International Journal of Antimicrobial Agents 62 (2023) 106869

Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

journal homepage: www.elsevier.com/locate/ijantimicag

Letter to the Editor

Antimicrobial Resistance Surveillance: China's Nearly 40-Year Effort

Editor: H. Sader

To the Editor,

The widespread emergence of multidrug-resistant bacteria worldwide has created major challenges for clinical anti-infective treatment [1]. The bacterial resistance surveillance network and performance standards for antimicrobial susceptibility testing play an important role in understanding the evolution of bacterial resistance and guiding rational clinical treatment.

Until now, China did not have its own performance standards and reference laboratory for antimicrobial susceptibility testing. As an authority with the highest technical capability of antimicrobial susceptibility testing, the lack of antimicrobial susceptibility testing standards and reference laboratories has led to several problems. First, there was no official channel or authoritative organisation, such as a reference laboratory, available for the verification and confirmation of rare multidrug-resistant phenotypes. Second, there has been an inability to guide the development of automated antimicrobial susceptibility testing systems that meet the actual clinical needs of China. Third, innovative drugs have been developed in China, such as nemonoxacin, norvancomycin [2], contezolid [3], for which neither the Clinical and Laboratory Standards Institute (CLSI) [4] nor the European Committee on Antimicrobial Susceptibility Testing (EUCAST) [5] have susceptibility testing standards. Fourth, if there is a difference between the CLSI and EUCAST standards, it is difficult to determine which standard is more appropriate for China's actual clinical needs. For example, the CLSI and EUCAST proposed different disk contents and breakpoints for ceftazidime-avibactam susceptibility testing by the disk diffusion method, and different interpretations of polymyxin susceptibility testing results (when the MIC $\leq$ 2 mg/L, CLSI only allows reporting of "intermediate", while EUCAST believes that "susceptible" can be reported). Finally, the lack of standardisation of susceptibility testing leads to the misuse of new antimicrobial agents, which is one of the factors contributing to the increase in resistance.

For almost 40 years, the Chinese government and social organisations have made great efforts to curb bacterial resistance and establish performance standards for antimicrobial susceptibility testing in China (Figure 1). In 1988, with the support from the World Health Organization Western Pacific Region and the Chinese Ministry of Health, the Antimicrobial Resistance Surveillance Network was formally established in Beijing and Shanghai, and the standard for antimicrobial susceptibility testing was developed. In 2005, the networks were expanded to cover the whole country, including the Centre for Antibacterial Surveillance (CAS, led by the National Health Commission), the China Antimicrobial Resistance Surveillance System (CARSS, led by the National Health Commission) (formerly Mohnarin, Ministry of Health National Antimicrobial Resistance Investigation Net) and the China Antimicrobial Surveillance Network (CHINET, led by Huashan Hospital, Fudan University). As a result, national-level systematic training platforms have been established to improve the skill level of clinicians, covering anti-infective treatment (Peiyuan Project), infection prevention and control professionals (SHIP Project), clinical pharmacist (Peiying Project), and clinical microbiologist (Peiwei Project).

In 2016, the National Health and Family Planning Commission (formerly the Ministry of Health) jointly released 'China's National Plan to Combat Antimicrobial Resistance 2016-2020' [6]. The action plan proposed, for the first time, the need to establish a reference laboratory for antimicrobial susceptibility testing in China. Subsequently, in 2017, the National Health and Family Planning Commission issued a document outlining the plan to establish a clinical microbiology reference laboratory in China. Meanwhile, the Peking Union Medical College Hospital took the lead in establishing the Chinese Committee on Antimicrobial Susceptibility Testing (ChiCAST). In May 2018, China's National Centre for Drug Evaluation officially released the 'Technical Guidelines for Antimicrobial Breakpoint Research', which for the first time stipulated that new antimicrobial agents must have antimicrobial susceptibility testing breakpoints (such as epidemiological cut-off values) before being approved for clinical marketing.

In the same year, the 'Expert Committee on Clinical Application and Management of Antimicrobial Agents of Shanghai Municipal Health and Family Planning Commission' was established to integrate the antimicrobial resistance surveillance network, the antimicrobial clinical application surveillance network and the nosocomial infection control network (i.e. 'triple network linkage'; this idea was first proposed by our group) [7]. As a result, the innovative 'Bacterial Resistance Index' was developed and published for the first time to assess the level of bacterial resistance in each hospital. This innovative model was quickly promoted throughout the country by the National Health Commission, namely: 'multiple networks for antimicrobial resistance'.

In August 2019, the China Antimicrobial Surveillance Network established the CHINET Committee on Antimicrobial Susceptibility Testing (CCAST). Subsequently, in June 2022, seven reference laboratories for CHINET antimicrobial susceptibility testing were established in six cities across the country. To date, breakpoints for 13 antimicrobial agents have been formulated or are in progress, including: nemonoxacin, contezolid, norvancomycin, cefoperazone-sulbactam, faropenem, cefoselis, cefathiamidine, cetirizine, cefotiam and cefotaxime-sulbactam (Table 1). In October 2022, a new round of China's national plan to combat antimicrobial resistance 2022–2025 was announced by the Chinese government [8].

The main tasks of the Committee on Antimicrobial Susceptibility Testing Committee and Reference Laboratories in China

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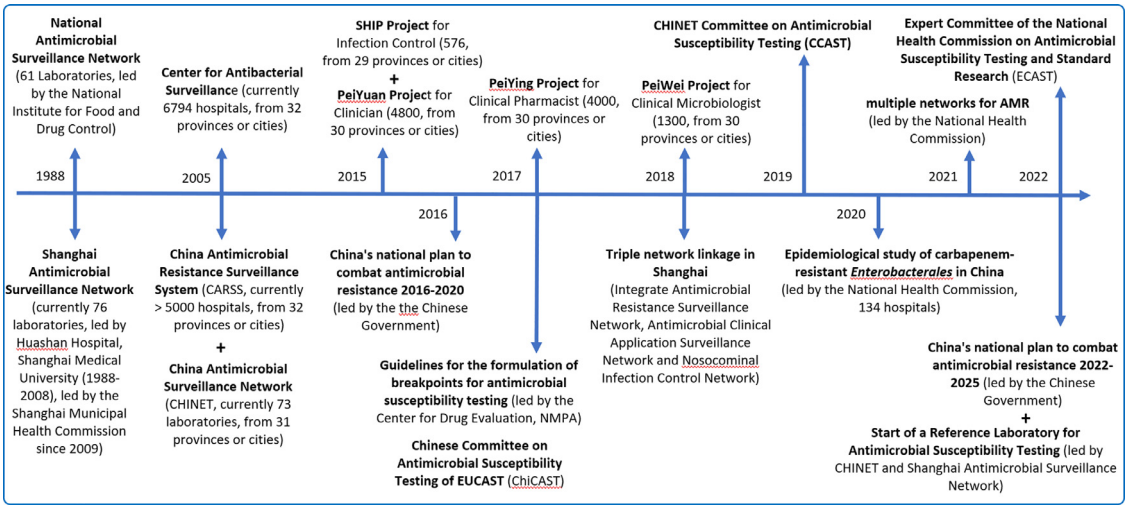

Figure 1. China's efforts to combat antimicrobial resistance and establish performance standards for antimicrobial susceptibility testing. AMR, antimicrobial resistance; NMPA, National Medical Products Administration.

Table 1
Completed or ongoing studies to establish breakpoints for antimicrobial susceptibility testing in China.

Antimicrobial agent	Manufacturer	Breakpoint	Isolate	Led by	Number of Laboratories	Year
Nemonoxacin	Zhejiang Medicine	ECOFF	*E. coli, K. pneumoniae, P. aeruginosa, S. aureus, H. influenzae, S. pneumoniae*	Huashan Hospital, Fudan University	3	2018
Norvancomycin	North China Pharmaceutical	ECOFF	*S. aureus, S. epidermidis, S. haemolyticus, S. hominis*	Peking Union Medical College Hospital	5	2018
Contezolid	MicuRx	ECOFF	*S. aureus, E. faecalis, S. pneumoniae*	Huashan Hospital, Fudan University	3	2019
Cefoperazone-sulbactam	Pfizer	ECOFF	*E. coli, K. pneumoniae, P. mirabilis, P. aeruginosa, A. baumannii*	Huashan Hospital, Fudan University	5	2019
Cefoselis	Jiangsu Hansoh Pharma	ECOFF	*E. coli, K. pneumoniae, E. cloacae, P. mirabilis, P. aeruginosa*	Peking Union Medical College Hospital	5	2019
Eravacycline	Everest Medicines	ECOFF, PK/PD breakpoint, Clinical breakpoint	*E. coli, K. pneumoniae, E. cloacae, A. baumannii, S. aureus*	Peking Union Medical College Hospital	5	2020
Faropenem	Hangzhou Hengtong Pharmaceutical	ECOFF	*E. coli, K. pneumoniae, H. influenzae, S. aureus, S. pneumoniae*	Huashan Hospital, Fudan University	4	2020
Cephathiamidine	Guangzhou Baiyunshan Pharmaceutical	ECOFF	*E. coli, K. pneumoniae, S. pyogenes, H. influenzae, M. catarrhalis*	Huashan Hospital, Fudan University	4	2021
Cetirizine	Guangzhou Baiyunshan Pharmaceutical	ECOFF	*E. coli, K. pneumoniae, S. pneumoniae, S. pyogenes, H. influenzae, M. catarrhalis*	Huashan Hospital, Fudan University	4	2021
Cefotiam	Zhejiang Yongning Pharma	ECOFF	*E. coli, K. pneumoniae, P. mirabilis, H. influenzae, S. pyogenes*	Huashan Hospital, Fudan University	4	2021
Sitafloxacin	Daiichi Sankyo Company Limited	ECOFF	*E. coli, K. pneumoniae, P. mirabilis, P. aeruginosa, A. baumannii, S. aureus, E. faecalis, E. faecium, S. pneumoniae*	Peking Union Medical College Hospital	5	2021
Cefotaxime-sulbactam	Welman Pharmaceutical	ECOFF	*E. coli, K. pneumoniae, E. cloacae, P. mirabilis, S. marcescens, A. baumannii, S. aureus, H. influenzae*	Peking Union Medical College Hospital	5	2021
Morinidazole	Hansoh pharmaceutical	ECOFF	*B. fragilis, C. difficile*	Huashan Hospital, Fudan University	5	2023

Abbreviations: ECOFF, epidemiological cut-off value; *E. coli, Escherichia coli; K. pneumoniae, Klebsiella pneumoniae; P. aeruginosa, Pseudomonas aeruginosa; S. aureus, Staphylococcus aureus; H. influenzae, Haemophilus influenzae; S. pneumoniae, Streptococcus pneumoniae; S. epidermidis, Staphylococcus epidermidis; S. haemolyticus, Staphylococcus haemolyticus; S. hominis, Staphylococcus hominis; E. faecalis, Enterococcus faecalis; P. mirabilis, Proteus mirabilis; A. baumannii, Acinetobacter baumannii; E. cloacae, Enterobacter cloacae; S. pyogenes, Streptococcus pyogenes; M. catarrhalis, Moraxella catarrhalis; S. marcescens, Serratia marcescens; E. faecium, Enterococcus faecium; B. fragilis, Bacteroides fragilis; C. difficile, Clostridium difficile*

include: (1) to study the breakpoints of antimicrobial agents; (2) to re-identify and confirm the detection of rare resistant phenotypes or genotypes; (3) to translate the latest international standard documents (such as CLSI and EUCAST documents), develop international cooperation and exchange, and conduct training to improve the overall level of antimicrobial susceptibility testing; (4) to work with reference laboratories to improve the level of competence of local clinical microbiology laboratories in antimicrobial susceptibility testing; (5) to work with pharmaceutical companies to guide the research and development of new antimicrobial agents, and with in vitro diagnostic companies to improve or develop new antimicrobial susceptibility testing systems; and (6) to take the lead in conducting multicentre epidemiological studies of important multidrug-resistant bacteria.

By staying true to its original aspirations and keeping its mission in mind, China will eventually develop its own performance

standards for antimicrobial susceptibility testing with Chinese characteristics to better guide anti-infective clinical practive in China.

Declaration Competing Interests: None to declare.

Declarations/Funding: This work was supported in part by the grants from the National Key Research and Development Program of China (2021YFC2701800, 2021YFC2701803), Shanghai 2021 Science and Technology Innovation Action Plan: Establishment of Technical Standards for the Epidemiological cut-off value for Antimicrobial agents (21DZ2200800) and the China Antimicrobial Surveillance Network (2018QD100).

Ethical Approval: Not required.

Sequence Information: None.

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Li Ding, Yan Guo, Fupin Hu*
Institute of Antibiotics, Huashan Hospital, Fudan University, Shanghai, China
Key Laboratory of Clinical Pharmacology of Antibiotics, Shanghai, China

*Correspondence to: Institute of Antibiotics, Huashan Hospital, Fudan University, Shanghai, 200040 China.
E-mail address: hufupin@fudan.edu.cn (F. Hu)