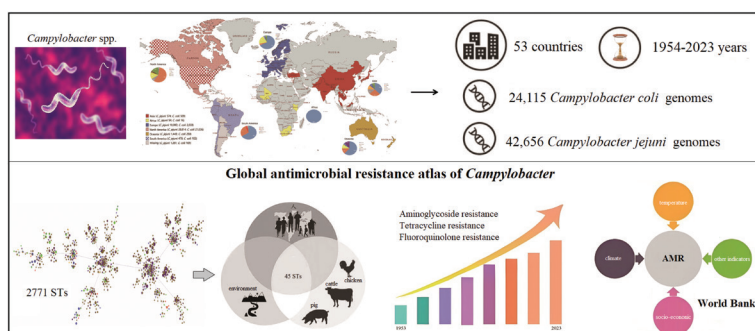




ORIGINAL ARTICLE

Longitudinal Trends and Drivers of Antimicrobial Resistance in *Campylobacter* Worldwide (1954-2023)

Graphical abstract



Authors

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Highlights

- Spatiotemporal atlas of AMR in *Campylobacter* from 53 countries during 1954–2023.
- Increased trends in critical antibiotics in both *C. jejuni* and *C. coli* were observed.
- Differences in AMR and virulent *Campylobacter* genes among sources.
- Socioeconomic factors driving AMR levels were observed.

Brief statement

This study highlights the global atlas of AMR-*Campylobacter*. Differences in AMR and virulent genes across different hosts, continents, and periods were identified. Positive correlations between socioeconomic factors and AMR levels were also observed. These findings contributed to understanding the transmission dynamics of AMR *Campylobacter* and policymakers for interventions in high-risk regions.

Longitudinal Trends and Drivers of Antimicrobial Resistance in *Campylobacter* Worldwide (1954-2023)

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Abstract

Objective: The zoonotic pathogen *Campylobacter* is a major foodborne bacterial species worldwide. The distribution and drivers of antimicrobial resistance (AMR) in global *Campylobacter* strains remain largely unknown. Therefore, a comprehensive analysis of longitudinal trends and driving factors of AMR in *Campylobacter* is necessary at a global level.

Methods: We downloaded from public repositories 66,771 *Campylobacter* genomes (24,115 from *C. coli* and 42,656 from *C. jejuni*) in 53 countries/regions during 1954–2023, and performed a comprehensive analysis.

Results: We categorized the *Campylobacter* isolates into 2,771 sequence types (STs), 45 of which were shared among humans, chickens, pigs, cattle, and the environment. We uncovered the spatial and temporal characteristics of resistance across antimicrobial classes on a global scale, and observed increased trends in the aminoglycoside, tetracycline, and fluoroquinolone resistance of *C. jejuni* during the past 23 years. Some of the antibiotic, climate, and socioeconomic indicators collected from the World Bank might potentially have driven the rise of AMR in various countries/regions to varying degrees.

Conclusions: In summary, we present a global genetic atlas of *Campylobacter*, which provides valuable insights for understanding the transmission dynamics of AMR in this species.

Keywords: *Campylobacter*, antimicrobial resistance (AMR), AMR gene, genomic mining, driving factor

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Received: November 4 2024

Revised: February 8 2025

Accepted: March 2 2025

Published Online: March 22 2025

INTRODUCTION

Campylobacter is a central cause of diarrhea worldwide. The incidence of gastroenteritis is increasing in both developed and developing countries [1]. *Campylobacter* infection has posed an enormous burden globally and was responsible for approximately 123,000 deaths in 2019

[2]. The most frequently identified species are *Campylobacter coli* (*C. coli*) and *Campylobacter jejuni* (*C. jejuni*), both of which are important triggers of human diarrheal diseases [3–5].

C. jejuni and *C. coli* usually live in the gut in animals including birds, swine, bovines, and domestic pets [6–10]. These bacteria are common in food animals

(e.g., poultry) and have developed resistance to several critical antibiotics, including fluoroquinolones and macrolides. These antibiotics are the primary treatments for *Campylobacter* infections in humans [11,12]. In addition, resistance to certain antimicrobials increase in farm animals and food, and the incidence of multidrug resistance (MDR) in *C. jejuni* has also increased [13]. However, understanding of the mechanisms of antimicrobial resistance (AMR) in *Campylobacter*, particularly in low-resource settings with limited data collection and surveillance, remains lacking.

AMR is among the top ten threats to global public health, and substantially damages both global health and economies. In response to the AMR crisis, the World Health Organization launched the Global Action Plan on Antimicrobial Resistance in 2015 and established the Bacterial Priority Pathogens List, which was released every year [14]. According to research statistics, in the next 25 years, more than 39 million people worldwide may die from infections caused by AMR bacteria [15]. Given the growing concerns regarding *Campylobacter* and the extensive availability of genomic data in public repositories, temporal and spatial monitoring of AMR trends in *Campylobacter* is needed. Nevertheless, most *Campylobacter* AMR monitoring studies are limited in geographic scope, temporal scope, or hosts, and have focused on phenotypic or point-prevalence surveys. For example, a study from Denmark in 2019 analyzed the dynamic occurrence of *Campylobacter* in chickens and its correlations with human populations with campylobacteriosis [16]. One-third of the clinical *Campylobacter* isolates matched the chicken isolates, but the study was limited to chickens and humans. Another study has described the AMR patterns of common pathogens causing childhood diarrhea in low- and middle-income countries from 1990 to 2020 [17]. Despite the increasing prevalence of campylobacteriosis, the global temporal and spatial distribution of AMR in *Campylobacter* in animals, humans, food, and the environment is not fully understood.

Whole genome sequencing has become an effective tool for studying AMR and tracking the transmission pathways of *Campylobacter* spp. This method enables detailed analysis of bacterial genomes, thus providing insights into the genetic mechanisms underlying AMR [18–21]. Whole genome sequencing has been used for monitoring AMR and the frequency of acquired ARGs, as well as mutations within and among microbial populations [22–28]. In addition, this technique can facilitate precise tracking of bacterial strains in epidemiological studies, and the pinpointing sources of outbreaks and transmission pathways [29]. The global drivers of bacterial AMR are multifaceted and involve a complex interplay of various factors. The major drivers include antibiotic overuse and misuse in medicine and agriculture, inadequate infection control measures, and the global movement of individuals and goods [30]. Poor hygiene conditions, particularly in low- and middle-income countries, exacerbate the spread of

resistant bacteria. Moreover, climate, social, and economic factors are positively associated with AMR in *Salmonella* [25]. Although a recent study has reported that climate change is closely associated with the spread of diarrhea caused by *Campylobacter* [31], full-scale associations of AMR in *Campylobacter* with global climate and socio-economic factors have rarely been investigated. Therefore, extensive and up-to-date real-time data are crucial for monitoring the worldwide spread of *Campylobacter*.

In this study, following the “One Health” strategy [32,33], we first constructed a high-quality dataset of *Campylobacter* by using 66,771 genomes covering 53 countries/regions from 1954 to 2023. Subsequently, we explored the temporal dynamics of AMR, ARGs, mobile genetic elements, and virulence genes (VGs) worldwide. In addition, we analyzed the correlations of AMR in *Campylobacter* with global climate and socio-economic indicators. The high-quality dataset generated herein should aid in development of effective intervention measures for the control and prevention of AMR in *Campylobacter*.

MATERIALS AND METHODS

Dataset collection

In this study, the 86,365 available *Campylobacter* genomes were downloaded from the NCBI database (<https://www.ncbi.nlm.nih.gov/assembly/>, as of May 20th, 2023). The genome accessions and metadata information were manually sorted and verified (S1 Table). The 86,365 assembled *Campylobacter* genomes included a range of human, animal, and environmental genomes in 53 countries/regions from 1954 to 2023. We screened the metadata of publicly available assembled *Campylobacter* genomes from the NCBI BioSample database (<https://www.ncbi.nlm.nih.gov/biosample/>), and further summarized the BioSample information for each genome (S2 Table). The publicly available *C. coli* and *C. jejuni* genomes were then filtered according to their BioSample information. At least two of the three columns of collection date, geographic location, and host were required to contain information. A total of 19,594 genomes were discarded because no clear background information regarding the collection time, isolation source, and sampling site had been simultaneously recorded. Following the One Health strategy, we focused on the following common types: humans, aquatic animals, chickens, cattle, pigs, food, turkey, wild animals, and the environment. A total of 66,771 high-quality genomes of *C. coli* and *C. jejuni* with detailed biosamples were retained for further analysis. These clean data covered 53 countries/regions from 1954 to 2023.

A total of 66,771 genomes of *Campylobacter* were further chosen for subsequent analysis. We extracted and arranged the information on geographic location, collection time, and isolation sources. The samples were systematically documented for each isolate, and the collection date, isolation source, and geographic locations were further detailed. The isolates from swine, pork, or pig feces were

classified into the pig category. The isolates from chicken ceca, chicken wings, whole chicken rinses, chicken throat swabs, chicken hams, or chicken breasts were classified into the chicken category. Other categories were classified similarly to the description above. The approach in this study was consistent with the methods used in previous studies [7,34,35].

Bioinformatics analysis

ST analysis was conducted with multi-locus sequence typing (MLST) v2.0 (<https://github.com/tseemann/mlst>) [36]. The ARG and AMR phenotypes were analyzed with ResFinder v4.1 (<https://bitbucket.org/genomicepidemiology/resfinder/src/master/>) [37] with the following parameters: identity $\geq 95\%$ and coverage $\geq 90\%$. *Campylobacter*-specific point mutations were screened with PointFinder (<https://bitbucket.org/genomicepidemiology/pointfinderdb/src/master/>) with parameters of identity $\geq 95\%$ and coverage $\geq 90\%$. All results were verified and used for subsequent analysis. ABRicate v1.0.1 (<https://github.com/tseemann/abricate>) was further applied to identify the VGs with default parameters. PlasmidFinder v2.0.1 [38] was used to detect putative plasmids with the parameters of identity $\geq 90\%$ and coverage $\geq 60\%$.

Data collection on indicators

To determine the associations of agriculture, antibiotics, climate, environment, and socioeconomic indicators with AMR in *Campylobacter*, we collected data including the animal husbandry production index, cereal production, CO₂ emissions, and GDP per capita. The primary dataset was sourced from the World Bank (<https://www.worldbank.org/en/home>). Additionally, the global average mean surface air temperature data were obtained from the Climate Change Knowledge Portal (<https://climateknowledgeportal.worldbank.org/download-data>). One representative country with the largest number of *Campylobacter* genomes in each of the six continents was selected and analyzed. World Bank data collected from five countries were used in the data analysis.

Statistical analyses and visualization

The geographical origins of the *Campylobacter* genomes were mapped and visualized with MapChart (<https://www.mapchart.net/>). Heatmap figures were generated with R 4.4.1 and associated R-tools. Pie charts and bar graphs were produced with GraphPad Prism version 9.0. A regression analysis was performed to investigate the associations of climate change and socioeconomic indicators with ARGs and AMR. Kruskal-Wallis tests, implemented in GraphPad Prism version 9.0, were used to evaluate differences in the counts of ARGs, plasmids, and VGs per isolate across various decade-specific datasets. The ImageGP online website (<http://www.ehbio.com/ImageGP/>) was used to generate the images. Additionally, the minimum spanning tree of STs was constructed with PHYLOViZ 2.0 (<http://www.phyloviz.net/>).

RESULTS

Global overview of *Campylobacter*

The assembled *Campylobacter* genomes included primarily *C. jejuni* (66%), *C. coli* (30%), and other *Campylobacter* species (4%). We focused on 42,656 genomes of *C. jejuni* and 24,115 genomes of *C. coli* (Fig 1A and S2 Table). The *Campylobacter* isolates derived from chickens were mainly from North America (29,062/66,771). The *Campylobacter* isolates derived from humans were distributed primarily in North America (29,716/66,771) and Europe (8,594/66,771). In contrast, the *Campylobacter* isolates from both humans and pigs were predominant in Europe (8,182/66,771) (Fig 1B and S3 Table).

We classified the isolates into the following periods for temporal analysis: before 2000 ($n = 224$), 2000–2004 ($n = 1,050$), 2005–2009 ($n = 2,166$), 2010–2014 ($n = 4,046$), 2015–2019 ($n = 37,885$), and 2020–2023 ($n = 20,331$) (Fig 1C and S4 Table). The strains were isolated primarily from humans ($n = 11,612$), chickens ($n = 30,213$), pigs ($n = 3,417$), turkeys ($n = 1,500$), and cattle ($n = 9,881$), and accounted for $\sim 84.8\%$ of the 66,771 genomes. However, only a small fraction was isolated from the environment ($n = 986$) (Fig 1D and S5 Table).

The 66,771 isolates were categorized into 2,771 different STs. Most of these STs were enriched predominantly in North America and Europe, and the top 20 STs composed 42.2% of the total (Fig 1E and S6–S8 Tables). Among the top 20 STs, the isolates ST829 ($n = 2,513$) and ST7818 ($n = 1,974$) had high proportions of *C. coli*. Similarly, in North America, ST353 ($n = 1,729$) and ST50 ($n = 1,416$) had high proportions of *C. jejuni* (S6 Table). The isolates originated primarily from the periods 2015–2019 (56.94%) and 2020–2023 (30.75%), whereas isolates before 2000 accounted for only a small fraction (0.36%) (S1A Fig). Most isolates originated from North America, where agriculture or industry was concentrated (76.9%) (S1B Fig). In contrast, ST45 and ST22 were more ubiquitous before 2000, and ST854 was the major type during 2005–2009 (Table 1). ST854 was the dominant type with pig origins, and was the main type originating from pigs in China (Table 1). ST353, ST829, and ST860 were frequently identified in Africa, North America, and Asia, respectively (Table 1). The ST2993 clonal complex (CC) was enriched in primarily Africa, whereas the ST45 CC was enriched primarily in Oceania (Table 1).

Among the 2,771 ST types, 45 STs were shared among humans, chickens, pigs, cattle, and the environment, and most of them originated from Europe ($n = 3,693$) and North America ($n = 23,991$) (S9 Table). In addition, the CCs of chicken specialists (enriched primarily in chicken) and generalists formed the largest group. ST-host specialization analysis of the most copious CCs revealed moderate levels of chicken-specific STs in the ST45 CC and highly chicken-specific STs in the ST50 and ST353 CCs (Table 1).

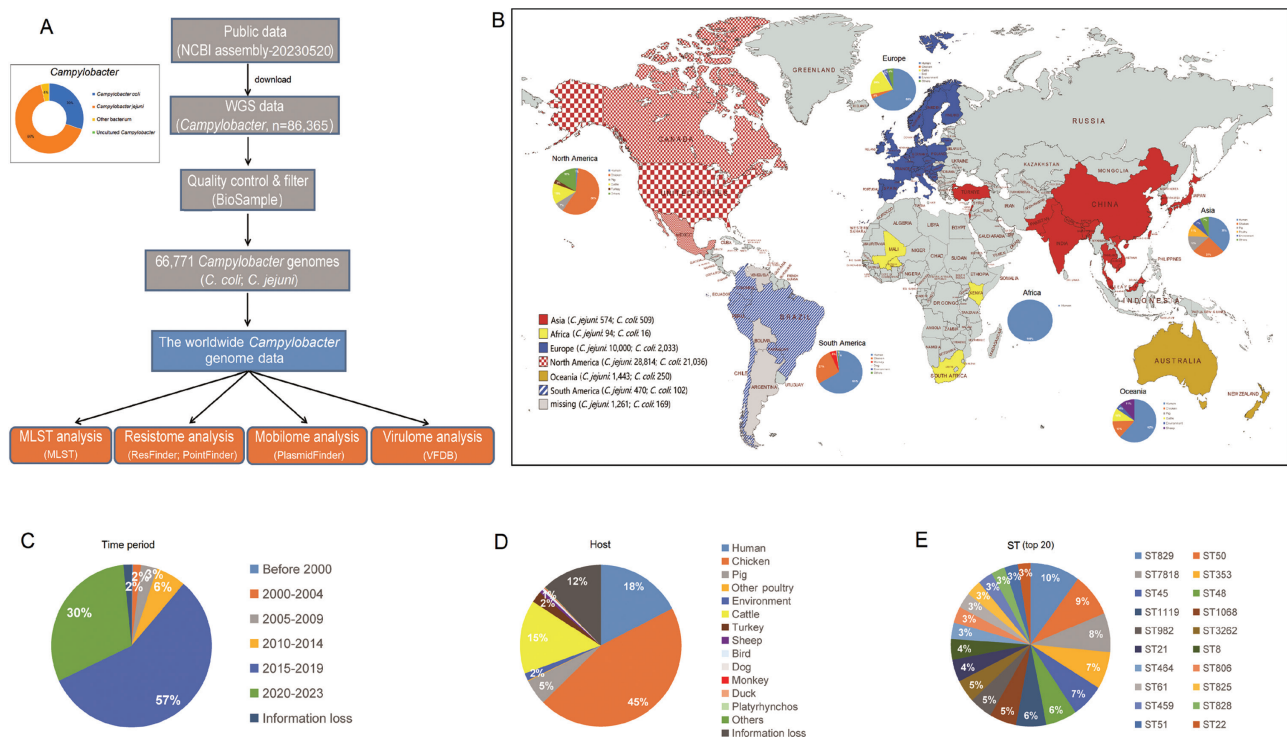


FIGURE 1 | Study design and summary of the global *Campylobacter* genome data. (A) Flowchart of study design. (B) Geographical distribution of the 66,771 *Campylobacter* isolates. (C–E), All isolates were grouped by (C) sampling time, (D) host, and (E) sequence type (ST). A total of 2,771 STs were detected. The 20 dominant STs were summarized and are shown in E.

Temporal variations in AMR

A total of 290,546 ARGs covering 68 types, as well as 11,524 *gyrA* (T86I) mutations mediating fluoroquinolone resistance were identified (S10 Table). An overall increasing trend of aminoglycoside, tetracycline, and fluoroquinolone resistance in *C. jejuni* in the past 23 years was observed (Fig 2A). For example, the prevalence of ARGs conferring fluoroquinolone resistance in *C. jejuni* markedly increased, from 3.45% before 2000 to 28.77% during 2015–2019 and to 22.81% during 2020–2023 (Fig 2A, B). Among *C. jejuni* genomes, the proportion with beta-lactam resistance decreased from 2005–2009 to 2020–2023 in North America but remained steady in Europe, in contrast to *C. coli* (Fig 2A, C). In Asia, no substantial alterations in fluoroquinolone resistance were observed in *C. jejuni* during the past 23 years, whereas tetracycline and beta-lactam resistance showed an increasing trend. Similarly, in Asia, the beta-lactam and aminoglycoside resistance in *C. coli* showed an increasing trend since 2009; although tetracycline resistance slightly decreased between 2015 and 2019, it also displayed an increasing trend (Fig 2A, C). Notably, in Europe, North America, and South America, we observed an increasing trend in the fluoroquinolone resistance of *C. jejuni* (Fig 2A, B).

In contrast, aminoglycoside and tetracycline resistance in *C. coli* showed an increasing trend until 2005–2009, then decreased until 2020–2023 (Fig 2C, D). We also examined resistance to phenicol, a key antimicrobial agent in veterinary medicine. However, although ARGs

conferring resistance to phenicols showed an increasing tendency over time, the proportion of ARGs was very low (Fig 2). In chicken isolates, an overall increasing trend in AMR level occurred before 2019, then remained steady until 2023 (S2 Fig). Although some fluctuations were observed, this trend remained steady in the *C. jejuni* genomes during the 23 years, whereas in the *C. coli* genomes, a decrease in beta-lactam, tetracycline, and aminoglycoside resistance was observed since 2010 (Fig 2). Although the beta-lactam resistance remained steady in the past 23 years, an increasing trend of tetracycline and fluoroquinolone resistance in *C. jejuni* genomes, and of beta-lactam, tetracycline, and aminoglycoside resistance in *C. coli* genomes, was observed since 2005 (Fig 2). In cattle, an overall increasing trend in AMR level observed before 2019, then decreased sharply thereafter. Notably, the distribution patterns of ARGs with human, chicken, and cattle origins were similar, thus indicating potential cross-transmission among these species. In contrast, in *C. jejuni* with pig origins, beta-lactam, tetracycline, and fluoroquinolone resistance sharply increased between 2005–2009 and 2010–2014, then decreased until 2023.

Characteristics of ARGs across sample times, hosts, and geographic locations

The prevalence of ARGs varied across hosts, continents, and time periods (Fig 3A–F; S11–S13 Tables). The *gyrA* (T86I) mutations *bla*_{OXA-61}, *bla*_{OXA-450}, *bla*_{OXA-453}, and *tet*(O) increased during 2010–2014 in *C. jejuni*, whereas

TABLE 1 | Sampling period, host, and continents distribution of STs in *Campylobacter*.

STs	Before 2000	2000–2004	2005–2009	2010–2014	2015–2019	2020–2023
ST21	1.84%	4.14%	3.58%	3.31%	2.06%	0.92%
ST22	8.76%	1.42%	1.11%	0.76%	1.41%	0.47%
ST45	11.98%	6.64%	3.14%	3.78%	3.29%	1.37%
ST353	2.30%	10.02%	0.86%	1.07%	3.06%	3.53%
ST854	0%	21.79%	10.36%	4.12%	0.35%	0.50%
ST982	0%	54.47%	2.10%	4.36%	2.22%	1.16%
ST827	0%	0.11%	0.99%	4.88%	0.71%	0.61%
ST50	6.45%	3.81%	1.97%	2.16%	4.11%	3.24%
ST829	0%	0.65%	0.99%	1.59%	3.53%	6.81%
STs	Human	Cattle	Chicken	Pig	Turkey	Environment
all STs	15.69%	14.84%	46.61%	5.07%	2.20%	1.48%
ST45	25.00%	14.42%	29.73%	0.71%	2.54%	1.48%
ST50	27.30%	5.30%	49.25%	0.09%	1.28%	1.69%
ST353	5.98%	2.03%	78.11%	0.16%	0.64%	0.21%
ST354	30.99%	7.79%	47.15%	0.19%	0.76%	0.76%
ST1068	0.29%	79.47%	5.17%	10.48%	1.15%	1.22%
ST828	5.21%	20%	39.44%	26.62%	2.39%	1.27%
ST829	1.32%	1.71%	84.77%	2.61%	5.96%	0.43%
ST854	1.84%	1.84%	12.89%	67.03%	0.92%	11.79%
STs	Asia	Africa	Europe	North America	South America	Oceania
ST860	4.66%	0%	0.28%	0.04%	0.64%	0.18%
ST50	3.74%	0%	6%	3.06%	1.49%	6.52%
ST353	0%	8.74%	0.88%	3.73%	5.53%	0.06%
ST829	1.01%	3.88%	0.21%	5.43%	2.13%	0.12%
ST2993	0.51%	0%	0.04%	0%	16.81%	0.06%
ST45	0.91%	0%	3.64%	2.45%	0.21%	10.36%

*bla*_{OXA-61} and *bla*_{OXA-450} slightly decreased in *C. coli* during 2010–2014 (Fig 3C, F). Notably, the *gyrA* (T86I) mutations from *C. jejuni* were concentrated in the periods of 2005–2009 and 2015–2019 (Fig 3C). Furthermore, temporal increases in *gyrA* (T86I) and *tet(O/W/O)* were observed in both humans and chickens (Fig 3B, E; S11–S13 Tables). We also detected 1,077 *C. jejuni* genomes with human and chicken origins carrying the MDR genotype of *bla*_{OXA-61}-*tet(O/W/O)*-*gyrA* (T86I), thus representing an increase in co-occurrence of ARGs (S11–S13 Tables).

Our findings indicated a notable increasing trend in beta-lactam resistance (Fig 3C). Among beta-lactam isolates, nine *bla*_{OXA} genes (*bla*_{OXA-446}, *bla*_{OXA-447}, *bla*_{OXA-448}, *bla*_{OXA-449}, *bla*_{OXA-465}, *bla*_{OXA-466}, *bla*_{OXA-184}, *bla*_{OXA-185}, *bla*_{OXA-193}) and one *bla*_{CTX-M-1} gene were identified. The *bla*_{OXA-61} gene was the predominant beta-lactam resistance determinant in *C. jejuni*, and most cases were reported in Asia and Oceania (S11 and

S12 Tables). The *gyrA* (T86I) mutations had the highest proportions in genomes from South America (77.2%), followed by Asia (72.5%) and Europe (40.5%) (Fig 3A). Notably, we identified 415 *Campylobacter* strains carrying the lincosamides resistance gene *lnu* (C), including 357 *C. coli* and 58 *C. jejuni*.

A total of 143 *Campylobacter* isolates—126 *C. coli* and 17 *C. jejuni*—carried macrolide resistance genes. Most of them were distributed in China (120/143), whereas only several were distributed in other countries. The macrolide resistance genes such as *erm(A)* (9/66,771), *erm(B)* (137/66,771), and *erm(C)* (5/66,771) were distributed primarily in ducks, humans, chickens, and other poultry. The number of *erm(B)* genes was higher in *C. coli* than *C. jejuni* (S3A Fig). The *gyrA* (T86I) mutation predominated in Europe (4,020/66,771) and North America (6,131/66,771), and were distributed mainly in the United Kingdom and the USA (S13 Table). Specifically, *C. coli*

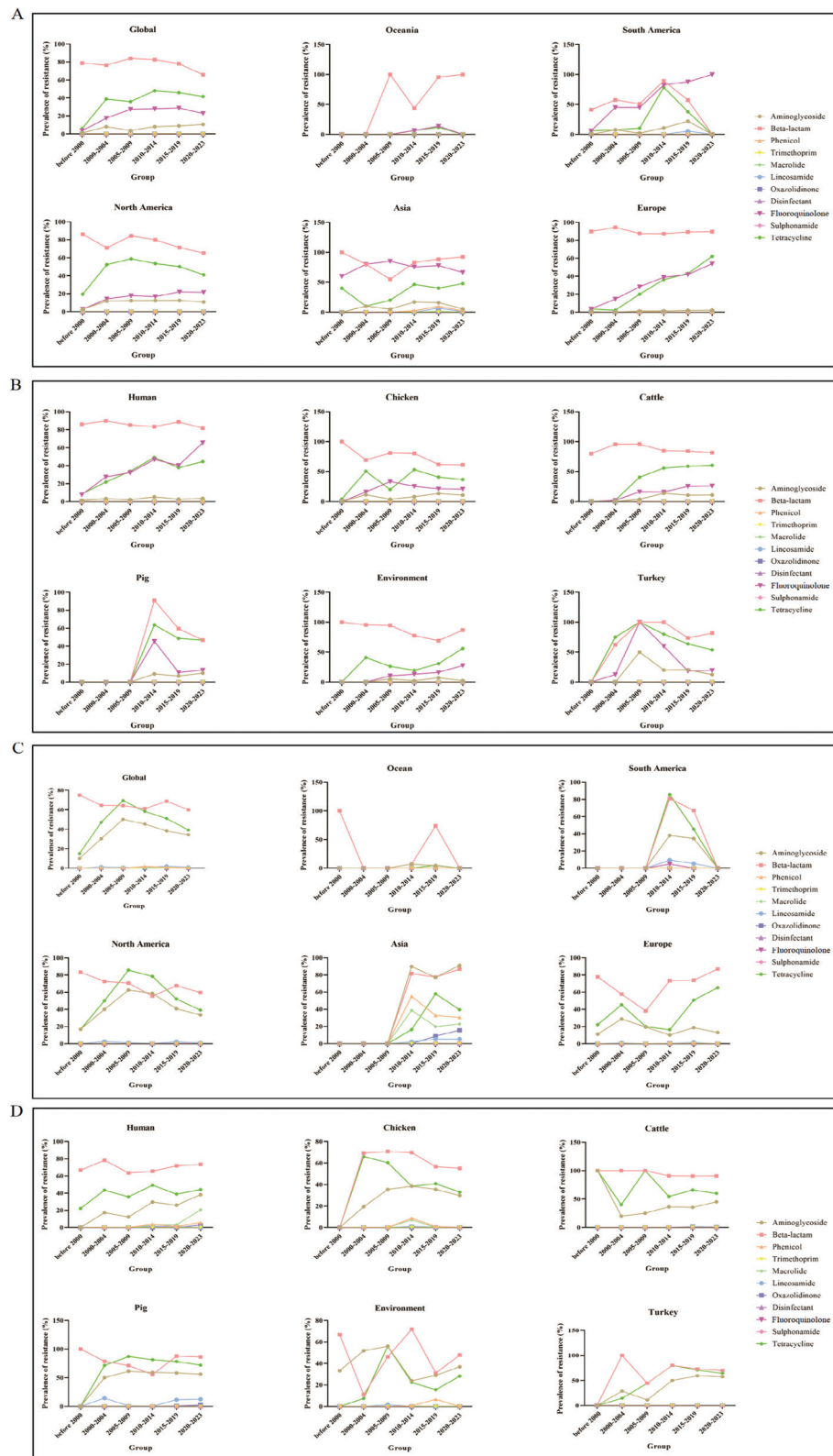


FIGURE 2 | Temporal changes in the resistomes of *C. jejuni* and *C. coli* genomes worldwide over the past 23 years. (A-B), Prevalence of AMR rates in *C. jejuni* genomes from different continents (A) and sources (B). (C-D), Prevalence of AMR in *C. coli* genomes from different continents (C) and sources (D).

(59.5%) with poultry origins in China carried more ARGs than *C. jejuni* (40.5%), thus indicating a shift in relative abundance from *C. jejuni* to *C. coli* in poultry from China.

Specific ARGs were found to be present in several hosts and periods. A total of 126 (0.2%, 126/66,771) *Campylobacter* strains carrying the *fexA* gene were identified

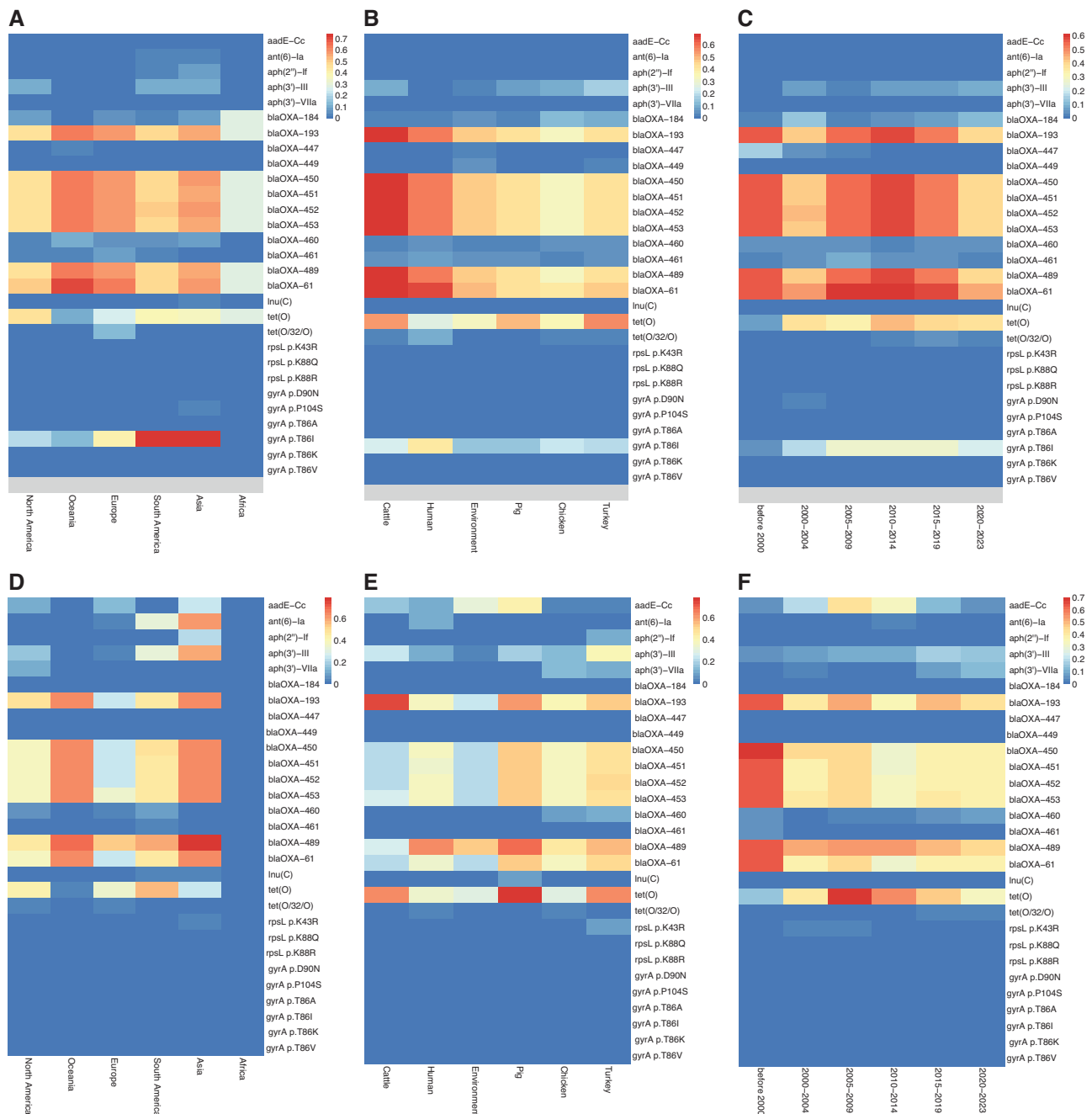


FIGURE 3 | Prevalence of global ARG in *C. jejuni* and *C. coli* genomes. (A-C), Global ARG prevalence in *C. jejuni* genomes, by continent (A), host (B), and sampling period (C). (D-F), Global ARG prevalence in *C. coli* genomes, grouped by continent (D), host (E) and sampling period (F).

from China, including those from chickens ($n = 67$), other poultry ($n = 26$), ducks ($n = 7$), geese ($n = 7$), the environment ($n = 3$), humans ($n = 3$), and pigs ($n = 2$). The *fexA*-positive isolates markedly increased between 2016 and 2021. Interestingly, we also detected several *fexA*-positive *Campylobacter* strains from humans ($n = 3$) and pigs ($n = 2$). These isolates were distributed in the United Kingdom, New Zealand, and China. Furthermore, the *optrA* gene was found primarily in *C. coli* with pig origins from China. The number of *optrA* was higher in *C. coli* than *C. jejuni* (S3B Fig). We also observed co-existence of

the *optrA* and *fexA* genes within 15 *Campylobacter* isolates from pigs, ducks, and chickens in China.

Temporal variations in VGs and plasmids

Most isolates carried abundant VGs (S14 Table). We examined 137 VGs in *Campylobacter*; the top 11 VGs were *cheV*, *flgE*, *cheW*, *cheA*, *fliG*, *fliF*, *fliH*, *motB*, *flhB*, *motA*, and *fliN*. Several genes associated with adhesion, colonization, invasion (*cadF*, *porA*, *ciaB*, and *jlplA*), and cytolethal distending toxin (*cdtA*, *cdtB*, and *cdtC*) were present in *C. jejuni*. The toxin *cdtB* was identified in 42,119 (63.08% of 66,771)

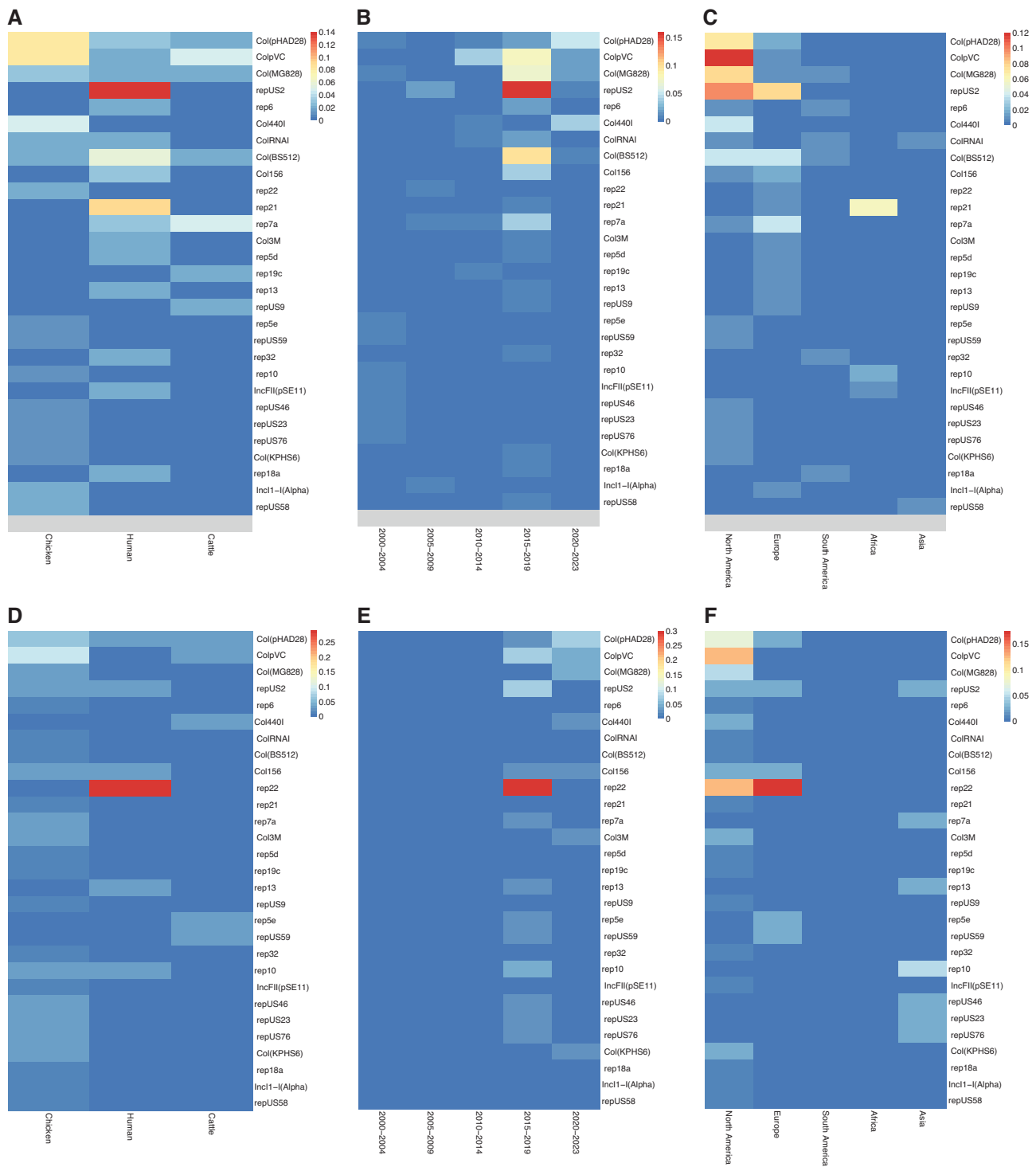


FIGURE 4 | Global plasmid repicon prevalence in *C. jejuni* and *C. coli* genomes, grouped by host, sampling period, and continent. (A–C), Global plasmid repicon prevalence in *C. jejuni*, grouped by host (A), sampling period (B), and continent (C). (D–F), Global plasmid repicon prevalence in *C. coli*, grouped by host (D), sampling period (E) and continent (F).

genomes distributed in 1,616 STs. The top five STs were ST50 ($n = 2,187$), ST353 ($n = 1,873$), ST45 ($n = 1,690$), ST48 ($n = 1,604$), and ST982 ($n = 1,188$) (S14 Table).

A total of 143 plasmid repicons categorized into 29 distinct types were identified (S15 Table). The prevalence of plasmid repicons varied among hosts, times, and countries (Fig 4A–F). Isolates derived from humans and

chickens exhibited a higher prevalence of plasmids than those from other sources (Fig 4A, D). Col (pHAD28) was dominant in humans, cattle, and chickens, whereas IncFII (pSE11) was dominant in humans (Fig 4A, D). The plasmid repicons were distributed in 66 STs, and most of them were dominant in North America and Europe during 2015–2019 (Fig 4B, C, E–F). However, the plasmid

replicon prevalence in *C. coli* showed no clear distribution in South America and Africa (Fig 4F).

Correlation analysis of driving factors and AMR

The correlations among antimicrobial, climate change, socioeconomic indicators, and AMR in *Campylobacter* with human origins showed different patterns from those with animal origins (Table 2, S4A–E Fig). The rural population and population growth in China, cereal production in the USA, and CO₂ emissions in Peru were positively correlated with ARGs of human origin (Table 2). In contrast, the food production index, cereal production, and GDP per capita in China; GDP per capita, and population growth in the United Kingdom; and rural population in Peru were negatively correlated with ARGs of human origin. Similarly, the CO₂ emissions in New Zealand; the average mean surface air temperature and GDP per capita in the United Kingdom; and the rural population and population growth in the USA were positively correlated with ARGs with animal origins (Table 2). In contrast, the animal husbandry production index, food production index, GDP per capita, average mean surface air temperature in the USA, and population growth in New Zealand were negatively correlated with ARGs with animal origins (Table 2).

Furthermore, the average mean surface air temperature in the USA was positively correlated with the number of *Campylobacter* genomes (S4D Fig). In contrast, the population growth in China and the USA, and CO₂ emissions in the United Kingdom and the USA, were negatively correlated with the number of *Campylobacter* genomes (S4D–E Fig). In the antibiotic consumption analysis, we observed that aminoglycoside, beta-lactam, fluoroquinolone, and tetracycline resistance in Peru, and aminoglycoside resistance in the USA, were positively associated with the annual ratio of resistant phenotypes with human origins, and fluoroquinolone resistance in China was positively associated with the annual ratio of resistant phenotypes with animal origins (Table 2, S4 Fig). In contrast, the aminoglycoside resistance in China and the fluoroquinolone resistance in the United Kingdom were negatively correlated with the annual ratio of resistant phenotypes with animal origins.

DISCUSSION

In this study, we provide a global AMR atlas for *Campylobacter*, encompassing 66,771 isolates from animals, humans, food, and the environment in 53 countries/regions from 1954 to 2023, according to the One health framework. The AMR profile established herein is the most current and largest dataset of *Campylobacter* worldwide, and presents a comprehensive genomic snapshot of the *C. coli* and *C. jejuni* to date. The results highlighted crucial spatial differences in the AMR of *Campylobacter*, and provided estimates for countries or regions lacking genomic surveillance data. To our knowledge, this study

provides the first comprehensive atlas of AMR across chickens, pigs, humans, cattle, aquatic animals, and the environment during the period of substantial industrial expansion of animal protein production.

The ARGs influencing tetracycline and beta-lactam resistance were observed predominantly in *C. jejuni* and *C. coli* genomes. The beta-lactam and tetracycline phenotypes were also the predominant AMRs of human pathogenic bacteria in hospital wastewater from megacities in China and were present in plasmid replicons [39]. Substantially more genomic data were used in this study than previous studies [21,23,35,40,41]. Most ARGs recently discovered in *Campylobacter* appear to have been from gene transfer from Gram-positive bacteria, which shared an ecological niche with *Campylobacter* in animal intestines [42].

In this work, *fexA*-positive strains were detected in the *Campylobacter* genomes from humans, the environment, pigs, chickens, ducks, and other sources. Acquisition of the *fexA* gene specifically promotes resistance to florfenicol in *C. jejuni*, and the *fexA* gene within *Campylobacter* is frequently associated with mobile genetic elements or MDR islands [43]. Notably, the observation of *fexA*-positive strains with human and pig origins provided a new perspective on the spread pattern, given that *fexA* had long been reported not to exist in these isolates [44]. Therefore, system monitoring should be implemented to prevent the spread of *fexA* to humans.

In addition, macrolide-resistant *Campylobacter* was more common in China than other countries. The *erm(B)* gene, the main contributor to macrolide resistance, was distributed in humans, chickens, and other origins. As reported, to date, *erm(B)*-mediated macrolide resistance has been limited primarily to *C. coli* in China, and the use of antimicrobials in China might have placed unique selection pressure on *Campylobacter* [45].

Fluoroquinolone and macrolide resistance have been found to be widely present worldwide [24], as further supported by our results. *Campylobacter* in ruminants might be transmitted to humans through unpasteurized milk and other means [42]. Although poultry remains the main source of human *Campylobacter* infections, ruminants, and companion animals might also play important roles in the spread of *Campylobacter* to humans.

Recently, several studies [9,10,46,47] have isolated *Campylobacter* from wild bird feces, and there observed overlap of strains among humans, livestock, and wild birds. These findings suggest that *Campylobacter* can rapidly spread worldwide, thus threatening human public health. In recent years, metagenomics technology has been applied to directly capture clinical *Campylobacter* genomes, for example, in humans [48] and chickens [49]. This method is worthy of future exploration.

Certain economic, climatic, and social indicators may drive the rise of AMR in *Campylobacter* in different countries. Examples include rural population and population growth in China, cereal production in the USA, and CO₂ emissions in Peru. Notably, the rural population and

TABLE 2 | Correlation analyses of AMR with agriculture, antimicrobial, climate, environment, and socioeconomic indicators in representative countries across five continents.

Climate, social, and economic factors		ARGs with human origins ^a					ARGs with animal origins ^b				
Class	Variable (driving factors)	China (Asia)	New Zealand (Oceania)	Peru (South America)	United Kingdom (Europe)	USA (North America)	China (Asia)	New Zealand (Oceania)	United Kingdom (Europe)	USA (North America)	
Agriculture and rural development	Animal husbandry production index (2014–2016 = 100)	0.421	0.459	0.362	0.278	0.25	0.562	0.131	0.247	0.007 (–)	
	Food production index (2014–2016 = 100)	0.03 (–)	0.447	0.411	0.178	0.098	0.888	0.137	0.146	0.021 (–)	
	Cereal production (metric tons)	0.01 (–)	0.726	0.115	0.249	0.03 (+)	0.872	0.283	0.461	0.138	
	Rural population	0.048 (+)	0.223	0.004 (–)	0.763	0.867	0.706	0.172	0.126	< 0.001 (+)	
Environment	Aquaculture production (metric tons)	0.165	0.734	0.398	0.69	0.48	0.834	0.876	0.295	0.735	
Climate change	CO ₂ emissions (metric tons per capita)	0.343	0.868	0.037 (+)	0.316	0.387	0.538	0.041 (+)	0.415	0.104	
	Average mean surface air temperature	0.267	0.158	0.752	0.284	0.667	0.554	0.376	0.035 (+)	0.014 (–)	
Economy and growth	GDP per capita (current US\$)	0.02 (–)	0.468	0.069	0.009 (–)	0.081	0.822	0.137	0.015 (+)	0.002 (–)	
	Renewable inland freshwater resources per capita (cubic meters)	0.167	0.207	0.125	0.796	0.065	0.853	0.179	0.273	0.088	
Health	Population growth (annual %)	0.004 (+)	0.72	0.357	0.035 (–)	0.289	0.254	0.045 (–)	0.067	0.012 (+)	
Antimicrobials	Aminoglycoside resistance (DDD/1,000/day)	0.215	0.813	0.003 (+)	0.163	0.006 (+)	0.011 (–)	-	0.375	0.96	
	Beta-lactam resistance (DDD/1,000/day)	0.192	0.813	0.003 (+)	0.402	0.151	0.826	0.092	0.082	0.106	
	Fluoroquinolone resistance (DDD/1,000/day)	0.1	0.339	<0.001 (+)	0.778	0.61	0.009 (+)	0.173	0.014 (–)	-	
	Tetracycline resistance (DDD/1,000/day)	0.115	0.347	<0.001 (+)	0.072	0.565	0.406	0.173	0.474	0.408	

a: Average count of ARGs with human origins.

b: Average count of ARGs with animal origins.

+: Positive associations with AMR ($p < 0.05$).–: Negative associations with AMR ($p < 0.05$).

population growth in the USA are positively correlated with ARGs with animal origins, because people with social and environmental disadvantages are more likely to have contact with animals, and human or animal waste, thus increasing the risk of multi-drug resistant urinary tract infections [50]. In contrast, the annual average temperature changes may be an important driving factor for changes in *Campylobacter* numbers in the USA; however, whether this relationship applies to other countries is unclear. This study provides the first report, to our knowledge, of associations between climatic change and socio-economic indicators and AMR in *Campylobacter*. Climate change has been found to be associated with the spread of diarrhea. Whereas rising temperatures, increased humidity, and prolonged sunlight have been associated with the spread of diseases caused by *Campylobacter*, the correlations with rainfall and wind speed are comparatively weaker [28]. This finding might be due to increased survival and transmission of pathogens under warm weather, or might be associated with human behavior and social patterns during this period.

Our study has several limitations. First, although 86,365 *Campylobacter* genomes were downloaded from the NCBI and analyzed, a total of 19,594 genomes were discarded because of a lack of detailed background information or the presence of quality control issues. Genomes without clear background information were discarded. Because genomes cannot be used for spatiotemporal analysis and outbreak investigation without detailed information on the collection time, location, and source, the quality of uploaded data must be improved in the future. Therefore, we recommend that all researchers deposit information on the data source. Second, only 223 genomes were collected before 2000. Moreover, a large proportion of genomes from North America were missing data pertaining to the year of isolation. Third, we did not obtain comprehensive data on antimicrobial consumption in both humans and animals worldwide. Antimicrobial consumption was obtained in two previous reports [51,52]. Finally, we did not explicitly investigate the indirect effects of factors driving AMR in *Campylobacter*. Thus, the use of current data and genome-based approaches may advance understanding of global bacterial infectious diseases and the spread of persistent bacterial foodborne hazards [53,54].

CONCLUSIONS

In summary, on the basis of the “One Health” concept, we mapped a comprehensive genetic atlas of *Campylobacter* worldwide. This study provides the previously undescribed landscape and drivers of AMR in *Campylobacter* globally, thus revealing the evolving patterns and dissemination mechanisms of AMR in *Campylobacter* over the past century. Beta-lactam, tetracycline, fluoroquinolone, and aminoglycoside resistance were the main AMR types in *Campylobacter*. A positive correlation was observed

between the dissemination of these AMR types and the use of antimicrobials in veterinary contexts, such as poultry production. This study is the first, to our knowledge, to investigate how several factors influence AMR in *Campylobacter* at the global level. Further strengthening of genomic surveillance and creating a large-scale surveillance dataset for AMR in *Campylobacter* is crucial for maintaining global health.

ACKNOWLEDGEMENTS

We gratefully acknowledge grants from the National Key Research and Development Program of China (2023YFC2307101), the Young TopNotch Talents Foundation of Henan Agricultural University (30501278), and the Major Program of the National Natural Science Foundation of China (NSFC81991534). The computational requirements for this work were supported partly by the High-performance Computing Platform of Tianjin Medical University and the Veterinary Big Data and Bioinformatics Center, Henan Agricultural University, which provided partial support for this study.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

SUPPLEMENTARY MATERIAL

Supplementary Material can be downloaded from https://zoonoses-journal.org/wp-content/uploads/2025/03/zoonoses20240060_Suppl.zip.

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