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Cross-sectional study of the use of antimicrobials following common infections by rural residents in Anhui, China

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Running title: Antimicrobials use in rural China

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Abstract

Objective: To describe help seeking behavior from medical doctors(HSMD) and antimicrobial use(AMU) for common infections among rural residents of Anhui province, China.

Design: A cross-sectional retrospective household study.

Setting: 12 administrative villages from rural Anhui, China.

Participants: 2760 rural residents selected through cluster-randomized sampling using an interviewer administered questionnaire.

Method: Logistic regression models were used to estimate associations between exposures(health insurance and antimicrobial-related knowledge), adjusted for confounders (sex, age and education), and HSMD and AMU following common infections, including acute respiratory tract infections(ARTIs), gastrointestinal tract infections(GTIs) and urinary tract infections(UTIs).

Results: A total of 2611(94.6%) rural residents completed the questionnaire. HSMD was highest for ARTIs (59.4%) followed by GTIs (42.1%), and UTIs (27.8%). Around two thirds (82.3% for ARTIs, 87.0% for GTIs and 66.0% for UTIs) of respondents sought help within 3 days following their infections and over three quarters (88% for ARTIs, 98% for GTIs and 77% for UTIs) reported complete recovery within 7 days. Of the respondents with HSMD, 94.5% of the visitors with ARTI symptoms recalled being prescribed either oral or intravenous(IV) antimicrobials (GTIs 81.7% and UTIs 70.4%). Use of antimicrobials bought from medicine shops without prescriptions ranged from 8.8% for GTIs to 17.2% for ARTIs; while use of antimicrobials leftover from previous illnesses or given by a relative ranged from

7.6% for UTIs to 13.4% for ARTIs. Multivariate logistic regression analysis revealed that respondents with higher antimicrobial-related knowledge score(ARKS) and lack of insurance were all associated with lower levels of HSMD for ARTIs; while respondents with a higher ARKS score were less likely to be prescribed either oral or IV antimicrobials.

Conclusions: Excessive AMU in primary care settings is still prevalent and there is a clear need for further studies on determinants of AMU in rural China.

Key Words: antimicrobial resistance, antimicrobial use, prescription, self-medication, pharmacoepidemiology

Strengths and limitations of this study

• The study added new data about the magnitude and determinants of antimicrobial use (AMU) in China.

• The study distinguished doctor- versus patient-dominated responses toward infections and revealed misperceptions of patients' demand for antimicrobials.

• The study collected data from healthcare users via a household survey whilst most of the existent research on antimicrobial 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 antimicrobials so as to meet relevant policy requirements.

• Self-reported AMU is prone to biases due to recall problems, inability to distinguish antimicrobials from other drugs, conformity to social norms and research expectations etc.

Introduction

Antimicrobial resistance (AMR) is a global health problem which claims at least 50,000 lives each year across Europe and the US, with many hundreds of thousands more dying in other parts of the world[1]. According to the World Health Organization, AMR is threatening our ability to treat common infections in both the community and health care settings[2]. Antimicrobial use (AMU), even when appropriate and conservative, contributes to the development of resistance, and inappropriate or excessive use should be avoided[2-3]. Countries consuming the highest amount of antimicrobials per capita have the highest rates of resistance[8].

Excessive use of antimicrobials is a widespread problem. Evidence suggests that half of antimicrobial prescriptions are unnecessary or inappropriate for the illness being treated[9-11]. For instance, it is known that the majority of acute respiratory tract infections (ARTIs) and gastrointestinal tract infections (GTIs) are caused by viruses[12], and yet antimicrobial treatment for such infections is common[13–15].

Inappropriate use of antimicrobials and AMR are prevalent in China. Studies published from 2009 to 2013 found that over half of outpatients and around 70% of inpatients of hospitals in China were prescribed one or more antimicrobials[16-21]. The problem was even more acute in primary care settings, particularly in rural areas. It had been estimated that, in the same period, 70-90% of patients visiting village clinics with symptoms of respiratory tract infection were prescribed antimicrobials[22-24]. Widespread overuse and misuse of antimicrobials parallels rapid growth of AMR in the nation[25-27]. Comparative studies on the patterns of AMR between

different countries indicate that China has one the highest levels and the fastest growth rates of AMR[26, 28-32].

The AMU/AMR problem in China has been attributed to a variety of factors[26, 33-36]. China has a long history of almost no charges being made for physician consultations with most patients only paying for prescribed medicines, making prescriptions the most important source of revenue for care providers. These remuneration mechanisms have provided a perverse financial incentive for health care practitioners resulting in excessive prescription of antimicrobials[33, 34], particularly in the lower levels of the health system. Other determinants of antimicrobial use include incorrect expectations and beliefs about antimicrobials among patients[35, 36]; diagnostic uncertainty, prescribing habits and clinicians' misperceptions that service-seekers are expecting them to prescribe antimicrobials.[37-39.]

China has witnessed fundamental reforms of its healthcare system during the past decade. In 2003, the Chinese government introduced a new rural cooperative medical system (NRCMS) available to rural residents at a relatively small per capita annual cost. By 2009, almost 96% of rural residents were covered by this insurance and, starting in 2011, the central government implemented a nation-wide Special Antimicrobials Use Rectification program. This program includes antimicrobial stewardship in hospitals, AMR monitoring systems, mandatory negative lists of clinical conditions and antimicrobial prescription limits[40-41]. There is some level from county and tertiary hospitals of reductions in AMU following these initiatives[42-44]. However, little is known about the effects of these reforms/programs on AMU in primary settings, especially in resource-poor rural areas.

Our study aimed to describe current AMU and help seeking from medical doctors (HSMD) for three common infections, ARTIs, urinary tract infections (UTIs) and GTIs among rural residents in Anhui province, China to assess current practice and help inform interventions to tackle the growing problem of AMR. Most previous studies examining AMU in rural China were based on extracted data from incomplete service logs preserved at primary care settings or exit surveys of patients to these caregivers. Studies using community samples in China are few and it is hoped that the findings of this survey will add to this literature and inform future policy reforms and interventions both in Anhui province and other rural settings in China.

Methods

Study design and population

Participants were recruited via a stratified-cluster randomized sampling among rural residents of Anhui province. Anhui is representative of over 80% of the population in the nation. Anhui is one of the three self-selected pilot provinces in China and as such has been proactive in implementing the New Health System Reformation which includes optimization of AMU. A sample size of 2760 was required to identify (n=140) cases of symptoms of ARTIs, GTIs and UTIs based on empirical incidence estimates of the infections (ARTIs=85%, GTIs=16%, UTIs=5%) adjusted for a 90% response rate. Participants were selected from 12 administrative villages (a purposive sample to ensure a wide range of villages) via a four step process. Step 1 classified all the counties in Anhui province into southern, northern and middle areas. Step 2 randomly selected 4 counties from each of the areas and then 1 township

from each of the counties and 1 administrative village from each of the townships. Step 3 randomly selected 230 households from each of the 12 administrative villages. Step 4 consisted of randomly selecting one eligible member from each household. The randomization used a web-based aid. Eligibility criteria included men and women who: a) were living in the sampled village when the survey was conducted; b) were aged 18 years and over; and c) deemed able to answer the survey questions.

Questionnaire

A structured questionnaire was developed to collect information on the prevalence of symptoms of common infections, HSMD in any setting and recall of antimicrobial prescription for those infections and potential determinants (Appendix 1). An annual rate of experience of possible ARTIs was determined based on self- reported symptoms. Rates of self-reported symptoms of GTIs and UTIs in the past 3 months were also calculated. Self-medication was defined as using of medicines without prescription including medicines: a) bought from a pharmacy or medicine shop; b) left-over from previous illnesses or given by relatives. An antimicrobials-related knowledge score (ARKS) was calculated using responses to a selected subset of tailored questions related to AMR. Responses to these questions were scored, post-hoc, as incorrect (score=0) or correct [score=1]. ARKS was derived by adding up all of the scores for the knowledge questions with a higher score indicative of better knowledge about antimicrobials (for detailed scoring system, please see Appendix 2). The questionnaire included questions on factors identified a priori as potential confounders (sex, age, education and health insurance cover (NRCMS, other health insurance systems).

Data collection

Data collection took place from 22 July to 11 August 2015. The structured questionnaire was administered face-to-face by selected students from Anhui Medical University at the households of the respondents. Twelve students were divided into two equal teams and led by a quality supervisor, with each team preforming data collection at 6 site villages consecutively. Data collection took about 3-4 days per village and each interview, about 15 minutes. Measures taken to ensure data quality included: a) piloting and revision of the questionnaire; b) training and examination of field data collectors (including questionnaire administration and taking informed consent); c) daily checks of all the questionnaires completed during the day by quality supervisors; d) retest of 5 % randomly selected subjects; and e) feedback of errors found via the daily checks and retests.

Data management and analysis

Questionnaire responses were double-entered into a database using EPI DATA 3.1 and then extracted and analyzed using SPSS 10.01 and Microsoft Excel 2013. Data analysis comprised descriptive estimations and multivariate logistic regression modeling to assess factors associated with help seeking from a medical doctor, use of prescribed oral antimicrobials, use of prescribed intravenous (IV) antimicrobials and use of prescribed oral or IV antimicrobials or both (oral/IV antimicrobials) adjusted by sex, age (years), education.

Patient and public involvement

Development of the research questions and outcome measures was based on qualitative

interviews and pilot tests of residents and village doctors in site communities purposefully selected from rural Anhui Province where the full survey was carried out. The study involved recruitment of and face-to-face interviews with residents after informed consent. Summary reports about the study results will be disseminated to the participating individuals and communities through relevant local websites, newspapers etc.

Results

Socio-demographic characteristics and reported symptoms of common infections

Of the 2760 sampled, 2611 (95%) rural residents completed the questionnaire. Participants had a mean age of 53 years, ranging from 18 to 95 years old (Table 1). Female rural residents made up 60% of the sample. One third (865, 33%) of the sample had no formal education and 2558 (98%) of them were insured. A total of 886 (33.9%) respondents scored 0 and only 317(12.1%) of them scored 3 or more (maximum score 6). Respondents who had reported symptoms of ARTI in the past year added up to 2223 (85%), and 425 (16%) and 133 (5%) reported GTI and UTI in the past three months respectively.

Help-seeking from medical doctor following reported symptoms of common infections

Out of the 2221 patients who had reported ARTI symptoms in the past year, 1319 (59.4%) had sought help from a medical doctor in response to the symptoms, compared with 28% of respondents reporting GTI and 42% of those reporting UTI, in the past three-months (Table 2). Around two thirds (82% for ARTIs, 87% for GTIs and 66% for UTIs) of respondents with symptomatic infections sought help from a medical doctor within three days of first experiencing symptoms. Of those participants who had recovered from the reported infection

when the survey was conducted, over three quarters (88% for ARTIs, 98% for GTIs and 77% for UTIs) reported complete recovery within 7 days. The median recovery period for ARTI type illness was 4 days, compared with 2 days for GTIs and 4 days for UTIs. Nonparametric tests revealed mixed differences in recovery period for the three categories of infections between participants who had sought help from a doctor and those who had not. Those who had sought help for ARTI reported a longer recovery period than those who hadn't ARTIs ($p<0.001$) but the period was shorter for GTIs ($p<0.001$); while no significant difference was found for UTIs ($p=0.073$). Appendix 3 gives details of HSMD for perceived symptoms of ARTIs by different subgroups. The proportion of respondents with ARTI symptoms who had HSMD increased steadily with age (OR=1.23, 95CI:1.16-1.31), but decreased with years of education (OR=0.72, 95CI:0.66-0.78). These trends were consistent between sex subgroups. The time-lag between ARTI onset and HSMD did not vary by age or education. A higher proportion of respondents recalled HSMD in day 2 and 3 of illness onset for all age and education subgroups.

Use of prescribed antimicrobials after infections

Of the respondents who recalled HSMD for their ARTI symptoms, 1059 (80%), 176 (13%), 60 (5%) and 29 (2%) reported visiting a village clinic, township health center, county hospital or higher level hospital, respectively. Of the respondents reporting HSMD, 1051 (95%) said that they had been prescribed oral, IV antimicrobials or both (Table 3). The proportion of respondents who recalled being prescribed antimicrobials for a GTI or UTI was slightly lower than for an RTI at 82% and 70% respectively. Oral antimicrobials were more frequently

prescribed than IV antimicrobials. There was no statistical evidence of an association between timing of help seeking and being prescribed antimicrobials.

Self-medication with antimicrobials following infections

354(17%) people reported self-medication with antimicrobials for ARTIs, 36 (9%) for GTIs and 22 (17%) for UTIs respectively (Table 4). Reported self-medication with antimicrobials left-over from previous illnesses or given by relatives to treat these symptoms was 290 (13%) for ARTIs, 43(11%) for GTIs and 10(8%) for UTIs. The majority of customers to medicine shops bought antimicrobials, being 354 out of 658 (63%) customers with ARTIs, 36 out of 83 (51%) customers with GTIs and 22 out of 33 (73%) customers with UTIs.

Determinants of help seeking from a medical doctor and antimicrobials use

Table 5 presents the results of the multivariate logistic regression models aimed at exploring determinant factors of HSMD, HSMD at village clinic, HSMD at township or higher level, oral/ IV AMU, prescribed oral AMU and IV AMU following an ARTI. We did not explore factors associated with HSMD for GTIs and UTIs due to the small number of cases. After controlling for a priori confounders (age, sex and education). HSMD was inversely associated with ARKS with people with greater knowledge about antimicrobials having lower odds of HSMD in response to their ARTI. There was no association between ARKS and reported prescription of oral or IV antimicrobials. However, respondents with a higher ARKS score (3 or more) were less likely to be prescribed oral/ IV antimicrobials compared with those with a score of 0 (OR=0.32, 95% CI: 0.13-0.78). Age displayed a negative association with prescribed oral AMU (OR=0.81, 95%CI: 0.71-0.93) but a positive relationship with

prescribed IV AMU (OR=1.21, 95%CI: 1.10-1.33). Health insurance was associated with HSMD (OR=0.33, 95% CI: 0.17-0.66). With insured respondents having higher odds of HSMD at village clinics but lower odds of HSMD from higher tier facilities compared with uninsured respondents (OR=0.17, 95% CI: 0.06-0.51 for HSMD at village clinics; OR=5.90, 95% CI: 1.99-17.47 for HSMD at township or higher levels).

Discussion

Key findings

This study has provided an important insight into HSMD for common infections in rural China. Symptoms of infections were commonly reported and most people sought help soon after developing symptoms. Most (94%) people seeking help from village clinics for ARTI recalled being prescribed either oral or IV AMU or a combination of both. The reported antimicrobials prescription rates for GTIs and UTIs were lower than that for ARTIs but was still very high at 82% and 70% respectively. Prescribed AMU was not associated with most of the patients' demographics except for ARKS and older patients were more likely to be prescribed with IV AMU. Self-medication with antimicrobials bought from medicine shops without prescriptions was reported by nearly 17% of people for ARTIs, 9% for GTIs, and 17% for UTIs; while self-medication with use of antimicrobials left-over from previous illnesses or given by relatives was reported by 13% for ARTIs, 11% for GTIs and 8% for UTIs. Greater knowledge about antimicrobials, greater educational attainment were all associated with lower levels of HSMD which suggests better education may reduce unnecessary attendances. As expected, lack of insurance was also associated with lower odds

of HSMD.

Implications in context of other research and for policy

The study findings have important implications. The very high reported rate of antimicrobial prescriptions in our study indicates that prescription rates remain high in rural areas and contradicts a common belief among policymakers in China that overuse and misuse of antimicrobials is being brought under control as a result of the nationwide Special Antimicrobials Use Rectification program (initiated in 2011) and the New Health System Reforms[42-44]. Given that about 57% of China's vast population lives in rural areas and over 70% of antimicrobial prescriptions occur at primary care settings[45, 46], there is a clear need for policies and interventions focused primarily on inappropriate AMU in primary care settings and communities. This is further supported by the finding of no apparent association between antimicrobials prescribing and days to service seeking after ARTIs.

The study also highlights the need for action to reduce self-medication with antimicrobials leftover from previous illnesses or given by relatives or bought over-the-counter without prescriptions. The consequences of self-medication are difficult to study but the risks are significant. The reported high level of self-medication with left-over antimicrobials from previous illnesses is likely to be indicative of both over prescription by clinicians, and poor compliance by patients, While reasons underlying the use of self-obtained antimicrobials may be complex, our study identified higher use of reported self-medication in the younger and more educated groups which is in line with previous studies[47] despite policies which ban the sale of antimicrobials without prescriptions. Future interventions to increase knowledge about

appropriate use of antimicrobials should include information about the harms of self-medication.

There may be benefit from differentiated strategies in tackling AMU-related behaviors. Our finding of an association between sex, education, health insurance and knowledge of antimicrobials with HSMD rather than use of prescribed AMU may suggest the former is dominated by patient-side factors, whilst the latter, may be more influenced by physician-side factors which were not measured in this study. Similarly, the variations in HSMD for ARTIs (59%), UTIs (42%) and GTIs (28%) may reflect the severity and pattern of progression of symptoms of the different infections with patients with acute and aggravating or persisting symptoms being more likely, than those with milder and diminishing symptoms, to seek professional healthcare. Albeit we did not investigate the reasons people chose either to seek, or not to seek professional help and it would be useful to explore this in further depth in future research.

Our findings also point to a need for understanding and tackling AMU/AMR in a socio-culturally sensitive way. Compared with findings from research in the UK and other western countries, our respondents reported more frequent symptoms of infections and higher and earlier HSMD following the infections. These variations may not be solely explained by differences in pathogens and host immunity between nations. Rather, China's strong culture of collectivism may have played an important role which requires each family member be sensitive to the health of other members and urges the sick to seek help from a doctor as soon as possible[48]. In addition, the relatively low HSMD for UTIs as compared to that for ARTIs

and GTIs may also be partly attributable to conservative values about sex, and consequently help-seeking for related conditions, held by Chinese, especially those in rural areas[49].

Strengths and limitations of the study

The study has both strengths and limitations. It is the first survey that collected data from healthcare users via a household survey whilst most of the existent research on AMU in China uses data from medical records or reports by medical care givers who may be incentivized to omit recording overuse or misuse of antimicrobials so as to meet relevant policy requirements[50]. As healthcare receivers, household members may be free from these concerns and hence more willing to report AMU. However, self-reported AMU may be prone to bias due, for example, to recall issues particularly among the elderly, inability to distinguish antimicrobials from other drugs which may be an issue among the less-well educated and over or under reporting by the respondents for reasons like perceived expectations from the researchers.

Next steps and future research required

Excessive prescribing of antimicrobials in primary care settings in rural Anhui is prevalent despite China's special rectification program and health systems reforms aimed at tackling the problem. There is a clear need to target existing interventions at primary care level and to develop bespoke, community appropriate interventions if we are to reduce antimicrobial prescribing in China. Further work is under way to identify pathways for optimizing AMU in rural Anhui and China via multidisciplinary qualitative research with specific attention being put on its key social, cultural, economic, clinical, health systems, behavioral and other

determinants to help inform future interventions.

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Table 1 Socio-Demographic Characteristics and Reported Symptoms of Common Infections among Rural Residents (N=2611)

Subgroups	Total in sample n (%)	Ranges of years of age (n/%)					
		≤30	31-40	41-50	51-60	61-70	≥71
Sex							
Male	1082(41.4)	76 (7.0)	106 (9.8)	244 (22.6)	190 (17.6)	289 (26.7)	177 (16.4)
Female	1529 (58.6)	164 (10.7)	186 (12.2)	382 (25.0)	327 (21.4)	309 (20.2)	161 (10.5)
Education							
No formal education	865 (33.1)	1 (0.1)	19 (2.2)	126 (14.6)	194 (22.4)	321 (37.1)	204 (23.6)
Primary school	694 (26.6)	7 (1.0)	58 (8.4)	239 (34.4)	122 (17.6)	189 (27.2)	79 (11.4)
Middle school	778 (29.8)	124 (15.9)	163 (21.0)	221 (28.4)	152 (19.5)	72 (9.3)	46 (5.9)
Higher School	274 (10.5)	108 (39.4)	52 (19.0)	40 (14.6)	49 (17.9)	16 (5.8)	9 (3.3)
Health insurance							
Insured	2558(98.3)	231(9.0)	290 (11.3)	612 (23.9)	507 (19.8)	587 (22.9)	331 (12.9)
Uninsured	45 (1.7)	7 (15.6)	1 (2.2)	11 (24.4)	10 (22.2)	9 (20.0)	7 (15.6)
ARKS † (max score 6)							
≥3 scores	317 (12.1)	81 (25.6)	69 (21.8)	85 (26.8)	43 (13.6)	31 (9.8)	8 (2.5)
1-2 scores	1408 (53.9)	141 (10.0)	175 (12.4)	368 (26.1)	289 (20.5)	295 (21.0)	140 (9.9)
No ARKS	886 (33.9)	18 (2.0)	48 (5.4)	173 (19.5)	185 (20.9)	272 (30.7)	190 (21.4)
Acute respiratory tract infections ‡							
Yes	2223 (85.1)	222 (10.0)	266 (12.0)	535 (24.1)	435 (19.6)	495 (22.3)	270 (12.1)
No	388 (14.9)	18 (4.6)	26 (6.7)	91 (23.5)	82 (21.1)	103 (26.5)	68 (17.5)
Gastro-intestinal tract infections §							
Yes	425 (16.3)	60 (14.1)	60 (14.1)	89 (20.9)	84 (19.8)	84 (19.8)	48 (11.3)
No	2186 (83.7)	180 (8.2)	232 (10.6)	537 (24.6)	433 (19.8)	514 (23.5)	290 (13.3)
Urinary tract infections §							
Yes	133 (5.1)	3 (2.3)	14 (10.5)	39 (29.3)	29 (21.8)	34 (25.6)	14 (10.5)
No	2477 (94.9)	237 (9.6)	278 (11.2)	586 (23.7)	488 (19.7)	564 (22.8)	324 (13.1)

Note. † Antimicrobials-related knowledge score; ‡ most recent episode within the past 12 months; § episode within the past 3 months.

Table 2 Help-Seeking from Medical Doctor Following Reported Symptoms of Selected Common Infections

Service use	Acute respiratory tract infections (ARTIs) †		Gastro-intestinal tract infections (GTIs) ‡ (n=425)		Urinary tract infections (UTIs) ‡ (n=133)	
	n	%	n	%	n	%
1) Help-seeking from medical doctor						
Yes	1319	59.4	118	27.8	56	42.1
No	902	40.6	307	72.2	77	57.9
Not stated	2	NA	0	NA	0	NA
2) Days until complete recovery after onset of symptoms						
Day 1	52	2.4	98	25.9	6	4.7
Day 2	262	12.3	114	30.2	18	14.1
Day 3	520	24.4	65	17.2	19	14.8
Day 4	301	14.1	30	7.9	10	7.8
Day 5	167	7.8	12	3.2	5	3.9
Day 6	64	3.0	4	1.1	1	0.8
Day 7	365	17.1	8	2.1	11	8.6
Day 8+	231	10.9	7	1.9	21	16.4
Not yet recovered	167	7.8	40	10.6	37	28.9
Not stated	94	NA	47	NA	5	NA
3) Days until first help-seeking from medical doctor after onset of symptoms §						
Day 1	257	19.8	41	35.7	4	7.5
Day 2	471	36.3	46	40.0	19	35.9
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Day 4+	230	17.7	15	13.0	18	34.0
Not stated	22	NA	3	NA	3	NA

Note. † most recent episode within the past 12 months; ‡ episode within the past 3 months; § includes only those who stated "yes" to use of professional health-care service; NA stands for not applicable.

Table 3 Reported Use of Prescribed Antimicrobials for Common Infections Following Help-Seeking from Medical Doctors

Antimicrobials use	Acute respiratory tract infections(ARTIs) † (n=1319)		Gastro-intestinal tract infections (GTIs) ‡ (n=118)		Urinary tract infections (UTIs) ‡ (n=56)	
	n	%	n	%	n	%
1) Respondents with clear memory of receiving prescribed oral antimicrobials						
Yes	638	72.7	34	49.3	32	74.4
No	240	27.3	33	50.7	11	25.6
Not clear	409	NA	43	NA	12	NA
Not stated	32	NA	8	NA	1	NA
2) Respondents with clear memory of receiving an intravenous antimicrobials						
Yes	705	54.7	48	42.5	12	22.6
No	584	45.3	65	57.5	41	77.4
Not clear	17	NA	3	NA	3	NA
Not stated	13	NA	2	NA	0	NA
3) Respondents with clear memory of receiving oral/intravenous antimicrobials						
Yes	1051	94.5	67	81.7	38	70.4
No	61	5.5	15	18.3	16	29.6
Not clear	197	NA	32	NA	1	NA
Not stated	10	NA	4	NA	1	NA
4) Prescribed oral/intravenous antimicrobials by days after onset of symptoms when the first professional service seeking took place §						
Day 1	178	91.8	20	80.0	1	25.0
Day 2	383	93.9	27	79.4	14	77.8
Day 3	286	96.0	8	88.9	8	66.7
Day 4+	189	95.9	12	85.7	13	76.5
Not stated	15	NA	0	NA	2	NA

Note. † most recent episode within the past 12 months; ‡ episode within the past 3 months; § includes only those who stated "yes" to clearly remembering receiving oral or intravenous antimicrobials or both; Oral/intravenous antimicrobials means oral or intravenous antimicrobials or both; NA stands for not applicable.

Table 4 Use of Self-Medication with Antimicrobials for Suspected Infections

Self-medication use	Acute respiratory tract infections(ARTIs) † (n=2223)		Gastro-intestinal tract infections (GTIs) ‡ (n=425)		Urinary tract infections (UTIs) ‡ (n=133)	
	N	%	N	%	N	%
1) Respondents who bought medicines for suspected infection without prescriptions						
Yes	658	29.8	83	19.8	33	24.8
No	1551	70.2	337	80.2	100	75.2
Not stated	14	NA	5	NA	0	NA
2) Antimicrobials bought for suspected infection without prescriptions §						
Yes	354	62.5	36	51.4	22	72.7
No	212	37.5	34	48.6	6	27.3
Not stated	92	NA	13	NA	5	NA
3) Respondents who bought antimicrobials for suspected infection without prescriptions						
Yes	354	16.7	36	8.8	22	17.2
No	1763	83.3	371	91.2	106	82.8
Not stated	106	NA	18	NA	5	NA
3) Use of antimicrobials leftover from previous illness or given by relatives						
Yes	290	13.4	43	10.8	10	7.6
No	1872	86.6	356	89.2	122	92.4
Not stated	61	NA	26	NA	1	NA

Note. † most recent episode within the past 12 months; ‡ episode within the past 3 months; § includes only those who stated "yes" to buy medicines for suspected infection without prescriptions; NA stands for not applicable.

Table 5 Help Seeking from a Medical Doctor (HSMD) and Use of Prescribed Antimicrobials Following Respiratory Tract Infections by Type of Health Insurance and Antimicrobials-Related Knowledge Score

Category	HSMD (n=2216)		HSMD at village clinic (n=1317)		HSMD at township or higher level (n=1317)		Use of prescribed oral/ IV antimicrobials (n=1111)		Use of prescribed oral antimicrobials (n=877)		Use of prescribed IV antimicrobials (n=1288)	
	n	OR (95% CI)	n	OR (95% CI)	n	OR (95% CI)	n	OR (95% CI)	n	OR (95% CI)	n	OR (95% CI)
Gender												
Female	1352	Ref.	780	Ref.	780	Ref.	666	Ref.	531	Ref.	764	Ref.
Male	864	1.40(1.15-1.70)**	537	0.98(0.68-1.40)	537	1.15 (0.84-1.56)	445	1.26(0.70-2.27)	346	1.13(0.80-1.58)	524	0.89(0.70-1.15)
Age group												
≤30	219	Ref.	107	Ref.	107	Ref.†	91	Ref.	73	Ref.†	106	Ref.
31-40	265	0.89(0.61-1.30)	139	0.84(0.42-1.68)	139	0.99 (0.52-1.90)	122	0.70(0.21-2.31)	108	1.90(0.92-3.92)	137	0.78(0.46-1.32)
41-50	534	0.77(0.54-1.10)	291	0.42(0.21-0.86)	291	0.58 (0.30-1.10)	249	0.66(0.21-2.09)	209	1.42(0.73-2.77)	289	0.91(0.55-1.48)
51-60	435	0.82(0.57-1.19)	254	0.84(0.42-1.65)	254	1.12 (0.60-2.08)	212	0.75(0.22-2.53)	173	1.16(0.59-2.30)	248	0.94(0.57-1.56)
61-70	494	0.93(0.62-1.38)	326	0.84(0.41-1.71)	326	1.22 (0.64-2.33)	282	0.64(0.18-2.23)	210	0.59(0.29-1.19)	319	1.81(1.07-3.07)*
≥71	269	1.30(0.83-2.04)	200	0.70(0.32-1.53)	200	1.24 (0.63-2.46)	155	0.48(0.13-1.82)	104	0.77(0.36-1.68)	189	1.77(1.00-3.11)
Education group												
No formal education	718	Ref.	492	Ref.	492	Ref.	405	Ref.	302	Ref.	476	Ref.
Primary school	596	0.78(0.61-1.00)	370	1.04(0.68-1.60)	370	1.10 (0.76-1.59)	317	0.70(0.34-1.43)	250	0.86(0.57-1.29)	364	0.98(0.72-1.32)
Middle school	658	0.58(0.44-0.76)**	344	0.84(0.50-1.41)	344	0.85 (0.55-1.33)	288	0.76(0.33-1.79)	235	0.80(0.49-1.30)	337	0.99(0.70-1.40)
Higher School	244	0.48(0.33-0.70)**	111	1.23(0.61-2.47)	111	1.51 (0.83-2.76)	101	0.61(0.20-1.88)	90	0.59(0.30-1.16)	111	1.25(0.75-2.08)
Health insurance												
Insured	2178	Ref.	1303	Ref.	1303	Ref.	1099	Ref.	9	Ref.	1274	Ref.
Uninsured	38	0.33(0.17-0.66)**	14	0.17(0.06-0.51)**	14	5.90 (1.99-17.47) **	12	0.55(0.07-4.42)	868	0.57(1.45-2.20)	14	0.77(0.27-2.25)
ARKS												
No ARKS	726	Ref.	498	Ref.	498		398	Ref.	302	Ref.	482	Ref.
1-2 scores	1208	0.77(0.63-0.95)*	707	1.18(0.82-1.71)	707	1.33 (0.97-1.82)	610	0.80(0.42-1.50)	484	1.13(0.81-1.59)	695	1.11(0.86-1.43)
≥3 scores	282	0.42(0.31-0.58)**	112	1.46(0.78-2.76)	112	1.30 (0.73-2.31)	103	0.32(0.13-0.78)*	91	1.16(0.64-2.11)	111	0.77(0.48-1.21)

Note. * or ** stand for p< 0.05 or p < 0.01 for the differences between the reference and study subgroup; †, p < 0.05 for the variable in the overall regression model; Oral/IV antimicrobials, oral or intravenous antimicrobials or both; ARKS, antimicrobial-related knowledge score

Household survey questionnaire on antimicrobial use by rural residents

Number of household：|__|__|__|__|__|__|__|__|

Name of local village：_____ county _____ townships _____ village _____ group

Part A Socio-demographics

1.1 Name: ____

1.2 Gender: 1=male; 2=female

1.3 Birth date: ____/_____/____（MM/DD/YY）

1.4 Days living in the local village in the past year: ____days.

1.5 Education: 0=illiterate; 1=primary schooling; 2=middle schooling; 3=secondary schooling; 4=higher schooling

1.6 Participants of the New Cooperative Medical System? 1=yes; 2=no

1.7 Enrollee of other health insurances? (please enter details)

Part B Symptoms of infections and service/antimicrobial use

2.1 Have you caught cold or presented with sneeze/cough etc during the past year?

- ☐ Yes
- ☐ No (skip to2.20)

2.2 Please recall the date of the last time when you caught cold or presented with sneeze cough etc.?

- ☐ ____/_____/____（MM/DD/YY）

2.3 Did you seek professional service for the illness?

- ☐ Yes
- ☐ No(Skip to 2.14)

2.4 How many times you had visited health care settings for the illness?

- ☐ ____times

2.5 Which kinds of settings you had sought service from?

- ☐ The village clinic
- ☐ Township health center
- ☐ County hospital
- ☐ Higher level hospital
- ☐ Others（please provide details）_____

2.6 How many days it took between you first felt the illness and you sought health care?

- ☐ ____days

2.7 How many kinds of antimicrobials in total had your doctor or doctors prescribed for you?

- ☐ No antibiotics
- ☐ ____kinds of atibiotics
- ☐ Not clear

2.8 How many kinds of traditional Chinese medicine in total had your doctor or doctors prescribed for you?

- ☐ ____kinds

☐ Not clear

2.9 Please proved the detailed drug name that you got from doctor or doctors

☐ _____

2.10 How many bottles of transfusions in total you had used for the illness?

☐ ____bottles

☐ Not clear

2.11 How many times of injections in total you had received?

☐ ____times

☐ Not clear

2.12 How many kinds of pills in total you had taken?

☐ ____kinds

☐ Not clear

2.13 Did your doctor or doctors do the following to you in treating the illness?

☐ Telling you that your illness need not any medications

☐ Telling you that you'd better wait for a few days and see wheather you need medications

☐ Discussing with you benefits and disbenefits of different therapies and then making a shared decision on what medication to use

2.14 Did you buy medicines from pharmacies without doctor's prescriptions for the illness?

☐ Yes

☐ No（skip to 2.17）

2.15 How many kinds of medicine in total you had buy from pharmacies?

☐ ____kinds

2.16 These medications includes how many kinds of antimicrobials?

☐ ____kinds

2.17 Did you use antimicrobials left behind from previous illness or given by relatives for the illness?

☐ Yes

☐ No

2.18 How many days it took for you to recover from the illness?

☐ _____days

☐ Not yet recovery

2.19 How much did you spent on the illness?

☐ _____Yuan

2.20 Did you get diarrhea and gastroenteritis in the past 3 monthes?

☐ Yes

☐ No（skip to 2.36）

2.21 Did you seek professional service for the illness?

☐ Yes

☐ No（skip to 2.30）

2.22 How many times you had visited health care settings for the illness?

☐ ____times

2.23 Which kinds of settings you had sought service from?

☐ The village clinic

☐ Township health center
☐ County hospital
☐ Higher level hospital
☐ Others（please provide details）_____

2.24 How many days it took between you first felt the illness and you sought health care?
☐ ____days

2.25 How many kinds of antimicrobials in total had your doctor or doctors prescribed for you?
☐ ____kinds
☐ Not clear

2.26 How many kinds of traditional Chinese medicine in total had your doctor or doctors prescribed for you?
☐ ____kinds
☐ Not clear

2.27 How many bottles of transfusions in total you had used for the illness?
☐ ____bottles
☐ Not clear

2.28 How many times of injections in total you had received?
☐ ____times
☐ Not clear

2.29 How many kinds of pills in total you had taken?
☐ ____kinds
☐ Not clear

2.30 Did you buy medicines from pharmacies without doctor's prescriptions for the illness?
☐ Yes
☐ No（skip to 2.33）

2.31 How many kinds of medicine in total you had buy from pharmacies?
☐ ____kinds

2.32 These medications includes how many kinds of antimicrobials?
☐ ____kinds

2.33 Did you use antimicrobials left behind from previous illness or given by relatives for the illness?
☐ Yes
☐ No

2.34 How many days it took you to recover from the illness?
☐ _____dyas
☐ Not yet recovery

2.35 How much did you spent on the illness?
☐ _____Yuan

2.36 Did you get urethritis in the past 3 monthes?
☐ Yes
☐ No（skip to 3.1）

2.37 Did you seek professional service for the illness?
☐ Yes
☐ No（skip to 2.46）

2.38 How many times you had visited health care settings for the illness?

☐ ____times

2.39 Which kinds of settings you had sought service from?

☐ The village clinic

☐ Township health center

☐ County hospital

☐ Higher level hospital

☐ Others（please provide details）_____

2.40 How many days it took between you first felt the illness and you sought health care?

☐ ____days

2.41 How many kinds of antimicrobials in total had your doctor or doctors prescribed for you?

☐ ____kinds

☐ Not clear

2.42 How many kinds of traditional Chinese medicine in total had your doctor or doctors prescribed for you?

☐ ____kinds

☐ Not clear

2.43 How many bottles of transfusions in total you had used for the illness?

☐ ____bottles

☐ Not clear

2.44 How many times of injections in total you had received?

☐ ____times

☐ Not clear

2.45 How many kinds of pills in total you had taken?

☐ ____kinds

☐ Not clear

2.46 Did you buy medicines from pharmacies without doctor's prescriptions for the illness?

☐ Yes

☐ No（skip to 2.49）

2.47 How many kinds of medicine in total you had buy from pharmacies?

☐ ____kinds

2.48 These medications includes how many kinds of antimicrobials?

☐ ____kinds

2.49 Did you use antimicrobials left behind from previous illness or given by relatives for the illness?

☐ Yes

☐ No

2.50 How many days it took for you to recover from the illness?

☐ _____days

☐ Not yet recovery

2.51 How much did you spent on the illness?

☐ _____Yuan

Part C antimicrobial-related knowledge

3.1 In your opinion antimicrobials can kill or control which of the following pathogens?

- ☐ Bacterier
- ☐ Virus
- ☐ Parasitic
- ☐ Don't kown

3.2 Do you think more kinds of antimicrobials more effective than fewer kinds of antimicrobials?

- ☐ Yes
- ☐ No
- ☐ It depends
- ☐ Not clear

3.3 What are the dis-benefits of using antimicrobials?

- ☐ Side-effects
- ☐ Drug resistance
- ☐ Economic burden
- ☐ Others（please provide details）

3.4 What do you think the main side-effects of antimicrobials?

- ☐ Allergic responses
- ☐ Liver damage
- ☐ Kidney damage
- ☐ Hearing damage
- ☐ Anemia and other blood problems
- ☐ Dizziness/headache
- ☐ Gastrointestinal discomfort
- ☐ Not clear
- ☐ Others（please provide details）

3.5 Which of the following symptoms do not need antimicrobials in general?

- ☐ Cold
- ☐ Sore throat
- ☐ Sneeze
- ☐ Cough
- ☐ Fever
- ☐ Bronchitis
- ☐ Sinusitis
- ☐ Otitis media
- ☐ Urinary infectious
- ☐ Diarrhea

3.6 Do you think frequent use reduces effectiveness of antimicrobials?

- ☐ No
- ☐ Not sure
- ☐ Yes

3.7 Traditional Chinese medicine is not effective for which of the following symptoms?

- ☐ Cold
- ☐ Sore throat
- ☐ Sneeze

- ☐ Cough
- ☐ Fever
- ☐ Bronchitis
- ☐ Sinusitis
- ☐ Otitis media
- ☐ Urinary infectious
- ☐ Diarrhea

Appendix 2 Scoring system and summary of antimicrobials-related knowledge

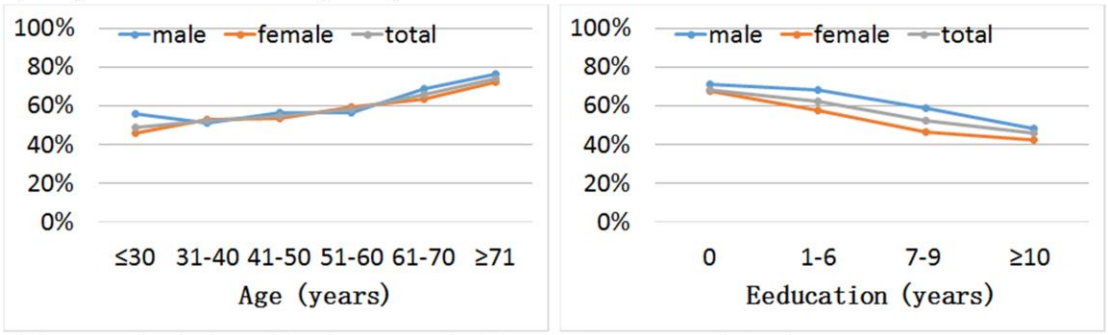
a) Scoring system of antimicrobials-related knowledge

Antimicrobials-related Knowledge	Score
Q1: In your opinion antimicrobials can kill or control Bacteria and Parasitic?	0-2
Q2: Do you think using a combination of antimicrobials is more effective than just one using?	0/1
Q3: Does unnecessary use of antimicrobials make drug resistance?	0/1
Q4: Does the common cold need antimicrobials in general?	0/1
Q5: Do you think frequent use reduces effectiveness of antimicrobials?	0/1
	Max score 6

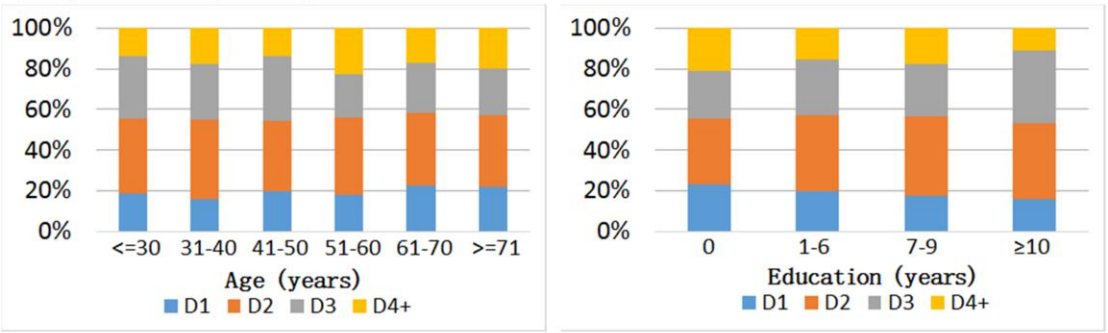
b) Antimicrobials-related Knowledge score (ARKS) by education group

ARKS	Total n (%)	Education group (n/%)			
		No formal education	Primary school	Middle school	Higher School
No ARKS	886 (33.9)	445 (50.2)	262 (29.8)	154 (17.4)	23 (2.6)
1-2 scores	1408 (53.9)	400 (28.4)	378 (26.8)	480 (34.1)	150 (10.7)
≥3 scores	317 (12.1)	20 (6.3)	52 (16.4)	144 (45.4)	101 (31.9)

1) Respondents who had sought help from a medical doctor



2) Days of first help seeking from a medical doctor after onset of infection



3) Days of complete recovery after onset of infection

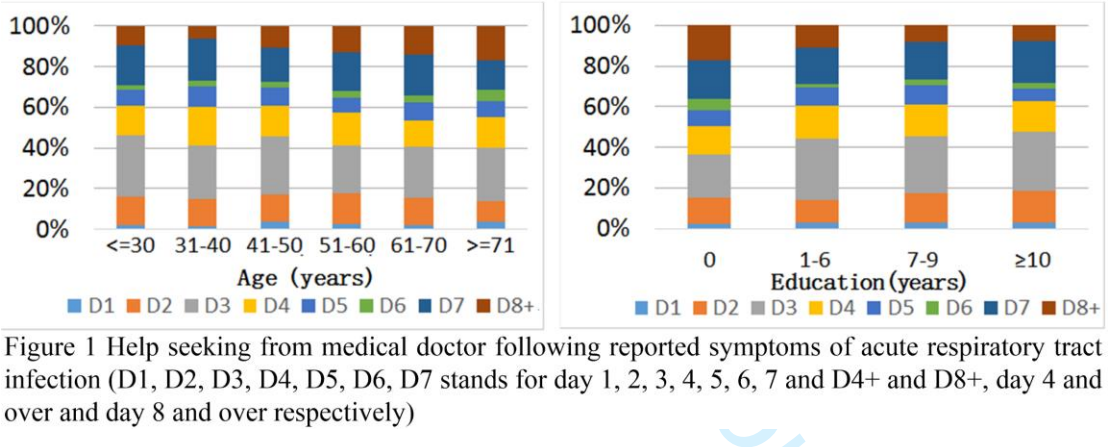


Figure 1 Help seeking from medical doctor following reported symptoms of acute respiratory tract infection (D1, D2, D3, D4, D5, D6, D7 stands for day 1, 2, 3, 4, 5, 6, 7 and D4+ and D8+, day 4 and over and day 8 and over respectively)

BMJ Open

Cross-sectional study of the use of antimicrobials following common infections by rural residents in Anhui, China

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Title: Cross-sectional study of the use of antimicrobials following common infections by rural residents in Anhui, China

Running title: Antimicrobials use in rural China

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Abstract

Objective: To describe help seeking behavior from a medical doctor and antimicrobial use for common infections among rural residents of Anhui province, China.

Design: A cross-sectional retrospective household survey.

Setting: 12 administrative villages from rural Anhui, China.

Participants: 2760 rural residents selected through cluster-randomized sampling using an interviewer administered questionnaire.

Method: Logistic regression models were used to estimate associations between exposures (health insurance and antimicrobial-related knowledge), adjusted for confounders (sex, age and education), and help seeking behavior from a medical doctor and antimicrobial use following common infections, including acute respiratory tract infections (ARTIs), gastrointestinal tract infections (GTIs) and urinary tract infections (UTIs).

Results: In total 2611(94.6%) rural residents completed the questionnaire. Help seeking from a medical doctor was highest for ARTIs (59.4%) followed by GTIs (42.1%), and UTIs (27.8%). Around two thirds (82.3% for ARTIs, 87.0% for GTIs and 66.0% for UTIs) of respondents sought help within 3 days following symptom onset and over three quarters (88% for ARTIs, 98% for GTIs and 77% for UTIs) reported complete recovery within 7 days. Of the help seeking respondents, 94.5% with ARTI symptoms recalled being prescribed either oral or intravenous(IV) antimicrobials (GTIs 81.7% and UTIs 70.4%). Use of antimicrobials bought from medicine shops without prescriptions ranged from 8.8% for GTIs to 17.2% for ARTIs; while use of antimicrobials leftover from previous illnesses or given by a relative ranged from 7.6% for UTIs to 13.4% for ARTIs. Multivariate logistic regression analysis

revealed that respondents with a higher antimicrobial-related knowledge score and lack of insurance were all associated with lower levels of help seeking for ARTIs; while respondents with a higher antimicrobial-related knowledge score were less likely to be prescribed either oral or IV antimicrobials.

Conclusions: Excessive antimicrobial use in the studied primary care settings is still prevalent.

Key Words: antimicrobial resistance, antimicrobial use, prescription, self-medication, pharmacoepidemiology

Strengths and limitations of this study

• The study added new data about the magnitude and determinants of antimicrobial use in China.

• The study distinguished doctor- versus patient-dominated responses toward infections and revealed misperceptions of patients' demand for antimicrobials.

• The study collected data from healthcare users via a household survey whilst most of the existent research on antimicrobial use in China uses data from medical records or reports by medical care givers.

• Self-reported antimicrobial use is prone to biases due to recall problems, inability to distinguish antimicrobials from other drugs, conformity to social norms and research expectations.

Introduction

Antimicrobial resistance (AMR) is a global health problem which claims at least 50,000 lives each year across Europe and the US, with many hundreds of thousands more dying in other parts of the world.[1] According to the World Health Organization, AMR is threatening our ability to treat common infections in both the community and health care settings.[2] Antimicrobial use, even when appropriate and conservative, contributes to the development of resistance, and inappropriate or excessive use should be avoided.[2-3] Numerous studies have reported the relationship between antimicrobial use and the development of resistance.[4-7] Countries consuming the highest amount of antimicrobials per capita have the highest rates of resistance.[8]

Excessive use of antimicrobials is a widespread problem. Evidence suggests that half of antimicrobial prescriptions are unnecessary or inappropriate for the illness being treated.[9-11] For instance, it is known that the majority of acute respiratory tract infections (ARTIs) and gastrointestinal tract infections (GTIs) are caused by viruses,[12] and yet antimicrobial treatment for such infections is common.[13–15]

Inappropriate use of antimicrobials and AMR are prevalent in China. Studies published from 2009 to 2013 found that over half of outpatients and around 70% of inpatients of hospitals in China were prescribed one or more antimicrobials.[16-21] The problem was even more acute in primary care settings, particularly in rural areas. It had been estimated that, in the same period, 70-90% of patients visiting village clinics with symptoms of respiratory tract infection were prescribed antimicrobials.[22-24] Widespread overuse and misuse of antimicrobials parallels

rapid growth of AMR in the nation.[25-27] Comparative studies on the patterns of AMR between different countries indicate that China has one of the highest levels and the fastest growth rates of AMR.[26, 28-32]

The antimicrobial use/AMR problem in China has been attributed to a variety of factors.[26, 33-36] China has a long history of nearly free consultations in which most patients only pay for prescribed medicines, making prescriptions an important source of revenue for care providers. These remuneration mechanisms have provided a perverse financial incentive for health care practitioners resulting in excessive prescribing of antimicrobials,[33, 34] particularly in the lower levels of the health system. Other determinants of antimicrobial use include expectations and beliefs about antimicrobials among patients;[35, 36] diagnostic uncertainty, prescribing habits and misperceptions among clinicians' about service-seekers expectations to receive antimicrobials.[37-39]

China has witnessed fundamental reforms of its healthcare system during the past decade. In 2003, the Chinese government introduced a new rural cooperative medical insurance system available to rural residents at a relatively small per capita annual cost. By 2009, almost 96% of rural residents were covered by this insurance. Starting in 2011, the central government implemented a nation-wide Special Antimicrobials Use Rectification program.[40,41] This program included antimicrobial stewardship in hospitals, AMR monitoring systems, mandatory negative lists of clinical conditions and antimicrobial prescription limits.[42,43] There is some evidence from county and tertiary hospitals of reductions in antimicrobial use following these initiatives.[44-46] However, little is known about the effects of these reforms and

programs on antimicrobial use in primary care settings, particularly those in resource-poor rural areas.

Our study aimed to describe current antimicrobial use and help seeking from a medical doctor for three common infections, including ARTIs, urinary tract infections (UTIs) and GTIs, among rural residents in Anhui province, China to help inform future interventions aimed at reducing AMR. Most previous studies examining antimicrobial use in rural China were based on extracted data from incomplete service logs preserved at primary care settings or exit surveys of patients visiting these caregivers.[47, 48] Studies using community samples in China are few and it is hoped that the findings of this survey will add to this literature and inform future policy reforms and interventions both in Anhui province and other rural settings in China.

Methods

Study design and population

Participants were recruited using a stratified-cluster randomized sampling approach targeting rural residents of Anhui province. Anhui is one of the three self-selected pilot provinces in China and as such has been proactive in implementing the New Health System Reformation which includes optimization of antimicrobial use. Being the baseline survey of a pilot intervention supported by the UK-China Strategic Prosperity Fund, the sample size was determined by the need to detect difference in antimicrobial use between intervention and control arms. A sample size of 2760 was required to identify (n=140) cases of UTIs (the lowest incidence among ARIs, GTIs and UTIs) based on empirical estimates of the infections

(UTIs=5%), use of antimicrobials following the infection (45%) and assumed effectiveness of the intervention (reduction in antimicrobial use by 30%) adjusted for a 90% response rate. Participants were randomly selected from 12 administrative villages via a four step process. Step 1 classified all the counties in Anhui province into southern, northern and middle areas. Step 2 randomly selected 4 counties from each area (n=12) and then 1 township from each of the counties and 1 administrative village from each of the townships. Step 3 randomly selected 230 households from each of the 12 administrative villages. Step 4 consisted of randomly selecting one eligible member from each household. The randomization used a web-based aid, a simple self-developed webpage which had an input box for entering the last number (say, n) of order (in terms of age) of eligible members within the household which randomly selecting a number between 1 and n. Eligibility criteria included men and women who were: a) living in the sampled village when the survey was conducted; b) aged 18 years or over; and c) deemed able to answer the survey questions.

Questionnaire

A structured questionnaire was developed to collect information on the prevalence of symptoms of common infections, help seeking from medical doctors in any setting and recall of antimicrobial prescription for those infections and other potential determinants (Appendix 1). An annual rate (R1) of experience of possible ARTIs was determined based on self-reported symptoms. Rates of self-reported symptoms of GTIs (R2) and UTIs (R3) in the past 3 months were also calculated. Here R1 (or R2 or R3) equals the number of respondents who had reported symptoms of ARTIs (or GTIs or UTIs) in the past year (or 3 months) divided by

the total number of respondents. Self-medication was defined as the use of medicines without prescription including those: a) bought from a pharmacy or medicine shop; b) left-over from previous illnesses or given by relatives. An antimicrobials-related knowledge score was calculated using responses to a selected subset of tailored questions related to AMR. Responses to these questions were scored, post-hoc, as incorrect (score=0) or correct (score=1). An antimicrobials-related knowledge score was derived by summing all of the scores for the knowledge questions with a higher score indicative of better knowledge about antimicrobials (for detailed scoring system, please see Appendix 2). Data was also collected on factors identified a priori as potential confounders including sex, age, education and health insurance cover (new rural cooperative medical system, other health insurance systems).

Data collection

Data collection took place from 22 July to 11 August 2015. The structured questionnaire was administered face-to-face by selected students from Anhui Medical University at the households of the respondents. Twelve students were divided into two equal teams and led by a quality supervisor, with each team conducting data collection at 6 study villages consecutively. Data collection took three to four days per village and each interview took about 15 minutes. Measures taken to ensure data quality included: a) piloting and revision of the questionnaire; b) training and examination of field data collectors (including questionnaire administration and taking informed consent); c) daily checks by quality supervisors of all the questionnaires completed during the day; d) retest of a 5% randomly selected sample of

subjects; and e) feedback of errors found via the daily checks and retests.

Data management and analysis

Questionnaire responses were double-entered into a database using EPI DATA 3.1 and then extracted and analyzed using SPSS 10.01 and Microsoft Excel 2013. Data analysis comprised descriptive estimations including nonparametric tests of association (Kruksal-Wallis) and multivariate logistic regression modeling to assess factors associated with help seeking from a medical doctor, use of prescribed oral antimicrobials, use of prescribed intravenous (IV) antimicrobials and use of prescribed oral or IV antimicrobials or both (oral/IV antimicrobials) adjusted by sex, age (years), education. Cases with missing data were excluded from the data analyses.

Patient and public involvement

Development of the research questions and outcome measures were informed by qualitative interviews and pilot tests with a purposively selected sample of rural residents and village doctors within the study site communities in Anhui province. The study involved recruitment of and face-to-face interviews with residents following informed consent. Summary reports about the study results will be disseminated to the participating individuals and communities through relevant local websites, newspapers and workshops.

Results

Socio-demographic characteristics and reported symptoms of common infections

Of the 2760 rural residents sampled, 2611 (95%) completed the questionnaire. Participants

had a mean age of 53 years, ranging from 18 to 95 years old (Table 1). Female rural residents made up 60% of the sample. One third (n=865) of the sample had no formal education and 2558 (98%) had health insurance. A third (n=886) of respondents had an antimicrobials-related knowledge score of zero, with only 317 (12.1%) participants scoring three or above (maximum score 6). A large proportion of respondents reported having symptoms of ARTI in the past year (n=2223; 85%), with smaller number, 425 (16%) and 133 (5%) reporting GTI and UTI symptoms in the past three months respectively.

Help-seeking from a medical doctor following reported symptoms of common infections

Of the respondents who had reported ARTI symptoms in the past year, 1319 (59.4%) reported seeking help from a medical doctor in response to the symptoms, compared with 28% of respondents reporting GTI symptoms and 42% of those reporting UTI symptoms, in the past three-months (Table 2). The proportion of respondents with symptomatic infections who sought help from a medical doctor within three days of first experiencing symptoms varied (82% for ARTIs, 87% for GTIs and 66% for UTIs). Of those participants who had recovered from the reported infection when the survey was conducted, over three quarters (88% for ARTIs, 98% for GTIs and 77% for UTIs) reported complete recovery within 7 days. The median recovery period for ARTI type illness was 4 days, compared with 2 days for GTIs and 4 days for UTIs. Kruskal-Wallis test revealed mixed differences in recovery period for the three categories of infections between participants who had sought help from a doctor and those who had not. Respondents who had sought medical help reported a longer recovery period for ARTIs than those who hadn't ($p<0.001$) but the recovery period was shorter for

GTIs ($p<0.001$); while no significant difference in recovery time was found for UTIs ($p=0.073$). Appendix 3 gives details of help seeking from a medical doctor for perceived symptoms of ARTIs by different subgroups. The proportion of respondents with ARTI symptoms who reported help seeking from a medical doctor increased by age-group (OR=1.23, 95% CI:1.16-1.31), but decreased with years of education (OR=0.72, 95% CI:0.66-0.78). These trends were consistent for males and females. The time-lag between ARTI onset and help seeking from a medical doctor did not vary by age or education. A higher proportion of respondents recalled seeking help from a medical doctor in day 2 and 3 following illness onset for all age and education subgroups.

Use of prescribed antimicrobials after infections

Of the respondents who recalled seeking help from a medical doctor for their ARTI symptoms, 1059 (80%) reported visiting a village clinic, 176 (13%) visited a township health center, 60 (5%) a county hospital and 29 (2%) a higher level hospital. Of the respondents who sought medical help for an ARTI 1051 (95%) said that they had been prescribed oral, IV antimicrobials or both (Table 3). The proportion of respondents who recalled being prescribed antimicrobials for a GTI or UTI was slightly lower at 82% and 70% respectively. Oral antimicrobials were more frequently prescribed than IV antimicrobials. There was no statistical evidence of an association between timing of help seeking and being prescribed antimicrobials.

Self-medication with antimicrobials following infections

Three-hundred and fifty-four (17%) people reported self-medication with antimicrobials for

ARTIs, 36 (9%) for GTIs and 22 (17%) for UTIs respectively (Table 4). Reported self-medication with antimicrobials left-over from previous illnesses or given by relatives to treat these symptoms was 290 (13%) for ARTIs, 43(11%) for GTIs and 10(8%) for UTIs. The majority of customers to medicine shops bought antimicrobials, being 354 out of 658 (63%) customers with ARTIs, 36 out of 83 (51%) customers with GTIs and 22 out of 33 (73%) customers with UTIs.

Determinants of help seeking from a medical doctor and antimicrobials use

Table 5 and Appendix 4 present the results of our descriptive analysis and multivariate logistic regression modeling respectively, aimed at exploring determinants of help seeking from a medical doctor at village clinic, township health center or higher level service, and determinants of prescribing of oral/ IV antimicrobials, oral antimicrobials only and IV antimicrobials only following an ARTI. We did not explore factors associated with help seeking from a medical doctor for GTIs and UTIs due to the relatively small number of cases. The descriptive analysis showed statistically significant differences in these healthcare behaviors between groups with different sex, age, education, insurance and knowledge status. After controlling for *a priori* confounders (age, sex and education). Help seeking from a medical doctor was inversely associated to the antimicrobial-related knowledge score with people with a higher knowledge score having a lower odds of help seeking from a medical doctor in response to their ARTI. There was no association between antimicrobial-related knowledge score and reported prescription of oral or IV antimicrobials. However, respondents with a higher antimicrobial-related knowledge score (3 or more) were less likely to be

prescribed oral/ IV antimicrobials compared with those with a score of zero (OR=0.32, 95% CI: 0.13-0.78). Age displayed a negative association with prescribed oral antimicrobial use (OR=0.81, 95%CI: 0.71-0.93) but a positive relationship with prescribed IV antimicrobial use (OR=1.21, 95%CI: 1.10-1.33). Health insurance was associated with help seeking from a medical doctor (OR=0.33, 95% CI: 0.17-0.66). Uninsured respondents had a lower odds of help seeking from a medical doctor at village clinics (OR=0.17, 95% CI: 0.06-0.51) but a higher odds of help seeking from a medical doctor from township or higher tier facility (OR=5.90, 95% CI: 1.99-17.47) compared with insured respondents.

Discussion

Key findings

This study has provided an important insight into help seeking from a medical doctor for common infections in rural China. Symptoms of infections were commonly reported and most people sought help soon after developing symptoms. The majority of people seeking help from village clinics for ARTI (94%) recalled being prescribed either oral or IV antimicrobials or a combination of both. The reported antimicrobial prescription rates for GTIs and UTIs were lower than that for ARTIs but were still very high at 82% and 70% respectively. We found evidence that receiving a prescription IV antimicrobials was associated with antimicrobial-related knowledge score and older age. Self-medication with antimicrobials bought from a medicine shop without prescription was reported by nearly 17% of people for ARTIs, 9% for GTIs, and 17% for UTIs; while self-medication with antimicrobials left-over from previous illness, or given by relatives, was reported by 13% of respondents for ARTIs,

11% for GTIs and 8% for UTIs. Greater knowledge about antimicrobials and higher level of educational attainment were associated with lower levels of help seeking from a medical doctor which suggests better education may reduce unnecessary attendances. As expected, lack of insurance was also associated with a lower odds of help seeking from a medical doctor.

Implications in context of other research and for policy

The study findings have important implications. The very high reported rate of antimicrobial prescriptions in our study indicates that prescription rates remain high in rural areas and contradicts a common belief among policymakers in China that overuse and misuse of antimicrobials is being brought under control as a result of the nationwide Special Antimicrobials Use Rectification program (initiated in 2011) and the New Health System Reforms.[44-46] Rates of antimicrobial prescribing at primary care settings in European countries range from 10% to 52% for respiratory tract infections, from 3% to 22% for genitourinary infections and from 1% to 55% for other infections.[49] Given that about 57% of China's vast population lives in rural areas and over 70% of antimicrobial prescriptions occur at primary care settings,[50-51] there is a clear need for policies and interventions focused primarily on inappropriate antimicrobial use in primary care settings and communities. This is further supported by the finding of no apparent association between antimicrobial prescribing and days to service seeking after ARTIs.

The study also highlights the need for action to reduce self-medication with antimicrobials leftover from previous illnesses or given by relatives or bought over-the-counter without

prescriptions. Self-medication of antimicrobials is very common worldwide.[52] It has been associated with the risk of inappropriate antimicrobial use which predisposes patients to drug interactions, masks symptoms of underlying disease and promotes the development of microbial resistance.[52] The reported high level of self-medication with left-over antimicrobials from previous illnesses is likely to be indicative of both over prescription by clinicians, and poor compliance by patients. While reasons underlying the use of self-obtained antimicrobials may be complex, our study identified higher use of reported self-medication in the younger and more educated groups which is in line with previous studies[53] despite policies which ban the sale of antimicrobials without prescriptions. Future interventions to increase knowledge about appropriate use of antimicrobials should include information about the harms of self-medication.

There may be benefit from differentiated strategies in tackling antimicrobial use behaviors. Our finding of an association between sex, education, health insurance and knowledge of antimicrobials with help seeking from a medical doctor rather than use of prescribed antimicrobial may suggest the former is dominated by patient-side factors, whilst the latter, may be more influenced by physician-side factors which were not measured in this study. Similarly, the variations in help seeking from a medical doctor for ARTIs (59%), UTIs (42%) and GTIs (28%) may reflect the severity and pattern of progression of symptoms of the different infections with patients with acute and aggravating or persisting symptoms being more likely, than those with milder and diminishing symptoms, to seek professional healthcare. Albeit we did not investigate the reasons people chose either to seek, or not to

seek professional help and it would be useful to explore this in further depth in future research.

Our findings also point to a need for understanding and tackling antimicrobial use and resistance in a socio-culturally sensitive way. Compared with findings from research in the UK and other western countries, our respondents reported more frequent symptoms of infections and higher and earlier help seeking from a medical doctor following an infection.[54-55] These variations may not be solely explained by differences in pathogens and host immunity between nations. Rather, China's strong culture of collectivism may have played an important role which requires each family member to be sensitive to the health of other members and urges the sick to seek help from a doctor as soon as possible.[56] In addition, the relatively low help seeking from a medical doctor for UTIs as compared to that for ARTIs and GTIs may also be partly attributable to conservative values about sex, and consequently help-seeking for related conditions, held by Chinese, especially those in rural areas.[57]

Strengths and limitations of the study

The study has both strengths and limitations. It is the first survey that collected data from healthcare users via a household survey whilst most of the existent research on antimicrobial 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 antimicrobials so as to meet relevant policy requirements[58]. As healthcare receivers, household members may be free from these concerns and hence more willing to report antimicrobial use. However, self-reported antimicrobial use may be prone to bias due, for example, to recall issues particularly among

the elderly, inability to distinguish antimicrobials from other drugs which may be an issue among the less-well educated and over or under reporting by the respondents for reasons such as perceived expectations from the researchers. The study asked respondents to recall symptomatic ARTIs in the past year but GTIs and UTIs in the past three months. Hence, more episodes of minor ARTIs than GTIs/UTIs may not have been recalled by respondents. In addition, readers are also cautioned about potential selection bias. The study allowed field data collectors to exclude the household members who were 'unable to answer the questionnaire'. This may result in under recruitment of senior and illiterate residents.

Next steps and future research required

Excessive prescribing of antimicrobials in the studied primary care settings in rural Anhui is prevalent despite China's special rectification program and health systems reforms aimed at tackling the problem. There is a clear need to target existing interventions at primary care level and to develop bespoke, community appropriate interventions if we are to reduce antimicrobial prescribing in China. Further work is under way to identify pathways for optimizing antimicrobial use in rural Anhui and China via multidisciplinary qualitative research with specific attention on its key social, cultural, economic, clinical, health systems, behavioral and other determinants to help inform future interventions.

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Contributors: JCha and DBW participated in conceptualizing the study. JCha directed study implementation and data collection, conducted data analysis and drafted the manuscript. DBW supervised the study and together with ZH provided expertise for overall design of the study. CC, JChe, IO and AK advised on study design, development of data collection materials and data analysis and together with DBW, JCha and ZH contributed to revising and finalizing the manuscript.

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Patient consent: Written informed consent was obtained from all voluntary participants. For an illiterate respondent, the researcher read out and explained the consent form to him/her and then asked him/her to a “tick (if he/she agreed)” or “cross (if disagreed)” on the form.

Ethics approval: The study protocol was approved by the Biomedical Ethics Committee of Anhui Medical University (reference number: 20150080).

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Data sharing statement: The data sets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Table 1 Socio-Demographic Characteristics and Reported Symptoms of Common Infections among Rural Residents (N=2611)

Subgroups	Total in sample n (%)	Age-range in years (n/%)					
		≤30	31-40	41-50	51-60	61-70	≥71
Sex							
Male	1082(41.4)	76 (7.0)	106 (9.8)	244 (22.6)	190 (17.6)	289 (26.7)	177 (16.4)
Female	1529 (58.6)	164 (10.7)	186 (12.2)	382 (25.0)	327 (21.4)	309 (20.2)	161 (10.5)
Education							
No formal education	865 (33.1)	1 (0.1)	19 (2.2)	126 (14.6)	194 (22.4)	321 (37.1)	204 (23.6)
Primary school	694 (26.6)	7 (1.0)	58 (8.4)	239 (34.4)	122 (17.6)	189 (27.2)	79 (11.4)
Middle school	778 (29.8)	124 (15.9)	163 (21.0)	221 (28.4)	152 (19.5)	72 (9.3)	46 (5.9)
Higher school	274 (10.5)	108 (39.4)	52 (19.0)	40 (14.6)	49 (17.9)	16 (5.8)	9 (3.3)
Health insurance							
Insured	2558(98.3)	231(9.0)	290 (11.3)	612 (23.9)	507 (19.8)	587 (22.9)	331 (12.9)
Uninsured	45 (1.7)	7 (15.6)	1 (2.2)	11 (24.4)	10 (22.2)	9 (20.0)	7 (15.6)
ARKS † (max score 6)							
≥3 score	317 (12.1)	81 (25.6)	69 (21.8)	85 (26.8)	43 (13.6)	31 (9.8)	8 (2.5)
1-2 score	1408 (53.9)	141 (10.0)	175 (12.4)	368 (26.1)	289 (20.5)	295 (21.0)	140 (9.9)
No ARKS	886 (33.9)	18 (2.0)	48 (5.4)	173 (19.5)	185 (20.9)	272 (30.7)	190 (21.4)
Acute respiratory tract infections ‡							
Yes	2223 (85.1)	222 (10.0)	266 (12.0)	535 (24.1)	435 (19.6)	495 (22.3)	270 (12.1)
No	388 (14.9)	18 (4.6)	26 (6.7)	91 (23.5)	82 (21.1)	103 (26.5)	68 (17.5)
Gastro-intestinal tract infections §							
Yes	425 (16.3)	60 (14.1)	60 (14.1)	89 (20.9)	84 (19.8)	84 (19.8)	48 (11.3)
No	2186 (83.7)	180 (8.2)	232 (10.6)	537 (24.6)	433 (19.8)	514 (23.5)	290 (13.3)
Urinary tract infections §							
Yes	133 (5.1)	3 (2.3)	14 (10.5)	39 (29.3)	29 (21.8)	34 (25.6)	14 (10.5)
No	2477 (94.9)	237 (9.6)	278 (11.2)	586 (23.7)	488 (19.7)	564 (22.8)	324 (13.1)

Note. † Antimicrobials-related knowledge score; ‡ most recent episode within the past 12 months; § episode within the past 3 months.

Table 2 Help-Seeking from Medical Doctor Following Reported Symptoms of Selected Common Infections

Service use	Acute respiratory tract infections (ARTIs) † (n=2223)		Gastro-intestinal tract infections (GTIs) ‡ (n=425)		Urinary tract infections (UTIs) ‡ (n=133)	
	n	%	n	%	n	%
1) Help-seeking from a medical doctor （Q2.3, Q2.21 and Q2.37）						
Yes	1319	59.4	118	27.8	56	42.1
No	902	40.6	307	72.2	77	57.9
Not stated	2	NA	0	NA	0	NA
2) Days until complete recovery after onset of symptoms (Q2.18, Q2.34 and Q2.50)						
Day 1	52	2.4	98	25.9	6	4.7
Day 2	262	12.3	114	30.2	18	14.1
Day 3	520	24.4	65	17.2	19	14.8
Day 4	301	14.1	30	7.9	10	7.8
Day 5	167	7.8	12	3.2	5	3.9
Day 6	64	3.0	4	1.1	1	0.8
Day 7	365	17.1	8	2.1	11	8.6
Day 8+	231	10.9	7	1.9	21	16.4
Not yet recovered	167	7.8	40	10.6	37	28.9
Not stated	94	NA	47	NA	5	NA
3) Days until first help-seeking from a medical doctor after onset of symptoms §(Q2.6, Q2.24 and Q2.40)						
Day 1	257	19.8	41	35.7	4	7.5
Day 2	471	36.3	46	40.0	19	35.9
Day 3	339	26.1	13	11.3	12	22.7
Day 4+	230	17.7	15	13.0	18	34.0
Not stated	22	NA	3	NA	3	NA

Note. † most recent episode within the past 12 months; ‡ episode within the past 3 months; § includes only those who stated “yes” to use of professional health-care service; NA stands for not applicable. Q plus a number stands for the reference number of question used in the questionnaire.

Table 3 Reported Use of Prescribed Antimicrobials for Common Infections Following Help-Seeking from a Medical Doctor

Antimicrobial use	Acute respiratory tract infections(ARTIs) † (n=1319)		Gastro-intestinal tract infections (GTIs) ‡ (n=118)		Urinary tract infections (UTIs) ‡ (n=56)	
	n	%	n	%	n	%
1) Respondents with clear memory of receiving prescribed oral antimicrobials (Q2.7, Q2.25 and Q2.41)						
Yes	638	72.7	34	49.3	32	74.4
No	240	27.3	33	50.7	11	25.6
Not clear	409	NA	43	NA	12	NA
Not stated	32	NA	8	NA	1	NA
2) Respondents with clear memory of receiving an intravenous antimicrobial (Q2.10, Q2.27 and Q2.43)						
Yes	705	54.7	48	42.5	12	22.6
No	584	45.3	65	57.5	41	77.4
Not clear	17	NA	3	NA	3	NA
Not stated	13	NA	2	NA	0	NA
3) Respondents with clear memory of receiving oral/intravenous antimicrobials (Q2.7, Q2.10, Q2.25 Q2.27, Q2.41 and Q2.43)						
Yes	1051	94.5	67	81.7	38	70.4
No	61	5.5	15	18.3	16	29.6
Not clear	197	NA	32	NA	1	NA
Not stated	10	NA	4	NA	1	NA
4) Prescribed oral/intravenous antimicrobials by days after onset of symptoms when the first professional service seeking took place § (Q2.6, Q2.7, Q2.10, Q2.24, Q2.25 Q2.27, Q2.40, Q2.41 and Q2.43)						
Day 1	178	91.8	20	80.0	1	25.0
Day 2	383	93.9	27	79.4	14	77.8
Day 3	286	96.0	8	88.9	8	66.7
Day 4+	189	95.9	12	85.7	13	76.5
Not stated	15	NA	0	NA	2	NA

Note. † most recent episode within the past 12 months; ‡ episode within the past 3 months; § includes only those who stated "yes" to clearly remembering receiving oral or intravenous antimicrobials or both; Oral/intravenous antimicrobials means oral or intravenous antimicrobials or both; NA stands for not applicable. Q plus a number stands for the reference number of question used in the questionnaire.

Table 4 Use of Self-Medication with Antimicrobials for Suspected Infections

Self-medication	Acute respiratory tract infections(ARTIs) † (n=2223)		Gastro-intestinal tract infections (GTIs) ‡ (n=425)		Urinary tract infections (UTIs) ‡ (n=133)	
	N	%	N	%	N	%
1) Respondents who bought medicines for suspected infection without prescriptions (Q2.14, Q2.30 and Q2.46)						
Yes	658	29.8	83	19.8	33	24.8
No	1551	70.2	337	80.2	100	75.2
Not stated	14	NA	5	NA	0	NA
2) Antimicrobials bought for suspected infection without prescriptions § (Q2.16, Q2.32 and Q2.48)						
Yes	354	62.5	36	51.4	22	72.7
No	212	37.5	34	48.6	6	27.3
Not stated	92	NA	13	NA	5	NA
3) Respondents who bought antimicrobials for suspected infection without prescriptions (Q2.14, Q2.16, Q2.30, Q2.32, Q2.46 and Q2.48)						
Yes	354	16.7	36	8.8	22	17.2
No	1763	83.3	371	91.2	106	82.8
Not stated	106	NA	18	NA	5	NA
3) Use of antimicrobials leftover from previous illness or given by relatives(Q2.17, Q2.33 and Q2.49)						
Yes	290	13.4	43	10.8	10	7.6
No	1872	86.6	356	89.2	122	92.4
Not stated	61	NA	26	NA	1	NA

Note. † most recent episode within the past 12 months; ‡ episode within the past 3 months; § includes only those who stated “yes” to buy medicines for suspected infection without prescriptions; NA stands for not applicable. Q plus a number stands for the reference number of question used in the questionnaire.

Table 5 Help Seeking from a Medical Doctor and Use of Prescribed Antimicrobials Following Respiratory Tract Infections by Type of Health Insurance and Antimicrobial-Related Knowledge Score

Category	Help seeking (Q2.3, n=2216)			Help seeking at village clinic (Q2.5, n=1317)			Help seeking at township or higher level (Q2.5, n=1317)			Use of prescribed oral/ IV antimicrobials (Q2.7 and Q2.10, n=1111)			Use of prescribed oral antimicrobials (Q2.7, n=877)			Use of prescribed IV antimicrobials (Q2.10, n=1288)		
	n	OR (95% CI)	P	n	OR (95% CI)	P	n	OR (95% CI)	P	n	OR (95% CI)	P	n	OR (95% CI)	P	n	OR (95% CI)	P
Gender																		
Female	1352	Ref.†		780	Ref.		780	Ref.		666	Ref.		531	Ref.		764	Ref.	
Male	864	1.40(1.15-1.70)	<0.01	537	0.83(0.61-1.13)	0.24	537	1.15 (0.84-1.56)	0.39	445	1.26(0.70-2.27)	0.44	346	1.13(0.80-1.58)	0.50	524	0.89(0.70-1.15)	0.38
Age group (years)																		
≤30	219	Ref.		107	Ref.		107	Ref.†		91	Ref.		73	Ref.†		106	Ref.†	
31-40	265	0.89(0.61-1.30)	0.55	139	0.84(0.42-1.68)	0.42	139	0.99 (0.52-1.90)	0.98	122	0.70(0.21-2.31)	0.56	108	1.90(0.92-3.92)	0.08	137	0.78(0.46-1.32)	0.35
41-50	534	0.77(0.54-1.10)	0.15	291	0.42(0.21-0.86)	<0.01	291	0.58 (0.30-1.10)	0.09	249	0.66(0.21-2.09)	0.48	209	1.42(0.73-2.77)	0.30	289	0.91(0.55-1.48)	0.69
51-60	435	0.82(0.57-1.19)	0.30	254	0.84(0.42-1.65)	0.14	254	1.12 (0.60-2.08)	0.73	212	0.75(0.22-2.53)	0.64	173	1.16(0.59-2.30)	0.67	248	0.94(0.57-1.56)	0.82
61-70	494	0.93(0.62-1.38)	0.70	326	0.84(0.41-1.71)	0.25	326	1.22 (0.64-2.33)	0.55	282	0.64(0.18-2.23)	0.48	210	0.59(0.29-1.19)	0.14	319	1.81(1.07-3.07)	0.03
≥71	269	1.30(0.83-2.04)	0.25	200	0.70(0.32-1.53)	0.19	200	1.24 (0.63-2.46)	0.54	155	0.48(0.13-1.82)	0.28	104	0.77(0.36-1.68)	0.52	189	1.77(1.00-3.11)	0.05
Education group																		
No formal education	718	Ref.†		492	Ref.		492	Ref.		405	Ref.		302	Ref.		476	Ref.	
Primary school	596	0.78(0.61-1.00)	0.05	370	1.04(0.68-1.60)	0.31	370	1.10 (0.76-1.59)	0.62	317	0.70(0.34-1.43)	0.32	250	0.86(0.57-1.29)	0.46	364	0.98(0.72-1.32)	0.87
Middle school	658	0.58(0.44-0.76)	<0.01	344	0.84(0.50-1.41)	0.22	344	0.85 (0.55-1.33)	0.48	288	0.76(0.33-1.79)	0.53	235	0.80(0.49-1.30)	0.36	337	0.99(0.70-1.40)	0.94
Higher school	244	0.48(0.33-0.70)	<0.01	111	1.23(0.61-2.47)	0.87	111	1.51 (0.83-2.76)	0.18	101	0.61(0.20-1.88)	0.39	90	0.59(0.30-1.16)	0.12	111	1.25(0.75-2.08)	0.40
Health insurance																		
Insured	2178	Ref.†		1303	Ref.†		1303	Ref.†		1099	Ref.		868	Ref.		1274	Ref.	
Uninsured	38	0.33(0.17-0.66)	<0.01	14	0.17(0.06-0.51)	<0.01	14	5.90 (1.99-17.47)	<0.01	12	0.55(0.07-4.42)	0.57	9	0.57(0.15-2.20)	0.42	14	0.77(0.27-2.25)	0.64
ARKS																		
No ARKS	726	Ref.†		498	Ref.		498			398	Ref.†		302	Ref.		482	Ref.	
1-2 scores	1208	0.77(0.63-0.95)	0.01	707	1.18(0.82-1.71)	0.05	707	1.33 (0.97-1.82)	0.08	610	0.80(0.42-1.50)	0.48	484	1.13(0.81-1.59)	0.47	695	1.11(0.86-1.43)	0.41
≥3 scores	282	0.42(0.31-0.58)	<0.01	112	1.46(0.78-2.76)	0.11	112	1.30 (0.73-2.31)	0.37	103	0.32(0.13-0.78)	0.01	91	1.16(0.64-2.11)	0.63	111	0.77(0.48-1.21)	0.25

Note. † stand for p < 0.05 for the variable in the overall regression model; Oral/IV antimicrobials, oral or intravenous antimicrobials or both; ARKS, antimicrobial-related knowledge score; Q plus a number stands for the reference number of question used in the questionnaire.

Appendix 1: Household survey questionnaire on antimicrobial use by rural residents

Number of household：|__|__|__|__|__|__|__|__|__|

Name of local village：_____ county _____ townships _____ village _____ group

Part A Socio-demographics

Q1.1 Name: ____

Q1.2 Gender: 1=male; 2=female

Q1.3 Date of birth: ____/_____/____（MM/DD/YY）

Q1.4 Days living in the local village in the past year: ____days.

Q1.5 Education: 0=illiterate; 1=primary schooling; 2=middle schooling; 3=secondary schooling; 4=higher schooling

Q1.6 Do you participate in the New Cooperative Medical System? 1=yes; 2=no

Q1.7 Do you participate in other health insurances? (if yes please enter details)

Part B Symptoms of infections, help-seeking and antimicrobial use

Q2.1 Have you caught cold or had cold symptoms such as sneezing, cough etc during the past year?

☐ Yes

☐ No (skip to Q2.20)

Q2.3 Did you seek professional help for the illness?

☐ Yes

☐ No(Skip to Q2.14)

Q2.5 Which kinds of setting(s) did you seek help from？Please tick all that apply.

☐ Village clinic

☐ Township health center

☐ County hospital

☐ Higher level hospital

☐ Other(s)（please provide details）_____

Q2.6 How many days was it from when you first experienced illness symptoms to when you first visited a health care setting?

☐ ____days

Q2.7 How many kinds of oral antimicrobials in total did your doctor(s) prescribe for you?

☐ No antibiotics

☐ ____kinds of antibiotics

☐ Not sure

Q2.10 How many bottles of transfusions with antimicrobials in total were you given for this illness？

☐ ____bottles

☐ Not sure

Q2.14 Did you buy medicines from a pharmacy without a doctor's prescription for this illness?

☐ Yes

☐ No（skip to Q2.17）

Q2.16 How many kinds of antimicrobial medications did this include?

☐ ____kinds

☐ Not sure

Q2.17 Did you use antimicrobials leftover from a previous illness or given by relatives for this illness?

☐ Yes

☐ No

Q2.18 How many days did it take for you to recover from this illness?

☐ _____days

☐ Not yet recovered

Q2.20 Did you experience diarrhea and/or gastroenteritis in the past 3 months?

☐ Yes

☐ No（skip to Q2.36）

Q2.21 Did you seek professional help for this illness?

☐ Yes

☐ No（skip to Q2.30）

Q2.24 How many days was it from when you first experienced illness symptoms to when you first visited a health care setting?

____days

Q2.25 How many kinds of oral antimicrobials in total did your doctor(s) prescribe for you?

☐ No antibiotics

☐ ____kinds of antibiotics

☐ Not sure

Q2.27 How many bottles of transfusions with antimicrobials in total were you given for this illness?

☐ ____bottles

☐ Not sure

Q2.30 Did you buy medicines from a pharmacy without a doctor's prescriptions for this illness?

☐ Yes

☐ No（skip to Q2.33）

Q2.32 How many kinds of antimicrobial medications did this include?

☐ ____kinds

☐ Not sure

Q2.33 Did you use antimicrobials leftover from a previous illness or given by relatives for this illness?

☐ Yes

☐ No

Q2.34 How many days did it take you to recover from this illness?

☐ _____dyas

☐ Not yet recovered

Q2.36 Did you experience urethritis in the past 3 monthes?

☐ Yes

☐ No（skip to Q3.1）

Q2.37 Did you seek professional help for this illness?

☐ Yes

☐ No（skip to Q2.46）

Q2.40 How many days was it from when you first experienced illness symptoms to when you first visited a health care setting?

☐ ____days

Q2.41 How many kinds of oral antimicrobials in total did your doctor(s) prescribe for you?

☐ No antibiotics

☐ ____kinds of antibiotics

☐ Not sure

Q2.43 How many bottles of transfusions with antimicrobials in total were you given for this illness?

☐ ____bottles

☐ Not sure

Q2.46 Did you buy medicines from a pharmacy without a doctor's prescriptions for this illness?

☐ Yes

☐ No（skip to Q2.49）

Q2.48 How many kinds of antimicrobial medications did this include?

☐ ____kinds

☐ Not sure

Q2.49 Did you use antimicrobials leftover behind from a previous illness or given by relatives for this illness?

☐ Yes

☐ No

Q2.50 How many days did it take you to recover from this illness?

☐ _____days

☐ Not yet recovered

Part C antimicrobial-related knowledge

Q3.1 In your opinion, which of the following pathogens can antimicrobials kill or control? (Please tick all that apply)

☐ Bacterial

☐ Viral

☐ Parasitic

☐ Don't know

Q3.2 Do you think a combination of antimicrobials is more effective than just one?

☐ Yes

☐ No

☐ It depends

☐ Not sure

Q3.3 What are the harms of using antimicrobials?

☐ Side-effects

☐ Drug resistance

☐ Economic burden
☐ Others（please provide details）

Q3.4 Which of the following symptoms do not need antimicrobials in general?

☐ Colds
☐ Sore throat
☐ Sneeze
☐ Cough
☐ Fever
☐ Bronchitis
☐ Sinusitis
☐ Otitis media
☐ Urinary infection
☐ Diarrhea

Q3.5 Do you think frequent use of antimicrobials reduces their effectiveness?

☐ No
☐ Not sure
☐ Yes

Appendix 2 Scoring system and summary of antimicrobials-related knowledge

a) Scoring system for antimicrobials-related knowledge

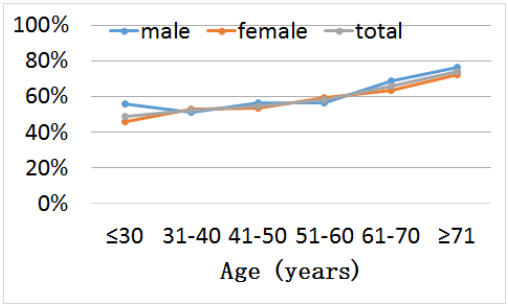
Antimicrobials-related knowledge	Score
Q1: In your opinion, can antimicrobials kill or control bacterial and parasitic illness?	0-2
Q2: Do you think a combination of antimicrobials is more effective than just one?	0/1
Q3: Does unnecessary use of antimicrobials lead to drug resistance?	0/1
Q4: Does the common cold need antimicrobials in general?	0/1
Q5: Do you think frequent use reduces effectiveness of antimicrobials?	0/1
	Max score 6

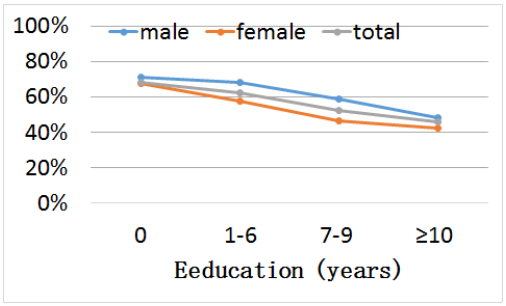
b) Antimicrobials-related knowledge score (ARKS) by education group

ARKS	Total n (%)	Education group (n/%)			
		No formal education	Primary school	Middle school	Higher School
No ARKS	886 (33.9)	445 (50.2)	262 (29.8)	154 (17.4)	23 (2.6)
1-2 scores	1408 (53.9)	400 (28.4)	378 (26.8)	480 (34.1)	150 (10.7)
≥3 scores	317 (12.1)	20 (6.3)	52 (16.4)	144 (45.4)	101 (31.9)

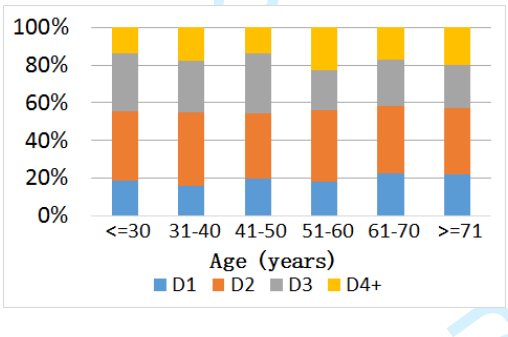
Appendix 3: Help seeking from medical doctor following reported symptoms of acute respiratory tract infection

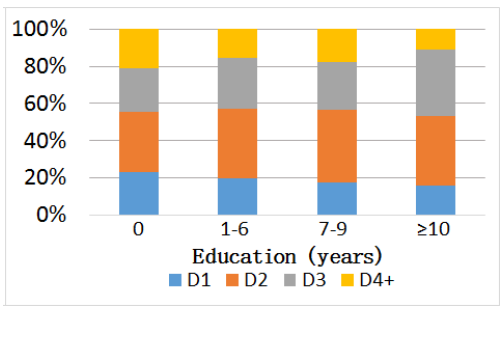
1) Respondents who had sought help from a medical doctor



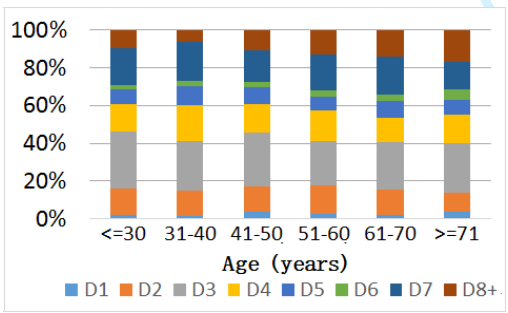


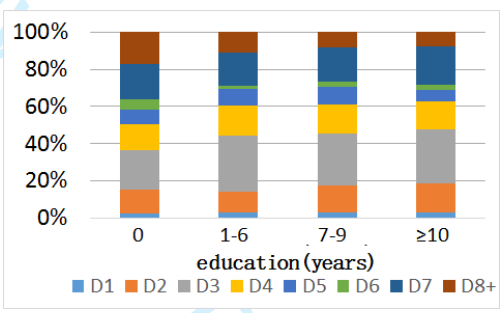
2) Days of first help seeking from a medical doctor after onset of infection





3) Days of complete recovery after onset of infection





D1, D2, D3, D4, D5, D6, D7 stands for day 1, 2, 3, 4, 5, 6, 7 and D4+ and D8+, day 4 and over and day 8 and over respectively.

Appendix 4 Help Seeking from a Medical Doctor and Use of Prescribed Antimicrobials Following Respiratory Tract Infections among different groups

Category	Help seeking (Q2.3, n=2216)				Help seeking at village clinic (Q2.5, n=1318)				Help seeking at township or higher level (Q2.5, n=1318)				Use of prescribed oral/ IV antimicrobials (Q2.7 and Q2.10, n=1112)				Use of prescribed oral antimicrobials (Q2.7, n=878)				Use of prescribed IV antimicrobials (Q2.10, n=1289)			
	n	n(%)	χ^2	P	n	n(%)	χ^2	P	n	n(%)	χ^2	P	n	n(%)	χ^2	P	n	n(%)	χ^2	P	n	n(%)	χ^2	P
Gender			4.41	0.04			1.43	0.23			1.52	0.22			0.01	0.91			0.05				0.03	0.86
Female	1355	781(57.6)			781	636(81.4)			781	143(18.3)			667	630(94.5)			532	388(72.9)		0.83	765	420(54.9)		
Male	866	538(62.1)			537	423(78.8)			537	113(21.0)			445	421(94.6)			346	250(72.3)			524	285(54.4)		
Age group			54.62	<0.001			10.70	0.06			12.45	0.03			0.83	0.98			22.84	<0.001			33.07	<0.001
≤30	221	108(48.9)			108	78(72.2)			108	24(22.2)			92	87(94.6)			74	51(68.9)			107	55(51.4)		
31-40	266	139(52.3)			139	108(77.7)			139	27(19.4)			122	114(93.4)			108	89(82.4)			137	61(44.5)		
41-50	535	292(54.6)			291	249(85.6)			291	36(12.4)			249	234(94.0)			209	165(78.9)			289	139(48.1)		
51-60	435	254(58.4)			254	205(80.7)			254	53(20.9)			212	202(95.3)			173	131(75.7)			248	123(49.6)		
61-70	495	326(65.9)			326	257(78.8)			326	72(22.1)			282	268(95.0)			210	131(62.4)			319	206(64.6)		
≥71	269	200(74.3)			200	162(81.0)			200	44(22.0)			155	146(94.2)			104	71(68.3)			189	121(64.0)		
Education group			59.33	<0.001			5.55	0.14			5.98	0.11			2.16	0.54			1.86	0.60			6.44	0.09
No formal education	719	492(68.4)			492	402(81.7)			492	96(19.5)			405	387(95.6)			302	215(71.2)			476	280(58.8)		
Primary school	596	370(62.1)			370	290(78.4)			370	73(19.7)			317	298(94.0)			250	181(72.4)			364	197(54.1)		
Middle school	661	345(52.2)			345	285(82.6)			345	57(16.5)			289	273(94.5)			236	179(75.8)			338	169(50.0)		
Higher school	245	112(45.7)			111	82(73.9)			111	30(27.0)			101	93(92.1)			90	63(70.0)			111	59(53.2)		
Health insurance			8.22	<0.01			12.67	<0.001			12.94	<0.001			0.19	0.66			1.33	0.25			1.28	0.72
Insured	2178	1304(59.9)			1303	1053(80.8)			1303	247(19.0)			1099	1039(94.5)			868	632(72.8)			1274	698(54.8)		
Uninsured	38	14(36.8)			14	6(42.9)			14	8(57.1)			12	11(91.7)			9	5(55.6)			14	7(50.0)		
ARKS			71.18	<0.001			5.09	0.08			1.95	0.38			8.76	0.01			2.28	0.32			5.55	0.06
No ARKS	726	498(68.6)			498	415(83.3)			498	87(17.5)			398	381(95.7)			302	210(69.5)			482	271(56.2)		
1-2 scores	1211	708(58.5)			708	559(79.0)			708	146(20.6)			611	579(94.8)			485	360(74.2)			695	385(55.3)		
≥3 scores	284	113(39.8)			112	85(75.9)			112	23(20.5)			103	91(88.3)			91	68(74.7)			111	49(44.1)		

Note. * or ** stand for p< 0.05 or p < 0.01 for the differences between the reference and study subgroup; †, p < 0.05 for the variable in the overall regression model; Oral/IV antimicrobials, oral or intravenous antimicrobials or both; ARKS, antimicrobial-related knowledge score. Q plus a number stands for the reference number of question used in the questionnaire.

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	P1-3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	P2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	P4-6
Objectives	3	State specific objectives, including any prespecified hypotheses	P6
Methods			
Study design	4	Present key elements of study design early in the paper	P7-8
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	P7-8
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	P7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	P7-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	P7-8
Bias	9	Describe any efforts to address potential sources of bias	P7-9
Study size	10	Explain how the study size was arrived at	P6-7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	NA
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	P9
		(*b*) Describe any methods used to examine subgroups and interactions	P9
		(*c*) Explain how missing data were addressed	P9
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	NA
		(*e*) Describe any sensitivity analyses	NA
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	P9-10
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	P10
		(b) Indicate number of participants with missing data for each variable of interest	P27-29

Outcome data	15*	Report numbers of outcome events or summary measures	P10-12
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	P12-13
		(*b*) Report category boundaries when continuous variables were categorized	P26
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	P13-14
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	P16-17
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	P14-17
Generalisability	21	Discuss the generalisability (external validity) of the study results	P16-17
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	P18

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.