Clinical symptoms and treatment of common respiratory tract infections in relation to microbiological profiles in rural health facilities in China: implications for antibiotic stewardship

Xingrong Shen
Anhui Medical University
Jilu Shen
the Fourth Affiliated Hospital of Anhui Medical University
Yaping Pan
the First Affiliated Hospital of Anhui Medical University
Jing Cheng
Anhui Medical University
Jing Chai
Anhui Medical University
Karen Bowker
Southmead Hospital
Alasdair MacGowan
Southmead Hospital
Isabel Oliver
Public Health England
Helen Lambert
University of Bristol
Debin Wang (dbwang@vip.sina.com)
Anhui Medical University https://orcid.org/0000-0002-5106-6427

Research

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Abstract

Background: This study aims to identify the extent to which current clinical practice in the treatment of common respiratory tract infections (RTIs) is consistent with presenting symptoms and microbiological characteristics at health care settings in rural China and implications for future antibiotic stewardship.

Methods: The study was implemented in one village clinic and one township health center in each of four rural residential areas in Anhui Province, China. Observations, structured and semi-structured interviews were conducted to investigate antibiotic use. Sputum and throat swabs were collected for bacterial culture and susceptibility testing.

Results: A total of 1068 completed the study. Antibiotics were prescribed for 87.8% of RTI patients. Of all the specimens tested, 329 (30.8%) specimens were isolated with bacteria. The most frequently detected bacteria were *K. pneumonia* (24.15% in all specimens), *H. influenza* (16.19%), *H. parainfluenzae* (14.77%), *S.aureus* (5.11%), *M. catarrhalis* (3.41%) and *S. pneumoniae* (2.27%). The bacteria detection was associated with age (OR=1.91), season (OR=0.41 to 0.60), days since infection onset (OR=1.54 to 1.81), and runny or blocked nose (OR=1.39 to 1.61), cough with green or white sputum (OR=1.47 to 1.59). Antibiotic use was only linked with limited non-specific clinical manifestations e.g., days since infection onset (OR=0.53) and sore throat (OR=1.64).

Conclusions: The study reveals that antibiotics prescription is still very common in rural China which is driven mainly by non-pathological factors rather than treatment of bacterial infections. The study establishes the feasibility of conducting microbiological testing outside Tier 2 and 3 hospitals in rural China.

Contributions To The Literature

- This study makes innovative use of observations in collecting data about antibiotics prescription at rural and township care settings in China for patients with respiratory tract infections.
- It is the first study in rural China that tries to triangulate antibiotics prescription and clinical symptoms and microbiological findings and reveals useful relations between them.
- It also establishes the feasibility of conducting microbiological testing outside Tier 2 and 3 hospitals in rural China.

Background

Antibiotic resistance (ABR) has become one of the biggest threats to global health [1−2]. It leads to higher financial costs, prolonged hospital stays and increased patient mortality. Data from 76 counties including China show that global antibiotics consumption grew by more than 39% between 2000 and 2015 and China consumes the second largest amount of antibiotics in the world [3] with a prescription rate twice that recommended by the World Health Organization (WHO) [4].Rural areas have higher antibiotic prescribing rates than urban areas[5]; according to a survey in rural areas of Shandong and Ningxia and 89.3% and 76.7% of the prescriptions contained antibiotics for patients clinically diagnosed as having upper respiratory tract infections [6]. Another survey of prescriptions from village clinics in middle-east China showed that the proportion of antibiotics prescribed for respiratory tract infections (RTIs) accounted for 87% [7]. The Chinese government has introduced a number of regulations to control antibiotic use in the last decade, but these have not played a significant role in rural areas [8].

The majority of people in China live in rural and township areas. Physicians in these areas mainly provide two kinds of services for residents, the treatment of common infectious diseases (mainly RTIs), and the management of chronic diseases. The excessive antibiotics prescriptions mostly occur in treating common RTIs. A range of possible reasons for unnecessary use of antibiotics from rural and township physicians have been identified. It is not uncommon for them to prescribe antibiotics 'just in case', due to a desire to reduce medical, legal and reputational risk in the face of diagnostic uncertainty [9]. Antibiotics may also be used unnecessarily under the driver of income interests, including prescribing of inappropriate antibiotics for particular diseases, unnecessary escalation (for example prescribing more expensive and broad spectrum antibiotics when cheaper and more specific antibiotics can give the same result) and intravenous use [10−11]. In addition, most rural and township physicians in China have to distinguish bacterial or virus infection based on patient-reported symptoms because microbiological facilities are not available at most front-line health care settings [12].

Most research on ABR in China has drawn on patient data collected in urban specialist hospitals. The often asserted high burden of ABR in China may be misleading since current assumptions are based on potential pathogens isolated in selected microbiology laboratories enrolled in the national surveillance system and it is uncertain if this reflects the incidence of resistance in non-hospitalized patients with mild to moderate infection receiving antibiotics, most of whom do not have samples sent to the laboratory [13–14]. UK data indicates that 1:35 patients presenting to their general practitioners with acute cough have microbiological sampling [15]. This data indicates that resistance rates to key antibiotics based on biased laboratory data may be over-emphasized [16–17]. Similarly, the often reported reduction in antibiotics prescription rate derived from paper or electronic medical records may also be misleading since such records in most primary clinics in China are incomplete or inaccurate and the bulk of antibiotics is used at primary care settings.

This study makes innovative use of observations in collecting data about antibiotics prescription at rural and township care settings in China. It tries to identify the extent to which current clinical practice in the treatment of common RTIs is consistent with presenting symptoms and microbiological characteristics and implications for future antibiotic stewardship.

Methods

This study is part of the ‘Pathways to optimizing antibiotic use in Anhui: Identifying key determinants in community and clinical settings’ project. The protocol has been published separately [18].

Setting

This study was implemented in one village clinic and one township health center in each of four rural residential areas in Anhui Province, China. Anhui Province is located in the middle east of China and has a population of 68.6 million of whom 57% live in rural areas. It has 968 hospitals, 1,941 community, 1,398 township health centers, and 15,288 village clinics (Annual Health Anhui Statistics 2018).

Participants

The study aimed to recruit 1,000 patients presenting with respiratory infection. For details of the sample size calculation, please refer to the aforementioned study protocol [18]. Inclusion criteria were male or female patients who were: a) 18 years or older and able to give consent to participate in the microbiological study and exit survey; b) presenting to the recruitment site for his/her current illness for the first time during the study period; and c) diagnosed by the attending doctor as having one or more of the following: exacerbation of chronic obstructive pulmonary disease, upper respiratory tract infection with productive cough, and sore throat. Patients were selected via “consecutive sampling” in which, when a start date had been determined, the recruitment continued daily (7 days a week) thereafter, between 8am-5 pm or 9am- 6 pm on alternate days, until the target numbers had been reached. All incoming patients to the site village clinics and township health centers who meet the inclusion criteria during any study day were invited to participate. This was a pragmatic approach to sampling since patient record systems do not allow the flexibility to carry out random sampling, and ongoing recruitment ensured the most efficient use of staff and resources in this setting.

Data collection

Semi-structured observations and exit surveys

A trained researcher was sent to each participating clinics and health centers to perform semi-structured observations. The observation focuses on daily operational routine including test ordering, prescribing, patient recall and other standard procedures using a pre-designed worksheet[18]. A brief exit survey using a semi-structured questionnaire was also completed to all patients who consented by the attending clinicians at clinics and health centers and recruited into the study. The questionnaire was completed when the episode of care had concluded. The questionnaire was informed by open-ended interviews undertaken in the study’s pilot phase and included information on social demographics, symptoms and diseases history.

Specimen collection and microbiological testing

The study collected sputum and throat swabs for bacterial culture, identification and susceptibility testing. Sputum was collected from patients presenting with productive cough and throat swabs from patients with sore throat. Samples were collected by the attending doctor using a sterilized container and according to a standard protocol. The tube containing the specimen was put immediately into a refrigerator and preserved at below−4°C pending transport to the Central Laboratory of Anhui Medical University (AMU). At about 12:00 am and 5:30 pm each day, the samples were transported in a portable case filled with ice bags which was sealed and handed over to a contracted bus company for delivery within a 4 hour time limit.

At AMU sputum and throat swab specimens were inoculated on four plates (a blood agar plate, a MacConkey agar plate, a chocolate agar plate and Candida color culture plate). The inoculated blood agar and chocolate agar plates were cultured in an incubator under 5% CO_2 and 35°C; and the MacConkey agar and the Candida color culture plate, in an incubator under 35°C. The culture duration was 24 hours plus an additional 24 hours if no bacteria were observed for the first period. Bacteria identification used automated methods i.e., the MicroscanWalkaway-96 System with PC33 (for gram positive bacteria) or NC50 (for gram negative bacteria) kits, and also according to different biochemical reactions as follows: a) S.pneumoniae optochin/ biochemistry; b) H.influenzae X + V factors or MALDI-TOF; and c) MALDI-TOF (BioMerieux, French). Antibiotic susceptibilities testing used automated methods (Vitek2 compact 2 by BioMerieux, French) and MicroScan Walk away 96 plus by Siemens, Germany) along with disk diffusion (according to CLSI).

Data analysis

This paper reports on descriptive analysis of: a) social demographics (sex, age and educations) of patients recruited; b) antibiotics use by clinical symptoms of RTIs; c) percentages of patients identified with specific types of bacteria by groups of clinical symptoms; and d) prevalence rates of resistance of top five strains of bacteria to commonly used antibiotics. The study also performed multiple logistic regression analysis using bacteria detection and antibiotics use as the dependent variable (1 = positive or yes and 0 = negative or no) respectively and patient social demographics, clinical symptoms as the independent variables.

Results

Social demographics of informants

A total of 1073 patients meeting our inclusion criteria were invited to participate and 1068 provided specimens and completed the face-to-face survey. Of these, 51.0% were male and 49.0%, female with an average age of 51.57 years (ranging from 18 to 89 years). Over half (54.5%) of them had less than 5 years of education with 25.8% being illiterate. There were statistically significant differences between gender groups with males being older and more educated (Table 1).

Table 1
Socio-demographic characteristics of respondents

	Male		***Female***		**Total**	
	N	**%**	**N**	**%**	**N**	**%**
Age						
<=39	120	22.0	152	29.1	272	25.5
40–53	120	22.0	162	31.0	282	26.4
54–64	129	23.7	123	23.5	252	23.6
>=65	174	31.9	86	16.4	260	24.3
Missing	2	0.4	0	0.0	2	0.2
p		0.000		0.000		0.000
Education						
0	89	16.3	187	35.8	276	25.8
1–5	157	28.8	149	28.5	306	28.7
6–8	155	28.4	74	14.1	229	21.4
> 8	141	25.9	109	20.8	250	23.4
Missing	3	0.6	4	0.8	7	0.7
p		0.000		0.000		0.000
Total	545	51.0	523	49.0	1068	100.0

Clinical symptoms and antibiotic use

Antibiotics were prescribed for 87.8% of all RTI patients and 35.5% of these prescriptions contained two or more types of antibiotics (Table 2). The most common symptoms of RTIs were sore throat (561, 34.2%), cough with white sputum (525, 49.2%) and breathing difficulties (365, 34.2%). The most commonly prescribed antibiotics were penicillin (404, 43.1%), followed by cephalosporins (359, 38.3%) and fluoroquinolones (335, 35.7%). Patients presenting cough with green sputum, dry throat/ burning throat/hoarse voice, and sore throat had higher antibiotics prescription rate as compared with those without these symptoms ($p < 0.05$). Fluoroquinolones was more commonly prescribed among patients with runny nose (clear/watery discharge), cough with white sputum, breathing difficulties, and weakness than patients without these symptoms. Use of cephalosporins was more frequent among patients with cough with green sputum, cough with white sputum, itchy throat, weakness and other symptoms and use of penicillins, more common among patients with weakness and fever. Patients with sore throat were more likely to be prescribed with a single antibiotic; while patients with breathing difficulties were more likely to get a prescription containing two or more types of antibiotics. An increasing number of symptoms was associated with prescribing of fluoroquinolones and with combined use of two or more types of antibiotics, but there was a mixed trend for prescription of any antibiotics.

Table 2
Antibiotic use by clinical symptoms

	Patients N (%)	Quinolones	Cephalosporins	Penicillins	Others	*Any*	Number of antibiotics used 1	2	3+
Symptom									
Blocked nose									
	257(24.06)	69(26.85)	82(31.91)	93(36.19)	0(0.00)	226(87.94)	146(56.81)	64(24.90)	16(6.23)
Runny nose (clear/watery discharge)									
	277(25.94)	106(38.27)	104(37.55)	108(38.99)	3(1.08)	245(88.45)	129(46.57)	90(32.49)	26(9.39)
Snotty nose (yellow/green discharge)									
	70(6.55)	19(27.14)	22(31.43)	19(27.14)	1(1.43)	59(84.29)	41(58.57)	13(18.57)	5(7.14)
Dry cough									
	137(12.83)	41(29.93)	45(32.85)	57(41.61)	2(1.46)	125(91.24)	77(56.20)	39(28.47)	9(6.57)
Cough with green sputum									
	250(23.41)	77(30.80)	95(38.00)	83(33.20)	1(0.40)	208(83.20)	121(48.40)	65(26.00)	22(8.80)
Cough with white sputum									
	525(49.16)	181(34.48)	194(36.95)	185(35.24)	2(0.38)	461(87.81)	265(50.48)	156(29.71)	40(7.62)
Dry throat / burning throat/hoarse voice									
	258(24.16)	68(26.36)	86(33.33)	101(39.15)	3(1.16)	216(83.72)	129(50.00)	67(26.00)	20(7.75)
Itchy throat									
	258(24.16)	79(30.62)	101(39.15)	87(33.72)	2(0.78)	224(86.82)	137(53.10)	65(25.19)	22(8.53)
Sore throat									
	561(52.53)	177(31.55)	187(33.33)	224(39.93)	6(1.07)	508(90.55)	308(54.90)	155(27.63)	45(8.02)
Breathing difficulties									
	365(34.18)	142(38.90)	126(34.52)	145(39.73)	4(1.10)	321(87.95)	159(43.56)	128(35.07)	34(9.32)
Headache									
	201(18.82)	69(34.33)	62(30.85)	77(38.31)	2(1.00)	173(86.07)	100(49.75)	55(27.36)	18(8.96)
Weakness									
	139(13.01)	50(35.97)	58(41.73)	36(25.90)	1(0.72)	120(86.33)	70(50.36)	41(29.50)	9(6.47)
Fever									
	146(13.67)	47(32.19)	55(37.67)	45(30.82)	1(0.68)	131(89.73)	84(57.53)	36(24.66)	11(7.53)
Other symptoms									
	213(19.94)	62(29.11)	54(25.35)	88(41.31)	3(1.41)	179(84.04)	105(49.30)	59(27.70)	15(7.04)
P		0.026	0.076	0.036	0.899	0.134	0.365		
Number of symptoms									
-1	83(7.77)	15(18.07)	23(27.71)	32(38.55)	2(2.41)	70(84.34)	49(59.04)	14(16.87)	7(8.43)
-2	221(20.69)	63(28.51)	66(29.86)	85(38.46)	2(0.90)	192(86.88)	119(53.85)	55(24.89)	18(8.14)
-3	287(26.87)	92(32.06)	96(33.45)	120(41.81)	2(0.70)	257(89.55)	151(52.61)	76(26.48)	30(10.45)
-4	222(20.79)	88(39.64)	86(38.74)	76(34.23)	1(0.45)	207(93.24)	115(51.80)	84(37.84)	8(3.60)

	Patients N (%)	Quinolones	Cephalosporins	Penicillins	Others	*Any*	Number of antibiotics used		
							1	2	3+
-5	164(15.36)	51(31.10)	50(30.49)	62(37.80)	2(1.22)	137(83.54)	82(50.00)	40(24.39)	15(9.15)
-6+	91(8.52)	26(28.57)	38(41.76)	29(31.87)	1(1.10)	75(82.42)	43(47.25)	24(26.37)	8(8.79)
P		0.046	0.146	0.310	0.661	0.020	0.003		
Total	1068(100)	335(35.7)	359(38.3)	404(43.1)	10(1.1)	938(87.8)	559(52.3)	293(27.4)	86(8.1)

Additional file 1 compares use of different kinds of antibiotics among patients with one of the 14 specific symptoms studied versus those without the symptom. Levofloxacin witnessed the greatest number of prescriptions for all of the symptoms, followed by amoxicillin, erythromycin and amoxicillin clavulanic acid. For patients without the specific symptoms, the same order of frequencies of prescriptions of these antibiotics was also observed.

Symptoms and bacteria identification

Of all the specimens tested, 329 (30.8%) specimens were isolated with pathogenic bacteria or conditional pathogens (pathogens that cause infections only under certain conditions), and 23 of them, with two strains of bacteria. These 352 isolates comprised 85 (24.15%) for K. pneumonia, 57 (16.19%) for *H. influenzae*, 52(14.77%) for *H. parainfluenzae*, 18 (5.11%) for *S.aureus*, 12 (3.41%) for *M. catarrhalis*, 8 (2.27%) for S. pneumoniae, and 6 (1.70%) for *B. haemolytic* streptococci. Table 3 provides bacterial detection results from sputum and throat swab specimens by symptoms (the results from sputum and throat swab specimens separately are given in Additional file 2 and 3). When all kinds of bacteria were concerned, patients with runny nose (clear/watery discharge), cough with green sputum and cough with white sputum were more likely to be tested positive than patients without these symptoms; while the chances of detecting bacteria were lower in patients with dry cough and sore throat than in those without these symptoms. Looking specific kinds of bacteria, greater chances were observed for: detecting *K.pneumonia* from patients with cough with white sputum but without dry cough and sore throat; *H. influenzae* from patients with Cough with green sputum; *H. parainfluenzae* from patients with blocked nose; and S. pneumoniae from patients with Snotty nose (yellow/green discharge) and Cough with green sputum. In addition, number of symptoms witnessed a general increasing trend with the chances of detecting *H. influenzae* and *H. parainfluenzae*.

Table 3
Bacterial detection by clinical symptoms (n = 1086, sputum and throat swabs)

	AB	KP	HI	HP	SA	MC	SP	BS
Symptom								
Blocked nose								
	86(33.46)	21(8.17)	22(8.56)	21(8.17)	7(2.72)	3(1.17)	0(0.00)	1(0.39)
Runny nose (clear/watery discharge)								
	100(36.10)	24(8.66)	17(6.14)	17(6.14)	3(1.08)	5(1.81)	1(0.36)	1(0.39)
Snotty nose (yellow/green discharge)								
	19(27.14)	5(7.14)	4(5.71)	2(2.86)	1(1.43)	1(1.43)	2(2.86)	0(0.00)
Dry cough								
	29(21.17)	5(3.65)	4(2.92)	7(5.11)	2(1.46)	1(0.73)	0(0.00)	1(0.73)
Cough with green sputum								
	90(36.00)	21(8.40)	24(9.60)	13(5.20)	7(2.80)	2(0.80)	4(1.60)	0(0.00)
Cough with white sputum								
	188(35.81)	55(10.48)	31(5.90)	30(5.71)	7(1.33)	8(1.52)	4(0.76)	1(0.19)
Dry throat / burning throat/hoarse voice								
	82(31.78)	17(6.59)	14(5.43)	16(6.20)	6(2.33)	4(1.55)	0(0.00)	1(0.39)
Itchy throat								
	73(28.29)	22(8.53)	15(5.81)	14(5.43)	3(1.16)	2(0.78)	1(0.39)	1(0.39)
Sore throat								
	152(27.09)	33(5.88)	27(4.81)	32(5.70)	6(1.07)	5(0.89)	3(0.53)	5(0.89)
Breathing difficulties								
	118(32.33)	24(6.58)	28(7.67)	21(5.75)	6(1.64)	4(1.10)	2(0.55)	1(0.27)
Headache								
	62(30.85)	14(6.97)	10(4.98)	12(5.97)	2(1.00)	2(1.00)	0(0.00)	1(0.50)
Weakness								
	48(34.53)	13(9.35)	5(3.60)	7(5.04)	2(1.44)	1(0.72)	2(1.44)	2(1.44)
Fever								
	46(31.52)	10(6.85)	6(4.11)	6(4.11)	0(0.00)	2(1.37)	1(0.68)	2(1.44)
Other symptoms								
	70(32.86)	16(7.51)	10(4.69)	11(5.16)	7(3.29)	1(0.47)	4(1.88)	0(0.00)
P	0.028	0.349	0.159	0.966	0.384	0.984	0.066	0.557
Symptom Numbers								
-1	28(33.73)	9(10.84)	5(6.02)	3(3.61)	1(1.20)	3(3.61)	0(0.00)	2(2.41)
-2	55(24.89)	19(8.60)	5(2.26)	3(1.36)	4(1.81)	1(0.45)	4(1.81)	1(0.45)
-3	85(29.62)	19(6.62)	13(4.53)	15(5.23)	5(1.74)	3(1.05)	2(0.70)	0(0.00)
-4	78(35.14)	21(9.46)	19(8.56)	11(4.95)	5(2.25)	2(0.90)	0(0.00)	2(0.90)
-5	51(31.10)	11(6.71)	7(4.27)	14(8.54)	2(1.22)	1(0.61)	2(1.22)	1(0.61)

	AB	KP	HI	HP	SA	MC	SP	BS
->=6	32(35.16)	6(6.59)	8(8.79)	6(6.59)	1(1.10)	2(2.20)	0(0.00)	0(0.00)
-P	0.226	0.695	0.0397078	0.040778	0.964	0.222	0.233	0.172
Total	**329(30.8)**	**85(24.15)**	**57(16.19)**	**52(14.77)**	**18(5.11)**	**12(3.41)**	**8(2.27)**	**6(1.70)**

Note: AB = detection of any bacteria, KP = *K.pneumonia*, HI = *H.influenzae*, HP = *H.parainfluenzae*, SA = *S.aureus*, MC = M.catarrhalis, SP = S.pneumoniae, BS = B.haemolytic streptococci.

Antibiotics prescription and bacteria sensitivity

Figure 1 portraits the prescription rate of specific antibiotics and resistance rate of 8 common bacteria isolated from sputum and swab specimens. These bacteria were tested sensitive to most of the antibiotics studied. The most frequently prescribed antibiotics were levofloxacin (31.0%), amoxicillin clavulanic acid (14.8%), and cefuroxime (9.8%), ceftriaxone (5.4%) and ceftazidime (5.1%). The highest resistance rate was estimated as 100% for *E.cloacae* to cefazolin, followed by 97.4% for K. pneumoniae to ampicillin and 92.3 for S. aureus to penicillin. There witnessed no clear associations between the frequency of antibiotics prescription and the rates of resistance. The highest resistance rate to the top five most frequently prescribed antibiotics was 30.0%.

Determinants of antibiotics use and bacteria identification

Table 4 summarizes main statistics of multiple logistic regression modeling of potential factors that may be associated with bacteria detection results or antibiotic prescription. In the model of detection of any bacteria from all specimens (model 1), variables found with statistical significance of bacteria detection included age (OR = 1.91 for age > = 65 group), season (OR = 0.50 and 0.55 for summer and winter group respectively), days since infection onset (OR = 1.18 for > = 5 days), runny nose (clear/watery discharge) (OR = 1.39), cough with green sputum (OR = 1.47) and cough with white sputum (OR = 1.51). For the model of detection of 7-bacteria (*H.influenzae, M.catarrhalis, S.pneumoniae, H.parainfluenzae, S.aureus, K. pneumonia* and *B.haemolytic streptococci*) from all specimens (model 2), the findings mirrored that of model 1 to a large extent. The differences in model 2 from model 1 included only: a) age and runny nose were not associated with bacteria detection; and b) males and patients presenting blocked nose were more likely to be tested with the 7-bacteria. With regard to detection of the 6-bacteria (the first six kinds of bacteria in model 2) from sputum (model 3) and the 6-bacteria (the first five kinds of bacteria in model 2 plus *B.haemolytic streptococci*) from throat swabs (model 4), only season was fond with statistical significance. As compared with that in spring, there witnessed a reduced likelihood in isolating bacteria from sputum in summer (OR = 0.50) and from throat swabs in winter (OR = 0.41). In the antibiotic use model (model 5), only days since infection onset (OR = 0.53) and sore throat (OR = 1.64) were found with statistical significance.

Table 4
Statistics of multiple logistic regression modeling of bacterial detection and antibiotic use

Independent variables	Any bacteria, all specimens		7-bacteria, all specimens		6-bacteria, Sputum		6-bacteria, throat swabs		Antibiotics prescription	
	OR	95%CI	OR	95%CI	OR	95%CI	OR	95%CI	OR	95%CI
Age (< = 39 as reference)										
40–53	1.34	[0.85,2.11]	1.40	[0.85,2.30]	1.50	[0.79,2.82]	1.14	[0.47,2.78]	1.23	[0.67,2.28]
54–64	1.41	[0.87,2.29]	1.30	[0.76,2.21]	1.39	[0.72,2.67]	0.89	[0.30,2.64]	0.97	[0.51,1.85]
>=65	1.91	[1.13,3.22]	1.39	[0.78,2.48]	1.30	[0.65,2.63]	1.80	[0.54,6.07]	1.19	[0.57,2.45]
Gender(Male as reference)										
female	0.83	[0.60,1.13]	0.65	[0.46,0.92]	0.66	[0.43,1.00]	0.57	[0.29,1.12]	0.78	[0.50,1.21]
Education *(0* as reference*)*										
1–5	0.75	[0.51,1.11]	0.85	[0.55,1.31]	1.02	[0.63,1.66]	0.41	[0.14,1.23]	0.91	[0.51,1.60]
6–8	0.89	[0.56,1.39]	0.82	[0.50,1.37]	0.84	[0.46,1.54]	0.84	[0.28,2.49]	0.9	[0.46,1.79]
> 8	0.98	[0.59,1.61]	1.10	[0.64,1.90]	1.13	[0.60,2.12]	1.06	[0.32,3.52]	0.57	[0.29,1.13]
Season(spring as reference)										
Summer	0.50	[0.35,0.70]	0.57	[0.39,0.83]	0.50	[0.33,0.78]	0.67	[0.30,1.53]	1.25	[0.75,2.08]
Winter	0.55	[0.39,0.78]	0.60	[0.41,0.89]	0.77	[0.49,1.22]	0.41	[0.19,0.90]	0.88	[0.54,1.42]
Days since infection onset(< = 2 as reference)										
2–4	1.31	[0.91,1.90]	1.33	[0.88,2.01]	1.14	[0.68,1.89]	2.11	[0.99,4.50]	0.88	[0.50,1.53]
>=5	1.81	[1.26,2.58]	1.54	[1.03,2.29]	1.50	[0.93,2.42]	1.20	[0.54,2.68]	0.53	[0.32,0.88]
Blocked nose	1.26	[0.91,1.75]	1.61	[1.13,2.29]	1.42	[0.94,2.15]	2.02	[0.98,4.17]	1.1	[0.69,1.75]
Runny nose (clear/ watery discharge)	1.39	[1.02,1.90]	1.16	[0.82,1.64]	1.21	[0.81,1.80]	0.76	[0.34,1.68]	0.91	[0.58,1.42]
Snotty nose (yellow/ green discharge)	0.78	[0.44,1.39]	0.95	[0.51,1.76]	0.98	[0.47,2.02]	0.59	[0.14,2.46]	0.91	[0.44,1.86]
Dry cough	0.97	[0.57,1.64]	1.00	[0.55,1.81]	0.80	[0.19,3.41]	1.15	[0.54,2.47]	1.49	[0.69,3.23]
Cough with green sputum	1.47	[1.01,2.15]	1.59	[1.05,2.41]	1.37	[0.80,2.35]	1.25	[0.47,3.33]	0.65	[0.39,1.06]
Cough with white sputum	1.51	[1.06,2.14]	1.56	[1.06,2.31]	1.26	[0.74,2.15]	1.94	[0.86,4.36]	0.91	[0.57,1.44]
Dry/burning throat/hoarse voice	1.21	[0.87,1.68]	1.12	[0.78,1.61]	1.35	[0.87,2.08]	0.81	[0.38,1.71]	0.66	[0.43,1.02]
Itchy throat	0.8	[0.57,1.12]	0.93	[0.65,1.34]	0.85	[0.56,1.29]	1.18	[0.52,2.71]	1.05	[0.66,1.65]
Sore throat	0.8	[0.59,1.07]	0.83	[0.59,1.15]	0.84	[0.57,1.25]	0.84	[0.41,1.73]	1.64	[1.07,2.50]
Breathing difficulties	0.83	[0.61,1.13]	0.89	[0.64,1.25]	0.88	[0.60,1.30]	0.88	[0.41,1.89]	1.23	[0.79,1.90]
Headache	1.15	[0.79,1.68]	1.01	[0.66,1.54]	0.84	[0.49,1.42]	1.67	[0.77,3.59]	0.69	[0.41,1.14]
Weakness	1.25	[0.82,1.89]	1.19	[0.75,1.88]	1.30	[0.76,2.23]	0.90	[0.33,2.48]	0.87	[0.49,1.53]
Fever	1.17	[0.76,1.80]	0.86	[0.53,1.42]	0.93	[0.51,1.67]	0.75	[0.28,2.03]	1.25	[0.66,2.36]
Other symptoms	1.28	[0.90,1.82]	1.27	[0.86,1.88]	1.20	[0.76,1.88]	1.39	[0.58,3.33]	0.7	[0.44,1.11]
Antibiotics prescription	1.23	[0.80,1.89]	1.26	[0.78,2.03]	1.41	[0.82,2.44]	0.94	[0.31,2.82]	NA	NA
Constant	0.31	NA	0.17	NA	0.19	NA	0.25	NA	17.38	NA

Independent variables	Any bacteria, all specimens		7-bacteria, all specimens		6-bacteria, Sputum		6-bacteria, throat swabs		Antibiotics prescription	
	OR	95%CI	OR	95%CI	OR	95%CI	OR	95%CI	OR	95%CI

Note: (1) the “7-bacteria” tested for all specimens included *H.influenzae, M.catarrhalis, S.pneumoniae, H. parainfluenzae, S.aureus, K.pneumonia* and *B.haemolytic streptococci*; (2) the “6-bacteria” tested for all sputum specimens included the first six kinds of bacteria of (1) ; (3) the “6-bacteria” tested for all throat swabs included the first five kinds of bacteria of (1) plus *B.haemolytic streptococci*.

Discussion

Key findings

This study reveals useful findings on antibiotic use and microbiological test results for patients presenting RTIs symptoms at rural and township care settings in rural Anhui, China. It documents an antibiotic prescription rate as high as 87.8% and that 35.5% of these prescriptions contained two or more kinds of antibiotics. The most commonly prescribed antibiotics were levofloxacin, amoxicillin and erythromycin. Nearly one third (30.8%) of the specimens were isolated with pathogenic bacteria or conditional pathogens with *K. pneumonia, H. influenza, H. parainfluenzae, P. aeruginosa and S. aureus* being the top five bacteria strains. *K. pneumoniae* witnessed the highest resistance rate to ampicillin followed by *S.pneumoniae* to Clindamycin, *H. influenzae* to Trimethoprim/Sulfaisoxazole and *H. parainfluenzae* to Ampicillin. The study also found, via logistic regression modeling, that bacteria detection was associated with age, season, days since infection onset, runny nose, cough with green sputum and cough with white sputum; while antibiotic use was only linked to days since infection onset and sore throat.

Implications in context of other research and for policy

The above study findings have important implications for antibiotics stewardship. The very high rate of antibiotics prescriptions contradicts a common belief among policymakers in China that excessive antibiotics use is being brought under control as a result of the nationwide Special Antibiotics Use Rectification program (initiated in 2011) and the New Health System Reforms [19–21]. These initiatives focus on antibiotics use at secondary and tertiary hospitals. Given that about 57% of China’s vast population lives in rural and township areas and over 70% of antibiotics prescriptions occur at settings in these areas[22, 23], there is a clear need for added attention on excessive antibiotics use at these settings and communities. Narrow (rather than broad) spectrum antibiotics are recommended whenever applicable. However, the most commonly prescribed antibiotics observed in this study belong to broad spectrum antibiotics and around one third of the prescriptions contained two or more types of antibiotics. This may be attributed mainly to medical uncertainty though decisions on which specific antibiotics to use depends on a variety of factors including availability, price, sensitivity, adverse effects and other characteristics of the antibiotics under concern[24–26]. Rural and township healthcare doctors in China work in a difficult situation in which microbiological tests are unavailable and it is hard to tell the pathogen and its sensitivity to specific antibiotics from clinical symptoms/history. So they tend to view broad spectrum or combined antibiotics as a safer strategy than narrow spectrum antibiotics since the former have greater chance of hitting the actual pathogen [27].

The study sheds new light on relations between clinical symptoms/history, microbiological tests and antibiotics use at rural and township care settings. Our multiple logistic regression modeling of bacteria detection indicates that patients who get RTIs in spring and who present runny nose and cough with green/white sputum, are older, and report a longer duration since onset of the infection, are more likely to test positive for bacterial pathogens. Given that antibiotics work only for patients with bacterial infections, the multiple logistic regression modeling of antibiotics use should result in similar associated factors as that of the aforementioned modeling of bacteria detection. However, our modeling found that only two variables, sore throat and days since onset of infection, were associated with antibiotics use. Of these two variables, one (sore throat) was not associated with bacteria detection and the other (days since onset of infection) showed an inverse correlation. These differences suggest that the doctors’ decision on antibiotics use were not driven mainly by considerations for controlling bacteria pathogens but for assuring the patients or relieving their sense of urgency [28]. Sore throat develops rapidly after onset of infection and is one of the most unpleasant symptoms of RTIs. Attendees with sore throat as a complaint may indicate that: a) their infection is at its early stage; and b) their symptoms are severe or intolerable enough to have driven them to visit the clinic so early. On the contrary, attendees with longer the time-lag between onset of infection and visit to the clinic may have less severe/ intolerable symptoms. Although patients with previous visits to other clinics may have longer time-lag, they account for only a small proportion [29].

The study also reveals a number of clues for leveraging microbiological tests, in rural and township areas, in tackling antibiotics use and resistance issues in China. First, the study has tested the feasibility of conducting microbiological tests for rural and township care attendees in resource-poor rural China. As specified in our separate protocol paper, the testing proceeded by collecting specimens at the rural and township care settings and sending the specimens to a tertiary hospital with a microbiological lab via existing transportation services. We collected and tested 1068 specimens out of 1073 RTI patients. Our overall rate of bacteria detection was 30.8%. This is compatible with published results for similar population groups [30]. These suggest that the testing is acceptable to both patients and physicians and test results are relatively reliable. Second, the study highlights the need for incorporating rural and township cares settings into China's national antibiotics use and resistance surveillance systems. Our study indicates that antibiotics prescription rate at rural and township care settings are much higher than that from current national surveillance system [31]; while antibiotics resistance rate among rural and township care attendees is substantially lower than that among patients of hospitals forming the national antibiotics resistance surveillance network [31]. Third, the study uncovers various possibilities in using microbiological tests to inform antibiotics prescription by rural and township care givers. For example, the specific strains of bacteria identified and their relative frequencies/compositions by different patient groups may be used to inform more tailored selection of specific types of antibiotics. The findings that antibiotic resistance rates are substantially lower among rural and township care attendees than patients of higher level hospitals and that the list of guideline-recommended antibiotics are all found with enough sensitivity (e.g., a resistance rate of lower than 15% as found in our study) may be used to convince rural and township practitioners that their guideline is valid and their appeal for authorization of more advanced antibiotics is not justified. More importantly, introduction of some monitoring indicators linking microbiological tests with clinical prescriptions may help in promoting a reorientation of decisions on antibiotics use from preventing “rare cases” or coping with patients' perceived urgency to controlling bacteria pathogens [32]. One of such indicators may be rate of antibiotics prescriptions with microbiological evidence, if it is linked to a policy that requires physicians not to prescribe antibiotics unless the patients are tested with pathogen bacteria.

Strengths and limitations of the study

This study has both strengths and limitations. It is the first study that collected data from healthcare providers and users via a non-participative observation whilst most of the existent research on antibiotics use in China uses data from medical records or reports by medical care givers who may be incentivized to omit recording overuse or misuse of antibiotics so as to meet relevant policy requirements [33]. It is also the first study that performed both microbiological testing and clinical data collection at rural and township care settings and thus enables cross-linking between data from different source. However, the study suffers from limited number of patients and site clinics. It involved only four counties and one village clinic and one township health center from each of the counties. Due to lack of enough number of specific bacteria isolates, the multiple regression models used only collective results (e.g., detection of any bacteria, 7-bacteria, 6-bacteria). In addition, the non-participative observation may also have intervened, to some extent, the routine encounters between the patients and doctors and the prescription behaviors being observed though we had arranged a two-week preparation for each site clinic to allow the field researchers to build trust with the doctors.

Conclusions

The study makes innovative use of observations in collecting data about antibiotics prescription at rural and township care settings in China for patients with respiratory tract infections. It reveals that antibiotics prescription is still very common in rural China which is driven mainly by patient reassurance and other non-pathological factors rather than treatment of bacterial infections. The study establishes the feasibility of conducting microbiological testing outside Tier 2 and 3 hospitals in rural China.

Declarations

Ethics approval and consent to participate

The study was approved by the Biomedical Ethics Committee of Anhui Medical University (reference number: 20170271). The patients and village doctors participated voluntarily, and written informed consent was obtained from all participants.

Consent for publication

Not applicable.

Availability of data and materials

Data are available from the University of Bristol or Anhui Medical University Data Access(contact via H.Lambert@bristol.ac.uk/dbwang@vip.sina.com) for researchers who meet the criteria for access to confidential data.

Competing interests

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Authors' contributions

XRS directed study implementation and data collection, conducted data analysis and drafted the manuscript. DBW conceptualized and supervised the study together with HL. JLS and YPP performed bacterial culture and drug sensitivity testing. KB and AMG provided expertise on microbiological studies and revised the manuscript together with IO. JC and JC developed data collection materials and collected data together with XR Shen.

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Abbreviations

ABR Antibiotic resistance

RTIs Respiratory tract infections

AMU Anhui Medical University

MALDI-TOF Matrix-Assisted Laser Desorption /Ionization Time of Flight

CLSI The Clinical & Laboratory Standards Institute

PC33 PosCombo33

NC50 NegCombo50

OR Odds ratio

AB Detection of any bacteria

KP K.pneumonia

HI H.influenzae

HP H.parainfluenzae

SA S.aureus

MC M.catarrhalis,

SP S.pneumoniae

BS B.haemolytic streptococci

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Figures

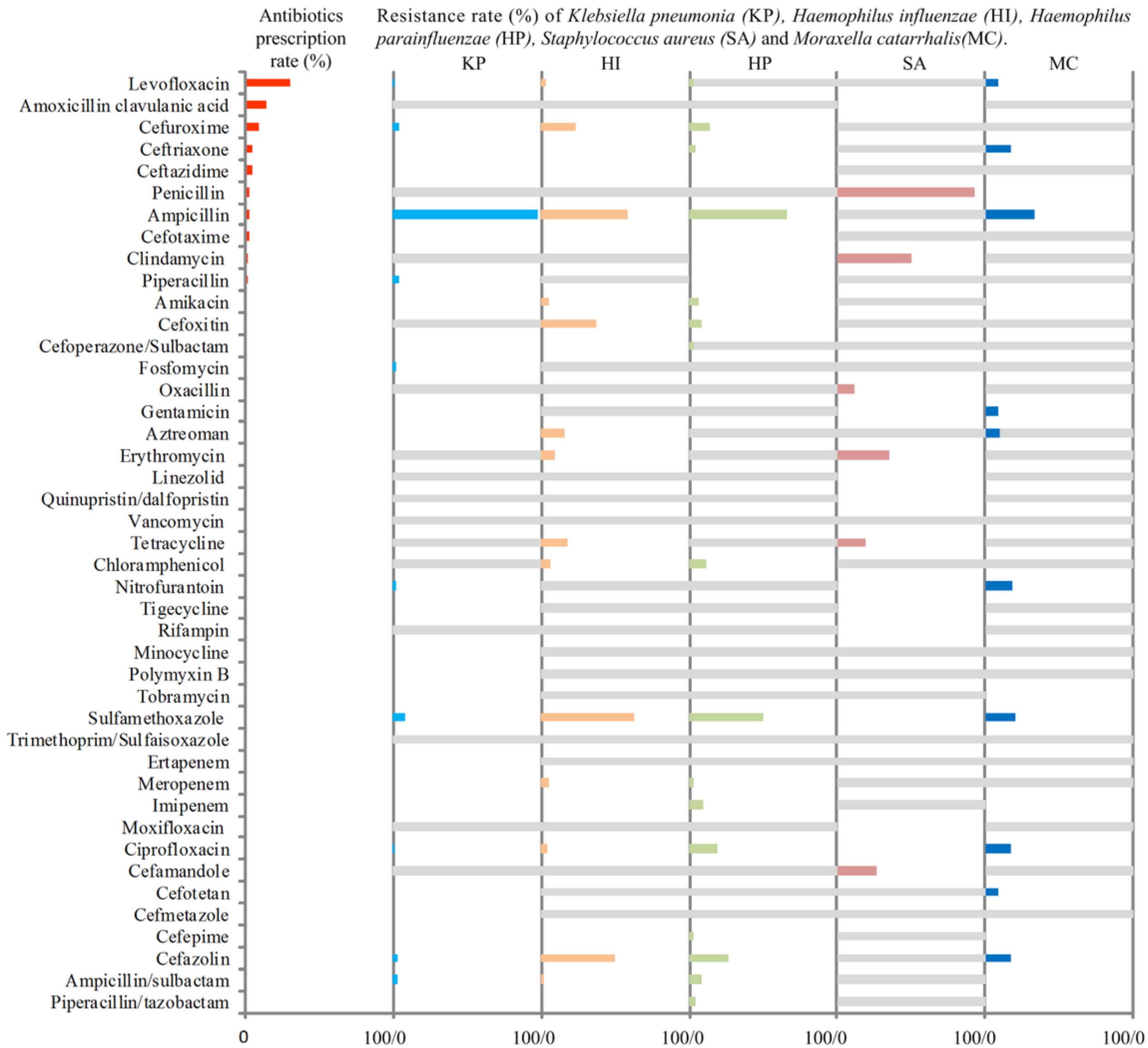

Figure 1

Antibiotics prescription rates compared with antibiotics resistance rates (grey bars represent not applicable or not performed tests)

Supplementary Files

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