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

DOI: https://doi.org/10.21203/rs.2.23498/v1

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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 guiding physicians in choosing the appropriate antibiotics and 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*. 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. Control of methicillin-resistant *Staphylococcus aureus* (MRSA) remains a major challenge, and in 2009–2017, the MRSA detection rate was 40–50%.

**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]. In 1998, the World Health Organization (WHO) sponsored and selected Dr. Peter Hockey (UK) and Dr. Martin Komican (Ireland) as clinical microbiologists to teach the Hubei WHO Advanced Training Course on Bacterial Resistance Monitoring. More than 20 professionals from Hubei Province were trained to establish a unified standard drug-sensitivity testing method. 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 and first-class 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 clinicians when selecting appropriate antibiotics to treat BSIs.

**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 cultivated, 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. Automated blood culture instruments, including the BD 9120, 9240 and FX 400 (BD Co., NJ, USA) or the 3D 120, 240 and 720 (BioMerier, 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 sensitivity 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 (BioMerier, Lyon, France) and the domestic drug-sensitivity testing system (Dier, Zhuhai, China). Antimicrobial susceptibility tests were performed strictly in accordance with 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.

**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 [7].
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 aureus* (Fig 2). 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]. The most common Gram-negative bacteria were *Escherichia coli* and *Klebsiella pneumoniae*. *Salmonella typhi* was prevalent in 1998–2003, and *Stenotrophomonas maltophilia* was prevalent in 2004–2005 (Fig 3).

Antimicrobial sensitivity 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. 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. 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 1 and 2). *S. typhi* showed resistance to third-generation cephalosporins and fluoroquinolones, but the resistance rate was less than 6%. The resistance rate of *S. typhi* to ampicillin increased significantly from 6.9% in 1998–2002 to 38.5% in 2013–2017 (Table 3).

Most resistance rates of *Pseudomonas aeruginosa* to common antibiotics were less than 30% (Table 4). The resistance rates of *Acinetobacter 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 5). *S. maltophilia* was not resistant to ceftazidime in 1998–2012 but then showed a resistance rate of 58.1% in 2013–2017 (Table 6).

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)
Most oxacillin resistance was mediated by mecA encoding PBP2a (also called PBP2'). Isolates that tested positive for mecA or PBP2a were considered oxacillin-resistant [7]. 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 [7, 9]. 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 4).

**Antimicrobial sensitivity 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 7 and 8).

**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 [10] but differed from reports from Malawi, Africa, which showed that non-typhoid *Salmonella, Salmonella 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 [11–15]. Typhoid fever is transmitted mainly through contaminated food and drinking water [16]. The incidence of *S. typhi*-related BSIs in rural children was reported to be 2–3 times higher than that in urban children [17]. 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.

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 [18]. *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
K. pneumoniae strains are significantly higher than those of patients infected with carbapenem-sensitive strains [19–20]. CR K. pneumoniae strains often exhibit combined resistance to cephalosporins, fluoroquinolones, aminoglycosides, beta-lactamase inhibitors and other antimicrobial agents [21]. Few antimicrobial agents, including tigecycline and polymyxin, can be used to treat CR K. pneumoniae [22].

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 sensitivity rate was 83.4% [23]. 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 [23]. 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 [7]. 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.

In our study, S. typhi was a predominant BSI-associated pathogen in 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 [24–25]. Reports from Africa showed that Salmonella was often resistant to first-line antibiotics such as chloramphenicol, sulfonamide and ampicillin [26–27]. 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 [28–29]. 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%.

MRSA infections are correlated with prolonged hospital stays and increased mortality and represent a significant healthcare burden [30]. In our study, MRSA detection rates were 10–30% in 1998–2003, 20–70% in 2004–2007 and 40–50% in 2009–2019. MRSA control requires following the guidelines issued by
the Centers for Disease Control and Prevention (CDC); other European agencies recommend contact precautions, which are strictly enforced by healthcare institutions [31–32]. Controlling the spread of MRSA remains a major challenge, and more research is needed in this area.

Surveillance data on BSIs from 1998–2017 showed that the resistance rate of \textit{A. baumannii} to common antibiotics has reached a high level, and the prevalence of CR \textit{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 use of this drug in recent years. Studies from China, South Korea and France have shown that the antimicrobial resistance rates of \textit{S. aureus}, \textit{K. pneumoniae}, \textit{E. coli}, \textit{P. aeruginosa} and \textit{Candida albicans} also decreased with the decreased clinical use of these antimicrobial agents [33–36]. Tigecycline and polymyxin can be used to empirically treat CR \textit{K. pneumoniae}, \textit{E. coli} and \textit{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.

**Conclusion**

CR \textit{K. pneumoniae}, extensively drug-resistant \textit{A. baumannii} and MRSA present major challenges to controlling BSIs.

**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 \textit{S. aureus}, CDC: Centers for Disease Control and Prevention

**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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References
1. Hu F, Zhu D, Wang F, Wang M: Current Status and Trends of Antibacterial Resistance in China. Clin Infect Dis 2018, 67(suppl_2):S128-S134.
2. Hubei Statistical Service. Statistical Yearbook of the Province; regional analytical report, Hubei Region—Hubei statistical service. Available at: www.tjj.hubei.gov.cn. Accessed 29 September 2019.
3. Iroh Tam PY, Musicha P, Kawaza K, Cornick J, Denis B, Freyne B, Everett D, Dube Q, French N, Feasey N et al: Emerging resistance to empiric antimicrobial regimens for pediatric bloodstream infections in
Malawi (1998-2017). Clin Infect Dis 2018.

4. Musicha P, Cornick JE, Bar-Zeev N, French N, Masesa C, Denis B, Kennedy N, Mallewa J, Gordon MA, Msefula CL et al: Trends in antimicrobial resistance in bloodstream infection isolates at a large urban hospital in Malawi (1998-2016): a surveillance study. Lancet Infect Dis 2017, 17(10):1042-1052.

5. Van Boeckel TP, Gandra S, Ashok A, Caudron Q, Grenfell BT, Levin SA, Laxminarayan R: Global antibiotic consumption 2000 to 2010: an analysis of national pharmaceutical sales data. Lancet Infect Dis 2014, 14(8):742-750.

6. Tang X, Xiao M, Zhuo C, Xu Y, Zhong N: Multi-level analysis of bacteria isolated from inpatients in respiratory departments in China. J Thorac Dis 2018, 10(5):2666-2675.

7. Clinical and Laboratory Standards Institute. Performance Standards for Antimicrobial Susceptibility Testing, Twenty-eighth Informational Supplement, M100-S28. Wayne, PA: Clin Lab Stand Institute; 2018.

8. Weinstein MP, Murphy JR, Reller LB, Lichtenstein KA: The clinical significance of positive blood cultures: a comprehensive analysis of 500 episodes of bacteremia and fungemia in adults. II. Clinical observations, with special reference to factors influencing prognosis. Rev Infect Dis 1983, 5(1):54-70.

9. Tsuzuki S, Matsunaga N, Yahara K, Gu Y, Hayakawa K, Hirabayashi A, Kajihara T, Sugai M, Shibayama K, Ohmagari N: National trend of blood-stream infection attributable deaths caused by Staphylococcus aureus and Escherichia coli in Japan. J Infect Chemother 2019.

10. Gagliotti C, Balode A, Baquero F, Degener J, Grundmann H, Gur D, Jarlier V, Kahlmeter G, Monen J, Monnet DL et al: Escherichia coli and Staphylococcus aureus: bad news and good news from the European Antimicrobial Resistance Surveillance Network (EARS-Net, formerly EARSS), 2002 to 2009. Euro Surveill 2011, 16(11).

11. Tack B, Phoba MF, Van Puyvelde S, Kalonji LM, Hardy L, Barbe B, Van der Sande MAB, Monsieurs E, Deborggraeve S, Lunguya O et al: Salmonella Typhi From Blood Cultures in the Democratic Republic of the Congo: A 10-Year Surveillance. Clin Infect Dis 2019, 68(Supplement_2):S130-S137.

12. Crump JA, Sjolund-Karlsson M, Gordon MA, Parry CM: Epidemiology, Clinical Presentation, Laboratory Diagnosis, Antimicrobial Resistance, and Antimicrobial Management of Invasive Salmonella Infections. Clin Microbiol Rev 2015, 28(4):901-937.

13. Buckle GC, Walker CL, Black RE: Typhoid fever and paratyphoid fever: Systematic review to estimate global morbidity and mortality for 2010. J Glob Health 2012, 2(1):010401.

14. Al-Emran HM, Eibach D, Krumkamp R, Ali M, Baker S, Biggs HM, Bjerregaard-Andersen M, Breiman RF, Clemens JD, Crump JA et al: A Multicountry Molecular Analysis of Salmonella enterica Serovar Typhi With Reduced Susceptibility to Ciprofloxacin in Sub-Saharan Africa. Clin Infect Dis 2016, 62 Suppl 1:S42-46.

15. Crump JA, Mintz ED: Global trends in typhoid and paratyphoid Fever. Clin Infect Dis 2010, 50(2):241-246.
16. Msemo OA, Mbwana J, Mahende C, Malabeja A, Gesase S, Crump JA, Dekker D, Lusingu JPA: Epidemiology and Antimicrobial Susceptibility of Salmonella enterica Bloodstream Isolates Among Febrile Children in a Rural District in Northeastern Tanzania: A Cross-sectional Study. *Clin Infect Dis* 2019, 68(Supplement_2):S177-S182.

17. Cruz Espinoza LM, Nichols C, Adu-Sarkodie Y, Al-Emran HM, Baker S, Clemens JD, Dekker DM, Eibach D, Krumkamp R, Boahen K *et al.*: Variations of Invasive Salmonella Infections by Population Size in Asante Akim North Municipal, Ghana. *Clin Infect Dis* 2016, 62 Suppl 1:S17-22.

18. Wang P, Hu F, Xiong Z, Ye X, Zhu D, Wang YF, Wang M: Susceptibility of extended-spectrum-beta-lactamase-producing Enterobacteriaceae according to the new CLSI breakpoints. *J Clin Microbiol* 2011, 49(9):3127-3131.

19. Falagas ME, Tansarli GS, Karageorgopoulos DE, Vardakas KZ: Deaths attributable to carbapenem-resistant Enterobacteriaceae infections. *Emerg Infect Dis* 2014, 20(7):1170-1175.

20. Fraenkel-Wandel Y, Raveh-Brawer D, Wiener-Well Y, Yinnon AM, Assous MV: Mortality due to blaKPC *Klebsiella pneumoniae* bacteraemia. *J Antimicrob Chemother* 2016, 71(4):1083-1087.

21. Gutierrez-Gutierrez B, Salamanca E, de Cueto M, Hsueh PR, Viale P, Pano-Pardo JR, Venditti M, Tumbarello M, Daikos G, Canton R *et al.*: Effect of appropriate combination therapy on mortality of patients with bloodstream infections due to carbapenemase-producing Enterobacteriaceae (INCREMENT): a retrospective cohort study. *Lancet Infect Dis* 2017, 17(7):726-734.

22. Tzouvelekis LS, Markogiannakis A, Psichogiou M, Tassios PT, Daikos GL: Carbapenemases in *Klebsiella pneumoniae* and other Enterobacteriaceae: an evolving crisis of global dimensions. *Clin Microbiol Rev* 2012, 25(4):682-707.

23. Zhang J, Zhao C, Chen H, Li H, Wang Q, Wang Z, Zhang F, Wang H, Network C: A multicenter epidemiology study on the risk factors and clinical outcomes of nosocomial intra-abdominal infections in China: results from the Chinese Antimicrobial Resistance Surveillance of Nosocomial Infections (CARES) 2007-2016. *Infect Drug Resist* 2018, 11:2311-2319.

24. Feasey NA, Dougan G, Kingsley RA, Heyderman RS, Gordon MA: Invasive non-typhoidal salmonella disease: an emerging and neglected tropical disease in Africa. *Lancet* 2012, 379(9835):2489-2499.

25. Uche IV, MacLennan CA, Saul A: A Systematic Review of the Incidence, Risk Factors and Case Fatality Rates of Invasive Nontyphoidal Salmonella (NTS) Disease in Africa (1966 to 2014). *PLoS Negl Trop Dis* 2017, 11(1):e0005118.

26. Crump JA, Heyderman RS: A Perspective on Invasive Salmonella Disease in Africa. *Clin Infect Dis* 2015, 61 Suppl 4:S235-240.

27. Kariuki S, Gordon MA, Feasey N, Parry CM: Antimicrobial resistance and management of invasive Salmonella disease. *Vaccine* 2015, 33 Suppl 3:C21-29.

28. Kalonji LM, Post A, Phoba MF, Falay D, Ngbonda D, Muyembe JJ, Bertrand S, Ceyssens PJ, Mattheus W, Verhaegen J *et al.*: Invasive Salmonella Infections at Multiple Surveillance Sites in the Democratic Republic of the Congo, 2011-2014. *Clin Infect Dis* 2015, 61 Suppl 4:S346-353.
29. Oneko M, Kariuki S, Muturi-Kioi V, Otieno K, Otieno VO, Williamson JM, Folster J, Parsons MB, Slutsker L, Mahon BE et al. *Emergence of Community-Acquired, Multidrug-Resistant Invasive Nontyphoidal Salmonella Disease in Rural Western Kenya, 2009-2013*. Clin Infect Dis 2015, 61 Suppl 4:S310-316.

30. de Kraker ME, Wolkewitz M, Davey PG, Koller W, Berger J, Nagler J, Icket C, Kalenic S, Horvatic J, Seifert H et al. *Clinical impact of antimicrobial resistance in European hospitals: excess mortality and length of hospital stay related to methicillin-resistant Staphylococcus aureus bloodstream infections*. Antimicrob Agents Chemother 2011, 55(4):1598-1605.

31. Muto CA, Jemigan JA, Ostrowsky BE, Richet HM, Jarvis WR, Boyce JM, Farr BM, Shea: SHEA guideline for preventing nosocomial transmission of multidrug-resistant strains of Staphylococcus aureus and enterococcus. Infect Control Hosp Epidemiol 2003, 24(5):362-386.

32. National Nosocomial Infections Surveillance S: *National Nosocomial Infections Surveillance (NNIS) System Report, data summary from January 1992 through June 2004, issued October 2004*. Am J Infect Control 2004, 32(8):470-485.

33. Wang H, Wang H, Yu X, Zhou H, Li B, Chen G, Ye Z, Wang Y, Cui X, Zheng Y et al. *Impact of antimicrobial stewardship managed by clinical pharmacists on antibiotic use and drug resistance in a Chinese hospital, 2010-2016: a retrospective observational study*. BMJ Open 2019, 9(8):e026072.

34. Zeng S, Xu Z, Wang X, Liu W, Qian L, Chen Y, Wei J, Zhu M, Gong Z, Yan Y: *Time series analysis of antibacterial usage and bacterial resistance in China: observations from a tertiary hospital from 2014 to 2018*. Infect Drug Resist 2019, 12:2683-2691.

35. Kim B, Kim Y, Hwang H, Kim J, Kim SW, Bae IG, Choi WS, Jung SI, Jeong HW, Pai H: *Trends and correlation between antibiotic usage and resistance pattern among hospitalized patients at university hospitals in Korea, 2004 to 2012: A nationwide multicenter study*. Medicine (Baltimore) 2018, 97(51):e13719.

36. Abbara S, Pitsch A, Jochmans S, Hodjat K, Cherrier P, Monchi M, Vinsonneau C, Diamantis S: *Impact of a multimodal strategy combining a new standard of care and restriction of carbapenems, fluoroquinolones and cephalosporins on antibiotic consumption and resistance of Pseudomonas aeruginosa in a French intensive care unit*. Int J Antimicrob Agents 2019, 53(4):416-422.

Tables
Table 1. Resistance of *Escherichia coli* from BSI to commonly used antibiotics

|                         | 1998-2002 | 2003-2007 | 2008-2012 | 2013-2017 |
|-------------------------|-----------|-----------|-----------|-----------|
|                         | n         | R (%)     | n         | R (%)     | n         | R (%)     | n         | R (%)     |
| **PENICILLINS**         |           |           |           |           |           |           |           |           |
| Ampicillin (100ug)      | 348       | 83.6      | 958       | 88.5      | 2411      | 89.3      | 7125      | 86.4      |
| Piperacillin (100ug)    | 343       | 71.1      | 948       | 79.4      | 2652      | 81.1      | 4883      | 79        |
| **β-LACTAM COMBINATION AGENTS** | | | | | | | | |
| Ampicillin clavulanic acid (20/10ug) | 328 | 22 | 859 | 17.2 | 2468 | 17.7 | 4968 | 14.1 |
| Cefoperazone sulbactam (75/75ug) | / | / | 930 | 9.2 | 2479 | 5.5 | 2962 | 7.6 |
| Piperacillin Tazobactam (100/10ug) | / | / | / | / | 2062 | 4.7 | 6619 | 3.7 |
| **CEPHEMS (Including cephalosporins I, II, III, and IV)** | | | | | | | | |
| Cefazolin (30ug)        | 350       | 34.9      | 941       | 58.8      | 1936      | 70.5      | 6277      | 47.5      |
| Cefuroxime (30ug)       | 304       | 31.9      | 893       | 57.7      | 2520      | 68.4      | 5228      | 61.5      |
| Ceftazidime (30ug)      | 352       | 10.5      | 1015      | 17.7      | 2904      | 30.1      | 7137      | 26.6      |
| Cefotaxime (30ug)       | 356       | 31.7      | 989       | 56.6      | 2611      | 67.3      | 4467      | 62.5      |
| Cefepime (30ug)         | /         | /         | 973       | 33.4      | 2812      | 48.8      | 7122      | 41.3      |
| Cefoxitin (30ug)        | /         | /         | 824       | 12.7      | 2393      | 11.5      | 5136      | 7.5       |
| **MONOBACTAMS**         |           |           |           |           |           |           |           |           |
| Aztreonam (30ug)        | 329       | 14.6      | 969       | 25.6      | 2684      | 40.9      | 5704      | 37        |
| **CARBAPENEMS**         |           |           |           |           |           |           |           |           |
| Imipenem (10ug)         | 341       | 2.3       | 1011      | 1.8       | 2850      | 1         | 7173      | 0.8       |
| Meropenem (10ug)        | /         | /         | 366       | 0.8       | 1988      | 1.2       | 6331      | 1.3       |
| **AMINOGYLCOSIDES**     |           |           |           |           |           |           |           |           |
| Amikacin (30ug)         | 352       | 9.1       | 964       | 6         | 2870      | 6.2       | 6900      | 2.4       |
| Gentamicin (10ug)       | 352       | 47.4      | 992       | 55.1      | 2775      | 52.5      | 7152      | 39.5      |
| **FLUOROQUINOLONES**    |           |           |           |           |           |           |           |           |
| Ciprofloxacin (5ug)     | 360       | 52.8      | 973       | 55.6      | 2448      | 54.3      | 7091      | 47.3      |
| Levofloxacin (5ug)      | /         | /         | 702       | 52.8      | 2190      | 54.6      | 6448      | 45.2      |
| FOLATE PATHWAY ANTAGONISTS | 351 | 72.1 | 980 | 72.2 | 2636 | 62.8 | 7101 | 56.6 |
|---------------------------|-----|------|-----|------|------|------|------|------|
| trimethoprim/sulfamethoxazole |  (1.25/23.75ug) |     |     |     |     |      |      |      |

Footnote: “/” indicated that the antibiotics had not been tested.
|                       | 1998-2002 | 2003-2007 | 2008-2012 | 2013-2017 |
|-----------------------|-----------|-----------|-----------|-----------|
|                       | n         | R(%)      | n         | R(%)      | n         | R(%)      | n         | R(%)      |
| **PENICILLINS**       |           |           |           |           |           |           |           |           |
| Ampicillin (10ug)     | 96        | 97.9      | 282       | 97.5      | 708       | 97.5      | 2505      | 94.5      |
| Piperacillin (100ug)  | 90        | 56.7      | 278       | 48.9      | 738       | 49.7      | 1960      | 52        |
| **β-LACTAM COMBINATION AGENTS** |           |           |           |           |           |           |           |           |
| Ampicillin clavulanic acid 20/10ug | 95       | 28.4      | 262       | 17.6      | 701       | 19.5      | 2005      | 29.6      |
| Cefoperazone sulbactam (75/75ug) | 48       | 18.8      | 259       | 12        | 688       | 9.3       | 1260      | 30.8      |
| Piperacillin Tazobactam (100/10ug) | /          | /         | 120       | 20.8      | 587       | 9.9       | 2560      | 20.4      |
| **CEPHEMS (Including cephalosporins I, II, III, and IV)** |           |           |           |           |           |           |           |           |
| Cefazolin (30ug)      | 96        | 47.9      | 281       | 43.4      | 556       | 46        | 2289      | 40.2      |
| Cefuroxime (30ug)     | 82        | 42.7      | 270       | 42.2      | 715       | 44.1      | 1889      | 45.8      |
| Ceftazidime (30ug)    | 96        | 24        | 290       | 25.9      | 810       | 27.7      | 2680      | 31.6      |
| Cefotaxime (30ug)     | 97        | 42.3      | 288       | 41.7      | 695       | 44.3      | 1814      | 49.7      |
| Cefepime (30ug)       | 38        | 39.5      | 279       | 29        | 780       | 30.1      | 2688      | 33.6      |
| Cefoxitin (30ug)      | /         | /         | 239       | 18        | 674       | 13.9      | 1866      | 25.2      |
| **MONOBACTAMS**       |           |           |           |           |           |           |           |           |
| Aztreonam (30ug)      | 90        | 34.4      | 278       | 25.9      | 745       | 30.2      | 2283      | 35.2      |
| **CARBAPENEMS**       |           |           |           |           |           |           |           |           |
| Imipenem (10ug)       | 88        | 9.1       | 289       | 2.4       | 802       | 3.7       | 2685      | 15.8      |
| Meropenem (10ug)      | /         | /         | 113       | 1.8       | 567       | 4.4       | 2372      | 17.5      |
| **AMINOGLYCOSIDES**   |           |           |           |           |           |           |           |           |
| Amikacin (30ug)       | 95        | 23.2      | 280       | 6.8       | 806       | 5.7       | 2620      | 12.7      |
| Gentamicin (10ug)     | 96        | 35.4      | 285       | 23.2      | 793       | 25.7      | 2694      | 28.8      |
| **FLUOROQUINOLONES**  |           |           |           |           |           |           |           |           |
| Ciprofloxacin (5ug)   | 97        | 18.6      | 285       | 19.3      | 722       | 18.1      | 2668      | 27.7      |
Table 3. Resistance of \emph{Salmonella typhi} from BSI to commonly used antibiotics

| Antibiotics                          | 1998-2002 n | 1998-2002 R (%) | 2003-2007 n | 2003-2007 R (%) | 2008-2012 n | 2008-2012 R (%) | 2013-2017 n | 2013-2017 R (%) |
|--------------------------------------|-------------|-----------------|-------------|-----------------|-------------|-----------------|-------------|-----------------|
| PENICILLINS                          |             |                 |             |                 |             |                 |             |                 |
| Ampicillin (10ug)                    | 202         | 6.9             | 116         | 15.5            | 69          | 26.1            | 52          | 38.5            |
| FLUOROQUINOLONES                     |             |                 |             |                 |             |                 |             |                 |
| Ciprofloxacin (5ug)                  | 194         | 4.1             | 119         | 4.2             | 66          | 3               | 54          | 3.7             |
| Levofloxacin (5ug)                   | 34          | 0               | 65          | 1.5             | 59          | 0               | 37          | 2.7             |
| FOLATE PATHWAY ANTAGONISTS           |             |                 |             |                 |             |                 |             |                 |
| trimethoprim/sulfamethoxazole (1.25/23.75ug) | 182      | 22              | 121         | 25.6            | 66          | 10.6            | 57          | 8.8             |
| CEPHEMS                              |             |                 |             |                 |             |                 |             |                 |
| Ceftazidime (30ug)                   | 192         | 3.6             | 109         | 1.8             | 62          | 3.2             | 42          | 0               |
| Cefatriaxone (30ug)                  | 41          | 2.4             | 62          | 1.6             | 38          | 5.3             | 23          | 0               |
| Cefotaxime (30ug)                    | 196         | 6.1             | 104         | 1.9             | 58          | 8.6             | 32          | 3.1             |
| PHENICOLS                            |             |                 |             |                 |             |                 |             |                 |
| Chloramphenicol (30ug)               | 83          | 6               | 68          | 7.4             | 33          | 9.1             | 41          | 7.3             |

Footnote: “/” indicated that the antibiotics had not been tested.

Table 4. Resistance of \emph{Pseudomonas aeruginosa} from BSI to commonly used antibiotics
|                      | 1998-2002 | 2003-2007 | 2008-2012 | 2013-2017 |
|----------------------|-----------|-----------|-----------|-----------|
|                      | n         | R (%)     | n         | R (%)     | n         | R (%)     | n         | R (%)     |
| **PENICILLINS**      |           |           |           |           |           |           |           |           |
| Piperacillin (100ug) | 99        | 24.2      | 189       | 29.1      | 473       | 23.7      | 1065      | 21.4      |
| **β-LACTAM COMBINATION AGENTS** | | | | | | | | |
| Piperacillin Tazobactam (100/10ug) | /         | /         | 89        | 19.1      | 334       | 13.2      | 1046      | 15.6      |
| **CEPHEMS**          |           |           |           |           |           |           |           |           |
| Ceftazidime (30ug)   | 100       | 26        | 191       | 18.8      | 471       | 21        | 1079      | 19        |
| Cefepime (30ug)      | /         | /         | 175       | 17.7      | 465       | 21.3      | 1081      | 19.9      |
| **MONOBACTAMS**      |           |           |           |           |           |           |           |           |
| Aztreonam (30ug)     | 92        | 33.7      | 187       | 22.5      | 451       | 26.6      | 859       | 22.7      |
| **CARBAPENEMS**      |           |           |           |           |           |           |           |           |
| Imipenem (10ug)      | 95        | 16.8      | 189       | 21.2      | 473       | 23.7      | 1079      | 30.6      |
| Meropenem (10ug)     | /         | /         | 87        | 14.9      | 381       | 21.8      | 935       | 25.6      |
| **AMINOGLYCOSIDES**  |           |           |           |           |           |           |           |           |
| Amikacin (30ug)      | 101       | 16.8      | 186       | 17.7      | 480       | 20.2      | 1063      | 14.3      |
| Gentamicin (10ug)    | 103       | 23.3      | 186       | 29.6      | 468       | 26.3      | 1075      | 21.2      |
| **FLUOROQUINOLONES** |           |           |           |           |           |           |           |           |
| Ciprofloxacin (5ug)  | 98        | 17.3      | 187       | 17.1      | 423       | 18.4      | 1069      | 17.5      |
| Levofloxacin (5ug)   | /         | /         | 107       | 21.5      | 326       | 13.8      | 939       | 17.3      |

Footnote: “/” indicated that the antibiotics had not been tested.
Table 5. Resistance of *Acinetobacter baumannii* from BSI to commonly used antibiotics

|                  | 1998-2002 |          |          | 2008-2012 |          |          | 2013-2017 |          |
|------------------|-----------|----------|----------|-----------|----------|----------|-----------|----------|
|                  | n  | R (%)  | n  | R (%)  | n  | R (%)  | n  | R (%)  |
| **PENICILLINS**  |   |        |   |        |   |        |   |        |
| Piperacillin (100ug) |  9 | 22.2   | 64 | 50     | 341 | 69.5   | 760 | 78.8   |
| **β-LACTAM COMBINATION AGENTS** |   |        |   |        |   |        |   |        |
| Cefoperazone sulbactam (75/75ug) | / | /  | 62 | 12.9   | 299 | 24.4   | 643 | 63.1   |
| Piperacillin Tazobactam (100/10ug) | / | /  | 36 | 41.7   | 245 | 62     | 876 | 74.9   |
| **CEPHEMS**      |   |        |   |        |   |        |   |        |
| Ceftazidime (30ug) |  10 | 30     | 68 | 42.6   | 351 | 63     | 879 | 76.5   |
| Cefepime (30ug)   | /   | /      | 65 | 38.5   | 310 | 62.9   | 986 | 75.4   |
| **CARBAPENEMS**  |   |        |   |        |   |        |   |        |
| Imipenem (10ug)   | /   | /      | 68 | 23.5   | 334 | 61.1   | 989 | 74.4   |
| Meropenem (10ug)  | /   | /      | 30 | 20     | 272 | 58.1   | 829 | 76.1   |
| **AMINOGLYCOSIDES**|   |        |   |        |   |        |   |        |
| Amikacin (30ug)   |  10 | 20     | 64 | 39.1   | 351 | 59.8   | 916 | 67.7   |
| Gentamicin (10ug) |  10 | 40     | 65 | 49.2   | 344 | 67.4   | 986 | 75.5   |
| **FLUOROQUINOLONES**|   |        |   |        |   |        |   |        |
| Ciprofloxacin (5ug) |  10 | 40     | 63 | 31.7   | 317 | 57.7   | 969 | 74.5   |
| Levofloxacin (5ug) | /   | /      | 46 | 28.3   | 273 | 57.9   | 928 | 69.6   |
| **FOLATE PATHWAY ANTAGONISTS**|   |        |   |        |   |        |   |        |
| trimethoprim/sulfamethoxazole (1.25/23.75ug) |  8 | 25     | 68 | 50     | 268 | 63.4   | 962 | 74.3   |

*Footnote: “/” indicated that the antibiotics had not been tested.*

Table 6. Resistance of *Stenotrophomonas maltophilia* from BSI to commonly used antibiotics
|                              | 1998-2002 | 2003-2007 | 2008-2012 | 2013-2017 |
|------------------------------|-----------|-----------|-----------|-----------|
|                              | n         | R (%)     | n         | R (%)     | n         | R (%)     | n         | R (%)     |
| **FLUOROQUINOLONES**         |           |           |           |           |           |           |           |           |
| Levofloxacin (5ug)           | 16        | 6.2       | 191       | 1         | 266       | 1.9       | 520       | 4.2       |
| **FOLATE PATHWAY ANTAGONISTS**|           |           |           |           |           |           |           |           |
| trimethoprim/sulfamethoxazole (1.25/23.75ug) | 38        | 10.5      | 243       | 9.5       | 268       | 22.4      | 531       | 11.1      |
| **CEPHEMS**                  |           |           |           |           |           |           |           |           |
| Ceftazidime (30ug)           | 41        | 0         | 171       | 0         | 102       | 0         | 365       | 58.1      |
| **PHENICOLS**                |           |           |           |           |           |           |           |           |
| Chloramphenicol (30ug)       | 24        | 0         | 90        | 0         | 19        | 0         | 259       | 5         |

Table 7. Resistance of *MRSA* from BSI to commonly used antibiotics
|                        | 1998-2002 | 2003-2007 | 2008-2012 | 2013-2017 |
|------------------------|-----------|-----------|-----------|-----------|
|                        | n        | R (%)    | n        | R (%)    | n        | R (%)    | n        | R (%)    |
| **AMINOGLYCOSIDES**    |          |          |          |          |
| Gentamicin (10ug)      | 89       | 38.2     | 345      | 55.4     | 442      | 56.6     | 520      | 77.9     |
| **FLUOROQUINOLONES**   |          |          |          |          |
| Levofloxacin (5ug)     | /        | /        | /        | /        | 380      | 53.9     | 455      | 82.6     |
| **FOLATE PATHWAY ANTAGONISTS** | | | |          |
| trimethoprim/sulfamethoxazole (1.25/23.75ug) | 83 | 69.9 | 379 | 64.9 | 435 | 41.1 | 504 | 3.8 |
| **LINCOSAMIDES**       |          |          |          |          |
| Clindamycin (2ug)      | 72       | 61.1     | 388      | 67.5     | 462      | 63.6     | 514      | 55.3     |
| **MACROLIDES**         |          |          |          |          |
| Erythromycin (15ug)    | 90       | 85.6     | 393      | 89.1     | 461      | 85.7     | 526      | 72.4     |
| **OXAZOLIDINONES**     |          |          |          |          |
| Linezolid (30ug)       | /        | /        | /        | /        | 487      | 0        |          |          |
| **GLYCOPEPTIDES**      |          |          |          |          |
| Vancomycin (30ug)      | 90       | 0        | 393      | 0        | 370      | 0        | 475      | 0        |
| Teicoplanin (30ug)     | /        | /        | 360      | 1.1      | 434      | 1.2      | 491      | 0.2      |

Footnote: "/" indicated that the antibiotics had not been tested.

Table 8. Resistance of *MSSA* from BSI to commonly used antibiotics
|                              | 1998-2002 | 2003-2007 | 2008-2012 | 2013-2017 |
|------------------------------|-----------|-----------|-----------|-----------|
|                              | n         | R(%)      | n         | R(%)      | n         | R(%)      | n         | R(%)      |
| PENICILLINS                  |           |           |           |           |           |           |           |           |
| Penicillin (10 units)        | 314       | 96.2      | 412       | 92.2      | 535       | 91.6      | 376       | 95.5      |
| AMINOGLYCOSIDES              |           |           |           |           |           |           |           |           |
| Gentamicin (10ug)            | 305       | 5.6       | 431       | 9.7       | 524       | 10.5      | 421       | 10.7      |
| FLUOROQUINOLONES             |           |           |           |           |           |           |           |           |
| Levofloxacin (5ug)           | /         | /         | /         | /         | 446       | 7.8       | 305       | 7.5       |
| FOLATE PATHWAY ANTAGONISTS   |           |           |           |           |           |           |           |           |
| trimethoprim/sulfamethoxazole (1.25/23.75ug) | 300       | 26.7      | 449       | 29.2      | 501       | 22.2      | 397       | 3.3       |
| LINCOSAMIDES                 |           |           |           |           |           |           |           |           |
| Clindamycin (2ug)            | 265       | 30.6      | 446       | 28.7      | 541       | 21.4      | 401       | 19.5      |
| MACROLIDES                   |           |           |           |           |           |           |           |           |
| Erythromycin (15ug)          | 313       | 62.3      | 451       | 54.8      | 540       | 54.1      | 422       | 46.2      |
| OXAZOLIDINONES                |           |           |           |           |           |           |           |           |
| Linezolid (30ug)             | /         | /         | /         | /         | /         | /         | 376       | 0         |
| GLYCOPEPTIDES                 |           |           |           |           |           |           |           |           |
| Vancomycin (30ug)            | 319       | 0         | 454       | 0         | 444       | 0         | 326       | 0         |
| Teicoplanin (30ug)           | /         | /         | 424       | 0         | 476       | 0.2       | 329       | 0         |

Footnote: ‘/’ indicated that the antibiotics had not been tested.

**Figures**
Figure 1

Demographic data and pathogens of BSI in Hubei Province, 1998-2017. Footnote: The number of permanent residents in the province is based on the information released by the Bureau of statistics.
Figure 2

Distribution of the main Gram-positive bacteria per year

Figure 3

Distribution of the main Gram-negative bacteria per year
Figure 4

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