Antimicrobial resistance among pathogens that infect the bloodstream: a multicenter surveillance report for 1998–2017

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Research article

Keywords: Hubei Province Antimicrobial Resistance Surveillance System (HBARSS), antimicrobial resistance, bloodstream infections, methicillin-resistant Staphylococcus aureus (MRSA), carbapenem-resistant

Posted Date: December 30th, 2020

DOI: https://doi.org/10.21203/rs.2.23498/v2

Abstract

Background Bloodstream infections (BSIs) are a common consequence of infectious diseases and cause high morbidity and mortality. Appropriate antibiotic use is critical for patients' treatment and prognosis. Long-term monitoring and analyzing of bacterial resistance are important for understanding the changes in bacterial resistance and infection control. Here, we report a retrospective study on antimicrobial resistance in BSI-associated pathogens.

Methods Data from the Hubei Province Antimicrobial Resistance Surveillance System (HBARSS) from 1998–2017 were retrospectively analyzed using WHONET 5.6 software.

Results Data from HBARSS (1998–2017) revealed that 40,518 Gram-positive bacteria and 26,568 Gram-negative bacteria caused BSIs, the most common of which were *Staphylococcus aureus* and *Escherichia coli*. *Salmonella typhi* was a predominant BSI-associated pathogen in 1998–2003. Drug susceptibility data showed that the resistance rates of *E. coli* and *Klebsiella pneumoniae* to cefotaxime were significantly higher than those to ceftazidime. Carbapenem-resistant (CR) *E. coli* and *K. pneumoniae* have also emerged. In 2013–2017, *K. pneumoniae* showed resistance levels reaching 15.8% and 17.5% to imipenem and meropenem, respectively, and *Acinetobacter baumannii* showed high resistance rates ranging from 60–80% to common antibiotics. The detection rate of *Salmonella typhi* resistance to third-generation cephalosporins and fluoroquinolones was less than 5%. Control of methicillin-resistant *Staphylococcus aureus* (MRSA) remains a major challenge, and in 2009–2017, the MRSA detection rate was 40–50%. The number of extensively drug-resistant *A. baumannii* and *P. aeruginosa* has been increasing since 2008. From 1998 to 2017, the total detection rates of extensively drug-resistant *A. baumannii* and *P. aeruginosa* were 34.38% (493/1434) and 7.45% (140/1879), respectively.

Conclusions Prevalence of CR *K. pneumoniae* has increased significantly in recent years. Resistance rates of *A. baumannii* to common antimicrobial agents have increased exponentially, reaching high levels. MRSA remains a challenge to control.

Background

Antimicrobial resistance is a major health-related issue of global concern. Long-term monitoring of bacterial resistance is important for implementing effective control measures. Monitoring systems for bacterial resistance in China operate at the national, provincial and hospital levels [1].

Hubei Province is located in central China and has 13 prefectural administrative regions under its jurisdiction. The Statistics Bureau of Hubei Province reports that in 1998, the permanent population of Hubei Province was 58.91 million, and by the end of 2018, this number was 59.17 million. Of this population, 35.68 million people lived in towns, and 23.49 million people lived in villages [2]. The Hubei Province Antimicrobial Resistance Surveillance System (HBARSS) was founded in 1998 and initially consisted of 15 tertiary hospitals in different regions of Hubei Province. Hospitals were added in 2003 and 2005, and 17 tertiary hospitals formed a monitoring network in Hubei Province. Since 2009, the

monitoring network has been extended to secondary and tertiary hospitals across the entire province, and more than 50 hospitals have joined the monitoring network to date. The proportion of network hospitals from the registered hospitals for all of Hubei Province reached 14.45% (50/346) in 2018. All hospital administrators log into the national bacterial resistance monitoring network of the Ministry of Health (http://www.carss.cn) using their own user name and password, then enter the provincial login to submit data.

Bloodstream infections (BSIs) are a major cause of morbidity and mortality in adults and children [3-4]. Appropriate use of antibiotics is critical for their treatment and prognosis. At present, China is one of the largest users of antibiotics worldwide [5], and antibiotic overuse remains a serious problem worldwide [6]. Here, we report a 20-year analysis of HBARSS for 1998–2017. Our findings provide a reference for monitoring changes of bacterial resistance and management of antibiotics.

Methods

Study design and procedures

To effectively analyze the accumulated susceptibility data and determine the trend in drug resistance for the major pathogens, only data from the initial 15 hospitals in 1998–2002, 16 hospitals in 2003–2004 and 17 hospitals in 2005–2017 were analyzed. Each network hospital independently cultured, identified and conducted susceptibility testing of the strains, and the data were submitted to HBARSS annually.

Blood culturing was performed on patients who satisfied the clinical standards [7]. Automated blood culture instruments, including the BD 9120, 9240 and FX 400 (BD Co., NJ, USA) or the 3D 120, 240 and 720 (Bio Mérieux, Lyon, France), were used in each hospital in the monitoring network. Strains were identified following each laboratory's protocol, which combined various automated instruments or an IVD-MALDI Biotyper (Bruker, Karlsruhe, Germany) with manual biochemical experiments. Either the disk-diffusion method or an automated instrument was used for the antimicrobial susceptibility tests. From 1998–2010, all hospitals used the disk-diffusion method for drug susceptibility testing. From 2011–2017, six hospitals used automated instruments, and 11 used the disk-diffusion method. Automated instruments for drug-sensitivity testing included the Vitek-2 Compact system (Bio Mérieux, Lyon, France) and the domestic drug-sensitivity testing system (Dier, Zhuhai, China). Antimicrobial susceptibility tests were performed strictly in accordance with Clinical Laboratory Standards Institute (CLSI) standards. Each hospital routinely carried out indoor quality control and participated in the External Quality Assessment of the Ministry of Health of China. Laboratory quality control experiments strictly followed the CLSI guidelines of the corresponding year, and standard strains were tested once weekly.

Because CNS, Corynebacterium, Bacillus, Propionibacterium and other potential skin contaminants frequently contaminate blood cultures, whether these organisms were colonizing, pathogenic or contaminating bacteria was determined from the available clinical data [8].

Statistical analysis

Data were analyzed using WHONET 5.6 software. To avoid the effects of repeated subculturing on bacterial resistance, only the first strain was used in the analysis. Interpretation criteria for the antimicrobial susceptibility results were based on CLSI 2018 Guidelines [9].

Results

Distribution of pathogenic bacteria

From 1998–2017, 40,518 Gram-positive bacterial strains and 26,568 Gram-negative bacterial strains were isolated from BSIs via HBARSS. The ratio of Gram-positive to Gram-negative bacteria was approximately 3:2 (Fig 1). The most common Gram-positive bacteria were coagulase-negative *Staphylococcus* (CNS) and *Staphylococcus S. aureus* (Fig 2). The most common Gram-negative bacteria were *Escherichia E. coli* and *Klebsiella (K.) pneumoniae*. *Salmonella (S.) typhi* was prevalent in 1998–2003, and *Stenotrophomonas (S.) maltophilia* was prevalent in 2004–2005 (Fig 3).

Antimicrobial susceptibility of Gram-negative bacteria

Both *E. coli* and *K. pneumoniae* showed higher resistance to the third-generation cephalosporin, cefotaxime, than to ceftazidime. The resistance rates of *E. coli* to ceftazidime and cefotaxime were 10.5–30.1% and 31.75–67.3%, respectively, whereas those of *K. pneumoniae* were 24–31.6% and 41.7–49.7%, respectively (Fig 4 and Fig 5). The resistance rate of *E. coli* to fluoroquinolones was significantly higher than that of *K. pneumoniae*. The resistance rates of *E. coli* to ciprofloxacin and levofloxacin were 47.3–55.6% and 45.2–52.8%, respectively, and those of *K. pneumoniae* were 18.1–27.7% and 11.9–25.5%, respectively (Fig 4 and Fig 5). The resistance rate of *K. pneumoniae* to carbapenems was significantly higher than that of *E. coli*. The resistance rates of *K. pneumoniae* to imipenem and meropenem were 2.4–15.8% and 1.8–17.5%, respectively, whereas those of *E. coli* were 0.8–2.3% and 0.8–1.3%, respectively (Tables S1 and S2). *S. typhi* showed resistance to third-generation cephalosporins and fluoroquinolones, but the resistance rate was less than 6% (Fig 6). The resistance rate of *S. typhi* to ampicillin increased significantly from 6.9% in 1998–2002 to 38.5% in 2013–2017 (Table S3).

Most resistance rates of *Pseudomonas (P.) aeruginosa* to common antibiotics were less than 30% (Table S4). The resistance rates of *Acinetobacter (A.) baumannii* to common antimicrobial agents increased significantly from less than 50% in 2003–2007 to 55–70% in 2008–2012 (except to cefoperazone sulbactam) and to 60–80% in 2013–2017 (Table S5). From 1998 to 2017, the detection rates of extensively drug-resistant *A. baumannii* and *P. aeruginosa* were 34.38% (493/1434) and 7.45% (140/1879), respectively (Fig 7 and Fig 8). *S. maltophilia* was not resistant to ceftazidime in 1998–2012 but then showed a resistance rate of 58.1% in 2013–2017 (Table S6).

Epidemiology of methicillin-resistant *Staphylococcus aureus* (MRSA)

MRSA strains included *S. aureus* that expressed mecA or another methicillin resistance mechanism such as changes in the affinity of penicillin-binding proteins (PBPs) for oxacillin (modified *S. aureus* strains)

[9]. Cefoxitin was tested as a surrogate for oxacillin. Isolates that tested resistant to cefoxitin on the minimum inhibitory concentration (MIC), disk, or oxacillin MIC tests were considered to be MRSA [9, 10]. The MRSA detection rate was 10–30% in 1998–2003, which increased to 20–70% in 2004–2007 and 40–50% in 2009–2017 (Fig 9).

Antimicrobial susceptibility of MRSA and methicillin-sensitive *S. aureus* (MSSA)

MSSA strains were *S. aureus* strains that tested sensitive to cefoxitin on MIC, disk, or oxacillin MIC tests. The resistance rate of MRSA to common antibiotics was significantly higher than that of MSSA. The resistance rate of MRSA to trimethoprim/sulfamethoxazole decreased significantly from 69.9% in 1998–2002 to 3.8% in 2012–2017, and that of MSSA decreased significantly from 29.2% in 2003–2007 to 3.3% in 2013–2017 (Tables S7 and S8).

Discussion

Surveillance data from 1998–2017 in Hubei Province showed that the most common BSI-associated Gram-negative and Gram-positive bacteria were *E. coli* and *S. aureus*, respectively. This finding was consistent with that of the European Antimicrobial Resistance Surveillance Network (EARS-Net, formerly EARSS) report for 2002–2009 [11] but differed from reports from Malawi, Africa, which showed that non-typhoid *Salmonella*, *S. typhi* and *Streptococcus pneumoniae* were the main BSI-associated pathogens [4].

Our study showed that *S. typhi* was also a main BSI-associated pathogen in Hubei Province from 1998–2003. Typhoid fever is a poverty-related disease, mainly occurring in Africa and Asia, with a low incidence in economically developed regions such as Europe and the United States [12-16]. Typhoid fever is transmitted mainly through contaminated food and drinking water [17]. The incidence of *S. typhi*-related BSIs in rural children was reported to be 2–3 times higher than that in urban children [18]. The different incidences in different areas may be related to local medical and health conditions and vaccination rates. These factors may also have contributed to the high incidence in Hubei Province during 1998–2003. Reports from Africa suggested that *S. typhi* and non-*S. typhi* were consistently the most common pathogens of BSIs [4]. *Salmonella* infections are frequently associated with human immunodeficiency virus infections, very young or elderly patients, clinical malaria and malnutrition, and can be fatal in up to 20–25% of patients [19-20]. Reports from Africa showed that *Salmonella* was often resistant to first-line antibiotics such as chloramphenicol, sulfonamide and ampicillin [21-22]. In our study, the resistance rate of *S. typhi* to ampicillin increased from 6.9% in 1998–2002 to 38.5% in 2013–2017, and resistance rates to other antibiotics were lower than 10% in 2013–2017. Resistance to fluoroquinolones and third-generation cephalosporins has also been reported in several African countries [23-24]. Our data showed that *S. typhi* resistance to third-generation cephalosporins and fluoroquinolones has emerged, but in 1998–2017, the detection rate was less than 5%.

Antibiotic susceptibility tests showed that the resistance rates of *E. coli* and *K. pneumoniae* to third-generation cefotaxime were significantly higher than those to ceftazidime, which is consistent with the 30-year data reported from CHINET in China [1]. Wang *et al*. showed that CTX-M was the most important

ESBL type in China and that cefotaxime resistance might be a sign of ESBL-producing bacterial strains [25]. *E. coli* and *K. pneumoniae* showed low resistance to amikacin, cefoperazone/sulbactam and imipenem; thus, these antibiotics might be used as empirical treatment options. Notably, in 2013–2017, the rates of *K. pneumoniae* resistance to imipenem and meropenem reached 15.8% and 17.5%, respectively. Studies have confirmed that mortality rates of patients infected with carbapenem-resistant (CR) *K. pneumoniae* strains are significantly higher than those of patients infected with carbapenem-sensitive strains [26-27]. CR *K. pneumoniae* strains often exhibit combined resistance to cephalosporins, fluoroquinolones, aminoglycosides, beta-lactamase inhibitors and other antimicrobial agents [28]. Few antimicrobial agents, including tigecycline and polymyxin, can be used to treat CR *K. pneumoniae* [29].

This study revealed that *P. aeruginosa* and *A. baumannii* were the most common non-fermentative Gram-negative bacteria that cause BSIs. Susceptibility tests showed that resistance rates of *P. aeruginosa* to most antibiotics were less than 30%. However, these results differed from those reported in a multicenter epidemiological study on the risk factors and clinical outcomes of nosocomial intra-abdominal infections in China (the Chinese antimicrobial resistance surveillance of nosocomial infections [CARES] 2007–2016), which indicated that *P. aeruginosa* showed high resistance to a variety of antimicrobial agents, except amikacin, whose susceptibility rate was 83.4% [30]. The antimicrobial susceptibility profiles of *A. baumannii* isolates from BSIs were similar to those of *A. baumannii* isolates from abdominal infections. *A. baumannii* was alarmingly resistant to diverse antibiotics, including third-generation cephalosporins, aminoglycosides, fluoroquinolones and carbapenems [30]. In this study, resistance rates of *A. baumannii* to common antibiotics increased significantly in 1998–2017. In 2003–2007, the antimicrobial resistance rate of *A. baumannii* was less than 50%, but by 2013–2017, the resistance rate reached 60–80%. The emergence of multidrug-resistant *A. baumannii*, especially extensively drug-resistant and fully drug-resistant strains, has made clinical treatment difficult. According to CLSI guidelines, *S. maltophilia* showed standard resistance levels to minocycline, levofloxacin and trimethoprim/sulfamethoxazole as determined by disk-diffusion tests, but MIC testing showed break points for ticarcillin/clavulanic acid, ceftazidime and chloramphenicol, minocycline, levofloxacin and trimethoprim/sulfamethoxazole [9]. Therefore, some hospitals could increase the drug sensitivity test results of some drugs after changing disk-diffusion tests to MIC tests. For example, for *S. maltophilia*, disk diffusion method had only three drug break points, while MIC method had six drug break points. As a result, clinicians had more choices in the empirical treatment. However, the disadvantage of the change of drug sensitivity test methodology was that the cumulative drug sensitivity data were inevitably biased when comparing data for many years. In this study, the resistance rate of *S. maltophilia* to ceftazidime increased to 58.1% in 2013–2017, whereas the resistance rates of *S. maltophilia* to other antimicrobial agents were less than 25%. Whether the increase in ceftazidime resistance was related to its wide clinical application requires further investigation and analysis.

Surveillance data on BSIs from 1998–2017 showed that the resistance rate of *A. baumannii* to common antibiotics has reached a high level, and the prevalence of CR *K. pneumoniae* has increased significantly, resulting in significant difficulties in clinical treatment. Our data show that vancomycin, teicoplanin, linezolid and trimethoprim/sulfamethoxazole can be used to treat MRSA. The resistance rate of MRSA to

trimethoprim/sulfamethoxazole has decreased significantly, possibly related to the decreased of use of this drug in recent years. Studies from China, South Korea and France have shown that the antimicrobial resistance rates of *S. aureus*, *K. pneumoniae*, *E. coli*, *P. aeruginosa* and *Candida albicans* also decreased with the decreased clinical use of these antimicrobial agents [31-34]. Tigecycline and polymyxin can be used to empirically treat CR *K. pneumoniae*, *E. coli* and *A. baumannii*.

This study had several limitations. The BSI incidence in Hubei Province was often reported from single research centers. We failed to find accurate data on the BSI incidence for all of Hubei Province from 1998–2017. Previous reports lacked demographic data. One shortcoming of this study was that the accurate BSI incidence was not calculated for Hubei Province. Another limitation was that different hospitals used different strain identification methods, including manual biochemical experiments and an IVD-MALDI Biotyper, and these results were undistinguishable once combined. Different hospitals adopted different drug sensitivity test methods, and the same hospital may change the drug sensitivity test method used between 1998 and 2017. Although each hospital strictly followed the CLSI guidelines, the inconsistency of test methods and the difference of drug sensitive consumables may lead to deviation in the analysis of drug resistance. The weakness of the analysis of the resistance mechanism involved in Gram-negative resistance to beta-lactams and more particularly to carbapenems was also a limitation of this study. We will increase the content of drug resistance mechanism research in the future.

Conclusion

CR *K. pneumoniae*, extensively drug-resistant *A. baumannii* and MRSA present major challenges to controlling BSIs. *S. typhi* resistant to the third generation cephalosporins and quinolones has emerged, but the drug resistance rates were all less than 5%.

Abbreviations

BSI: Bacterial bloodstream infection, HBARSS: Hubei Province Antimicrobial Resistance Surveillance System, CR：Carbapenem-resistant；CNS: coagulase-negative staphylococcus, EARS-Net: European Antimicrobial Resistance Surveillance Network, CARES: Chinese antimicrobial Resistance surveillance of nosocomial Infections, MRSA: Methicillin-resistant S. aureus, CDC: Centers for Disease Control and Prevention, CLSI: Clinical Laboratory Standards Institute

Declarations

Ethics approval and consent to participate

The study protocol was approved by the Tongji Hospital ethics committee for research in health. The Tongji Hospital ethics committee also approved the waiver of informed consent to participate in this study due to its retrospective design. All patient data were anonymous prior to the analysis.

Consent to publish

Not applicable.

Availability of data and materials

The datasets used and analyzed during the current study are stored in the website http://www.carss.cn. The datasets could be available from the corresponding author upon reasonable request. The results from analysis of the datasets are presented in this published article as tables and figures.

Competing interests

The authors declare that they have no competing interest.

Funding

This work was supported by research grants from the National Mega Project on Major Infectious Disease Prevention (2017ZX10103005-007). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Author Contributions

ZS designed the study. LT analyzed the data and wrote the article. ZZ revised the manuscript. All authors reviewed the manuscript prior to submission.

Acknowledgement

We thank all members of HBARSS for their participation in these studies. We thank Traci Raley, MS, ELS, from Liwen Bianji, Edanz Editing China (www.liwenbianji.cn/ac) for editing a draft of this manuscript.

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Figures

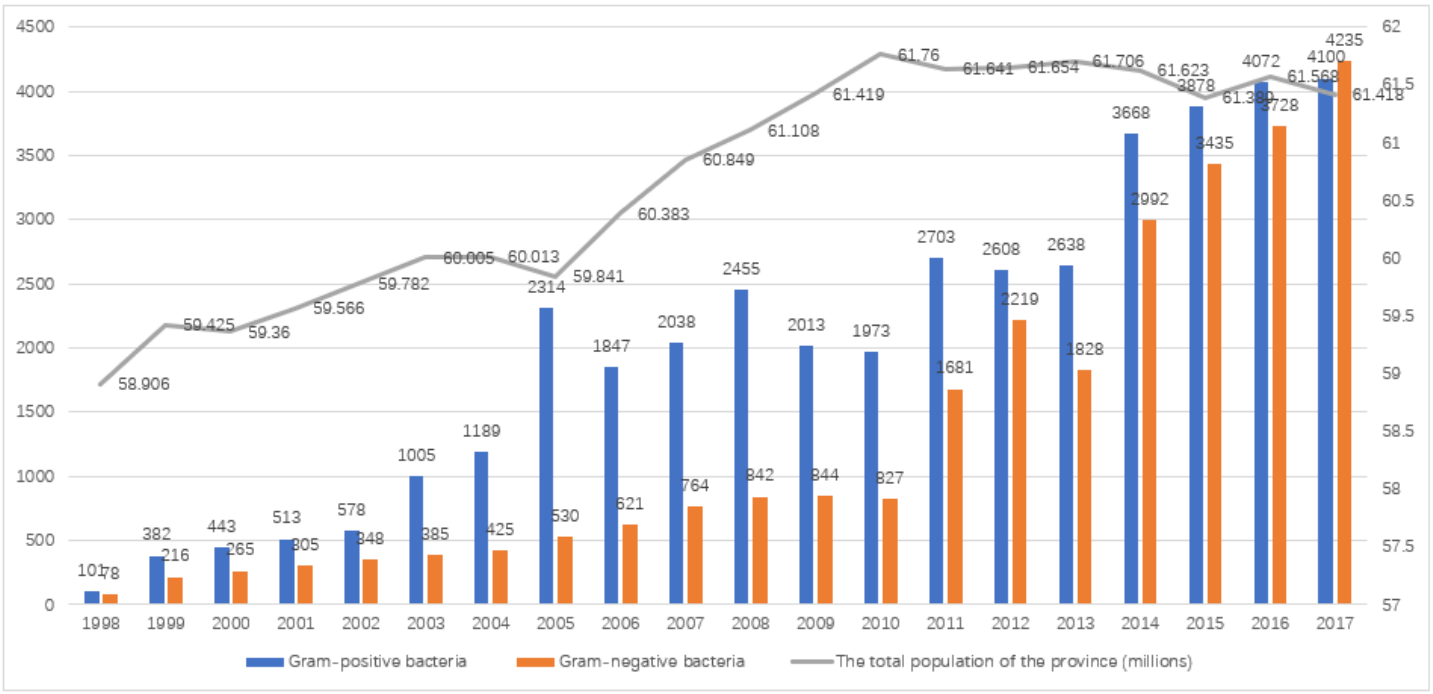

Figure 1

Demographic data and pathogens of BSI in Hubei Province, 1998-2017.

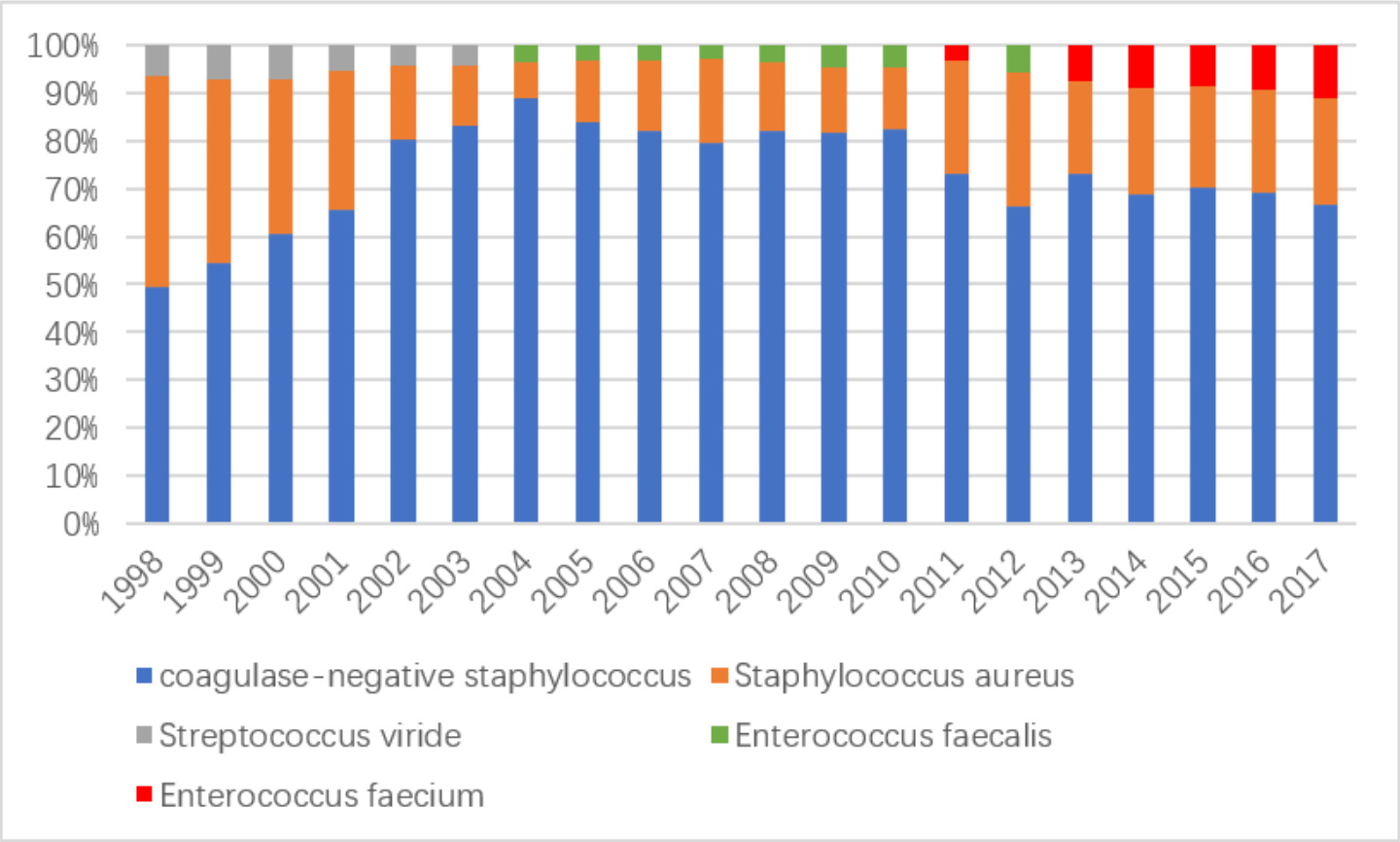

Figure 2

Distribution of the main Gram-positive bacteria per year

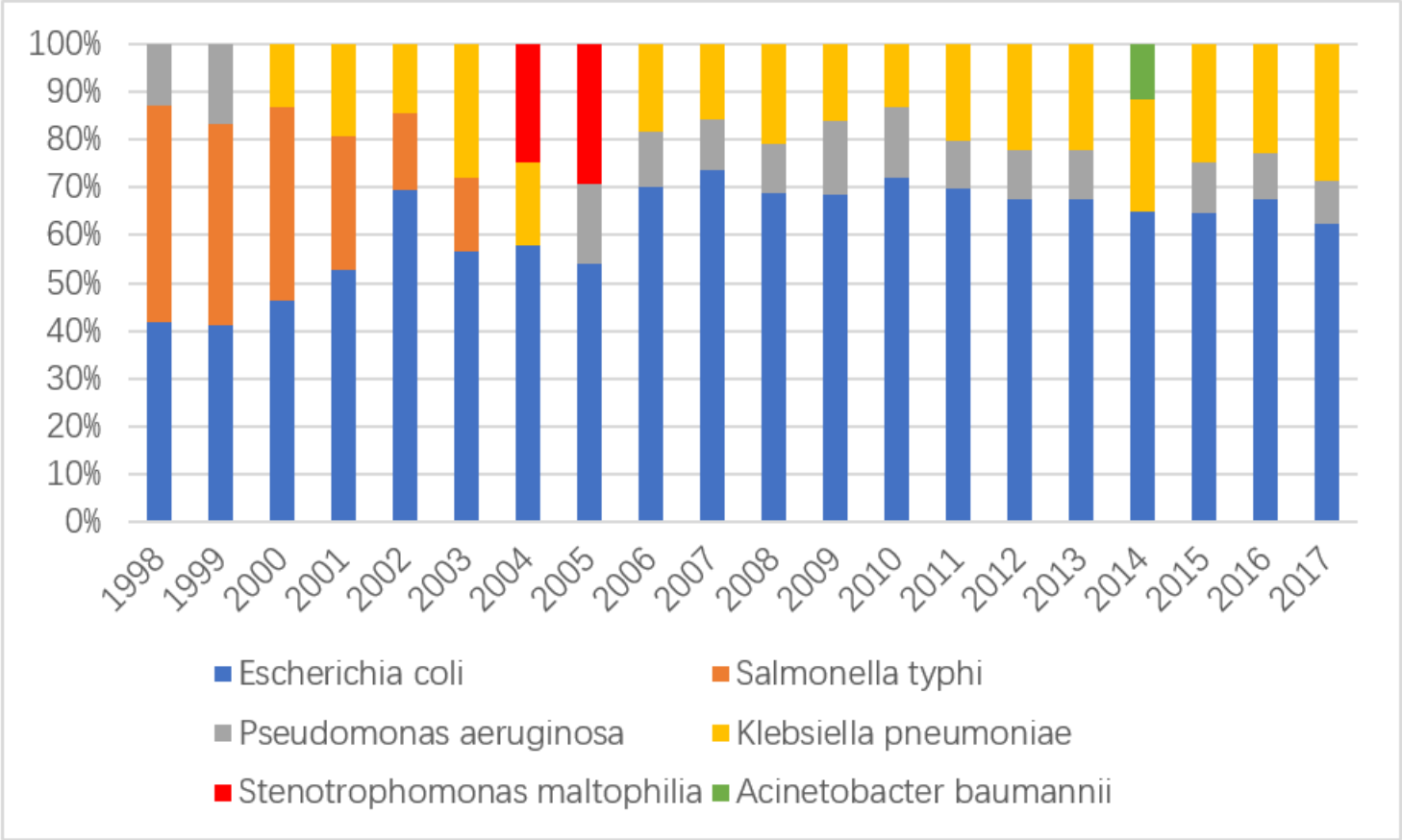

Figure 3

Distribution of the main Gram-negative bacteria per year

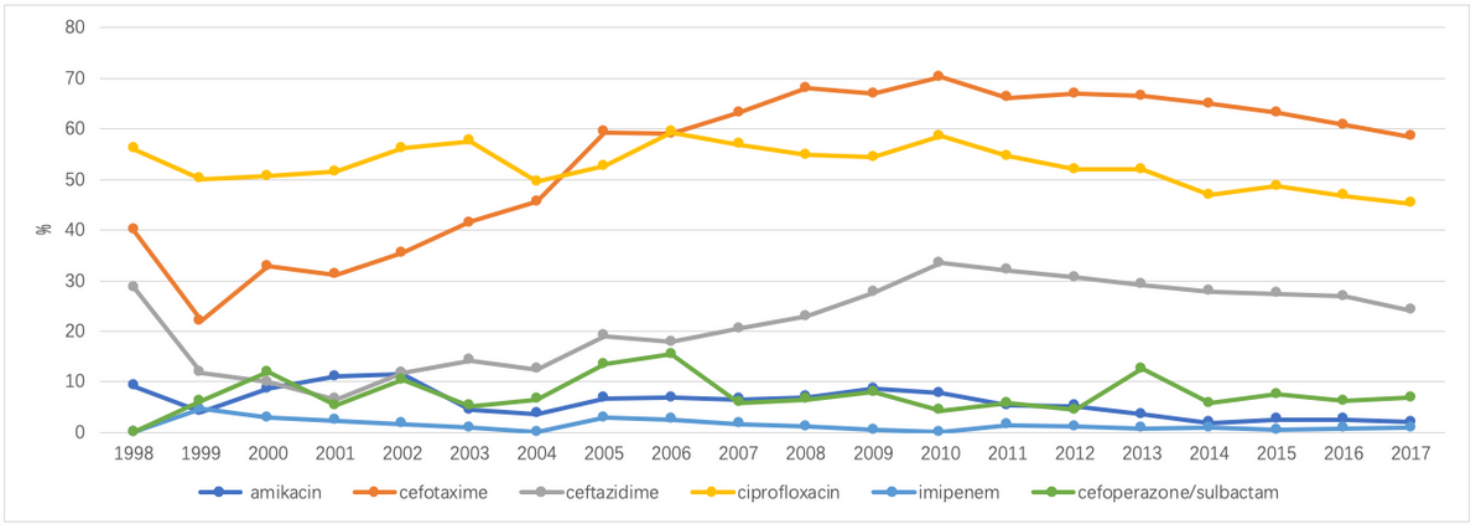

Figure 4

Resistance profile of Escherichia coli for 6 commonly used antimicrobials from 1998 to 2017

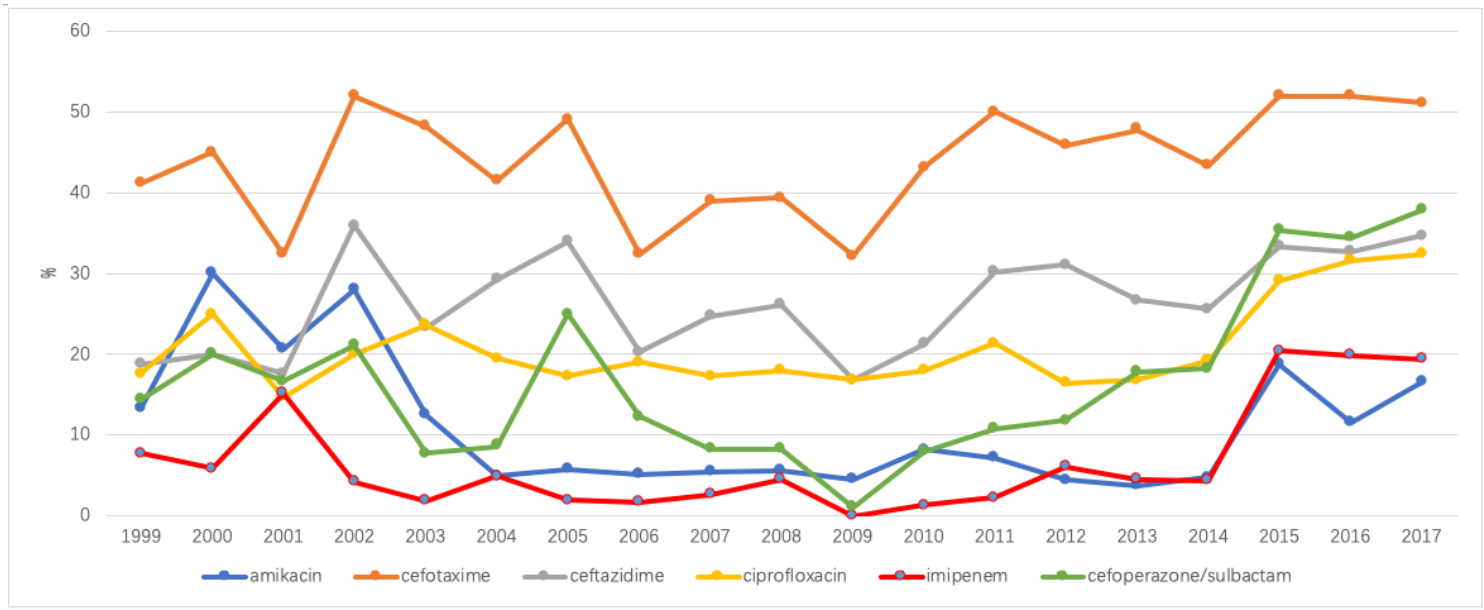

Figure 5

Resistance profile of Klebsiella pneumoniae for 6 commonly used antimicrobials

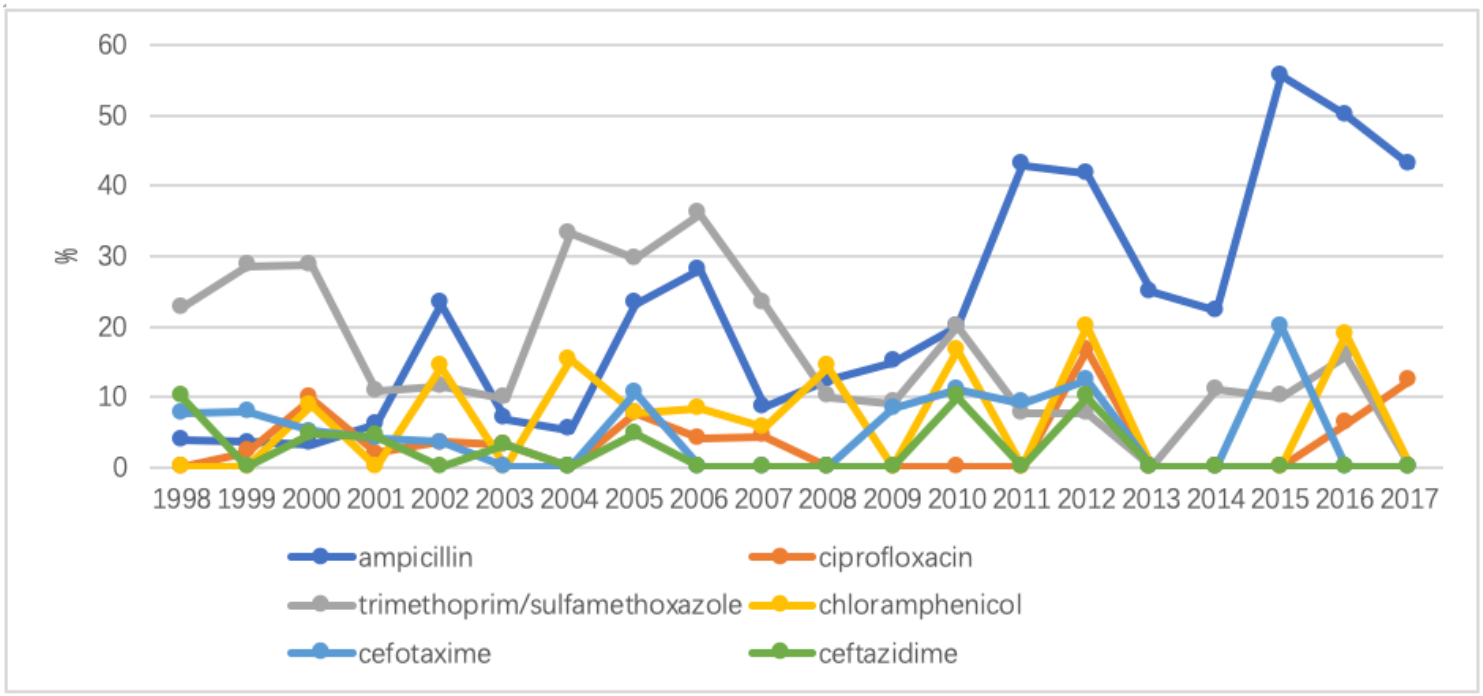

Figure 6

Resistance profile of Salmonella typhi for 6 commonly used antimicrobials

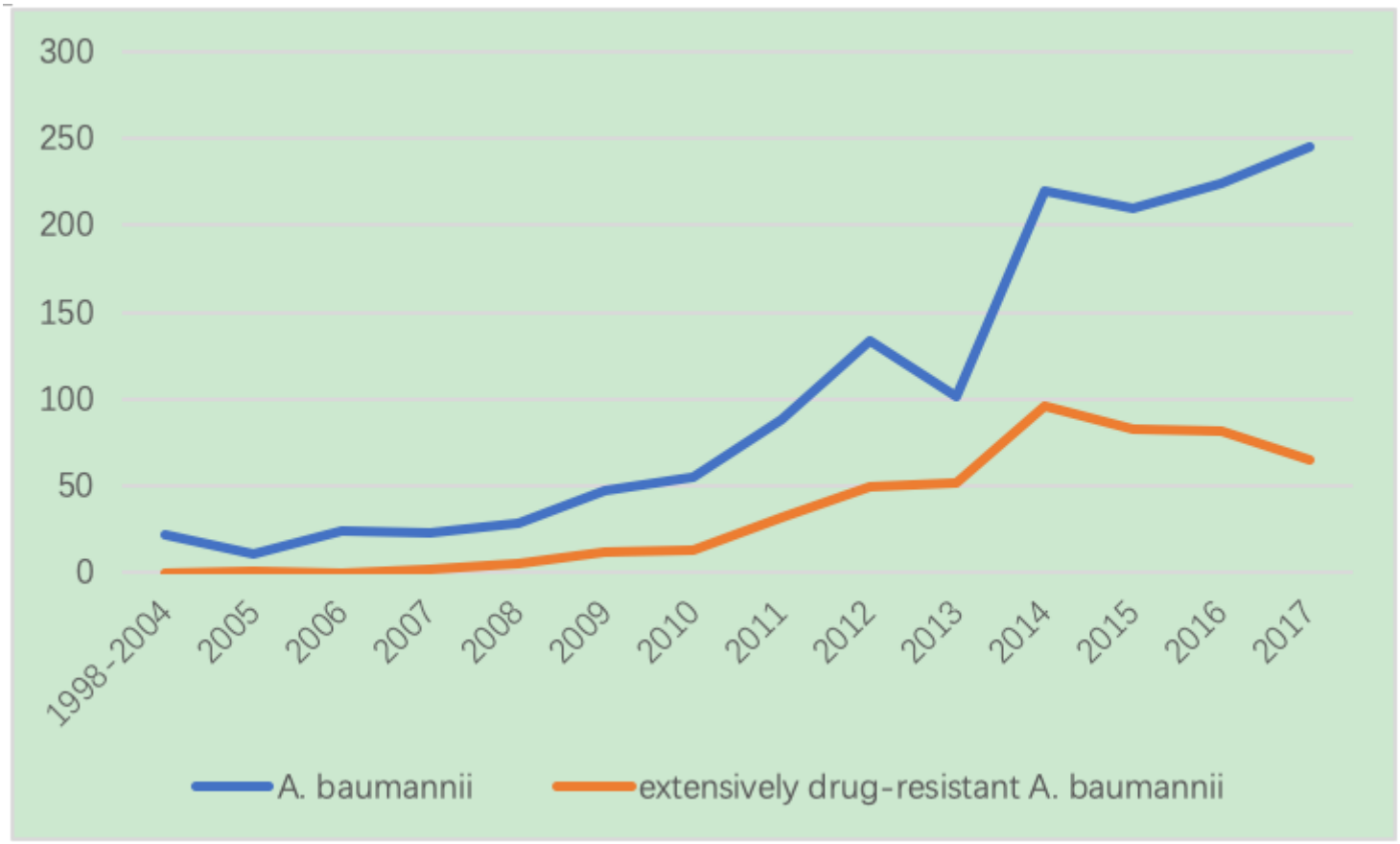

Figure 7

Temporal treads of extensively drug-resistant A. baumannii isolates

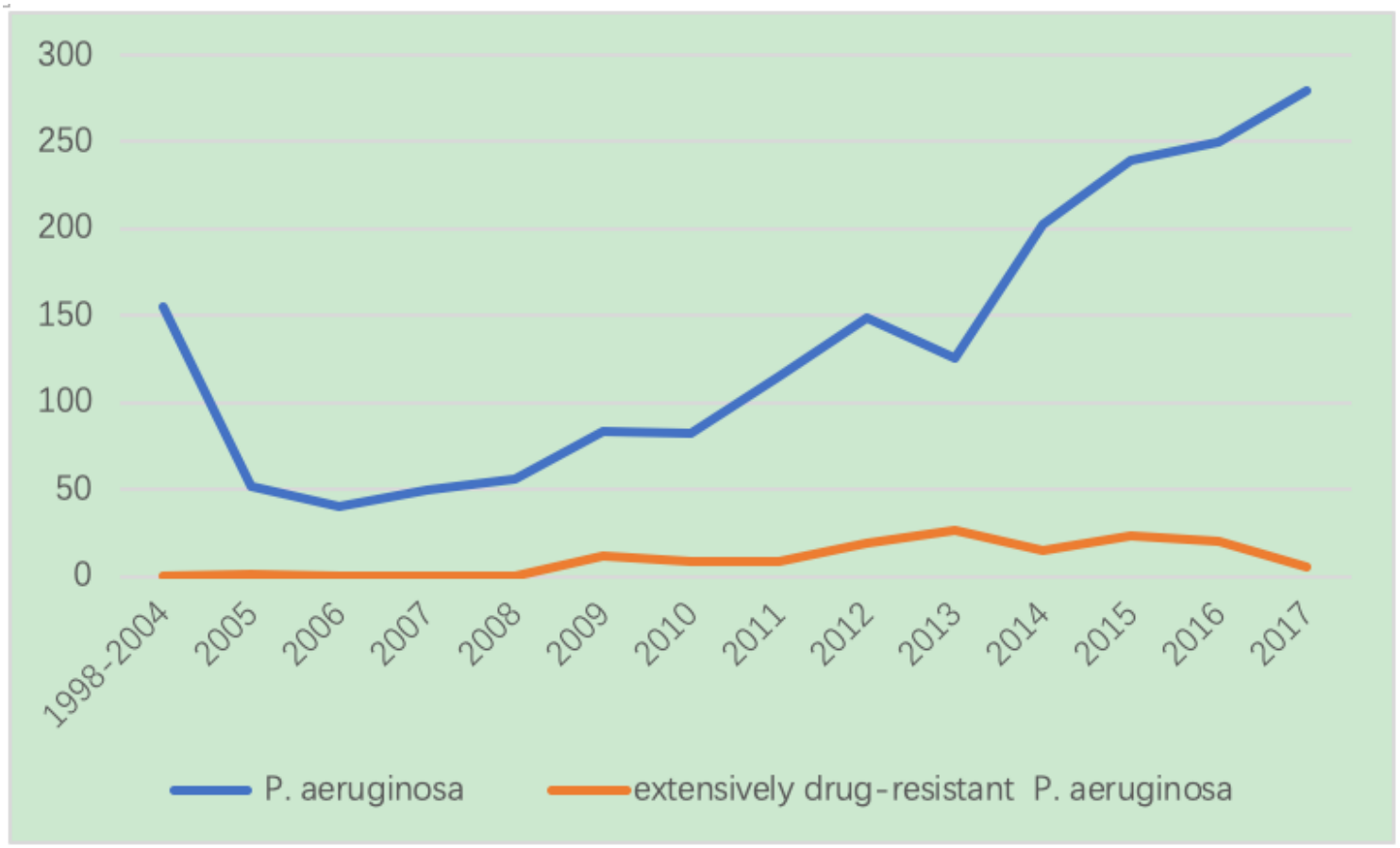

Figure 8

Temporal treads of extensively drug-resistant P. aeruginosa isolates

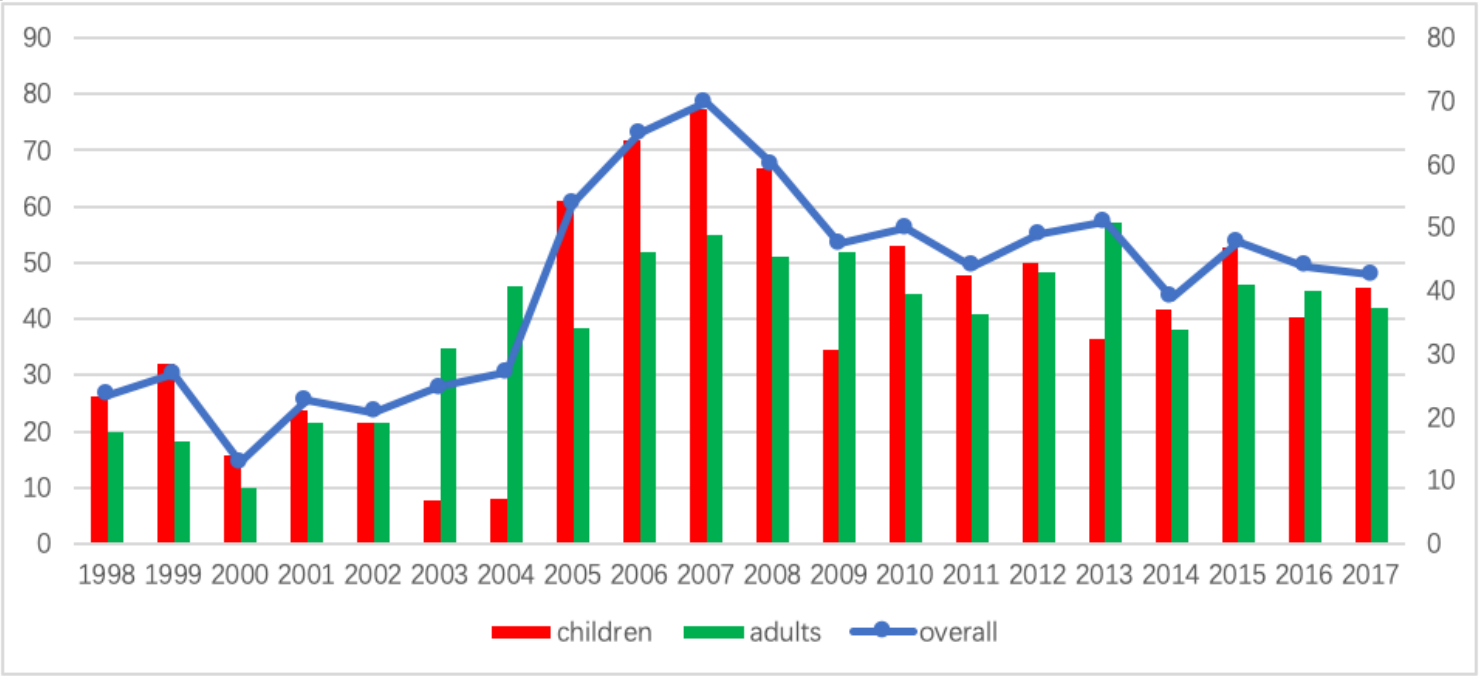

Figure 9

Prevalence of MRSA (%) in adults (≥18 years old) and children (<18 years)

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- tableS1ECO.docx
- tableS2KPN.docx
- tableS3sat.docx
- tableS4pae.docx
- tableS5aba.docx
- tableS6pma.docx
- tableS7MRSA.docx
- tableS8MSSA.docx