail nosocomial transmission, although the existing burden locally plus the contribution of community outbreaks from regional countries where these organisms have been found in environmental sources will make control challenging.

Antimicrobial stewardship is not well developed in Asia. Broad-spectrum antimicrobial use in Singapore is higher than in most developed countries, but so is antimicrobial resistance [57]. It is difficult to tease out cause and effect. Up to 38% of antibiotic prescriptions in Singaporean hospitals could be considered inappropriate (mostly failure to de-escalate after culture results were available) [58]. Antimicrobial stewardship is now practiced in all major Singaporean hospitals, with evidence of a resulting shorter length of stay and fewer infection-related readmissions [59]. The effect on antimicrobial resistance is yet to be shown. No data currently exist on community prescribing. In the community in Singapore, antibiotics require a prescription, in contrast to most other countries in Asia.

Surveillance remains undeveloped in most Asian countries. Singapore has escalated surveillance to provide leadership in the region, and help to identify emerging resistance patterns. All hospitals report rates to the Ministry of Health for MRSA, VRE, carbapenem-resistant *A. baumannii* and *P. aeruginosa*, and third-generation cephalosporin-resistant and carbapenem-resistant *E. coli* and *K. pneumoniae*, as well as levels of broad-spectrum antibiotic use. A National Antimicrobial Task Force coordinates the response to antimicrobial resistance in hospitals and long-term care facilities. This initiative aims to monitor the clinical and molecular epidemiology and formalize lines of communication between the healthcare facilities to better prepare for future challenges.

We can expect future resistant organisms to spread quickly, independent of international boundaries. Containment requires a coordinated global approach. As well as improving infection control, surveillance, and antimicrobial stewardship, a recent World Health Organization report recommends reducing antimicrobial use in animal husbandry [60]. Although ESBL-producing gram-negative organisms have repeatedly been identified on fresh meat and vegetables, the true implications of this for human health are not known [61]. Almost all meat for human consumption in Singapore is imported from farms that are preaccredited through a process which includes screening for antibiotic residues. Finally, the development of new antibiotics, diagnostics, and vaccines can no longer be relied upon. The approval of new antibiotics in the United States has fallen from 30 between 1983 and 1992, to just 12 between 1998 and 2009 [62].

While historically, antibiotic resistance has followed the introduction of novel antibiotics in the West, the recent trend toward the emergence of highly drug-resistant community-associated strains in developing Asian countries where medical resources are scarce is a cause for concern. There is potential for unrecognized global spread of these organisms. Globally connected cities such as Hong Kong and Singapore are uniquely positioned to act as sentinels for the emergence of resistant strains. At the same time, their modern healthcare facilities offer unique opportunities for research into novel approaches to controlling the spread of these organisms.

**Notes**

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