

Antimicrobial Resistance Trends of the Most Common Causative Pathogens Associated with Community-acquired Respiratory Infections in China: 2009–2018

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Background: Emergence of antimicrobial resistance poses new challenges in the management of community acquired respiratory tract infections (CARTIs). Therefore, surveillance on the antimicrobial susceptibilities of common respiratory pathogens is valuable and guides empirical therapeutic choices in management of CARTIs.

Objective: The objective of the current study is to summarize the antimicrobial resistance trends in common respiratory tract pathogens isolated from patients with CARTIs in China, over a 10-year period (2009–2018).

Methods: *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Moraxella catarrhalis* strains were collected from multicenter, and antimicrobial susceptibility testing was performed in the research central laboratory of each study period from 2009–2018. The pathogens that accounted for CARTIs in the adult population was considered and summarized.

Results: From 2009–2018 a total of 3750 isolates were collected from 22 cities located across different regions of China. Among these the most common bacterial isolates include *S. pneumoniae* (53.7%) followed by *H. influenza* (32.4%), *M. catarrhalis* (13.9%). *S. pneumoniae* exhibited reduction in susceptibility and increase in resistance to penicillin, cephalosporins (cefaclor, cefuroxime, ceftriaxone) during the surveillance period. Invasive and noninvasive *S. pneumoniae* showed similar resistance. In the case of *H. influenzae* susceptibility to β -lactam and β -lactamase inhibitors (ampicillin, amoxicillin and AMC), SXT, clarithromycin and cephalosporins (cefuroxime, cefaclor, ceftazidime) was reduced over the past 10 years with an exception of ceftriaxone. Overall, moxifloxacin and levofloxacin have the highest susceptibility rates against *S. pneumoniae* (>95%) and *H. influenza* (>90%). *M. catarrhalis* exhibited susceptibility to almost all the tested antimicrobials.

Conclusion: In China the 10-year trends showed a substantial increase in resistance to β -lactam drugs and reduction in sensitivity. However, certain antimicrobial agents namely fluoroquinolones including moxifloxacin and levofloxacin maintained low resistance rates with better susceptibility. Further, with few exceptions decline in susceptibility rates to macrolides and cephalosporins was observed among the tested pathogens.

Keywords: Community-acquired respiratory tract infections, antimicrobial resistance, susceptibility, *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*

Introduction

Globally, community-acquired respiratory tract infections (CARTIs) are a serious public health problem representing a leading cause of hospitalization and accounts for a significant proportion of antimicrobial prescriptions.^{1,2} Typically, there are three major bacterial pathogens namely *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Moraxella catarrhalis* that account for CARTIs.^{3,4} Treatment for CARTI is often empirical as isolation, identification, and local drug susceptibility test to guide treatment is not feasible for each individual patient.⁵ Furthermore, β -lactam and other substitute

antibiotics are the common principal therapeutic agents used in the empiric management of CARTIs.^{6,7} Community-acquired respiratory infection is a common type of community-acquired infection in China. There are usually no conditions for etiological testing in community hospitals, so it mainly relies on empirical treatment. The guidelines in China also recommend empirical treatment as the first choice for community-acquired respiratory infections.⁸ At this juncture, several studies reported high resistance rates of these pathogens to the more commonly used antimicrobial agents thereby complicating the empirical therapy in CARTIs management.^{9,10} However, the distribution of these major bacterial pathogens and development of antimicrobial resistance varies across different regions.¹¹

Surveillance is the cornerstone in understanding and controlling antimicrobial resistance. Although there were many drug resistance surveillance programs in mainland China, Taiwan, and other Asian regions, there were few drug resistance surveillance programs dedicated to monitoring the main pathogens of community-acquired respiratory infections. Furthermore, knowledge of local resistance patterns and predominant mechanisms underlying the resistance development plays a pivotal role in success of empiric therapy.¹² In this context, the main objective of the current community-acquired respiratory tract infection pathogen surveillance (CARTIPS) study is to summarize the susceptibility and resistance trends of various primary CARTI pathogens (*S. pneumoniae*, *H. influenzae* and *M. catarrhalis*) against conventional antimicrobials in the adult Chinese population. The CARTIPS study published two articles, in 2011¹⁰ and 2016.⁹ Combined with previous studies, changes in antimicrobial resistance over long timescales (2009–2018) can be clearly demonstrated, providing solid evidence for future empirical treatment and prevention of the emergence of drug-resistant strains.

Materials and Method

Participating Centers and Profile of Strains

Between 2009 and 2018 around 34 hospitals from 22 cities of China (Beijing, Changchun, Changsha, Chengdu, Chongqing, Guangzhou, Hangzhou, Harbin, Hefei, Hohhot, Jinan, Kunming, Nanchang, Nanning, Shanghai, Shenyang, Tianjin, Urumchi, Wuhan, Xian, Yinchuan, Zhengzhou) took part in this study (Figure 1).

Patients aged >18 years with clinically diagnosed CARTIs, such as community-acquired pneumonia, acute attack of chronic bronchitis, acute attack of chronic obstructive pulmonary disease, acute and/or chronic tonsillitis, pharyngitis and sinusitis occurring in the community or within 48 hour after hospital admission were included. Patients aged <18 years, nonpathogenic strains, duplicate isolates, colonization by bacteria without any clinical evidence of infection and noncommunity-acquired pathogenic strains isolated from patients who had been hospitalized for >48 h were excluded from the study.

Strains isolated from specimens obtained by invasive procedures were considered as pathogenic strains. The most majority of noninvasive strains were cultured from sputum, and the quality of sputum specimens were assessed to determine whether the isolates were pathogenic. For some cases imaging evidence (such as X-ray) was also used to determine pathogenicity of cultured strains. During the study period major bacterial pathogens namely *S. pneumoniae* (2015 isolates), *H. influenzae* (1215 isolates), *M. catarrhalis* (520 isolates) that are deemed pathogenic for CARTIs were collected from the Chinese adult patients. Further, based on combined results of culture test and immunopathology the isolates were judged to be pathogenic bacteria or colonized bacteria and the pathogenic bacteria were included in the study. Specimens from nasal and pharyngeal swab, sputum with white blood cells (WBC) >25 and squamous epithelial cells <10 under low power microscopy were considered as qualified. Other specimens such as blood, pleural effusion and cerebrospinal fluid (CSF) were considered as sources for invasive bacterial infections. The number of strains from every center collected in each monitoring year was presented in [Supplementary Table 1](#).

The Ethics Statement

All the adult patients participating in this study signed informed consent. The study protocols of different years were approved by the Ethics Committee of the Peking University People's Hospital (No. 2010PHB065, No. 2013PHB188, No. 2014PHB104, No. 2016PHB135, No. 2018PHB129), and all procedures were conducted according to the Declaration of Helsinki revised in 2008.

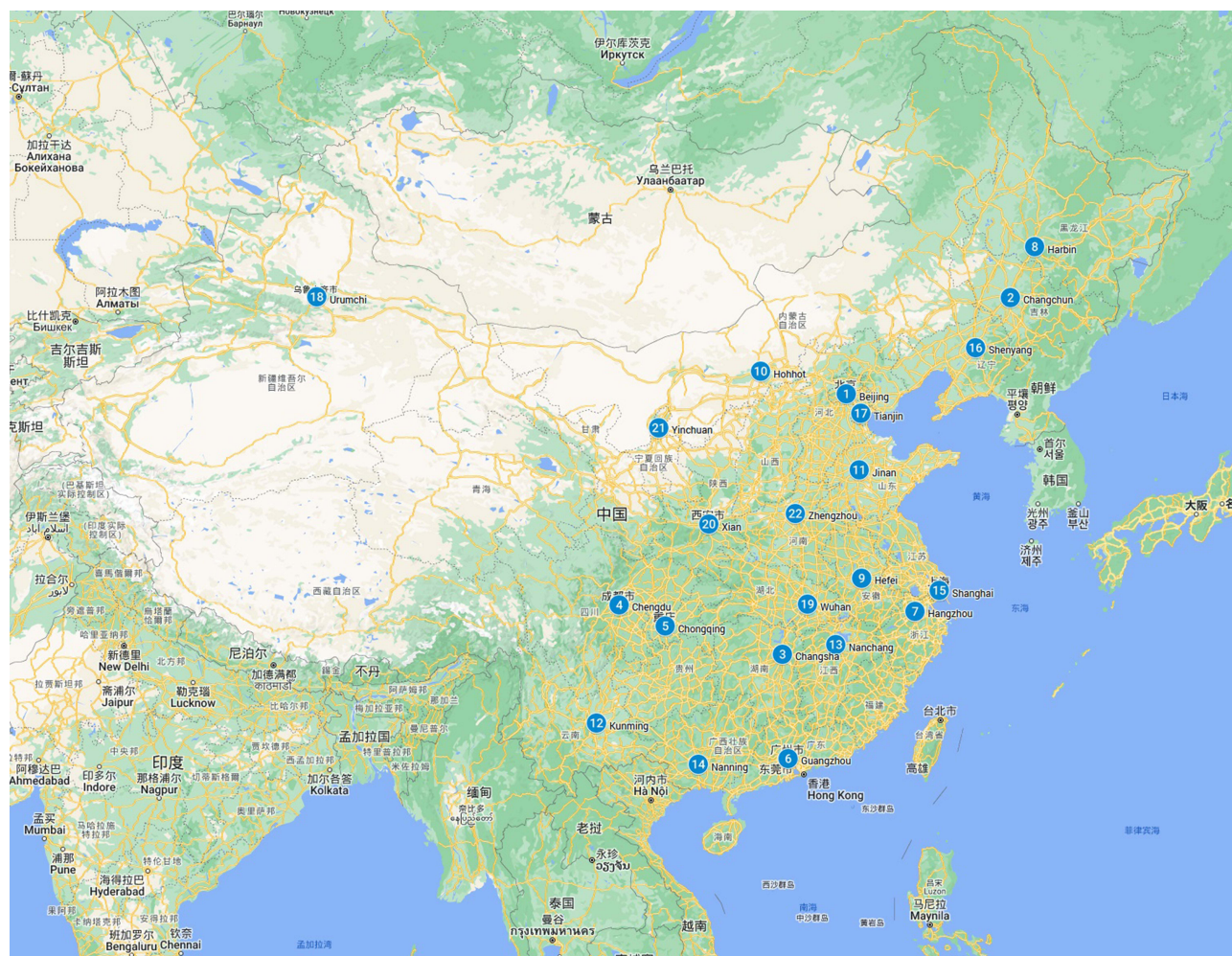


Figure 1 Geographical location of different cities participating in this study.

In vitro Antimicrobial Susceptibility Testing

The agar dilution method was used to determine the minimum inhibitory concentrations (MICs) of all *S. pneumoniae* isolates against antibiotics commonly used in community. For *H. influenzae* and *M. catarrhalis*, broth microdilution method was used for the determination of MICs of different antibiotics. All the tests were strictly in accordance with the guidelines established by the Clinical and Laboratory Standards Institute (CLSI).¹³

In China, combined with the distribution characteristics of pathogenic bacteria and the antibacterial spectrum of antibacterial drugs, β -lactams, macrolides and fluoroquinolones were usually used for empirical treatment of community-acquired respiratory infections in adults.¹⁴ There were 16 antibiotics tested in this study includes penicillin (only for *S. pneumoniae*), amoxicillin-clavulanic acid, ampicillin (only for *H. influenzae*), cefaclor, cefuroxime, ceftriaxone, vancomycin (only for *S. pneumoniae*), erythromycin (only for *S. pneumoniae*), azithromycin, clarithromycin, tetracycline, levofloxacin, moxifloxacin (for *S. pneumoniae* and *H. influenzae*), sulfamethoxazole-trimethoprim, chloramphenicol, and clindamycin. All drug standards used in the current study were purchased from the National Institute for the Control of Pharmaceutical and Biological Products, China. For *S. pneumoniae* and *H. influenzae*, the CLSI 2017 criteria were applied to classify isolates as susceptible (S), intermediate (I), or resistant (R).

For *S. pneumoniae*, the oral penicillin breakpoint was used to classify isolates as penicillin-susceptible (MIC ≤ 0.06 $\mu\text{g/mL}$), penicillin-intermediate (MIC between 0.12 and 1 $\mu\text{g/mL}$), and penicillin-resistant (MIC ≥ 2 $\mu\text{g/mL}$). Penicillin non-meningitis breakpoints (susceptible, MIC ≤ 2 $\mu\text{g/mL}$; resistant, MIC ≥ 8 $\mu\text{g/mL}$) and penicillin meningitis breakpoints (susceptible, MIC ≤ 0.06 $\mu\text{g/mL}$; resistant, MIC ≥ 0.12 $\mu\text{g/mL}$) were also applied to evaluation the susceptibilities. For

ceftriaxone, the non-meningitis breakpoints (susceptible, MIC ≤ 1 $\mu\text{g/mL}$; resistant, MIC ≥ 4 $\mu\text{g/mL}$) and meningitis breakpoints (susceptible, MIC ≤ 0.5 $\mu\text{g/mL}$; resistant, MIC ≥ 2 $\mu\text{g/mL}$) were used to classify isolates as susceptible and resistant.¹⁵ For *M. catarrhalis*, resistance was interpreted according to the breakpoints in CLSI M45-A2.¹⁶

S. pneumoniae ATCC 49619 was used as the quality control strain and was included in each batch of tests to ensure accurate results. MIC₅₀ and MIC₉₀ (MICs that inhibit 50% and 90% of the isolates, respectively) were calculated by R. Multidrug-resistance was defined as tested strains which were resistant to at least three different antibiotic classes simultaneously. Nitrocefin disk (Oxoid, UK) was used for the detection of β -lactamase production¹⁷ by *H. influenzae* and *M. catarrhalis*. For *S. pneumoniae* strains that tested erythromycin-resistant and clindamycin-susceptible or -intermediate, the D-zone test was performed to detect inducible clindamycin resistance in accordance with CLSI guidelines.¹³ Moreover, differences in the antibiotic susceptibility patterns between the earlier and later study years for a given antimicrobial agent were compared to the resistance profiles of respiratory isolates of the period 2009–10, 2012, 2013–14, 2016 and 2018.

Statistical Analysis

Data from the antibiotic susceptibility tests were analyzed using WHONET 5.6 software, a Windows-based database software developed by the World Health Organization for managing and analyzing microbiological laboratory data with a special focus on the analysis of antimicrobial susceptibility test results. The chi-squared and Fisher's exact probability tests were performed using R version 4.0.2 to compare proportions. Data visualization was done with ggplot2 package version 3.3.2.¹⁸ A *p*-value less than 0.05 was considered statistically significant.

Results

Profile of Pneumococcal Isolates

During the surveillance period 2009–2018, a total of 3750 nonduplicated isolates were collected from 34 representative hospitals located across 22 different regions of mainland China. All the strains were divided into East (788), Middle (357), North (1392), Northeast (320), Northwest (282), South (292) and Southwest (319) by their geological locations. Among these the most common bacterial isolates include *S. pneumoniae* (2015, 53.7%) followed by *H. influenza* (1215, 32.4%), *M. catarrhalis* (520, 13.9%). The strains were mainly isolated from elderly patients, 48% (1800/3750) of the strains were isolated from patients over 60 years old; only 20.4% (764/3750) of the strains were isolated from patients under 40 years old. Sputum was the most important specimen type (3071 strains, 81.9%), followed by bronchoalveolar lavage fluid (269 strains, 7.2%), throat swab (165 strains, 4.4%) and blood (152 strains, 4.1%). The specific number of strains collected by various centers in different regions in different years were summarized in [Supplementary Table 1](#).

Antimicrobial Susceptibility of *S. pneumoniae*

The overall in vitro activities of the tested antimicrobial agents against *S. pneumoniae* strains during the study periods were shown in [Table 1](#). Based on the MIC breakpoints of oral penicillin criteria, the overall rate of penicillin-resistant *S. pneumoniae* (PRSP), penicillin-intermediate *S. pneumoniae* (PISP), and penicillin-susceptible *S. pneumoniae* (PSSP) isolates was 40.8% (822/2015), 17.8% (359/2015), and 41.4% (834/2015), respectively. Macrolide and tetracycline exhibited limited antibacterial effects against *S. pneumoniae* during the study periods. The resistant rate of *S. pneumoniae* to erythromycin, azithromycin, clarithromycin, clindamycin, and tetracycline was 93.3%, 91.4%, 90.4%, 86.7%, and 91.5%, respectively. Furthermore, 1880 (93.3%) strains were resistant to erythromycin, and of these, 1588 were resistant to clindamycin simultaneously. For PSSP strains, all β -lactams except cefaclor showed excellent antibacterial activity, with susceptibility rates of >99%. Most PISP strains were susceptible to AMC, ceftriaxone, quinolones and chloramphenicol with susceptibility rates of >89%. However, compared with PSSP and PISP, the sensitivity of PRSP to ceftriaxone and AMC decreased to 47.9% and 34.8% respectively. In regard to PRSP isolates, cefuroxime, cefaclor, SXT, macrolides, tetracycline and clindamycin showed very low antibacterial activity ([Table 2](#)). Ceftriaxone had a good antibacterial activity against *S. pneumoniae*, but the average resistance rate of *S. pneumoniae* to cefaclor had exceeded 50%, as well as cefuroxime. vancomycin, fluoroquinolones and chloramphenicol have high antibacterial activity against

Table I The Overall Resistance Rate of *S. pneumoniae* to Different Antibacterial Agents, from 2010 to 2018

Antibiotics	Sensitive %	Intermediate %	Resistant %	MIC ₅₀	MIC ₉₀	Range	Strain Number
Penicillin oral	41.4	17.8	40.8	0.5	4	0.004 – 64	2015
Penicillin meningitis	41.4	0.0	58.6	0.5	4	0.004 – 64	2015
Penicillin non-meningitis	76.2	22.2	1.6	0.5	4	0.004 – 64	2015
Amoxicillin-clavulanic acid	73.1	8.7	18.3	0.5	8	0.008 – 64	2015
Cefaclor	39.8	5.7	54.5	16	>256	0.016 – >256	2015
Cefuroxime	49.2	3.8	47.0	2	32	0.016 – >256	2015
Ceftriaxone	78.0	6.7	15.3	0.5	4	0.016 – >64	2015
Ceftriaxone meningitis	57.5	20.5	22.0	0.5	4	0.016 – >64	2015
Vancomycin	100.0	0.0	0.0	0.25	0.25	0.016 – 1	2015
Erythromycin	6.0	0.7	93.3	256	>256	0.016 – >256	2015
Azithromycin	7.4	1.2	91.4	>16	>256	0.016 – >256	2015
Clarithromycin	7.8	1.8	90.4	128	>256	0.016 – >256	2015
Tetracycline	7.1	1.4	91.5	32	64	0.032 – >128	2015
Levofloxacin	97.6	0.2	2.2	1	1	0.016 – >32	2015
Moxifloxacin	98.4	1.0	0.6	0.125	0.25	0.016 – >32	2015
Trimethoprim-sulfamethoxazole	25.3	8.0	66.7	4	16	0.016 – 128	2015
Chloramphenicol	87.9	0.0	12.1	4	8	0.016 – 32	2015
Clindamycin	12.2	1.1	86.7	128	256	0.016 – >256	2015

S. pneumoniae. No *S. pneumoniae* strains resistant to vancomycin have been found. The resistance rate of *S. pneumoniae* to fluoroquinolones was less than 3%, and the resistance rate to moxifloxacin was less than 1%. Compared to levofloxacin, moxifloxacin usually have lower MIC₅₀ and MIC₉₀ values against *S. pneumoniae* (1 µg/mL vs 0.125 µg/mL and 1 µg/mL vs 0.25 µg/mL). The resistance rate of *S. pneumoniae* to fluoroquinolones remained constant in the whole time span. Of all *S. pneumoniae* strains 60.9% (1227/2015) showed multi-drug resistance (MDR, [Supplementary Table 2](#)). Invasive and non-invasive strains demonstrated parallel resistance rate in all antibiotics tested in this study and the differences were not statistically significant ([Table 3](#)). The most common drug-resistant phenotype was simultaneously resistant to β-lactams, macrolides, tetracycline and sulfonamides, accounting for 53.1% (651/1227) of all multidrug resistant strains. *S. pneumoniae* strains showed a higher rate of resistance to β-lactams in age groups younger than 40 years than in age groups older than 60 years, most notably in penicillin, cefuroxime and ceftriaxone ([Figure 2](#)).

During the study period, a striking uptrend of resistance was observed, especially for β-lactams. The resistance to penicillin (oral) raised from 24.4% in 2010 to 61.6% in 2018, and other β-lactams shared the similar trend. Although the resistance rate was relatively low in cephalosporins, a clear and definitive upward trend of the resistance rate was observed. For macrolides, the resistance rate remains at high level during the entire study period. ([Figure 3](#)).

Antimicrobial Susceptibility of *H. influenzae*

For *H. influenzae*, most of the tested antimicrobial agents showed excellent activity against isolates from different years from China ([Table 4](#)). SXT and ampicillin showed relatively lower activity against *H. influenzae*, with resistance rates of 36.6% and 60.5%, respectively. Ceftriaxone, levofloxacin, moxifloxacin, azithromycin and chloramphenicol demonstrated high activity (>90%) against all *H. influenzae* strains. During all research periods, there were 319 (26.3%) β-lactamase positive strains, among all 1215 *H. influenzae* strains. The rates of β-lactamase producing strains have shown a clear upward trend, from 14.5% in 2010 to 35.1% in 2018.

Rates of β-lactamase producing *H. influenzae* varied with geographical regions, with the highest rate of 42.2% (46/109) in Southwest, followed by 29.9% (23/77) in Northeast, 27.5% (25/91) in Northwest, 27.1% (92/340) in East, 23.6% (93/394) in North, 20.6% (21/102) in Middle and 18.6% (19/102) in South. In addition, for β-lactamase negative strains, there were 79 strains demonstrated resistance to ampicillin, regarding as β-lactamase-negative ampicillin-resistant (BLNAR) strains. Resistance rates of BLNAR strains to ampicillin, AMC, cefaclor and cefuroxime were 100%, 67.5%, 77.5% and 55.0%, respectively. Compared with β-lactamase negative strains, β-lactamase positive *H. influenzae* usually exhibited higher

Table 2 The Overall Resistance Rate of PSSP, PISP and PRSP to Different Antibacterial Agents, from 2010 to 2018

Antibiotics	PSSP ^a (N=834)						PISP ^b (N=359)						PRSP ^c (N=822)					
	S ^d	I ^e	R ^f	MIC ₅₀	MIC ₉₀	Range	S	I	R	MIC ₅₀	MIC ₉₀	Range	S	I	R	MIC ₅₀	MIC ₉₀	Range
Penicillin oral	100	0	0	0.032	0.064	0.004 – 0.064	0	100	0	0.5	I	0.125 – I	0	0	100	4	4	2 – 64
Penicillin meningitis	100	0	0	0.032	0.064	0.004 – 0.064	0	0	100	0.5	I	0.125 – I	0	0	100	4	4	2 – 64
Penicillin non-meningitis	100	0	0	0.032	0.064	0.004 – 0.064	100	0	0	0.5	I	0.125 – I	41.7	54.4	3.9	4	4	2 – 64
Amoxicillin-clavulanic acid	99.8	0	0.2	0.016	0.032	0.008 – 32	98.6	1.1	0.3	0.5	I	0.008 – 8	34.8	20.8	44.4	4	8	0.016 – 64
Cefaclor	87.9	10.4	1.7	I	2	0.016 – >256	18.9	7.8	73.3	16	>64	0.125 – >256	0	0	100	>256	>256	16 – >256
Cefuroxime	99.5	0.2	0.2	0.032	0.125	0.016 – 16	44	17.8	38.2	2	4	0.032 – >16	0.4	1.2	98.4	8	32	0.125 – >256
Ceftriaxone	99.8	0.1	0.1	0.016	0.064	0.016 – 4	96.1	2.5	1.4	0.5	I	0.016 – >64	47.9	15.2	36.9	2	8	0.125 – >32
Ceftriaxone meningitis	99.6	0.1	0.2	0.016	0.064	0.016 – 4	74.9	21.2	3.9	0.5	I	0.016 – >64	7.1	40.9	52.1	2	8	0.125 – >32
Vancomycin	100	0	0	0.25	0.25	0.064 – 0.5	100	0	0	0.25	0.25	0.016 – I	100	0	0	0.25	0.25	0.064 – I
Erythromycin	12.7	1.2	86.2	128	>256	0.016 – >256	5.7	1.7	92.6	128	>256	0.016 – >256	0.3	0	99.7	>128	>256	0.032 – >256
Azithromycin	15.1	2.2	82.7	32	>256	0.016 – >256	5.3	0.8	93.9	>16	>256	0.016 – >256	0.5	0.4	99.1	>256	>256	0.032 – >256
Clarithromycin	15.5	2.4	82.1	>4	>256	0.016 – >256	7.2	3.3	89.4	>4	>256	0.016 – >256	0.4	0.5	99.1	>256	>256	0.032 – >256
Tetracycline	12.2	3	84.8	32	64	0.032 – 128	7.4	1.3	91.3	32	64	0.125 – 256	2.5	0.1	97.3	32	64	0.25 – >128
Levofloxacin	98.3	0.1	1.6	I	I	0.016 – 32	96.7	0.3	3.1	I	I	0.016 – 32	97.2	0.4	2.4	I	I	0.125 – >32
Moxifloxacin	98.9	0.7	0.4	0.125	0.125	0.016 – 16	98.3	0.6	1.1	0.125	0.125	0.016 – 8	97.9	1.5	0.6	0.125	0.25	0.032 – >32
Trimethoprim-sulfamethoxazole	47.4	7.4	45.1	I	8	0.016 – 128	24.3	15.7	60	4	8	0.016 – 128	6.7	5.9	87.4	8	16	0.125 – 128
Chloramphenicol	78.4	0	21.6	4	8	0.016 – 16	89.1	0	10.9	2	8	0.064 – 32	95.6	0	4.4	4	4	0.125 – 16
Clindamycin	25.9	2.3	71.8	64	256	0.016 – >256	12.2	1.4	86.5	64	256	0.016 – >256	1.4	0	98.6	256	256	0.064 – >256

Abbreviations: ^aPSSP, penicillin-susceptible *Streptococcus pneumoniae*; ^bPISP, penicillin-intermediate *Streptococcus pneumoniae*; ^cPRSP, penicillin-resistant *Streptococcus pneumoniae*; ^dS, Sensitive percentage; ^eI, intermediate percentage; ^fR, resistant percentage.

Table 3 The Differences in Drug Resistance Rates Between Invasive and Noninvasive *S. pneumoniae*

Antibiotics	Invasive (N=145)						Noninvasive (N = 1870)						P-value
	S%	I%	R%	MIC ₅₀	MIC ₉₀	Range	S%	I%	R%	MIC ₅₀	MIC ₉₀	Range	
Penicillin oral	44.1	17.2	38.6	0.25	4	0.004 – 8	41.2	17.9	41	0.5	4	0.004 – 64	0.780733
Penicillin meningitis	44.1	0	55.9	0.25	4	0.004 – 8	–	–	–	–	–	–	–
Penicillin nonmeningitis	–	–	–	–	–	–	76.1	22.2	1.7	0.5	4	0.004 – 64	–
Amoxicillin/clavulanic acid	74.5	6.9	18.6	0.25	8	0.008 – 32	72.9	8.8	18.2	0.5	8	0.008 – 64	0.729767
Cefaclor	40.7	6.2	53.1	16	>256	0.016 – >256	39.7	5.7	54.7	16	>256	0.016 – >256	0.922137
Cefuroxime	50.3	3.4	46.2	0.5	32	0.016 – >256	49.1	3.8	47.1	2	32	0.016 – >256	0.946579
Ceftriaxone	79.3	7.6	13.1	0.25	4	0.016 – >32	77.9	6.6	15.5	0.5	4	0.016 – >64	0.695279
Ceftriaxone meningitis	60	19.3	20.7	0.25	4	0.016 – >32	–	–	–	–	–	–	–
Vancomycin	100	0	0	0.25	0.25	0.125 – 0.5	100	0	0	0.25	0.25	0.016 – 1	–
Erythromycin	7.4	0	92.6	256	>256	0.016 – >256	5.8	0.8	93.4	256	>256	0.016 – >256	0.490743
Azithromycin	8.3	0	91.7	>16	>256	0.016 – >256	7.3	1.3	91.4	>16	>256	0.016 – >256	0.363069
Clarithromycin	8.3	2.1	89.7	>128	>256	0.016 – >256	7.8	1.8	90.4	64	>256	0.016 – >256	0.943526
Tetracycline	7.4	2.5	90.1	32	64	0.032 – 128	7	1.3	91.6	32	64	0.032 – >128	0.582572
Levofloxacin	96.6	0	3.4	1	1	0.016 – >32	97.6	0.3	2.1	1	1	0.016 – >32	0.461022
Moxifloxacin	97.2	1.4	1.4	0.125	0.25	0.016 – >32	98.5	1	0.5	0.125	0.25	0.016 – 16	0.392802
Trimethoprim/sulfamethoxazole	28.1	5	66.9	4	16	0.016 – 32	25.1	8.2	66.7	4	16	0.016 – 128	0.388543
Chloramphenicol	86	0	14	4	8	0.016 – 16	88.1	0	11.9	4	8	0.016 – 32	0.592261
Clindamycin	11	1.2	87.8	128	256	0.016 – >256	12.4	1.1	86.6	128	256	0.016 – >256	0.929252

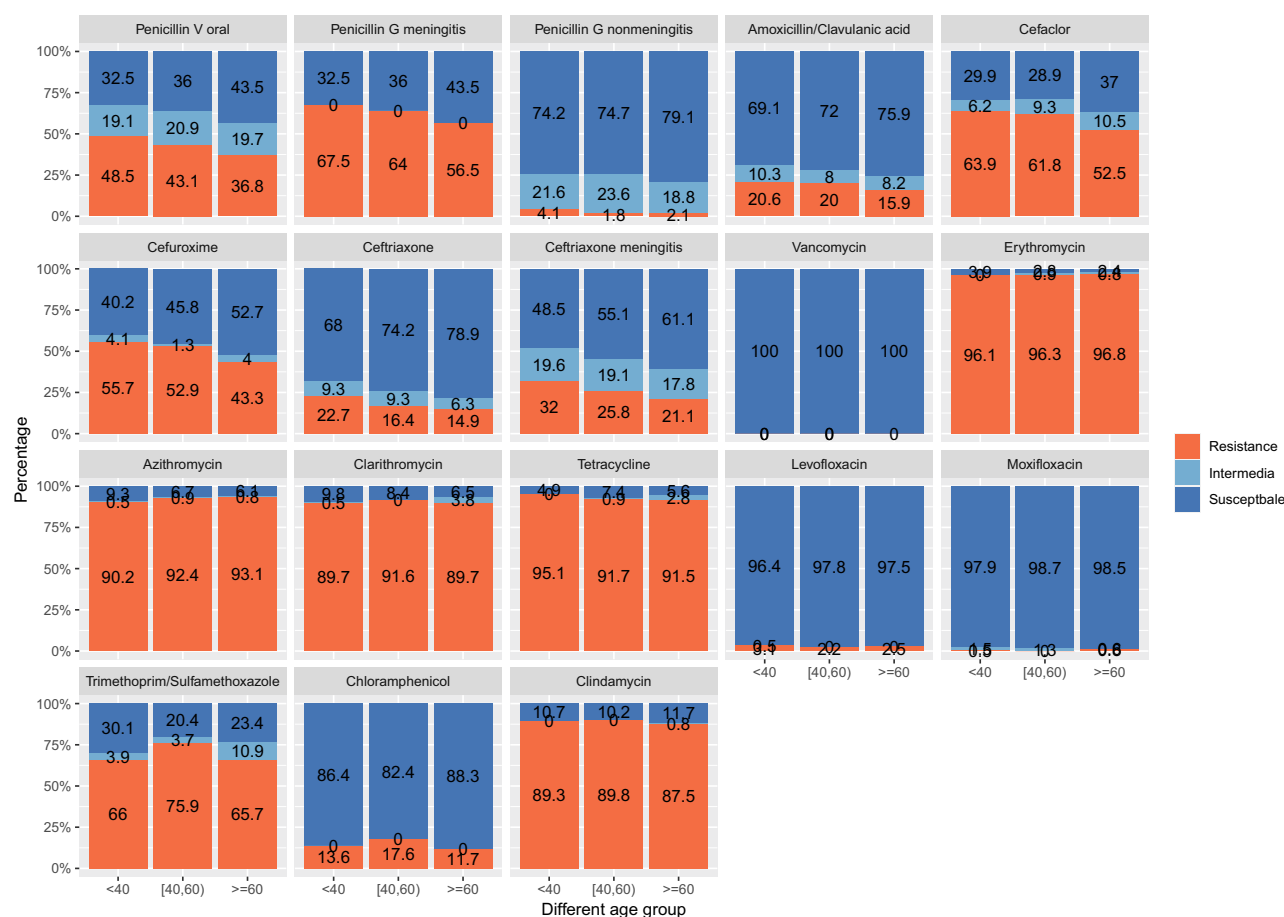


Figure 2 Changes in resistance rates of *S. pneumoniae* to various drugs in different age groups.

resistance rates to β -lactams agents (Table 5). Although *H. influenzae* strains were sensitive to a variety of antibacterial agents tested, a remarkable upward trend of resistance rate was still observed during the entire study periods, especially in ampicillin, AMC, cefaclor and cefuroxime (Figure 4). The incidence of multidrug resistance (MDR) in *H. influenzae* was 10.0% (122/1215), and the most important multidrug resistance pattern was simultaneously resistant to β -lactams, macrolides and co-sulfonamides, accounting for 41.0% (50/122) of all MDR strains (Supplementary Table 3).

Antimicrobial Susceptibility of *M. catarrhalis*

Most of the antimicrobial agents showed excellent activities against 520 isolates of *M. catarrhalis*, with susceptibility rates of >90%. *M. catarrhalis* strains from this study were 100% sensitive to amoxicillin-clavulanic acid, ceftriaxone, azithromycin, clarithromycin, and levofloxacin. However, clindamycin, trimethoprim-sulfamethoxazole and cefaclor showed relatively low activity against *M. catarrhalis* (Table 6). In addition, 90.8% of *M. catarrhalis* isolates produced a β -lactamase in this study. During the study period, the β -lactamase positive rate rose from 82.6% in 2010 to 94.4% in 2018 (Figure 5). The MDR in *M. catarrhalis* was much lower compared with *S. pneumoniae* and *H. influenzae*. The important patterns of MDR in *M. catarrhalis* isolates were summarized in Supplementary Table 4.

The three bacteria in this study showed different drug resistance in different regions, and the drug resistance rate in northwest China was higher than that in other regions, especially for β -lactams. Supplementary Figures 1–3 show the resistance rates of *S. pneumoniae*, *H. influenzae* and *M. catarrhalis* to different drugs, respectively.

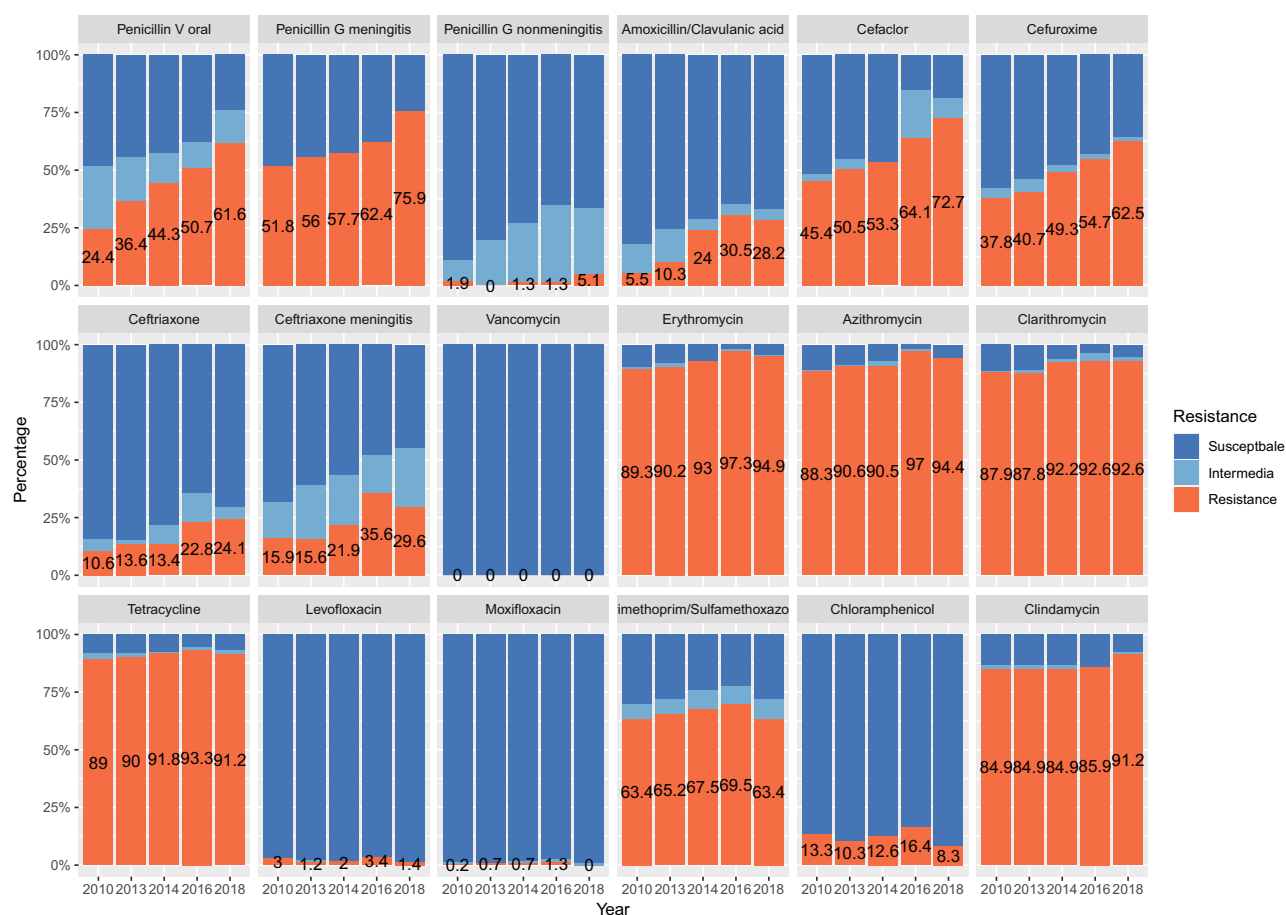


Figure 3 Resistance of *S. pneumoniae* to routine antibiotics in different years.

Discussion

This study updated the antimicrobial resistance trend of the major pathogens that cause CARTI in Chinese adults. *S. pneumoniae*, *H. influenzae* and *M. catarrhalis* were the most frequently isolated bacterial pathogens associated with CARTIs and were becoming more and more resistant to commonly used antimicrobial agents, according to the findings of this long-term research. Successful management and treatment of CARTIs requires timely administration of effective therapeutic agents. At this juncture, clinical decisions on empirical therapy require knowledge of possible pathogens and their susceptibilities to antimicrobials. However, such knowledge can be gained in result of clinical practice experience over time, but more objectively and robustly through surveillance. Moreover, the prevalence of resistance rates to commonly used antimicrobials in the management of CARTIs is alarming. Furthermore, there are fewer drug resistance monitoring surveillance studies focused on CARTIs in China and the majority of studies reported results from nosocomial infections. The current monitoring of nosocomial infection shows that the drug resistance rate is also increasing year by year, especially the proportion of CRE (carbapenem resistant Enterobacteriaceae) is increasing.¹⁹ Although the pathogens of community-acquired infection and nosocomial infection are different, they all show a trend of increasing drug resistance.

Based on the MIC breakpoints of oral penicillin, the percentage of PRSP in this study increased drastically from 24.2% in 2010 to 61.6% in 2018. Previous study suggested the high resistance due to clonal spread of resistance clones, such as 19F-ST271 and 19A-ST320 strains.^{20,21} In this study, *S. pneumoniae* strains demonstrated a high drug resistant rate to β -lactam drugs as well as to macrolides, which posed a severe challenge to actual clinical treatment and may cause

Table 4 The Overall Resistance Rate of *H. influenzae* to Different Antibacterial Agents, from 2010 to 2018

Antibiotics	Sensitive %	Intermediate %	Resistant %	MIC ₅₀	MIC ₉₀	Range	Strain Number
Ampicillin	60.5	7.3	32.2	1	>16	0.016 – >64	1215
Amoxicillin-Clavulanic acid	89.5	0	10.5	0.5	8	0.008 – >32	1215
Cefaclor	65.3	6.7	28	4	>32	0.016 – >32	1215
Cefuroxime	80.2	4.3	15.5	1	32	0.016 – 128	1215
Ceftriaxone	100	0	0	0.032	0.125	0.016 – 0.5	1215
Azithromycin	100	0	0	1	2	0.016 – 4	1215
Clarithromycin	84.8	7.7	7.6	4	16	0.064 – >64	1215
Tetracycline	89.2	2.2	8.6	0.5	4	0.016 – >64	1215
Levofloxacin	100	0	0	0.016	0.5	0.008 – 2	1215
Moxifloxacin	100	0	0	0.032	0.5	0.008 – 1	1215
Trimethoprim-sulfamethoxazole	36.6	9.2	54.2	4	32	0.016 – >32	1215
Chloramphenicol	92.2	1.9	5.9	0.5	2	0.016 – 32	1215

clinical treatment failure in actual clinical practice. Fluoroquinolones maintained high sensitivity to *S. pneumoniae* in this study, and can be applied as the first choice for the treatment of CARTI in appropriate populations, such as adults.

In addition to the weak antibacterial activities of macrolides against *S. pneumoniae* in this study, macrolides showed strong antibacterial activity against both *H. influenzae* and *M. catarrhalis* isolates. Although the antibacterial activity against *S. pneumoniae* was relative weaker in this study, considering the higher safety boundary and strong tissue penetration of macrolides,²² especially in lung tissue, macrolides can be used as multi-therapy in combination with β -lactam or amoxicillin-clavulanate.²³ The MIC results of erythromycin and clindamycin suggested MLS_B phenotype was the most prevalent phenotype in China and this result was consistent with previous research.^{24,25}

For the prevention and treatment of *S. pneumoniae*, in addition to the standardized application of conventional antibacterial regents, pneumococcal vaccine was also an important supplementary measurement, especially in groups with risk factors for pneumococcal infection.²⁶ As the pneumococcal vaccine has not been included in the Chinese immunization program, the pneumococcal vaccine has not been widely used in China. PCV-7 vaccine had been introduced in China since 2008, and it was replaced by PCV-13 vaccine in 2016, which can prevent pneumococcal infection of 13 different serotypes.^{27,28} Previous studies have shown that the current pneumococcal vaccine PCV-13 can effectively cover the main drug-resistant serotypes in China, and the vaccine coverage rate in adults was 62%.²¹ If the vaccine were widely used, it will definitely impose a significant impact on the distribution of pneumococcal serotypes and resistant clones, and this will be a new opportunity for the rational use of antibacterial drugs.

Ampicillin and amoxicillin were the drugs of choice for the treatment of *H. influenzae* infection. The data of this study showed that the resistance rate of *H. influenzae* to ampicillin rose rapidly from 17.2% in 2010 to 43.9% in 2018. This study showed that the resistance rate of *H. influenzae* to ampicillin was 32.2%, and the positive rate of β -lactamase was 26.3%. There were 79 β -lactamase-negative ampicillin resistant (BLNAR) strains in this study, which were considered to be resistant to β -lactams such as AMC, ampicillin-sulbactam, cefaclor and cefuroxime, although they were susceptible to some of the antimicrobials in vitro.²⁹ In this study, ceftriaxone, levofloxacin, moxifloxacin, azithromycin, chloramphenicol and tetracycline showed high activity against BLNAR strains, with susceptibility rates of >92.2%.

In the case of *M. catarrhalis*, although the rate of β -lactamase positivity was very high, the antibacterial drug susceptibility testing results show that *M. catarrhalis* strains were still highly susceptible to β -lactam agents, indicating that the effect used for the β -lactamase produced by *M. catarrhalis* was relatively weak and that current β -lactam drugs remained stable against it, thus allowing for the application of such antibiotics in empirical clinical treatment. Further research and testing is needed to determine exactly what type of β -lactamases are produced by *M. catarrhalis* in China.

In this study, strains from the north-western region showed high resistance rates, while strains isolated from the east and south showed relatively low resistance rates. The possible reasons for this phenomenon are, firstly, the small number

Table 5 The Sensitivities of β -Lactamase Negative and Positive *H. influenzae* to Different Antibacterial Agents, from 2010 to 2018

Antibiotics	β -Lactamase Negative (N=896)					β -Lactamase Positive (N=319)				
	Sensitive %	Resistant %	MIC ₅₀	MIC ₉₀	Range	Sensitive %	Resistant %	MIC ₅₀	MIC ₉₀	Range
Ampicillin	81.5	8.8	0.25	2	0.016 – >64	1.6	97.8	>8	>32	0.016 – >64
Amoxicillin-clavulanic acid	93.1	6.9	0.5	4	0.008 – >32	79.3	20.7	1	16	0.016 – 32
Cefaclor	73.3	22	2	>32	0.016 – >32	42.6	44.8	16	>32	0.016 – >32
Cefuroxime	84.2	11.4	0.5	16	0.016 – 128	69.2	27	2	>32	0.016 – >32
Ceftriaxone	100	0	0.016	0.064	0.016 – 0.5	100	0	0.032	0.25	0.016 – 0.5
Azithromycin	100	0	1	2	0.016 – 4	100	0	1	2	0.016 – 4
Clarithromycin	89.5	2.6	4	16	0.25 – >64	71.5	21.5	8	>32	0.064 – >64
Tetracycline	93.8	4.9	0.5	2	0.016 – 32	79	17	1	8	0.064 – >64
Levofloxacin	100	0	0.016	0.5	0.008 – 2	100	0	0.016	0.5	0.008 – 2
Moxifloxacin	100	0	0.016	0.5	0.008 – 1	100	0	0.032	0.5	0.008 – 1
Trimethoprim-sulfamethoxazole	43.4	46.7	2	32	0.016 – >32	21.6	70.9	8	32	0.016 – >32
Chloramphenicol	96.2	2.6	0.5	1	0.016 – 32	83	13.3	0.5	8	0.016 – 32

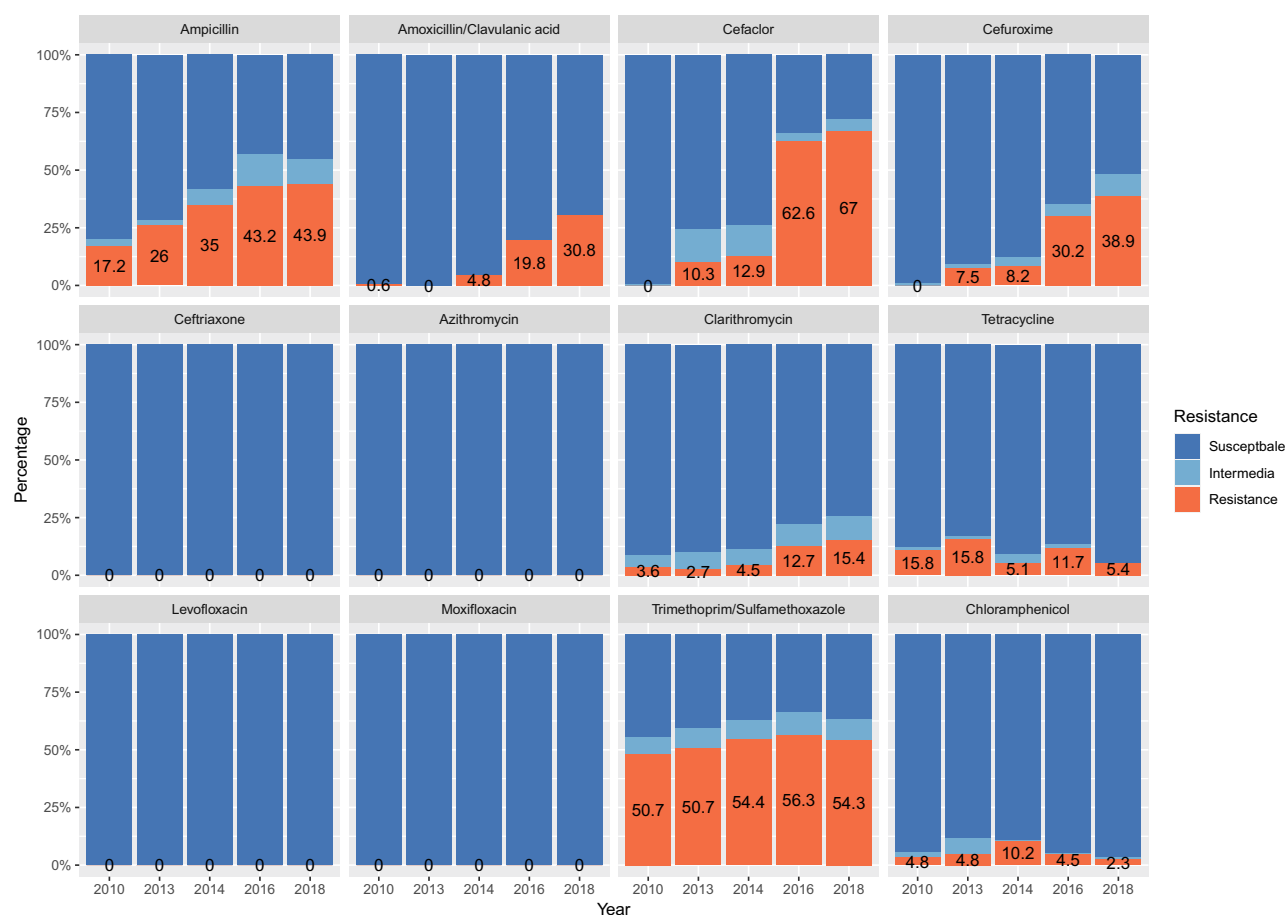


Figure 4 Resistance of *H. influenzae* to routine antibiotics in different years.

of hospitals participated in the north-west included in the study, such differences being due to random errors, and secondly, the association with antibiotics use habits and vaccination rates (especially for *S. pneumoniae*). The north-western region of China is relatively economically less developed, whereas in the eastern and southern coastal regions the level of economic development is high. *S. pneumoniae* vaccination is not included in the national immunization in China and vaccines need to be paid for themselves. The serotypes covered by the PCV13 are mostly those with high resistance rates, and because of the relatively high vaccination rates in the east and south, the proportion of

Table 6 The Overall Resistance Rate of *M. catarrhalis* to Different Antibacterial Agents, from 2010 to 2018

Antibiotics	Sensitive %	Intermediate %	Resistant %	MIC ₅₀	MIC ₉₀	Range
Amoxicillin-clavulanic acid	100	0	0	0.125	0.5	0.008 – 4
Cefaclor	85.2	5.4	9.4	2	16	0.016 – >32
Cefuroxime	97.3	1.3	1.3	1	4	0.016 – >32
Ceftriaxone	100	0	0	0.25	1	0.016 – 2
Azithromycin	100	0	0	0.064	0.125	0.016 – 0.25
Clarithromycin	100	0	0	0.25	1	0.016 – 1
Tetracycline	91	0.2	8.8	0.25	1	0.016 – >64
Levofloxacin	100	0	0	0.064	0.125	0.008 – 2
Trimethoprim-sulfamethoxazole	67.7	26.3	6	0.25	2	0.016 – >64
Chloramphenicol	95.6	1.4	3	0.5	0.5	0.016 – 32
Clindamycin	19	48	33	2	64	0.016 – >256

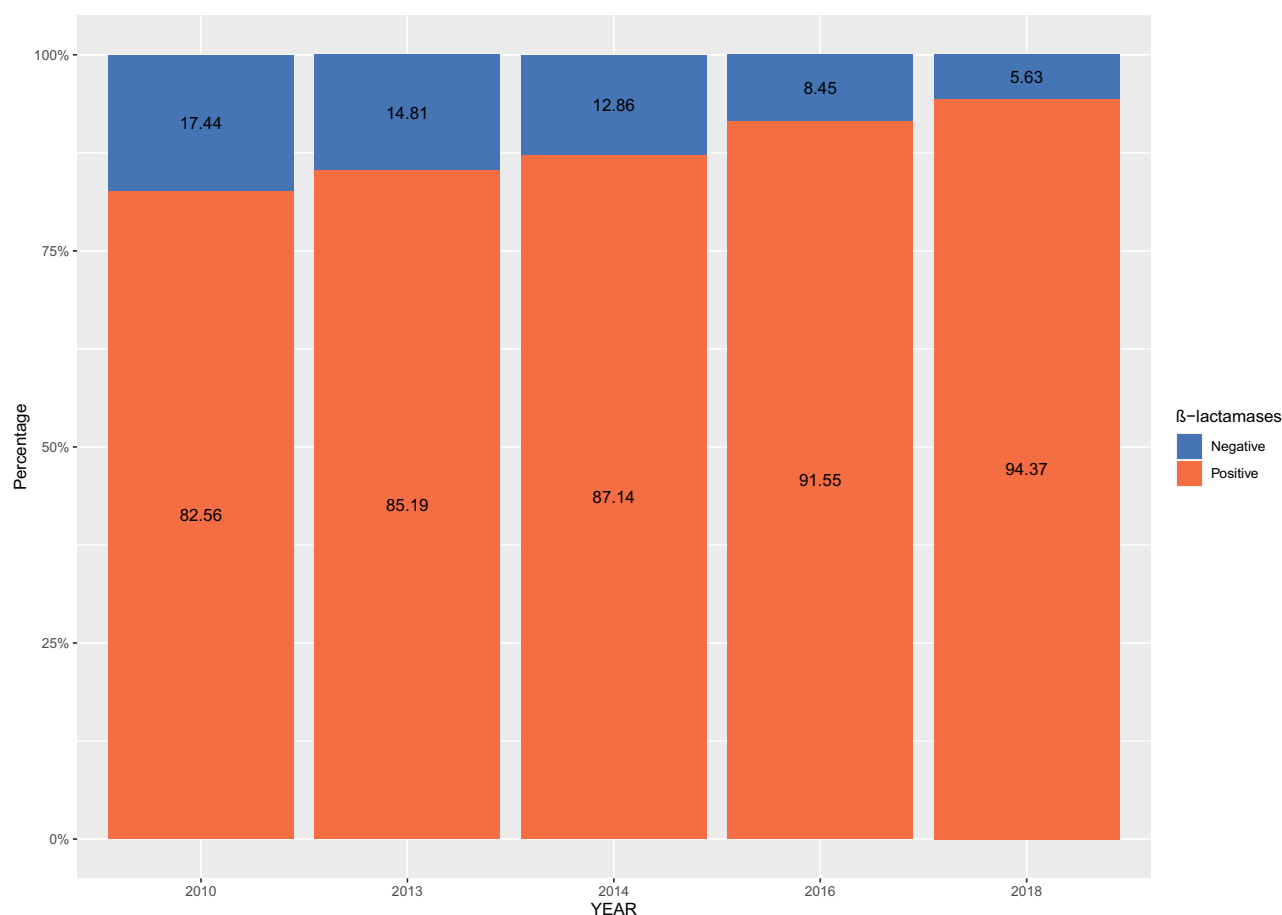


Figure 5 The prevalence of β -lactamase positive *M. catarrhalis* in different years.

S. pneumoniae with high resistance serotypes decreases, resulting in lower resistance rates. Previous studies have also confirmed the impact of the level of economic development on *S. pneumoniae* antibiotic resistance rates.²¹

Although this research mainly focused on the changes in the drug resistance of the main pathogens in community-acquired respiratory infections, it was difficult to conduct standardized pathogenic diagnosis in communities. The pathogens collected in this study are mainly from large medical centers in huge cities. Strains may not fully represent the true resistance properties of strains from communities especially in remote rural areas. For example, relatively serious infections that the community cannot deal with will be finally diagnosed and treated in a sophisticated hospital. The pathogens isolated in this way may be more resistant than the strains in the real communities. This is called survivorship bias and results of this study could overestimate the actual resistance rate of pathogens in the real community.

In conclusion, the results of this study confirmed the excellent activities of fluoroquinolones, including levofloxacin and moxifloxacin, against *S. pneumoniae*, *H. influenzae* and *M. catarrhalis*. However, the susceptibilities to azithromycin, clarithromycin, erythromycin and β -lactams among these pathogens were on the decrease. Regional variations were also found in the antimicrobial susceptibilities of these CARTI pathogens. Given the high rate of resistance and limited data from rural areas, continuous national surveillance of the epidemiology of CARTIs is strongly warranted in China.

Abbreviations

CARTIs, community-acquired respiratory tract infections; CARTIPS, community-acquired respiratory tract infection pathogen surveillance; BALF, bronchoalveolar lavage fluid; CSF, cerebrospinal fluid; WBC, white blood cells; CLSI, Clinical and Laboratory Standards Institute; MIC, minimum inhibitory concentration; PSSP, penicillin-susceptible

S. pneumoniae; PISP, penicillin-intermediate *S. pneumoniae*; PRSP, penicillin-resistant *S. pneumoniae*; AMC, amoxicillin and clavulanic acid; SXT, sulfamethoxazole and trimethoprim.

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Disclosure

The authors report no conflicts of interest in this work.

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