Clinical Infectious Diseases

SUPPLEMENT ARTICLE

Current Status and Trends of Antibacterial Resistance in China

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The bacterial resistance surveillance system is relatively well established at the national, provincial, and hospital levels in China. Two representative national surveillance networks for bacterial resistance are the China Antimicrobial Resistance Surveillance System (CARSS) and the China Antimicrobial Surveillance Network (CHINET), both established in 2005. CARSS data show the different bacterial resistance rates among different provinces and autonomous regions for each specific bacterium. CHINET data mainly represent the bacterial resistance profiles of teaching hospitals and show the changing trends of bacterial resistance in China. For clinical isolates, the ratio of gram-negative bacilli to gram-positive cocci is approximately 7 to 3. In general, gram-negative bacilli have higher antimicrobial resistance profiles in China. Regarding different bacterial species, antimicrobial resistance is multifaceted. The prevalence of extended-spectrum β-lactamases is high; *Acinetobacter baumannii* has a high antimicrobial resistance profile; and, notably, the prevalence of CRKP has been showing a marked increase since 2005. In addition, the prevalence of vancomycin-resistant Enterococcus is low, and the prevalence of methicillin-resistant *Staphylococcus aureus* and antimicrobial resistance in *Pseudomonas aeruginosa* showed decreasing trends from 2005 to 2017

Keywords. antibacterial resistance; surveillance; China.

Antibacterial resistance is a global problem that threatens public health. In 2016, 14 ministries of China led by the National Health and Family Planning Commission jointly issued the National Action Plan for Containing Antibacterial Resistance (2016–2020). Surveillance of bacterial resistance is one of the major tasks indicated in this action plan for tackling antibacterial resistance [1]. In this review, we will briefly introduce the bacterial resistance surveillance system, review the current status and trends of antibacterial resistance, and discuss the impact of bacterial resistance on clinical practice in China.

BACTERIAL RESISTANCE SURVEILLANCE IN CHINA

In China, the bacterial resistance surveillance system is relatively well established at the national, province, and hospital levels. The antibiotic susceptibilities of clinical isolates were determined using the disk diffusion method or automated system according to the Clinical and Laboratory Standards Institute (CLSI) criteria, and the results were interpreted according to CLSI criteria. The data, in a unified format, were collected from microbiology laboratories and input into a central database using WHONET software [2].

There are several operational national surveillance networks for bacterial resistance, with 2 well known in China: CARSS (China Antimicrobial Resistance Surveillance System) and CHINET (China Antimicrobial Surveillance Network). CARSS was established in 2005 and organized by the Expert Committee on Rational Use of Drugs, National Health Commission of the People's Republic of China (Formerly Health and Family Planning Committee of China). In 2016, 1273 hospitals from all provinces and autonomous regions participated, including tertiary hospitals (75%) and secondary hospitals (25%). In 2016, a total of 2 727 605 bacterial strains were included for analysis. The surveillance data show the different bacterial resistance rates among different provinces and autonomous regions for each specific bacterium in China [3].

CHINET was also founded in 2005, and currently there are 34 hospitals involved, including 30 tier 3 hospitals, of which 5 are children's hospitals, and 4 tier 2 hospitals, which represent 25 provinces and autonomous regions covering 960 million members of the population in China. In 2017, 190 610 bacterial strains in total were included for analysis. The surveillance data are published annually in the *Chinese Journal of Infection and Chemotherapy* [4]. The CHINET data mainly represent the bacterial resistance profiles of teaching hospitals and show the changing trends of bacterial resistance since 2005 in China [5].

Province-level bacterial surveillance networks have gradually been set up over the past 30 years in all provinces and autonomous regions. Usually, each province-level network includes tens of hospitals from all regions in each province and has an annual report of the resistance data. The Shanghai Bacterial Resistance Surveillance Network is the earliest

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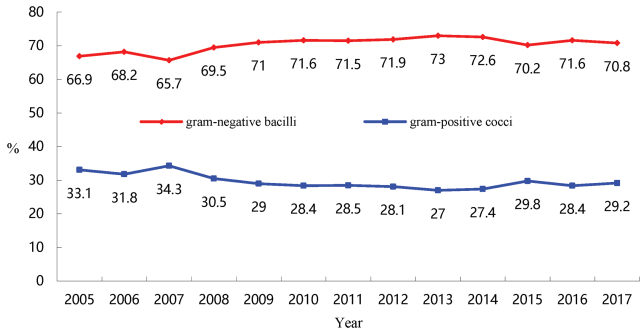

Figure 1. Percentages of gram-positive cocci and gram-negative bacilli of clinical isolates in China (China Antimicrobial Surveillance Network [CHINET] data).

province-level network in China and was established in 1988 with the assistance of the World Health Organization Western Pacific Region Office. The Shanghai network has been running continuously for 30 years, and the annual data are published in the *Chinese Journal of Infection and Chemotherapy* each year [6].

Hospital-level bacterial resistance surveillance is required as a part of antimicrobial stewardship measures in China, as local antimicrobial resistance data are critical for guiding the rational use of antimicrobials such as the empirical use of antimicrobials in hospital-acquired and ventilator-associated pneumonia [7]. It is required that the surveillance data be fed back automatically to clinical physicians via the hospital intranet every 3 months or half a year, and/or that the data are available in a booklet each year for distribution in hospitals.

DISTRIBUTION OF CLINICAL ISOLATES

Many more gram-negative bacilli were isolated than gram-positive cocci were, approximately 70% vs 30%, respectively, according to CHINET surveillance from 2005 to 2017 (Figure 1). Similar results, 70.9% vs 29.1%, respectively, were obtained through CARSS surveillance in 2016 [3].

The top 10 most frequently isolated strains in CHINET in 2017 were *Escherichia coli* (19.3%), *Klebsiella* species (14.7%), *Acinetobacter* species (10.1%), *Staphylococcus aureus*

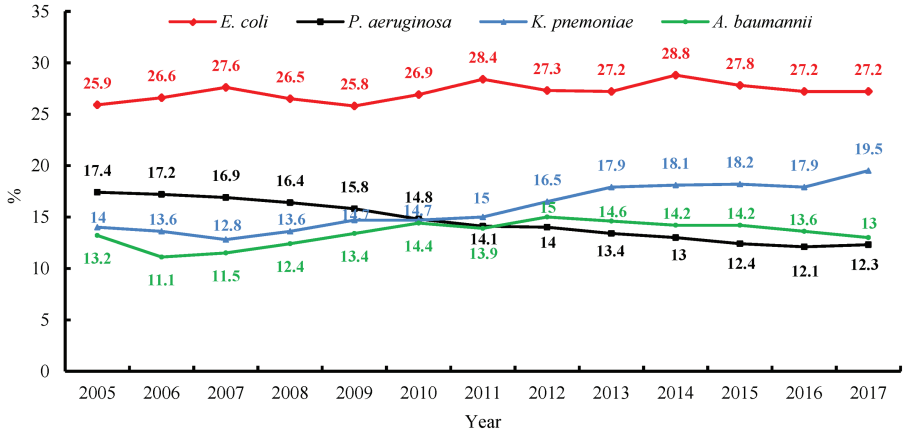

Figure 2. Percentages of the top 4 gram-negative bacilli (China Antimicrobial Surveillance Network [CHINET] data). The numbers represent the percentages of each isolate among all gram-negative clinical isolates.

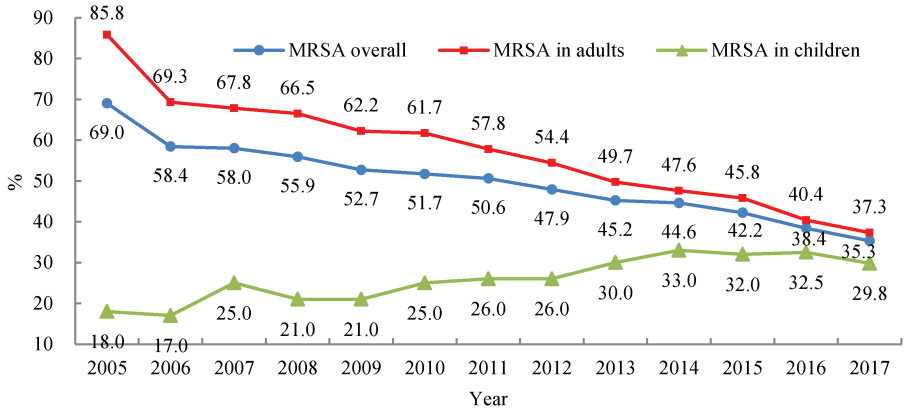

Figure 3. Prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA) overall and in adults (≥18 years old) and children (<18 years) (China Antimicrobial Surveillance Network [CHINET] data).

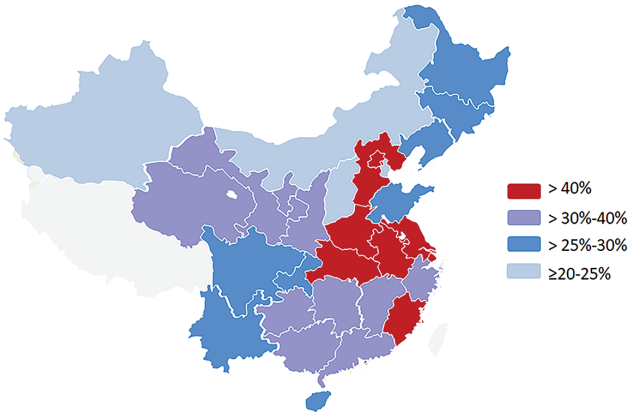

Figure 4. Prevalence of methicillin-resistant *Staphylococcus aureus* among different provinces in China (China Antimicrobial Resistance Surveillance System [CARSS] data).

Figure 6. Prevalence of vancomycin-resistant *Enterococcus faecium* among different provinces in China in 2016 (China Antimicrobial Resistance Surveillance System [CARSS] data).

(9.0%), *Pseudomonas aeruginosa* (8.7%), *Enterococcus* species (8.4%), coagulase-negative staphylococci (4.4%; only the isolates collected from blood and other sterile fluids were included), *Enterococcus* species (3.9%), β-hemolytic streptococci (3.6%), and *Stenotrophomonas maltophilia* (2.9%). The top 10 most common isolates in CARSS in 2016 were similar to those in CHINET, with only slightly changes in the order: *Streptococcus pneumoniae* was listed as the ninth most common isolate in CARSS instead of β-hemolytic streptococci as in CHINET.

Among gram-negative bacilli, the top 4 most frequent isolates were *E. coli*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, and *P. aeruginosa* in CHINET. *E. coli* was always listed as the first most common isolate from 2005 to 2017, representing 26%–29% of all gram-negative bacilli, while the percentage of *A. baumannii* increased from 13.2% in 2005 to 15.0% in 2012, and thereafter slightly decreased to 13% in 2017. The percentage of *K. pneumoniae* showed an increasing trend, from 14% in 2005 to 19.5% in 2017, whereas *P. aeruginosa* showed a decreasing trend from 17.4% in 2005 to 12.3% in 2017 (Figure 2).

BACTERIAL RESISTANCE AND TRENDS IN GRAM-POSITIVE COCCI

Staphylococcus aureus

The prevalence of methicillin-resistant *S. aureus* (MRSA) showed a markedly decreasing trend from 69.0% in 2005 to 35.3% in 2017 in CHINET. MRSA prevalence in adults aged ≥18 years decreased from 85.8% in 2005 to 37.3% in 2017, whereas the prevalence in children aged <18 years increased from 18.0% to 29.8% during the same period of time (Figure 3). The decreasing trend of MRSA prevalence may be related to good implementation of infection control measures such as hand hygiene and antimicrobial stewardship measures in clinical practice in China. Since the 2011 special rectification program, aiming at achieving rational use of antimicrobials around the country, the total defined daily dose per 100 patient-days including adult and pediatric patients decreased from 85.9 in 2010 to 49.7 in 2017 according to the National Surveillance Network of Antimicrobial Clinical Use. However, the marked increase in bacterial resistance in children is a cause for concern. The increasing

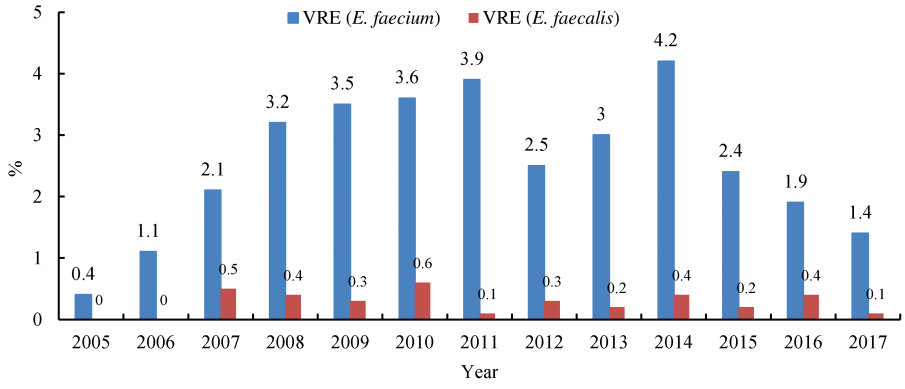

Figure 5. Prevalence of vancomycin-resistant *Enterococcus faecalis* and *Enterococcus faecium* (China Antimicrobial Surveillance Network [CHINET] data).

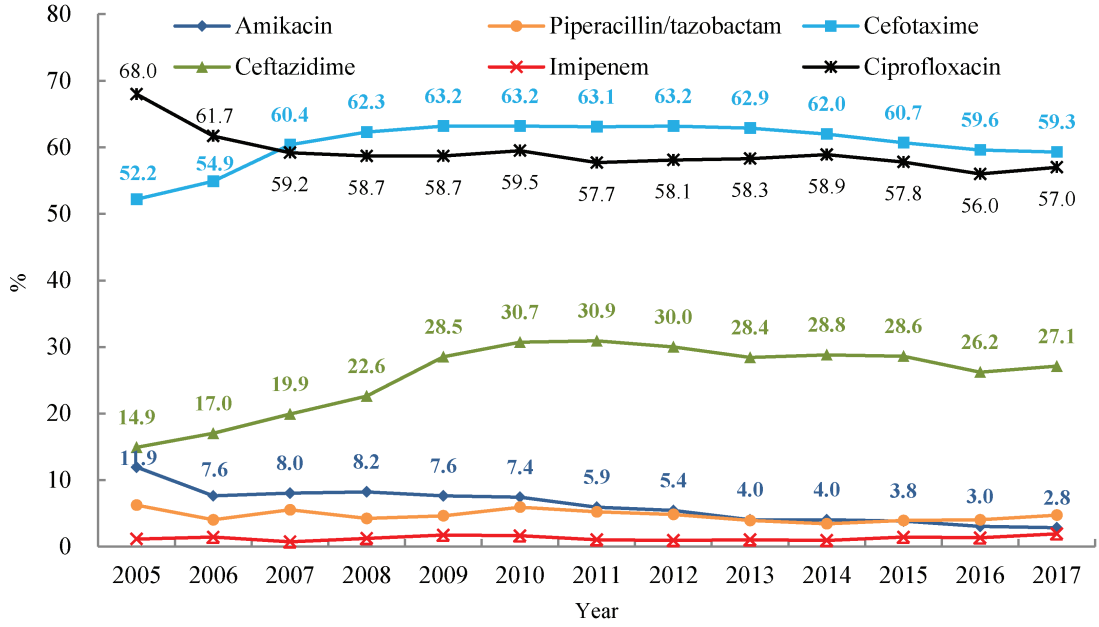

Figure 7. Resistance profile of *Escherichia coli* for 6 commonly used antimicrobials (China Antimicrobial Surveillance Network [CHINET] data).

trend in children may be related to the increasing intensive care unit beds in children's hospitals or departments that usually had higher bacterial resistance rates including prevalence of MRSA; limited choices of antimicrobials comparing with adults may also be related to the increasing trend of MRSA prevalence.

The prevalence of MRSA ranged from 20% to 49% among different provinces according to CARSS surveillance in 2016 [3] (Figure 4).

Enterococci

The prevalence of vancomycin-resistant enterococci (VRE) is fairly low in China: <5% for *Enterococcus faecium* and <1% for *Enterococcus faecalis* in CHINET surveillance from 2005 to 2017 (Figure 5). In CARSS surveillance, VRE prevalence was from 0 to 8.7% among different provinces, with an average of 2.0% [3] (Figure 6). The prevalence of VRE is much lower than that in many countries around the world. The low VRE prevalence may be partially related to the infrequent use of

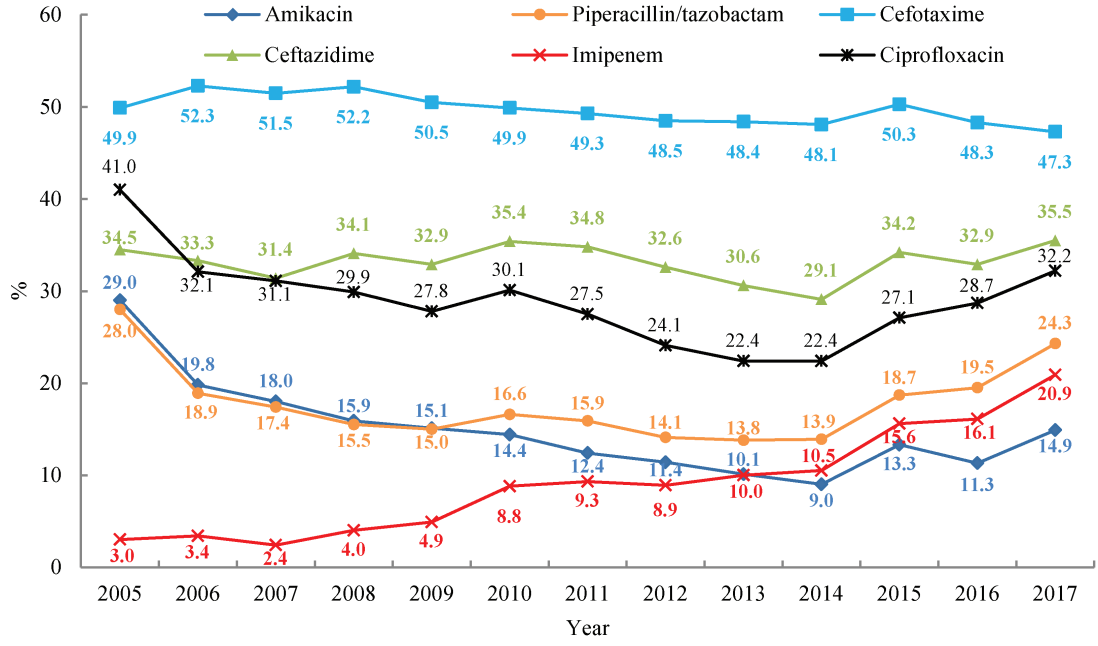

Figure 8. Resistance profile of *Klebsiella pneumoniae* for 6 commonly used antimicrobials (China Antimicrobial Surveillance Network [CHINET] data).

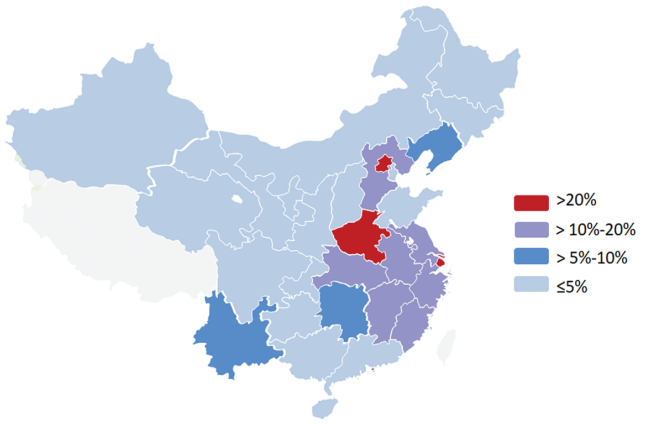

Figure 9. Prevalence of carbapenem-resistant *Klebsiella pneumoniae* among different provinces in China in 2016 (China Antimicrobial Resistance Surveillance System [CARSS] data).

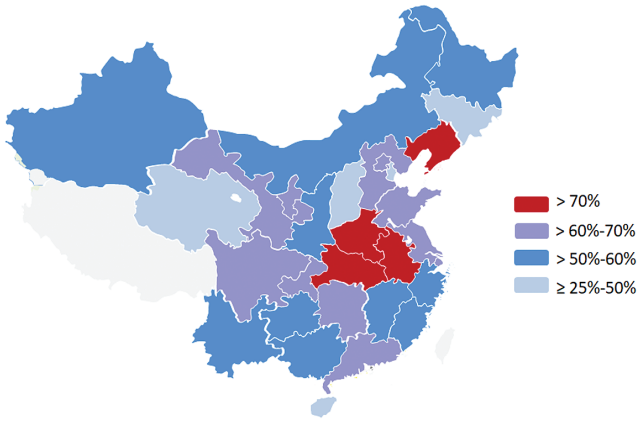

Figure 11. Prevalence of carbapenem-resistant *Acinetobacter baumannii* among different provinces in China in 2016 (China Antimicrobial Resistance Surveillance System [CARSS] data).

vancomycin oral preparations, which are not available in China. Intravenous preparations are administered orally for the treatment of *Clostridium difficile* infections if needed in China.

Streptococcus pneumoniae

The prevalence of penicillin-nonsusceptible *S. pneumoniae* (PNSP), including penicillin-resistant *S. pneumoniae* and penicillin-intermediate *S. pneumoniae*, in children is higher than that in adults. The prevalence of PNSP fluctuated between 10.5% and 13.5% in children from 2015 to 2017, while it was 4.6% to 8.2% in adults in CHINET surveillance. More than 90% of the *S. pneumoniae* isolates were resistant to erythromycin or clindamycin both in children and adults [5]. Another common community-acquired pneumonia (CAP) pathogen, *Mycoplasma pneumoniae*, also showed resistance rates as high as 80% to erythromycin [8]; therefore, macrolides alone are not recommended as an empirical therapy for CAP in China. Less than 5% of the *S. pneumoniae* isolates were resistant to levofloxacin and <2% to moxifloxacin in adults, and even lower resistance rates were found in children [5].

Escherichia coli

Cefotaxime resistance rates in *E. coli* were relatively stable from 2007, ranging from 59% to 63%, while ceftazidime-resistance rates were lower than those of cefotaxime, ranging from 26% to 31% from 2009. The main genotypes of extended-spectrum β-lactamases (ESBLs) in China are CTX-M groups, and almost all ESBL-producing Enterobacteriaceae are resistant to cefotaxime, ceftriaxone, cefuroxime, and cefazolin, so cefotaxime resistance may be used as a marker of ESBL-producing isolates [9]. The prevalence of ESBLs in tier 2 hospitals may be higher than that in tier 3, which may be related to the intensive use

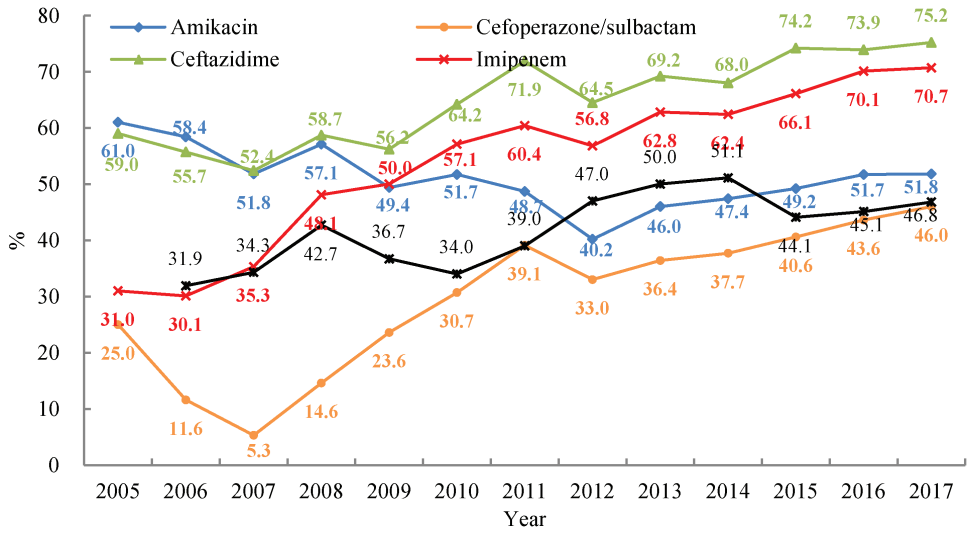

Figure 10. Resistance profile of *Acinetobacter* species for 5 commonly used antimicrobials (China Antimicrobial Surveillance Network [CHINET] data).

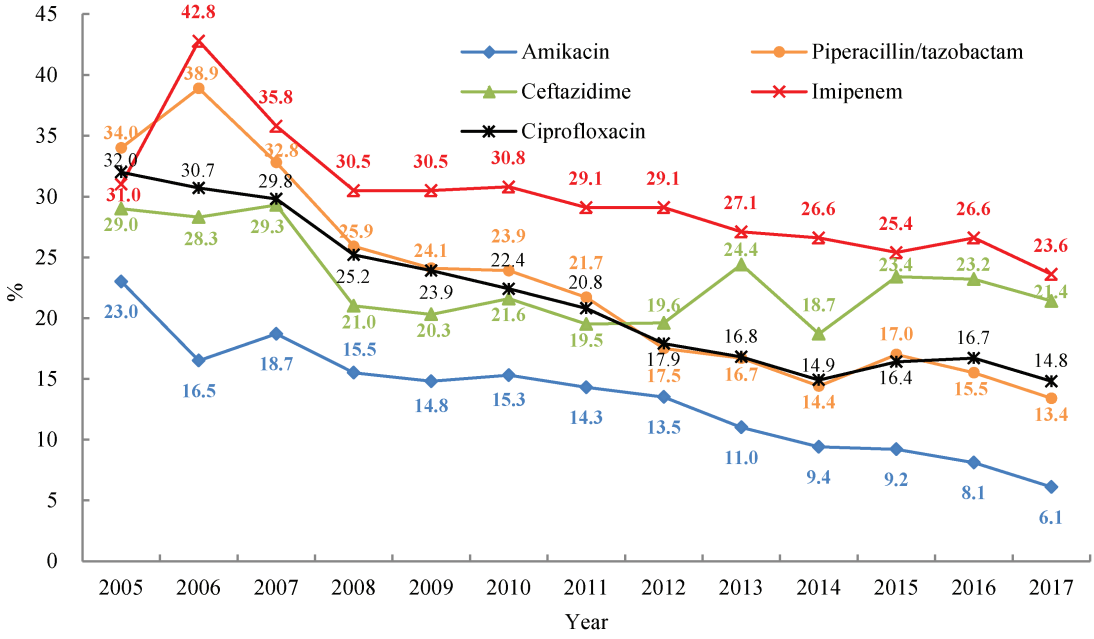

Figure 12. Resistance profile of *Pseudomonas aeruginosa* for 5 commonly used antimicrobials (China Antimicrobial Surveillance Network [CHINET] data).

of cephalosporins in tier 2 hospitals [6]. Ciprofloxacin resistance rates decreased from 68% in 2005 to 57% in 2017, while amikacin resistance decreased from 11.9% to 2.8%. The resistance rates to piperacillin-tazobactam and imipenem were low in *E. coli*, ranging from 4% to 6% and 0.7% to 1.9%, respectively, from 2005 to 2017 (Figure 7).

Klebsiella pneumoniae

Cefotaxime resistance rates in *K. pneumoniae* deceased slightly from 52.3% in 2006 to 47.3% in 2017, means that about 50% of *K. pneumoniae* strains produced ESBLs. A marked change is that carbapenem-resistant *K. pneumoniae* (CRKP) increased from 3.0% in 2005 to 20.9% in 2017. The resistance rates to ceftazidime, ciprofloxacin, piperacillin-tazobactam, and amikacin showed a deceasing trend from 2005 to 2014 and thereafter had a markedly increasing trend from 2015, which was consistent with the marked increase in CRKP (Figure 8). In China, the dominant genotypes of CRKP were *Klebsiella pneumoniae* carbapenemase-2 (KPC-2), accounting for approximately 70% [10]. The dominant clone of CRKP is sequence type (ST) 11, which usually carries multiple resistance genes via plasmids [11]. The spread of ST11 may contribute to the increasing trend of multiple, even extensive drug resistance in *K. pneumoniae* since 2015.

The prevalence of CRKP (defined by resistance to any of the carbapenems) ranged from 0.9% to 23.6% in different provinces, with an average rate of 8.7%, in CARSS surveillance in 2016 [3] (Figure 9).

Acinetobacter Species

In general, the resistance rates against 5 commonly used antimicrobials were very high and showed increasing trends except for amikacin. Imipenem resistance increased from 31% in 2005 to 70.7% in 2017. Resistance rates to cefoperazone-sulbactam, one of the most commonly used antimicrobials for the treatment of MDR *Acinetobacter* species infections in China, also increased from 31% in 2005 to 46% in 2017 (Figure 10). The susceptibility of polymyxins and tigecycline is not tested routinely in clinical microbiology departments in China, but showed high susceptibility according to 2 studies done using microdilution methods [12, 13].

Carbapenem-resistant *A. baumannii* varied among provinces, from the lowest prevalence of 25% in Tianjin to the highest of 81% in Henan province, with an average of 60% according to the results of CARSS in 2016 [3] (Figure 11).

Pseudomonas aeruginosa

In general, *P. aeruginosa* showed a relatively low resistance profile and trends of decreasing resistance to the 5 most commonly used antimicrobials listed in Figure 12. Resistance rates of amikacin decreased from 23.0% in 2005 to 6.1% in 2017. The piperacillin-tazobactam and ciprofloxacin resistance rates were 13.4% and 14.8%, respectively, in 2017, according to CHINET surveillance (Figure 12).

Carbapenem-resistant *P. aeruginosa* ranged from 9.8% in Hainan province to 31.6% in Liaoning province with an average rate of 22.3% in CARSS in 2106 [3], which was close to the rate of 23.6% in CHINET in 2017.

In summary, gram-negative bacilli clinical isolates are much more common than gram-positive cocci, with a ratio of approximately 7 to 3, and in general, gram-negative bacilli have higher antimicrobial resistance profiles; therefore, the bacterial resistance of gram-negative bacilli is a major problem in China. Regarding different bacterial species, antimicrobial resistance is multifaceted in China: The prevalence of MRSA and antimicrobial resistance in *P. aeruginosa* showed decreasing trends from 2005 to 2017, the prevalence of VRE is low; the prevalence of ESBLs is high, and *A. baumannii* has a high antimicrobial resistance profile. In addition, notably, the prevalence of CRKP has been showing an increasing trend since 2005.

Notes

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References

1. National Health and Family Planning Commission. National action plan for containing bacterial resistance. Available at: http://www.nhfpc.gov.cn/yzygj/s3593/201608/f1ed26a0c8774e1c8fc89dd481ec84d7.shtml. Accessed 31 October 2018.
2. Hu FP, Guo Y, Zhu DM, et al. Resistance trends among clinical isolates in China reported from CHINET surveillance of bacterial resistance, 2005-2014. Clin Microbiol Infect **2016**; 22(Suppl 1):S9–14.
3. China Antimicrobial Resistance Surveillance System. Available at: http://www.carss.cn/. Accessed 31 October 2018.
4. Hu F, Guo Y, Zhu D, et al. CHINET surveillance of bacterial resistance across China: report of the results in 2016. Chin J Infect Chemother **2017**; 17:481–91.
5. China Antimicrobial Surveillance Network. Available at: www.chinets.com. Accessed 31 October 2018.
6. Guo Y, Zhu D, Hu F, et al. Surveillance of bacterial resistance in Shanghai hospitals during 2016. Chin J Infect Chemother **2017**; 17:609–22.
7. Kalil AC, Metersky ML, Klompas M, et al. Management of adults with hospital-acquired and ventilator-associated pneumonia: 2016 clinical practice guidelines by the Infectious Diseases Society of America and the American Thoracic Society. Clin Infect Dis **2016**; 63:e61–111.
8. Yin YD, Wang R, Zhuo C, et al. Macrolide-resistant *Mycoplasma pneumoniae* prevalence and clinical aspects in adult patients with community-acquired pneumonia in China: a prospective multicenter surveillance study. J Thorac Dis **2017**; 9:3774–81.
9. Wang P, Hu F, Xiong Z, et al. Susceptibility of extended-spectrum-beta-lactamase-producing Enterobacteriaceae according to the new CLSI breakpoints. J Clin Microbiol **2011**; 49:3127–31.
10. Zhang R, Liu L, Zhou H, et al. Nationwide surveillance of clinical carbapenem-resistant Enterobacteriaceae (CRE) strains in China. EBioMedicine **2017**; 19:98–106.
11. Qi Y, Wei Z, Ji S, Du X, Shen P, Yu Y. ST11, the dominant clone of KPC-producing *Klebsiella pneumoniae* in China. J Antimicrob Chemother **2011**; 66:307–12.
12. Jones RN, Castanheira M, Hu B, et al. Update of contemporary antimicrobial resistance rates across China: reference testing results for 12 medical centers (2011). Diagn Microbiol Infect Dis **2013**; 77:258–66.
13. Li Y, Guo Q, Wang P, et al. Clonal dissemination of extensively drug-resistant *Acinetobacter baumannii* producing an OXA-23 β-lactamase at a teaching hospital in Shanghai, China. J Microbiol Immunol Infect **2015**; 48:101–8.