ORIGINAL ARTICLE

Resistance trends among clinical isolates in China reported from CHINET surveillance of bacterial resistance, 2005–2014

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Abstract

With the aim of gathering temporal trends on bacterial epidemiology and resistance from multiple laboratories in China, the CHINET surveillance system was organized in 2005. Antimicrobial susceptibility testing was carried out according to a unified protocol using the Kirby-Bauer method or automated systems. Results were analyzed according to Clinical and Laboratory Standards Institute (CLSI) 2014 definitions. Between 2005 and 2014, the number of bacterial isolates ranged between 22 774 and 84 572 annually. Rates of extended-spectrum β-lactamase production among *Escherichia coli* isolates were stable, between 51.7 and 55.8%. Resistance of *E. coli* and *Klebsiella pneumoniae* to amikacin, ciprofloxacin, piperacillin/tazobactam and cefoperazone/sulbactam decreased with time. Carbapenem resistance among *K. pneumoniae* isolates increased from 2.4 to 13.4%. Resistance of *Pseudomonas aeruginosa* strains against all of antimicrobial agents tested including imipenem and meropenem decreased with time. On the contrary, resistance of *Acinetobacter baumannii* strains to carbapenems increased from 31 to 66.7%. A marked decrease of methicillin resistance from 69% in 2005 to 44.6% in 2014 was observed for *Staphylococcus aureus.* Carbapenem resistance rates in *K. pneumoniae* and *A. baumannii* in China are high. Our results indicate the importance of bacterial surveillance studies.

Keywords: *Acinetobacter baumannii*, antimicrobial resistance, carbapenems, CHINET surveillance of bacterial resistance, *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*

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Introduction

In 2005, with the aim of gathering bacterial resistance information from multiple laboratories in China on temporal trends

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and epidemiology, the CHINET surveillance system was organized. The data, in a unified format, were collected from microbiology laboratories and input into a central database using WHONET software [1]. These data provided a comprehensive national picture of resistance. In this analysis, we reported the significant changes and trends in antimicrobial resistance of clinically important pathogens from the CHINET surveillance system.

Materials and Methods

Bacterial strains, culture media and species identification

All aerobic bacteria (excluding anaerobic bacteria, fungi and mycobacteria) collected from outpatients and inpatients in 19 hospitals were obtained in the CHINET surveillance system for a 10-year period between 2005 and 2014 (two hospitals dropped out in 2012). Most of the hospitals included are the largest in each province or city; altogether, they represent 14 provinces or cities (about six hundred million population). In order to avoid duplicate counts, only one isolate from the same species was included per patient, based on the personal identifying code and hospital, per year. For coagulase-negative *Staphylococcus* and viridans *Streptococci,* only isolates collected from blood and cerebrospinal fluid were included in the analysis. Species identification of the isolates was performed by standard biochemical methods, the API 20E system or the Vitek 2 automated system (bioMérieux, Marcy l'Etoile, France).

Antimicrobial susceptibility testing

The antibiotic susceptibilities of clinical isolates were determined using the disk diffusion method according to the Clinical and Laboratory Standards Institute (CLSI) criteria (http://ncipd.org/control/images/NCIPD_docs/CLSI_M100-S24.pdf), or the Vitek 2 compact automated system (bioMérieux) following the instrument specifications, and the results were interpreted according to CLSI criteria (http://ncipd.org/control/images/NCIPD_docs/CLSI_M100-S24.pdf). During the 10-year sampling period, the methodologies used were consistent in all participating hospitals. Extended-spectrum β-lactamase (ESBL) production was identified by clavulanic acid synergy test (http://ncipd.org/control/images/NCIPD_docs/CLSI_M100-S24.pdf). No minimum inhibitory concentration data were available.

Reference strains

Staphylococcus aureus ATCC 25923, *Enterococcus faecalis* ATCC 29212, *Escherichia coli* ATCC 25922 and *Pseudomonas aeruginosa* ATCC 27853 were included to ensure reproducibility of the antibiotic susceptibility testing procedure.

Results

Percentage of targeted five species

The total number of bacterial isolates was between 22 774 and 84 572 annually. There were no changes in the ratio between specimen types during the study period. The percentage of the targeted five species among total number of all reported isolates is shown in Table 1. The five selected species accounted for 51.9 to 60.3% of all isolates (Table 1).

Escherichia coli

The rate of ESBL-producing isolates was stable, from 51.7% in 2006 to 55.8% in 2014 (Fig. 1). A marked decrease of resistance was seen for amikacin from 11.9 to 4%. However, a marked increase of resistance was seen for cefotaxime and ceftazidime from 52.2 to 63.2% and from 14.9 to 30.9%, respectively. Piperacillin/tazobactam, cefoperazone/sulbactam and ciprofloxacin resistance levels decreased from 6.2 to

TABLE 1. Percentage of targeted five species among total number of all reported isolates (isolated from both inpatients and outpatients)

Year	No. hospitals	Total	*Escherichia coli*		*Klebsiella pneumoniae*		*Pseudomonas aeruginosa*		*Acinetobacter baumannii*		*Staphylococcus aureus*		Total percentage of targeted five species
			n	%	*n*	%	*n*	%	*n*	%	*n*	%	
2005	8	22 774	3758	16.5	2234	9.8	2323	10.2	2095	9.2	1440	6.3	52.0
2006	9	33 945	6072	17.9	3452	10.2	4752	14.0	2968	8.7	1799	5.3	56.1
2007	12	36 001	6524	18.1	3037	8.4	3988	11.1	3157	8.8	1963	5.5	51.9
2008	12	36 216	6678	18.4	3435	9.5	4130	11.4	3625	10.0	1987	5.5	54.8
2009	14	43 670	7992	18.3	4556	10.4	4912	11.2	4796	11.0	2167	5.0	55.9
2010	14	47 850	9225	19.3	5529	11.6	5080	10.6	5523	11.5	2302	4.8	57.8
2011	15	59 287	11 860	20.0	6981	11.8	6012	10.1	6723	11.3	3033	5.1	58.4
2012	15	72 397	14 154	19.6	9621	13.3	7271	10.0	8739	12.1	3519	4.9	59.8
2013	16	84 572	16 794	19.9	12 121	14.3	8257	9.8	10 120	12.0	3672	4.3	60.3
2014	17	78 955	16 511	20.9	11 308	14.3	7471	9.5	8769	11.1	3172	4.0	59.8

TABLE 2. Resistance rates (%) of *Escherichia coli* to antimicrobial agents

Antimicrobial agent	2005 (*n* = 3758)	2006 (*n* = 6072)	2007 (*n* = 6524)	2008 (*n* = 6678)	2009 (*n* = 7992)	2010 (*n* = 9225)	2011 (*n* = 11 860)	2012 (*n* = 14 154)	2013 (*n* = 16 794)	2014 (*n* = 16 511)
Amikacin	11.9	7.6	8.0	8.2	7.6	7.4	5.9	5.4	4.0	4.0
Gentamicin	61.0	54.9	55.0	52.6	52.4	52.2	48.2	48.0	47.3	46.6
Piperacillin	76.9	76.9	76.0	77.1	76.9	75.3	75.7	76.0	73.5	71.6
Piperacillin/tazobactam	6.2	4.0	5.5	4.2	4.6	5.9	5.2	4.8	3.9	3.4
Cefazolin	68.8	66.5	70.2	70.6	72.7	69.2	70.8	70.5	72.8	71.1
Cefuroxime	52.8	55.5	61.6	63.0	63.9	64.1	63.9	63.3	64.4	62.8
Cefotaxime	52.2	54.9	60.4	62.3	63.2	63.2	63.1	63.2	62.9	62.0
Ceftazidime	14.9	17.0	19.9	22.6	28.5	30.7	30.9	30.0	28.4	28.8
Cefepime	31.2	32.2	35.4	37.6	40.2	42.1	40.7	38.5	31.6	28.1
Cefoperazone/sulbactam	9.0	5.8	2.9	4.0	5.3	6.5	7.9	7.6	6.0	5.4
Cefoxitin	13.0	11.6	10.8	10.9	10.9	13.5	12.0	15.5	16.3	13.6
Imipenem	1.1	1.4	0.7	1.2	1.7	1.6	1.0	0.9	1.0	0.9
Meropenem	1.4	0.8	0.8	0.9	1.0	1.4	1.2	1.0	3.0	1.0
Ertapenem						2.4	2.5	1.5	1.6	1.2
Ciprofloxacin	68.0	61.7	59.2	58.7	58.7	59.5	57.7	58.1	58.3	58.9
Sulfamethoxazole/ trimethoprim	71.0	66.0	66.5	64.7	66.2	66.8	66.4	60.1	57.6	59.1
Fosfomycin[a]							6.7	6.5	6.5	7.3

[a]Results only from urine isolates.

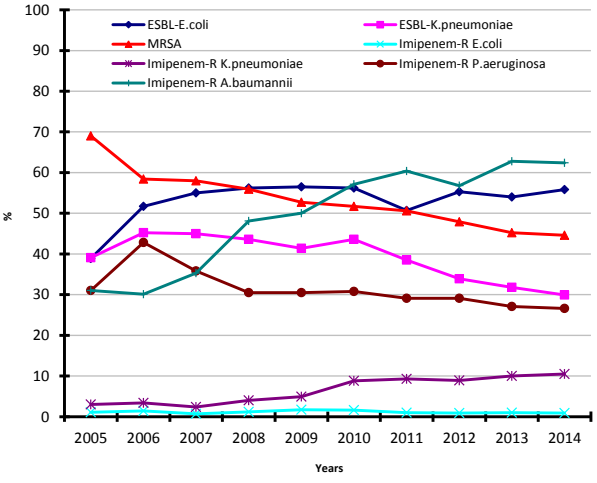

FIG. 1. Rates of methicillin-resistant *Staphylococcus aureus*, extended-spectrum β-lactamase-producing *Escherichia coli* and *Klebsiella pneumoniae*, imipenem-resistant Gram-negative bacilli clinical isolates from 2005 to 2014.

3.4%, from 9 to 5.4% and from 68 to 58.9%, respectively. Imipenem, meropenem and ciprofloxacin resistance rates essentially fluctuated around 1.0, 2.2 and 11%, respectively (Table 2).

Klebsiella pneumoniae

The rate of ESBL-producing isolates decreased from 39.1% in 2005 to 29.9% in 2014 ($p < 0.001$). A marked increase of resistance was seen for imipenem and meropenem from 2.4 to 10.5% and from 2.6 to 13.4%, respectively. Piperacillin/tazobactam and cefoperazone/sulbactam resistance levels decreased from 28 to 13.9% and from 23 to 16.1%, respectively. Amikacin, ciprofloxacin, ceftazidime and cefepime resistance levels decreased from 29 to 9%, 41 to 22.4%, 34.5 to 29.1% and 33.0 to 22.6%, respectively. Cefotaxime resistance levels were stable from 49.9 to 48.1%. Gentamicin and cefoxitin resistance rates essentially fluctuated around 16.4 and 9.6%, respectively (Table 3).

TABLE 3. Resistance rates (%) of *Klebsiella pneumoniae* to antimicrobial agents

Antimicrobial agent	2005 (*n* = 2234)	2006 (*n* = 3452)	2007 (*n* = 3037)	2008 (*n* = 3435)	2009 (*n* = 4556)	2010 (*n* = 5529)	2011 (*n* = 6981)	2012 (*n* = 9621)	2013 (*n* = 12 121)	2014 (*n* = 11 308)
Amikacin	29.0	19.8	18.0	15.9	15.1	14.4	12.4	11.4	10.1	9.0
Gentamicin	41.0	35.7	34.8	34.9	35.0	34.0	33.5	28.5	28.2	24.6
Piperacillin	58.0	58.4	59.1	59.5	56.1	57.5	55.2	52.0	50.2	48.2
Piperacillin/tazobactam	28.0	18.9	17.4	15.5	15.0	16.6	15.9	14.1	13.8	13.9
Cefazolin	59.6	58.7	59.5	59.2	57.3	56.8	56.9	53.7	59.1	52.3
Cefuroxime	49.4	51.7	52.0	52.9	50.8	50.3	50.4	50.1	48.9	47.3
Cefotaxime	49.9	52.3	51.5	52.2	50.5	49.9	49.3	48.5	48.4	48.1
Ceftazidime	34.5	33.3	31.4	34.1	32.9	35.4	34.8	32.6	30.6	29.1
Cefepime	33.0	34.1	32.0	31.7	33.1	35.1	34.5	29.6	25.7	22.6
Cefoperazone/sulbactam	23.0	12.7	8.7	8.8	10.8	14.8	15.8	17.0	15.8	16.1
Cefoxitin	16.0	18.3	17.4	17.5	13.0	21.7	19.0	16.0	15.5	12.1
Imipenem	3.0	3.4	2.4	4.0	4.9	8.8	9.3	8.9	10.0	10.5
Meropenem	2.9	2.6	2.9	3.8	4.8	8.9	9.4	10.8	13.5	13.4
Ciprofloxacin	41.0	32.1	31.1	29.9	27.8	30.1	27.5	24.1	22.4	22.4
Sulfamethoxazole/ trimethoprim	49.0	43.9	44.2	43.9	45.4	44.3	46.4	31.9	30.1	29.2

P. aeruginosa

The resistance level decreased for all of antimicrobial agents. A marked decrease of resistance was seen for gentamicin and piperacillin from 46 to 14.9% and from 44 to 19.8%, respectively. Piperacillin/tazobactam, ciprofloxacin and amikacin resistance levels decreased from 34 to 14.4%, from 32 to 14.9% and from 23 to 9.4%, respectively (Table 4).

Acinetobacter baumannii

A marked resistance increase was seen for imipenem and meropenem from 31% in 2005 to 62.4% in 2014, from 39% in 2005 to 66.7% in 2014, respectively. Cefoperazone/sulbactam and minocycline resistance levels increased from 25 to 37.7% and from 33 to 49.7%, respectively. Amikacin and sulfamethoxazole/trimethoprim resistance levels decreased from 61 to 47.4% and from 69 to 50.5%, respectively (Table 5).

Staphylococcus aureus

A marked decrease of the methicillin resistance rate was seen from 69% in 2005 to 44.6% in 2014 (Fig. 1). No isolate was found resistant to vancomycin, linezolid or teicoplanin. For methicillin-resistant *S. aureus* isolates, a resistance increase was seen for rifampin from 34.9 to 47.2%. Clindamycin and sulfamethoxazole/trimethoprim resistance levels decreased from 90.1 to 52.9% and from 36.3 to 7.0%, respectively. Erythromycin resistance levels decreased from 92.7 to 77.1% (Table 6).

Discussion

The trends of resistance levels among *E. coli* and *K. pneumoniae* were similar. A decrease of resistance with time was seen for amikacin, ciprofloxacin, piperacillin/tazobactam and cefoperazone/sulbactam and an increase in resistance was observed for cefotaxime. For *P. aeruginosa,* resistance levels decreased for all of antimicrobial agents, including imipenem and meropenem. However, resistance of *A. baumannii* increased to many important antimicrobial agents, especially imipenem and meropenem.

Carbapenems are the most potent and reliable β-lactam antibiotics for the treatment of serious infections caused by multidrug-resistant *Enterobacteriaceae* [2,3]. However,

TABLE 4. Resistance rates (%) of *Pseudomonas aeruginosa* to antimicrobial agents

Antimicrobial agent	2005 (n = 2323)	2006 (n = 4752)	2007 (n = 3988)	2008 (n = 4130)	2009 (n = 4912)	2010 (n = 5080)	2011 (n = 6012)	2012 (n = 7271)	2013 (n = 8257)	2014 (n = 7471)
Amikacin	23.0	16.5	18.7	15.5	14.8	15.3	14.3	13.5	11.0	9.4
Gentamicin	46.0	44.2	39.2	27.7	26.9	25.9	23.5	20.9	17.5	14.9
Piperacillin	44.0	46.5	40.1	32.6	30.9	30.3	29.3	24.6	23.7	19.8
Piperacillin/tazobactam	34.0	38.9	32.8	25.9	24.1	23.9	21.7	17.5	16.7	14.4
Cefoperazone	41.0	45.3	40.3	32.3	29.1	29.5	31.7	34.5	29.8	30.9
Cefoperazone/sulbactam	23.0	25.7	22.8	14.8	18.2	17.9	19.8	19.8	16.6	15.5
Ticarcillin/clavulanic acid	51.0	56.2	50	43.6	41.1	41.2	38.7	38.3	35.5	35.1
Ceftazidime	29.0	28.3	29.3	21.0	20.3	21.6	19.5	19.6	24.4	18.7
Cefepime	28.0	26.3	26.0	17.6	19.7	19.3	19.0	18.3	16.4	16.0
Aztreonam	37.0	32.8	31.2	26.3	29.9	32.4	38.9	29.4	26.2	26.2
Imipenem	31.0	42.8	35.8	30.5	30.5	30.8	29.1	29.1	27.1	26.6
Meropenem	32.0	34.1	28.5	24.5	25.2	25.8	25.0	27.1	25.1	24.3
Ciprofloxacin	32.0	30.7	29.8	14.8	23.9	22.4	20.8	17.9	16.8	14.9
Levofloxacin						26.1	24.6	20.5	16.5	12.9

TABLE 5. Resistance rates (%) of *Acinetobacter baumannii* to antimicrobial agents

Antimicrobial agent	2005 (n = 2095)	2006 (n = 2968)	2007 (n = 3157)	2008 (n = 3625)	2009 (n = 4796)	2010 (n = 5523)	2011 (n = 6723)	2012 (n = 8739)	2013 (n = 10 120)	2014 (n = 8769)
Amikacin	61.0	58.4	51.8	57.1	49.4	51.7	48.7	40.2	46.0	47.4
Gentamicin	71.0	67.4	62.5	64.8	59.9	64.0	64.8	60.9	63.3	62.5
Piperacillin	70.0	65.9	66.7	70.7	69.7	69.4	69.8	69.6	67.0	71.0
Piperacillin/tazobactam	59.0	56.3	54.4	62.4	58.5	64.6	63.9	58.3	63.2	62.4
Cefoperazone/sulbactam	25.0	11.6	5.3	14.6	23.6	30.7	39.1	33.0	36.4	37.7
Ceftazidime	59.0	55.7	52.4	58.7	56.2	64.2	71.9	64.5	69.2	68.0
Cefepime	62.0	54.8	55.0	61.6	57.7	64.1	64.6	59.4	64.5	67.6
Aztreonam	84.0	80.1	91.4	81.7	92.6	84.7	92.2	72.6	82.2	76.4
Imipenem	31.0	30.1	35.3	48.1	50.0	57.1	60.4	56.8	62.8	62.4
Meropenem	39.0	40.9	39.9	49.3	52.4	58.3	61.4	61.4	59.4	66.7
Ciprofloxacin	62.0	61.8	60.0	66.9	63.0	68.3	67.3	60.8	66.1	65.4
Sulfamethoxazole/ trimethoprim	69.0	67.0	66.7	67.8	68.8	73.4	70.9	56.8	51.7	50.5
Minocycline	33.0	31.4	32.9	25.3	26.7	25.2	27.3	42.2	41.8	49.7
Polymyxin B							1.6	1.4	0.7	1.9
Polymyxin E							6.3	2.6	0.0	0.0

TABLE 6. Resistance rates (%) of Staphylococcus aureus to antimicrobial agents

Antimicrobial agent	2005		2006		2007		2008		2009		2010		2011		2012		2013		2014	
	MSSA (n = 619)	MRSA (n = 1440)	MSSA (n = 1258)	MRSA (n = 1799)	MSSA (n = 1397)	MRSA (n = 1963)	MSSA (n = 1538)	MRSA (n = 1987)	MSSA (n = 1755)	MRSA (n = 2167)	MSSA (n = 2150)	MRSA (n = 2302)	MSSA (n = 2954)	MRSA (n = 3033)	MSSA (n = 3686)	MRSA (n = 3519)	MSSA (n = 4620)	MRSA (n = 3672)	MSSA (n = 4022)	MRSA (n = 3172)
Vancomycin	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Linezolid	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Teicoplanin	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Rifampin	4.3	34.9	4.2	54.4	2.9	49.2	2.9	56.0	3.2	58.3	3.2	58.0	2.6	57.2	1.7	57.5	5.1	53.9	1.5	47.2
Sulfamethoxazole/trimethoprim	6.5	36.3	4.6	26.9	4.7	26.2	7.4	24.4	6.5	18.5	10.7	20.9	16.6	20.1	13.7	11.5	14.2	7.1	12.6	7.0
Levofloxacin	8.3	81.0	7.5	83.3	8.7	88.0	7.0	88.3	7.0	85.3	6.7	80.0	7.6	83.0	6.2	80.6	11.8	77.6	8.9	71.7
Ciprofloxacin	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	12.7	86.9	12.5	88.2	11.0	85.4	15.5	75.9	11.2	68.3
Gentamicin	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	11.9	77.3	14.3	75.5	15.1	74.2	16.1	69.5	10.8	62.3
Clindamycin	28.2	90.1	26.9	89.0	27.7	87.4	24.8	82.4	26.4	80.7	25.7	73.4	25.5	67.5	25.6	71.3	27.1	55.9	23.5	52.9
Erythromycin	46.3	92.7	50.9	93.4	53.1	92.2	50.8	88.4	50.9	89.4	50.4	86.2	48.7	85.3	51.1	85.7	52.1	76.1	51.4	77.1
Penicillin G	85.7	100.0	92.1	100.0	90.9	100.0	92.5	100.0	90.9	100.0	92.1	100.0	90.7	100.0	89.9	100.0	88.6	100.0	88.4	100.0
Oxacillin	0.0	100.0	0.0	100.0	0.0	100.0	0.0	100.0	0.0	100.0	0.0	100.0	0.0	100.0	0.0	100.0	0.0	100.0	0.0	100.0

MRSA, methicillin-resistant S. aureus; MSSA, methicillin-susceptible S. aureus.

carbapenem resistance has been emerging and increasing in a wide variety of *Enterobacteriaceae* species worldwide [4–7]. In Europe, five of the 24 reporting countries had significant increasing trends of carbapenem-resistant *K. pneumoniae* in the period between 2009 to 2012. None of the countries had a significant decreasing trend. In 2012, the percentage of *K. pneumoniae* isolates resistant to carbapenems ranged from zero (seven countries) to 60.5% (Greece), and for *Acinetobacter* spp., more than half of isolates reported by these countries were resistant to all antimicrobial groups under surveillance (carbapenems, fluoroquinolones and aminoglycosides) [4].

The results of the present study show that the carbapenem resistance rates among *K. pneumoniae* and *A. baumannii* are higher in comparison with antibiotic resistance in *E. coli* and *P. aeruginosa*. Because carbapenem-resistant Gram-negative bacilli are usually extensively drug resistant, infections caused by these strains present a serious clinical challenge for physicians in healthcare settings [8]. Treatment options for these infections are limited, and few clinical data are available on which to base antibiotic recommendations. Moreover, the use of inappropriate empirical antibiotic therapy or delayed appropriate antibiotic therapy can lead to worse outcomes. Previous studies have found crude mortality rates ranging from 30 to 44% for diverse infections caused by carbapenem-resistant *Enterobacteriaceae* [9]. These results suggest that prompt detection is critical for containing carbapenem-resistant strains and preventing nosocomial transmission. Because only few novel antimicrobials are in development for the treatment of these extensively drug-resistant infections, further studies should focus on the judicious use of available antibiotics and implementation of strict infection control measures to avoid the rapid spread or clonal dissemination of carbapenems-resistant *K. pneumoniae* and *A. baumannii* in healthcare facilities [10].

Although many surveillance projects of antibiotic resistance are carried out, they usually cover only shorter time periods [11,12]. We found large fluctuations over time in our study, indicating that it is important to perform antibiotic resistance surveillance studies over longer time periods. This is especially important for some antimicrobial agents, such as carbapenems. These fluctuations might be explained partly as a result of outbreaks of nosocomial infections. The present study has two limitations. One is that participating hospitals do not cover all of the provinces or cities in China. Currently, there are 34 provinces or cities in China, and the CHINET surveillance system covers 14 of them. Another limitation is we collected only the routine susceptibility testing results by Kirby-Bauer or automated systems. In the future, we should expand this surveillance system to cover at least one hospital in each province or city. We also have a plan to collect the clinical isolates from each hospital involving the CHINET surveillance system and to

carry out agar dilution or broth microdilution to determine the minimum inhibitory concentration of antimicrobial agents, since the reporting of minimum inhibitory concentration values is important for hospital-based surveillance and will improve the reliability of the current surveillance system [13].

Transparency declaration

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