JIDC | THE JOURNAL OF INFECTION IN DEVELOPING COUNTRIES

Original Article

Antibiotic resistance in East Asia: current status, risks, and response strategies

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Abstract

Introduction: This study investigates the current status and regional disparities of resistance to novel antibiotics in East Asia, exploring links to socioeconomic factors and identifying high-risk resistance determinants.

Methodology: Metagenomic sequencing was performed on 1024 human fecal samples (25 local, 999 public) from 12 regions across China and Japan. Antibiotic resistance genes (ARGs) were identified by aligning sequences against a comprehensive antibiotic resistance database, focusing on 8 novel antibiotic classes. The relationship between regional per capita GDP and resistance rates for clinically relevant novel antibiotics was statistically analyzed.

Results: Significant regional variation in resistance rates was observed for clinically used novel antibiotics (aminocoumarins, glycylcyclines, oxacephems, oxazolidinones, pleuromutilins). A significant inverse correlation was found between per capita GDP and resistance rates for aminocoumarins, glycylcyclines, and oxacephems, particularly pronounced within inland regions. Oxacephem resistance was alarmingly high (> 55% in all regions, > 90% in some). Oxazolidinone resistance remained low (< 28%). Pleuromutilin resistance showed a strong negative GDP correlation only inland. Analysis revealed 24 high-frequency ARGs (5 exceeding 45% coverage: CfxA, IsaB, MexB, abeS, IsaE). Minimal shared resistance determinants existed among novel antibiotic classes, except between oxazolidinones and pleuromutilins.

Conclusions: Resistance to novel antibiotics in East Asia exhibits significant regional heterogeneity, strongly influenced by local economic development levels. Resistance rates for specific agents (e.g., oxacephems) critically limit their clinical utility, necessitating mandatory susceptibility testing. High-frequency ARGs linked to traditional antibiotic misuse pose cross-resistance risks. Surveillance and stewardship strategies must be regionally tailored, prioritizing vulnerable areas and tracking critical resistance loci for novel agents.

Key words: New antibiotics; antibiotic resistance genes; regional disparities; metagenomic sequencing; economic development; public health surveillance.

J Infect Dev Ctries 2026; 20(1):43-51. doi:10.3855/jidc.21637

(Received 21 March 2025 – Accepted 18 June 2025)

Introduction

Overview of antibiotics

The discovery and application of antibiotics in the early 20th century marked a pivotal advancement in the history of medicine [1]. Bacteria can develop resistance through various mechanisms, including the production of antibiotic-degrading enzymes, alterations to drug targets, and the enhancement of drug efflux pumps. Consequently, the research and application of novel antibiotics have become increasingly critical [2].

In the face of the increasingly severe problem of antimicrobial resistance, comprehensive big data analysis is essential for effectively monitoring the use of new antibiotics and scientifically tailoring responses to regional resistance profiles in real-time. Consequently, in a context where traditional antibiotics are widely resistant and new antibiotics are increasingly subject to resistance, the utilization of big data to monitor the usage patterns of new antibiotics and to rationalize their regional application is of paramount importance in addressing the escalating challenge of antimicrobial resistance.

Usage of novel antibiotics

By integrating public databases and locally collected human fecal metagenomic data (totaling 1,024 samples), a total of 5,227 antibiotic resistance determinants spanning 29 antibiotic classes were identified. From these, eight classes of novel antibiotics (glycylcyclines, oxazolidinones, oxycephems, promicins, aminocoumarins, diarylquinolines, zoliflodacin-like agents, and tetracyclines) were

selected for comprehensive analysis. Figure 1 illustrates the heatmap of resistance rates to these novel antibiotics in selected cities across East Asia from 2019 to 2024.

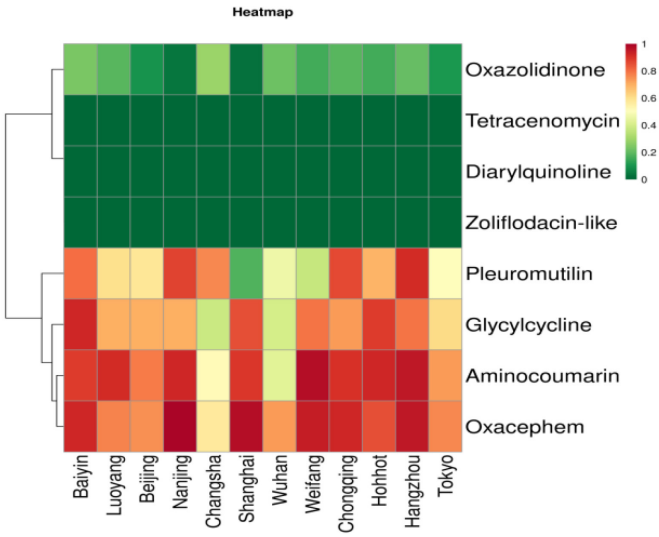
Glycylcycline antibiotics: Tigecycline, a broad-spectrum glycylcycline antibiotic, exhibits efficacy against a wide range of pathogens, including multidrug-resistant organisms such as methicillin-resistant *Staphylococcus aureus (*MRSA) and vancomycin-resistant *Enterococcus (*VRE). [3]. It is indicated for the treatment of complicated skin and soft tissue infections, complicated intra-abdominal infections, and infections due to *Clostridioides difficile* [4].

Oxazolidinone antibiotics: Linezolid is associated with side effects such as thrombocytopenia, optic and peripheral neuropathy, and lactic acidosis [5]. This agent is approved for the treatment of infections caused by vancomycin-resistant *Enterococcus faecium*, hospital-acquired pneumonia due to *Staphylococcus aureus*, and complex skin and skin structure infections (SSSIs) [6].

Oxacephem antibiotics: Latamoxef is a semi-synthetic, broad-spectrum oxacephem antibiotic primarily utilized for the treatment of infectious diseases, including respiratory, biliary, and urinary tract infections. This compound demonstrates efficacy against a variety of Gram-negative bacteria [7].

Pleuromutilin antibiotics: Lefamulin is a novel semi-synthetic pleuromutilin antibiotic primarily indicated for the treatment of community-acquired bacterial pneumonia (CABP). It represents the first systemically administered pleuromutilin antibiotic and exhibits activity against Gram-positive bacteria, including methicillin-resistant strains, as well as atypical pathogens [8].

Figure 1. Heatmap of resistance rates to novel antibiotics in selected cities across East Asia from 2019 to 2024.



Aminocoumarin antibiotics: 6-Aminocoumarin has demonstrated considerable potential in the realms of anticancer, antibacterial (both aerobic and anaerobic), and antifungal activities [9]. Nonetheless, detailed clinical application data for this compound are yet to be fully investigated.

Diarylquinoline antibiotics: Bedaquiline is the first new anti-tubercular drug to be marketed in nearly 50 years. It is characterized by its unique mechanism of action, potent activity against *Mycobacterium tuberculosis* (MTB), and favorable clinical efficacy [10].

Zoliflodacin-like antibiotics: Zoliflodacin is a novel antibiotic currently undergoing clinical trials, which is intended for the treatment of gonorrhea and other potential infectious diseases. It demonstrates efficacy against *Neisseria gonorrhoeae* and other pathogens with a high risk of antimicrobial resistance (AMR) [11].

Tetracenomycin antibiotics: Tetracenomycins and isoepoxydon are polyketide natural products produced by various actinomycetes with antimicrobial and anticancer activities. These compounds exhibit antimicrobial and anticancer activities by inhibiting ribosomal translation by binding to the polypeptide exit tunnel of the large ribosomal subunit [12].

Methodology

Ethics

This study was approved by the Medical Ethical Considerations Committee of Baiyin First Hospital (The Third Affiliated Hospital of Gansu University of Chinese Medicine) (Approval No. YL-KY-2024-051; Approval Date: 19 March 2024). Informed consent was obtained from all participants.

Materials

This study analyzed 1,024 fecal metagenomic samples. Twenty-five samples were collected from outpatient volunteers in Baiyin, Gansu Province, China. Individuals with complex hospitalization histories or potential nosocomial infections were excluded to focus on community-acquired antimicrobial resistance (AMR). The remaining 999 samples were obtained from public databases and represent 11 geographically distinct regions across China, as well as the Kanto region of Japan.

By utilizing the diverse Chinese samples under a unified national policy framework, the impact of socioeconomic conditions on AMR patterns was assessed. Samples from the socioeconomically developed Kanto population (Japan) served as an external reference cohort to evaluate potential effects of

differing national policies on AMR within genetically similar populations.

Sequencing experiments and bioinformatics analysis

Experimental procedure

Fecal specimens were collected under controlled conditions from donors who provided written informed consent approved by the Ethics Committee of Baiyin Municipal First People's Hospital (informed consent forms are attached). To ensure sample representativeness, specimens were specifically selected from outpatient clinic patients, excluding those hospitalized due to complex nosocomial infections. Total genomic DNA was subsequently extracted following standardized protocols and subjected to strict quality control. Finally, qualified DNA libraries underwent metagenomic sequencing on a high-throughput sequencing platform.

Bioinformatics analysis

Following the sequencing of 25 local samples and the integration of raw sequencing data from multiple public databases, all data underwent rigorous quality control using fastp [13] to remove low-quality reads and adapter sequences. Subsequently, assembly of the quality-controlled reads was performed using MEGAHIT [14], and the quality of the assembled contigs was assessed using QUAST [15]. Protein-coding genes within the contigs were predicted using Prodigal [16], which generated corresponding amino acid sequences (.faa). The predicted protein-coding gene sequences were functionally annotated by aligning against the Comprehensive Antibiotic Resistance Database (CARD) [17]. This analysis identified genes conferring distinct resistance phenotypes covering 29 antibiotic classes within the study samples, 8 of which correspond to novel antibiotic classes.

Results

Analysis of the resistance rates to novel antibiotics in selected cities across East Asia

Utilizing the ARO data from the CARD database, this study analyzed the antibiotic resistance profiles from 1024 human fecal samples collected from 12 different geographical regions in East Asia, incorporating both self-collected and publicly available datasets (Table 1).

Analysis of the relationship between per capita GDP and resistance to different novel antibiotics

Given the limited market application and research regarding resistance loci for diarylquinoline antibiotics, tetracenomycin antibiotics, and zoliflodacin-like antibiotics —which have comparatively few identified effective resistance loci—and considering that an insufficient number of resistance samples were reported within the the sample population of this study's sample population, this section focuses on analyzing the relationship between the economic development (as measured by per capita GDP) and resistance to aminocoumarin antibiotics, glycylcycline antibiotics, oxazolidinone antibiotics, pleuromutilin antibiotics, and oxacephem antibiotics. The objective is to elucidate strategies for the effective use and monitoring of resistance to them in regions with varying levels of economic development.

To account for regional development factors influencing GDP, the data were categorized the data into two groups: coastal or capital regions and inland regions. The coastal/capital regions include Beijing, Nanjing, Weifang, Hangzhou, Shanghai, and Tokyo, while the inland regions comprise Baiyin, Chongqing, Hohhot, Luoyang, Changsha, and Wuhan.

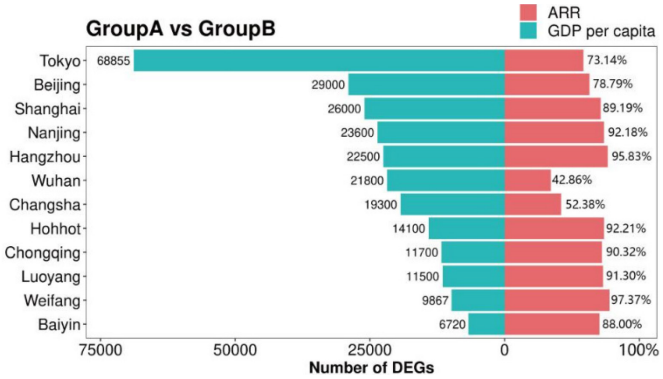
The results support the notion that regions with higher economic development may possess superior medical resources, public health systems, and antibiotic stewardship, thereby reducing resistance rates. However, this negative correlation does not imply a direct causal link between GDP per capita and antibiotic resistance but rather reflects the complex interplay of antibiotic use, healthcare quality, and public health policies. Consequently, the development of strategies for the use of new antibiotics should consider regional disparities and tailor treatment plans accordingly.

Figures 2-4 reveal that Tokyo, Beijing, Shanghai, Nanjing, and Hangzhou —either capital cities or economically developed coastal provincial capitals— exhibit significant locational advantages in economic development. Their comprehensive economic development levels and per capita GDP are generally higher than those of inland regions. In contrast, cities

Table 1. Data statistics of cholera carriers in East Asia.

Sample number	Region	Valid samples (n)
A1-Z8	Baiyin	25
CRR559598-CRR559725	Chongqing	127
CRR625388-CRR625467	Hohhot	79
CRR1000138-CRR1000234	Luoyang	95
CRR1238506-CRR1238527	Changsha	21
CRR342332-CRR342499	Wuhan	73
CRR1091478-CRR1091614	Beijing	135
CRR119984-CRR120050	Nanjing	65
CRR503890-CRR503927	Weifang	38
CRR933860-CRR933887	Hangzhou	27
CRR314259-CRR314334	Shanghai	74
DRR127476-DRR173017	Tokyo	285

Figure 2. Comparison of the impact of economic levels across different regions on the resistance to aminocoumarin antibiotics.



such as Baiyin, Luoyang, Changsha, Wuhan, Weifang, Chongqing, and Hohhot, located in China's interior, have comparatively lower levels of economic development. After controlling for the impact of locational advantages on GDP, a significant negative correlation is observed between resistance to these three types of antibiotics and GDP levels.

Nationwide, the negative correlation between per capita GDP and resistance rates to the novel antibiotics aminocoumarin, glycylcycline, and oxacephem is weak. However, in coastal and inland regions, this negative correlation becomes significantly stronger, indicating that in these areas, increased per capita GDP is associated with a reduction in antibiotic resistance. Specifically, the Pearson correlation coefficient for aminocoumarin resistance is -0.8643 in coastal or capital regions and -0.8733 in inland regions; for glycylcycline, it is -0.7537 in coastal or capital regions and -0.8820 in inland regions; and for oxacephem, it is -0.6594 in coastal or capital regions and -0.7636 in inland regions. Nationwide, the Pearson correlation coefficients for resistance to aminocoumarin, glycylcycline, and oxacephem are -0.2669, -0.2829, and -0.2255, respectively (Table 2).

For aminocoumarin and glycylcycline antibiotics —widely used with extensive research on their resistance loci, resistance levels inversely correlate with per capita GDP within regions of similar economic potential (Figures 2 and 3). In the context of resistance prevention efforts, and where locational economic advantages are comparable, attention should be directed

Figure 3. Comparison of the impact of economic levels across different regions on the resistance to glycylcycline antibiotics.

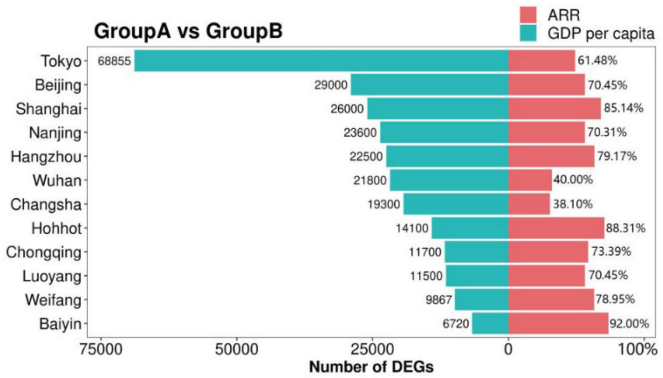
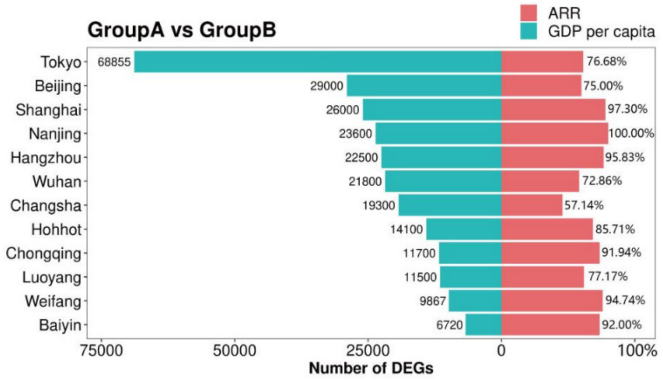


Figure 4. Comparison of the impact of economic levels across different regions on the resistance to oxacephem antibiotics.



towards the risk of antibiotic resistance in relatively less economically developed areas within these cities.

Oxacephem antibiotics exhibit high resistance rates across 12 regions, with all areas reporting resistance rates exceeding 55% (Figure 4). Notably, the resistance rate in Nanjing reaches 100%, while in Shanghai and Hangzhou, also located within the Yangtze River Delta economic region, resistance rates surpass 95%. Even in Changsha, which has the lowest resistance rate among the surveyed areas, resistance to oxacephem antibiotics stands at 57%.

Oxazolidinone antibiotics generally exhibit low resistance rates, not exceeding 28%. These antibiotics possess complex chemical structures, and their antimicrobial effects are achieved by inhibiting bacterial protein synthesis. This unique mechanism of

Table 2. Pearson correlation coefficient.

Antibiotic Name	Pearson correlation coefficient across 12 regions	Pearson correlation coefficient for 6 coastal or capital regions	Pearson correlation coefficient for 6 inland regions
Aminocoumarin Antibiotics	-0.2669	-0.8643	-0.8733
Glycylcycline Antibiotics	-0.2829	-0.7537	-0.8820
Oxacephem Antibiotics	-0.2255	-0.6594	-0.7636
Oxazolidinone Antibiotics	-0.4109	-0.1986	0.2557
Pleuromutilin Antibiotics	-0.2314	-0.0401	-0.5873

action reduces the likelihood of bacteria developing resistance through genetic mutation.

Nationwide, the Pearson correlation coefficient between per capita GDP and resistance to oxazolidinone antibiotics is -0.4109, indicating a significant negative correlation. However, the correlation coefficient for coastal or capital regions is -0.1986, suggesting a weaker correlation, while for inland regions, it is 0.2557, indicating a positive correlation. This may be related to the lower usage of these antibiotics, resulting in less pronounced regional differences (Table 2).

Figure 6 reveals marked antibiotic resistance in the developed regions of both countries. The situation differs somewhat for pleuromutilin antibiotics. Nationwide, the Pearson correlation coefficient between per capita GDP and resistance is -0.2314, suggesting a weak negative correlation. In coastal or capital regions, the coefficient is -0.0401, indicating a negligible correlation; in inland regions, the coefficient is -0.5873, revealing a strong negative correlation between resistance and per capita GDP. These discrepancies likely reflect heterogeneity in the distribution of medical resources, public health policies, and health awareness among residents across different regions. Therefore, the development of targeted antibiotic management strategies should consider regional economic disparities and geographical factors

Figure 7. Rose diagram of the distribution of resistance loci with high carriage frequency.

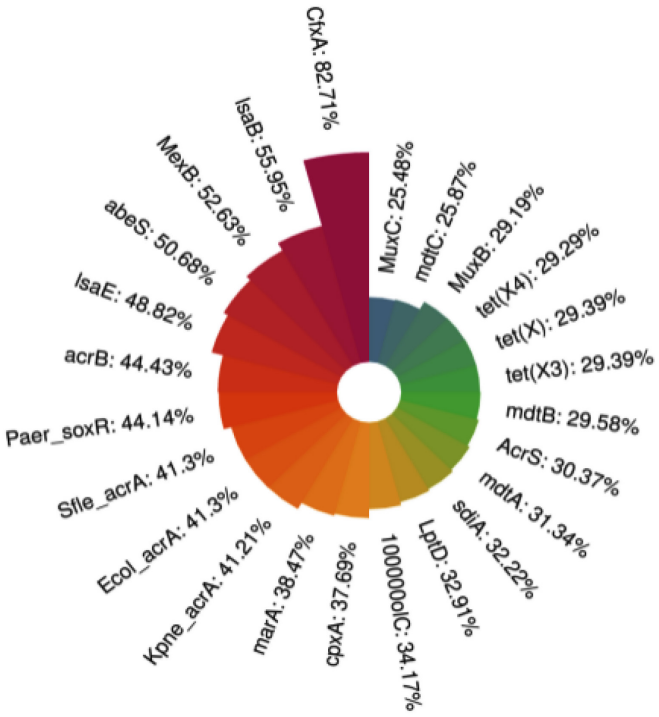
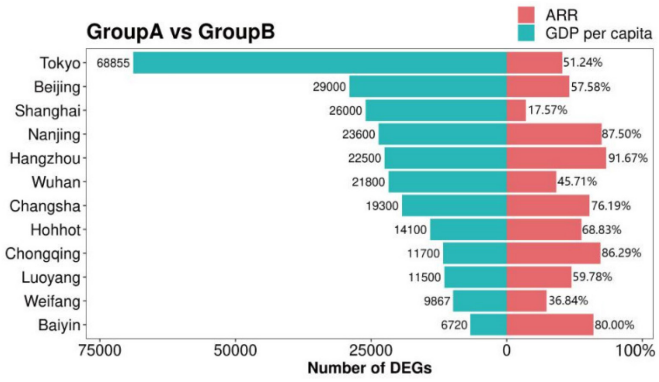


Figure 6. Comparison of the impact of economic levels across different regions on the resistance to pleuromutilin antibiotics.



(Table 2).

Analysis based on high-frequency carriage gene loci

In the in-depth investigation of antibiotic resistance, 24 out of 5,227 antibiotic resistance gene loci were identified as exhibiting coverage rates exceeding 25%, a finding that has attracted significant attention (Figure 7). Notably, the coverage probabilities of five gene loci—CfxA, IsaB, MexB, abeS, and IsaE—surpassed 45%. This may be attributed to certain antibiotics inducing high resistance at specific gene loci, thereby impacting other novel antibiotics; despite use, these have also shown marked resistance.

The high coverage rate of 82.71% at the CfxA gene locus indicates not only its widespread presence in novel antibiotics but also its significant resistance to cephalosporins. The potent efficacy of the CfxA gene locus also extends to Prevotella species in the oral cavity, gut, and vagina, which exhibit resistance to β-lactam antibiotics commonly used for infection treatment [18]. This phenomenon highlights that the misuse of cephalosporins has led to the spread and accumulation of resistance genes among bacteria, posing considerable challenges to clinical therapy.

Similarly, the high coverage rate of 55.95% at the IsaB gene locus suggests its presence not only in aminocoumarin and lincosamide antibiotics but also its role as a surface antigen B in *Staphylococcus aureus,* conferring an immune advantage [19]. This could reduce the host's ability to clear *S. aureus*, thereby increasing the risk of faecal-oral transmitted diseases [20].

The widespread distribution of the MexB gene locus has attracted significant attention, as its presence in various conventional antibiotics indicates that misuse of these antibiotics has increased resistance loci in novel antibiotics. The MexB multidrug efflux pump plays a pivotal role in bacterial resistance development

by expelling antibiotics through the MexA-OprM complex-like mechanism, enabling bacterial survival under antibiotic pressure [21].

Additionally, the IsaE gene is associated with the resistance of Group B Streptococcus (GBS). GBS, a common opportunistic pathogen, primarily colonizes the urogenital and lower gastrointestinal tracts of humans [22]. A study analyzed 85 *Group B Streptococcus* (GBS) isolates from pregnant women in Porto Velho, Rondônia, Brazil, for their serotypes, virulence genes, and antimicrobial resistance profiles. The analysis demonstrated that all isolates remained susceptible to β-lactam antibiotics (including penicillins and cephalosporins) and glycopeptide antibiotics [23].

Analysis of the association degree of resistance to novel antibiotics

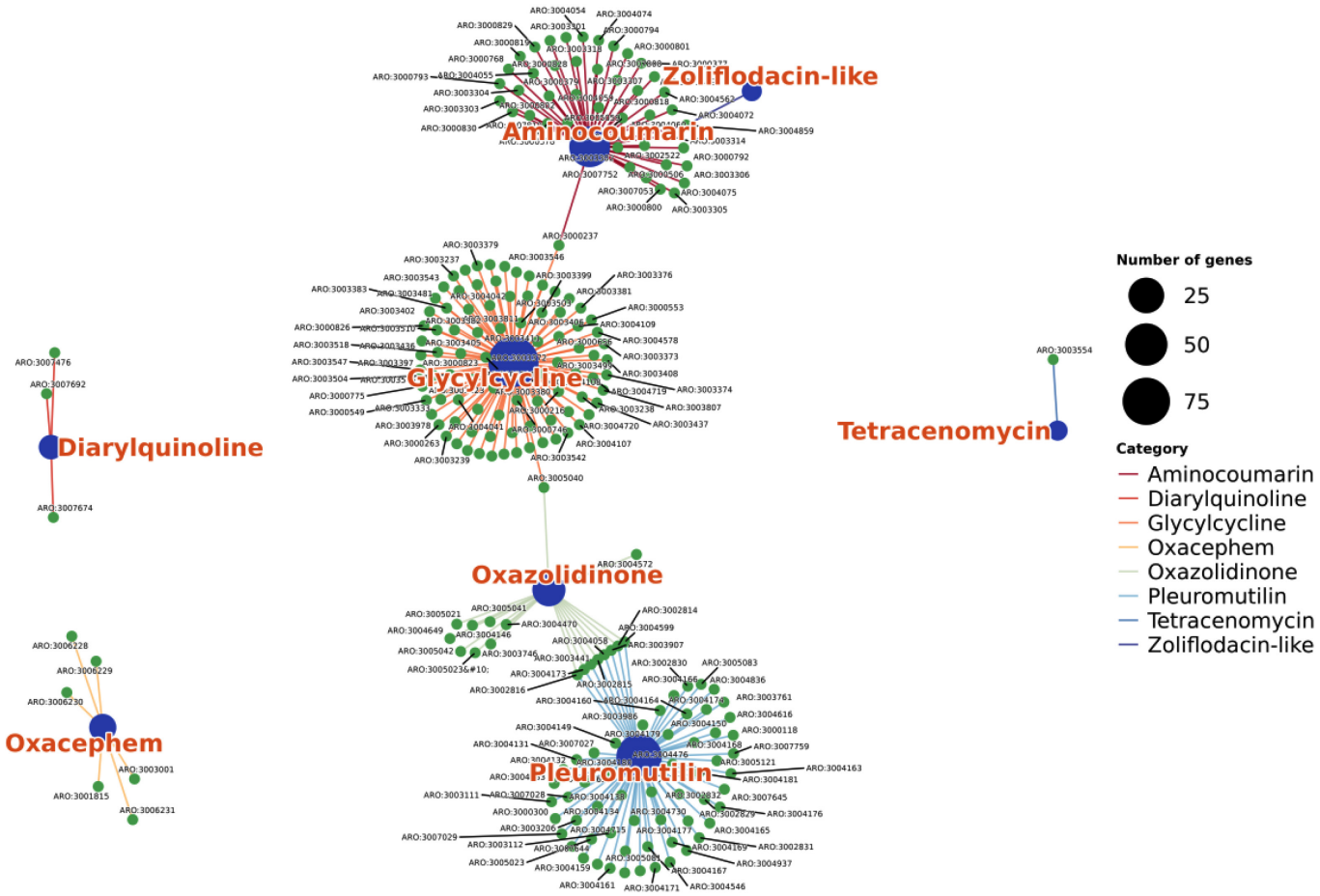
Presently, research on the resistance loci and mechanisms of novel antibiotics remains in its infancy compared to that of traditional antibiotics. A complex network diagram, as shown in Figure 8, was constructed for this study.

Among the eight novel antibiotics examined, only one to three resistance loci were identified in diarylquinoline antibiotics, zoliflodacin-like antibiotics, and tetracenomycin antibiotics —and these loci did not confer significant resistance. In contrast, resistance loci in aminocoumarin antibiotics, glycylcycline antibiotics, oxazolidinone antibiotics, and pleuromutilin antibiotics have been more thoroughly investigated. In terms of association, the overall correlation among the eight classes of novel antibiotics was low; only oxazolidinone antibiotics and pleuromutilin antibiotics exhibited a more pronounced association, sharing eight common resistance gene loci. The remaining antibiotic classes either shared only one common resistance locus or none at all, reducing the likelihood of a cascading resistance response.

Discussion

This study reveals significant differences in resistance patterns for novel antibiotics compared to traditional agents in East Asia. Unlike the widespread

Figure 8. Network analysis diagram of resistance gene loci in novel antibiotics.



resistance observed for traditional antibiotics, clinically deployed novel antibiotics—specifically oxacephem antibiotics, oxazolidinone antibiotics, aminocoumarin antibiotics, glycylcycline antibiotics, and pleuromutilin antibiotics—demonstrate marked regional heterogeneity. This divergence not only underscores the specificity of resistance mechanisms for newer agents but strongly suggests that clinical utilization strategies should prioritize regional resistance profiles over universal guidelines.

Inverse Correlation Between Regional Economic Development and Resistance: Analysis indicates that higher per capita GDP is generally associated with lower resistance rates, a correlation particularly pronounced in inland regions. This trend likely reflects more robust healthcare infrastructure, stricter antibiotic stewardship, and more effective public health interventions in developed areas. This observation implies that underserved regions face disproportionately elevated risks of novel antibiotic resistance, necessitating urgent reinforcement of training on rational antibiotic use and public education on antimicrobial stewardship.

Significant Regional Variability in Clinical Applicability of Novel Antibiotics: Oxacephem antibiotics exhibited exceedingly high resistance rates (over 70% in most regions and exceeding 90% in some), severely limiting their viability as first-line agents. Mandatory susceptibility testing prior to administration is therefore essential. Oxazolidinone antibiotics demonstrated low overall resistance, particularly in developed regions (Figure 5), which highlights their potential as preferred therapeutic options—especially in economically advanced areas.

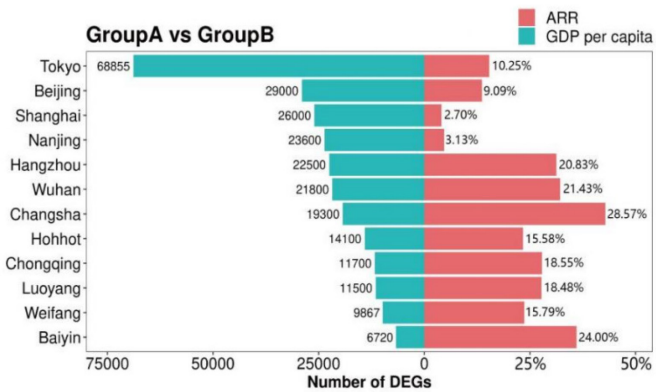
Three pre-approval agents (diarylquinoline antibiotics, tetracenomycin antibiotics, and zoliflodacin-like antibiotics) have shown no detectable resistance to date, suggesting considerable promise as future first-line therapies. However, vigilant post-marketing surveillance of resistance is crucial.

Aminocoumarin antibiotics, glycylcycline antibiotics, and pleuromutilin antibiotics displayed elevated resistance in most areas, coupled with significant inter-regional fluctuations—emphasizing the critical need for individualized treatment regimens.

The study identified widespread distribution of high-frequency resistance-associated genetic loci (e.g., cfxA, isaB, mexB), indicating that misuse of traditional antibiotics may indirectly compromise the efficacy of novel antibiotics through cross-resistance mechanisms.

Notably, shared resistance determinants among different novel antibiotic classes were minimal; a stronger association was observed only between oxazolidinone antibiotics and pleuromutilin antibiotics. This reduces the near-term risk of broad cross-resistance emergence and underscores the importance of surveillance focused on class-specific critical resistance loci, as well as monitoring of their mutational dynamics.

Figure 5. Comparison of the impact of economic levels across different regions on the resistance to oxazolidinone antibiotics.



Conclusions

In summary, this research provides new insights into the resistance of novel antibiotics in East Asia and underscores the importance of regional antibiotic surveillance. Recommendations for the scientific and rational use of novel antibiotics are also proposed, with future efforts suggested to continue exploring therapeutic strategies for novel antibiotics and developing specific inhibitors targeting highly prevalent virulence genes—aimed at addressing the challenge of antibiotic resistance.

Acknowledgements

The authors declare that this study received no funding from any external sources. All the resources utilized in this research were provided by The Third Affiliated Hospital of Gansu University of Chinese Medicine. All authors contributed their time and expertise without financial compensation from grants or other funding mechanisms.

Data availability statement

Some data used in this paper are from public databases.
Chongqing:
https://ngdc.cncb.ac.cn/bioproject/browse/PRJCA011396;
Hohhot:
https://ngdc.cncb.ac.cn/bioproject/browse/PRJCA013710
Luoyang:
https://ngdc.cncb.ac.cn/biosample/browse/SAMC3177292
Changsha:
https://ngdc.cncb.ac.cn/bioproject/browse/PRJCA028326

Wuhan:
https://ngdc.cncb.ac.cn/bioproject/browse/PRJCA007087
Beijing:
https://ngdc.cncb.ac.cn/bioproject/browse/PRJCA024368
Nanjing:
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Shanghai:
https://ngdc.cncb.ac.cn/bioproject/browse/PRJCA006197
Tokyo, Japan:
https://ddbj.nig.ac.jp/search/entry/sra-submission/DRA006684
and
https://ddbj.nig.ac.jp/search/entry/sra-submission/DRA008156.

Authors Contributions

JDZ conceived the idea and designed the study; JDZ, JHF, DFL, GLL, ZQC, ZHC, NY, HMQ, TXS, XSW collected the data; JDZ, JHF, DFL, GLL, ZQC, ZHC analyzed the data and drafted the manuscript. All authors commented on the paper and approved the final manuscript.

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Conflict of interest

No conflict of interest is declared.

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