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Vital Surveillances

Characteristics and Influencing Factors of Antimicrobial Resistance in *Salmonella* Isolated from Asymptomatic Workers — Yulin City, Guangxi Zhuang Autonomous Region, China, 2013–2024

Yao Peng[1,2,&]; Ming Luo[3,&]; Ziyu Liu[2,4]; Changyu Zhou[3]; Hongqun Zhao[2]; Zhenpeng Li[2,4];
Biao Kan[1,2,#]; Ning Jiang[3,#]; Xin Lu[4,#]

ABSTRACT

Introduction: Asymptomatic carriers of antibiotic-resistant *Salmonella* constitute a significant yet frequently overlooked public health threat. This study aimed to characterize antimicrobial resistance (AMR) patterns in *Salmonella* isolated from asymptomatic workers in Yulin, China, over a 12-year period (2013–2024) and to identify the potential influence of natural and socioeconomic factors.

Methods: Antimicrobial susceptibility testing was performed against 11 antimicrobial agents. We analyzed temporal trends in AMR rates using the Mann-Kendall test and assessed associations between AMR rates and natural or socioeconomic variables using Spearman's rank correlation, Principal Component Regression (PCR), and Least Absolute Shrinkage and Selection Operator (LASSO) regression. An Autoregressive Integrated Moving Average (ARIMA) model was employed to forecast future resistance trends.

Results: Resistance to tetracycline (TET) was most prevalent (mean rate: 66.2%). The overall multidrug resistance (MDR) rate was 41.9%, exhibiting a significant increasing trend ($P<0.05$). Most alarmingly, the tigecycline (TGC) resistance rate surged from 0% to 24.4% by 2024. PCR model analysis revealed that a composite "Socioeconomic and Healthcare Development Index" served as the primary predictor of this increase, explaining 54.9% of the variance in TGC resistance rates. The ARIMA model forecasted a continued upward trajectory for TGC resistance through 2025–2026.

Conclusion: Our findings demonstrate a significant rise in MDR *Salmonella* among asymptomatic workers in Yulin, establishing them as important reservoirs of antibiotic-resistant *Salmonella*. The emergence and rapid escalation of TGC resistance is strongly associated with regional socioeconomic and healthcare development. These results underscore the urgent need for integrated surveillance within the One Health framework to effectively address AMR transmission.

Salmonella represents a leading cause of diarrheal disease worldwide and constitutes a major pathogen in foodborne outbreaks throughout China (*1*–*2*). The emergence of antimicrobial resistance (AMR) in *Salmonella* has substantially intensified this public health challenge. An alarming global increase in multidrug-resistant strains has been documented, particularly among isolates resistant to critically important antibiotics such as fluoroquinolones and third-generation cephalosporins, thereby elevating the risk of treatment failure (*3*–*4*).

Although clinically based surveillance systems for AMR are well established, they frequently overlook a critical transmission reservoir: asymptomatic carriers. These individuals, particularly food workers (FWs), function as silent reservoirs and play a pivotal role in disseminating resistant pathogens throughout the food supply chain. Food workers may acquire asymptomatic carriage through exposure to contaminated food products, subsequently transmitting these pathogens to additional food items and consumer populations, potentially causing disease in susceptible individuals (*5*–*7*).

The One Health framework provides an essential paradigm for addressing AMR by recognizing the intricate interconnections among human, animal, and environmental health. Multiple factors — including antimicrobial use in livestock production, environmental contamination, climatic conditions, and socioeconomic development — collectively shape the complex epidemiology of AMR (*8*–*9*). However, the specific influence of these macro-level determinants on long-term AMR trends remains poorly characterized, particularly within asymptomatic carrier populations.

This study conducted 12-year (2013–2024) longitudinal surveillance of asymptomatic individuals in Yulin, China, to investigate the dynamic influence of natural and socioeconomic factors on *Salmonella* antimicrobial resistance. By integrating antimicrobial resistance data with environmental and socioeconomic variables, we aimed to develop evidence-based strategies for containing AMR transmission within the One Health framework.

METHODS

Sample Collection and Isolate Identification

Between January 2013 and December 2024, we collected 488,409 fecal samples from asymptomatic workers (aged 18–65 years) in Yulin, China. Samples were cultured for *Salmonella* spp. according to established protocols (*10*). Species identification was confirmed using Matrix-Assisted Laser Desorption/Ionization Time-of-Flight Mass Spectrometry (MALDI-TOF MS), and confirmed isolates were stored at −80 °C for subsequent analysis.

Antimicrobial Susceptibility Testing

Antimicrobial susceptibility testing was performed on all *Salmonella* isolates using the Phoenix NMIC803 panel (Becton, Dickinson Co., Franklin Lakes, NJ, USA) on the BD Phoenix$^{\mathrm{TM}}$ automated system. Minimum inhibitory concentrations (MICs) were determined for 11 antimicrobial agents: amikacin (AMK), ceftazidime (CAZ), chloramphenicol (CHL), ciprofloxacin (CIP), colistin (COL), ertapenem (ETP), meropenem (MEM), ampicillin-sulbactam (SAM), tetracycline (TET), tigecycline (TGC), and trimethoprim-sulfamethoxazole (SXT). Resistance profiles were interpreted according to the Clinical and Laboratory Standards Institute (CLSI) M100 guidelines (30th Edition) (*11*). *Escherichia coli* ATCC 25922 served as the quality control strain. Multidrug resistance (MDR) was defined as acquired non-susceptibility to at least one agent in three or more antimicrobial categories (*12*).

Collection of Data on Natural and Socioeconomic Factors

To identify potential drivers of temporal changes in *Salmonella* antimicrobial resistance rates, we collected data on environmental conditions and socioeconomic variables. Monthly meteorological data, including mean temperature (℃) and precipitation (mm), were obtained from the China Meteorological Data Service Center. Annual economic and public health indicators from 2013 to 2023 were sourced from the Guangxi Zhuang Autonomous Region Bureau of Statistics (http://tjj.gxzf.gov.cn). This dataset encompassed gross domestic product (GDP), per capita GDP, urbanization rate, number of hospitals, number of hospital beds, number of public toilets, water consumption, and the production and consumption of pork and poultry. Additionally, national antibiotic consumption data were acquired from the One Health Trust's ResistanceMap platform (https://resistancemap.onehealthtrust.org/AntibioticUse.php).

Statistical Analysis

All statistical analyses were performed using R software (version 4.3.3, R Foundation for Statistical Computing, Vienna, Austria). Temporal trends in annual antimicrobial resistance rates were evaluated using the Mann-Kendall test. Associations between antimicrobial resistance rates and natural or socioeconomic variables were assessed through Spearman's rank correlation analysis. To address multicollinearity among predictor variables, particularly when modeling annual tigecycline resistance rates, we employed two complementary regression approaches: Principal Component Regression (PCR) and Least Absolute Shrinkage and Selection Operator (LASSO) regression. Subsequently, an Autoregressive Integrated Moving Average (ARIMA) model was constructed to project future trends in tigecycline resistance. Statistical significance was defined as a two-sided P<0.05 for all analyses.

RESULTS

Overall Antimicrobial Resistance Trend

According to our previous study (*13*), between 2013 and 2024, a total of 9,276 non-duplicate *Salmonella* strains were isolated from 488,409 fecal samples collected from asymptomatic workers in Yulin. Antimicrobial susceptibility testing revealed substantial and rising resistance rates across several key antimicrobial agents (Figure 1A). Resistance to TET was the most prevalent, with a mean rate of 66.2% across the study period. Resistance rates for CHL

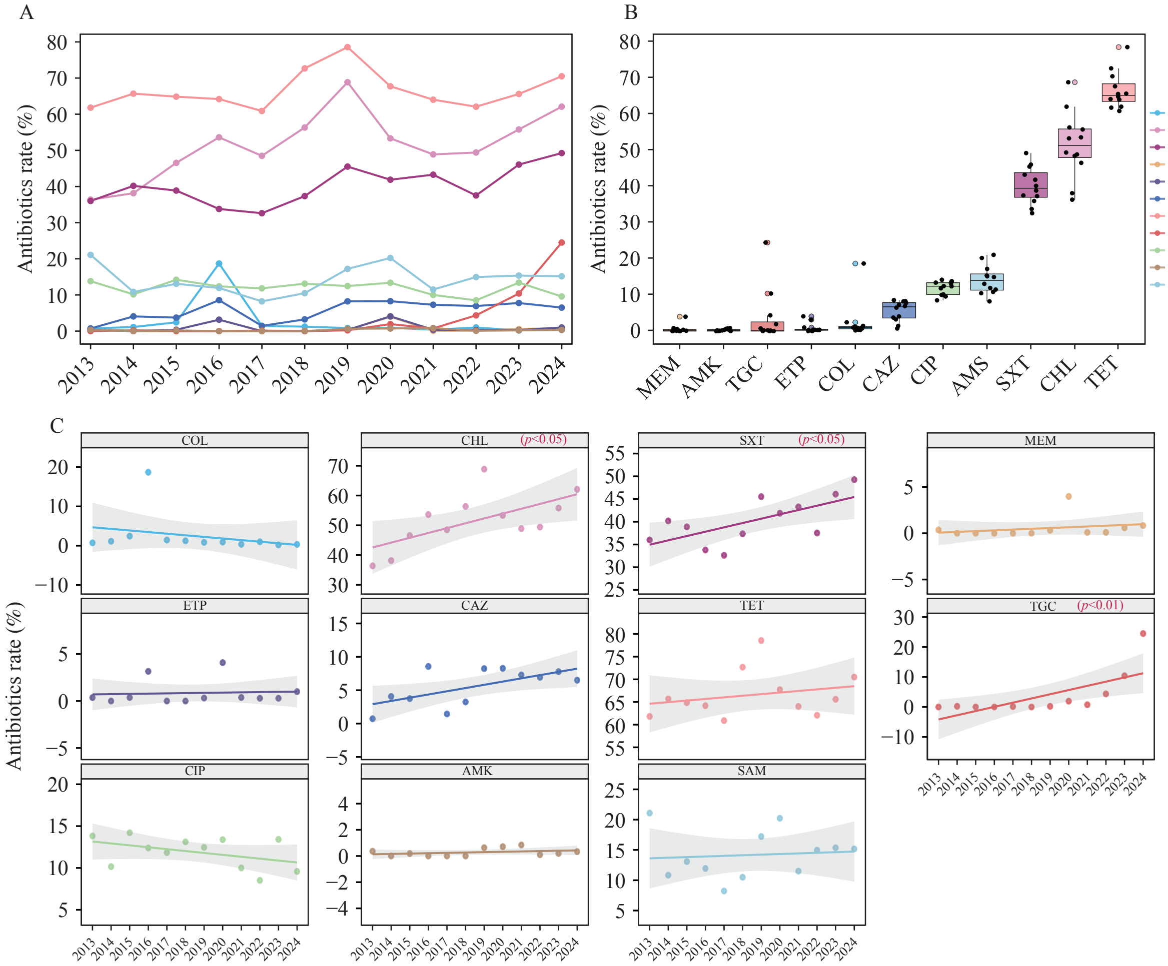

FIGURE 1. Temporal trends and overall rates of antimicrobial resistance (2013–2024). (A) Line chart illustrating the annual resistance rates (%) for 11 different antimicrobials over the 12-year study period. (B) Overall distribution of resistance rates for each antimicrobial over the 12-year period, showing the median (line), interquartile range (box), and annual values (dots). (C) Linear regression plots showing resistance trends over time.

Note: For (A), Each colored line represents a specific antimicrobial agent. For (C), The shaded area is the 95% confidence interval. *P* values indicate a significant increasing trend of the annual resistance rates for CHL, SXT, and TGC.

Abbreviation: CHL=chloramphenicol; SXT=trimethoprim-sulfamethoxazole; TGC=tigecycline; AMK=amikacin; CAZ=ceftazidime; CIP=ciprofloxacin; COL=colistin; ETP=ertapenem; MEM=meropenem; SAM=ampicillin-sulbactam, TET=tetracycline.

(mean 49.6%) and SXT (mean 38.9%) were also substantial and demonstrated significant upward trends (*P*<0.05 for both). Although resistance to carbapenems (MEM and ETP) and COL remained comparatively low (0.8% and 2.6%, respectively), their detection indicates that the efficacy of last-line antibiotics is threatened (Figure 1A).

A critical finding was the rapid increase in TGC resistance from 0% in 2021 to 24.5% in 2024, highlighting a significant and emerging public health concern. In contrast, COL resistance declined significantly after peaking at 17% in 2016 (Figure 1A). This downward trend is potentially attributable to the 2017 governmental regulatory change that banned the use of colistin as an animal growth-promoting feed additive, as implemented by the Ministry of Agriculture of China (*11*).

Trends in Multidrug Resistance

The overall MDR rate was 41.86% (3,883/9,276), demonstrating a significant upward trend (*P*<0.05) with an 11.8% increase over the decade. The MDR rate remained relatively stable through 2018, then surged to 49.5% in 2019, followed by a slight decline from 2020 to 2022, before rising again to exceed 45% from 2023 to 2024. This pattern suggests an exacerbation of the resistance burden in recent years (Figure 2A).

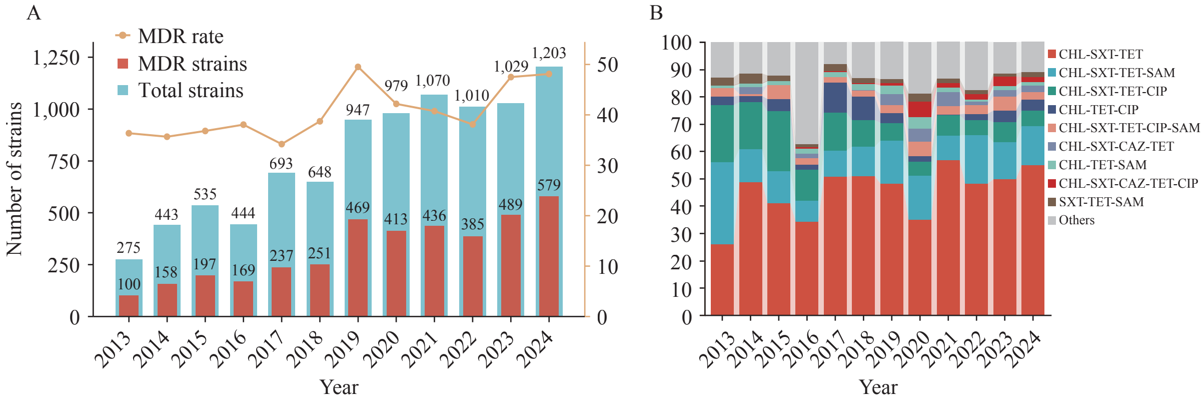

FIGURE 2. Trends in multidrug-resistant *Salmonella* isolations and MDR profiles in Yulin City, 2013–2024. (A) Annual trends of multidrug-resistant *Salmonella* isolates. (B) Temporal distribution of major MDR profiles among the resistant isolates.

Note: For (A), the bar chart displays the total number of isolates (light blue) and the subset of multidrug-resistant isolates (red) collected each year (left y-axis). The orange line indicates the corresponding annual MDR rate (%, right y-axis). For (B), the 100% stacked area chart illustrates the relative annual proportion of different resistance patterns. The dominant CHL-SXT-TET profile is highlighted in red. The "Others" category includes all other less frequent MDR combinations.

Abbreviation: MDR=multidrug resistance; CHL=chloramphenicol; SXT=trimethoprim-sulfamethoxazole; TET=tetracycline; CAZ=ceftazidime; CIP=ciprofloxacin; SAM=ampicillin-sulbactam; TET=tetracycline.

Analysis of resistance patterns revealed that CHL-SXT-TET was the most dominant MDR profile, accounting for 47.7% of all MDR isolates. The next most prevalent profiles were CHL-SXT-TET-SAM (13.7%) and CHL-SXT-TET-CIP (8.8%). Notably, the prevalence of the CHL-SXT-TET-CIP pattern exhibited a downward trend (Figure 2B). Seventeen isolates demonstrated resistance to both quinolones and third-generation cephalosporins. More alarmingly, eight of these isolates were also resistant to carbapenems and colistin, representing a critical threat to last-resort treatment options.

Correlations Between Resistance Rates and Natural and Socioeconomic Factors

Spearman's rank correlation analysis identified significant associations between AMR patterns and both natural and socioeconomic variables. Among natural factors, resistance rates to CHL, TET, AMK, and SAM exhibited weak positive correlations with temperature (*r*= 0.244–0.262). To investigate temporal dynamics, we conducted a time-lag analysis examining temperature effects on resistance rates. The strongest associations occurred when comparing resistance rates with concurrent monthly temperatures (0-month lag). These correlations diminished rapidly when temperature values were lagged by one or two months prior to resistance measurement (1-month lag/2-month lag), with only the AMK resistance rate maintaining significance at a 1-month lag (Supplementary Table S1, available at https://weekly.chinacdc.cn/). Regarding precipitation, only the SAM resistance rate demonstrated a significant correlation with rainfall patterns.

TGC resistance rates exhibited particularly strong positive correlations with multiple socioeconomic indicators, including GDP (*r*=0.805), per capita GDP (*r*=0.805), urbanization rate (*r*=0.791), number of hospitals (*r*=0.840), number of hospital beds (*r*=0.833), and agricultural water usage (*r*=0.819). Additionally, meropenem resistance rates correlated positively with poultry production in Yulin (*r*=0.801), while the overall MDR rate showed positive correlations with both poultry production and consumption (Figure 3A).

Identifying Influencing Factors of Tigecycline Resistance

Five socioeconomic factors demonstrated significant associations with TGC resistance rates. To address the substantial multicollinearity among these variables, we employed both PCR and LASSO regression models. The PCR analysis identified a single principal component, designated the "Socioeconomic and Healthcare Development Index (SHDI)", which accounted for 89.5% of the total variance across the original factors. This composite index exhibited a strong positive correlation with TGC resistance rates, explaining 54.9% of the observed variance. Component loading analysis revealed that all six variables contributed positively to this index. The primary drivers of the SHDI were the number of

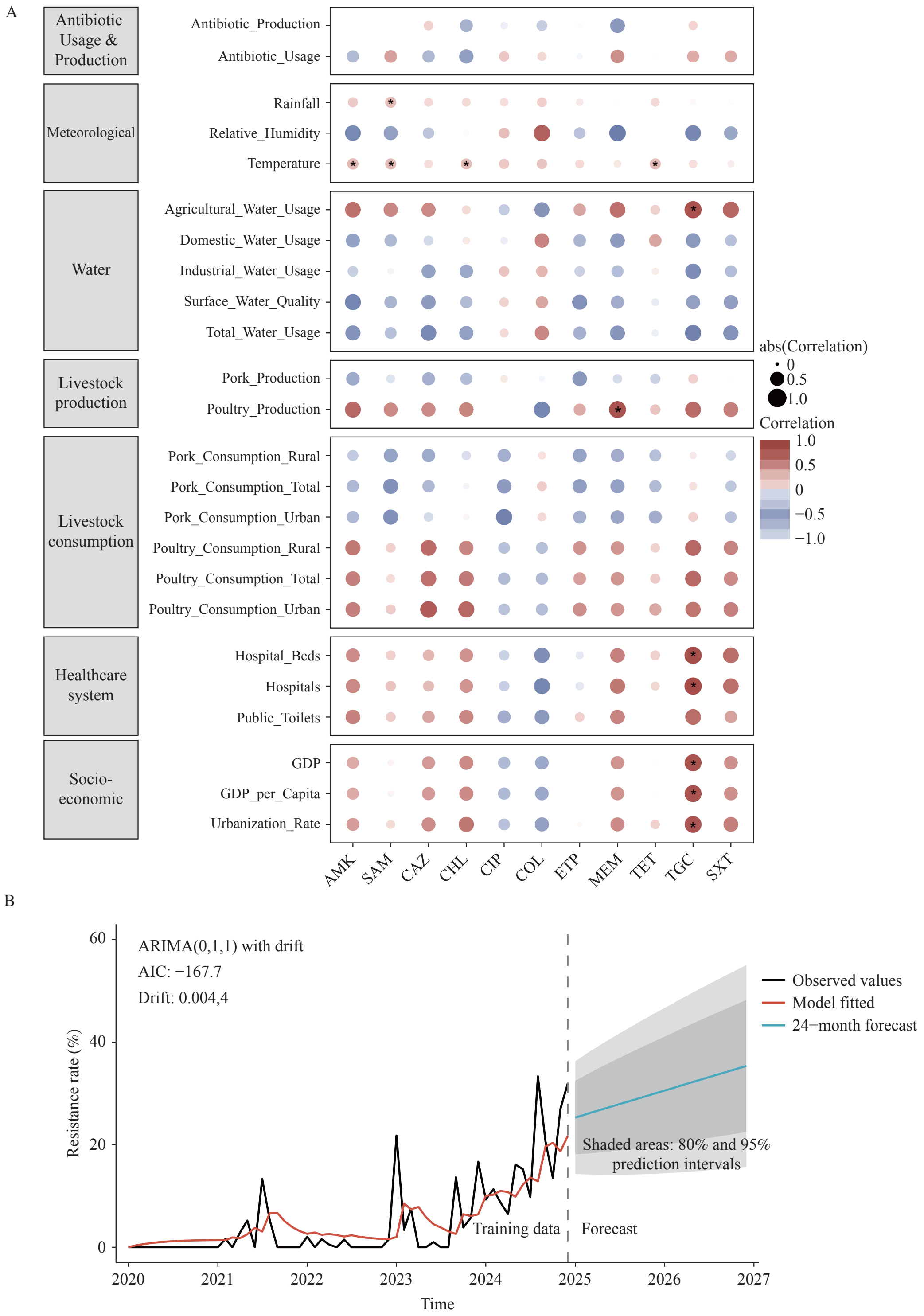

FIGURE 3. Correlation between the resistance rates to 11 antibiotics and natural/socioeconomic factors, and forecasting of TGC resistance. (A) Spearman correlation matrix between potential influencing factors and antimicrobial resistance rates. (B) Time-series forecast for TGC resistance based on an ARIMA (0,1,1) model with drift.

Note: For (A), the color and size of the circles represent the direction and magnitude of the correlation, respectively. For (B), the black line shows actual data, while the blue line and shaded areas show the point forecast with 80% and 95% prediction intervals.

Abbreviation: CHL=chloramphenicol; SXT=trimethoprim-sulfamethoxazole; TGC=tigecycline; AMK=amikacin; CAZ=ceftazidime; CIP=ciprofloxacin; COL=colistin; ETP=ertapenem; MEM=meropenem; SAM=ampicillin-sulbactam, TET=tetracycline; abs=absolute value; ARIMA= Autoregressive Integrated Moving Average; AIC=Akaike Information Criterion.

* Significance (*P*<0.05).

hospital beds (loading=0.425), GDP (0.417), GDP per capita (0.416), urbanization rate (0.415), number of hospitals (0.402), and agricultural water usage (0.373). This composition confirms that the index effectively captures the convergent trends of economic growth, urbanization, and healthcare infrastructure expansion. In contrast, the LASSO regression penalized all individual factor coefficients to zero, indicating that no single variable independently predicted resistance when accounting for multicollinearity. The combined results from both analytical approaches strongly indicate that the rise in TGC resistance rates is driven by an integrated set of underlying socioeconomic factors rather than any single determinant.

Forecasting Tigecycline Resistance Rate

The resistance rate to TGC has demonstrated a significant upward trajectory in recent years, prompting the development of an ARIMA model to forecast potential future threats. Initial modeling using TGC resistance data from January 2013 to December 2024 yielded a significant Ljung-Box test result (P=0.03), indicating residual autocorrelation. Given that TGC resistance rates were negligible before 2020, we refined the model using only data from January 2020 to December 2024. The optimal model specification, determined by the Akaike Information Criterion (AIC=−167.74), was ARIMA (0,1,1) with a drift term of 0.004. This refined model produced a non-significant Ljung-Box test result (P=0.08), confirming the absence of substantial residual autocorrelation and indicating that residuals approximated white noise. The model demonstrated strong predictive performance, with a Root Mean Square Error (RMSE) of 0.05 and a Mean Absolute Error (MAE) of 0.04, supporting its utility for trend identification and informing targeted public health interventions, including enhanced surveillance protocols and strategic resource allocation.

DISCUSSION

This 12-year surveillance study of asymptomatic workers revealed a significant increase in the prevalence of MDR *Salmonella*, with the CHL-SXT-TET resistance profile emerging as the most dominant pattern. Notably, our findings demonstrate the emergence of TGC resistance, which is strongly associated with a composite index of regional socioeconomic and healthcare development. The ARIMA model's forecast of continued increases in TGC resistance serves as a critical warning that demands immediate public health attention and intervention.

The persistently high resistance rate to TET (66.2%) and the increasing resistance to CHL align with other studies (*14*–*16*) and are likely attributable to their historical overuse in both agricultural and clinical settings (*17*). Of greater concern is the detection of isolates resistant to TGC, COL, and the carbapenems (ETP and MEM). The emergence of resistance to these last-line agents within a community setting, particularly among food workers, represents a serious public health challenge with implications for treatment options.

Temperature serves as a key driver of AMR dissemination. Higher temperatures have been shown to accelerate the frequency of horizontal gene transfer (HGT), the principal mechanism for the dissemination of resistance genes among bacterial communities, primarily through conjugation (*18*–*19*). Warmer temperatures are also associated with higher insect populations, which contribute to disseminating resistant bacteria (*20*). These mechanisms explain the positive correlations observed between temperature and resistance to CHL, TET, AMK, and SAM in our study. Although a positive relationship was identified for AMK, this result should be interpreted cautiously due to the small sample size of AMK-resistant isolates (n=31), which reduces statistical power and may affect the reliability of the correlation analysis. Despite this limitation, our findings suggest that rising global temperatures may exacerbate the spread of resistant phenotypes. Therefore, increased attention must be directed toward understanding the impact of global warming on AMR dynamics.

The strong positive correlation between the “Socioeconomic and Healthcare Development Index” and TGC resistance rates provides novel insight into the macro-level drivers of AMR. This finding aligns with previous research demonstrating that socioeconomic factors — including health investment, out-of-pocket health costs, access to water, sanitation, and hygiene (WASH) services, and immunization coverage — contribute to the rise of AMR (*21*). Tigecycline, a glycylcycline antibiotic, is often reserved as a last-resort treatment for severe infections caused by MDR pathogens, such as carbapenem-resistant Enterobacteriaceae (CRE) and *Acinetobacter baumannii* (*22*–*23*). Importantly, tigecycline use is prohibited in all food-producing animals (*24*–*25*). This regulatory context strongly supports our finding that the rise in TGC resistance is linked to the "Socioeconomic and Healthcare Development Index" (which encompasses hospital numbers and bed capacity) and is driven by human healthcare pressures rather than agricultural practices. The positive correlation between MDR rates and poultry production and consumption further reinforces the One Health framework, highlighting the critical role of food chain pathways in disseminating AMR and antibiotic resistance genes (ARGs) from animals to humans, as emphasized in global analyses (*26*).

Several limitations warrant consideration. First, our data originate from a single region, which may limit generalizability to other geographic contexts. Second, we did not perform genomic analyses (e.g., whole-genome sequencing) to trace specific resistance genes or elucidate transmission pathways at the molecular level. Future research should integrate comprehensive genomic surveillance to identify the genetic mechanisms and transmission dynamics underlying the observed resistance trends.

In conclusion, this 12-year surveillance study demonstrates that AMR *Salmonella* isolated from asymptomatic carriers represents a growing public health threat in Yulin, characterized by increasing MDR rates and emerging TGC resistance. These resistance patterns are influenced by both natural and socioeconomic factors. Our findings underscore the urgent need for integrated surveillance and management strategies to contain AMR transmission. Specifically, surveillance programs must address the critical issue of asymptomatic carriage and silent transmission of antibiotic-resistant pathogens in healthy populations, particularly among food handlers who serve as key reservoirs in the transmission chain.

Conflicts of interest: No conflicts of interest.

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[#] Corresponding authors: Ning Jiang, ylcdcjn@163.com; Biao Kan, kanbiao@icdc.cn; Xin Lu, luxin@icdc.cn.

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[1] School of Public Health, Nanjing Medical University, Nanjing City, Jiangsu Province, China; [2] National Key Laboratory of Intelligent Tracking and Forecasting for Infectious Diseases, National Institute for Communicable Disease Control and Prevention, Chinese Center for Disease Control and Prevention, Beijing, China; [3] Yulin Center for Disease Control and Prevention, Yulin City, Guangxi Zhuang Autonomous Region, China; [4] Department of Microbiomics, National Institute for Communicable Disease Control and Prevention, Chinese Center for Disease Control and Prevention, Beijing, China.
[&] Joint first authors.

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SUPPLEMENTARY MATERIAL

SUPPLEMENTARY TABLE S1. Correlation between temperature and antibiotic resistance rates.

Antibiotics	Temperature		Temperature adjustment			
			One-month lag		Two-month lag	
	r	*P*	*r*	*P*	*r*	*P*
AMK	0.2621	0.0133*	0.2497	0.0443*	0.1599	0.3808
SAM	0.2496	0.0133*	0.1942	0.0962	0.0983	0.5846
CAZ	0.1082	0.2869	0.0941	0.4478	0.0705	0.5846
CHL	0.2439	0.0133*	0.1707	0.1411	0.103	0.5846
CIP	0.1956	0.0551	0.0604	0.5423	−0.0375	0.7394
COL	0.2035	0.0524	0.1283	0.3172	0.0755	0.5846
ETP	0.1213	0.2608	0.0837	0.4699	0.0194	0.8264
MEM	0.0723	0.4512	0.0705	0.5180	0.0812	0.5846
SXT	0.0492	0.5756	−0.0475	0.5899	−0.0608	0.6017
TET	0.2476	0.0133 *	0.2182	0.0676	0.1948	0.2899
TIG	0.1041	0.2869	0.1088	0.3963	0.0784	0.5846

*Significance ($P<0.05$).

Abbreviation: CHL=chloramphenicol; SXT=trimethoprim-sulfamethoxazole; TIG=tigecycline; AMK=amikacin; CAZ=ceftazidime; CIP= ciprofloxacin; COL=colistin; ETP=ertapenem; MEM=meropenem; SAM=ampicillin-sulbactam; TET=tetracycline.