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Results from the Survey of Antibiotic Resistance (SOAR) 2009–11 and 2013–14 in China

F. Hu[1,2], D. Zhu[1,2], F. Wang[1,2], I. Morrissey[3], J. Wang[4] and D. Torumkuney[5]*

[1]Institute of Antibiotics, Huashan Hospital, Fudan University, Building No. 6, 12 Middle Urumqi Road, Shanghai, China; [2]Key Laboratory of Clinical Pharmacology of Antibiotics, Ministry of Health, Building No. 6, 12 Middle Urumqi Road, Shanghai, China; [3]IHMA Europe Sàrl, 9A route de la Corniche, Epalinges 1066, Switzerland; [4]GlaxoSmithKline, The Headquarters Building, No. 168 Middle Tibet Road, Shanghai 200001, China; [5]GlaxoSmithKline, 980 Great West Road, Brentford, Middlesex TW8 9GS, UK

*Corresponding author. Tel: +44-20-8047-1671; Email: didem.x.torumkuney@gsk.com

Objectives: To compare antibiotic susceptibility of community-acquired respiratory bacteria in China during 2009–11 and 2013–14.

Methods: Susceptibility was determined by Etest® (bioMérieux) or disc diffusion according to CLSI, EUCAST and pharmacokinetic/pharmacodynamic (PK/PD) breakpoints, except for azithromycin where Etest® breakpoints (in CO_2 incubation) were used in place of standard CLSI breakpoints. Statistical significance of differences in susceptibility across time periods was evaluated using Fisher's exact test.

Results: During 2009–11, 434 *Streptococcus pneumoniae*, 307 *Haemophilus influenzae* and 140 *Moraxella catarrhalis* were collected from eight centres and during 2013–14, 208 *S. pneumoniae*, 185 *H. influenzae* and 80 *M. catarrhalis* were collected from five centres. Penicillin-non-susceptible isolates remained stable at ∼66% over both time periods but susceptibility decreased significantly for amoxicillin/clavulanic acid (or amoxicillin) and cefaclor. For *H. influenzae*, the proportion of β-lactamase-positive isolates and β-lactamase-negative ampicillin-resistant strains (CLSI definition) was higher in 2013–14 (25.4% and 7.0%, respectively) than in 2009–11 (16.3% and 3.6%, respectively), with decreased ampicillin and cephalosporin susceptibility. By 2009–11 and 2013–14, only amoxicillin/clavulanic acid (amoxicillin), levofloxacin, penicillin (intravenously) and chloramphenicol inhibited >70% of *S. pneumoniae*. During 2013–14, *M. catarrhalis* showed increasing resistance, with cefaclor and levofloxacin susceptibility decreasing significantly. However, amoxicillin/clavulanic acid, cefuroxime and levofloxacin continued to inhibit >90% of isolates.

Conclusions: On the whole, antimicrobial susceptibility decreased in China between 2009–11 and 2013–14. In 2013–14, amoxicillin/clavulanic acid, levofloxacin and chloramphenicol were the most active antibacterial agents tested against community-acquired respiratory pathogens when assessed by CLSI, EUCAST or PK/PD breakpoints. Resistance to other antibacterials in China was generally high. Our data demonstrate the need to harmonize breakpoints for these pathogens.

Introduction

Community-acquired pneumonia (CAP) and other lower respiratory tract infections are the second most frequent cause of all-age premature deaths.[1] *Streptococcus pneumoniae* and *Haemophilus influenzae* are the most common bacterial species associated with CAP. A smaller percentage of *Moraxella catarrhalis* isolates are recovered from patients with this disease. These pathogens are recovered from patients of all age groups but remain a serious threat to young children, the elderly and those with an immunocompromised status. Managing patients with CAP requires risk-scoring systems and reliable and effective empirical therapy due to the rapid progression of this disease.[2,3] While advances have been made in determining patients at highest risk of developing progressive disease, antimicrobial resistance among common CAP pathogens has been increasing. Empirical treatment options include β-lactams, macrolides and fluoroquinolones. However, resistance to each of these agents is now common, or increasing, among CAP pathogens collected in most areas of the world and treatment failures have been reported using standard-of-care therapies.[3–7]

Resistance surveillance programmes are important in that detection of regional variations can be observed, giving care providers knowledge of bacterial resistance rates in their environments. One such study is the ongoing Survey of Antibiotic Resistance (SOAR), which is an antimicrobial resistance surveillance study of key respiratory pathogens conducted in the Middle East, Africa, Latin America, Asia-Pacific and Commonwealth of Independent States countries and has been running since 2002. Here, we report recent data from SOAR for three major respiratory tract pathogens collected from hospital sites in China.

Materials and methods

Collaborating centres

The following eight centres took part in the study in 2009–11: Beijing Hospital, Zhejiang Provincial College of Medicine, Jiangxi Provincial People's Hospital, Peking Union Medical College Hospital, Shanghai Children's Hospital, Shanghai Huashan Hospital, Shanghai Ruijin Hospital and Tongji Hospital. Five centres participated in 2013–14: Beijing Hospital, Jiangxi Provincial People's Hospital, Peking Union Medical College Hospital, Shanghai Children's Hospital and Shanghai Huashan Hospital.

Clinical isolates

During 2009–11, a total of 434 isolates of *S. pneumoniae*, 307 isolates of *H. influenzae* and 140 isolates of *M. catarrhalis* were collected and during 2013–14, a total of 208 isolates of *S. pneumoniae*, 185 isolates of *H. influenzae* and 80 isolates of *M. catarrhalis* were collected (all isolates were from community-acquired infections and provided by a university hospital). In 2009–11, paediatric patients (≤12 years old) accounted for 240 isolates (27.2%), adult patients (13–64 years old) for 405 (46.0%) and the elderly (≥65 years) for 227 isolates (25.8%). A small number (nine isolates, 1.0%) were from patients whose age was not provided. In 2013–14, the collection comprised 248 isolates from paediatric patients (52.4%), 136 from adult patients (28.8%) and 89 isolates from the elderly (18.8%). Pathogens were obtained from a variety of specimen types including sputum, bronchoalveolar lavage, bronchial brush and blood. Organisms were identified using conventional methods (optochin susceptibility/bile solubility for *S. pneumoniae* and X and V factor requirement for *H. influenzae*). Duplicate isolates from the same patient were not accepted.

Susceptibility testing

MICs were determined using the Etest® susceptibility method according to the manufacturer's instructions (bioMérieux, Marcy l'Etoile, France). Disc diffusion susceptibility testing was carried out according to CLSI methodology.[8] Study drugs for *H. influenzae* evaluated by Etest® included amoxicillin/clavulanic acid, ampicillin, ampicillin/sulbactam, azithromycin, cefaclor, cefuroxime and levofloxacin. Trimethoprim/sulfamethoxazole, tetracycline and chloramphenicol were evaluated by disc diffusion. Study drugs for *S. pneumoniae* evaluated by Etest® included penicillin, amoxicillin/clavulanic acid, cefaclor, cefuroxime and levofloxacin. Erythromycin, clindamycin, trimethoprim/sulfamethoxazole, tetracycline and chloramphenicol were evaluated by disc diffusion. For *M. catarrhalis*, study drugs included amoxicillin/clavulanic acid, azithromycin, cefaclor, cefuroxime and levofloxacin and all were evaluated by Etest®. β-Lactamase production was determined for each *H. influenzae* and *M. catarrhalis* isolate using chromogenic cephalosporin (nitrocefin) discs according to the manufacturer's instructions (BD Diagnostics, Sparks, MD, USA) using *E. coli* ATCC 35218 and *H. influenzae* ATCC 49247 as the positive and negative controls, respectively. Quality control strains *S. pneumoniae* ATCC 49619, *H. influenzae* ATCC 49247, *H. influenzae* ATCC 49766, *Escherichia coli* ATCC 25922 and *E. coli* ATCC 32518 were included on each day of testing. Results of susceptibility testing were accepted if the results of the control strains were within published limits. Susceptibility to the study drugs was calculated based on CLSI breakpoints,[9,10] except for azithromycin where bioMérieux Etest® breakpoints for incubation in CO_2 were used. In addition, susceptibility based on EUCAST and pharmacokinetic/pharmacodynamic (PK/PD) breakpoints was analysed where applicable[11,12] to assess if adoption of these breakpoints would affect susceptibility. EUCAST and PK/PD breakpoints were not evaluated for azithromycin because, unlike CLSI, these are not adjusted for incubation in CO_2 by Etest®. The MIC breakpoints used are shown in Table 1 and the disc diffusion zone diameter breakpoints are shown in Table 2.

Statistical analysis

Differences in susceptibility between time periods were assessed with Fisher's exact test, using XLSTAT version 2015.2.02. A P value <0.05 was considered statistically significant. For this analysis only, the five sites that participated in both time periods were included.

Table 1. MIC breakpoints (mg/L) used for *S. pneumoniae*, *H. influenzae* and *M. catarrhalis* isolates

	S. pneumoniae						*H. influenzae*						*M. catarrhalis*						
	CLSI			EUCAST			CLSI			EUCAST			CLSI			EUCAST			PK/PD
Antimicrobial agent	S	I	R	S	I	R	S	I	R	S	I	R	S	I	R	S	I	R	(S only)
AMC[a]	≤2	4	≥8	NA	NA	NA	≤4	—	≥8	≤2	—	≥4	≤4	—	≥8	≤1	—	≥2	≤2 (≤4)
Ampicillin	NT	NT	NT	NT	NT	NT	≤1	2	≥4	≤1	—	≥2	NT	NT	NT	NT	NT	NT	NA
Ampicillin/sulbactam	NT	NT	NT	NT	NT	NT	≤2	—	≥4	≤1	—	≥2	NT	NT	NT	NT	NT	NT	NA
Azithromycin[b]	NT	NT	NT	NT	NT	NT	≤8	—	—	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Cefaclor	≤1	2	≥4	≤0.03	0.06–0.5	≥1	≤8	16	≥32	NA	NA	NA	≤8	16	≥32	NA	NA	NA	≤0.5
Cefuroxime[c]	≤1	2	≥4	≤0.25	0.5	≥1	≤4	8	≥16	≤0.12	0.25–1	≥2	≤4	8	≥16	≤0.12	0.25–4	≥8	≤1
Levofloxacin	≤2	4	≥8	≤2	—	≥4	≤2	—	—	≤1	—	≥2	≤2	—	—	≤1	—	≥2	≤2
Penicillin (oral)	≤0.06	0.12–1	≥2	≤0.06	0.12–2	≥4	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NA
Penicillin (iv)[d]	≤2	4	≥8	[e]	NA	NA	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NT	NA

AMC, amoxicillin/clavulanic acid; S, susceptible; I, intermediate; R, resistant; NT, not tested; NA, not applicable.
[a]Amoxicillin/clavulanic acid was tested at a 2:1 amoxicillin/clavulanic acid ratio; breakpoints are expressed as the amoxicillin component. PK/PD breakpoint based on high dose (4 g of amoxicillin with 250 mg of clavulanic acid per day for adults) is shown in parentheses.[4]
[b]bioMérieux Etest® breakpoints for incubation in CO_2.
[c]Breakpoints used are for cefuroxime axetil.
[d]Parenteral non-meningitis breakpoints.
[e]EUCAST give iv susceptible breakpoints for pneumonia based on three doses: 1.2 g×4 (MIC ≤0.5 mg/L=susceptible), 1.2 g×6 or 2.4 g×4 (MIC ≤1 mg/L=susceptible) and 2.4 g×6 (MIC ≤2 mg/L=susceptible).

Table 2. Zone diameter breakpoints (mm) used for *S. pneumoniae* and *H. influenzae* isolates

	S. pneumoniae						*H. influenzae*					
	CLSI			EUCAST			CLSI			EUCAST		
Antimicrobial agent	R	I	S	R	I	S	R	I	S	R	I	S
Chloramphenicol	≤20	—	≥21	≤20	—	≥21	≤25	26–28	≥29	≤27	—	≥28
Clindamycin	≤15	16–18	≥19	≤18	—	≥19	NT	NT	NT	NT	NT	NT
Erythromycin	≤15	16–20	≥21	≤18	19–21	≥22	NT	NT	NT	NT	NT	NT
Tetracycline	≤24	25–27	≥28	≤21	22–24	≥25	≤25	26–28	≥29	≤21	22–24	≥25
SXT	≤15	16–18	≥19	≤14	15–17	≥18	≤10	11–15	≥16	≤19	20–22	≥23

SXT, trimethoprim/sulfamethoxazole; NT, not tested.

Results

S. pneumoniae

A total of 434 *S. pneumoniae* were collected in China from 2009 to 2011. Nearly all of the pneumococci were collected from sputum cultures ($n=421$, 97.0%). Comparing age groups, 139 isolates (32.0%) were collected from paediatric patients (aged ≤12 years old), 107 (24.7%) were from elderly patients (aged ≥65 years old) and 181 (41.7%) were from adults (aged 13–64 years old). Seven isolates were collected from patients whose age was unknown. In 2013–14, 208 *S. pneumoniae* isolates were collected, with 188 (90.4%) isolates from sputum, 12 (5.8%) isolates from blood and 8 (3.8%) from bronchoalveolar lavage. Paediatric patients accounted for 86 (41.3%) isolates, adult patients for 73 (35.1%) isolates and the elderly for 49 (23.6%) isolates. Summary MIC and susceptibility data for all *S. pneumoniae* are shown in Table 3. MIC distribution data are given in Table 4.

In 2009–11, using CLSI oral or EUCAST breakpoints (these being identical), only 36.2% of the pneumococci were penicillin susceptible. However, due to differing intermediate and resistant breakpoints, 35.5% were penicillin intermediate and 28.3% penicillin resistant by CLSI oral breakpoints and 53.9% penicillin intermediate and 9.9% penicillin resistant by EUCAST. Using the CLSI intravenous (iv) (non-meningitis) breakpoints, 90.1% of isolates were susceptible to penicillin. These susceptibility level results decreased slightly in 2013–14, with 32.2% of isolates susceptible using the CLSI oral/EUCAST breakpoints and 83.7% susceptible at the CLSI iv breakpoint (Table 3).

Using CLSI or low-dose PK/PD breakpoints, susceptibility to amoxicillin/clavulanic acid (and by inference amoxicillin) was 89.2% but using the high-dose PK/PD breakpoint, 95.2% of pneumococci were susceptible in 2009–11. Apart from high levofloxacin susceptibility (97.5% by all breakpoints) and high chloramphenicol susceptibility (85.9% by CLSI/EUCAST criteria), the other tested antimicrobials exhibited low activity (≤44%) against pneumococci. In 2013–14, amoxicillin/clavulanic acid (amoxicillin) susceptibility decreased to 75.0% by CLSI and low-dose PK/PD breakpoints and to 88.5% using the high-dose PK/PD breakpoint. Levofloxacin and chloramphenicol susceptibility was more stable and actually increased slightly to 99.0% and 90.9% susceptible, respectively. As in 2009–11, susceptibility levels for all other antimicrobials were low (<44%) in 2013–14 (Table 3).

CLSI guidelines indicate that isolates susceptible to penicillin G (MIC ≤0.06 mg/L) can be reported as susceptible to amoxicillin/clavulanic acid, ceftriaxone, cefaclor, cefepime, cefpodoxime and cefuroxime. Data from this study (both periods combined) confirmed this, as in most cases penicillin-susceptible *S. pneumoniae* ($n=224$) were also susceptible to the β-lactams listed above. The exception was with cefaclor, where 20 penicillin-susceptible isolates were intermediate to cefaclor and 4 were cefaclor resistant. However, the reverse was not always found. Of the 418 penicillin-non-susceptible isolates, 319 (76.3%) were amoxicillin/clavulanic acid susceptible and 58 (13.9%) were cefuroxime susceptible. Only a small number of penicillin-non-susceptible isolates ($n=22$, 5.3%) were cefaclor susceptible. A similar 'expert rule' is provided by EUCAST but for penicillins only, i.e. amoxicillin/clavulanic acid (amoxicillin) in this study. However, unlike by CLSI, individual breakpoints are not provided by EUCAST for amoxicillin/clavulanic acid to make this comparison.

H. influenzae

A total of 307 *H. influenzae* were collected in China from 2009 to 2011. These isolates were obtained mostly from patient sputum cultures ($n=294$, 95.8%). Isolates of *H. influenzae* came from paediatric patients ($n=72$, 23.5%), the elderly ($n=84$, 27.4%) and adults ($n=151$, 49.2%). In 2013–14, 185 *H. influenzae* isolates were collected; all but 3 isolates were from sputum (98.4%). The majority of isolates ($n=113$, 61.1%) were from paediatric patients, 47 (25.4%) came from adults and 25 (13.5%) from the elderly.

In 2009–11, 16.3% (50/307) were β-lactamase positive and 83.7% (257/307) were β-lactamase negative, of which 11 (3.6% of all *H. influenzae*) were β-lactamase negative, ampicillin resistant (BLNAR) by the CLSI definition (ampicillin MIC ≥4 mg/L) and 40 (13.0% of all *H. influenzae*) by the EUCAST definition (ampicillin MIC ≥2 mg/L). In 2013–14, the percentage of β-lactamase-positive isolates was higher at 25.4% (47/185) and by CLSI and EUCAST definitions 13 (7.0%) and 31 (16.8%) BLNAR isolates were found, respectively. For analysis, the BLNAR were included within the β-lactamase-negative population.

Summary MIC and susceptibility data and MIC distributions for all *H. influenzae* isolates are shown in Tables 5 and 6, respectively.

In 2009–11, *in vitro* susceptibility to amoxicillin/clavulanic acid was high at 98.4% for all *H. influenzae* by CLSI breakpoints and by high-dose PK/PD breakpoints (Table 5). However, CLSI guidelines state that all BLNAR should be considered non-susceptible to amoxicillin/clavulanic acid, thereby reducing clinical susceptibility to 97.4%. Similarly, BLNAR corrections have been made for

Table 3. MIC and susceptibility data for *S. pneumoniae* isolates collected during 2009–11 and 2013–14

						Susceptibility						
		MIC (mg/L)				CLSI			PK/PD	EUCAST		
Years/antimicrobial agent	*N*	50%	90%	min.	max.	%S	%I	%R	%S	%S	%I	%R
2009–11												
AMC[a,b]	434	1	4	≤0.015	128	89.2	6.0	4.8	89.2 (95.2)	NA	NA	NA
cefaclor	434	16	>256	0.12	>256	40.3	2.1	57.6	35.3	0.0	35.3	64.7
cefuroxime[c]	434	2	16	≤0.015	>256	44.2	9.9	45.9	44.2	41.2	3.7	58.8
levofloxacin	434	1	1	0.12	>32	97.5	0.2	2.3	97.5	97.5	—	2.5
penicillin (oral)	434	1	2	≤0.015	32	36.2	35.5	28.3	NA	36.2	53.9	9.9
penicillin (iv)	434	1	2	≤0.015	32	90.1	6.5	3.4	NA	49.1–90.1	NA	NA
chloramphenicol[d]	434	NA	NA	NA	NA	85.9	0.0	14.1	NA	85.9	0.0	14.1
clindamycin[d]	434	NA	NA	NA	NA	9.2	0.5	90.3	NA	9.2	0.0	90.8
erythromycin[d]	434	NA	NA	NA	NA	7.8	0.7	91.5	NA	7.8	0.2	91.9
tetracycline[d]	434	NA	NA	NA	NA	6.0	3.2	90.8	NA	9.2	4.2	86.6
SXT[d]	434	NA	NA	NA	NA	24.2	5.3	70.5	NA	27.0	3.0	70.1
2013–14												
AMC[a,b]	208	1	8	≤0.015	64	75.0	13.5	11.5	75.0 (88.5)	NA	NA	NA
cefaclor	208	>256	>256	0.25	>256	22.6	13.0	64.4	7.7	0.0	7.7	92.3
cefuroxime[c]	208	2	32	≤0.015	>256	43.3	10.5	46.2	43.3	36.5	4.8	58.7
levofloxacin	208	1	2	0.25	>32	99.0	0.0	1.0	99.0	99.0	—	1.0
penicillin (oral)	208	1	4	≤0.015	32	32.2	33.2	34.6	NA	32.2	51.5	16.3
penicillin (iv)	208	1	4	≤0.015	32	83.7	13.4	2.9	NA	49.5–83.7	NA	NA
chloramphenicol[d]	208	NA	NA	NA	NA	90.9	0.0	9.1	NA	90.9	0.0	9.1
clindamycin[d]	208	NA	NA	NA	NA	6.2	0.5	93.3	NA	6.2	0.0	93.8
erythromycin[d]	208	NA	NA	NA	NA	4.3	1.9	93.8	NA	4.3	1.0	94.7
tetracycline[d]	208	NA	NA	NA	NA	0.0	0.0	100	NA	0.0	6.2	93.8
SXT[d]	208	NA	NA	NA	NA	26.4	4.3	69.2	NA	28.4	2.4	69.2

AMC, amoxicillin/clavulanic acid; NA, no breakpoint data available; SXT, trimethoprim/sulfamethoxazole.
[a]AMC, amoxicillin/clavulanic acid PK/PD susceptibility at high dose is shown in parentheses.
[b]Susceptibility for amoxicillin alone can be inferred from amoxicillin/clavulanic acid.
[c]Breakpoints used are for cefuroxime axetil.
[d]CLSI disc diffusion testing method used.

Table 4. MIC distribution data for *S. pneumoniae* isolates collected during 2009–11 and 2013–14

		Number of isolates at MIC (mg/L)														
Years/antimicrobial agent	*N*	≤0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	≥256
2009–11																
AMC	434	111	37	13	8	15	22	92	89	26	12	7	0	0	2	0
cefaclor	434	0	0	0	1	15	137	22	9	11	8	18	62	66	24	61
cefuroxime	434	21	36	37	32	37	16	13	43	78	57	32	16	11	0	5
levofloxacin	434	0	0	0	1	4	97	297	24	1	0	0	2	0	0	0
penicillin	434	87	50	20	17	12	27	98	80	28	10	4	1	0	0	0
2013–14																
AMC	208	31	30	12	3	11	9	33	27	28	16	6	1	1	0	0
cefaclor	208	0	0	0	0	1	15	31	27	5	3	3	4	2	3	114
cefuroxime	208	11	30	11	8	16	10	4	22	30	22	15	15	12	0	2
levofloxacin	208	0	0	0	0	3	62	121	20	0	0	0	2	0	0	0
penicillin	208	31	22	14	9	8	19	33	38	28	4	1	1	0	0	0

AMC, amoxicillin/clavulanic acid.

Table 5. MIC and susceptibility data for *H. influenzae* isolates collected during 2009–11 and 2013–14

			MIC (mg/L)				Susceptibility						
							CLSI			PK/PD	EUCAST		
Years/antimicrobial agent	Isolate group	*N*	50%	90%	min.	max.	%S	%I	%R	%S	%S	%I	%R
2009–11													
AMC[a,b]	all	307	1	2	0.06	512	98.4 (97.4)[c]	—	1.6 (2.6)[c]	93.5 (98.4)	93.5 (85.0)[c]	—	6.5 (15.0)[c]
	BL−	257	0.5	2	0.06	8	98.8	—	1.2	94.2 (98.8)	94.2	—	5.8
	BL+	50	1	2	0.12	512	96.0	—	4.0	90.0 (96.0)	90.0	—	10.0
ampicillin[d]	all	307	0.5	64	0.06	>256	71.3	9.5	19.2	NA	71.3	—	28.7
	BL−	257	0.5	2	0.06	>256	84.4	11.3	4.3	NA	84.4	—	15.6
	BL+	50	64	>256	0.5	>256	4.0	0.0	96.0	NA	4.0	—	96.0
azithromycin[e]	all	104	2	4	≤0.015	>256	91.4	—	—	NA	NA	NA	NA
	BL−	85	4	4	≤0.015	8	92.9	—	—	NA	NA	NA	NA
	BL+	19	2	>256	≤0.015	>256	84.2	—	—	NA	NA	NA	NA
cefaclor[b]	all	307	2	32	0.25	>256	78.5 (77.5)[c]	7.8 (7.2)[c]	13.7 (15.3)[c]	2.0	NA	NA	NA
	BL−	257	2	32	0.25	>256	79.4	7.8	12.8	2.3	NA	NA	NA
	BL+	50	4	32	1	>256	74.0	8.0	18.0	0.0	NA	NA	NA
cefuroxime[b,f]	all	307	1	4	0.06	64	94.8 (92.8)[c]	2.9 (2.0)[c]	2.3 (5.2)[c]	65.5	1.0 (1.0)[c]	64.5 (62.9)[c]	34.5 (36.2)[c]
	BL−	257	1	4	0.06	64	94.6	3.1	2.3	66.9	1.2	65.8	33.1
	BL+	50	1	4	0.25	32	96.0	2.0	2.0	58.0	0.0	58.0	42.0
levofloxacin	all	307	0.06	4	0.008	>32	78.2			78.2	71.7	—	28.3
	BL−	257	0.06	4	0.008	>32	79.8	—	20.2	79.8	72.4	—	27.6
	BL+	50	0.03	8	0.008	>32	70.0	0	30	70.0	68.0	—	32.0
chloramphenicol[g]	all	307	NA	NA	NA	NA	90.6	1.3	8.1	NA	91.5	—	8.5
	BL−	257	NA	NA	NA	NA	96.1	1.2	2.7	NA	96.9	—	3.1
	BL+	50	NA	NA	NA	NA	62.0	2.0	36.0	NA	64.0	—	36.0
tetracycline[g]	all	292	NA	NA	NA	NA	74.3	9.9	15.8	NA	85.3	2.7	12.0
	BL−	242	NA	NA	NA	NA	79.8	10.3	9.9	NA	90.9	2.5	6.6
	BL+	50	NA	NA	NA	NA	48.0	8.0	44.0	NA	58.0	4.0	38.0
SXT[g]	all	307	NA	NA	NA	NA	41.0	2.6	56.4	NA	34.2	4.6	61.2
	BL−	257	NA	NA	NA	NA	46.3	3.1	50.6	NA	38.5	5.1	56.4
	BL+	50	NA	NA	NA	NA	14.0	0.0	86.0	NA	12.0	2.0	86.0
2013–14													
AMC[a,b]	all	185	1	4	0.12	16	95.7 (89.1)[c]	—	4.3 (10.9)[c]	78.4 (95.7)	78.4 (73.0)[c]	—	21.6 (27.0)[c]
	BL−	138	1	2	0.12	8	97.8	—	2.2	81.9 (97.8)	81.9	—	18.1
	BL+	47	2	8	0.5	16	89.4	—	10.6	68.1 (89.4)	68.1	—	31.9
ampicillin[d]	all	185	1	>256	0.12	>256	58.4	9.7	31.9	NA	58.4	—	41.6
	BL−	138	1	2	0.12	>256	77.5	13.1	9.4	NA	77.5	—	22.5
	BL+	47	256	>256	1	>256	2.1	0.0	97.9	NA	2.1	—	97.9
ampicillin/sulbactam[b]	all	97	1	4	0.12	8	86.6 (80.4)[c]	—	13.4 (19.6)[c]	NA	63.9 (58.9)[c]	—	36.1 (41.1)[c]
	BL−	73	1	2	0.12	8	93.2	—	6.8	NA	82.2	—	17.8
	BL+	24	2	8	0.25	8	66.7	—	33.3	NA	8.3	—	91.7

Continued

Table 5. *Continued*

			MIC (mg/L)				Susceptibility						
							CLSI			PK/PD	EUCAST		
Years/antimicrobial agent	Isolate group	*N*	50%	90%	min.	max.	%S	%I	%R	%S	%S	%I	%R
azithromycin[e]	all	185	2	16	≤0.015	>256	89.7	—	—	NA	NA	NA	NA
	BL−	138	2	4	≤0.015	>256	97.8	—	—	NA	NA	NA	NA
	BL+	47	4	>256	≤0.015	>256	66.0	—	—	NA	NA	NA	NA
cefaclor[b]	all	185	16	>256	1	>256	49.2 (47.6)[c]	13.0 (13.0)[c]	37.8 (39.5)[c]	0.0	NA	NA	NA
	BL−	138	8	>256	1	>256	52.9	10.9	36.2	0.0	NA	NA	NA
	BL+	47	16	>256	1	>256	38.3	19.2	42.5	0.0	NA	NA	NA
cefuroxime[b,f]	all	185	2	32	0.25	>256	75.1 (73.0)[c]	7.1 (7.0)[c]	17.8 (20.0)[c]	43.8	0.0 (0.0)[c]	43.8 (42.2)[c]	56.2 (57.8)[c]
	BL−	138	2	32	0.25	>256	76.8	7.3	15.9	46.4	0.0	46.4	53.6
	BL+	47	2	64	0.25	>256	70.2	6.4	23.4	36.2	0.0	36.2	63.8
levofloxacin	all	185	0.015	4	0.008	>32	89.2	—	—	89.2	82.7	—	17.3
	BL−	138	0.015	2	0.008	8	90.6	—	—	90.6	83.3	—	16.7
	BL+	47	0.03	4	0.008	>32	85.1	—	—	85.1	80.9	—	19.2
chloramphenicol[g]	all	185	NA	NA	NA	NA	91.4	2.1	6.5	NA	91.9	—	8.1
	BL−	138	NA	NA	NA	NA	96.4	1.4	2.2	NA	97.1	—	2.9
	BL+	47	NA	NA	NA	NA	76.6	4.3	19.1	NA	76.6	—	23.4
tetracycline[g]	all	185	NA	NA	NA	NA	86.5	3.8	9.7	NA	90.3	1.6	8.1
	BL−	138	NA	NA	NA	NA	92.0	2.9	5.1	NA	94.9	0.0	5.1
	BL+	47	NA	NA	NA	NA	70.2	6.4	23.4	NA	76.6	6.4	17.0
SXT[g]	all	185	NA	NA	NA	NA	41.1	3.2	55.7	NA	38.9	1.6	59.5
	BL−	138	NA	NA	NA	NA	45.7	2.9	51.4	NA	42.8	2.1	55.1
	BL+	47	NA	NA	NA	NA	27.7	4.2	68.1	NA	27.7	0.0	72.3

NA, no breakpoint data available; BL−, β-lactamase negative; BL+, β-lactamase positive; AMC, amoxicillin/clavulanic acid; SXT, trimethoprim/sulfamethoxazole.
[a]Amoxicillin/clavulanic acid PK/PD susceptibility at high dose is shown in parentheses.
[b]In the clinical setting, isolates of BLNAR are considered resistant to amoxicillin/clavulanic acid, ampicillin/sulbactam, cefaclor and cefuroxime (see main text).
[c]Clinical susceptibility to amoxicillin/clavulanic acid ampicillin/sulbactam, cefaclor and cefuroxime reduced (data in parentheses) due to corrections according to BLNAR (see main text).
[d]In clinical setting, all β-lactamase-positive *H. influenzae* should be considered resistant.
[e]bioMérieux Etest® breakpoints for incubation in CO_2.
[f]Breakpoints used are for cefuroxime axetil.
[g]CLSI disc diffusion testing method used.

Table 6. MIC distribution data for *H. influenzae* isolates collected during 2009–11 and 2013–14

Years/antimicrobial agent	*N*	Number of isolates at MIC (mg/L)														
		≤0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	≥256
2009–11																
AMC	307	0	0	2	5	30	108	101	41	15	3	1	0	0	0	1
ampicillin	307	0	0	2	8	48	98	63	29	7	4	7	8	7	1	25
azithromycin	104	7	0	0	0	0	6	8	32	42	6	0	0	0	0	3
cefaclor	307	0	0	0	0	2	4	29	125	54	27	24	20	4	8	10
cefuroxime	307	0	0	1	2	19	59	120	57	33	9	2	3	2	0	0
levofloxacin	307	100	46	15	23	10	9	17	20	49	10	2	6	0	0	0
2013–14																
AMC	185	0	0	0	4	4	40	49	48	32	5	3	0	0	0	0
ampicillin	185	0	0	0	4	27	34	43	18	10	8	8	4	1	3	25
ampicillin/sulbactam	97	0	0	0	5	12	20	25	22	9	4	0	0	0	0	0
azithromycin	185	20	1	0	6	1	3	10	65	55	5	1	0	4	4	10
cefaclor	185	0	0	0	0	0	0	4	32	31	24	24	16	18	9	27
cefuroxime	185	0	0	0	0	8	31	42	32	26	13	11	7	6	1	8
levofloxacin	185	105	11	2	20	1	7	7	12	16	1	0	3	0	0	0

AMC, amoxicillin/clavulanic acid.

susceptibility to cefaclor and cefuroxime (Table 5). Using EUCAST and low-dose PK/PD breakpoints, *in vitro* susceptibility to amoxicillin/clavulanic acid was reduced slightly to 93.5%. With a similar BLNAR correction, susceptibility is reduced to 85%. In 2013–14, *in vitro* susceptibility to amoxicillin/clavulanic acid remained high (95.7%) using CLSI/high-dose PK/PD breakpoints (89.1% with BLNAR correction), but decreased to 78.4% (73.0% with BLNAR correction) by EUCAST/low-dose PK/PD criteria. Interestingly, susceptibility to ampicillin/sulbactam (2013–14 only) was lower than that seen with amoxicillin/clavulanic acid. High *in vitro* susceptibility (94.8%) was observed in 2009–11 for cefuroxime by CLSI breakpoints (92.8% with BLNAR correction). However, with PK/PD and EUCAST breakpoints, susceptibility to cefuroxime was reduced considerably to 65.5% and 1.0%, respectively. By 2013–14, susceptibility to cefuroxime had been reduced to 75.1% (73.0% corrected) using CLSI breakpoints and was even lower by PK/PD (43.8%) and EUCAST (0%) breakpoints. Similarly, cefaclor showed wide variation in susceptibility if different breakpoints are used, with 78.5% (77.5% corrected) of *H. influenzae* susceptible in 2009–11 by CLSI breakpoints, but virtually zero susceptibility using PK/PD breakpoints. EUCAST does not provide breakpoints for cefaclor against *H. influenzae*, but using BLNAR prevalence as a marker, 87.0% appeared susceptible. Again, susceptibility decreased in 2013–14 with only 49.2% (47.6% corrected) of isolates susceptible by CLSI criteria (Table 5).

Using CLSI breakpoints, susceptibility was seen in 91.4% and 90.6% of *H. influenzae* isolates, respectively, in 2009–11. This proved to be relatively stable across time periods with 89.7% and 91.4% susceptible in 2013–14 (Table 5).

By CLSI or EUCAST breakpoints, 71.3% of *H. influenzae* isolates were susceptible to ampicillin in 2009–11 and 58.4% in 2013–14. As would be expected, ampicillin was inactive against the β-lactamase-positive strains. Levofloxacin and tetracycline were active against 78.2% and 74.3% (by CLSI criteria) of *H. influenzae* isolates in 2009–11, but susceptibility levels were higher in 2013–14 (89.2% and 86.5%, respectively). Trimethoprim/sulfamethoxazole was poorly active (41% susceptible) against *H. influenzae* in both time periods using CLSI breakpoints (Table 5).

M. catarrhalis

A total of 140 *M. catarrhalis* were collected in China from 2009 to 2011. These isolates were obtained mostly from patient sputum cultures ($n=138$, 98.6%). Isolates of *M. catarrhalis* came from paediatric patients ($n=29$, 20.7%), the elderly ($n=36$, 25.7%) and adults ($n=73$, 52.1%). Two isolates were collected from patients where age is unknown. In 2013–14, 80 *M. catarrhalis* isolates were collected, all of them from sputum. Paediatric patients accounted for 49 isolates (61.3%), adults for 16 (20.0%) and the elderly for 15 (18.8%). All *M. catarrhalis*, except for three isolates collected in 2009–11, were β-lactamase positive.

Summary MIC and susceptibility data and MIC distributions for *M. catarrhalis* are shown in Tables 7 and 8.

In 2009–11, all isolates were susceptible to amoxicillin/clavulanic acid and levofloxacin using CLSI and PK/PD breakpoint criteria. Levofloxacin susceptibility was reduced to 96.4% when EUCAST breakpoints were applied. In 2013–14, amoxicillin/clavulanic acid susceptibility remained at 100%, but levofloxacin activity had decreased to 91.3% by all three breakpoints. Dramatic differences in susceptibility were observed across breakpoints (but not across time periods) for cefuroxime. Using CLSI breakpoints, susceptibility was 90.0% and 93.8% in 2009–11 and 2013–14, respectively, whereas it was 27.1% and 20.0%, respectively, using PK/PD breakpoints and 0% and 1.3%, respectively, using EUCAST breakpoint criteria. Cefaclor showed similar differences between CLSI and PK/PD breakpoints, but also a decrease in activity over time. In 2009–11, susceptibility was 91.4% by CLSI criteria compared with 1.4% by PK/PD breakpoints, with respective values of 63.8% and 2.5% in 2013–14 (Table 7).

Table 7. MIC and susceptibility data for *M. catarrhalis* isolates collected during 2009–11 and 2013–14

						Susceptibility						
		MIC (mg/L)				CLSI			PK/PD	EUCAST		
Years/antimicrobial agent	*N*	50%	90%	min.	max.	%S	%I	%R	%S	%S	%I	%R
2009–11												
AMC	140	0.25	0.25	0.03	1	100	—	0.0	100 (100)	100	—	0.0
azithromycin	140	0.25	>256	0.03	>256	NA	NA	NA	NA	NA	NA	NA
cefaclor	140	2	8	0.5	32	91.4	4.3	4.3	1.4	NA	NA	NA
cefuroxime[a]	140	2	8	0.5	8	90.0	10.0	0.0	27.1	0.0	90.0	10.0
levofloxacin	140	0.06	0.5	0.03	2	100	—	—	100	96.4	—	3.6
2013–14												
AMC	80	0.25	0.25	0.03	0.5	100	—	0.0	100 (100)	100	—	0.0
azithromycin	80	0.03	0.5	≤0.015	>256	NA	NA	NA	NA	NA	NA	NA
cefaclor	80	4	16	0.25	32	63.8	26.3	10.0	2.5	NA	NA	NA
cefuroxime[a]	80	2	4	0.06	8	93.8	6.3	0.0	20.0	1.3	92.5	6.3
levofloxacin	80	0.06	1	0.015	>32	91.3	—	—	91.3	91.3	—	8.8

AMC, amoxicillin/clavulanic acid; NA, no breakpoint data available.
[a]Breakpoints used are for cefuroxime axetil.

Table 8. MIC distribution data for *M. catarrhalis* isolates collected during 2009–11 and 2013–14

		Number of isolates at MIC (mg/L)													
Years/antimicrobial agent	*N*	≤0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	≥256
2009–11																
AMC	140	0	19	15	25	69	11	1	0	0	0	0	0	0	0	0
azithromycin	140	0	2	4	31	36	23	7	6	2	1	0	0	0	0	28
cefaclor	140	0	0	0	0	0	2	42	66	8	10	6	6	0	0	0
cefuroxime	140	0	0	0	0	0	12	26	48	40	14	0	0	0	0	0
levofloxacin	140	0	27	93	3	1	4	7	5	0	0	0	0	0	0	0
2013–14																
AMC	80	0	3	9	20	41	7	0	0	0	0	0	0	0	0	0
azithromycin	80	9	36	18	6	1	5	1	0	0	1	0	1	0	0	2
cefaclor	80	0	0	0	0	1	1	2	30	14	3	21	8	0	0	0
cefuroxime	80	0	0	1	0	5	5	5	26	33	5	0	0	0	0	0
levofloxacin	80	3	20	36	9	2	1	2	0	0	0	0	7	0	0	0

AMC, amoxicillin/clavulanic acid.

Comparison of susceptibility in 2009–11 versus 2013–14

An analysis was performed comparing antimicrobial susceptibility between 2009–11 and 2013–14, using only the five sites that participated in both time periods. Susceptibility according to CLSI breakpoints by time period is given in Figures 1–3 for *S. pneumoniae*, *H. influenzae* and *M. catarrhalis*, respectively. For *S. pneumoniae*, from 2009–11 to 2013–14, susceptibility decreased significantly to amoxicillin/clavulanic acid (from 88.6% to 75.0%), cefaclor (from 41.3% to 22.6%) and tetracycline (from 6.4% to 0%; all $P < 0.05$). Statistically significant changes were more numerous for *H. influenzae*, where susceptibility to ampicillin (from 71.3% to 58.4%), cefaclor (from 78.5% to 49.2%) and cefuroxime (from 94.8% to 75.1%) decreased significantly, whereas levofloxacin (from 78.2% to 89.2%) and tetracycline (from 74.3% to 86.5%) showed significant increases in activity. For *M. catarrhalis*, cefaclor and levofloxacin showed significant changes, decreasing from 91.4% to 63.8% and from 100% to 91.3%, respectively.

Discussion

The increasing prevalence of antimicrobial resistance among common pulmonary pathogens including *S. pneumoniae* and *H. influenzae* is worrisome. In *S. pneumoniae*, resistance to antibiotics has been a growing problem that has been monitored since penicillin resistance was observed in this species several decades ago. *H. influenzae* and *M. catarrhalis* have been associated

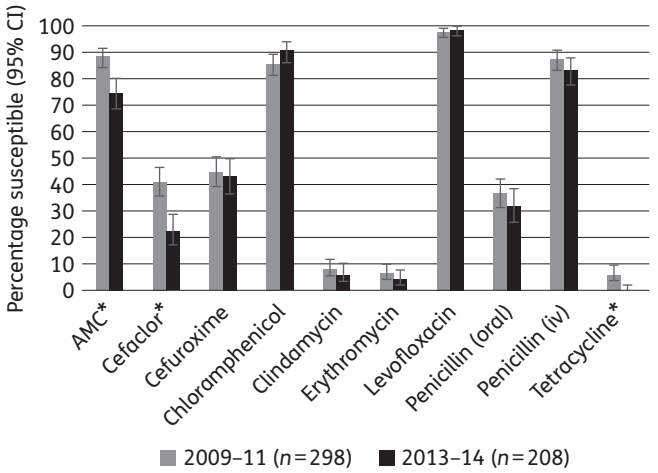

Figure 1. Percentage susceptibility rates (with 95% CI) for antimicrobials against *S. pneumoniae* according to CLSI breakpoints, comparing 2009–11 and 2013–14 using only sites that participated in both time periods. AMC, amoxicillin/clavulanic acid (it can be assumed that amoxicillin activity alone is the same). An asterisk indicates a statistically significant difference between time periods ($P<0.05$).

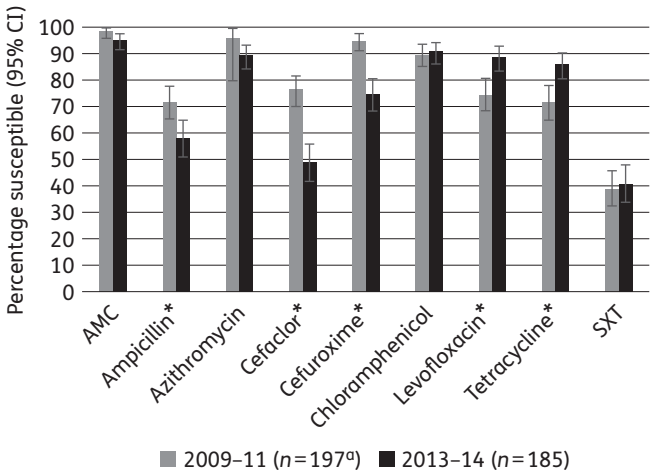

Figure 2. Percentage susceptibility rates (with 95% CI) for antimicrobials against *H. influenzae* according to CLSI breakpoints, comparing 2009–11 and 2013–14 using only sites that participated in both time periods. AMC, amoxicillin/clavulanic acid; SXT, trimethoprim/sulfamethoxazole. An asterisk indicates a statistically significant difference between time periods ($P<0.05$). [a]Sample sizes in 2009–11 were: azithromycin, $n=27$; tetracycline, $n=183$.

with β-lactam resistance due to production of β-lactamase enzymes. β-Lactamase production can be quite variable among *H. influenzae*, but is usually ≥90% among *M. catarrhalis* isolates. Unfortunately, contemporary isolates of both of these species are now becoming resistant to agents other than β-lactams. Macrolide and fluoroquinolone resistance is becoming a growing concern.

Data from this current China SOAR study report highlight numerous important features with respect to a countrywide contemporary surveillance over two distinct time periods. For *S. pneumoniae*, based on CLSI oral and standard EUCAST penicillin

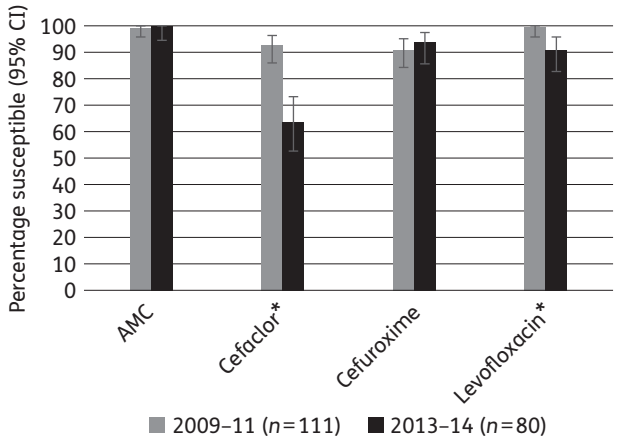

Figure 3. Percentage susceptibility rates (with 95% CI) for antimicrobials against *M. catarrhalis* according to CLSI breakpoints, comparing 2009–11 and 2013–14 using only sites that participated in both time periods. AMC, amoxicillin/clavulanic acid. An asterisk indicates a statistically significant difference between time periods ($P<0.05$).

breakpoints, activity of penicillin was quite stable but about two-thirds of pneumococci were penicillin non-susceptible during both time periods. However, using the CLSI iv penicillin breakpoints, about 84% may be considered to be susceptible to penicillin. Higher-dose amoxicillin/clavulanic acid (amoxicillin) increased susceptibility when the PK/PD breakpoint was applied. Therefore, the use of relevant breakpoints and dosing of penicillin and amoxicillin/clavulanic acid (amoxicillin alone as would be expected to have identical activity) are important factors to consider when assessing appropriate antimicrobial use. Other β-lactams (cefaclor and cefuroxime) were less active (<44% susceptible in 2013–14) than amoxicillin/clavulanic acid (amoxicillin) or penicillin iv as determined by any breakpoint method. Other classes of antimicrobial, including macrolides, were also poorly active. The exceptions to this were levofloxacin and chloramphenicol. By 2013–14, only amoxicillin/clavulanic acid (by PK/PD high-dose breakpoint amoxicillin alone as would be expected to have identical activity), levofloxacin and chloramphenicol showed ∼90% or higher susceptibility rates in *S. pneumoniae* from China.

The data from this study confirm that isolates of *S. pneumoniae* susceptible to penicillin G are also susceptible to other penicillins as inferred by CLSI and EUCAST guidelines and to cephalosporins as inferred by CLSI guidelines. Interestingly, the data from this study found the reverse was not always correct using CLSI breakpoints, i.e. most penicillin-non-susceptible *S. pneumoniae* were susceptible to amoxicillin/clavulanic acid (amoxicillin). This warrants further investigation.

For *H. influenzae*, both the proportion of β-lactamase-positive isolates and the proportion of BLNAR strains were higher in 2013–14 than in 2009–11. As a result, susceptibility was lower for ampicillin and the cephalosporins, a finding confirmed in the direct comparison of isolates from the five sites that participated during both time periods. Interestingly, susceptibility to levofloxacin and tetracycline appeared to increase over the same time period. However, by 2013–14, only amoxicillin/clavulanic acid, azithromycin, levofloxacin and chloramphenicol inhibited ∼90% or more of *H. influenzae* isolates using CLSI breakpoints.

M. catarrhalis also showed increasing resistance over time, with cefaclor and levofloxacin susceptibility decreasing significantly. However, three of the four agents with available breakpoints continued to inhibit >90% of isolates: amoxicillin/clavulanic acid, cefuroxime and levofloxacin.

This study demonstrated the differences observed when comparing the susceptibility of respiratory tract pathogens using CLSI, EUCAST and PK/PD breakpoints. For example, cefaclor and cefuroxime breakpoint differences had a dramatic effect on percentage susceptibility. It is important to understand these breakpoint differences as some non-European laboratories may utilize EUCAST breakpoints for determining susceptibility or, alternatively, laboratories currently using CLSI breakpoints may consider changing to EUCAST breakpoints. A concerted effort should be made to better align these different breakpoints to avoid confusion among clinicians and to allow for better comparison of surveillance data across geographical regions and over time.

Several studies have also documented high antibiotic resistance among CAP pathogens in China. In 2011, Jones *et al.*[13] reported pneumococcal resistance to ceftriaxone at an alarming 35.1% in China. Another study group found <50% penicillin susceptibility in six cities located in China during 2009–10.[14] In a further study from China over the same time period, significant regional differences in antimicrobial susceptibilities were observed including penicillin-non-susceptibility rates ranging from 46% to 100% and macrolide resistance ranging from 0% to 88%.[15] Although the high prevalence of antibiotic resistance could be due to overuse of antibiotics and their availability without prescription in China, the antimicrobial resistance rates in pneumococci have been attributed to the capsular serotypes and international clones that are circulating in China. Close monitoring of pneumococcal resistance will be required as various polyvalent pneumococcal conjugate vaccines are introduced into the Chinese population.[7,16]

A study conducted during 2000–04, in the outpatient paediatric department of a single Chinese hospital, demonstrated that *H. influenzae* remained highly susceptible to oral cephalosporins and amoxicillin/clavulanic acid.[17] During 1999–2000 in Beijing, high rates of resistance to *H. influenzae* were observed for tetracycline and trimethoprim/sulfamethoxazole, whereas amoxicillin/clavulanic acid and cefuroxime were uniformly active.[18] In agreement with these findings, our more recent study data showed that *H. influenzae* had reduced susceptibility to tetracycline and trimethoprim/sulfamethoxazole and isolates were highly susceptible to amoxicillin/clavulanic acid. However, cefuroxime activity was much lower at 75% in the current study in 2013–14 than in the older study from Beijing.

The data presented from this SOAR study highlight the importance of antimicrobial resistance surveillance in China. Resistance to common antimicrobial agents among CAP pathogens is relatively high in this country and is increasing (based upon previously published literature in this region and the current study). Future data from China will further assist in understanding the implications of longitudinal trends related to antimicrobial resistance in this country.

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