Association between antibiotic resistance and increasing ambient temperature in China: An ecological study with nationwide panel data

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Summary

Background Antibiotic resistance leads to longer hospital stays, higher medical costs, and increased mortality. However, research into the relationship between climate change and antibiotic resistance remains inconclusive. This study aims to address the gap in the literature by exploring the association of antibiotic resistance with regional ambient temperature and its changes over time.

Methods Data were obtained from the China Antimicrobial Surveillance Network (CHINET), monitoring the prevalence of carbapenem-resistant *Acinetobacter baumannii* (CRAB), *Klebsiella pneumoniae* (CRKP) and *Pseudomonas aeruginosa* (CRPA) in 28 provinces/regions over the period from 2005 to 2019. Log-linear regression models were established to determine the association between ambient temperature and antibiotic resistance after adjustment for variations in socioeconomic, health service, and environmental factors.

Findings A 1 °C increase in average ambient temperature was associated with 1.14-fold increase (95%-*CI* [1.07–1.23]) in CRKP prevalence and 1.06-fold increase (95%-*CI* [1.03–1.08]) in CRPA prevalence. There was an accumulative effect of year-by-year changes in ambient temperature, with the four-year sum showing the greatest effect on antibiotic resistance. Higher prevalence of antibiotic resistance was also associated with higher antibiotic consumption, lower density of health facilities, higher density of hospital beds and higher level of corruption.

Interpretation Higher prevalence of antibiotic resistance is associated with increased regional ambient temperature. The development of antibiotic resistance under rising ambient temperature differs across various strains of bacteria.

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Introduction

Antibiotic resistance has become one of the biggest threats to global health, due to rapid spread of antibiotic resistance and slow discovery of new antibiotics. Antibiotic resistance occurs when bacteria evolve over time and cease to respond to previously effective antibiotics. Antibiotic resistance leads to longer hospital stays, higher medical costs and increased mortality.[1,2] It was estimated that antibiotic resistance may have caused 1.27 million deaths in 2019, with 929,000 deaths attributable to the six leading pathogens: *Escherichia coli*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Strepto-*

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Research in context

Evidence before this study

Antibiotic resistance and climate change have become the two biggest threats to global health. We searched in the PubMed between April 1, 2012 and April 1, 2022 with the terms “climate change” or “climate warming” or “temperature”, “antibiotic” or “antimicrobial” and“resistance”. Two reviews explored the potential impact of climate warming on antibiotic resistance, while three articles investigated the link between antibiotic resistance and temperature in the United States and Europe. Most available researches discussed common drug-resistant bacteria, accounting for several recognized resistance drivers like antibiotic consumption and population density. Few studies have looked at the long-term effects of increasing temperature on antibiotic resistance.

Added value of this study

We looked at the impact of a number of socioeconomic and environmental factors on three multidrug-resistant strains that require urgent research and intervention development. We discovered the prevalence of antibiotic resistance increases with higher regional ambient temperature, and highlighted year-by-year changes in ambient temperature have an accumulative effect on antibiotic resistance, with the four-year sum showing the greatest effect. These findings have added to the growing body of information from China regarding the link between antibiotic resistance and global warming.

Implications of all the available evidence

Our study revealed that fighting against antibiotic resistance is a long-term battle, as potential reduction in antibiotic resistance from reduced antibiotic use may be far slower than we expected due to the effect of climate change. More collaborative cooperation and cooperative action from the government and all sectors of the society need to be encouraged.

coccus pneumoniae, *Acinetobacter baumannii*, and *Pseudomonas aeruginosa*.[3] Uncontrolled antibiotic resistance also has significant implications on food and feed production, which can result in increased population poverty and inequality.[4]

Antibiotic resistance can be developed intrinsically or acquired by absorbing certain genetic codes from others or through self-mutation.[5] Antibiotic use is the primary selective pressure promoting the genetic evolution of antibiotic resistance. Excessive and inappropriate use of antibiotics is believed to have hastened the emergence of resistant bacteria.[6–8]

Many socioeconomic and environmental factors have been found to be associated with the development of antibiotic resistance. Overcrowded living conditions and low income are linked to high prevalence of drug-resistant bacterial infections, such as methicillin-resistant *S. aureus* (MRSA).[9,10] In China, the rapid socioeconomic development has witnessed increasing prevalence of antibiotic resistance. Gross domestic product (GDP) per capita, out of pocket (OOP) health expenditure, and physician density were found to be positively correlated with the prevalence of MRSA and *E. coli* (3GCREC) and *K. pneumoniae* (3GCRKP) that are resistant to the third-generation cephalosporin.[11] Non-compliance with common laws and corruption are often blamed for the lack of control over antibiotic resistance.[12,13]

In recent years, researchers started to pay attention to the link between climate change and antibiotic resistance. Kaba and colleagues[12] noticed a significant association between the warm-season change in temperature and the prevalence of carbapenem-resistant *P. aeruginosa*. Theoretically, bacterial activities are inextricably tied to temperature. Temperature has long been recognized to influence bacterial growth and its transfer of genomic material encoding antibiotic resistance.[14,15] Global warming is usually accompanied by increased weather events such as rainstorm and flood. Heavy rainfall helps bacterial mutagenesis and expression of antibiotic resistance genes.[16] MacFadden and colleagues[17] revealed that the rise of local temperature in the US is linked to population level increase in antibiotic resistance from *E. coli*, *K. pneumoniae*, and *S. aureus*. Similar studies in Europe indicate that ambient temperature may be a key modulator of changes in antibiotic resistance rate.[18] However, research into the relationship between climate change and antibiotic resistance remains inconclusive. Antibiotic resistance is likely to be developed over a certain period of time after repeated exposure to warmer ambient temperature. Therefore, this study aims to address the gap in the literature by exploring the link between local ambient temperature and its population prevalence of antibiotic resistance in China, and testing the potential accumulative effect of increased temperature.

Methods

Sample sources

Data were obtained from the China Antimicrobial Surveillance Network (CHINET, http://www.chinets.com/Chinet), which was established in 2005. The antibiotic susceptibility testing followed the guidelines and quality control requirements specified in the Clinical and Laboratory Standards Institute (CLSI) document. CHINET totally covered 28 provinces and autonomous regions during the study period of 2005–2019. In 2019, the CHINET had covered 49 hospitals

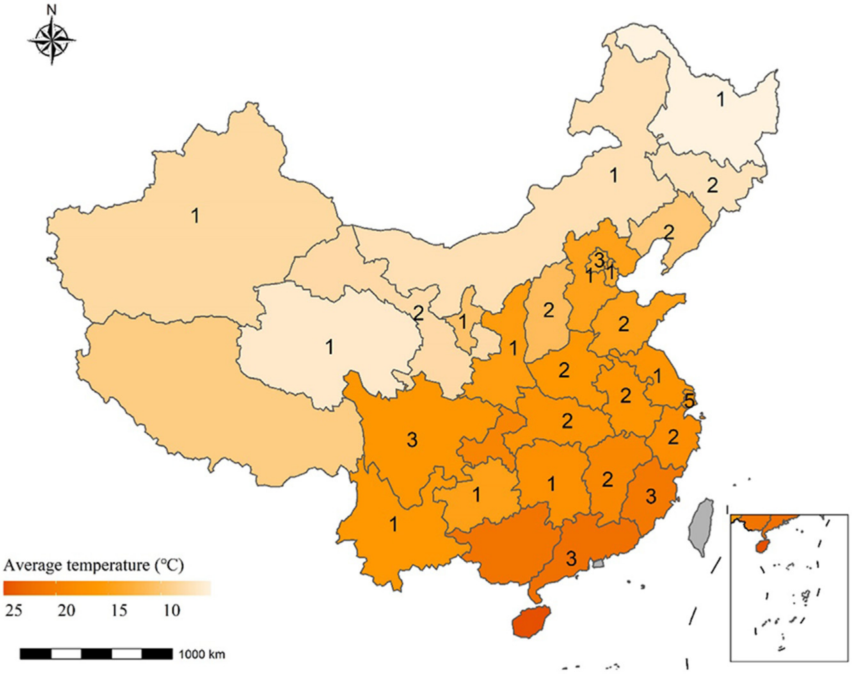

Fig. 1: Map with average ambient temperature. The numbers indicate the number of participating hospitals in 2019 in the China Antimicrobial Surveillance Network (CHINET) from each province or autonomous region.

(36 tertiary and 13 secondary) across 27 provinces and autonomous regions in China (Fig. 1), and reported 0.14 million tests for the isolates of *A. baumannii*, 0.18 million for *K. pneumoniae*, and 14 million for *P. aeruginosa*, respectively (Table 1). The 15-year (2005–2019) panel dataset used in this study contained 603 observation records of annual prevalence of antibiotic resistance of the three isolates in the 27 provinces/regions of China.

Dependent variables

Prevalence of antibiotic resistance was measured by the detection rates of carbapenem-resistant *A. baumannii* (CRAB), *K. pneumoniae* (CRKP), and *P. aeruginosa* (CRPA) in each year by province/region. The three carbapenem-resistant Gram-negative bacteria (GNB) were chosen as our target species based on the following reasons: Firstly, they are the prominent causes of hospital-acquired infections (HAIs) leading to increased

Year	No. of hospitals	Tested isolates			
		Total	*A. baumannii*	*K. pneumoniae*	*P. aeruginosa*
2005	8	22,774	2095	2234	2323
2006	9	33,945	2968	3452	4752
2007	12	36,001	3157	3037	3988
2008	12	36,216	3625	3435	4130
2009	14	43,670	4796	4556	4912
2010	14	47,850	5523	5529	5080
2011	15	59,287	6723	6981	6012
2012	15	72,397	8739	9621	7271
2013	16	84,572	10,120	12,121	8257
2014	17	78,955	8769	11,308	7471
2015	20	88,778	8875	11,532	7700
2016	30	153,059	14,930	19,611	13,254
2017	34	190,610	17,602	26,268	16,562
2018	44	244,843	21,813	21,805	23,431
2019	49	270,497	23,534	39,379	23,607

Table 1: **Numbers of participating hospitals and tested isolates in the China Antimicrobial Surveillance Network (CHINET) from 2005 to 2019.**

mortality. The World Health Organization (WHO) has labeled them as critical pathogens in need of urgent drug research and development.[19,20] Secondly, carbapenems are the most reliable last-resort treatment for bacterial infections due to their broad spectrum of antibacterial activity against Gram-positive and Gram-negative bacteria and remarkable stability against most beta-lactamases.[21] Thirdly, the CHINET has monitored CRAB, CRKP and CRPA over the past 15 years and made the dataset openly accessible.[22–28]

Independent and control variables

The independent variable, ambient temperature, was measured using two indicators: annual average ambient temperature (EQ1) and year-by-year change in average ambient temperature (EQ2). We also calculated the sum of year-by-year ambient temperature change of the current year and preceding years (Table 2).

Historical data of monthly average ambient temperature (°C) for each province in which the participating hospitals were located, were extracted from the China Statistical Yearbook (http://www.stats.gov.cn/tjsj/ndsj/), which was calculated based on the average of major cities within each province.

Control variables

Previous studies showed that sociodemographic profiles,[11] economic status,[1] medical services (in particular antibiotic consumptions),[1,12] environmental factors[6,14,16–18] and corruption[12] are associated with the development of antibiotic resistance.

China has a vast territory characterized by diversities in environmental, economic, and sociocultural contexts, as well as regional disparities in health resources and health services. In this study, population density, gross domestic production (GDP) per capita, number of health facilities, physicians and hospital beds per 10,000 population, annual average rainfall (mm), and annual average humidity (%) of the provinces in which the participating hospitals were located were extracted from the China Statistical Yearbooks and served as control variables. Annual antibiotic consumption measured by defined daily doses (DDDs) nationwide as reported by the National Health Commission was also included as a control variable. Corruption was measured by year-by-year Corruption Perceptions Index (CPI) reported by the Transparency International. CPI describes the national level of corruption of the public sector perceived by experts and businesspeople using a scale ranging from 0 to 100, with a lower score indicating higher corruption (Table 3).

No.	Equation
EQ1[a]	$\text{aver\_temp} = [\overline{T}(\text{January} \ldots \text{December})]_{2005–2019}$ $\text{summer\_temp} = [\overline{T}(\text{June, July, August})]_{2005–2019}$ $\text{winter\_temp} = [\overline{T}(\text{January, February, December})]_{2005–2019}$
EQ2[b]	$\text{net\_warming\_lag1} = [\overline{T}(\text{January} \ldots \text{December})]_{2005–2019} - [\overline{T}(\text{January} \ldots \text{December})]_{2004–2018}$ $\text{net\_warming\_lag2} = \text{net\_warming\_lag1} + [\overline{T}(\text{January} \ldots \text{December})]_{2004–2018} - [\overline{T}(\text{January} \ldots \text{December})]_{2003–2017}$
	$\text{net\_warming\_lag3} = \text{net\_warming\_lag2} + [\overline{T}(\text{January} \ldots \text{December})]_{2003–2017} - [\overline{T}(\text{January} \ldots \text{December})]_{2002–2016}$
	$\text{net\_warming\_lag4} = \text{net\_warming\_lag3} + [\overline{T}(\text{January} \ldots \text{December})]_{2002–2016} - [\overline{T}(\text{January} \ldots \text{December})]_{2001–2015}$
	$\text{net\_warming\_lag5} = \text{net\_warming\_lag4} + [\overline{T}(\text{January} \ldots \text{December})]_{2001–2015} - [\overline{T}(\text{January} \ldots \text{December})]_{2000–2014}$
	$\text{net\_warming\_lag6} = \text{net\_warming\_lag5} + [\overline{T}(\text{January} \ldots \text{December})]_{2000–2014} - [\overline{T}(\text{January} \ldots \text{December})]_{1999–2013}$
	$\text{net\_warming\_lag7} = \text{net\_warming\_lag6} + [\overline{T}(\text{January} \ldots \text{December})]_{1999\sim2013} - [\overline{T}(\text{January} \ldots \text{December})]_{1998–2012}$

[a] EQ1: annual average ambient temperature over the period from 2005 to 2019.[b] EQ2: lag1 refers to change in average ambient temperature of the current year in contrast with the previous year; lag2 to lag7 refers to the sum of year-by-year changes in average ambient temperature of the current year and preceding years.

Table 2: **Calculation of average ambient temperature and changes in average ambient temperature.**

Statistical modelling

Statistical modelling on antibiotic resistance was established for the three tested isolates, respectively. The prevalence of CRAB, CRKP and CRPA (dependent variables) was transformed using the natural logarithm "LN(ABR)" function for log-linear regression modelling, because classical linear regression models could not fit proportion values between zero and one. Two types of models were established: one tested the effect of average ambient temperature adjusting for variations in the control variables; and the other tested the long-term accumulative effect of climate change on the prevalence of antibiotic resistance by adding changes in average ambient temperature. The addition of changes in average ambient temperature could help control the effect of years unrelated to ambient temperature. The sum of up to seven years of year-by-year changes in ambient temperature was considered in the modelling tests. Multicollinearity of the independent and control variables was defined as a *VIF* greater than 10 and a two-sided p value less than 0.05.

We used the panel data to address potential spatial–temporal heterogeneity, but found poorer model fitting results than pooled ones as indicated by the lower adjusted R^2 (Supplementary Tables S1, S2, and S3). Thus, we decided to present the pooled modelling results in the manuscript.

Model validation

We predicted the 2019 prevalence (and 95% confidence interval) of antibiotic resistance in the non-participating regions (Tibet, Guangxi, Hainan and Chongqing) of the CHINET, using the established regression models, and compared the predicting values with the published data extracted from the China Antimicrobial Resistance Surveillance System (CARSS).

Variables	Description
DDDs	National total antibiotic consumption measured in defined daily doses per day per 100 population by year
CPI	National Corruption Perceptions Index by year
Population density	Provincial population per square kilometer by year
GDP	Provincial GDP (in current Chinese currency value) per capita, log-scale transformed, by year
Health facility	Provincial health facility density per 10,000 population by year
Physician	Provincial physician density per 10,000 population by year
Hospital bed	Provincial hospital bed density per 10,000 population by year
Humidity	Annual average humidity of major cities in each province (%)
Rainfall	Annual average rainfall of major cities in each province (mm)

Table 3: **Control variables used for statistical analysis.**

We performed sub-group modelling by restricting the sample to the 22 provinces (Supplementary Fig. S1), dividing the provinces/regions into northern (colder) and southern (warmer) using Qinling Mountains and Huaihe River as borderline (Supplementary Fig. S2), and testing summer (June, July, August) and winter (December, January, February) data separately.

Results

Antibiotic resistance over time

The prevalence of CRAB and CRKP showed a clear upward trend over time; whereas, the prevalence of CRPA showed a slightly downward trend. Higher prevalence of antibiotic resistance appeared in the provinces with a higher average ambient temperature, particularly for CRKP and CRPA (Fig. 2).

Correlation between antibiotic resistance and average ambient temperature

The prevalence of CRKP and CRPA increased with the rise of average ambient temperature ($p < 0.001$), although no such significant ($p = 0.44$) correlation was found for CRAB (Fig. 3).

Factors associated with antibiotic resistance

The log-linear regression models showed that average ambient temperature was a significant predictor of the prevalence of CRKP and CRPA, but not for CRAB (Table 4). An increase of 1 °C in average ambient temperature was associated with a rise of 1.14-fold ($p < 0.001$, 95%-*CI* [1.07–1.23]) of CRKP prevalence and 1.06-fold ($p < 0.001$, 95 %-*CI* [1.03–1.08]) of CRPA prevalence, respectively, after adjustment for variations of the control variables. Higher antibiotic consumption was also associated with higher CRPA prevalence, despite a lack of significant association with CRAB prevalence and CRKP prevalence. Lower health facility density and higher hospital bed density (larger numbers of beds in fewer facilities) were associated with higher prevalence of antibiotic resistance across all of the three target species. Higher perceived corruption (i.e. lower CPI) was associated with higher prevalence of CRPA (Table 4).

Positive associations between ambient temperature and the prevalence of antibiotic resistance remained significant for CRAB, CRKP and CRPA in northern China, for CRKP and CRPA in the 22 provinces, for CRKP and CRPA in winter, and for CRKP in summer. Negative associations between ambient temperature and the prevalence of CRAB and CRKP were found in southern China (Fig. 4).

CRAB was highly prevalent in Tibet, Guangxi, Hainan and Chongqing, compared with very low prevalence of CRKP and CRPA. The unstandardized estimations of modelling produced a higher prediction accuracy for CRAB as indicated by the Index of Estimation Deviation in comparison with CRKP and CRPA (Supplementary Table S4). The vast majority of predicting values fell within the 95% of the prediction interval even though the interval exceeded 100%, indicating a high level of uncertainty of prediction (Supplementary Table S5).

Accumulative effects of ambient temperature

Changes in average ambient temperature showed an accumulative effect, with the four-year sum in year-by-year changes in ambient temperature having the greatest effect: RR = 1.09 ($p = 0.016$, 95%-*CI* [1.02–1.18]) for CRPA. Average ambient temperature remained a significant stable predictor of antibiotic resistance for CRKP prevalence and CRPA prevalence regardless what indicators of changes in average ambient temperature were introduced in the models (Fig. 5).

Discussion

Our study shows that population level prevalence of antibiotic resistance increases with rising regional ambient temperature and year-by-year accumulative warming. These results are consistent with the findings of studies conducted in the US and Europe.[12,17,18] We found that a 1 °C increase in regional-level average ambient temperature is associated with 1.14-fold increase in CRKP prevalence and 1.06-fold increase in CRPA prevalence in China. In comparison, a 0.5 °C increase in year-wise temperature change was found to be associated with 1.02-fold increase in CRPA prevalence in Europe.[12] It is important to note that some target species (such as CRPA and CRKP) are more

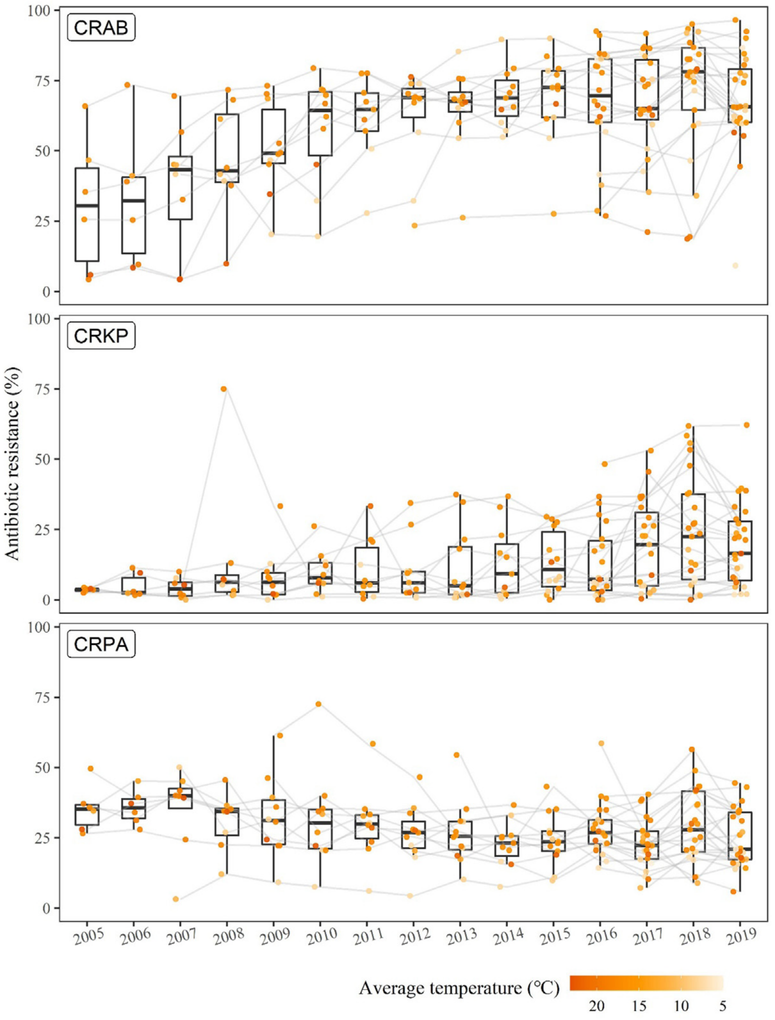

Fig. 2: Prevalence of antibiotic resistance by province over the period from 2005 to 2019. Each point represents a province colored by its annual average ambient temperature. A lighter color indicates a lower average ambient temperature. The grey lines link the same province over time.

sensitive to changes in ambient temperature than others (such as CRAB) according to the findings of our study. Using *K. pneumoniae* as a target strain, a 10 °C increase in ambient temperature was found to be associated with 2.2% increase in antibiotic resistance in the US[17] and 1.2% increases in European countries.[18]

From a microcosmic perspective, the link between temperature and antibiotic resistance can be explained by their physiological similarities in triggering cell responses. Both aminoglycosides (a class of antibiotics) and heat stress enhance misfolded proteins in cells.[29,30] As a result, heat exposure can stimulate bacteria to develop antibiotic resistance through a process known as cross-tolerance.[31–33]

We found a negative association between ambient temperature and the prevalence of antibiotic resistance in southern China. Southern China has warm weathers all year around. The growth of bacteria and their development of antibiotic resistance may be hampered by high temperature[34,35] due to varied production of biofilm.[36] Ambient temperature in southern China also fluctuates within a relatively small range, with most of the annual average ranging from 15 to 20 °C, which can jeopardize the reliability of modelling. Further studies are needed to explore the potential nonlinear association between ambient temperature and antibiotic resistance.

There is an accumulative effect of increasing ambient temperature on the development of CRPA, according to the findings of our study. The widespread distribution of *P. aeruginosa* in nature[37] and its fast response to selective pressure imposed by antibiotic use provides a potential explanation.[38] Another possible explanation may be related to the temperature-regulated

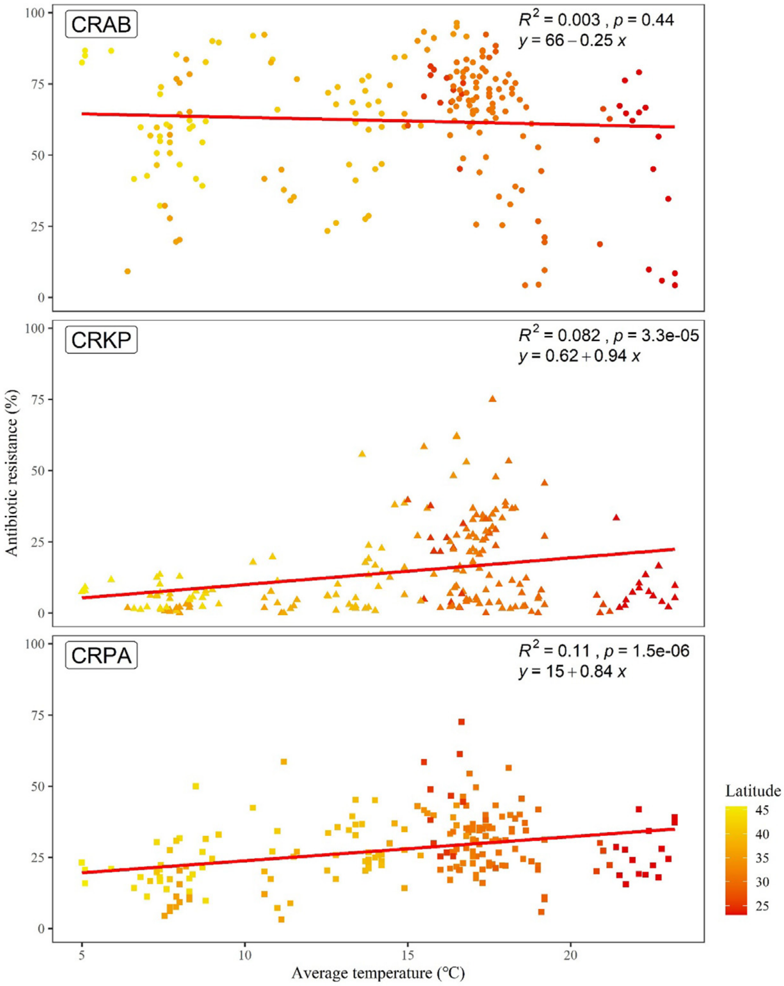

Fig. 3: Unadjusted linear trend line estimating the linear relationship between annual average ambient temperature and antibiotic resistance. Each point represents a province colored by latitude. The three pathogens were represented as geometric shapes.

Predictor	**CRAB**			**CRKP**			**CRPA**		
	RR[a]	*p*	VIF	RR	*p*	VIF	RR	*p*	VIF
Antibiotic consumption (DDDs)	1.00	0.275	3.00	1.01	0.326	3.01	1.01	0.012	2.94
Corruption Perceptions Index (CPI)	1.02	0.341	2.72	1.08	0.160	2.71	0.96	0.037	2.71
Population density (person/km^2)	1.00	0.270	2.52	1.00	0.237	2.53	1.00	0.515	2.52
GDP per capita (Yuan)	0.95	0.679	4.66	0.71	0.258	4.53	1.09	0.434	4.62
Health facilities per 10,000 population	0.95	0.026	2.70	0.75	<0.001	2.61	0.96	0.021	2.59
Physicians per 10,000 population	1.00	0.247	4.46	1.00	0.961	4.45	1.00	0.636	4.50
Hospital beds per 10,000 population	1.01	0.025	5.00	1.07	<0.001	5.06	1.02	0.002	4.92
Annual average humidity (%)	1.01	0.226	5.14	0.97	0.105	4.94	1.00	0.545	4.81
Annual average rainfall (mm)	1.00	0.367	4.71	1.00	0.528	4.61	1.00	0.064	4.60
Average ambient temperature (°C)	1.00	0.862	4.18	1.14	<0.001	4.13	1.06	<0.001	4.13
R^2		0.277			0.366			0.315	
adj.-R^2		0.239			0.332			0.278	

[a] Rate ratio was obtained from the estimated coefficient of each predictor through exponential conversion.

Table 4: **Rate ratios (RR)[a] of predictors on prevalence of antibiotic resistance.**

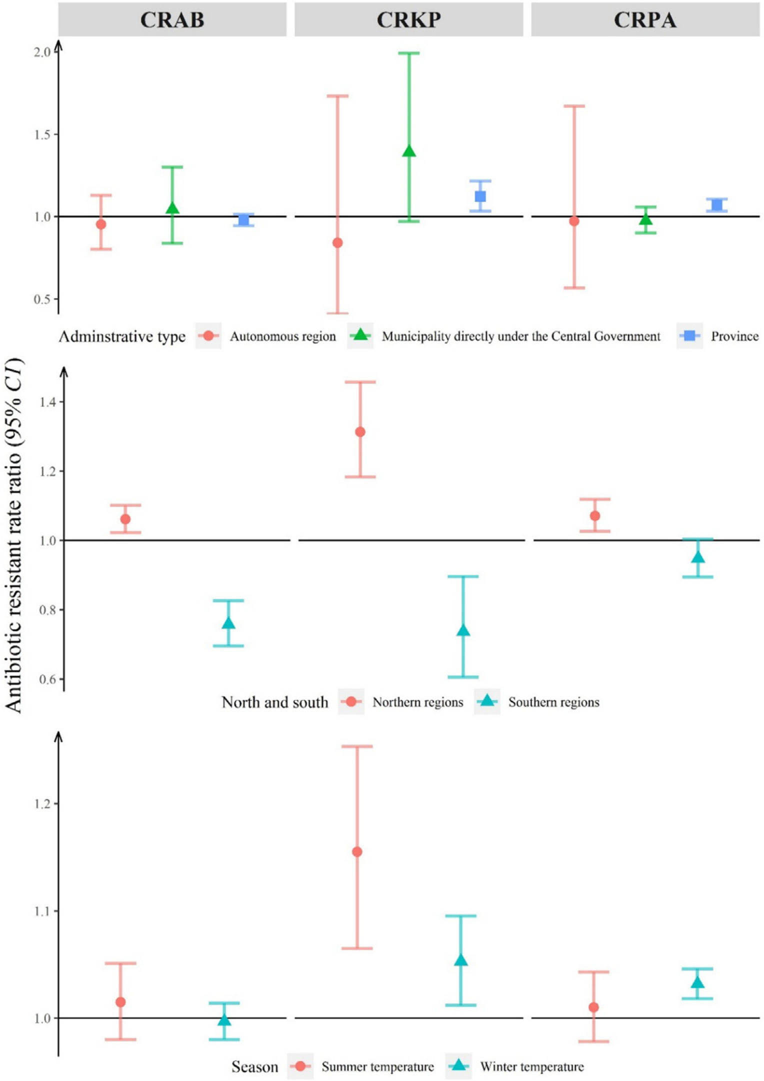

Fig. 4: Rate ratios of antibiotic resistance associated with ambient temperature: results of sub-group modelling.

acyltransferase (PA3242) and temperature-regulated 2-OH-lauroytransferase (PA0011). Both play a key part in changes in the composition of outer membrane of bacteria, strengthening their ability to adapt to environmental stimuli.[39,40] The most likely scenario is that bacteria are exposed to antibiotics and stressful temperature simultaneously or in sequential, resulting in gradual changes over the course of their lifetime. It may take a few generations to develop antibiotic resistance. More time is needed to allow the antibiotic-resistant bacteria to become a dominant strain, displacing the susceptible ones.[6] Heat shock mechanism generated by high ambient temperature can help with the process through enhancing gene expression, inducing phenotypic heterogeneity, and producing persistent antibiotic-resistant bacteria.[41,42] In the long run, ambient temperature also plays a role in gene mutation and maintenance of antibiotic resistance.[6,43] Higher temperature can reduce the fitness cost of mutation while preserving its resistance to antibiotics after removal of antibiotics.[44–47]

It is undeniable that over- and inappropriate use of antibiotics remains to be an important challenge in addressing the problem of antibiotic resistance. We found that CRPA prevalence increases with antibiotic consumption even after adjustment for variations in other factors, including ambient temperature. Serious abuse of antibiotic usage is evident in China,[48] which has been proved to be associated with antibiotic resistance from bacteria like *E. coli* and *S. aureus*.[49] Over the past few decades, China has taken great efforts to reduce antibiotic use. In this study, we

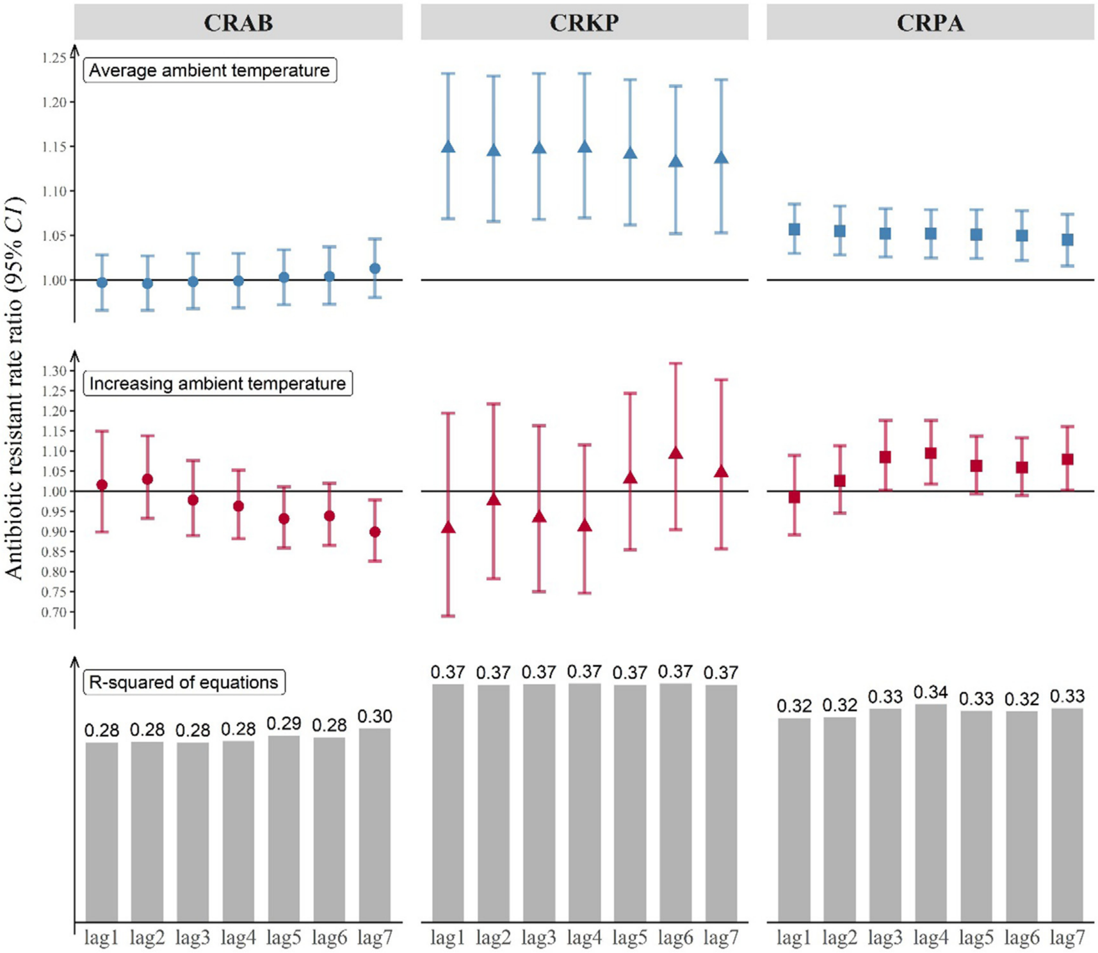

Fig. 5: Rate ratios of antibiotic resistance for the three target species (CRAB, CRKP, CRPA) when average ambient temperature and changes in average ambient temperature jumped by 1 °C. The bars represent the R-squared of the equations.

found that lower health facility density and higher hospital bed density are associated with higher prevalence of antibiotic resistance across all three target species. This is concerning as medical resources have been increasingly concentrated in large hospitals in metropolitan areas in China, which reduces the competition effect that may improve antibiotic prescribing practices.[50] Indeed, hospital size in China is usually large, and inappropriate prescription of antibiotics in these hospitals is highly prevalent.[51,52] Our findings about the association of corruption with antibiotic resistance is consistent with that in the European area.[12] Corruption could be considered as a cultural determinant of non-compliance to common regulations, and several antibiotic–species pairs resistance was found to be associated with the corruption.[13] Furthermore, association of corruption with antibiotic use was confirmed somehow, indicating that corruption might confound the influence of antimicrobial use on antibiotic resistance.[53]

There are several limitations in this study. Data used in this study came from the hospital monitoring system. Antibiotic products have been widely used in agriculture and animal husbandry, which are also associated with antibiotic resistance.[54] Primary care facilities were not included in this study either, which served about half of outpatient visits. However, access to antibiotics in primary care is restricted to those included in the essential medicines list only. Our analysis did not consider time trends in antibiotic resistance; instead, we focused on the effect of year-by-year changes in ambient temperature. The models established in our study also have low R^2 values. Further studies are needed to establish the causal relationship between climate change and antibiotic resistance and its underlying mechanisms.

Conclusion

Population level prevalence of antibiotic resistance increases with regional higher ambient temperature in China. Year-by-year changes in ambient temperature have an accumulative effect on antibiotic resistance, with the four-year sum showing the greatest effect. Variations exist among bacteria in developing antibiotic resistance under rising ambient temperature.

In light of the global warming and climate change, we have to prepare for a long-term fight against antibiotic resistance. Potential reduction in antibiotic resistance resulting from lower use of antibiotics may be far slower than we expected due to the effect of climate change.

Contributors

WBL, LS, YCZ, XYY, QXH, YP, CJL, HCH, CRH and LPY have substantial contributions to conception and design, acquisition of funding, data and interpretation of data; WBL and LPY analyzed the data, WBL and LPY drafted the article, CJL, LPY, HCH and CRH revised it critically for important intellectual content, WBL and LPY was responsible for the decision to submit the manuscript, and all authors contributed to final approval of the paper.

Data sharing statement

The datasets analyzed during the current study are publicly available at the CHINET (https://www.chinets.com/). YP is an employee of one of the CHINET member hospitals.

CHINET is not responsible for the correctness of the data and for data management, data merging and data collation. The accuracy of the authors' statistical analysis and the findings they report are not the responsibility of CHINET.

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Declaration of interests

All authors declare no competing interests.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lanwpc.2022.100628.

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