Emerging Microbes & Infections
2024, VOL. 13, 2317915 (21 pages)
https://doi.org/10.1080/22221751.2024.2317915

REVIEW ARTICLE

OPEN ACCESS Check for updates

ESKAPE in China: epidemiology and characteristics of antibiotic resistance

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ABSTRACT

The escalation of antibiotic resistance and the diminishing antimicrobial pipeline have emerged as significant threats to public health. The ESKAPE pathogens – Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, and Enterobacter spp. – were initially identified as critical multidrug-resistant bacteria, demanding urgently effective therapies. Despite the introduction of various new antibiotics and antibiotic adjuvants, such as innovative β-lactamase inhibitors, these organisms continue to pose substantial therapeutic challenges. People's Republic of China, as a country facing a severe bacterial resistance situation, has undergone a series of changes and findings in recent years in terms of the prevalence, transmission characteristics and resistance mechanisms of antibiotic resistant bacteria. The increasing levels of population mobility have not only shaped the unique characteristics of antibiotic resistance prevalence and transmission within People's Republic of China but have also indirectly reflected global patterns of antibiotic-resistant dissemination. What's more, as a vast nation, People's Republic of China exhibits significant variations in the levels of antibiotic resistance and the prevalence characteristics of antibiotic resistant bacteria across different provinces and regions. In this review, we examine the current epidemiology and characteristics of this important group of bacterial pathogens, delving into relevant mechanisms of resistance to recently introduced antibiotics that impact their clinical utility in China.

ARTICLE HISTORY Received 21 December 2023; Revised 26 January 2024; Accepted 8 February 2024

KEYWORDS ESKAPE; antimicrobial resistance; epidemiology; China

Introduction

Antimicrobial resistance (AMR) has emerged as a major public health threat in the twenty-first century and caused serious societal and economic burden [1,2]. If AMR is not controlled, 10 million people could die from bacterial infections by 2050 [3]. The irrational use of antimicrobial agents is a significant and critical issue in China, contributing to the development of severe bacterial resistance [4]. In recent years, China has issued two "National Action Plans for Combating Bacterial Resistance (2016–2020, 2022–2025)", implementing effective antimicrobial stewardship, rational use policies and surveillance [5,6]. China's efforts to combat antimicrobial resistance have shown significant results. The rate of antibiotic use has notably decreased, and the detection rate of some commonly encountered clinically resistant bacteria has either decreased or remained stable [7,8]. However, numerous challenges persist in China's current landscape of AMR, including the escalating antibiotic resistance rates of certain common bacteria [9], continual discovery of new resistance mechanisms [10–12], and dynamic changes in prevalent clones [13,14]. Comprehensive control of nosocomial infections is still a pending task.

Surveillance and mechanistic studies of bacterial resistance are the most important measures in terms of controlling the spread of resistant bacteria [15–17]. There are several nationwide surveillance networks in China nowadays. CARSS (China Antimicrobial Resistance Surveillance System), currently managed by the National Health Commission, evolved from Mohnarin [18]. BRICS established by Zhejiang University, focused on surveillance of antimicrobial resistance in national bloodstream infection [9]. CHINET established by Fudan University, included more than 70 tertiary and second-class hospitals in China [18,19] (Figure 1). Besides the national surveillance networks, there are several independently established hospitals and local surveillance programmes, and some other special surveys including children hospitals [20]. These initiatives contribute valuable data that can aid in formulating strategies for the rational use of antimicrobial agents. With the establishment and development of these antimicrobial resistance surveillance networks, the quantity and quality

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Figure 1. Surveillance networks. Geographical distribution of sentinel hospitals of BRICS and CHINET. Due to the extensive number of sentinel hospitals in CARSS (exceeding 1,500), it is impractical to display them individually on the map. Therefore, CARSS sentinel hospitals have not been marked on the map.

of research output on antimicrobial resistance in China has remarkably increased [18], including molecular epidemiology and the underlying and genetic basis and evolution of antimicrobial resistance [21,22]. These studies make a significant and valuable contribution to the scientific community engaged in researching antimicrobial resistance, offering insights that inform strategies for mitigating antimicrobial resistance.

We published a review paper related to epidemiology and characteristics of antimicrobial resistance in China in the first decade of 21th [23]. From the second decade of 21th to now, dynamic changes have made in epidemiology, underlying mechanisms and evolution of antimicrobial resistance. To comprehensively illustrate the extent and dynamics of antimicrobial resistance in China over the last decade, we examined data mainly on ESKAPE pathogens (including *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* species) that often trigger severe nosocomial infections in critically ill and immunocompromised individuals [24] (Figure 2), and are notable for their propensity to develop antibiotic resistance mechanisms. Most of the data came from CARSS, BRICS and CHINET, which covered all the regions of China.

Enterococcus faecium

Enterococcus, mainly consisted by *Enterococcus faecalis* and *Enterococcus faecium*, is a globally important opportunistic pathogen, and can persist in the gastrointestinal tract for an extended period without causing any symptoms of infection, similarly enduring in the hospital environment [25,26]. The widespread use of antimicrobial agents in clinical treatment has led to the emergence and global spread of antibiotic-resistant enterococci, particularly multi-drug resistant (MDR) isolates such as vancomycin-resistant *Enterococci* (VRE) and linezolid-resistant *Enterococci* (LRE) [25]. Although ten years ago the isolation rate of *E. faecium* was significantly lower than that of *E. faecalis* in China, now the two are comparable as each around 50% (CARSS data in 2022). The antimicrobial resistance of *E. faecium* was more severe than that of *E. faecalis*, such as fosfomycin (30.3% *vs.* 4.8%), ciprofloxacin (85.4% *vs.* 30.6%) and nitrofurantoin (46.4% *vs.* 1.6%), except for chloramphenicol (5.2% *vs.* 22.6%), linezolid (0.6% *vs.* 3.4%) and contezolid (0% *vs.* 1.1%) (CHINET data in 2022) (Figure 3).

The prevalence of VRE in China is relatively low, with a stable low resistance around 0.1% in *E. faecalis*, while the nationwide incidence of

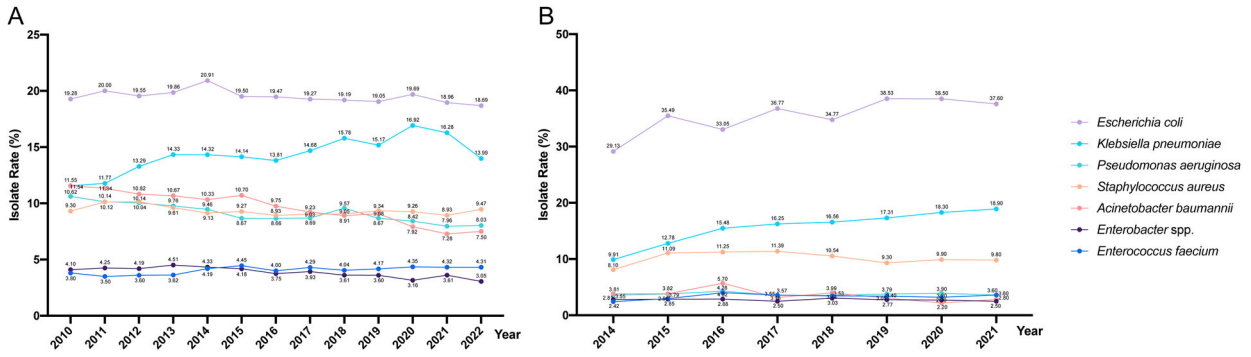

Figure 2. Trends in the prevalence of the predominant antimicrobial resistant bacteria in China. (A) data from CHINET. (B) data from BRICS.

vancomycin-resistant *E. faecium* (VREfm) was fluctuate downtrend from 2010 (3.6%) to 2018 (1.2%), and a slow upward trend from 2019 (1.0%) to 2022 (2.2%) [27–30] (Figure 3). Of note, the prevalence of VREfm in Beijing and Guangdong province were markedly higher, and increased to 11.7% and 8% in 2022, respectively (CARSS data). Yan et al., reported an extremely high prevalence of VRE in patients admitted to ICUs in tertiary hospitals in Beijing, with 31.1% (46/148) patients carried VRE and 91.3% among them being *E. faecium* [32]. Compared to the globally predominant *vanA* and *vanB* genes associated with vancomycin resistance, the most prevalent vancomycin resistance genes in China are *vanA* and *vanM* [30–32]. Among these, *vanA* has the highest prevalence, reported to be in the range of 78.3% −81.7% [30,32]. *vanM* has been predominant in VRE strains since 2011 and showing a greater prevalence than *vanA* in Shanghai, and later spread to other regions such as Zhejiang and Beijing, becoming the second most prevalent vancomycin resistance gene in China [30,32]. The isolation rate of *vanM* has gradually increased, with recent reports indicating around 15.3%−16.7% [30,32]. Generally, both *vanA* and *vanM* genotype are characterized by an acquired high-level of resistance to both vancomycin and teicoplanin. The horizontal transfer capability of antibiotic resistance plasmids plays a crucial role in the dissemination of VRE strains. Multi-locus sequence type (ST) 78 VREfm are predominant in China, ranging from 47.6% to 57.1% in studies [30,32]. In contrast to Europe and Australia, where the VRE subtype ST80 has isolation rates ranging from 40% to 67.1%, ST80 has been rarely reported in clinical cases in China. However, recent findings by Li et al. have documented an outbreak of ST80 in a hospital in Shenzhen, suggesting that ST80 may be emerging in China [34]. Clonal expansion and horizontal transfer of resistance genes have contributed to VREfm increased prevalence in hospitals in China, which deserved further study.

Linezolid serves as one of the final lines of defense against Gram-positive bacteria. Before 2010, linezolid-resistant enterococci (LRE) was not found in any national survey. In recent years, with the widespread application of linezolid in clinics, the gradual increasing reports of linezolid resistant gram-positive pathogens highlights the enhanced risk of linezolid resistance transmission [35,36]. From 2010 on, the escalating emergence of LRE has evolved into a significant concern in nosocomial infections. LREfm was 0.1% in 2011 increased to 0.6% in 2022, and LREfs was 0.2% from 2011 increase to 3.4% in 2022 (CHINET data) (Figure 3). Several genes are related to linezolid resistance, but *optrA* and *poxtA*, is a growing concern, as it is being increasingly reported in both human and veterinary medicine [37]. OptrA was primary mechanism in LRE that was first detected in a

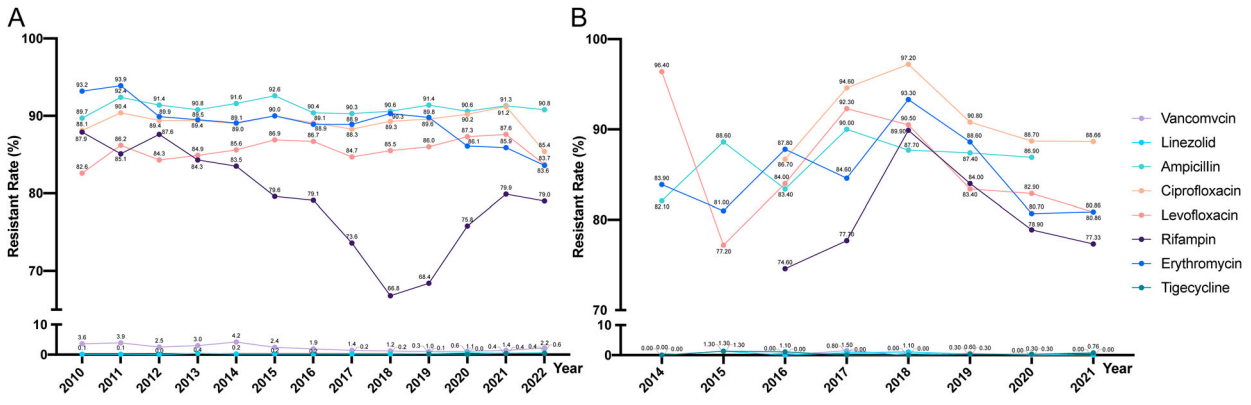

Figure 3. Antimicrobial resistance trends for *E. faecium*. (A). data from CHINET. (B). data from BRICS.

clinical *E. faecalis* from China in 2015, and was commonly localized within chromosomes or plasmids and can be transmitted through horizontal gene transfer (HGT) via mobile genetic elements such as transposons, integrative and conjugative elements, and insertion sequences [38,39]. The recently reported *poxtA* gene, mediating resistance to oxazolidinones, tetracyclines, and phenicols, was first described in an MRSA isolate from an Italian patient [40]. Yi et al. reported that 46.7% (7/15) of linezolid-resistant clinical isolated *E. faecium* were positive for *optrA*, and 13.3% (2/15) of isolates had *poxtA* in China [41]. Besides, Tn558 and IS*1216Es* may play an important role in the dissemination of *optrA* and *poxtA*, respectively [41]. *poxtA* is found more in the environment or food-producing animals than human samples and *E. faecium* has higher prevalence than *E. faecalis*, indicating the necessity of applying the "One Health" perspective to analyse the evolutionary dynamics of *poxtA*-positive *E. faecium* in clinical and non-clinical settings worldwide [42,43]. Although linezolid is currently effective in the treatment of Enterococcal infections, advanced monitoring of changes in the resistance mechanism of linezolid is needed in the future.

Staphylococcus aureus

S. aureus is a commensal bacterium in humans, but it also serves as a pathogen responsible for various infections, ranging from mild skin and soft tissue infections to more severe conditions like endocarditis, pneumonia, and sepsis. Approximately 30% of healthy individuals harbour *S. aureus* in their anterior nares. The global prevalence of *S. aureus* in human populations has been on the rise, potentially attributed to the continual emergence of antibiotic-resistant strains, particularly methicillin-resistant *S. aureus* (MRSA).

Epidemiology of antimicrobial resistance

The high prevalence of MRSA was once a critical antimicrobial resistance issue for *S. aureus* in China, with an isolation rate exceeding 50% before 2010 [23] (Figure 4). This is attributed to the effective implementation of antimicrobial stewardship and rational use policies in China [4]. The isolation rates of MRSA vary geographically, with rates in regions such as Tibet, Shanghai, and Jiangsu remaining above 40% in recent years (CARSS data). The resistance rate of MRSA to antimicrobial agents is higher than that of methicillin-sensitive *S. aureus* (MSSA), except for trimethoprim-sulfamethoxazole (6.4% *vs.* 12.4% in 2022, CHINET data). MRSA is higher resistance rates to macrolides, clindamycin, aminoglycosides and quinolones compared with MSSA [44]. The rate of rifampicin resistance in MRSA, which was about 50% in 2010, has sharply declined to about 3% in 2022, though it remains higher than in MSSA (Figure 4). The rate of sulfamethoxazole-trimethoprim resistance in MSSA has remained stable around 15% from 2011 to 2022, whereas in MRSA, it decreased from 20.1% to 6.4% (CHINET data). *S. aureus* is still highly sensitive to vancomycin, linezolid, teicoplanin, contizolamide and tigecycline. Among the major treatment options for MRSA, no vancomycin, linezolid or teicoplanin resistant strains were reported in the surveillance data in China. Whereas in-host evolution of daptomyxin resistance and heteroresistance in MRSA were reported with mutations in *mprF* and *yycH* [45,46]. The role of *mprF* mutations in seesaw effect of daptomyxin resistance MRSA provides fundamental insights into the combination therapy of beta-lactam antibiotics and daptomycin for treating MRSA infections [46]. Nevertheless, as these antibiotics are widely utilized, there has been a rising number of reports on the emergence of drug non-susceptible strains among these antibiotics called the "MIC creep" phenomenon [47,48].

Susceptibility tests on four major MRSA STs (ST239, ST5, ST59, and ST398) isolated from 61 hospitals in China from 2014 to 2019 discovered that all strains maintained resistance to penicillin and all MRSA exhibited sensitivity to vancomycin, daptomycin, and linezolid [49]. The susceptibility of other antibiotics changed between STs [49]. Overall, ST239 clone showed a high (>66%) and increasing trend of resistance rate in tetracycline and quinolones. The ST5 clone maintained a consistently high resistance rate (>78%) to quinolones and erythromycin. The ST59 clone exhibited high resistance rates (>80%) only to erythromycin and clindamycin, with an overall decreasing trend for moxifloxacin, and the resistance rates to amikacin and tetracycline began to decline after reaching their peak in 2016. The ST398 clone showed relatively low overall resistance rates to antimicrobial drugs, with a generally increasing trend for clindamycin and high fluctuation for erythromycin and tetracycline [49].

To date, at least 15 major *staphylococcal* cassette chromosome *mec* (SCC*mec*) types (I–XV) have been identified [49–51]. Over the past decade, MRSA-SCC*mec* IV and SCC*mec* V has spread widely in China, gradually replacing previously prevalent hospital-acquired MRSA-SCC*mec* II and III types [53,53]. While MRSA-SCC*mec* II has shown a declining trend in recent years, it still dominates in the East China region [54,55]. SCC*mec* elements IV (21–24 kb) and V (27 kb), being relatively smaller, facilitate their transfer among *S. aureus* strains, enhancing their potential for dissemination. MRSA carrying IV and V SCC*mec* elements typically show sensitivity to many non-β-lactam antibiotics and are predominantly found in community-acquired MRSA (CA-MRSA)

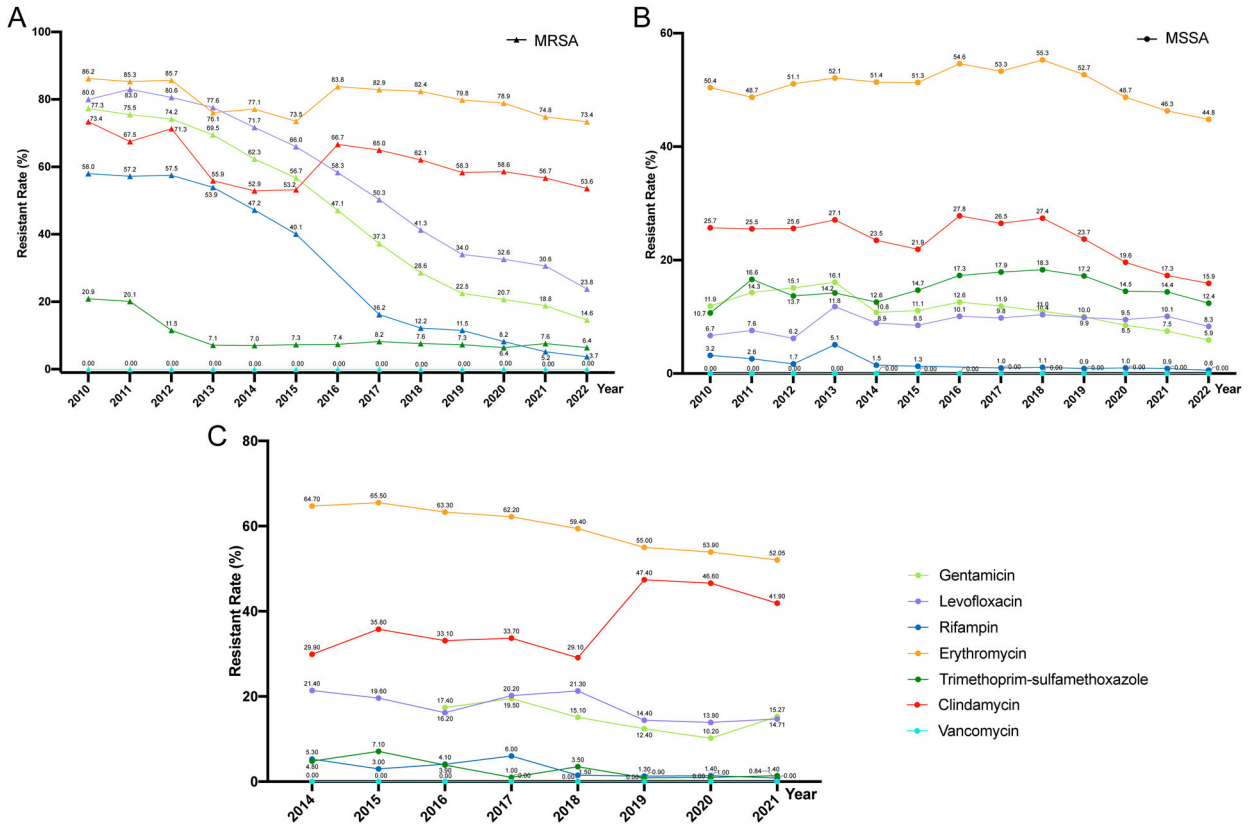

Figure 4. Antimicrobial resistance trends for *S. aureus*. (A, B). data from CHINET. (C). data from BRICS.

in China [49]. In China, the recently prevalent ST59 clone is primarily associated with SCC*mec* IV [56,57]. IV and V elements are also present in some widely distributed healthcare-aquired (HA)-MRSA clones, such as ST22-MRSA-IV, ST45-MRSA-IV, and ST5-MRSA-VI [58]. A rising number of variants of SCC*mec* elements that harbour composite cassettes and pseudo-SCC*mec* elements but do not harbour *ccr* genes, have also been detected in recent years. This reflected the ongoing intra/interspecies genetic rearrangements [59]. Among the 1,006 MRSA strains collected between 2014 and 2020 in China, a total of 25 non-duplicate MRSA strains with non-typeable SCC*mec* elements were detected, provide evidence for the ongoing evolution of SCC*mec* elements within MRSA [60]. *mecA*-positive but phenotypically susceptible to oxacillin, suggesting potential frameshift mutations or single base substitutions in nucleotide repeat regions within *mecA*, with the capability to revert to resistance when exposed to antibiotics [61].

Reshaping the epidemiology of MRSA

Between 2005 and 2010, the ST239 clone dominated MRSA clones in China (50–80.8%), followed by the ST5 clone (15.5%) [54,61]. Since 2010, multiple studies have confirmed a decrease in the prevalence of the dominant MRSA ST239 and ST5 clones in China, while ST59 has been steadily increasing [21,62]. The isolation rate of ST59-MRSA increased from 25.09% in 2014 to 35.58% in 2019 [63,64]. Jin et al. discovered that in bloodstream infections, the ST59 clone becoming the dominant clone in most Chinese hospitals (33%−36.98%), with varying prevalence rates among different provinces ranging from 17.86% to 80.95%; the ST239 clone causing decreased from 10.29% in 2014 to 3.05% in 2019, while ST5 sharply declined from 39.71% to 9.64% during the same period [49].

In the past decade, the “main battlefield” of MRSA has shifted from hospitals to the community, with a reciprocal influence from the community to hospitals [65–67]. The boundary between HA-MRSA and CA-MRSA has become increasingly blurred. With the rapid development of whole-genome sequencing, CA-MRSA is defined based on microbiological and molecular characteristics, utilizing SCC*mec* typing and phylogenetic methods [21,68]. The prevalence of CA-MRSA in China has become significant, reaching a rate of 24%, with the unique Chinese CA-MRSA clone CC59 (mainly ST59) has been steadily increasing [52,62]. Studies reported that HA-MRSA strains belonged to the CC59-MRSA-IV/V-t437 clone, exhibiting characteristics of traditional Chinese CA-MRSA, carrying SCC*mec* IVa, and being PVL-positive [52,63]. However, HA-MRSA ST59 displayed higher resistance to compound sulfamethoxazole and gentamicin, while CA-MRSA ST59 was more likely to be resistant to clindamycin and levofloxacin. The *sak* and *chp* genes carried by MRSA ST59 and higher toxin gene content may be associated with the

increased transmission success of this clone [49,64]. It's worth noting that Chen et al. found that almost all CC59 isolates in China (91%) exhibited sensitivity to the combination of penicillin and clavulanic acid due to the susceptible genotype [52]. The increasing prevalence of ST59 clones in Chinese hospitals highlights the multifaceted adaptive evolution of MRSA as a pathogen, extending beyond the community healthcare environment.

ST5 HA-MRSA clone is considered a representative epidemic clone in East China, with high prevalence reported in Shanghai and Zhejiang [55,69]. Wu et al. reported that ST5-t311-II lineage has become the predominant ST5 clone in Zhejiang Province (65%) [55]. The expansion and structurally unstable nature of the CC5 population were noted, with ST5-t311-II, ST764-t1084-II, ST5-t2460-II and ST764-t002-II existing complex competition [63]. The intra-hospital dissemination of ST5-MRSA has led to nosocomial outbreaks [70]. Simultaneously, the proportion of some sporadic STs, such as ST30, ST4513, ST1821, and ST5529, causing bloodstream infections in China increased from 5.88% in 2014 to 20.30% in 2019, demonstrating a rising diversity of MRSA strains over the years. It is noteworthy that, despite its lower prevalence, the ST398 clone has shown an increasing trend; as reported, an increase in the isolation rate of the ST398 clone from 1.47% in 2014 to 9.14% in 2019 [49,69].

As the isolation rate of HA-MRSA declines, increasing attention is being directed towards MRSA's animal hosts [71]. The livestock-associated MRSA (LA-MRSA) is predominantly associated with CC398 (in Europe) and CC9 (in Asia), causing infections primarily among individuals engaged in livestock farming [71]. However, recent observations indicate that LA-MRSA can also infect some individuals who have not had direct contact with animals. Phylogenetic analysis along with the distribution of resistance genes demonstrated that HA-ST9 MRSA and LA-ST9 MRSA share similar genetic backgrounds, which provides evidence that multidrug-resistant LA-MRSA-ST9, evolved in the livestock industry, spreads to communities and clinical settings through trade chains [60].

Vancomycin-intermediate S. aureus *(VISA) and heterogeneous VISA (hVISA)*

hVISA/VISA infections, reported since 1996, have been linked to poor patient outcomes. A meta-analysis reveals that Vancomycin-resistant *S. aureus* (VRSA), VISA and hVISA isolates have a worldwide prevalence of 1.5%, 1.7% and 4.6% in *S. aureus*, respectively [72]. No VRSA cases have been reported in China; however, VISA and hVISA are present at rates of 0.5% and 10.0%, respectively, with hVISA showing a significantly higher isolation rate compared to global levels [72]. Moreover, there is a growing concern due to the increasing prevalence of hVISA in recent years. Shen et al. identified 7.6% (36/476) hVISA among *S. aureus* isolated in 2010–2011 [73], while Liang et al. discovered 10.8% (22/204) hVISA among isolates from inpatients and outpatients in 2019–2021 [74]. With the recent decrease in MRSA isolation rates, the proportion of MRSA among VISA/hVISA has also declined [73,74]. Liang et al. reported 22.7% of hVISA isolates belonged to ST72 and CC5 (ST5/965/7197), followed by CC59 (ST59) and ST25 (18.2%, respectively), which indicated that previous dominant hVISA/VISA clone ST239 in China is changed [74].

Klebsiella pneumoniae

Klebsiella pneumoniae rose from about 15% to around 20% in all the clinical isolated bacteria nationwide (CARSS data). In the nationwide bloodstream infections surveillance (BRICS), *K. pneumoniae* increased from 9.91% in 2014–18.9% in 2021 (Figure 2). Over the past decade, no matter in all clinical samples or in bloodstream infection samples, *K. pneumoniae* has exhibited an overall steady rise of resistance to cephalosporins, aminoglycosides, fluoroquinolones, polymyxins and tigecycline [9,19]. In special, the increasing isolation rate of carbapenem-resistant *K. pneumoniae* (CRKP) is concerning [75]. Furthermore, *K. pneumoniae* demonstrates relatively high sensitivity to tigecycline, polymyxin, and ceftazidime-avibactam, with nationwide surveillance in 2022 indicating resistance rates of 2.6%, 2.8%, and 6.2% for these antibiotics (CHINET data) (Figure 5), respectively. The issue of drug resistance in *K. pneumoniae* has become one of the most challenging among Enterobacteriaceae worldwide [76].

Resistance to carbapenems

With widespread clinical use, resistance to carbapenems among Enterobacteriaceae, particularly CRKP, has become increasingly serious in China [76–78]. According to CHINET, the resistance rates of *K. pneumoniae* to imipenem and meropenem have straightly climbed from 8.8% and 8.9% in 2010–25.0% and 26.3% in 2018. However, a stabilizing trend is observed from 2019 onwards, with rates of 22.6% and 24.2% in 2022. This suggests a plateauing of carbapenem resistance development, potentially influenced by optimized antimicrobial drug use in China and a reduction in nosocomial infections due to the COVID-19 pandemic since 2019 [19]. Regional variations in resistance rates are substantial, with resistance predominantly concentrated in eastern China [19,79]. Similarly, the incidence of CRKP in BRICS countries sharply increased from 2014 to 2018 (5.2% to 21.4%) and has been slowly declining from 2018 to 2021 (21.4% to 15.8%) [9] (Figure 5).

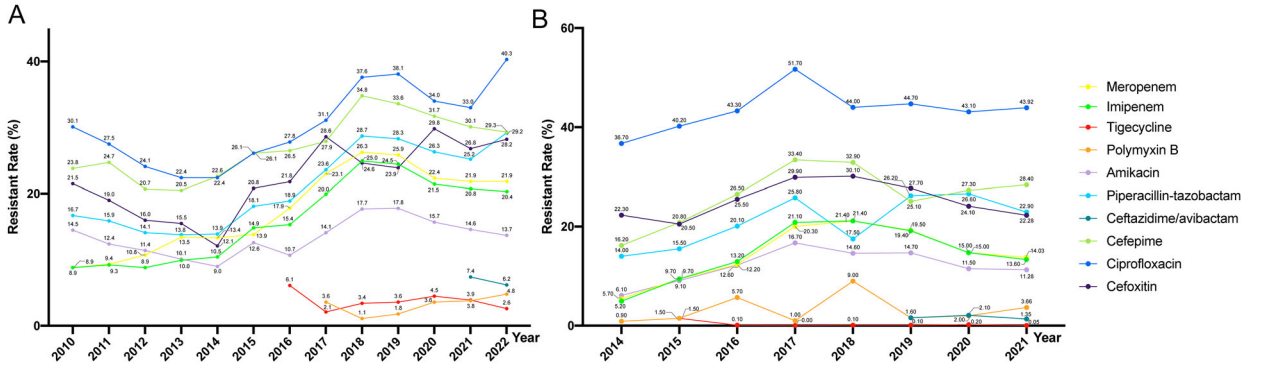

Figure 5. Antimicrobal resistance trends for *K. pneumoniae*. (A). data from CHINET. (B). data from BRICS.

KPC enzymes account for more than 70% of CRKP, followed by NDM-producing strains, while the prevalence of IMP, VIM, and OXA-48 enzymes is relatively low in China [79,80]. China reported the first KPC-producing CRKP in 2007 [81], and the prevalent genotype is $bla_{\text{KPC-2}}$, most commonly associated with the epidemic clone ST11, accounting for approximately 60–80% of the CRKP isolation rate [82]. Different from the classical Tn4401 background reported in the United States, China identified unique genetic backgrounds for $bla_{\text{KPC-2}}$, such as Tn3 transposon and partial Tn4401 fragments [83]. New structures like Tn1721-$bla_{\text{KPC-2}}$-Tn3 and Tn1721-$bla_{\text{KPC-2}}$-ΔTn3-IS*26* have been discovered in China [84,85]. The predominant plasmid carrying $bla_{\text{KPC-2}}$ in ST11 CRKP in China is IncFII type [86,87]. In contrast, in other international regions, diverse plasmids like IncFIA, IncX, IncP, IncN, and IncC are common carriers of $bla_{\text{KPC-2}}$, indicating the diversity and widespread dissemination of KPC-2 resistance plasmids between regions [88,89]. These plasmids, containing $bla_{\text{KPC-2}}$, often carry genes conferring resistance to other antibiotics, resulting in the multidrug resistance of CRKP [89].

Another representative of the epidemic CRKP strains carries NDM enzymes, belonging to class B metallo-β-lactamases dependent on zinc. These enzymes can hydrolyze all β-lactam antibiotics except aztreonam and are not inhibited by β-lactamase inhibitors. In China, the main genotypes are $bla_{\text{NDM-1}}$ and $bla_{\text{NDM-5}}$, and although the isolation proportion is lower than that of KPC-2, it is more common in CRKP isolated from pediatric patients [90–92]. Furthermore, there has been an increase in the reported incidence of $bla_{\text{OXA-48}}$-like genes in China in recent years. Individual regions have experienced small-scale outbreaks, with $bla_{\text{OXA-232}}$ being the most prevalent, mainly associated with ST15 CRKP and carried by ColKP3-type plasmids [93]. In Taiwan, $bla_{\text{OXA-48}}$ has been reported in ST11 *K. pneumoniae* [94]. Moreover, in China, the combination of bla_{NDM} and bla_{KPC} is prevalent among *K. pneumoniae* [78,95].

In recent years, it has been observed that CRKP in China is undergoing evolution with the acquisition of high virulence traits, and there is an increasing number of reports on highly virulent CRKP [96–102]. Current studies suggest that the emergence of highly virulent CRKP is primarily the result of bidirectional evolution involving both high virulence and high resistance [14,103,104]. One pathway involves classic high-virulence *K. pneumoniae* (hvKP) acquiring plasmids or mobile elements containing carbapenem-resistant genes. Another pathway is CRKP acquiring virulence plasmids or mobile elements containing virulence genes [83,105–107]. It is noteworthy that through widespread transposon-mediated transposition or the fusion of resistance plasmids and virulence plasmids, virulence and resistance genes can be located on the same conjugative plasmid [108,109]. In recent years, an alternating trend of sub-clones has been observed among the prevalent ST11-type CRKP strains in China, with KL64 gradually replacing the earlier KL47 type [14,104]. KL64 carries a series of virulence genes associated with high pathogenicity, contributing to a high mortality rate in clinical infections [14]. An analysis of 1,052 CRKP strains from 19 regions and 56 centres in China between 2015 and 2017 revealed that 34.2% of CRKP strains carried virulence genes, primarily iron carrier genes (*iucA*, *iroN*), and capsular polysaccharide expression regulatory genes (*rmpA* and *rmpA2*). 80% of these strains belonged to the ST11-KL64 clone carrying the $bla_{\text{KPC-2}}$ gene [96]. Zhou et al. revealed the gradual replacement of the once prevalent sub-clone OL101: KL47 by O2v1: KL64, with the latter exhibiting an increased abundance of mobile genetic elements. Additionally, a specific point mutation in the *recC* of O2v1: KL64 significantly enhances recombination proficiency [104]. The prevalent ST11 clone of CRKP in China is undergoing rapid evolution, forming a pathogenic and highly transmissible high-risk sub-clone, posing significant challenges to clinical diagnosis and treatment as well as infection control in healthcare settings [110,111].

Resistance to ceftazidime/avibactam

Ceftazidime/avibactam (CAZ/AVI) is currently the first novel β-lactam/β-lactamase inhibitor combination available for the treatment of infections caused by KPC-producing Enterobacteriaceae [112]. It was officially launched in China in early September 2019. Avibactam, within this combination, inhibits KPC and OXA-48 enzymes but does not inhibit metallo-enzymes like NDM. With its clinical application, there have been reported cases of non-metallo-enzyme CRKP resistance to CAZ/AVI [113]. The resistance rates to CAZ/AVI in China have been monitored since 2020, with resistance rates decreasing from 11.8% and 14.9% in 2020 to 6.2% and 9.1% in 2022 for *K. pneumoniae* and CRKP, respectively. Moreover, resistance rates were higher in children compared to adults, possibly due to a higher prevalence of metallo-enzymes like NDM in children.

CAZ/AVI resistance primarily due to mutations in the bla_{KPC} gene and alterations in outer membrane porins [75,113]. To date, over 150 variants of bla_{KPC} have been reported globally, with the majority of new variants identified in the last three years, warranting public concern [75]. The variant KPC protein increases its affinity to ceftazidime while reducing its affinity to avibactam through structural changes, thereby facilitating bacterial resistance to CZA [75]. Zhang et al. reported that resistance against CAZ/AVI in CRKP emerged before clinical use of CAZ/AVI in China, although most of the CRKP isolates maintained the susceptibility [113]. Among the resistant isolates, 53.1% (17/32) were metallo-blactamase-producing *K. pneumoniae* (MBL-KP), 40.6% (13/32) were KPC-producing *K. pneumoniae* (KPC-KP) and 6.3% (2/32) produced both MBL and KPC [113]. MBL production, bla_{KPC-2} point mutation and high KPC expression played an important role in CAZ/AVI resistance [113]. Shi et al. reported CAZ/AVI resistance caused by the change from KPC-2 to KPC-33 carbapenemase via the D179Y variant [12]. Plasmid-mediated novel CMY-type AmpC β-lactamase, leading to high-level resistance to CAZ/AVI, was discovered [114]. Therefore, enhanced monitoring is essential to prevent the spread of novel CAZ/AVI -resistant strains in China.

Resistance to polymyxins

Polymyxins (polymyxin B and polymyxin E) were officially introduced into clinical use in China in 2018. Prior to its clinical use, there was a lack of attention to polymyxins resistance in China's clinical antimicrobial resistance monitoring system. However, it had been closely monitored in the country's animal bacterial resistance monitoring system because polymyxins had been widely used in livestock farming before being reintroduced for clinical use [10,115]. Due to prolonged exposure to low concentrations of polymyxins, there has been a selection pressure leading to the prevalence and spread of low-level polymyxin-resistant strains mediated by the mobile resistance gene *mcr* [115].

The continuous increase in polymyxins resistance among clinically isolated strains, especially in countries with a high proportion of MDR and carbapenem-resistant strains, is a particularly concerning issue [116]. Research data from the European Antimicrobial Resistance Surveillance Network (EARS-Net) indicates that CRKP exhibits a much higher resistance rate to polymyxins than carbapenem-sensitive strains, especially in countries with a high prevalence of CRKP, such as Greece and Italy. In China, the resistance rates of *K. pneumoniae* to polymyxin B and polymyxin E have increased from 1.1% and 1.2% in 2018–4.8% and 2.8% in 2022, respectively. The resistance rate of CRKP to polymyxins has increased from 3.6% in 2020–8.2% in 2022 (CHINET data). In recent years, the increase in polymyxins resistance among *K. pneumoniae* has been significantly greater than that observed in other Gram-negative bacteria (BRICS and CHINET data) (Figure 5). It can be anticipated that without the proper use of polymyxins, the resistance rates of Gram-negative bacteria in China, especially CRKP, to polymyxins will continue to rise, leading to a further loss of effective antibiotic treatment options [116].

The resistance mechanisms of different bacterial species to polymyxin can be broadly classified into chromosome gene mutation-mediated and plasmid *mcr* gene-mediated [117]. Chromosome gene mutations associated with polymyxin resistance that have been reported include *pmrCAB*, *phoPQ*, *mgrB*, *pmrD*, *etc* [118]. Additionally, mutations in the *crrAB* two-component regulatory system have been reported in *K. pneumoniae* [119,120]. What's more, one significant factor contributing to the increasing trend of polymyxins resistant CRKP is the high proportion of heteroresistance characteristics in *K. pneumoniae*, making them prone to mutations that induce full-resistance [121]. Therefore, the resistance of clinical isolates to polymyxins underscores the importance of addressing chromosomal gene mutations leading to heteroresistance as a consequence of clinical polymyxin use.

Resistance to tigecycline

In recent years, the heavy use of tigecycline (TGC) in clinical settings has resulted in the global emergence of resistance [122]. Tigecycline was introduced to the clinical in China at the end of 2011. The tigecycline resistance rate of clinical isolated *K. pneumoniae* in China has increased from 2.1% in 2017–3.9% in

2022. Tigecycline resistant rate of CRKP was higher, reaching to 5% in 2022 (Figure 5).

The mechanisms underlying TGC resistance in Enterobacteriaceae are complicated and have not been fully elucidated. Studies revealed that TGC resistance is primarily due to chromosome-encoding mechanisms, including overexpression of efflux pumps and ribosome protection [123–125]. An uncommon mechanism of TGC resistance is provided by enzymatic inactivation mediated by the flavin-dependent monooxygenase Tet(X) [11,126]. Fortunately, the mobile tigecycline-resistance *tet*(X) genes currently are rarely found in clinical isolates. A nationwide epidemiological analysis discovered no *K. pneumoniae* isolates were positive to *tet*(X) genes though 4% isolates were resistant to TGC [127].

Resistance to aminoglycosides

Aminoglycosides are important options for treating life-threatening infections and are generally administered in combination with β-lactam agents [128]. In China, the resistance rate of *K. pneumoniae* to gentamicin decreased from 34.0% in 2010–25.1% in 2022, possibly attributed to a reduction in the usage of gentamicin. In contrast, the resistance rate to amikacin showed a slow decrease from 14.4% in 2010–13.7% in 2022. Additionally, in 2022, CRKP exhibited resistance rates of 75.8% to gentamicin and 62.2% to amikacin (CHINET data) (Figure 5).

The predominant mechanism of aminoglycoside resistance involves the activity of aminoglycoside-modifying enzymes (AMEs) [129]. However, a significant mechanism mediating resistance to nearly all clinically available aminoglycosides is the production of 16S rRNA methyltransferase (16S-RMTase) [130]. *rmtB* and *armA* are the most widespread 16S rRNA methylase genes [131]. Furthermore, there is an emerging trend of high-level aminoglycoside resistance (HLAR) in *K. pneumoniae* isolates in China, where they carry 16S rRNA methylase genes (*armA* and *rmtB*), resulting in aminoglycoside MIC values exceeding 256 μg/mL [132]. Zhang et al. reported an incidence of 13.7% (40/292) HLAR strains, with *rmtB* being the predominant resistance gene (70%, 28/40), identified in a Chinese teaching hospital, and discovered conjugative *armA* and AME genes carrying plasmid [132].

Resistance to fosfomycin

Fosfomycin, an old antibiotic, has been re-introduced to fight infections caused by CRKP. However, the trend of fosfomycin resistance among CRKP is increasing dramatically in China, and becomes an emerging problem. CHINET data indicates that the resistance rate of CRKP to fosfomycin has remained consistently around 50% from 2019 to 2022. However, data from BRICS reveals that the resistance rate of all bloodstream *K. pneumoniae* isolates to fosfomycin has shown a linear increase, rising from 0.4% in 2014–11.57% in 2021 (Figure 5). Huang et al. reported that 80.0% (64/80) carbapenemase-producing *K. pneumoniae* (KPC-KP) were resistant to fosfomycin from three tertiary hospital in China (2014–2017) [133], and is similar to the report by a systematic review of the literature (73.5%) [134].

Bacterial resistance to fosfomycin can be caused by multiple mechanisms, including transporter defect (i.e. GlpT- or Uhp-deficient strains), target modification and FosA-mediated inactivation [133]. Most *fosA3*-carrying KPC-KP strains are highly resistant to fosfomycin (MIC > 2048mg/L) [133]. Huang et al. and Xiang et al. reported that 36.3% (29/80) and 45.4% (44/97) of the KPC-KP were positive for the mobile fosfomycin resistance gene *fosA3*, respectively, in China [133,135]. All *fosA3*-positive strains belonged to the dominant ST11-pulse type [135]. Findings indicate that the two major mechanisms of resistance identified were plasmid-mediated fosfomycin resistance gene *fosA3* and mutation of the target gene *glpT* [133,135].

Escherichia coli

Although *E. coli* is not included in the ESKAPE pathogens, its clinical isolation rate (accounting for stable approximately 29% of Gram-negative bacteria, CARSS data) has consistently been 8–10 percentage points higher than that of *K. pneumoniae* in China. It has remained the most prevalent species in terms of isolation rates among Gram-negative bacteria and displayed important MDR phenotypes. Therefore, we included *E. coli* in this review. The bloodstream infection isolation rate of *E. coli* has increased in recent years, rising from 29.13% in 2014–37.60% in 2021 (BRICS data) (Figure 2). However, this growth trend, while notable, has not been as rapid as the nearly twofold increase observed in *K. pneumoniae* during the same period.

As two of the most representative species within the Enterobacteriaceae family, *E. coli* exhibits similar antibiotic resistance characteristics compared with *K. pneumoniae*. However, in recent years, the resistance trend in *E. coli* has shown a more moderate increase compared to *K. pneumoniae*. From various clinical isolation sources, *E. coli* has shown a generally stable or decreasing trend in resistance rates to most antibiotics in recent years. In 2022, *E. coli* exhibited high resistance rates to ciprofloxacin (61.4%) and cefepime (25.1%). However, resistance rates to ceftriaxone, fosfomycin, piperacillin-tazobactam, polymyxin B, and tigecycline were relatively low, at 9.7%, 4.4%, 4.3%, 2.2%, 1.0%, and 0.1% in 2022, respectively

(CHINET data). From 2014 to 2021, the resistance rates of bloodstream-isolated *E. coli* to imipenem and meropenem have consistently remained between 1% and 1.6%. The resistance to polymyxin B (0.5% to 3.1%) and ceftazidime-avibactam (0.56% to 1.2%), and tigecycline (0% to 0.3%) have consistently been low. The resistance to ciprofloxacin varied from 27% to 30.4%. Over the same period, resistance to cefperazone-sulbactam (15.3% to 5%) and cefoxitin (19.5% to 9.15%) decreased, while resistance to fosfomycin increased from 0.1% to 3.57% in bloodstream-isolated *E. coli*. The bloodstream-isolated *E. coli* has exhibited a notable upward trend in resistance to fosfomycin, mirroring the trend observed in bloodstream-isolated *K. pneumoniae* (BRICS data) (Figure 6). This contrasts with the generally stable or decreasing resistance rates to most antibiotics, highlighting a divergent pattern that warrants continued attention and further research into the mechanisms underlying fosfomycin resistance.

Carbapenem-resistant *E. coli* (CRECO) in China typically carry the NDM gene. Bi et al. reported that 70.83% (102/144) CRECO isolates that produced various NDMs. In addition, CRECO also produced KPC-2 ($n = 15$), IMP-4 ($n = 3$), and OXA-48 ($n = 3$) [136]. The bla_{NDM} gene is rarely found on the chromosome but is predominantly located on plasmids, with plasmid types covering IncX3, IncFII, IncC, IncFIB, IncHI1B, and others [137]. This indicates that various plasmids can acquire bla_{NDM} and facilitate horizontal transfer through plasmid mediation [137]. In China, IncX3 is the most common plasmid type carrying bla_{NDM}, suggesting that IncX3 plasmids may be the primary vehicles mediating the dissemination of bla_{NDM} in China [138,139]. An analysis of all NDM-1 gene sequences revealed the consistent presence of the IS*Aba125* sequence in the upstream 100 bp region of the $bla_{\mathrm{NDM\text{-}1}}$ gene, indicating that the $bla_{\mathrm{NDM\text{-}1}}$ gene likely first appeared in *A. baumannii*, mediated by IS*Aba125* [140,141]. Furthermore, downstream of the $bla_{\mathrm{NDM\text{-}1}}$ gene, there is a consistent presence of the ble_{MBL} gene, conferring resistance to bleomycin [140]. Other bla_{NDM} variants share a similar genetic background with $bla_{\mathrm{NDM\text{-}1}}$, often associated with upstream IS*Aba125* (complete or truncated) and downstream ble_{MBL} [142]. *E. coli* exhibits resistance mechanisms to antibiotics such as polymyxins, aminoglycosides, and fosfomycin that are similar to those observed in *K. pneumoniae* [143]. Reports suggest that the prevalence of the *fosA3* gene in fosfomycin-resistant *E. coli* may be higher than *K. pneumoniae*. Li et al. reported that 83.3% of fosfomycin-resistant *E. coli* carry the *fosA3* gene, with 70% of the *fosA3* genes located on transferable resistant plasmids [144]. This indicates that the dissemination of fosfomycin resistance in *E. coli* is likely to be a significant concern.

Acinetobacter resistance

Acinetobacter baumannii is an opportunistic human pathogen that infected particularly in critically ill patients, mainly causing hospital-acquired (HAP) and ventilator-associated pneumonia (VAP) [145,146]. *A. baumannii* is now considered a global threat in the healthcare setting mainly owing to its propensity to acquire multidrug resistance phenotypes and to thrive in the healthcare environment at previously unforeseen rates [147,148]. What's more, *A. baumannii* globally exhibits a high MDR rate, reaching approximately 45% [149]. The overall mortality rate estimate for *A. baumannii* infection reach up to 45% and is a major concern for nosocomial infection control [149,150]. Studies estimated that in 2019, carbapenem-resistant *A. baumannii* (CRAB) ranked as the fourth most burdensome pathogen–drug combination in high-income regions and the third in South Asia [2,151]. In China, CRAB consistently demonstrating pan-drug resistance and susceptibility only to polymyxins and tigecycline, has an isolation rate of around 70%, which has been increasing in recent years [152].

According to the CHINET monitoring results from 2015 to 2021, *A. baumannii* maintains an absolute dominance among all clinically isolated *Acinetobacter* species, with an average composition ratio of 89.6% over the seven years [19]. Apart from minocycline,

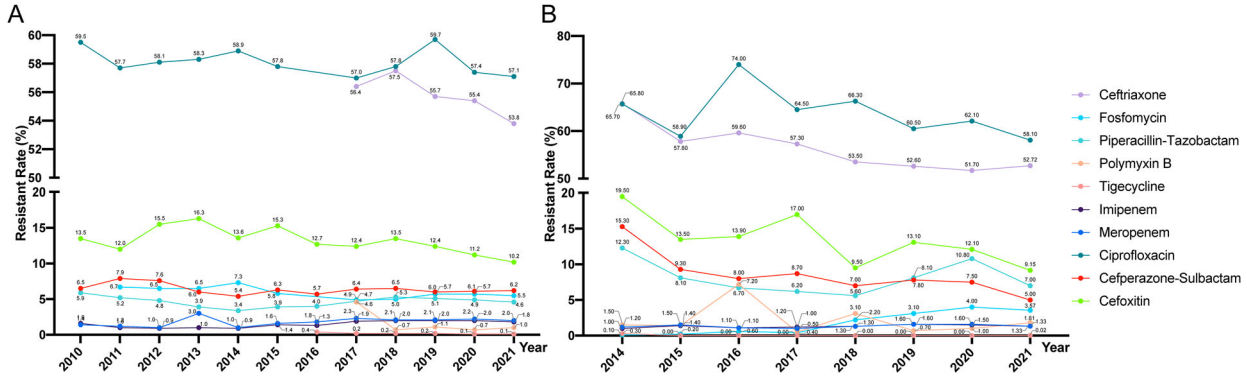

Figure 6. Antimicrobial resistance trends for *E. coli*. (A). data from CHINET. (B). data from BRICS.

tigecycline, and polymyxin B, *A. baumannii* exhibit higher resistance rates to other antimicrobial agents such as β-lactams, aminoglycosides, and fluoroquinolones [9]. From 2015 to 2021, there was an increasing trend in the resistance of *A. baumannii* to cefoperazone-sulbactam (from 40.6% to 52.8%) and piperacillin-tazobactam (from 64.5% to 73.2%), while a decreasing trend was observed in resistance to tigecycline (from 10.3% to 2.8%) and minocycline (from 30.4% to 21.0%) (Figure 7).

A study of nationwide and genome-based surveillance on CRAB strains collected from intensive care units (ICUs) in hospitals in different provinces in China found that CRAB strains were prevalent in 71.4% (55/77) of the ICUs surveyed. The study further indicated that CRAB isolates exhibited a notably low resistance rate to colistin (0.4%) and tigecycline (2.5%), while displaying a high resistance rate to ceftazidime–avibactam (70.2%) [153]. 59% among the GenBank available genomes of *A. baumannii* belongs of global clone (GC)2 according to the Institut Pasteur MLST scheme [154], which is mainly clonal complex (CC)92 according to the Oxford MLST. ST195, ST191 and ST208 are the most prevalent *A. baumannii* STs belonging to CC92 [155–158]. Clonal dissemination of CRAB was identified in 37.6% (29/77) of ICUs, revealing a total of 22 distinct clones and majority of these clones demonstrated transmissibility within a single ICU [153].

The major mechanism of carbapenem resistance in *A. baumannii* occurs through the action of acquired OXA-type carbapenem-hydrolyzing class D β-lactamases, which are encoded by $bla_{\text{OXA-23}}$-like, $bla_{\text{OXA-40}}$-like, $bla_{\text{OXA-58}}$-like, $bla_{\text{OXA-143}}$-like, and $bla_{\text{OXA-235}}$-like genes [159,160]. CRAB is less commonly mediated by MBLs and only exceptionally by class A KPC and GES beta-lactamases [160]. The AdeABC efflux pump system contributed to CRAB isolates, as evidenced by the high expression of some of its encoding genes [150]. CRAB from the global T.E.S.T. worldwide surveillance between 2012 and 2016 (data from hospitals in 47 countries representing a total population of around 2.2 billion people spread over five geographical regions) that acquired OXA-type carbapenemase genes were found in 300 (96%) isolates with $bla_{\text{OXA-23}}$-like and $bla_{\text{OXA-40}}$-like predominating, which constitutes a significant increase compared to their findings from 2010 [161].

Polymxyins and tigecycline are commonly regarded as potent first-line agents for treating infections caused by CRAB [162]. While most CRAB strains remain highly sensitive to colistin and tigecycline, there has been a growing number of reports on *A. baumannii* strains resistant to these antibiotics in recent years. In 2022, CHINET revealed CRAB exhibited 1.2% resistance to polymyxins and 3.1% resistance to tigecycline (Figure 7). However, currently, over 50% of clinical *A. baumannii* strains demonstrate resistance to CAZ-AVI [112]. Presently, mutations in the *pmrA*/*pmrB* and *lpxACD* genes are the primary mechanisms of *A. baumannii* resistance to colistin [163,164]. Conversely, mutational changes in the *tet*(X) gene and the overexpression of resistance-nodulation-cell division (RND) efflux pumps are the major mechanisms observed in tigecycline-resistant *A. baumannii* isolates [165].

Pseudomonas aeruginosa

The isolation rate of *P. aeruginosa* has seen a relatively stable trend in China, from 12.7% in 2014 to 11.9% in 2022, and still ranks third among clinically isolated Gram-negative bacteria in China. MDR and extensively drug-resistant XDR *P. aeruginosa* poses an increasing global threat of nosocomial infections [166]. According to CHINET, *P. aeruginosa* shows a generally stable or decreasing trend in resistance to most drugs in China, and decreased for almost all antibiotics, during the five-year period. Resistance to imipenem and meropenem decreased in *P. aeruginosa* nationwide. From 2010 to 2022, the rates of imipenem and meropenem resistant isolates decreased from 30.8% to 22.1% and from 25.8% to 17.6%, respectively. However, CRPA in Zhejiang Province increased annually from 22% in 2015–38.67% in 2017 and that Zhejiang had the highest rates of CRPA of all

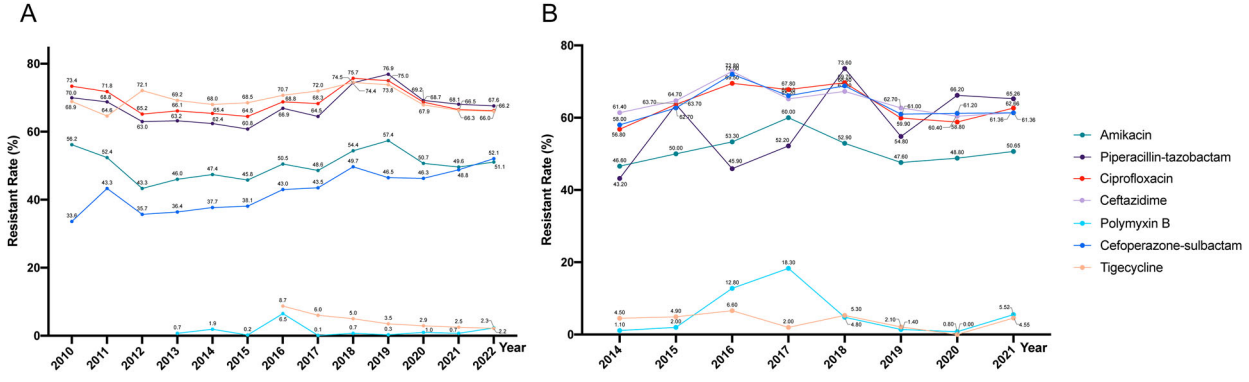

Figure 7. Antimicrobial resistance trends for *A. baumannii*. (A). data from CHINET. (B). data from BRICS.

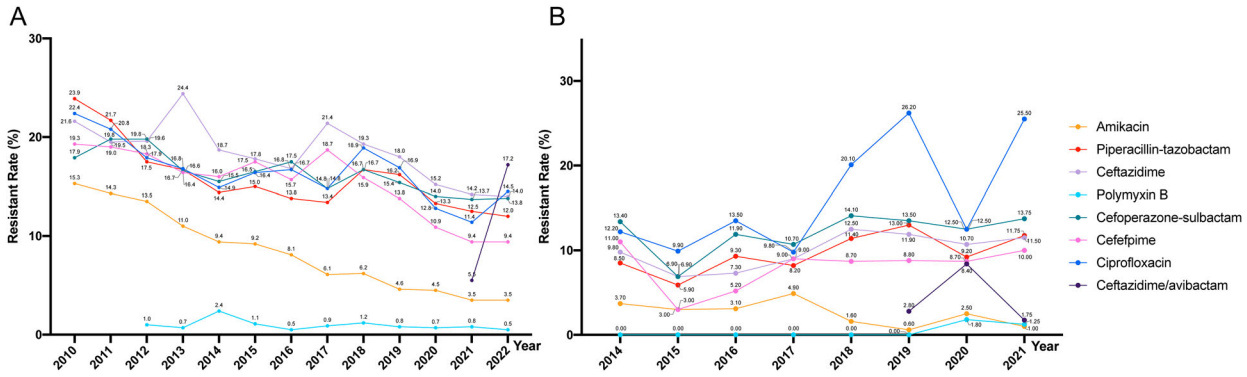

Figure 8. Antimicrobial resistance trends for *P. aeruginosa*. (A). data from CHINET. (B). data from BRICS.

provinces in China in 2017 [167]. Resistance to CAZ/AVI in *P. aeruginosa* significantly decreased from 11.1% in 2018–6.3% in 2022 [19]. Furthermore, in the recent five-years, the resistance rates to cefoperazone-sulbactam, piperacillin-tazobactam, ceftazidime, ciprofloxacin and amikacin decreased from 17.1% to 15%, 16.7% to 13.5%, 19.3% to 14.9%, 24.1% to 15.3%, and 6.2% to 3.8%, respectively. The resistance rates of colistin and polymyxin B fluctuated around 1.5% and 0.5% respectively (CHINET data). Nevertheless, the nationwide bloodstream surveillance system BRICS discovered an increase of *P. aeruginosa* in resistance to piperacillin-tazobactam (from 8.5% in 2014 to 11.75% in 2021), fosfomycin (from 0% in 2014 to 6.5% in 2021) and meropenem (from 6.1% in 2014 to 13.5% in 2021) (BRICS data) (Figure 8). Therefore, we still cannot relax our vigilance against the antibiotic resistance of *P. aeruginosa*.

P. aeruginosa demonstrates diverse characteristics in the prevalence of its clones [168]. Several STs of *P. aeruginosa*, including ST235, ST111, ST463 *etc*, are of special concern [168,169]. These infamous STs are strongly linked to adverse clinical outcomes and harbour a multitude of horizontally acquired resistance determinants. In recent years, prevalent clones have emerged in various regions across China. In Zhejiang, ST463 poses a potential health threat due to its unique combination of pyocyanin production and virulence genes [170]. In Shenzhen, the detection of $bla_{\text{NDM-1}}$ and *mcr*-1 in MDR *P. aeruginosa* underscores the need for continuous surveillance in pediatric patients [171]. In Shanghai, a low prevalence of polymyxin-resistant *P. aeruginosa*, including the globally disseminated ST277, was observed following polymyxin administration in a tertiary teaching hospital [172]. Furthermore, CRPA strains were reported in Shandong (ST244), Sichuan (ST277), and Hainan (ST357), respectively [173].

Enterobacter species

Enterobacter species rank fifth in the isolation rate of Gram-negative bacteria, comprising 3–5% of all bacterial isolates in China (CARSS data). Enterobacter species extracted from clinical samples are usually reported as *E. cloacae*, and sometimes *E. asburiae*, *E. hormaechei*, or *E. kobei*. They are all members of *E. cloacae* complex (ECC) [174,175]. The resistance rates of Enterobater species to imipenem and meropenem increased from 5.2% and 4.8% in 2010 to 9.7% each in 2022. Enterobacter species are highly sensitive to amikacin (resistant rate 1.6% in 2022), and tigecycline (resistant rate 1.9% in 2022) (CHINET data). Additionally, Enterobacter species exhibit a very high resistant rate (93.6%) to cefotaxime. Regarding the resistance of Enterobacter species to polymyxins, there is a discrepancy between the CHINET and BRICS data. CHINET data indicates that the resistance rate of *Enterobacter* species to polymyxin ranged from 2% to 5% from 2019 to 2022. However, BRICS data shows a different trend, with the resistance rate increasing from 1.5% in 2014 to 29.58% in 2021 (Figure 9). Although the exact prevalence of polymyxins resistance is uncertain, *Enterobacter* appears to exhibit a higher resistance rate than *Escherichia* and *Klebsiella* (usually <2% for both) [176,177]. What's more, *Enterobacter* species often exhibit heteroresistance to polymyxins [178], may cause the "skipped wells" phenomenon in broth microdilution, potentially influencing the observed resistance rate.

Strains of carbapenem-resistant Enterobacter (CR-Ent) have emerged in the last two decades that contributing majorly by carbapenemases, with 99.9% of *Enterobacter* clinical strains reported to be carbapenem-susceptible prior to 2001 [177]. A variety of carbapenemases have been found in *Enterobacter* with geographic specificity. KPC is prevalent in the Americas, VIM is most common in Europe, NDM is mostly encountered in India and mainland China [177]. *Enterobacter* has demonstrated faster carbapenem penetration via porins compared with *Klebsiella*, suggesting that porins may play an important role in carbapenem resistance in *Enterobacter* [179].

Clinical laboratories commonly categorize *Enterobacter* species as the ECC, leading to challenges in correlating antimicrobial resistance with specific

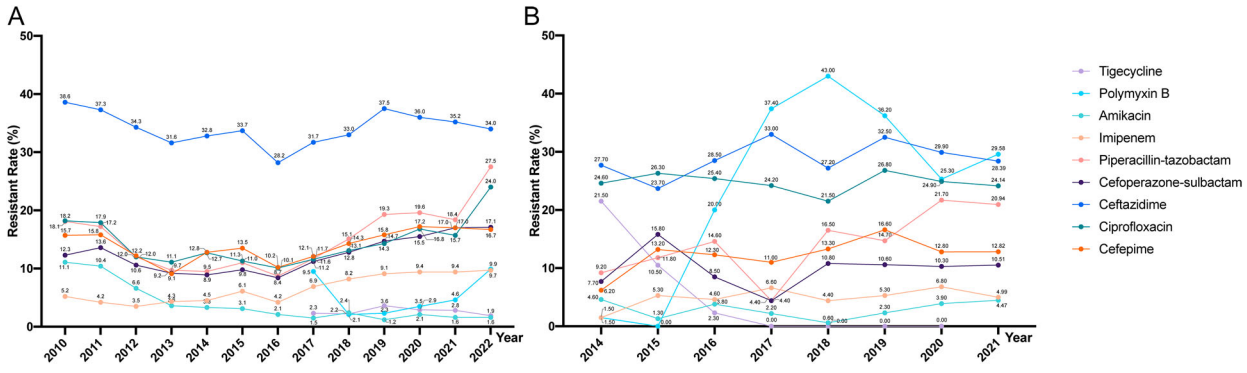

Figure 9. Antimicrobial resistance trends for *Enterobacter* species. (A). data from CHINET. (B). data from BRICS.

Enterobacter species. The widespread adoption of genomic sequencing analysis technology has made the classification ECC strains more convenient and accurate. Zong et al. analysed 4,899 *Enterobacter* genomes from GenBank, and revealed that *E. xiangfangensis* is the most prevalent species worldwide, with the bla_{NDM} gene predominantly found in China [177]. Study revealed that the most common human-source CR-Ent species in China was *E. xiangfangensis* (66/92, 71.93%), and the proportion of carbapenemase-producing Enterobacter (CP-Ent) in CR-Ent was high (72/92, 78.26%) in comparison to other global regions [177]. The high risk of carbapenemase-producing ST171 and ST116 *E. xiangfangensis*, and the bla_{NDM}-harbouring IncX3-type plasmid were detected and emphasized in China [180]. Furthermore, globally distributed strains, such as ST90, ST93, and ST114 *E. xiangfangensis*, and ST78 *E. hoffmannii*, are associated with multiple carbapenemases (VIM, NDM, KPC, and OXA-48) [181]. ECC is conventionally regarded as a low-virulence pathogen. However, an epidemic hypervirulent clone of *Enterobacter hormaechei*, ST133, showing high invasiveness and mortality in clinical settings was reported [182,183].

Concluding remarks and future directions

From the second decade of 21th, although the resistance rates of clinically isolated bacteria in China to common antibiotics continue to exhibit an increasing trend, there has been a slight stabilization or even a modest decline in resistance to certain antibiotics among some bacteria in recent years [19]. Moreover, the detection rates of critically important carbapenem-resistant bacteria, such as CRKP and CRPA, which have shown a continuous increase over many years, have recently demonstrated a consecutive decline [9,19]. This suggests the importance of enhancing bacterial resistance monitoring and implementing multidisciplinary collaboration, along with hospital infection prevention and control measures, as effective strategies to curb the epidemic spread of antibiotic resistant bacteria [4,5]. What's more, the variation in antibiotic resistant rates in China during the three-year period of COVID-19 pandemic control (from late 2019 to the end of 2022) may be influenced by differences in nosocomial infection control strategies [184]. Therefore, ongoing monitoring and attention are needed to assess the trend in antibiotic resistant rates in Chinese clinical settings starting from 2023.

In recent years, there has been a continuous evolution of prevalent antibiotic resistant bacterial clones. For instance, the prevalence of CA-MRSA strain ST59 invading clinical settings has gradually surpassed that of HA-MRSA ST239 and ST5 [49,53,62]. The proportion of *A. baumannii* ST208 in bloodstream infections has been steadily increasing [185,186], while the prevalence of high-virulence CRKP strains, such as ST11-KL64, is on the rise, with a simultaneous decrease in the prevalence of ST11-KL47 strains [104]. The emergence of next-generation sequencing has facilitated the development of advanced tools for monitoring and addressing the dissemination of antibiotic resistant bacteria [187,188]. Leveraging the advancements in high-throughput sequencing technology to study their systematic evolutionary dynamics and resistance evolution trends will aid in predicting the future direction of antibiotic resistant bacteria, providing essential insights for proactive monitoring and effective resistance control.

Data from the Centre for Antibacterial Surveillance in China indicates that in recent years, the utilization of antibiotics among outpatients and inpatients has significantly decreased. However, there is a continuous increase in the use or intensity of cephalosporin/beta-lactamase inhibitor combinations, carbapenems, and tigecycline [189]. The persistent high concentration of antibiotic usage is likely to have a direct impact on bacterial resistance [189]. Ongoing efforts in the antibiotic stewardship will play a crucial role in preventing and controlling antibiotic resistance.

The prevention and control of antibiotic resistance are not limited to clinical concerns; they also involve issues related to animal farming, environmental

pollution, food safety, and more [189,190]. Resistant bacteria in areas such as animals, the environment, and food can be transmitted to humans, as seen in the case of MRSA [191,192]. The use of antibiotics in animal farming and other sectors can lead to resistant bacteria, impacting the selection of antibiotics in clinical settings, such as the resistance issue with polymyxins [10,115]. Therefore, it is essential to adopt a One Health strategy to address antibiotic resistance in clinical settings, fostering collaboration across various sectors and optimizing the use of antibiotics in both human and animal contexts.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

This work was supported by The National Key Research and Development Program of China (2021YFC2300300). This work was partially supported by grants from the Key Research and Development program of Zhejiang province (No. 2021C03068), the Natural Science Foundation of Zhejiang Province, China (No. LY24H190002), the National Natural Science Foundation of China (No. 81971984).

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