Original Article

Multi-level analysis of bacteria isolated from inpatients in respiratory departments in China

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Background: With the different situation for clinical antibiotic usage and its management in different regions and medical institutions, the antimicrobial resistance varied in different level. However, the epidemiological data of multi-drug resistant (MDR) strains from the department of respiration is limited. Thus, this study aims to investigate the epidemiology of bacteria isolated from inpatients of respiratory departments, and analyze the distribution variation of major multi-drug resistant bacteria in China.

Methods: Based on data from China Antimicrobial Resistance Surveillance System (CARSS) in 2015, 50,417 non-duplicate isolates obtained from inpatients of respiratory departments from 91 general hospitals in seven regions of China were enrolled in the study. The distribution of methicillin-resistant *Staphylococcus aureus* (MRSA), carbapenem-resistant *Escherichia coli* (CREC) and *Klebsiella pneumoniae* (CRKP), carbapenem-resistant *Pseudomonas aeruginosa* (CRPA) and *Acinetobacter baumannii* (CRAB), extended-spectrum β-lactamases-producing *E. coli* (ESBL-EC) and *K. pneumoniae* (ESBL-KP), were further analyzed by geographic regions, age groups, wards and specimen types.

Results: The major specimens type were sputum (81.6%, 41,131/50,417), followed by blood (5.3%, 2,649/50,417), urine (4.5%, 2,249/50,417) and bronchoalveolar lavage fluid (BALF) (3.2%, 1,620/50,417). The top four bacteria species isolated from sputum and BALF were similar: *K. pneumonia* (18.9% and 14.8%, respectively), *P. aeruginosa* (13.6% and 22.2%, respectively), *A. baumannii* (11.3% and 11.9%, respectively) and *S. pneumonia* (11.1% and 9.6%, respectively). The four most common bacteria species were *K. pneumonia* (17.2%), *P. aeruginosa* (12.1%), *A. baumannii* (10.4%) and *S. pneumonia* (10.1%) in tertiary hospitals but *K. pneumonia* (20.8%), *P. aeruginosa* (16.3%), *E. coli* (11.3%) and *A. baumannii* (6.9%) in secondary hospitals. The top four bacteria species in respiratory intensive care unit (RICU) were *A. baumannii* (25.8%), *P. aeruginosa* (13.1%), *K. pneumonia* (12.2%) and *S. aureus* (9.2%). The prevalence of CRKP, CRPA and CRAB in tertiary hospitals was significantly higher than that in secondary hospitals (5.2% *vs.* 2.5%, 23.8% *vs.* 12.8% and 53.5% *vs.* 33.9%, respectively) (all P<0.05). However, the prevalence of ESBL-EC in secondary hospitals was higher than in tertiary ones (63.9% *vs.* 55.0%, P=0.011). The prevalence of MRSA, CRKP, CRAB, CRPA, ESBL-EC, ESBL-KP in RICU were higher than that in non-ICU respiratory departments (76.5% *vs.* 35.7%, 20.1% *vs.* 4.1%, 90.6% *vs.* 45.5%, 64.2% *vs.* 19.3%, 47.2% *vs.* 28.3% and 43.0% *vs.* 11.2%, respectively) (all P<0.01). Among seven regions in China, central area had the highest detection rates of MRSA (70.3%, 237/337), CRPA (30.9%, 376/1,218), CRAB (71.8%, 487/678) and ESBL-KP (38.8%, 241/621). The prevalence of ESBL-EC and ESBL-KP in pediatric group (68.2% and 55.3%, respectively) was higher than that in geriatric group (54.2% and 27.1%, respectively) and adult group (51.1% and 15.1%, respectively) (all P<0.001).

Conclusions: In China, the predominant bacterial pathogens in the respiratory ward were *Enterobacteriaceae* and non-fermentative bacteria. High prevalence of ESBL-EC and ESBL-KP isolated from lower respiratory tract (LRT) was revealed in primary hospitals and pediatric patients.

Keywords: Respiratory departments; multi-drug resistant (MDR); multi-level analysis

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Introduction

Respiratory tract infections are the most common infectious disease of respiratory tract, and irrational use of antimicrobial agents has introduced serious antibiotic resistance (1-4). In United State, although there were strict regulations for the use of antimicrobial agents for respiratory infections, such as bronchitis, pharyngitis, sinusitis and common cold, 41% of antimicrobial agents were prescribed for respiratory diseases (5,6). In China, the irrational use of antibiotics was still severe. Researches revealed that over 50% outpatients, including 80% outpatients with upper respiratory tract infections were prescribed antibiotics (7,8). This problem was more significant in the primary hospitals, as less than 40% outpatients and less than 25% inpatients conformed to the principle of antibiotics; more than 93% patients with upper respiratory tract infections, most of which were supposed to be viral infections, were prescribed antibiotics (9). To date, China has become one of largest consumer of antibiotics in the world (10). A multicenter epidemiology survey on hospital acquired pneumonia revealed that the detection rates of carbapenem-resistant *Acinetobacter baumannii* (CRAB) and *Pseudomonas aeruginosa* (CRPA) were 78.9% and 70.7%, respectively, while the rate of methicillin-resistant *Staphylococcus aureus* is 87.8% (MRSA) (11). China is a vast country with a huge number of medical institutions. Mainly due to the disparities in socioeconomic development, the situation for clinical antibiotic usage and its management varied in different regions and amongst medical institutions of different level (12). However, the epidemiological data of multi-drug resistant (MDR) strains from the department of respiration is limited. Therefore, this study aims to analyze the distribution and epidemic characteristics of the target MDR isolates from department of respiration in China via different levels and to provide the basis for the antibiotic regulation.

Methods

Bacteria source

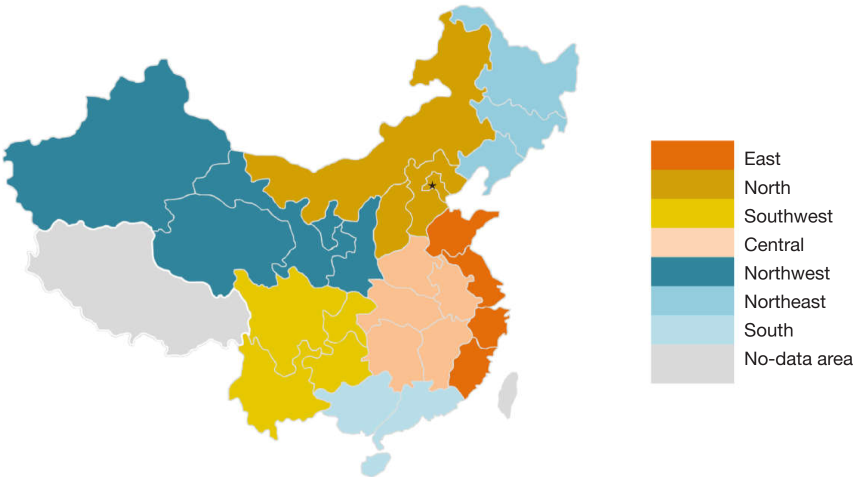
Based on the data of China Antimicrobial Resistance Surveillance System (CARSS) in 2015, 50,417 non-duplicated bacterial strains from inpatient in respiratory departments from 91 general hospitals (9 in Northeast China, 16 in the north region of China, 14 in East China, 9 in southern China, 15 in Central China, 14 in Northwest China, 14 in Southwest China) in seven regions of China were enrolled in the study (*Figure 1*). Briefly, 90.2% (45,491/50,417) strains were obtained from 63 tertiary hospitals, and 9.8% (4,926/50,417) strains from 28 secondary hospitals. Meanwhile, 6.2% (3,129/50,417) strains were isolated from respiratory intensive care units (RICUs) and 93.8% (47,288/50,417) were isolated from non-ICU respiratory department. Furthermore, age groups were classified as: neonatal (age ≤28 days), pediatric (age from 29 days to 14 years old), adult (age from 15 to 65 years old) and geriatric groups (age >65 years old). The number of isolates from geriatric group accounted for 46.0% (23,177/50,417), followed by adult group (29.9%, 15,092/50,417) and pediatric group (24.0%, 12,112/50,417).

Species identification and quality control

Species identification and antimicrobial susceptibility testing were performed in locally. The species identification was performed by standard biochemical methods including API 20E system, Vitek 2 compact (bioMérieux, Marcy l'Etoile, France) and Matrix-assisted Laser Desorption/Ionization Time of Flight Mass Spectrometry (MALDI-TOF MS, bioMérieux, Marcy l'Etoile, France), etc. The antimicrobial susceptibility test was interpreted according to clinical and laboratory standards institute (CLSI) 2015 guidelines (13). Quality control of the dataset was conducted by Peking Union Medical College Hospital, the national quality control center of antimicrobial resistance.

Statistically analysis

Distribution of methicillin-resistant *S. aureus* (MRSA), carbapenem-resistant *Escherichia coli* (CREC), carbapenem-resistant *Klebsiella pneumoniae* (CRKP), CRPA, CRAB and extended-spectrum β-lactamases-producing *E. coli* (ESBL-



Region	MRSA	MRCON	CREC	CRKP	CRPA	CRAB	ESBL-KP	ESBL-EC
National	39.2	85.4	2.3	4.9	22.3	52.1	24.3	55.9
Northeast	44.6	78.2	0.4	2.1	18.2	63.5	21.5	65.1
North	46.9	85.9	3.2	5.9	24.6	43.7	18.6	58.2
East	40.0	90.5	2.4	6.6	20.0	40.2	17.5	41.1
South	25.8	86.2	1.5	3.4	15.6	43.6	31.2	50.7
Central	70.3	82.7	2.6	6.5	30.9	71.8	38.8	70.0
Northwest	40.4	29.3	3.0	5.0	27.3	73.5	26.5	63.6
Sortheast	29.6	85.9	1.8	3.9	13.8	36.3	29.5	70.8

Figure 1 Prevalence of multi-drug resistant bacteria (%) in seven regions in China. MRSA, methicillin-resistant *Staphylococcus aureus*; MRCONS, methicillin-resistant coagulase-negative *Staphylococcus*; CREC, carbapenem-resistant *Escherichia coli*; CRKP, carbapenem-resistant *Klebsiella pneumoniae*; CRAB, carbapenem-resistant *Acinetobacter baumannii*; CRPA, carbapenem-resistant *Pseudomonas aeruginosa*; ESBL-KP, extended-spectrum β-lactamases-producing *Klebsiella pneumoniae*; ESBL-EC, extended-spectrum β-lactamases-producing *Escherichia coli*.

EC) and *K. pneumoniae* (ESBL-KP) were analyzed by the WHONET 5.6 software. Statistical analysis was performed by IBM SPSS software (version 16.0; IBM SPSS Inc., New York, USA). Categorical variables were compared using the Chi-square test. P values of 0.05 were considered significant.

Results

Prevalence of different bacterial species in respiratory departments in China

Overall, a total of 50,417 non-duplicated isolates were collected from the respiratory department of 91 general hospitals, with the top four species being *K. pneumoniae* (17.5%, 8,835/50,417), *P. aeruginosa* (12.5%, 6,323/50,417), *A. baumannii* (10.1%, 5,076/50,417) and *S. pneumoniae* (9.5%, 4,810/50,417). Meanwhile, the top four species in secondary hospitals were *K. pneumoniae* (20.8%, 1,027/4,926), *P. aeruginosa* (16.3%, 803/4,926), *E. coli* (11.3%, 557/4,926) and *A. baumannii* (6.9%, 340/4,926). Additionally, the leading top four species in RICU were *A. baumannii* (25.8%, 808/3,129), *P. aeruginosa* (13.1%, 410/3,129), *K. pneumoniae* (12.2%, 381/3,129) and *S. aureus* (9.2%, 289/3,129) (*Table 1*).

For the detection rate of fastidious bacteria in various regions, the highest isolation rate of *Streptococcus pneumoniae* was in the South region (17.7%, 837/4,736), while the lowest was in the Northeast (1.1%, 55/4,853). The highest detection rate of *Haemophilus influenzae* was found in East China (10.3%, 1,081/10,463) (*Figure S1*).

Specimen types

The main specimen types of the collection were sputum (81.6% 41,131/50,417), followed by blood sample (5.3%, 2,649/50,417), urine (4.5%, 2,249/50,417) and

Table 1 Distribution of bacterial species of 91 general hospitals in China

Species	National		Hospital				Hospital ward			
			Tertiary hospital		Secondary hospital		RICU		Non-ICU respiratory departments	
	N	%	N	%	N	%	N	%	N	%
K. pneumoniae	8,835	17.5	7,808	17.2[a]	1,027	20.8[a]	381	12.2[b]	8,454	17.9[b]
P. aeruginosa	6,323	12.5	5,520	12.1[a]	803	16.3[a]	410	13.1	5,913	12.5
A. baumannii	5,076	10.1	4,736	10.4[a]	340	6.9[a]	808	25.8[b]	4,268	9.0[b]
S. pneumoniae	4,810	9.5	4,580	10.1[a]	230	4.7[a]	22	0.7[b]	4,788	10.1[b]
E. coli	4,511	8.9	3,954	8.7[a]	557	11.3[a]	180	5.8[b]	4,331	9.2[b]
S. aureus	3,627	7.2	3,380	7.4[a]	247	5.0[a]	289	9.2[b]	3,338	7.1[b]
Enterobacter	2,203	4.4	2,056	4.5[a]	147	3.0[a]	81	2.6[b]	2,122	4.5[b]
H. influenzae	1,884	3.7	1,669	3.7	215	4.4	4	0.1[b]	1,880	4.0[b]
S. maltophilia	1,651	3.3	1,508	3.3	143	2.9	142	4.5[b]	1,509	3.2[b]
Enterococcus	1,403	2.8	1,306	2.9[a]	97	2.0[a]	212	6.8[b]	1,191	2.5[b]
Others	10,094	20.0	8,974	19.7[a]	1,120	22.7[a]	600	19.2	9,494	20.1
Total	50,417	100.0	45,491	100.0	4,926	100.0	3,129	100.0	4,7288	100.0

[a], species comparison (secondary hospital *vs*. tertiary hospital) P<0.01; [b], species comparison (RICU *vs*. non-ICU respiratory departments) P<0.01. RICU, respiratory intensive care unit.

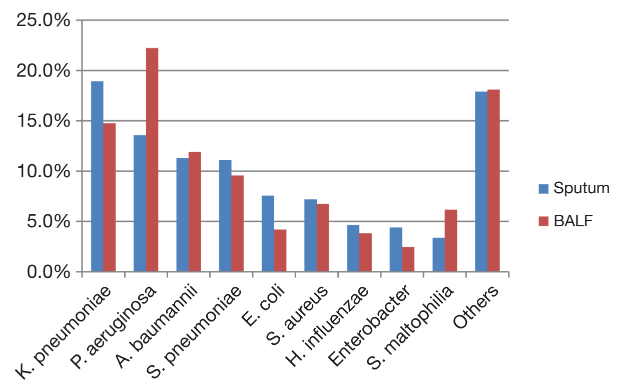


Figure 2 Isolation rate of different bacteria species in sputum and bronchoalveolar lavage fluid from respiratory departments in China. BALF, bronchoalveolar lavage fluid.

bronchoalveolar lavage fluid (BALF) (3.2%, 1,620/50,417) (For detail information of specimen type and the distribution of MDR bacteria by specimens, please refer to *Tables S1,S2*). In BALF and sputum specimens, the top four species were similar: *K. pneumonia* (18.9% and 14.8%, respectively), *P. aeruginosa* (13.6% and 22.2%, respectively), *A. baumannii* (11.3% and 11.9%, respectively) and *S. pneumonia* (11.1% and 9.6%, respectively). The proportion of non-fermentative bacteria, i.e., *P. aeruginosa* and *S. maltophilia* in BALF was higher than that in sputum 22.2% *vs.* 13.6% and 6.2% *vs.* 3.4%, respectively, while the rate of *K. pneumoniae* and *E. coli* in sputum was higher than that in BALF (18.9% *vs.* 14.8% and 7.6% *vs.* 4.2%, respectively) (all P<0.05) (*Figure 2*).

Distribution of MDR bacteria by hospital ranks

The overall detection rate of MRSA in the secondary hospitals was higher than that in the tertiary hospitals (46.8% *vs.* 38.6%) (P=0.013). Additionally, the rates of CRKP, CRPA, CRAB and ESBL-KP in the tertiary hospitals were higher than that in secondary hospitals (5.2% *vs.* 2.5%, 23.8% *vs.* 12.8%, 53.5% *vs.* 33.9% and 25% *vs.* 17.5%), respectively (all P<0.01). The detection rate of ESBL-KP in tertiary hospitals was lower than that in secondary hospital (55.0% *vs.* 63.9%) (P=0.01) (*Figure 3*).

Distribution of MDR bacteria in RICUs and non-ICU respiratory departments

The detection rates of MRSA, CRKP, CRAB, CRPA, ESBL-EC and ESBL-KP in RICUs were significantly

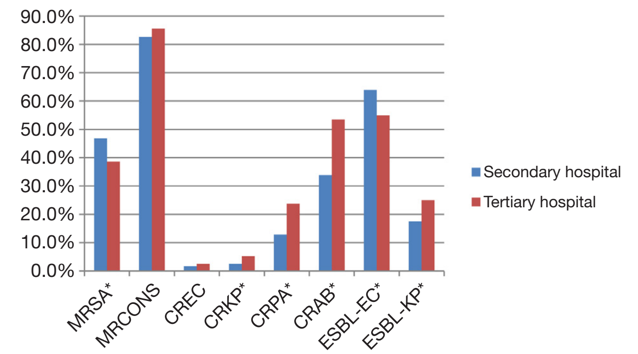


Figure 3 Distribution of multi-drug resistant bacteria from respiratory departments by rank of hospitals in China. *, statistically significant difference (MRSA, P=0.013; CRKP, P<0.01; CRPA, P<0.01; CRAB, P<0.01; ESBL-EC, P=0.011; ESBL-KP, P<0.01). MRSA, methicillin-resistant *Staphylococcus aureus*; MRCONS, methicillin-resistant coagulase-negative *Staphylococcus*; CREC, carbapenem-resistant *Escherichia coli*; CRKP, carbapenem-resistant *Klebsiella pneumoniae*; CRAB, carbapenem-resistant *Acinetobacter baumannii*; CRPA, carbapenem-resistant *Pseudomonas aeruginosa*; ESBL-KP, extended-spectrum β-lactamases-producing *Klebsiella pneumoniae*; ESBL-EC, extended-spectrum β-lactamases-producing *Escherichia coli*.

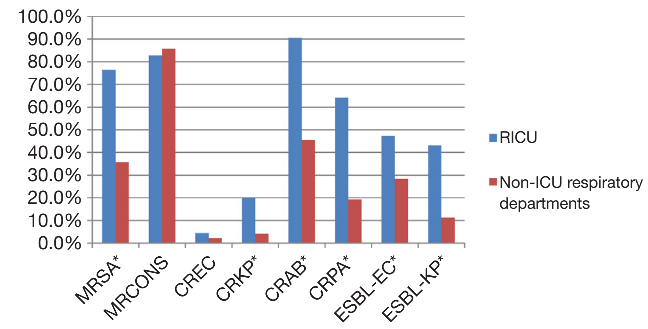


Figure 4 Distribution of multi-drug resistant bacteria in RICUs and non-ICU respiratory departments in China. *, statistically significant difference (P<0.01). MRSA, methicillin-resistant *Staphylococcus aureus*; MRCONS, methicillin-resistant coagulase-negative *Staphylococcus*; CREC, carbapenem-resistant *Escherichia coli*; CRKP, carbapenem-resistant *Klebsiella pneumoniae*; CRAB, carbapenem-resistant *Acinetobacter baumannii*; CRPA, carbapenem-resistant *Pseudomonas aeruginosa*; ESBL-KP, extended-spectrum β-lactamases-producing *Klebsiella pneumoniae*; ESBL-EC, extended-spectrum β-lactamases-producing *Escherichia coli*; RICU, respiratory intensive care unit.

higher than that in non-ICU respiratory departments (76.5% *vs.* 35.7%, 20.1% *vs.* 4.1%, 90.6% *vs.* 45.5%, 64.2% *vs.* 19.3%, 47.2% *vs.* 28.3% and 43.0% *vs.* 11.2%, respectively) (all P<0.01) (*Figure 4*).

Regional distribution of MDR bacteria in respiratory departments

The national average detection rate of MRSA was 39.2% (1,316/3,356), of which the highest rate was detected in Central region (70.3%, 237/337), and lowest in Southern region (25.8%, 163/632). The national average detection rate of CREC was 2.3% (99/4,215), with rates fluctuating at a low level (0.4–3.0%) in varied regions. The national average detection rate of CRKP was 4.9% (408/8,412), with the highest rate in East (6.6%, 75/1,144) and the lowest in Northeast region (2.1%, 28/1,327). The national average detection rate of CRPA was 22.3% (1,361/6,091), with highest rate in Center China (30.9%, 376/1,218) and the lowest in Southwest region (13.8%, 102/737). The national average detection rate of CRAB was 52.1% (2,368/4,546), with high rates in Northwest (73.5%, 391/532) and Central region (71.8%, 487/678). The national average detection rate of ESBL-KP was 24.3% (1,080/4,443), with most prevalence (38.8%, 241/621) in Central and lowest in East region (17.5%, 172/984). The national average detection rate of ESBL-EC was 55.9% (1,286/2,301), with high rate in Southwest (70.8%, 243/343) and Central China (70.0%, 217/310) (*Figure 1*).

Distribution of MDR bacteria in respiratory departments by age groups

The detection rate of MRSA in geriatric group (57.9%, 608/1,050) was significant higher than that in adult (36.8%, 285/775) and pediatric group (27.7%, 423/1,529) (all P<0.01), whilst no MRSA strains were found in neonatal group. Additionally, the rates of CREC in geriatric group (2.8%, 60/2,119) were higher than that in pediatric group (1.3%, 12/951) (P=0.008). Similarly, the rates of CRKP in geriatric group (6.6%, 284/ 4,301) were higher than that in adult (3.0%, 97/3,225) and pediatric group (3.2%, 27/849) (all P<0.001), whilst no CRKP strain were found in neonatal group. The detection rates of ESBL-EC and ESBL-KP in pediatric group (68.2% and 55.3%, respectively) were higher than that in geriatric group (54.2% and 27.1%, respectively) and adult group (51.1% and 15.1%, respectively) (all P<0.001). For non-fermentative bacteria,

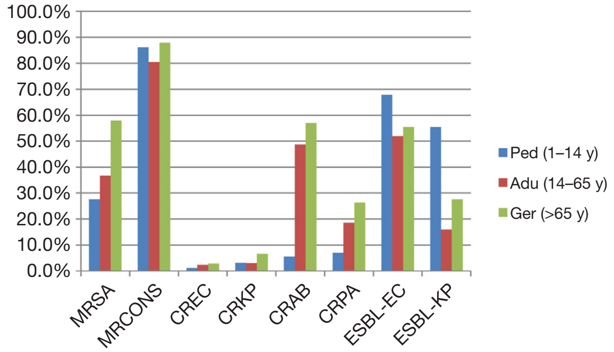


Figure 5 Age distribution of multi-drug resistant bacteria from respiratory departments in China. MRSA, methicillin-resistant *Staphylococcus aureus*; MRCONS, methicillin-resistant coagulase-negative *Staphylococcus*; CREC, carbapenem-resistant *Escherichia coli*; CRKP, carbapenem-resistant *Klebsiella pneumoniae*; CRAB, carbapenem-resistant *Acinetobacter baumannii*; CRPA, carbapenem-resistant *Pseudomonas aeruginosa*; ESBL-KP, extended-spectrum β-lactamases-producing *Klebsiella pneumoniae*; ESBL-EC, extended-spectrum β-lactamases-producing *Escherichia coli*; Ped, pediatric; Aud, adult; Ger, geriatric.

the rates of CRAB and CRPA in geriatric group (57.0% and 26.3%, respectively) were higher than that in adult (48.7% and 18.6%, respectively) and pediatric group (5.5% and 6.9%, respectively) (all P<0.001) (*Figure 5*).

In vitro susceptibility of specific agents

For the major clinical antimicrobial agents against CRKP, all of strains (30/30) were susceptible to polymyxin B, with minimal inhibitory concentration $(MIC)_{90}$ 4.000 μg/mL, whilst 5.8% (3/52) of the strains were resistant to tigecycline, with MIC_{90} 4.000 μg/mL (*Table 2*). For susceptibility of CRAB, the resistance rate of polymyxin B and tigecycline were 2.0% (4/205; MIC_{90} 2.000 μg/mL) and 4.3% (22/515; MIC_{90} 4.000 μg/mL), respectively. As for CRPA, the resistance rate of Polymyxin B was 4.1% (10/243), with MIC_{90} 2.000 μg/mL (*Table 3*). For the major clinical antimicrobial agents against fastidious bacteria (*Streptococcus Haemophilus influenzae*), ESBL-EC and ESBL-KP, please refers to supplementary material *Tables S3-S5*).

Discussion

MDR has been a public health problem. In order to cope with the threat posed by MDR bacteria with high resistance against major clinical antibiotics, WHO first enumerated twelve MDR bacteria in 2017 (14), including the ones associated with the common community-acquired pneumonia and Hospital acquired pneumonia in the respiratory departments in China. Therefore, multi-level epidemiological analysis of isolates from respiratory department in China is significant and instructive, not only for a better understanding of antimicrobial resistance in China, but also for the improvement of the rational use of antimicrobial agents.

In our study, the distribution of species from qualified sputum specimens were basically consistent with BALF, with consistency for top four species, i.e., *K. pneumonia*, *P. aeruginosa*, *A. baumannii* and *S. pneumonia*. Interestingly, the proportion of *P. aeruginosa* and *S. maltophilia* in BALF was significantly higher than that in sputum. The reasons for this phenomenon may be as follow: (I) due to the differences sensitivity rate of sputum culture of varied bacteria (15), moderate consistency was found between sputum and BALF (16); (II) meanwhile, invasive procedure, including BALF, was commonly conducted in qualified hospitals and patients from these hospitals had received antibiotic treatment before taking sample, which resulted in the increase of MDR strains including *P. aeruginosa* and *S. maltophilia* (15). Furthermore, the high inspection rate of sputum culture from numerous local primary hospitals before prescribing antimicrobial agents may result in the increase of specie types and the relative decrease of MDR bacteria in sputum, i.e., *P. aeruginosa* and *S. maltophilia*. Therefore, in view of the recognition of qualified semi quantitative sputum culture by Infectious Diseases Society of America (IDSA) and the advance of microbial laboratory in China, high quality sputum specimens and sterile specimens obtained by bronchoscopy are essential for the etiology diagnosis.

For hospital distribution of varied MDR strains, the detection rates of CRKP, CRAB, and CRPA in tertiary hospitals were significant higher than the secondary hospitals. There were two reasons for this phenomenon. On one hand, due to the irrational use of antibiotics and the selective pressure of antibiotics in primary hospitals or secondary hospitals, the multidrug-resistant bacteria might be likely emerged before the submission into tertiary hospitals and prescribed a more broad-spectrum antibiotic in tertiary hospital. On the other hand, the irrational use and overuse of antibiotics still existed in some tertiary hospitals in the well-developed cities, which was one of the important factors for the emergence and prevalence of

Table 2 Resistance of common clinical drugs for CREC and CRKP

Antibiotics	CREC				CRKP			
	%R	MIC50 (μg/mL)	MIC90 (μg/mL)	MIC range (μg/mL)	%R	MIC50 (μg/mL)	MIC90 (μg/mL)	MIC range (μg/mL)
Ampicillin	95.5	32.000	32.000	16.000–64.000	98.9	32.000	32.000	16.000–64.000
Cefoperazone/sulbactam	50.0	32.000	128.000	16.000–128.000	70.6	64.000	128.000	16.000–128.000
Piperacillin/tazobactam	61.5	128.000	128.000	4.000–256.000	76.6	128.000	128.000	4.000–256.000
Cefazolin	100.0	64.000	64.000	8.000–64.000	96.7	64.000	64.000	2.000–128.000
Cefuroxime	78.9	64.000	64.000	4.000–64.000	89.1	32.000	64.000	4.000–128.000
Ceftazidime	90.2	32.000	64.000	1.000–64.000	86.0	32.000	64.000	1.000–128.000
Ceftriaxone	92.5	64.000	64.000	0.120–64.000	93.3	64.000	64.000	0.120–128.000
Cefotaxime	86.7	64.000	64.000	0.120–64.000	95.1	64.000	64.000	0.120–64.000
Cefepime	90.0	64.000	64.000	1.000–64.000	86.0	64.000	64.000	0.120–128.000
Cefotetan	78.6	64.000	64.000	4.000–64.000	80.9	64.000	64.000	4.000–128.000
Cefoxitin	57.1	32.000	64.000	8.000–64.000	76.0	32.000	64.000	2.000–64.000
Ertapenem	95.8	8.000	8.000	0.120–16.000	95.1	8.000	8.000	0.500–16.000
Imipenem	89.6	8.000	16.000	0.500–16.000	91.4	≥16.000	≥16.000	0.250 to ≥16.000
Meropenem	70.4	8.000	16.000	0.060–16.000	89.8	≥16.000	≥16.000	0.250 to ≥16.000
Amikacin	13.2	8.000	64.000	1.000–64.000	54.3	64.000	64.000	1.000–128.000
Gentamicin	59.3	16.000	16.000	1.000–32.000	69.8	16.000	16.000	0.500–32.000
Ciprofloxacin	77.3	4.000	4.000	0.250–8.000	72.3	4.00	4.000	0.060–8.000
Levofloxacin	73.4	8.000	16.000	0.250–16.000	66.0	8.00	8.000	0.060–16.000
Polymyxin B	0	0.500	2.000	0.500–2.000	0	2.00	4.000	0.500–4.000
Minocycline	20.0	2.000	16.000	1.000–16.000	17.4	4.00	16.000	1.000–16.000
Tigecycline	0	0.500	2.000	0.500–2.000	5.8	2.00	4.000	0.500–8.000

%R, resistant rate; CREC, carbapenem-resistant *Escherichia coli*; CRKP, carbapenem-resistant *Klebsiella pneumoniae*; MIC, minimal inhibitory concentration.

MDR bacteria (8,17). Notably, in this study, the detection rates of ESBL-EC and ESBL-KP were high in the secondary hospitals and the rate of ESBL-EC in secondary hospitals was significant higher than that in the tertiary hospitals. This phenomenon is consistent with another epidemiological study on community-acquired bloodstream infections in China, indicating a high prevalence of ESBL-EC in Chinese community, which was up to 51.0% (18). The prevalence of ESBL-EC and ESBL-KP in secondary hospitals might be associated with the high utilization of cephalosporins. Compared to the tertiary hospitals in well-developed cities, the use and misuse of antibiotics were more serious in primary hospitals and community hospitals in less-developed areas. Some studies showed that the utilization rate of antibiotics for outpatient in primary hospitals and secondary hospitals were 53.4% and 49.2% respectively, higher than the tertiary hospital (47.1%) (8,9,19). As for the outpatients with upper respiratory tract infections, the antibiotic usage rate in secondary hospitals was 84.8% and over 90% of the patients with acute upper respiratory infections were treated with antibiotics, among which 28% of the patients were treated with cephalosporins (7,9). In addition, in the livestock area with high ESBL detection rate, including Northeast and West regions,

Table 3 Resistance of common clinical drugs for CRAB and CRPA

Antibiotics	CRAB				CRPA			
	%R	MIC50 (μg/mL)	MIC90 (μg/mL)	MIC range (μg/mL)	%R	MIC50 (μg/mL)	MIC90 (μg/mL)	MIC range (μg/mL)
Ampicillin	92.3	32.000	32.000	2.000–64.000	93.4	32.000	32.000	16.000–64.000
Cefoperazone/sulbactam	38.7	32.000	64.000	16.000–128.000	28.9	32.000	128.000	4.000–128.000
Piperacillin/tazobactam	86.7	128.000	128.000	1.000–256.000	34.6	64.000	128.000	1.000–256.000
Cefazolin	96.6	64.000	64.000	4.000–128.000	100.0	64.000	64.000	16.000–128.000
Cefuroxime	91.8	32.000	64.000	16.000–128.000	98.3	64.000	64.000	4.000–128.000
Ceftazidime	95.7	32.000	64.000	1.000–128.000	41.5	16.000	64.000	1.000–128.000
Ceftriaxone	95.6	64.000	64.000	0.500–128.000	96.6	64.000	64.000	1.000–128.000
Cefotaxime	95.4	64.000	64.000	0.500–128.000	98.3	64.000	64.000	2.000–128.000
Cefepime	95.2	64.000	64.000	1.000–128.000	42.0	16.000	64.000	1.000–128.000
Cefotetan	100.0	64.000	64.000	64.000–128.000	97.5	64.000	64.000	4.000–128.000
Cefoxitin	93.7	64.000	64.000	8.000–64.000	98.3	32.000	64.000	8.000–64.000
Aztreonam	85.9	64.000	64.000	1.000–128.000	45.6	16.000	64.000	1.000–128.000
Imipenem	99.3	16.000	16.000	1.000–32.000	92.2	16.000	16.000	0.500–64.000
Meropenem	99.3	16.000	16.000	1.000–64.000	85.4	16.000	16.000	0.250–32.000
Amikacin	69.3	64.000	64.000	1.000–256.000	24.0	8.000	64.000	1.000–256.000
Gentamicin	88.4	16.000	16.000	0.500–64.000	42.2	4.000	32.000	0.500–64.000
Ciprofloxacin	95.2	4.000	4.000	0.250–16.000	44.8	2.000	8.000	0.125–16.000
Levofloxacin	71.8	8.000	8.000	0.060–32.000	43.3	4.000	16.000	0.250–16.000
Polymyxin B	2.0	1.000	2.000	0.500–8.000	4.1	2.000	2.000	0.500–8.000
Minocycline	24.6	4.000	16.000	1.000–32.000	0	8.000	16.000	4.000–16.000
Tigecycline	4.3	2.000	4.000	0.500–8.000	84.6	8.000	8.000	0.500–8.000

%R, resistant rate; CRAB, carbapenem-resistant *Acinetobacter baumannii*; CRPA, carbapenem-resistant *Pseudomonas aeruginosa*; MIC, minimal inhibitory concentration.

animal-mediated ESBL infections were associated with the high prevalence of ESBL in local primary hospitals. Our study also revealed that a high detection rate of ESBL-EC and ESBL-KP in pediatric population. This phenomenon might be associated with the high utilization rate of cephalosporin antibiotics in pediatric outpatients, as the usage of cephalosporins, especially the third generation cephalosporin, was one of the risk factors for children infected with ESBL-KP and ESBL-EC (20). Therefore, it is particularly important for primary hospitals to strengthen the standardized and rational use of antibiotics in multiple links.

In this study, the distribution of multi-drug resistant bacteria in RICU was significantly higher than that in the non-ICU respiratory departments. On one hand, the patients in RICU with severe disease, including cancer, kidney failure, heart disease, chronic obstructive pulmonary disease, etc., were commonly prescribed broad-spectrum antibiotics for empirical therapy, posing the risk of MDR bacterial infections to patients (21-23). On the other hand, the risk of ventilator-associated pneumonia (VAP) increased due to the prolonged hospitalization in ICU and routine invasive procedures such as intubation and respiratory support. The IDSA 2016 guidelines also point out that, the usage of intravenous broad-spectrum antibiotics is one of the risk factors for MDR infections in VAP patients, making VAP more difficult to treat (23,24). Meanwhile, the special environment of the ICU departments provided convenient conditions for the transmission of MDR clones, including CC22 of CRAB, ST11 of CRKP, ST239 of MRSA, etc., which poses a great risk for ICU patients (25-28). Therefore, in view of the high prevalence of MDR bacterial in RICU, the establishment of RICU monitoring system, including the monitoring of MDR clones with high pathogenicity, was an urgent need to provide relevant basis for clinical treatment and for related control measures making.

Compared with the national data in 2014, the detection rate of MDR strains in 2015, including MRSA (39.2% *vs.* 44.6%), CRKP (4.9% *vs.* 10.5%), CRPA (22.3% *vs.* 26.6%), CRAB (52.0% *vs.* 62.4%) and ESBL-KP (24.3% *vs.* 29.9%) were lower, while the rate of CREC and ESBL-EC were similar (29). Notably, the AMR in Central region was serious, with the highest rates of MRSA, CRPA, ESBL-KP and second highest rates of CRKP, CRAB and ESBL-EC. Studies on the usage of antibiotics in China revealed that 87.3% outpatients in respiratory departments were prescribed one antibiotics, which is significantly higher than the west China and the east China (7). Meanwhile, it is worth noticing that the high detection rate of ESBL-EC was found not only in the Central region, but also in Southwest, Northwest and Northeast region of China whereas possesses prosperous livestock industry. And this finding basically consistent with the results of another ESBL bloodstream infection research (18). The irrational use of antibiotics in these areas promotes the transmission of ESBL-producing strains between humans and animals (18,19,30). Therefore, strengthening the management of antibiotic use and continuous monitoring of MDR bacteria in these drug-resistant epidemic areas were highly needed

Our study also has some limitations. On one hand, since not all the respiratory departments of general hospitals were enrolled in this study, the detection rates of resistant bacteria can not accurately reflect the resistance in various regions. However, the overall detection rates of MDR bacteria from the respiratory departments in this study remain a high degree of consistency with the available national data. On the other hand, contamination of sputum was unavoidable completely, which would slightly affect the regional distribution of MDR bacteria.

Conclusions

In China, the predominant bacterial pathogens in the respiratory ward were *Enterobacteriaceae* and non-fermentative bacteria. High prevalence of ESBL-EC and ESBL-KP isolated from lower respiratory tract (LRT) was revealed in primary hospitals and pediatric patients.

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Footnote

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Supplementary

Table S1 Specimen type of bacteria from inpatients in respiratory in China

Specimen type	N	%
Sputum	41,131	81.6
Blood	2,649	5.3
Urine	2,249	4.5
BALF	1,620	3.2
Secretion	545	1.1
Pleural effusions	420	0.8
Others	1,803	3.6
Total	50,417	100.0

BALF, bronchoalveolar lavage fluid.

Table S2 Prevalence of MDR bacteria in sputum and BALF

Bacteria	Sputum		BALF	
	N	%	N	%
MRSA	1,109	39.1	39	46.4
CREC	44	1.9	1	2.5
CRKP	305	5.4	8	5.7
CRPA	1,148	21.7	53	23.7
CRAB*	2,093	51.3	89	80.2
ESBL-KP	892	23.9	26	28.3
ESBL-EC	778	57.5	8	47.1

*, statistically significant difference with P<0.001. MDR, multi-drug resistant; BALF, bronchoalveolar lavage fluid; CREC, carbapenem-resistant *Escherichia coli*; CRKP, carbapenem-resistant *Klebsiella pneumoniae*; CRAB, carbapenem-resistant *Acinetobacter baumannii*; CRPA, carbapenem-resistant *Pseudomonas aeruginosa*; ESBL-KP, extended-spectrum β-lactamases-producing *Klebsiella pneumoniae*; ESBL-EC, extended-spectrum β-lactamases-producing *Escherichia coli*.

Table S3 Resistance of major clinical drugs for *S. pneumoniae*

Antibiotics	%R	MIC50 (μg/mL)	MIC90 (μg/mL)	MIC range (μg/mL)
Penicillin G	4.2	2.000	4.000	0.004–64.000
Ampicillin	0	0.250	16.000	0.120–32.000
Oxacillin	54.5	0.500	2.000	0.250–16.000
Amoxicillin/Clavulanic acid	6.5	2.000	4.000	0.016–8.000
Ceftriaxone	10.6	0.500	4.000	0.006–8.000
Cefotaxime	11.5	1.000	4.000	0.014–8.000
Levofloxacin	1.7	0.500	2.000	0.250–16.000
Clindamycin	92.4	2.000	2.000	0.030–16.000
Azithromycin	80.6	2.000	2.000	0.500–4.000
Erythromycin	95.7	1.000	8.000	0.060–80.000
Vancomycin	0	1.000	1.000	0.250–32.000

MIC, minimal inhibitory concentration; %R, resistant rate.

Table S4 Resistance of major clinical drugs for *H. influenzae*

Antibiotic	%R	MIC50 (μg/mL)	MIC90 (μg/mL)	MIC range (μg/mL)
Ampicillin	48.8	2.000	4.000	0.120–16.000
Ampicillin/sulbactam	16.7	2.000	4.000	0.120–8.000
Cefuroxime	35.1	4.000	16.000	0.500–16.000
Ceftriaxone	0*	2.000	2.000	0.120–2.000
Levofloxacin	0*	0.125	2.000	0.008–8.000
Trimethoprim/sulfamethoxazole	44.9	1.000	4.000	0.120–8.000
Azithromycin	0*	4.000	4.000	0.250–8.000

*, drug non-sensitive rate. %R, resistant rate.

Table S5 Resistance of major clinical drugs for ESBL isolates

Antibiotic	ESBL-EC		ESBL-KP	
	%R	MIC_{90} (μg/mL)	%R	MIC_{90} (μg/mL)
Ampicillin	95.5	32.000	97.3	32.000
Amoxicillin/clavulanic acid	14.7	32.000	43.5	32.000
Cefoperazone/sulbactam	8.7	32.000	47.3	64.000
Ampicillin/sulbactam	64.1	32.000	80.3	32.000
Piperacillin/tazobactam	5.7	32.000	18.1	128.000
Cefazolin	99.2	64.000	96.9	64.000
Cefuroxime	98.0	64.000	96.8	64.000
Ceftazidime	50.9	32.000	58.8	64.000
Ceftriaxone	97.9	64.000	94.4	64.000
Cefotaxime	98.9	64.000	97.3	64.000
Cefepime	45.7	64.000	44.4	64.000
Cefoxitin	21.3	32.000	34.6	64.000
Aztreonam	63.4	64.000	66.5	64.000
Ertapenem	0.7	0.500	3.1	0.5.000
Imipenem	1.1	1.000	6.7	1.000
Meropenem	0.7	1.000	9.5	2.000
Amikacin	5.3	16.000	13.5	64.000
Gentamicin	55.9	16.000	58.8	16.000
Ciprofloxacin	69.9	4.000	52.4	4.000
Levofloxacin	69.1	16.000	42.8	8.000
Polymyxin B	0	1.000	0	2.000
Tigecycline	0	0.500	8.9	4.000

%R, resistant rate; ESBL-KP, extended-spectrum β-lactamases-producing *Klebsiella pneumoniae*; ESBL-EC, extended-spectrum β-lactamases-producing *Escherichia coli.*

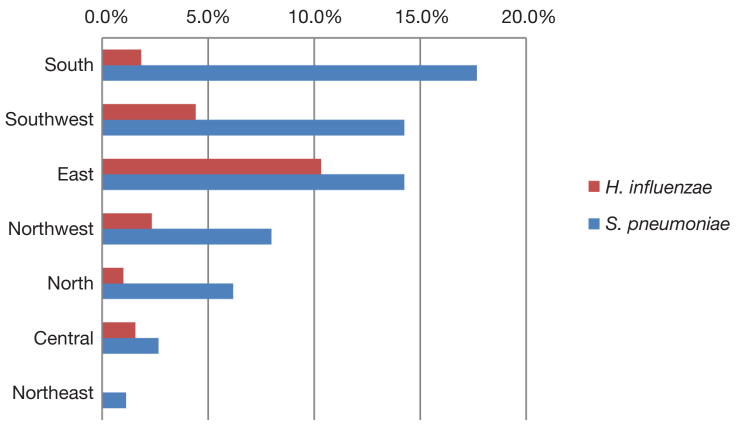

Figure S1 Isolation rates of fastidious bacteria (i.e., *S. pneumoniae* and *H. influenzae*) in seven regions of China.