Causal Effects of Climatic and Socioeconomic Drivers on Antimicrobial Resistance

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Abstract

Antimicrobial resistance (AMR) is a rapidly escalating global health crisis threatening human, animal, and environmental well-being. While its spread is often linked to antibiotic use, the complex, nonlinear nature of its environmental and socioeconomic drivers remains poorly understood, rendering traditional analyses insufficient. This study moves beyond simple correlation to investigate the causal relationships between four distinct E. coli resistance phenotypes and key socioeconomic and climatic factors across the United States, employing the powerful Peter and Clark Momentary Conditional Independence (PCMCI) and Transfer Entropy (TE) methods. This analysis reveals a highly heterogeneous landscape of AMR dynamics, where causal drivers differ significantly by both phenotype and geographical location. Results show that drivers such as extreme temperatures, precipitation, and income levels exert significant causal effects on AMR in specific states, demonstrating that this crisis is intrinsically linked to climatic and socioeconomic conditions, not just healthcare practices. These findings point to the urgent need for dynamic, phenotype-specific, and regionally tailored strategies developed under a One Health lens, highlighting that only a multidisciplinary approach can truly address the complexity of AMR.

Keywords: Antimicrobial Resistance (AMR), Climate Change, E. Coli, One Health, Causality, US

1. Introduction

Antimicrobial resistance (AMR) refers to the capacity of microorganisms, including bacteria, viruses, or parasites, to withstand the effects of antibiotics, hence rendering them ineffective. The health of people, animals, and ecosystems can be severely impacted by bacteria that become persistent and spread when antibiotics employed in treatments prove unsuccessful and infections endure.

The World Health Organization (WHO), referencing Murray et al. (2022), reports that bacterial AMR directly caused 1.27 million deaths worldwide in 2019 and led to a total of 4.95 million fatalities. Current projections indicate that AMR will result in roughly 1.14 million fatalities in 2021, with this figure anticipated to increase to 1.91 million by 2050. AMR affects countries in all parts of the world and at all income levels. However, poverty and inequality make its causes and effects worse, especially in low- and middle-income countries, which are the most affected (Naghavi et al., 2024).

According to the 2019 Antibiotic Resistance Threats Report by the Centers for Disease Control and Prevention (CDC), over 2.8 million AMR infections occur annually in the US, resulting in more than 35,000 deaths (CDC, 2019). Furthermore, the CDC indicates that AMR incurs an additional $20 billion in direct healthcare expenses in the US, excluding around $35 billion in annual productivity losses (Dadgostar, 2019). In consideration of the facts, during the 79th United Nations General Assembly (UNGA) HLM on AMR in 2024, global leaders pledged to decrease human fatalities from AMR by 10% by 2030 (United Nations General Assembly, 2024). In summary, AMR poses a significant threat to global health, necessitating study and mitigation initiatives. Despite the current surge in AMR research (see Figure 1), scant investigation has been undertaken, especially in low- and middle-income nations, regarding the dynamic interplay of AMR with climate change and socioeconomic factors (Kirby and Herbert, 2013; Booth and Wester, 2022; Li et al., 2025; Moon et al., 2025).

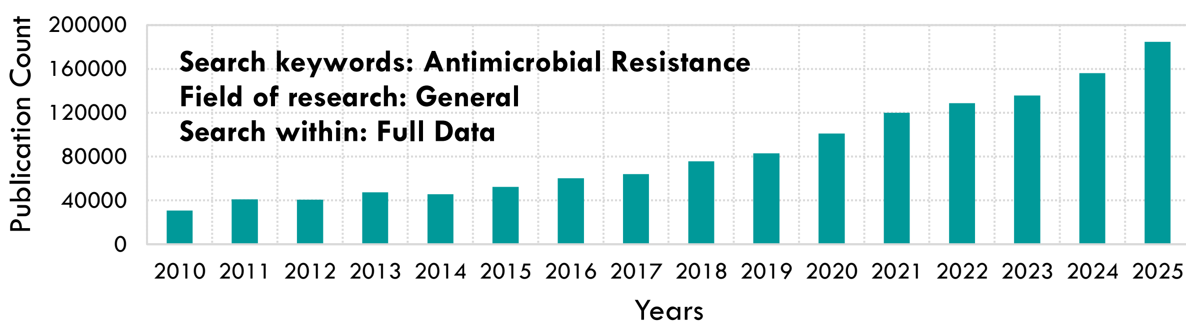


Figure 1. From 2010 to 2025, searching within full data: the number of publications per year mentioning “antimicrobial resistance” as a search keyword in the general field (data source: https://www.dimensions.ai/).

Although there are studies investigating the correlation between AMR and meteorological, environmental, social, and political factors, research focusing on causative links is notably scarce. Zhao et al. (2024) used bioinformatics and AI to predict antibiotic resistance gene traits. Causal-ARG, a CNN framework with Gaussian Mixture Model (GMM), stresses gene causality, encompassing mechanism, phenotype, and antibiotic class. Using a dataset from 70 middle- and high-income countries, Awasthi et al. (2022) analyzed AMR determinants using Bayesian Network and counterfactual analysis. Structural changes in countries with poor healthcare systems may lower resistance by 50%, according to their research. Donaghy et al. (2019) examined how cleaning and disinfectants affect AMR. The study compared laboratory trials with food processing facility field studies using literature synthesis and scientific review. The authors noted that while bacteria can evolve resistance to low doses of disinfectants in a lab, there is no compelling evidence that disinfectants used at correct quantities contribute to the global AMR crisis. Martínez et al. (2025) studied the dynamic interaction and temporal lag effects of AMR in primary care and hospitals. Their approach included multivariable logistic regressions, vector autoregressive models, and Granger (Granger, 1969) causality analyses. Resistance rates in primary care and hospitals were positively correlated, showing that as community resistance rises, so does hospital resistance. Hospital E. coli resistance was predicted by community resistance changes. To visualize how AMR works, Huebner et al. (2025) used a Causal Loop Diagram to map the reinforcing and balancing relationships between various elements. This study used questionnaires, semi-structured interviews, and interactive workshops to obtain data. Environmental factors like wastewater treatment plant-derived resistance genes and bacteria fertilizing soil and groundwater were evaluated. Since each region has unique agricultural, health, and environmental characteristics, the authors conclude that the global AMR crisis must be tackled regionally.

Some of the methods employed in causality studies include Granger causality; transfer entropy (TE) (Schreiber, 2000; Yeşilköy et al., 2026), which is grounded in information theory (Shannon, 1948; Baydaroğlu and Koçak, 2019); cross convergent mapping (CCM) (Sugihara et al., 2012), based on Takens' theorem (Takens, 2006; Baydaroğlu et al., 2024; Baydaroğlu, 2025; Yeşilköy et al., 2026); and the stochastic framework for testing conditional independence known as PCMCI (Peter and Clark Momentary Conditional Independence) (Runge et al., 2015; Delforge, 2022; Yeşilköy 2026). A test for momentary conditional independence (MCI) is conducted after PCMCI, a sequential process based on the PC (Peter–Clark) algorithm (Spirtes and Glymour, 1991) (Runge et al., 2019b).

Adopting a One Health approach, this study investigates the causal relationship between AMR—characterized by four distinct resistance phenotypes in E. coli, namely carbapenem-resistant, multidrug (MDR)-resistant, cephalosporin-resistant, and fluoroquinolone-resistant strains—and key drivers such as meteorological variables (maximum temperature, minimum temperature, and precipitation) and socioeconomic factors (per capita personal income - PCPI) using PCMCI and TE. This critical threat to human, animal, and ecosystem health is analyzed at the state level across the US.

2. Background

AMR is a global concern impacting the health of both humans and animals. Although AMR predominantly arises from the excessive and improper use of antibiotics and antimicrobials, compelling evidence indicates that the broader dissemination of resistance is exacerbated by additional factors, including insufficient local sanitation (Ljungqvist et al., 2025), environmental contamination, agricultural applications (Csorba et al., 2025), and climate change, with the natural environment serving as a crucial vector in this phenomenon (Woolhouse et al., 2015; Graham et al., 2019; Al-Khalaifah et al., 2025).

Li et al. (2025) used 4,502 AMR surveillance records from 101 countries to examine the impact of environmental and social variables on AMR and developed prediction models based on diverse socioeconomic pathways, including antimicrobial consumption reduction, sustainable development, and climate change. The AMR gap between high-income and low- and middle-income nations is growing, according to their findings.

Zambrano (2023) notes that antibiotic resistance genes existed before clinical antibiotic use, but anthropogenic activities have accelerated their global catastrophe. Environmental contaminants like heavy metals, disinfectants, and microplastics selectively favor resistance strains, according to the study. Extreme weather and land-use changes like deforestation help wildlife and humans share resistance reservoirs. Wastewater, agricultural runoff, and waterways are 'highways' that transport antibiotic resistance genes to remote locations, according to Zambrano. Pollution-induced biodiversity loss helps these genes survive.

Climate change affects AMR through three mechanisms, according to Kalanxhi and Laxminarayan (2026). Rising temperatures increase bacterial proliferation, mutation, and horizontal gene transfer. Second, more frequent and severe natural disasters like droughts and floods increase infectious disease burden. Higher antibiotic intake increases selective pressure for resistance. Third, excessive rainfall and flooding disseminate wastewater and animal waste, promoting resistance gene transmission into water and soil ecosystems.

Wang et al. (2025) found a global AMR rise across all six continents using 208,233 Salmonella genomes from 148 countries. Their research shows that human isolates are more resistant than animal or environmental isolates. Beyond clinical antibiotic consumption, socioeconomic indicators like GDP, healthcare expenditure, and education, climate change, environmental pollution, and global trade and travel pressures were found to be critical determinants of resistance trends.

The investigations into the correlation among climate change, environmental pollutants, and AMR indicate that ambient temperature (Zeng et al., 2023; Kou et al., 2025), air temperature (MacFadden et al., 2018; Rodríguez-Verdugo et al., 2020; Meinen et al., 2023; Ching et al., 2025; Yang et al., 2026; Kalanxhi and Laxminarayan, 2026), precipitation (Ching et al., 2025), extreme weather events (Usman Qamar and Aatika, 2023; Csorba et al., 2025; Kalanxhi and Laxminarayan, 2026), agricultural applications (Gao et al., 2024), water (Booth and Wester, 2022; Gao et al., 2024; Zhou et al., 2024; Díaz-Zaragoza et al., 2025; Chayña et al., 2025), soil (Yazdankhah et al., 2018) and air pollution (Kou et al., 2025; Özbek, 2026; Matijašević, 2026) are increasingly detrimental to the emergence and proliferation of AMR.

Untreated or insufficiently treated drinking water is a major source of Escherichia coli (E. coli). In many middle-income countries, inadequate wastewater and sanitation management increases the prevalence of resistant E. coli. Resistant strains can spread through the food chain, particularly from cattle exposed to antibiotics, reaching humans via meat and dairy products. Direct contact with animals or the use of manure as fertilizer may also contaminate crops. In addition, wastewater treatment plants may fail to fully remove resistant bacteria, releasing resistance genes into rivers and oceans, while precipitation can transport urban and agricultural contaminants into water bodies. Socioeconomic factors further influence this process: violations of food and water safety regulations, weak healthcare systems, poor hygiene practices, and inappropriate antibiotic use increase transmission risks (Booth and Wester, 2022).

E. coli is a leading cause of both community- and hospital-acquired infections, particularly urinary tract and bloodstream infections. Resistant strains are associated with more severe outcomes and reduce the effectiveness of empirical antibiotic treatments. Consequently, increased diagnostic testing, prolonged hospitalizations, and higher treatment costs place a substantial financial burden on healthcare systems (MacKinnon et al., 2020).

Below are some notable research on E. coli, this study's primary organism, and antibiotic resistance (AMR): In their 2020 study, Rodríguez-Verdugo et al. investigated how temperature affects E. coli antibiotic resistance. Researchers observed that E. coli strains grown at higher temperatures developed antibiotic resistance mutations faster.

Leekitcharoenphon et al. (2021) studied E. coli evolution and AMR gene dissemination in European livestock. The study found that resistant bacteria are varied and pervasive. The study found poultry to be the best AMR indicator group.

Kou et al. (2025) examined the regional distribution of AMR in E. coli in China and its factors throughout a decade. A spatial durbin model was used to examine how resistance in one area affects neighboring provinces. The data show that AMR clusters in certain locations, contrary to Leekitcharoenphon et al. (2021). A province with high resistance rates increases resistance in neighboring provinces. Higher ambient temperature enhances all types of resistance, whereas PM 2.5 air pollution spreads resistant bacteria.

Collignon et al. (2015) argue that antibiotic use cannot explain global AMR differences. They studied how government, corruption, and socioeconomic factors propagate resistance. The authors investigated antibiotic use, GDP, and governance factors including corruption and the rule of law using a multivariate regression model and national econometric analysis. The study's key finding is that corruption predicts antibiotic resistance better than antibiotic use. Corruption leads to over-the-counter antibiotics, counterfeit or low-quality drugs, hospital infection control failures, and food chain monitoring. Insufficient regulation and monitoring allow resistant germs to spread swiftly.

3. Materials and Methods

3.1 Study Area

The study covers all US states with the exception of Washington, D.C., and Wyoming. These jurisdictions were excluded from the analysis due to the unavailability of required data.

3.2 Data

This study utilizes state-level data spanning from 2011 to 2024, focusing on the dynamics of AMR in E. coli, a key coliform bacterium. The dataset (provided by the CDC) comprises state-level observations across the US, specifically analyzing the 'percent resistant' metric for all infectious event types. The analysis is categorized into four distinct resistance phenotypes: carbapenem-resistant, multidrug (MDR)-resistant, cephalosporin-resistant, and fluoroquinolone-resistant strains.

The meteorological parameters utilized in this study consist of monthly maximum and minimum temperatures (°F) and total monthly precipitation (inches), all sourced from the NOAA National Centers for Environmental Information (NCEI). To account for socioeconomic factors, monthly per capita personal income (PCPI) data were obtained from the U.S. Bureau of Economic Analysis (BEA).

All datasets were integrated to investigate the causal drivers of AMR within a One Health framework. The combined analysis of E. coli AMR rates, averaged each month by state and including all types of resistance, shows a notable yearly rise in resistance levels as shown in Figure 2. The significant declines observed in 2012 and 2021, along with the stagnant rates between 2017 and 2019, are particularly noteworthy. Figure 3 (a-d) displays the AMR rates of E. coli separately for each phenotype.

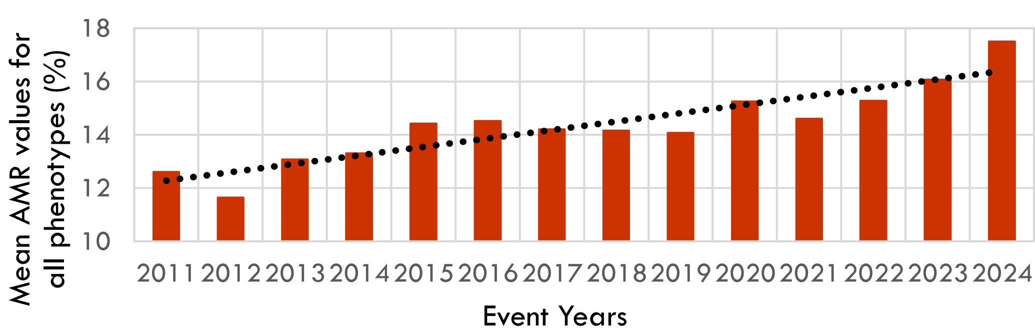
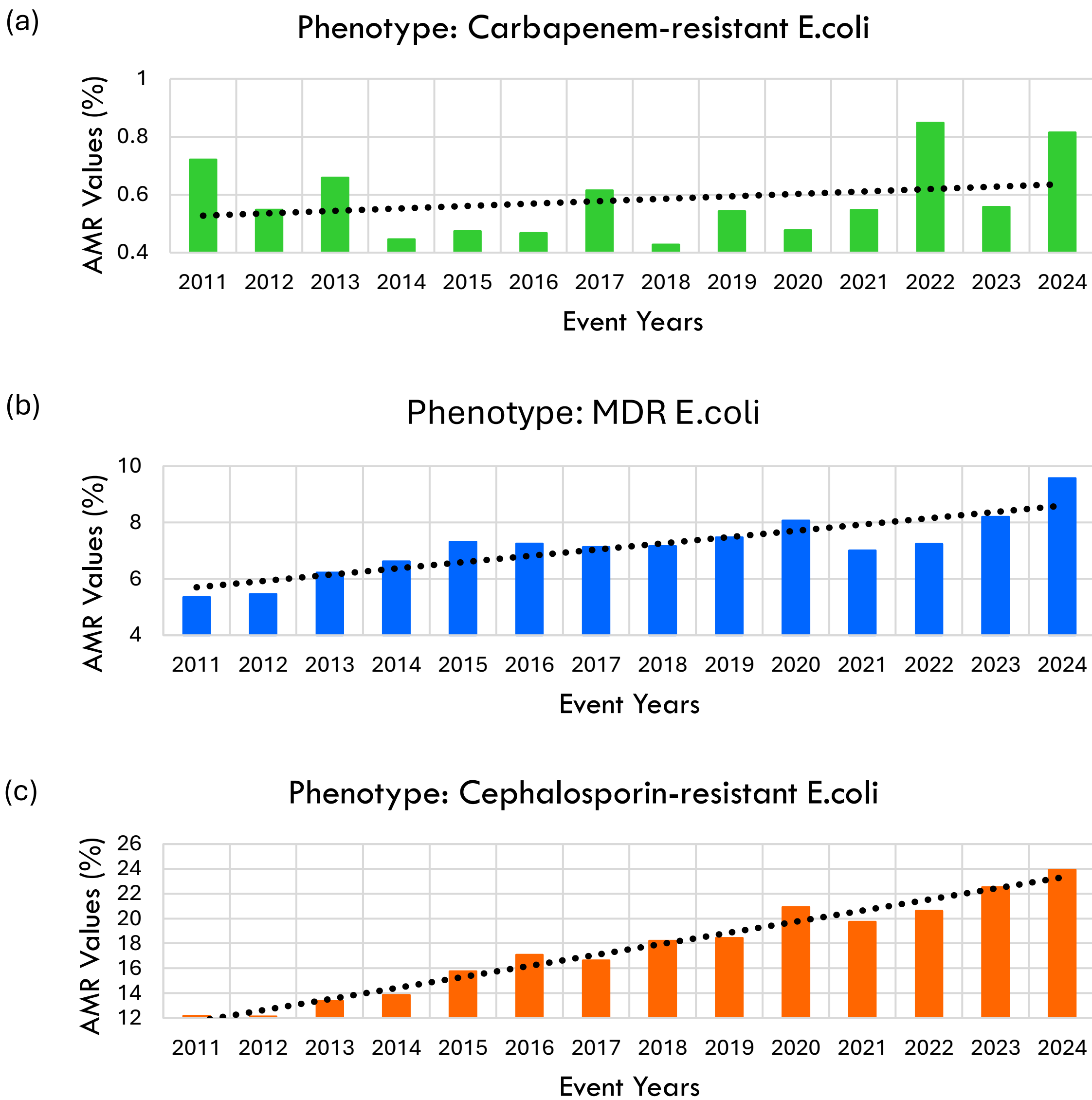


Figure 2. Mean AMR values for all phenotypes based on event years.

In Figure 2, the results show notable declines in E. coli AMR levels in 2012 and 2021. The reduction in 2012 corresponds with the implementation of FDA's Guidance for Industry #209, which initiated a voluntary framework to limit the subtherapeutic use of medically important antibiotics in livestock (FDA, 2012; Alvy, 2014; Deb et al., 2023). Furthermore, the 2021 decrease likely reflects the secondary effects of the COVID-19 pandemic. As highlighted by the CDC (2022), unprecedented improvements in hygiene, social distancing, and changes in healthcare utilization during the pandemic may have temporarily interrupted the transmission cycles of resistant bacteria.



(d)

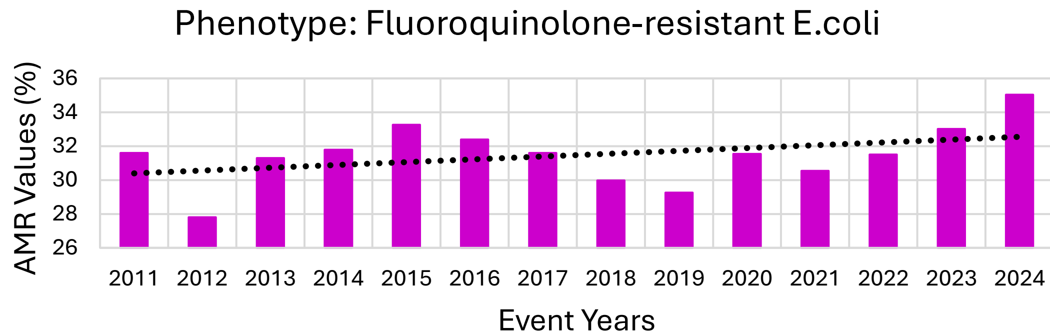


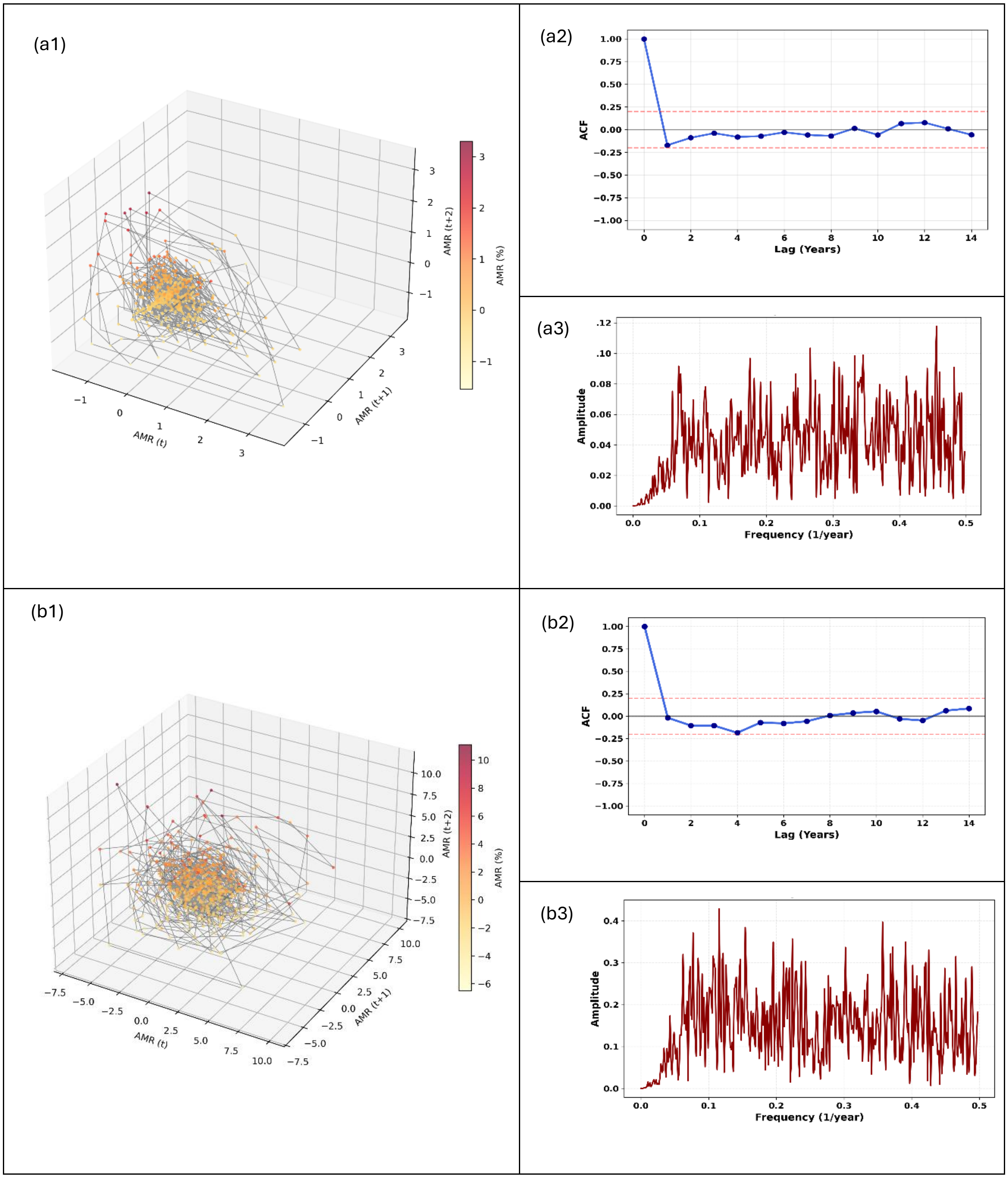
Figure 3. Between the years 2011 and 2024, AMR values for (a) Phenotype: Carbapenem-resistant E.coli (b) Phenotype: MDR E.coli (c) Phenotype: Cephalosporin-resistant E.coli (d) Phenotype: Fluoroquinolone-resistant E.coli.

The analysis of the alterations in resistance phenotypes of E. coli to four distinct antibiotic classes over time reveals a rise in AMR rates for each phenotype (see Figure 3a-d). Figure 3 (a-d) indicates that the AMR rates of E. coli across all phenotypes demonstrate an increasing trend over the years. The rise is more significant for MDR-resistant and cephalosporin-resistant E. coli, but the AMR values for carbapenem-resistant and fluoroquinolone-resistant E. coli exhibit fluctuation. The resistance percentages of MDR-resistant and cephalosporin-resistant E. coli exhibit a steadily increasing trend.

As highlighted by Bartsev et al. (2021) and Bonotto et al. (2022), the presence of underlying trends and seasonality in time-series data can lead to spurious causality. To mitigate this risk, the AMR data were detrended prior to analysis. Given that the dataset consists of annual observations, seasonality was not considered a factor influencing the time-series characteristics.

A phase space reconstruction is essential for determining the complexity of the underlying dynamics. Every point in the phase space represents a state of the system, whereas each trajectory indicates the temporal evolution of the system under different initial conditions. Points or clusters of points create distinct patterns, which are referred to as attractors (Baydaroğlu and Koçak, 2014). Figure 4 illustrates the attractors of E. coli linearly detrended AMR values for the four phenotypes. In the phase space reconstruction (Takens, 2006), a time delay of 1 was utilized to attain optimal resolution for the embedding (Bonotto et al., 2022; Yeşilköy et al., 2026), alongside an embedding dimension of 3.

In addition, autocorrelation functions (ACFs) and power spectra facilitate understanding of the data's nonlinearity, chaotic nature, or, alternatively, its predictability. The observed dynamics suggest a chaotic structure within the data. This is evidenced by the attractors, which exhibit a high density at the center and trajectories that undergo continuous folding. Furthermore, the autocorrelation functions (ACFs) drop rapidly to zero without significant dampening, and the power spectra display a broadband structure rather than isolated or few discrete peaks (Anishchenko et al., 2003; Zou et al., 2007). To further validate these findings, more comprehensive datasets could be employed for extensive nonlinear analysis, including the computation of Lyapunov exponents.



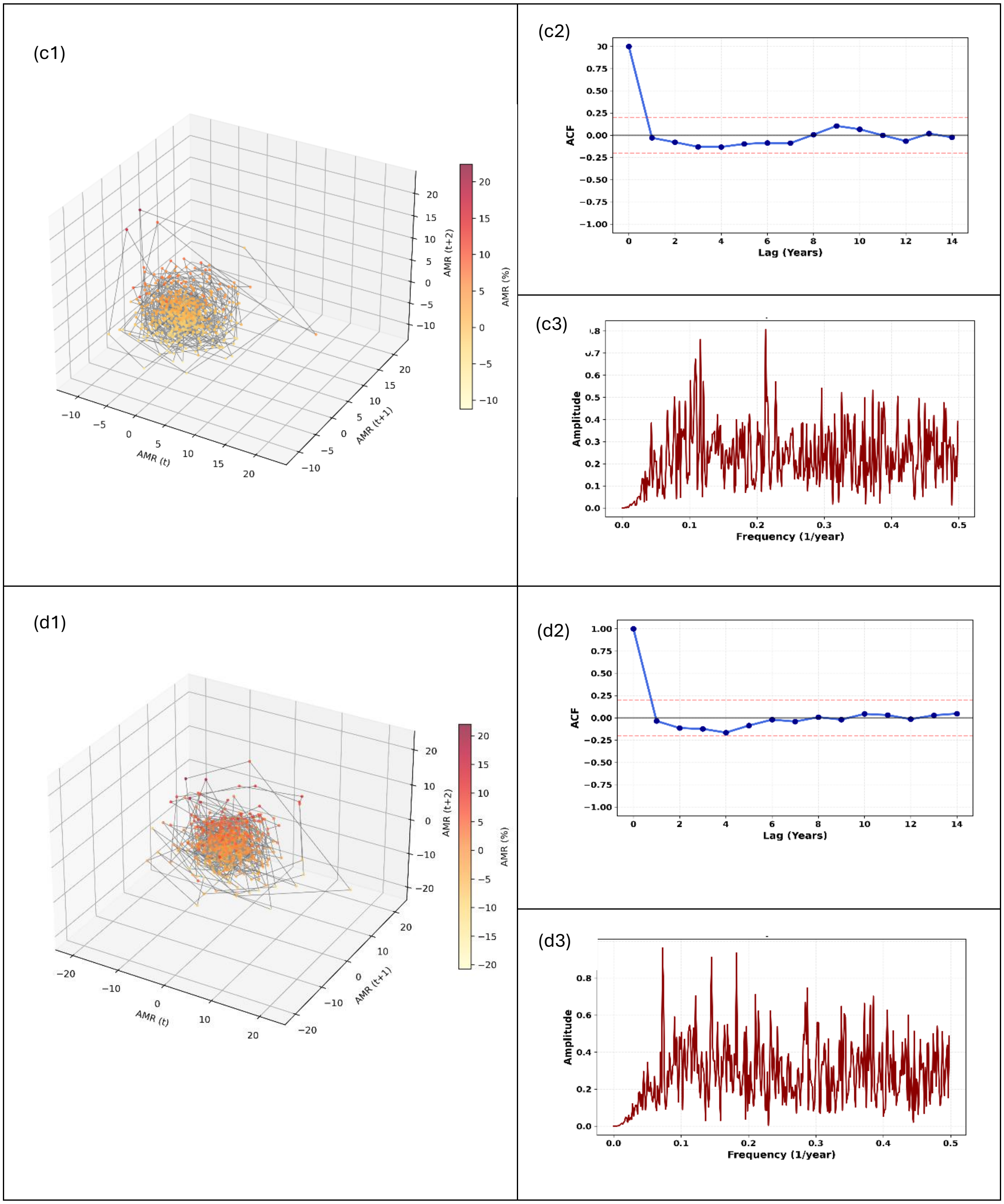


Figure 4. Attractors (1), ACFs (2) and power spectra (3) of the (a) Carbapenem-resistant E.coli (b) MDR-resistant E.coli (c) Cephalosporin-resistant E.coli (d) Fluoroquinolone-resistant E.coli.

3.3 Methods

This research has two case studies as a methodological framework. In the first case study, data for the four phenotypes were separated to perform a comprehensive causality analysis between AMR in E. coli and potential drivers, including climatic factors (precipitation, maximum temperature, and minimum temperature) and a socioeconomic indicator (per capita personal income - PCPI) to capture specific dynamics. In the second case study, causality was examined with aggregated data for all phenotypes. AMR data was detrended in both case studies, and PCMCI and TE were employed for causal discovery. Furthermore, Pearson correlation coefficients were given.

3.3.1 Peter and Clark Momentary Conditional Independence (PCMCI)

PCMCI (Runge et al., 2019) is an algorithm developed to uncover causal linkages within multivariate time series data. This method is extensively utilized in the analysis of complex systems, especially in earth (Runge et al., 2019; Muszynski et al., 2026) and climate sciences (Krich et al., 2020; Docquier et al., 2024; Yeşilköy, 2026), and microbiome (Ruiz-Perez et al., 2024; Kardish et al., 2025).

The main target of PCMCI is to ascertain whether one variable affects another by eliminating spurious correlations and time-series-specific autocorrelation effects. PCMCI employs conditional independence testing to eliminate these spurious correlations. It constitutes a two-stage methodology. Initially, potential parental relationships are determined by discarding superfluous links, including historical influences that do not directly impact the target variable, can be elucidated through other variables, or may induce misleading causation. In the subsequent stage, it establishes a significant causal network by the execution of conditional independence tests.

According to Runge et al. (2009), the following equation can be used to represent a time-dependent complex system $X_t = (X_t^1, X_x^2, \ldots, X_t^N)$:

$$X_t^j = f_j\left[P\left(X_t^j\right), \varepsilon_t^j\right] \tag{1}$$

Where f_j shows potential nonlinear functional dependencies, and ε_t^j indicates mutually independent dynamic noise while X_t^j represents different lagged temporal variables. The PCMCI approach is founded on conditional independence framework $X_t^j = \hat{P}^{\alpha}(X_t^j)\beta$ (where α and β are a threshold based on Bayesian Information Criterion (BIC) or Akaike Information Criterion (AIC) and effect size, respectively), making it appropriate for processing highly interdependent time series data. It comprises the subsequent stages:

1) Stage of Feature Selection (PC)

The PC condition selection procedure is employed to determine the relevant conditions $\hat{P}(X_t^j)$ within $X_t^j \in \{X_t^1, X_x^2, \ldots, X_t^N\}$ across time series variables. The PC algorithm is a Markov set discovery algorithm derived from the stable-PC algorithm, which iteratively tests for independence to eliminate unrelated conditions for each variable in the set of N variables.

2) Stage of Momentary Conditional Independence Test (MCI)

Based on the results from the prior stage, the MCI method is utilized to assess if the relationship $X_{t-\tau}^{i} \rightarrow X_{t}^{j}$ (where τ is time lag) meets the following criterion (Runge et al. (2009; Liu et al., 2025):

$$MCI: \left(\hat{P}\left(X_{t}^{j}\right) \setminus \{X_{t-\tau}^{i}\}, \hat{P}\left(X_{t}^{i}\right)\right) \quad (2)$$

In this part of the study, the Tigramite Python package (Runge et al., 2019b) was used.

3.3.2 Transfer Entropy (TE)

Based on the concepts of information theory, TE is a unique measure for measuring the transfer of information (Shannon, 1948). According to the original idea, entropy originates from the stationary probability of states, whereas the transition probabilities are used to determine the entropy rate. Based on the second idea, regardless of the historical data from Y, the transition probabilities of X stay unchanged when there is no information flow from Y to X (Sironen, 2020). Schreiber (2000) proposed employing Markov processes to approximate the two time series, $X = x_t$ and $Y = y_t$, and thereafter calculating the deviation from the generalized Markov condition as an indicator of causation.

$$p(y_t^n, x_t^m) = p(y_t^n) \quad (3)$$

where $x_t^m = (x_t, \ldots, x_{t-m+1})$, $y_t^n = (x_t, \ldots, x_{t-n+1})$, m and n are the orders of X and Y's Markov processes, respectively. The transfer entropy from X to Y is determined by computing the expected Kullback-Leibler divergence (Kullback, 1951) between the probability distributions on either side of Equation (4) to measure causality (Vicente et al., 2011).

$$TE\ (X \rightarrow Y) = \sum_{y_{t+1}, y_t^n, x_t^m} p(y_{t+1}, y_t^n, x_t^m) log\left(\frac{p(y_t^n, x_t^m)}{p((y_t^n)}\right) \quad (4)$$

In this part of the study, PyInform was used as a Python library.

4. Results and Discussions

To investigate causal inference, in the first case study, separated AMR datasets based on phenotypes were used, whereas in the second case study, aggregated AMR data without regard to phenotypes was utilized. In both studies, the significance level (p-value) was set at 0.05.

The causal relationships between AMR and drivers were analyzed separately for each phenotype. The results are presented through both integrated and individual mapping approaches. In the integrated maps, the dominant drivers affecting each state are distinguished by color: green for PCPI, blue for precipitation, yellow for minimum temperature, and orange for maximum temperature. For the individual driver maps, a color gradient from light to dark represents the increasing strength of causality. Furthermore, states where multiple drivers significantly influence a specific phenotype are marked with an asterisk (*) next to their abbreviations.

The TE score is an absolute value quantified in entropy units (bits), originating from information theory (Shannon, 1948), and it assesses the directional flow and amount of information between two time series. A TE value of zero signifies the absence of information transfer, whereas a positive value implies information flow, with greater values denoting stronger causality (Yeşilköy, 2026).

The causality between the variables can be discussed if the causality strength, as determined by the PCMCI and TE, exceeds 0.2 (20%).

1st Case Study: Causal discovery with separated data based on phenotypes

- *Carbapenem-resistant E.coli*

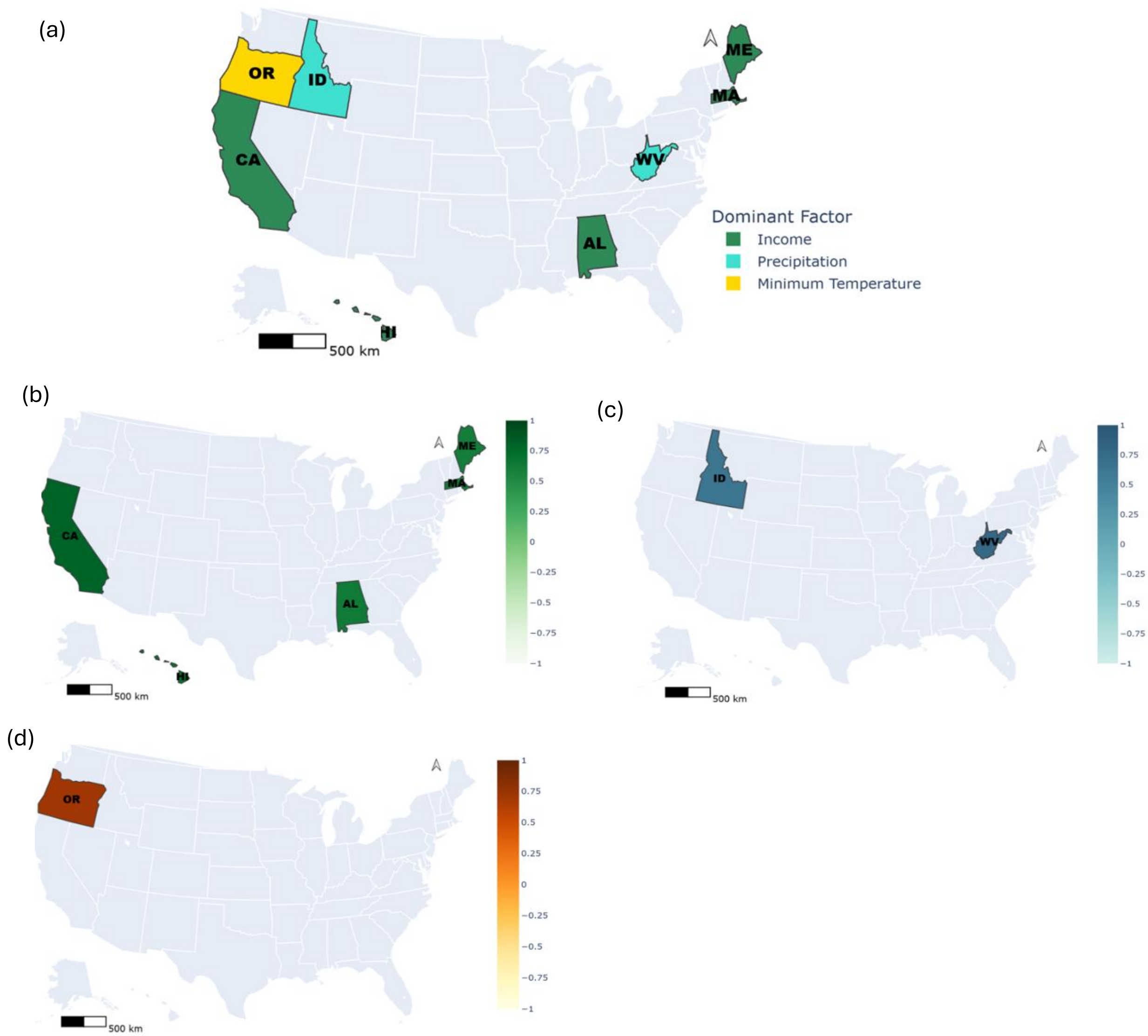


Figure 5. For carbapenem-resistant E.coli (a) Integrated causal drivers map (b) the causal map of AMR and PCPI (c) the causal map of AMR and precipitation (d) the causal map of AMR and minimum temperature.

Figure 5 illustrates that PCPI, precipitation, and minimum temperature are influential drivers in the emergence of AMR for carbapenem-resistant E. coli. The causal relationship between PCPI values and AMR is particularly noteworthy. While previous studies (Awasthi et al., 2022; Naghavi et al., 2024; Li et al., 2025) typically report a negative correlation between income and AMR—albeit without utilizing a causal framework as in this study—our findings indicate a positive causal strength between PCPI and AMR. At first glance, this positive link may seem counterintuitive, as it is generally anticipated that higher income will be associated with more robust healthcare systems and lower resistance levels. However, this dynamic can be reversed in the case of resistance to 'last-resort' (or last-line) antibiotics, such as carbapenems (Paterson, 2000; Torres et al., 2007; Papp-Wallace et al., 2011).

Carbapenems are not routinely employed to treat infections; they are predominantly reserved for critically ill patients in intensive care units (ICUs) who demonstrate multi-drug resistance. It is common for high-income regions to have a higher density of ICUs that are well-equipped to perform complex surgical procedures such as organ transplants and aggressive treatments like chemotherapy. These medical interventions increase the susceptibility of patients to complex infections, thereby requiring the frequent administration of last-line antibiotics. As a result, a larger patient population exposed to these specific environments is associated with higher income, which in turn creates a higher selective pressure for carbapenem resistance. That is, the utilization of carbapenems—and consequently the prevalence of resistance—may increase in parallel with an increase in income.

Furthermore, agricultural practices may play a role. While lower-income regions often utilize older and cheaper antibiotics for growth promotion in livestock, high-income regions may have stricter regulations on such practices. Nevertheless, industrial agriculture in wealthy regions may employ advanced, more powerful generations of antibiotics to address diseases, so indirectly augmenting the reservoir of resistance.

A further contributing aspect may be inequality in healthcare facilities and diagnostic capabilities. Wealthy states generally exhibit superior laboratory testing capabilities, resulting in increased sampling frequency and enhanced reporting of resistant cases. Conversely, lower-income states may report 'zero' or minimal values not due to a lack of resistance, but rather as a result of insufficient testing.

Finally, income inequality—rather than merely low absolute income—is a substantial determinant, as emphasized by Ljungqvist et al. (2025). Hygiene issues and antibiotic misuse among lower-income subgroups may induce resistance, even if the average state-level PCPI remains high, if the dataset includes states with high intrastate wealth differentials.

Table 1. For carbapenem-resistant E.coli, causality strength values determined via PCMCI and TE, and Pearson correlation coefficients.

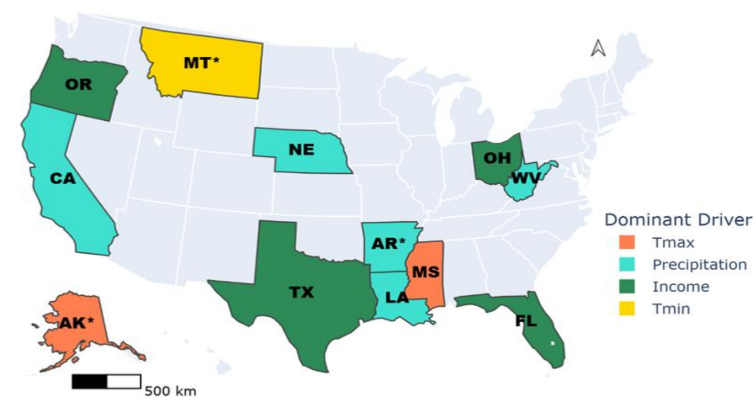
Driver	PCPI			Precipitation			Maximum Temperature			Minimum Temperature		
State	PCMCI	TE	Corr	PCMCI	TE	Corr	PCMCI	TE	Corr	PCMCI	TE	Corr
Alabama	0.63	0.64	**0.44**	x	x	x	x	x	x	x	x	x
California	0.80	0.67	**0.64**	x	x	x	x	x	x	x	x	x
Hawaii	0.71	0.06	**-0.30**	x	x	x	x	x	x	x	x	x
Idaho	x	x	x	x	x	x	0.64	0.10	-0.10	x	x	x
Maine	0.61	0.22	0.12	x	x	x	x	x	x	x	x	x
Massachusetts	0.62	0.37	**0.39**	x	x	x	x	x	x	x	x	x
Oregon	x	x	x	x	x	x	x	x	x	0.72	0.18	-0.03
West Virginia	x	x	x	x	x	x	0.78	0.29	**0.44**	x	x	x

Table 1 displays the causality strength values obtained by PCMCI and TE, in addition to the Pearson correlation coefficients. All tables in this paper specifies causality strengths found by PCMCI (highlighted in blue) and TE values (highlighted in green) that meet or exceed a threshold of 0.2. Additionally, correlation coefficients that statistically validate the PCMCI and TE results are highlighted in bold. Figure 5 and Table 1 reveals that PCPI is a critical determinant of AMR, especially in Alabama, California, Hawaii, Maine, and Massachusetts. Moreover, although maximum temperature is a key factor for AMR in Idaho and West Virginia, minimum temperature is identified as a crucial driver for Oregon.

Finally, for carbapenem-resistant E. coli, precipitation did not show a causal effect on AMR in any of the states analyzed.

- *Multidrug-resistant (MDR) E.coli*

(a)



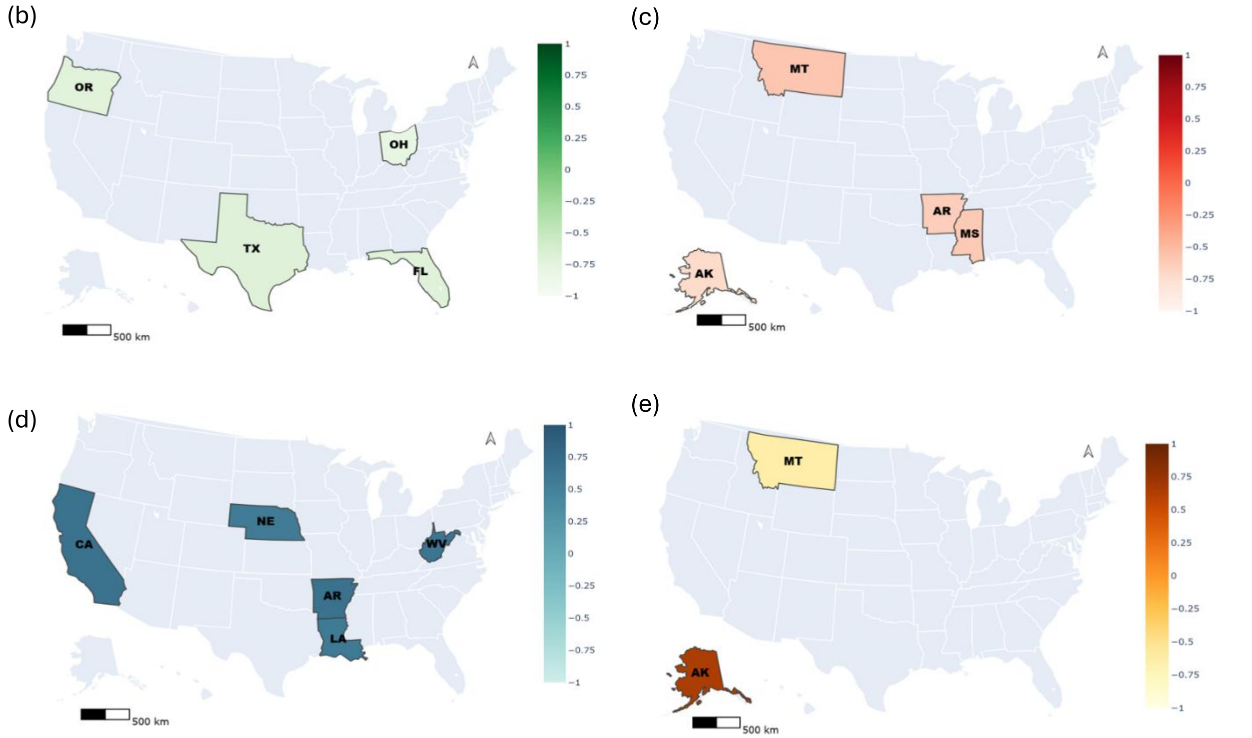


Figure 6. For multidrug-resistant (MDR) E.coli (a) Integrated causal drivers map (b) the causal map of AMR and PCPI (c) the causal map of AMR and maximum temperature (d) the causal map of AMR and precipitation (e) the causal map of AMR and minimum temperature. In this figure, states with multiple drivers for AMR (such as AK*, AR*, MT*) are denoted with an asterisk over their abbreviations.

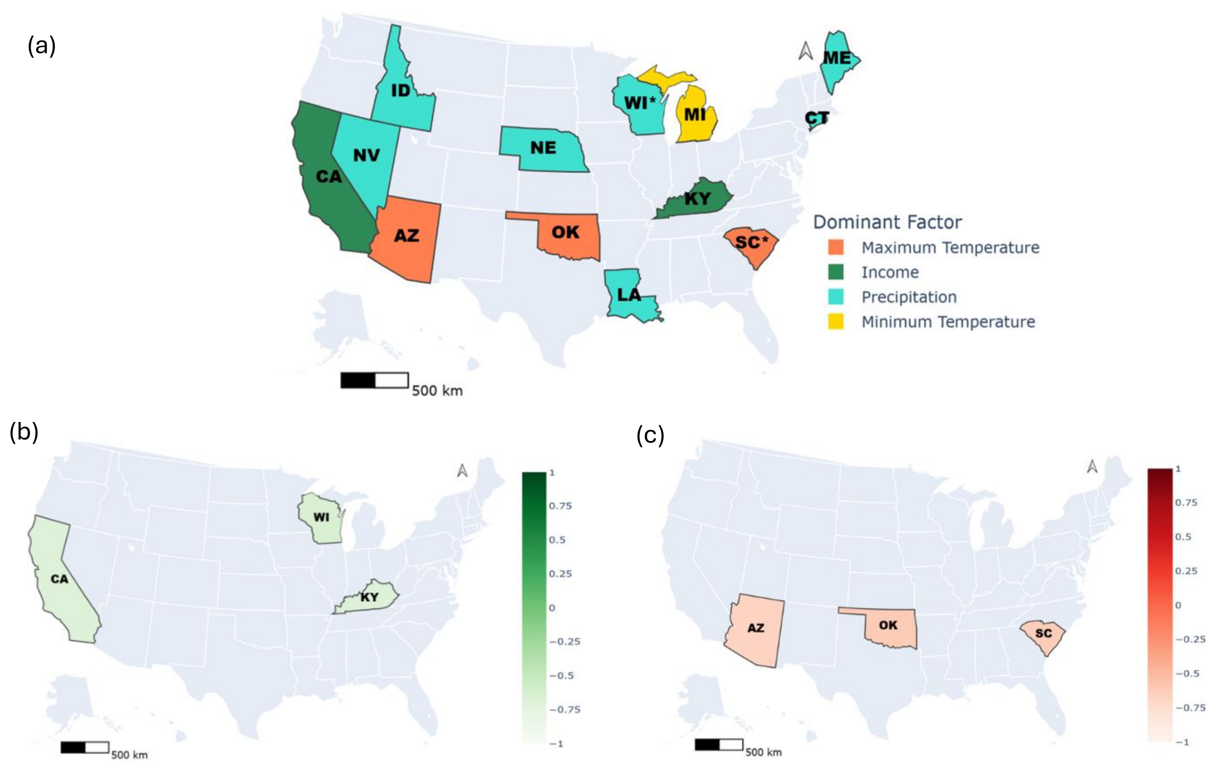
Table 2. For multidrug-resistant (MDR) E.coli, causality strength values determined via PCMCI and TE, and Pearson correlation coefficients.

Driver	PCPI			Precipitation			Maximum Temperature			Minimum Temperature		
State	PCMCI	TE	Corr	PCMCI	TE	Corr	PCMCI	TE	Corr	PCMCI	TE	Corr
Alaska*	x	x	x	x			-0.72	0.56	0.03	0.65	0.40	**0.47**
Arkansas*	x	x	x	0.67	0.61	**0.51**	-0.63	0.58	0.01	x	x	x
California	x	x	x	0.67	0.70	0.12	x	x	x	x	x	x
Florida	-0.71	0.22	**0.68**	x	x	x	x	x	x	x	x	x
Louisiana	x	x	x	0.58	0.26	-0.06	x	x	x	x	x	x
Mississippi	x	x	x	x	x	x	-0.60	0.83	0.09	x	x	x
Montana*	x	x	x	x	x	x	-0.57	0.18	0.04	-0.64	0.40	-0.16
Nebraska	x	x	x	0.57	0.71	0.18	x	x	x	x	x	x
Ohio	-0.79	0.20	**0.74**	x	x	x	x	x	x	x	x	x
Oregon	-0.71	0.53	**0.47**	x	x	x	x	x	x	x	x	x
Texas	-0.70	0.26	**0.75**	x	x	x	x	x	x	x	x	x
West Virginia	x	x	x	0.63	0.29	-0.08	x	x	x	x	x	x

According to Table 2 and Figure 6, PCPI is a notable determinant of AMR in Florida, Ohio, Oregon, and Texas. Precipitation is the main driver for Arkansas, California, Louisiana, Nebraska, and West Virginia, and maximum temperature is recognized as a significant factor for Alaska, Arkansas, Mississippi, and Montana. Furthermore, minimum temperature is crucial in Alaska and Montana. Alaska, Arkansas, and Montana display several drivers that significantly impact AMR dynamics.

In states where PCPI is effective on AMR, AMR levels are noted to diminish as income increases. When examining the causal relationship with precipitation, an increase in precipitation is found to lead to higher AMR values. A negative causal link was shown between AMR values and maximum temperature; specifically, increasing maximum temperatures led to a reduction in AMR. The effect of minimum temperature on AMR varies between Alaska and Montana: an increase in minimum temperature raises AMR in Alaska, but it decreases in Montana. Additionally, Alaska, Arkansas, and Montana exhibit many key drivers for AMR.

- *Cephalosporin-resistant E.coli*



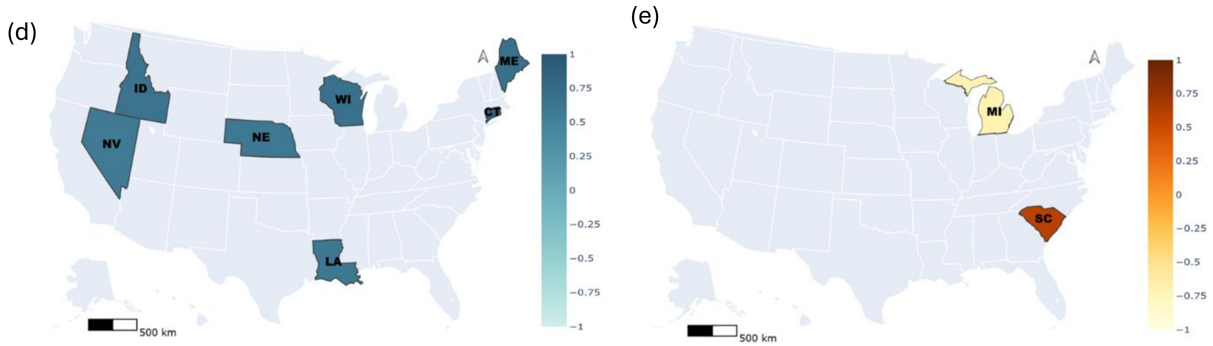


Figure 7. For cephalosporin-resistant E.coli (a) Integrated causal drivers map (b) the causal map of AMR and PCPI (c) the causal map of AMR and maximum temperature (d) the causal map of AMR and precipitation (e) the causal map of AMR and minimum temperature. In Figure 6, states with multiple drivers for AMR (such as WI*, SC*) are denoted with an asterisk over their abbreviations.

Table 3. For cephalosporin-resistant E.coli, causality strength values determined via PCMCI and TE, and Pearson correlation coefficients.

Driver	PCPI			Precipitation			Maximum Temperature			Minimum Temperature		
State	PCMCI	TE	Corr	PCMCI	TE	Corr	PCMCI	TE	Corr	PCMCI	TE	Corr
Arizona	x	x	x	-0.67	0.49	**0.28**	x	x	x	x	x	x
California	-0.69	0.25	**0.92**	x	x	x	x	x	x	x	x	x
Connecticut	x	x	x	x	x	x	0.86	0.67	-0.02	x	x	x
Idaho	x	x	x	x	x	x	0.66	0.40	-0.08	x	x	x
Kentucky	-0.69	0.10	**0.44**	x	x	x	x	x	x	x	x	x
Louisiana	x	x	x	x	x	x	0.61	0.35	**0.23**	x	x	x
Maine	x	x	x	x	x	x	0.68	0.33	**0.23**	x	x	x
Michigan	x	x	x	x	x	x	x	x	x	-0.69	0.27	**0.49**
Nebraska	x	x	x	x	x	x	0.61	0.31	**0.30**	x	x	x
Nevada	x	x	x	x	x	x	0.59	0.22	0.16	x	x	x
Oklahoma	x	x	x	-0.61	0.53	**-0.35**	x	x	x	x	x	x
South Carolina	x	x	x	-0.63	0.28	0.19	x	x	x	0.61	0.27	**0.21**
Wisconsin	-0.65	0.26	**0.44**	x	x	x	0.69	0.45	**-0.28**	x	x	x

As illustrated in Figure 7 and Table 3, PCPI is a key driver for AMR in California, Kentucky, and Wisconsin, while precipitation serves as the primary driver in Arizona, Oklahoma, and South Carolina. Furthermore, maximum temperature is identified as a key driver for Connecticut, Idaho, Louisiana, Maine, Nebraska, Nevada, and Wisconsin, whereas minimum temperature is the critical parameter for Michigan and South Carolina. Notably, South Carolina and Wisconsin are among the states characterized by multiple drivers.

In states where PCPI is influential, AMR levels are observed to decrease as income rises. While an increase in precipitation leads to a decline in AMR, rising maximum temperatures are associated with an increase in resistance levels.

The impact of minimum temperature exhibits divergent trends: an increase in minimum temperature leads to a decrease in AMR in Michigan, whereas it results in an increase in South Carolina.

- *Fluoroquinolone-resistant E.coli*

Figure 8. For Fluoroquinolone-resistant E.coli (a) Integrated causal drivers map (b) the causal map of AMR and PCPI (c) the causal map of AMR and maximum temperature (d) the causal map of AMR and precipitation (e) the causal map of AMR and minimum temperature. In this figure, states with multiple drivers for AMR (such as VT*) are denoted with an asterisk over their abbreviations.

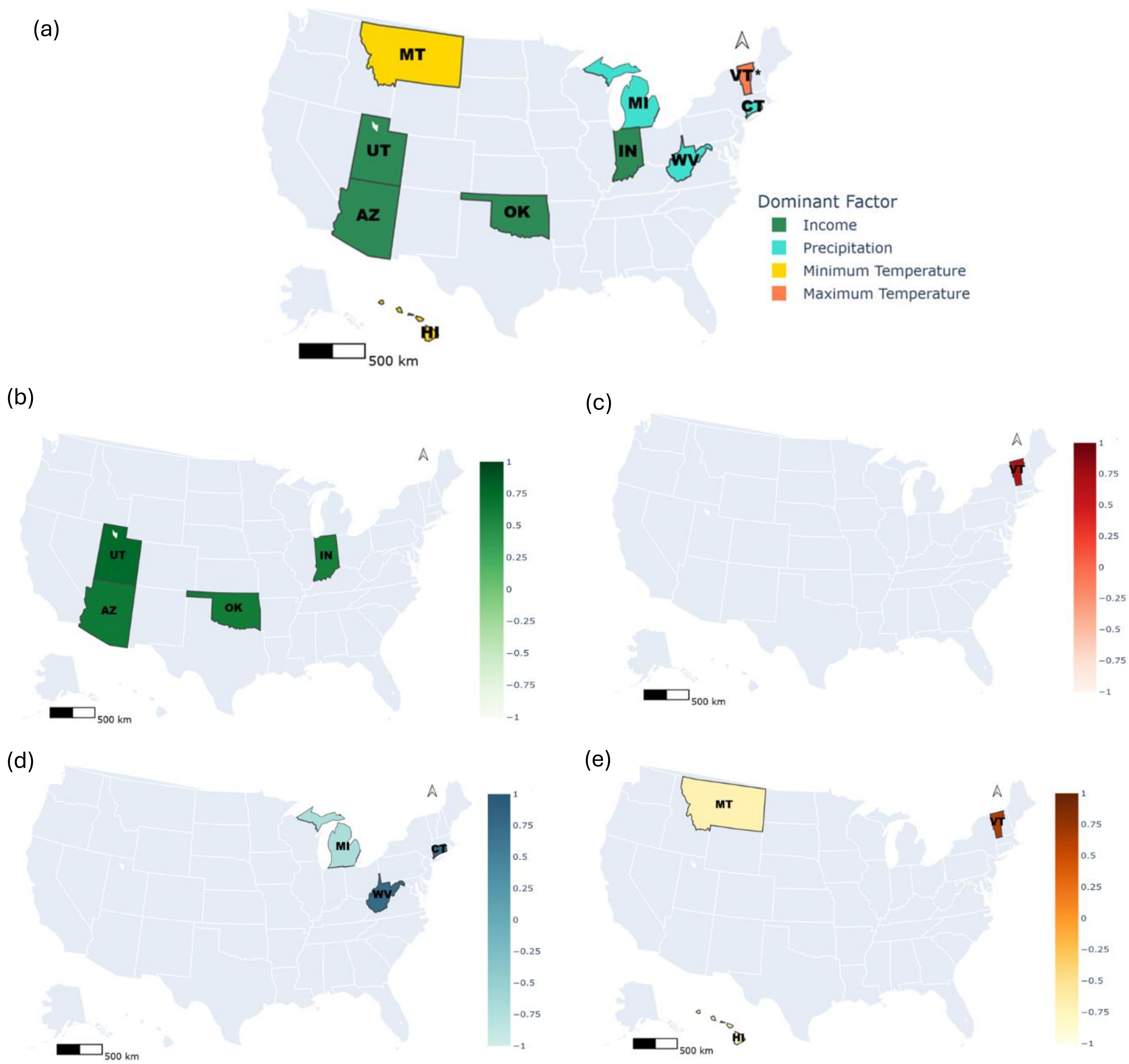


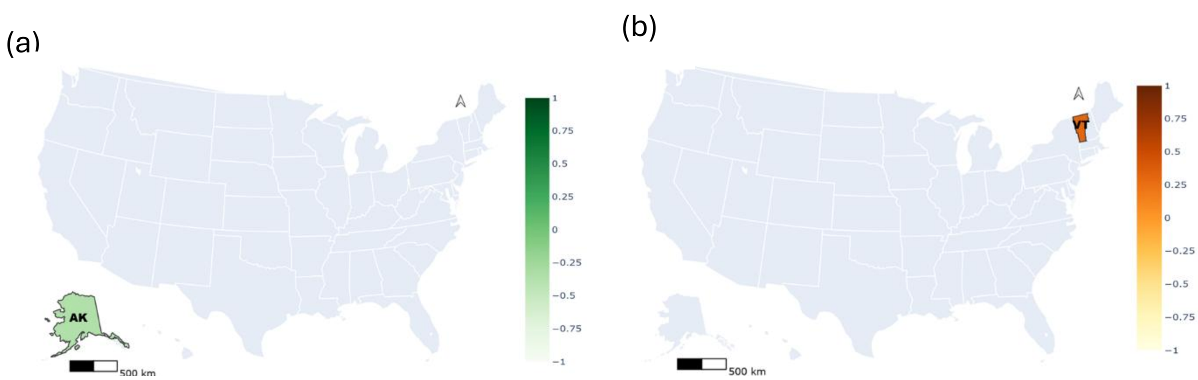
Table 4. For Fluoroquinolone-resistant E.coli, causality strength values determined via PCMCI and TE, and Pearson correlation coefficients.

Driver	PCPI			Precipitation			Maximum Temperature			Minimum Temperature		
State	PCMCI	TE	Corr	PCMCI	TE	Corr	PCMCI	TE	Corr	PCMCI	TE	Corr
Arizona	0.64	0.21	**0.86**	x	x	x	x	x	x	x	x	x
Connecticut	x	x	x	0.77	0.72	**-0.27**	x	x	x	x	x	x
Hawaii	x	x	x	x	x	x	x	x	x	-0.71	0.42	**-0.29**
Indiana	0.59	0.32	**-0.28**	x	x	x	x	x	x	x	x	x
Michigan	x	x	x	-0.71	0.20	**-0.44**	x	x	x	x	x	x
Montana	x	x	x	x	x	x	x	x	x	-0.69	0.43	-0.11
Oklahoma	0.62	0.46	**0.32**	x	x	x	x	x	x	x	x	x
Utah	0.76	0.62	**0.83**	x	x	x	x	x	x	x	x	x
Vermont	x	x	x	x	x	x	0.69	0.54	**0.47**	0.65	0.23	**0.43**
West Virginia	x	x	x	0.76	0.78	-0.14	x	x	x	x	x	x

Figure 8 and Table 4 demonstrate a positive causal link between PCPI and AMR in Arizona, Indiana, Oklahoma, and Utah, reflecting the trends seen in carbapenem-resistant E. coli. Iacobucci (2024) and the FDA Drug Safety Communication of July 26, 2016 (URL-1) classify fluoroquinolones as medications to be avoided unless essential. The causality between precipitation and AMR is positive in Connecticut and West Virginia, while it is negative in Michigan. In Vermont, AMR demonstrates a causal relationship with both maximum and minimum temperatures. Furthermore, minimum temperature and AMR exhibit a negative a causal connection in Hawaii and Montana, with a similar inverse causal relationship observed in Vermont.

2nd Stage: Causal discovery with aggregated data without regard to phenotype

Figure 9. For all phenotypes-resistant E. coli (a) the causal map of AMR and PCPI (b) the causal map of AMR and minimum temperature.



Upon applying causal analysis to the aggregated AMR data, regardless of specific phenotypes (refer to Figure 9 and Table 5), only two principal drivers and two impacted states were identified. The findings indicate that in Alaska, AMR levels decrease with an increase in PCPI, but in Vermont, increasing minimum temperatures are anticipated to result in a rise in AMR.

Table 5. For all phenotypes-resistant E. coli, causality strength values determined via PCMCI and TE, and Pearson correlation coefficients.

Driver	PCPI			Precipitation			Maximum Temperature			Minimum Temperature		
State	PCMCI	TE	Corr	PCMCI	TE	Corr	PCMCI	TE	Corr	PCMCI	TE	Corr
Alaska	-0.36	0.20	-0.07	x	x	x	x	x	x	x	x	x
Vermont	x	x	x	x	x	x	x	x	x	0.31	0.20	0.11

Last of all, as presented in Table 6, the results of this study reveal distinct causal patterns for each phenotype. Specifically, a positive causal relationship was identified between AMR and PCPI for carbapenem-resistant E. coli and fluoroquinolone-resistant E. coli. Conversely, for multi-drug resistant (MDR) E. coli, cephalosporin-resistant E. coli, and the aggregate dataset (all phenotypes combined), the causal link between AMR and PCPI was found to be negative. This difference can be attributed to the status of carbapenems and fluoroquinolones as last-resort medications. These antibiotics are more frequently utilized in high-income regions characterized by advanced hospital infrastructures and well-equipped intensive care units, thereby driving the positive causal association with PCPI. Moreover, it is conceivable that data collecting and reporting are conducted more systematically in rich regions. It can be concluded that rising income levels may lead to lifestyle changes, higher travel frequency, and greater environmental exposure, which could further affect AMR dynamics and contribute to the observed trends.

In carbapenem-resistant E. coli, precipitation does not influence AMR levels; nevertheless, a positive causal association exists between AMR and both maximum and minimum temperatures. Concerning MDR E. coli, the findings suggest that AMR levels diminish with an increase in the PCPI. Moreover, increased precipitation is observed to elevate AMR, while a rise in maximum temperature results in reduced resistance levels. The causal link between minimum temperature and AMR for the MDR phenotype is notably site-specific, exhibiting considerable variation across different regions.

The relationship with maximal temperature is positive for cephalosporin-resistant E. coli, despite the fact that both PCPI and precipitation share a negative causal link with AMR. It is intriguing that the causal effect of minimal temperature on AMR does not adhere to a consistent pattern; rather, it is contingent upon the particular region under investigation.

For fluoroquinolone-resistant E. coli, the analysis reveals that AMR levels are positively correlated with both PCPI and maximum temperature. Conversely, it is found an inverse relationship between AMR and both precipitation and minimum temperature. When it comes to the aggregate analysis—where all phenotypes are combined regardless of their specific type—the results show a positive causal link between AMR and both PCPI and maximum temperature. However, the influence of precipitation and minimum temperature becomes highly inconsistent, varying significantly by region. Interestingly, this phenotype-independent approach only produced results for two states and two drivers. Compared to the phenotype-specific analysis, this broad aggregate method proved to be insufficient in capturing the full complexity of the AMR and its drivers' causal pattern.

Table 6. Causal relationships between AMR and its drivers

Phenotypes	Causal Relationship			
	AMR-PCPI	AMR-Precipitation	AMR-Maximum temperature	AMR-Minimum temperature
Carbapenem-resistant E.coli	+	x	+	+
Multi-drug (MDR) E.coli	-	+	-	+/-
Cephalosporin-resistant E.coli	-	-	+	+/-
Fluoroquinolone-resistant E.coli	+	+/-	+	+/-
All phenotypes combined	-	x	x	+

In addition, Tables (1-5) demonstrate a clear alignment between PCMCI and TE results across nearly all states. In several instances, these causality values are supported by correlation coefficients, with the strongest correlations highlighted in bold for emphasis. The results also reveal that for certain states, AMR dynamics are influenced by more than one driver simultaneously.

5. Conclusion

AMR is poised to become one of the most significant challenges of our future, impacting not only public health but also the global economy. The existing literature makes it clear that the drivers of AMR are incredibly diverse, demanding a truly comprehensive approach. Understanding, predicting, and modeling AMR is a challenging task. Its drivers are numerous and diverse, exhibiting nonlinear and sometimes even chaotic behavior across different temporal and spatial scales. Therefore, effectively grasping the dynamics of AMR—and identifying the causal relationships with its drivers—requires a holistic perspective. Planning the necessary interventions and protective measures is only possible by integrating a wide array of factors. This includes various climate variables and scenarios, climate-environment interactions, all agricultural and livestock activities, and the full spectrum of relevant demographic, social, and economic perspectives.

Several eye-opening studies on AMR have illuminated the path forward, highlighting what needs to be done. In their 2023 work, Usman Qamar and Aatika argue that a solution is impossible if we focus solely on human health. They offer compelling examples: rising temperatures cause stress in animals, lowering their resistance to disease. This, in turn, leads to increased antibiotic use and a subsequent rise in drug-resistant bacteria originating from livestock. Furthermore, they point out that soil and water act as vast reservoirs for resistance genes. Climate change, they warn, is effectively opening up pathways for this reservoir to "leak" into human and animal populations, threatening the health of both.

In their 2022 report, Klümper et al. emphasize the critical importance of environmental surveillance. They argue that current monitoring systems are predominantly focused on clinical (human) and livestock settings, largely overlooking the environment. Given the crucial role that water, soil, and waste play in the spread of resistant bacteria, they advocate for establishing an international, standardized monitoring network. Echoing this sentiment, Gao et al. (2024) similarly contend that managing AMR risk in rivers requires moving beyond local measures. They call for the creation of integrated monitoring systems that incorporate global microbiome data. Their work powerfully suggests that rivers should be evaluated not just for their water quality, but for the "resistance load" they carry.

Nguyen-Thanh et al. (2024) argue that simply restricting antibiotics is not enough. They urge policymakers to treat AMR as a multi-sectoral crisis, stressing that the fight against it must also include tackling poverty, protecting the environment, and ensuring good governance. Similarly, Huebner et al. (2025) emphasize that while AMR is a global problem, solutions must be tailored to regional dynamics, like local agriculture and healthcare systems. Their work shows AMR moving in a nonlinear cycle—for instance, from livestock back to humans through the environment. They conclude that the disconnect between medicine, veterinary science, and environmental science hinders progress, and call for these sectors to work from a shared system map.

In their comprehensive review, Ljungqvist et al. (2025) note that low income and income imbalance affect AMR. They underline that unregulated antibiotic access increases abuse in low-GDP areas. Insufficient public awareness of antibiotic efficacy leads to inappropriate use, underscoring that patient and provider education considerably alter prescribing behaviors. The report proposes a "One Health" plan that unites human, animal, and environmental health, supported by strong social policies and international collaboration, to combat AMR.

In light of all this information, the drivers of AMR—which are the focus of this study—clearly warrant further investigation. In this work, the causal links between AMR in the U.S. (characterized by four distinct E. coli resistance phenotypes) and a set of meteorological variables (maximum temperature, minimum temperature, and precipitation) and socioeconomic factors (per capita personal income—PCPI) are explored, using both PCMCI and TE methods. As shown in Table 6, our results reveal that each phenotype responds to different drivers. Furthermore, a review of the map-based figures indicates that these causal relationships vary significantly from state to state. A key takeaway is that meteorological factors, such as precipitation and temperature extremes, are definitive causal drivers of either increases or decreases in AMR. This finding underscores the necessity of conducting AMR and climate change research in parallel. Moreover, income level also demonstrates a powerful, phenotype-dependent causal relationship with AMR.

Drawing from this study and the broader literature, several key conclusions about AMR research can be made. First, data availability stands out as a primary obstacle. This issue is rooted in legal and political barriers to data sharing among countries, the relatively short time span of available AMR data (roughly the last 15 years), and the low temporal and spatial resolution of this data. Compounding the problem is the difficulty of accessing information from a single platform, as many nations use their own disparate data portals.

Second, as previously highlighted, tackling AMR demands a remarkably comprehensive approach. It must be multisectoral (integrating policy, economics, health, environment, agriculture, livestock and tourism), multivariate (including meteorological, environmental, demographic, and socioeconomic drivers), and multistakeholder (involving all countries and a wide range of professionals from politicians, municipalities, decision-makers to health, environment, climate, water, agriculture, livestock, tourism professionals). This approach must be built on a foundation of shared data, following the FAIR (Findable, Accessible, Interoperable, and Reusable) principles.

Furthermore, we must account for complex interactions like cascading or compound effects. For example, a change in an environmental factor might influence AMR after a significant time lag, or a variable that seems insignificant on its own could have a major impact when combined with another. From the perspective of climatic drivers, this means we must investigate not only meteorological variables but also the causal links between AMR and extreme or compound events like floods, droughts, and heatwaves (Yeşilköy, 2026). This requires building multivariate causal networks that incorporate these time lags. Finally, AMR data should be collected and shared not just at the national level but at much finer spatial and temporal scales.

To conclude, future work must be grounded in the One Health approach. AMR needs to be studied holistically, with the full participation of all stakeholder domains. Data and findings must be shared transparently to enable comprehensive planning that accounts for all influential drivers, both for today and for the future.

Acknowledgement

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Data Availability

E. coli data from Centers for Disease Control and Prevention (CDC): https://arpsp.cdc.gov/profile/antibiotic-resistance?tab=antibiotic-resistance

Meteorological (Tmax, Tmin and Precipitation) Data from NOAA:
https://www.ncei.noaa.gov/access/monitoring/climate-at-a-glance/statewide/time-series/

PCPI data from U.S. Bureau of Economic Analysis (BEA): https://www.bea.gov/itable/

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