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Impact of Demographic Trends on Antimicrobial Resistance

Roshen Fernando

Australian National University

Crawford School of Public Policy

CAMA

Centre for Applied Macroeconomic Analysis

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Roshen Fernando
Centre for Applied Macroeconomic Analysis (CAMA), ANU
Australian Research Centre of Excellence in Population Ageing Research (CEPAR), UNSW

Abstract

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Keywords

Antimicrobial resistance, Infectious diseases, Demographic Trends, Population Growth, Population Aging, Urbanization, Econometrics, Machine Learning

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Address for correspondence:

(E) cama.admin@anu.edu.au

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IMPACT OF DEMOGRAPHIC TRENDS ON ANTIMICROBIAL RESISTANCE

Roshen Fernando[1]

Centre for Applied Macroeconomic Analysis (CAMA), The Australian National University

Australian Research Centre of Excellence in Population Ageing Research (CEPAR)

ABSTRACT

Medical advancements in the twenty-first century significantly contribute to increased longevity and the current global demographic trends, including population aging. While rising antimicrobial resistance (AMR) threatens the sustainability of longevity prospects, the current demographic trends also contribute to worsening AMR. We investigate the role of four demographic indicators (population growth, population aging, population density, and urbanization) in the resistance growth of seven pathogens against twelve antimicrobials in 30 countries from 2000 to 2020. We observe heterogeneous responses of different antimicrobial drug-pathogen combinations to demographic trends. We observe that the demographic trends could affect resistance growth more than antimicrobial consumption growth in some antimicrobial-drug pathogen combinations. We emphasize the importance of a broader exploration of factors affecting AMR evolution from a one-health approach and enhanced AMR surveillance, among others, to produce effective policy responses to tame AMR.

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1 INTRODUCTION

The global population exceeded eight billion by the end of 2022. The remarkable population growth accompanies significant changes in the global population composition. On one hand, some parts of the world, such as Sub-Saharan Africa, will continue to experience a burgeoning youth population, enabling them to harvest a demographic dividend. On the other hand, other parts of the world, such as Australia, Europe, and Eastern Asia, will observe an aging population amidst declining fertility. The global increase in longevity is attributable to the decline in mortality from infectious diseases due to the medical advancements led by the discovery of antimicrobial medicine, improved access to clean water, and improvements in nutrition, hygiene, and sanitation (United Nations [UN] 2023; Bloom & Cadarette 2019).

The role of antimicrobial medicine in increasing human longevity is uncontested. The revolutionary discovery of penicillin in the late 1920s and the golden age of antibiotics that followed reduced mortality and morbidity from infectious diseases enabled effective surgical procedures and enhanced the means to prevent diseases before infection. Consequently, an increase of 23 years in the average human life span is attributable to the advancements in antimicrobial medicine (Hutchings et al. 2019).

Yet, suboptimal antimicrobial consumption, both in healthcare and agriculture settings and resulting selective pressure on pathogens, has given rise to antimicrobial resistance (AMR). At least 1.27 million lives were lost in 2019 due to existing antimicrobial medicine failing to treat known infections due to AMR (Murray et al. 2022). Amidst worsening AMR, preventing and treating new infections that emerge and treating existing infections, especially among those who are aging, are testing the global health systems and economies.

AMR and demographic trends share a two-way relationship. On one hand, worsening AMR threatens the effectiveness of the existing medical advancements and, thereby, the ability to sustain longevity. On the other hand, continuing population growth and population aging will further aggravate AMR without effective health policies to reduce such effects. While the health and economic burden of worsening AMR is being studied, little is also known about the contribution of demographic trends to aggravate AMR.

This paper estimates the impact of demographic trends, represented via a set of demographic indicators, on AMR. The rest of the paper is organized as follows. Section 2 introduces the data and empirical estimation approach used to derive the impact of demographic indicators on AMR. Section 3 presents a framework to understand the AMR linkages with demographic trends and discusses the empirical estimates with reference to the existing understanding of the impact of demographic trends on AMR. We also present the average near-term AMR growth variation under ten demographic scenarios. Section 4 concludes by outlining the research and policy implications and future directions for research.

2 THE IMPACT OF DEMOGRAPHIC TRENDS ON AMR

2.1 Data on Antimicrobial Consumption and Resistance

Systematic global surveillance of AMR commenced only in 2015 (WHO 2015). Therefore, the availability of global AMR data is limited. However, the European Centre for Disease Prevention and Control (ECDC) (2023a, b) has been gathering data on the resistance of eight pathogens to 12 antimicrobial drugs across 30 countries from 2000 to 2020[2]. Even though some data for several other developed countries outside Europe, such as Australia, Canada, and the US, are available, they are not for comparable pathogens and antimicrobial drugs ECDC covers. Therefore, this paper focuses on the 30 countries ECDC covers to assess the impact of demographic indicators on AMR using the consistent data available from the ECDC.

One of the main approaches to measuring a pathogen's resistance to a given antimicrobial drug involves observing the antimicrobial drug concentration required to inhibit the growth of a desired proportion of the pathogen population. Depending on the inhibitory concentration levels, pathogens will be identified with different levels of susceptibilities to the antimicrobial drugs. The proportion of the population that requires extensive antimicrobial concentrations is drug-resistant.

Observing pathogenic molecular structures could also reveal whether a pathogen is no longer responsive to a drug. Furthermore, resistance could be identified by monitoring different pathogenic activities, such as reproduction, responsiveness to external disturbances, etc. Ultimately, these experiments produce the percentage of a pathogen population resistant to a given drug.

ECDC (2023b) data on AMR distinguishes three categories of pathogens: (1) the proportion of the population that is susceptible to a given drug; (2) the proportion of the population that is susceptible and has received increased exposure to a given drug, and (3) the proportion of the population resistant to a given drug. This paper uses the data on the proportion of pathogens resistant to a given drug out of these three categories. The data covers the resistance of eight pathogens to 12 antimicrobial drug classes.

ECDC (2023a) data covers the consumption of Antibacterials for Systemic Use (J01 class), according to the Anatomical Therapeutic Chemical (ATC) Classification System. The data is expressed in Daily Defined Dosages per 1,000 inhabitants per day and is already adjusted for the populations of the countries covered. Following the guidelines from the WHO Collaborating Centre for Drug Statistics Methodology (WHO 2023a), we map the antimicrobial consumption data for 1,284 drugs to the 12 antimicrobial drug classes covered in the ECDC data.

[2] Supplementary Annexure 1 lists the 30 countries covered in the paper, the five United Nations (UN) subregions they belong to, and their ISO codes. It is noteworthy that geographically, the countries belong to Northern, Eastern, Southern, and Western Europe, as well as Western Asia.

Tables 1 and 2 summarize the pathogens and antimicrobial drugs. The pathogens and antimicrobial drugs result in 26 combinations. However, we avoid the resistance of Methicillin against *Staphylococcus aureus* (MRSA) due to the lack of availability of antimicrobial consumption data[3].

Table 1: Pathogens

	Pathogen		Pathogen
1	Acinetobacter spp	5	Klebsiella pneumoniae
2	Enterococcus faecalis	6	Pseudomonas aeruginosa
3	Enterococcus faecium	7	Staphylococcus aureus
4	Escherichia coli	8	Streptococcus pneumoniae

Source: ECDC (2023b).

Table 2: Antimicrobial Drug Classes

	Antimicrobial Drug	Corresponding ATC-4 Drug Classes
1	Aminoglycoside	J01GA and J01GB (excluding High-level gentamicin)
2	Aminopenicillin	J01CA
3	Carbapenem	J01DH
4	Ceftazidime	J01DD
5	Fluoroquinolone	J01MA
6	High-level gentamicin	J01GB
7	Macrolide	J01FA
8	Methicillin	J01CF
9	Penicillin	J01CE, J01CF (excluding Methicillin), J01CG, and J01CR
10	Piperacillin Tazobactam	J01CA
11	Third-generation cephalosporin	J01DD
12	Vancomycin	J01XA

Source: ECDC (2023a).

2.2 Demographic Indicators

Population growth, population aging, growth in population density, urbanization, and migration are the widely discussed demographic indicators in the existing literature in relation to AMR. However, due to the lack of availability of annual data on migration, we only focus on assessing the responsiveness of AMR to the first four demographic indicators in this paper.

Specifically, the four indicators account for the growth in population[4], population aging via the old-age dependency ratio, population density, and urbanization via urban population as a proportion of the total population, respectively. Table 3 summarizes the measures with their data sources[5].

[3] Supplementary Annexure 2 lists the 25 antimicrobial drug-pathogen combinations considered in this paper. Supplementary Annexures 3 and 4 present the descriptive statistics for historical antimicrobial consumption and resistance, respectively. The online dashboard illustrates, and Supplementary Annexures 5 and 6 discuss the historical variation in antimicrobial consumption and resistance, respectively, across the 30 countries this paper focuses on.

[4] We refer to population as all the inhabitants of a given country, irrespective of nationality, following the definition of the World Population Prospects (UN 2022).

[5] The online dashboard illustrates and Supplementary Annexure 7 discusses the historical variation in the demographic indicators across the 30 countries this paper focuses on, aggregated for five UN regions, from 2000 to 2020.

Table 3: Demographic Indicators

	Demographic Indicator	Description	Data Source
1	Growth in Population	Annual growth in the total population of a country	World Population Prospects (UN 2022)
2	Growth in Old-age Dependency Ratio	Annual growth in the ratio of the population above the age of 65 compared to the working-age population (15-64 years).	
3	Growth in Population Density	Annual growth in the midyear population divided by land area (km^2).	World Bank (2023)
4	Growth in Urban Population	Annual growth in the number of people living in urban areas, as defined by national statistical offices, as a proportion of the total population.	

Source: Constructed by the Author using information from World Population Prospects (UN 2022) and World Bank (2023).

2.3 Empirical Estimation Approach

In this paper, using the data on antimicrobial consumption and resistance for 30 countries, we first calculate the consumption growth for 12 antimicrobial drug classes and the resistance growth for seven pathogens against the 12 antimicrobial drug classes. We aim to understand how the demographic indicators (introduced in Section 2.3) historically affected the antimicrobial consumption and resistance growth in those countries. There, we encounter two challenges.

Firstly, some of the demographic indicators are linked to the same distributions, although their methods of construction are independent[6]. Secondly, we have a considerably higher number of demographic indicators as predictors (especially compared to existing studies that have primarily used one or two demographic indicators, at most). Accordingly, both accounting for collinearity and retaining the features are central to our estimations. Therefore, we estimate a regularized panel regression model, the Ridge regression model, illustrated in Equation 1[7].

GDP per capita growth in the empirical estimation model captures the impact of the national economic growth adjusted for the population on AMR. Per capita economic growth also acts as a proxy to indicate the level of private and public healthcare expenditure, the existence of public health and sanitation infrastructure, and the development of the health and sanitation practices, standards, and policies, including those targeting AMR, in the absence of consistent measures for them for all countries across the period.

We include drug-specific fixed effects (α_i) to control for unobserved time-invariant heterogeneity in resistance growth. We also include additional country- and year-specific fixed effects (γ_j and δ_k, respectively) to control for unobserved time-invariant heterogeneities, such as those in demographic indicators, and any additional unobserved time-variant effects. These fixed effects also account

[6] For example, the growth in population, urban population, and population density share the same population distribution.

[7] Supplementary Annexure 8 introduces regularized regression models and illustrates how they help overcome certain limitations of linear regression models.

for the effect of any time-variant and/or time-invariant historical health and population policies on resistance growth[8].

We estimate the same regression model for individual antimicrobial drug-pathogen combinations, omitting the drug-specific fixed effects. Equation 2 presents the specific model we estimate. This allows for breaking down the average resistance of a pathogen against multiple antimicrobial drugs for individual antimicrobial drugs.

Equation 1: Estimated Model for AMR Growth in a Given Pathogen against Antimicrobial Drug *i* in Country *j* and Year *k*.

$$AMR\ Growth_{i,j,k} = \beta_0 + \beta_{AMC} * Antimicrobial\ Consumption\ Growth_{i,j,k} + \beta_{GDP} * GDP\ Per\ Capita\ Growth_{j,k} + \sum_{n=1}^{4} \beta_n * Growth\ in\ the\ Demographic\ Indicator_{n,j,k} + \alpha_i + \gamma_j + \delta_k + \varepsilon_{i,j,k}$$

Equation 2: Estimated Model for AMR Growth for a Given Pathogen-Antimicrobial Drug Combination in Country *j* and Year *k*.

$$AMR\ Growth_{j,k} = \beta_0 + \beta_{AMC} * Antimicrobial\ Consumption\ Growth_{j,k} + \beta_{GDP} * GDP\ Per\ Capita\ Growth_{j,k} + \sum_{n=1}^{4} \beta_n * Growth\ in\ the\ Demographic\ Indicator_{n,j,k} + \gamma_j + \delta_k + \varepsilon_{j,k}$$

3 RESULTS & DISCUSSION

3.1 Associations between AMR and Demographic Trends

Figure 1 presents the average Pearson's correlation coefficients among AMR, demographic indicators, antimicrobial consumption, and GDP per capita for the 25 antimicrobial drug-pathogen combinations. Notably, the correlation coefficients illustrate the average relationship AMR had with its confounders from 2001 to 2020 in the 30 countries this paper focuses on. Therefore, while the correlation coefficients capture the resistance heterogeneity a pathogen may illustrate towards various antimicrobial drugs, they do not reflect the heterogeneity across time and countries.

Overall, the correlation coefficients of AMR and demographic indicators lie within those of AMR and antimicrobial consumption. The correlation coefficients vary between 0.15 and -0.1. However, the correlations are quite heterogeneous. For example, the correlations among resistance growth, urban population growth, and population density growth could vary across the whole range of the correlation coefficients. The resistance of the same pathogen to different antimicrobial drugs could also have different correlations with various demographic indicators. For example, while the resistance growth of *Pseudomonas aeruginosa* to Aminoglycosides is positively correlated with the growth in population density, the correlation is almost null for that to Carbapenems.

[8] The objective of the empirical estimation in this paper is not to comprehensively explain the resistance growth patterns of a pathogen towards an antimicrobial drug but to estimate the sensitivity of resistance growth to demographic trends. Therefore, the omitted variables (that could contribute to explaining resistance growth patterns), especially other demographic indicators, could affect the estimates only to the extent they are correlated with the demographic indicators. For example, as mentioned in Section 2.3, the lack of annual data on migration prevents us from incorporating that into our empirical estimation approach. Its effect may partly be captured in other demographic indicators, such as population density or urbanization.

We also observe that the antimicrobial consumption growth and GDP per capita could have heterogeneous correlations with resistance growth. While the resistance growth of *Pseudomonas aeruginosa* to Carbapenems is positively correlated with antimicrobial consumption growth, its resistance growth against Piperacillin is mildly negatively correlated with antimicrobial consumption growth. While GDP per capita has some negative correlations with the resistance growth in *Acinetobacter spp.* and Enterococci, the correlations of GDP per capita with *Klebsiella pneumoniae* and *Escherichia coli* are quite close to zero.

3.2 Impact of Demographic Trends on AMR

3.2.1 Overview

As explained in Section 2.3, we estimate empirical models to capture the impact of demographic indicators on the resistance growth of pathogens against specific antimicrobial drugs and the average resistance growth across all the antimicrobial drugs. The empirical results are presented in the online dashboard for each pathogen and Figures 2A to 2F for each indicator[9]. With the existing evidence of how demographic indicators affect AMR, we construct a framework to illustrate their linkages with AMR. Figure 3 presents the framework. Sections 3.2.2 to 3.2.7 discuss the empirical estimates of the impacts of demographic trends on AMR with reference to the framework.

3.2.2 Population Growth

Population growth affects resistance growth both directly and indirectly (via antimicrobial consumption). Population growth directly affects resistance growth via two main pathways. Firstly, a larger population allows for faster infection transmission, provides a broader pool of hosts for pathogens, and increases the probability of interactions among various pathogens, enabling resistance acquisition via horizontal gene transfer. Secondly, a larger, younger population, particularly children, with their behavioral differences compared to adults and the lack of immunity at early growth stages, become more vulnerable hosts and facilitate resistance acquisition via horizontal gene transfer[10].

Population growth indirectly affects resistance growth via antimicrobial consumption in two main ways. Firstly, a growing population and infections burden the existing health and sanitation infrastructure and services, leading to higher antimicrobial consumption. The resulting increase in selective pressure promotes resistance growth. Secondly, unless the capacity of the existing health and sanitation infrastructure and services is expanded to accommodate the population growth, the pressure on health systems may deprive some fractions of the population of access to those systems due to various reasons, including the lack of financial resources. They may choose to access suboptimal treatments via informal and unregulated pharmaceutical markets. Thus, the lack of universal access

[9] The diagnostics for the empirical models and the Variance Inflation Factors for the confounders are available from Supplementary Annexures 9 and 10, respectively.
[10] See ReAct (2019) for a detailed discussion, and McDonnell and Klemperer (2022) and Medernach and Logan (2019) for a synthesis of evidence.

to optimal preventive and therapeutic care also promotes resistance growth via the underuse and misuse of antimicrobials.

However, in Figure 2A, we do not observe the resistance growth of all the pathogens promoted by population growth. Following our understanding of the impact pathways, the resistance growth of *Klebsiella pneumoniae* and *Streptococcus pneumoniae* for all the drugs is incentivized by population growth, where the resistance grows by up to 0.5 percentage points due to a one percentage increase in population growth. Yet, the resistance growth of other pathogens is negatively affected by population growth. For example, the resistance growth of *Escherichia coli* is reduced by up to 0.15 percentage points from a percentage increase in population growth. The resistance of *Enterococcus faecalis* against Gentamicin is reduced by up to 0.5 percentage points from a percentage increase in population growth. We attribute these observations to several factors specific to the sample of countries considered in this paper.

Firstly, as discussed in Supplementary Annexure 7, population growth was stagnant in most regions from 2000 to 2020. However, the significant growth in the old-age dependency ratio during the same period illustrates that the population growth is more attributable to the increased longevity of elderly populations[11]. Secondly, as most countries are high-income countries, they potentially expanded and improved their healthcare infrastructure and services as the fraction of the elderly population increased, hence managing the potential burden on the healthcare systems[12]. Thirdly, although elderly populations could have increased antimicrobial consumption due to their vulnerability to infections, our empirical estimation strategy includes other indicators, such as population aging and antimicrobial consumption, to capture those effects[13].

Therefore, as we control for population aging, antimicrobial consumption, and GDP per capita in this paper, the reasons for the negative effect of population growth on resistance growth should be independent of those factors. We expect the residual pathway to be via the reduction in the younger fraction of the population, particularly children (as the growing population is skewed towards the elderly), and the reduced scope for transmission of infections and resistance via them[14].

3.2.3 Population Aging

Population aging is a direct consequence of declining fertility and increasing longevity, implying a higher proportion of the elderly population compared to the working-age population. Among the demographic trends discussed in this paper, population aging has a notable two-way relationship with AMR.

[11] Pneumococcal infections are disproportionately prevalent among the elderly (e.g., see Wroe et al. (2012) for evidence from the US). Therefore, perhaps the increased fraction of the elderly population is also the reason for observing incentivized resistance growth of *Klebsiella pneumoniae* and *Streptococcus pneumoniae* species.
[12] We observe that GDP per capita negatively impacts the resistance growth of most pathogens, as discussed in Section 3.37.
[13] These effects are discussed in Sections 3.3.3 and 3.3.6, respectively.
[14] See Baker et al. (2021) for a discussion on the impact of children on the transmission dynamics of infectious diseases.

On one hand, medical advancements in the twenty-first century, including the discovery of antimicrobials, have contributed to increased longevity. Hence, resistance growth threatens longevity. Given the physiological changes associated with aging and age-related immunosenescence (which reduces both innate and adaptive responses of human systems to pathogens), the elderly become attractive hosts for pathogens and, hence, are disproportionately vulnerable to diseases[15]. Resistance growth reduces the effectiveness of existing medicine and, thus, reduces the success rates of antimicrobial drugs and medical procedures on which the elderly rely to prevent and treat those diseases. Therefore, resistance growth could reduce longevity.

On the other hand, aging populations could exacerbate resistance growth. Firstly, physiological changes, age-related immunosenescence, and the impact on nutrition from the dietary changes with aging and increased exposure to chronic health conditions increase their vulnerability to diseases, necessitating higher antimicrobial consumption to prevent and treat those diseases. Secondly, limited mobility and functional disabilities prevent the elderly from seeking medical care promptly to prevent and treat those diseases. These pathways together result in suboptimal antimicrobial consumption, increasing the selective pressure on the pathogens (Baker et al. 2021; Du et al. 2021; Gavazzi et al. 2004).

In addition to these pathways, multimorbidity and increased exposure to long-term care facilities and both primary and secondary healthcare settings also contribute to resistance growth. Firstly, multimorbidity, or prevalence of multiple health conditions and receiving multiple antimicrobial treatments, increases the probability of horizontal gene transfer among pathogens. Secondly, concentration in long-term healthcare facilities for long periods and frequent exposure to primary and secondary healthcare further increase their exposure to infections and pathogens. This increases the probability of horizontal gene transfer across the elderly and potential spillovers to other age groups (Nguyen et al. 2019; Church 2004).

In contrast to high-income countries, population aging could exacerbate resistance growth in developing countries via additional pathways. The widespread lack of financial resources, education, awareness, and nutrition, and the concentration of elderly populations in rural settings reduce the access to healthcare facilities for the elderly. These could lead to suboptimal antimicrobial consumption, promoting resistance growth (Du et al. 2021; Gavazzi et al. 2004).

As the existing population, predominantly the elderly population, has benefited from antimicrobial medicine advancements in the twenty-first century and improved their longevity, we do not expect the current data to reflect the first direction of the relationship where AMR affects longevity. Therefore, in this paper, we focus on the second direction of the relationship, which is the impact of aging populations on AMR.

[15] See Xu et al. (2020) for a detailed discussion of aging and immunosenescence and how age-related immunosenescence could affect different human organs differently, and Chang et al. (2019) for a systematic analysis of the global burden of disease and injuries across older (aged 70+) adults.

From Figure 2B, we observe that for most of the antimicrobial drug-pathogen combinations, the growth in population aging promotes resistance growth. The effects are relatively high for the resistance growth of *Enterococcus faecium* and *Klebsiella pneumoniae*, where the highest resistance growth reaches a 0.28 percentage point increase in response to a percentage increase in the growth of the old-age dependency ratio. Although not as high as *Enterococcus faecium* or *Klebsiella pneumoniae,* resistance growth of *Acinetobacter spp.* and *Enterococcus faecalis* also consistently responds positively to growth changes in the old-age dependency ratio.

However, for certain combinations, especially those related to *Escherichia coli.* and *Streptococcus pneumoniae*, we observe population aging to reduce resistance growth. For example, the resistance growth of *Streptococcus pneumoniae* reduces by about 0.21 percentage points due to a percentage increase in the growth of the old-age dependency ratio. The infections of those pathogens are more prevalent among children and the elderly. Therefore, the reduced scope for incidence and transmission of those infections among children from reduced fertility may have influenced the resistance growth decrease, as the population distribution gets skewed towards the elderly.

3.2.4 Population Density

Population density affects resistance growth via two main pathways. Firstly, from an epidemiological perspective, densely concentrated populations increase the contact rate among citizens, which enables pathogens to find new hosts and spread infections faster across the population. Secondly, a higher population density implies more interactions with shared facilities, such as public transportation services and public places (Cave et al. 2021). Similar to disease spreading, higher interactions across the population enable faster acquisition of resistance, primarily via horizontal gene transfer. Accordingly, dense populations promote resistance growth.

As observed in Figure 2C, the growth in population density incentivizes resistance growth across almost all pathogens. The effect is considerably higher among the resistance growth of *Pseudomonas aeruginosa,* where a percentage increase in population density growth increases resistance growth by 0.38 percentage points. The resistance growth of *Streptococcus pneumoniae* and *Escherichia coli.* also increases with the growth in population density. The effects could vary between 0.04 – 0.24 and 0.02 – 0.19 percentage points, respectively, in response to a percentage increase in population density growth. The resistance growth of *Acinetobacter spp.*, *Enterococcus faecium*, and *Klebsiella pneumoniae* against some antimicrobial drugs has mixed responses to population density growth.

3.2.5 Urbanization

Urbanization is the concentration of human populations into discrete areas, which could transform the land for residential, commercial, industrial, and transportation purposes (United States Environmental Protection Agency (USEPA) 2023). In this paper, we capture the effect of urbanization on resistance growth via the growth in the proportion of people living in urban areas.

Urbanization could also increase population density. Therefore, some impact pathways discussed in Section 3.2.4 could also apply to urbanization. However, the population density measure in this

paper is an independent indicator of the distribution of the total population across a given country rather than their concentration in urban areas. Therefore, we expect urbanization to capture additional effects that population density could not capture, and our empirical estimation approach, discussed in Section 2.3, enables extracting the independent effects of the two indicators separately despite their correlation.

Firstly, in addition to increasing the proximity between people, urbanization could also increase the proximity between people and livestock, given the space constraints often accompanying urbanization. This could also facilitate the spillover of pathogens from animals to humans and enable zoonoses. Secondly, the various services shared by the masses, such as accommodation, food and beverage, recreation, and transportation, could also aggravate disease transmission and pathogenic spillovers without widespread hygienic practices. Thirdly, if the health and sanitation infrastructure are being burdened due to urbanization, they would retain pathogenic genes longer and enable mixing with the broader environment. Fourthly, the urban environments could also be more exposed to travelers and migrants, enabling the introduction of foreign pathogenic genes into the domestic environment. Thus, growth in urbanization could promote resistance growth (Baker et al. 2021; Cave et al. 2021; Tapsall & Limnios 2007; Church 2004; Bruinsma et al. 2003).

In line with the existing evidence, we observe that resistance growth of most of the pathogens increases in response to the growth in the urban population. As presented in Figure 2D, the resistance growth of *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* is quite responsive to changes in the urban population, where the resistance growth could vary between 0.05 to 0.5 percentage points in response to a percentage increase in the urban population growth. The resistance growth of *Escherichia coli* is also positively affected by the rise in urban population growth.

However, the resistance growth of several pathogens, *Acinetobacter spp., Enterococcus faecalis, Enterococcus faecium, and Streptococcus pneumoniae,* tend to reduce in response to the growing urban population. This effect is potentially attributable to broader access to better health and sanitation systems as rural populations migrate to urban settings.

3.2.6 Antimicrobial Consumption

In line with the general notion of selective pressure exerted by antimicrobial consumption on resistance growth, we observe that the resistance growth of some pathogens is positively affected by antimicrobial consumption growth. As reported in Figure 2E, *Pseudomonas aeruginosa* demonstrates the strongest responsiveness, where a percentage increase in consumption growth increases its resistance growth by about 0.02 percentage points. The resistance growth of *Streptococcus pneumoniae* and *Acinetobacter spp.* also positively responds to antimicrobial consumption growth.

However, the resistance growth of some pathogens reduces in response to antimicrobial consumption. The resistance growth of *Enterococcus faecium*, *Enterococcus faecalis*, and *Escherichia coli* reduces amidst antimicrobial consumption growth. We attribute this effect to two factors. Firstly, this effect could be due to the efficiency of the antimicrobials from 2001 to 2020 across the 30 countries con-

sidered in this study. Secondly, as antimicrobial consumption is correlated with other demographic factors, such as population growth and population aging, this could be the residual effect antimicrobial consumption has once the contemporaneous effect attributable to population growth or population aging is reduced, given the ability of our empirical estimation strategy to handle such effects.

3.2.7 GDP Per Capita Growth

GDP per capita growth is a proxy for the standards of health and sanitation systems and socioeconomic development. Therefore, in general, the growth in GDP per capita could reduce the resistance growth. However, resistance growth could still increase if antimicrobial consumption outside the healthcare sector, such as livestock, increases with the GDP per capita growth. The observations from Figure 2F align with this hypothesis for the resistance growth of almost all the pathogens except Streptococcus pneumonia.

3.2.8 Summary

Overall, we observe that the impact of demographic indicators on AMR varies across pathogens and antimicrobial drugs. Most of our empirical estimates align with the existing evidence on the directionality of the effects of demographic indicators on different pathogenic activities. The impacts could be either positive or negative depending on the evidence from the historical data, which covers antimicrobial consumption and resistance across 30 countries from 2000 to 2020.

We illustrate that including potentially correlated demographic indicators, antimicrobial consumption, and GDP per capita within the same empirical model and estimating the contemporaneous responsiveness of resistance growth to those indicators yields exciting insights, which may not be implied directly from the existing evidence.

Most of our estimates for the impact of antimicrobial consumption on resistance growth agree with the general notion of the effect of selective pressure on resistance growth exerted by antimicrobial consumption. However, independent of this impact on antimicrobial consumption, demographic indicators strongly affect resistance growth. We also observe that the GDP per capita growth predominantly contributes to reducing the resistance growth.

3.3 Near-term Resistance Growth Projections

3.3.1 Demographic Scenarios

We project the near-term resistance growth variations under ten demographic scenarios from the World Population Prospects (UN 2022). The scenarios assume a mix of assumptions about fertility, mortality, and migration, as presented in Table 4 (not in any particular order).

Given the enormous evolutionary power and adaptability of pathogens, we only project the near-term variation in resistance growth rates for the 30 years from 2021 to 2050. Although highly probable, we do not assume any additional adaptation of pathogens to demographic trends other than any historical adaptation trends built into the empirical estimates through historical observations.

We also project the resistance growth changes only as a function of population and population aging growth changes. Thus, we inherently do not assume any additional effects on resistance growth from growth changes in population density, urbanization, GDP per capita, and antimicrobial consumption.

Most importantly, we do not attribute any likelihood to any of the scenarios and consider any of them to be a counterfactual case. We use all the scenarios only to obtain a range of resistance growth trajectories. Given the uncertainty involved also in population projections, this exercise is speculative. Notwithstanding the limitations, to contribute to the discussions on managing AMR amidst the demographic trends, we illustrate how the changing demographic indicators could influence the near-term resistance growth trajectories.

3.3.2 Projected Resistance Growth

We apply the empirical estimates obtained in Section 2.3 and discussed in Section 3.2 to the projected demographic indicators, illustrated in the online dashboard and discussed in Supplementary Annexure 11, to project the near-term resistance growth variations under demographic scenarios. The online dashboard presents the average of the resistance growth variations from all the scenarios for the seven pathogens we focus on in this paper. Table 5 summarizes the projected average resistance growth of the pathogens by the end of 2030, 2040, and 2050 in each region.

Table 4: Demographic Scenarios

	Scenario	Fertility	Mortality	International Migration
1	Medium fertility	Medium*	Medium*	Medium
2	Low fertility	Low	Medium	Medium
3	High fertility	High	Medium	Medium
4	Constant fertility	Constant as of 2022	Medium	Medium
5	Instant replacement	Instant replacement as of 2022	Medium	Medium
6	Constant mortality	Medium	Constant as of 2022	Medium
7	Constant fertility and Constant mortality	Constant as of 2022	Constant as of 2022	Medium
8	Zero migration	Medium	Medium	Zero from 2022
9	Instant replacement and Zero migration	Instant replacement as of 2022	Medium	Zero from 2022
10	Momentum	Instant replacement as of 2022	Constant as of 2022	Zero from 2022

Source: World Population Prospects (UN 2022).

*Based on median probabilistic fertility.

The average resistance growth variations are derived from three steps. Firstly, the effects of individual demographic indicators on the resistance growth of each pathogen are projected under each demographic scenario. Specifically, the projections are based on the empirical estimates from the model presented in Equation 1 for the growth in population and population aging. Secondly, the estimates are aggregated for each pathogen under each scenario. Thirdly, we obtain the average resistance growth rate of each pathogen across all the demographic scenarios. The online dashboard

also illustrates the decomposition of the aggregate effect to identify the individual contribution from the growth changes in population and population aging under different demographic scenarios.

The resistance growth variations are primarily influenced by three factors: (1) the non-linear variation in the demographic indicators across demographic scenarios, (2) the differential exposure of a given region to different demographic indicators under different demographic scenarios, and (3) the differential responsiveness of resistance growth to different demographic indicators. Therefore, the ultimate resistance growth variations could differ from the results expected from a linear extrapolation involving a single demographic indicator.

The resistance growth of *Acinetobacter and Enterococcus spp.* generally increases across all the regions. Eastern and Western Europe experience the highest and lowest growth rates, respectively. The highest growth rates across the three pathogens are observed in *Enterococcus faecium*. The resistance growth of *Pseudomonas aeruginosa* minimally increases across all the regions. The resistance growth of *Escherichia coli* remains almost constant compared to the other pathogens, and Southern Europe and Western Asia experience the highest positive and the lowest (rather negative) resistance growth, respectively. The resistance growth of *Klebsiella pneumoniae* and *Streptococcus pneumoniae* decreases on average, while the latter decreases faster.

A breakdown of the results illustrates that the growth in population and population aging contribute differently to the resistance patterns. The contributions depend on the fertility, mortality, and migration assumptions in the scenarios. For example, under a low fertility scenario, the contribution of population growth to resistance growth is higher, while under a low mortality scenario, the contribution of population aging to resistance growth is higher.

3.4 Summary

Section 3 discussed two sets of results from this paper. Firstly, we discussed the results from the empirical estimation of the impact of demographic indicators on AMR. The results included the impacts on the average resistance of a given pathogen and specific resistance to different antimicrobial drugs. We illustrated that the responsiveness of resistance growth to various demographic indicators could be different. The responsiveness of the specific resistance growth in a given pathogen towards different antimicrobial drugs could also be different from the average resistance growth. Where possible, we also situated our estimates within the existing understanding of the responsiveness of AMR to demographic trends. We also demonstrated that demographic indicators are crucial for explaining the resistance growth in almost all pathogens, in addition to antimicrobial consumption, which is currently considered the primary driver of AMR.

Secondly, we applied the empirical estimates to projected demographic indicators to speculate how the resistance growth of different pathogens could change on average under ten demographic scenarios. We illustrated the net effect on resistance growth as the demographic risks evolve differently, changing their proportional contribution to net resistance growth. However, given the uncertain-

ty in demographic projections and the vast potential of pathogens to adapt to evolving demographic trends, we restricted our projections to a 30-year horizon (2021-2050).

In the discussion of those projections, we illustrated that, given the historical adaptation of pathogens to demographic indicators and without any additional growth changes in population density, urbanization, antimicrobial consumption, and GDP per capita, the resistance patterns could either change positively or negatively[16]. While these patterns varied across pathogens, the demographic drivers of those changes were also diverse. Therefore, we reiterate the importance of considering a more comprehensive range of demographic indicators when assessing the impacts of demographic indicators on AMR and that the holistic variation in resistance growth may be much different from what could be linearly predicted using a single demographic indicator.

Table 5: Changes in Average Resistance by 2030, 2040, and 2050

Region	Pathogen	2030	2040	2050
Eastern Europe	*Acinetobacter spp.*	0.13	0.13	0.13
	Enterococcus faecalis	0.23	0.24	0.25
	Enterococcus faecium	0.39	0.39	0.39
	Escherichia coli	-0.01	0.00	0.00
	Klebsiella pneumoniae	0.07	0.06	0.05
	Pseudomonas aeruginosa	0.08	0.08	0.08
	Streptococcus pneumoniae	-0.53	-0.55	-0.57
Northern Europe	*Acinetobacter spp.*	0.03	0.04	0.05
	Enterococcus faecalis	0.05	0.08	0.11
	Enterococcus faecium	0.19	0.19	0.19
	Escherichia coli	-0.04	-0.03	-0.01
	Klebsiella pneumoniae	0.11	0.07	0.03
	Pseudomonas aeruginosa	0.02	0.03	0.03
	Streptococcus pneumoniae	-0.13	-0.18	-0.24
Southern Europe	*Acinetobacter spp.*	0.06	0.09	0.12
	Enterococcus faecalis	0.11	0.17	0.23
	Enterococcus faecium	0.22	0.25	0.28
	Escherichia coli	-0.02	0.01	0.03
	Klebsiella pneumoniae	0.06	0.01	-0.03
	Pseudomonas aeruginosa	0.04	0.06	0.08
	Streptococcus pneumoniae	-0.25	-0.38	-0.51
Western Asia	*Acinetobacter spp.*	0.03	0.05	0.07
	Enterococcus faecalis	0.04	0.08	0.12
	Enterococcus faecium	0.29	0.30	0.31
	Escherichia coli	-0.08	-0.06	-0.04
	Klebsiella pneumoniae	0.21	0.17	0.13
	Pseudomonas aeruginosa	0.02	0.03	0.04
	Streptococcus pneumoniae	-0.11	-0.20	-0.28
Western Europe	*Acinetobacter spp.*	0.02	0.04	0.07
	Enterococcus faecalis	0.03	0.08	0.13
	Enterococcus faecium	0.17	0.19	0.20
	Escherichia coli	-0.05	-0.02	0.00
	Klebsiella pneumoniae	0.12	0.07	0.02
	Pseudomonas aeruginosa	0.01	0.03	0.04
	Streptococcus pneumoniae	-0.07	-0.18	-0.29

Source: Constructed by the Author.

[16] This observation should not be interpreted as a positive effect of demographic changes on health consequences.

4 CONCLUSION & POLICY IMPLICATIONS

4.1 Summary

Demographic change and AMR are two complex and interrelated challenges humanity is facing. Ensuring sustained demographic changes requires managing the effects of infectious diseases and AMR on the populations. As AMR is contributed by the suboptimal consumption of antimicrobials, primarily for healthcare and agriculture applications, sustained demographic changes are also likely to aggravate AMR and its already dire consequences on populations. Given the criticality of these linkages to developing policies to manage both challenges, this paper investigates the impact of demographic indicators on AMR.

Section 2 explained the data sources used to obtain antimicrobial consumption and resistance data and demographic variables. The antimicrobial consumption and resistance data covered the resistance of eight pathogens to 12 antimicrobial drugs in 30 countries from 2000 to 2020. It further explained the demographic indicators and data. The empirical estimation approach of penalized regressions coupled with machine learning was also introduced there.

Section 3 discussed the results from empirical estimations and projected the near-term variation in the resistance growth of different pathogens under ten demographic scenarios. The averaged results across the scenarios illustrated a wider heterogeneity in the responsiveness of AMR to different demographic scenarios, depending on the drivers of the scenarios, such as fertility, mortality, or migration. The responsiveness also varied for different antimicrobial drugs a given pathogen was resisting. Even though the different regions were exposed to demographic indicators somewhat similarly, the ultimate effect was determined both by the responsiveness of resistance to various demographic indicators and the exposure of the regions to those demographic indicators under the respective demographic scenarios.

4.2 Implications for Research

This paper has four main implications for AMR research. Firstly, it illustrates the importance of considering a wider group of factors when modeling resistance growth in addition to antimicrobial consumption. Specifically, this paper demonstrates the more substantial effects demographic indicators have on resistance, even compared to antimicrobial consumption, which is currently considered the primary driver of AMR. Fernando and McKibbin (2022) summarize several other factors, and Fernando (Forthcoming) discusses climate risks that should be considered when understanding the evolution of AMR.

Secondly, this paper highlights the importance of incorporating a broader range of demographic indicators to understand their contemporaneous effects on AMR. For example, even though population growth is widely believed to promote resistance growth, we illustrated that the contribution of population growth to resistance growth may change when controlled for other demographic indicators.

Thirdly, we emphasize the importance of preserving heterogeneity. Specifically, we observed the different responsiveness of antimicrobial drug-specific resistance compared to the average resistance of a pathogen to different demographic indicators. In our near-term projections under the demographic scenarios, we also illustrated how the resistance growth could differ across various regions, even though they faced similar demographic challenges.

Fourthly, we illustrate the potential of penalized regression coupled with machine learning to help reduce the limitations in conventional estimation techniques to handle high dimensionality and multicollinearity.

4.3 Implications for Policy

We identify three main policy implications arising from this paper. Firstly, it highlights the importance of perceiving global challenges from a systems perspective and appreciating the broad linkages between and within natural and socioeconomic systems. The quadripartite initiative on AMR, which brings together the Food and Agriculture Organization (FAO), the World Organization for Animal Health (OIE), and the United Nations Environment Program (UNEP), alongside the World Health Organization (WHO), recognizes the importance of addressing AMR within a one-health approach which acknowledges the interactions between the environment, plants, animals, and humans (WHO 2023b). As Fernando and McKibbin (Forthcoming) argue, via the illustration of the global economic impacts of AMR, the initiative should also be extended to include development institutions and other economic policy institutions, given the transboundary nature of AMR and its development, growth, and welfare consequences. The consequences of AMR are disproportionately felt by the fractions of the world, which are already struggling with poverty, poor institutions, and many other development challenges, including climate change and infectious diseases.

Secondly, we illustrate the importance of strengthening AMR surveillance and making AMR data widely available and accessible. Our ability to extend the study is constrained by the lack of consistent data from other developed countries and the lack of antimicrobial consumption and resistance observations from developing countries. With informal pharmaceutical markets, developing countries will continue aggravating AMR risks, which will spill over to the rest of the world, given its transboundary nature. Thus, developing their institutional capabilities, including those for AMR surveillance, and improving their health system resilience will be vital for taming AMR.

Thirdly, this paper reiterates various sources of uncertainty AMR (and also demographic trends) involves. These are primarily related to the pathways via which demographic indicators affect AMR, data availability, and the methodologies used to process and model the data to derive estimates. In this paper, we presented a comprehensive framework synthesizing the existing knowledge on how demographic trends could affect AMR to reduce uncertainty. Yet, research into factors affecting AMR within a broader one-health context should be expanded. Improved access to AMR and antimicrobial consumption data would be a vital enabler of such studies. Furthermore, studies em-

ploying a variety of methodologies should be accommodated and considered to navigate through methodological uncertainties.

4.4 Suggestions for Future Research

Future research could extend this paper to other parts of the world, particularly developing countries, incorporating additional antimicrobial drugs and pathogens, as far as the data warrants. Future studies could also incorporate additional demographic indicators, such as population composition and migration, and other factors (such as climate, health, sanitation, and socioeconomic and governance indicators) affecting AMR to measure their contemporaneous effects as well as persistent effects of all factors through dynamic estimations.

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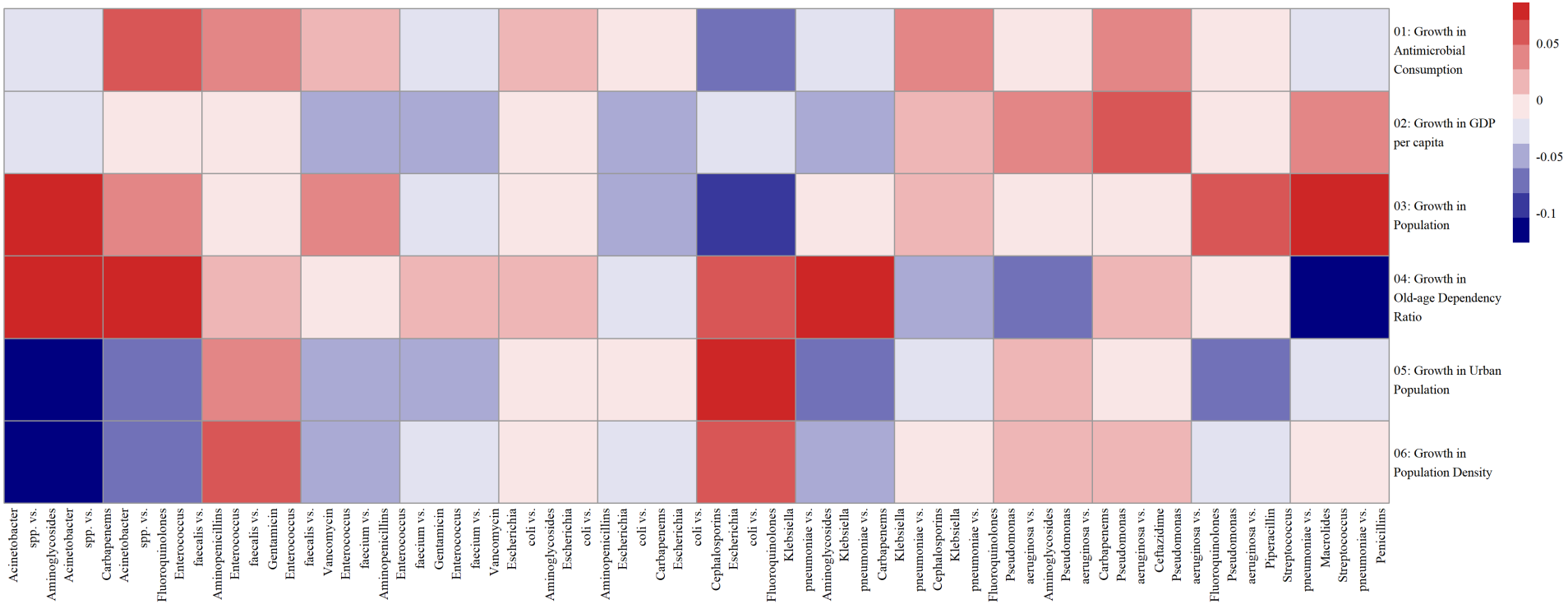
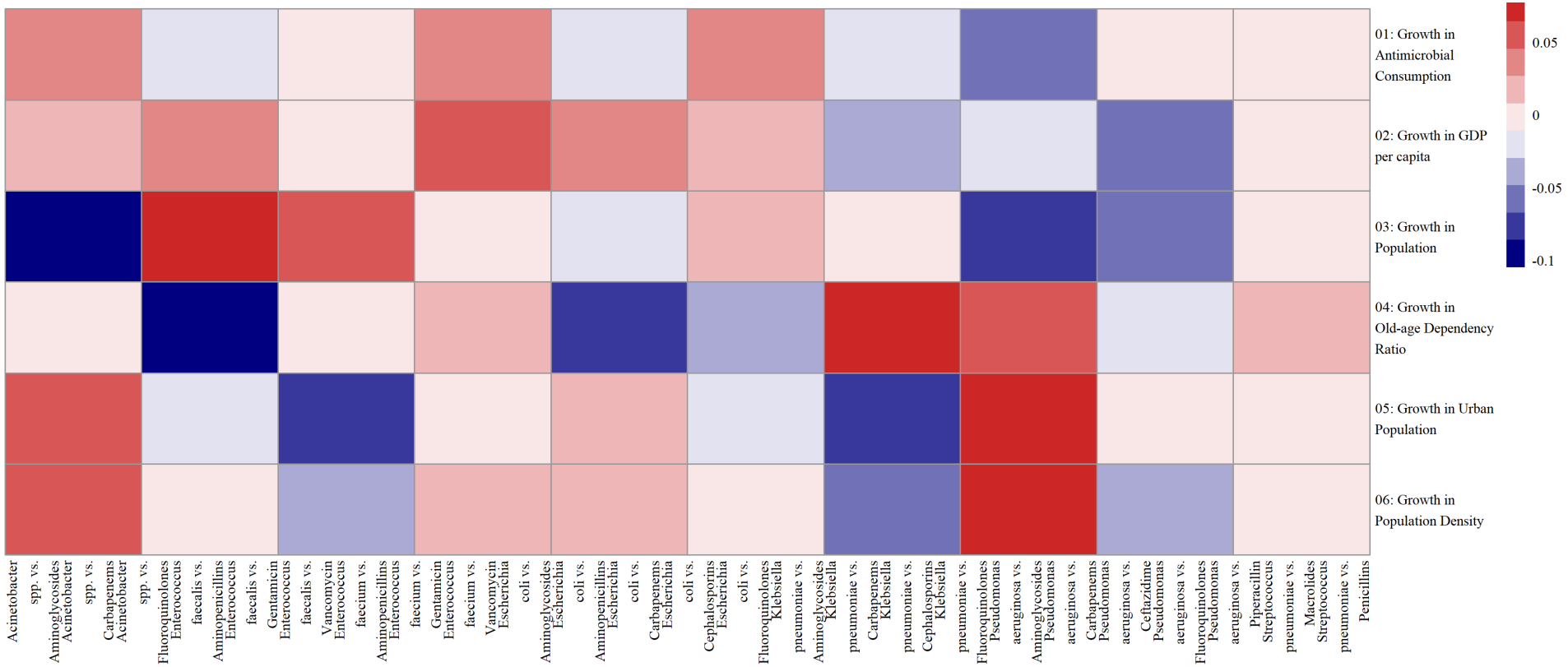
Figure 1: Association between Demographic Indicators and AMR



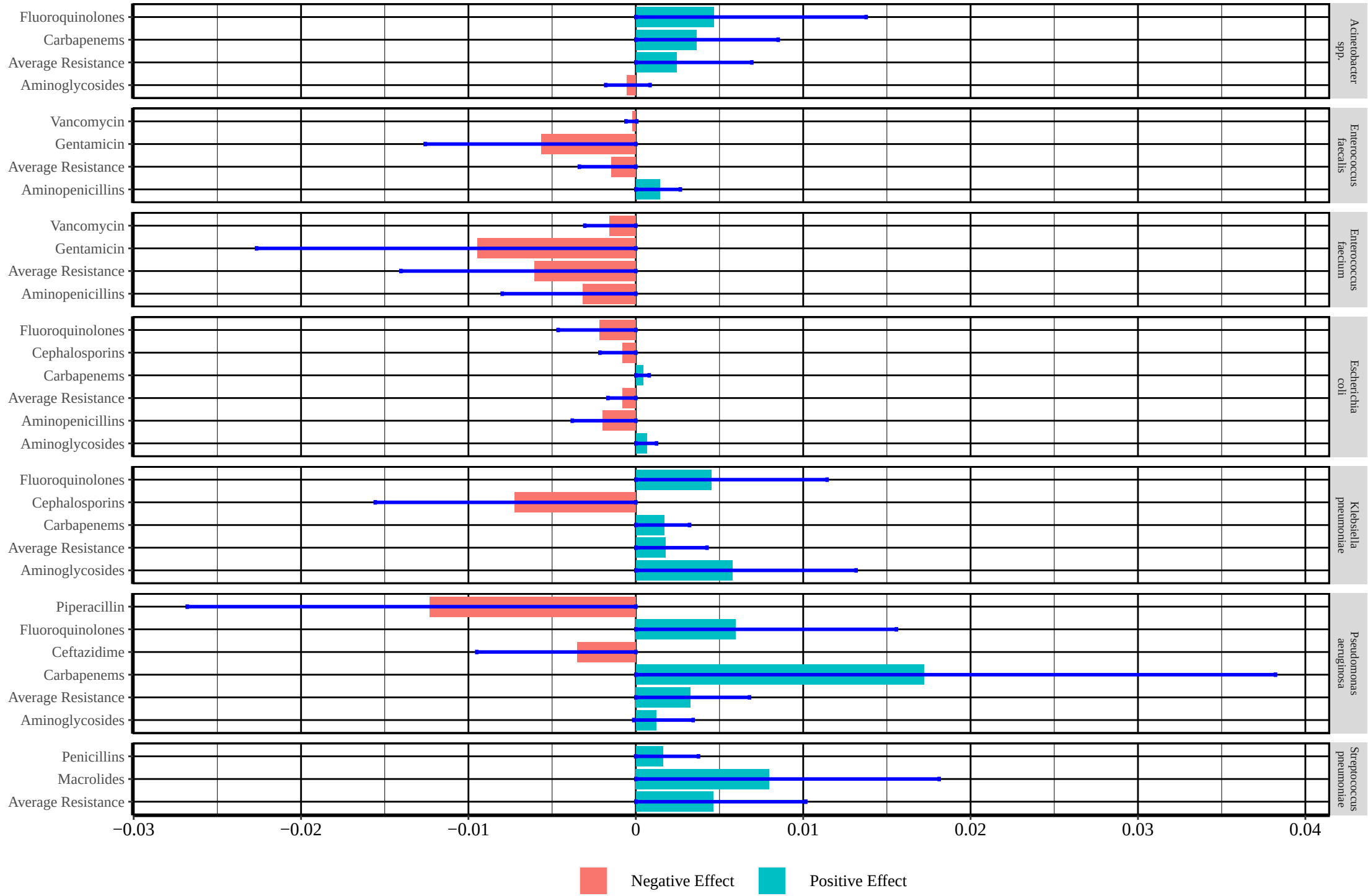
Source: Constructed by the Author.

Figure 1 (Contd.): Association between Demographic Indicators and AMR



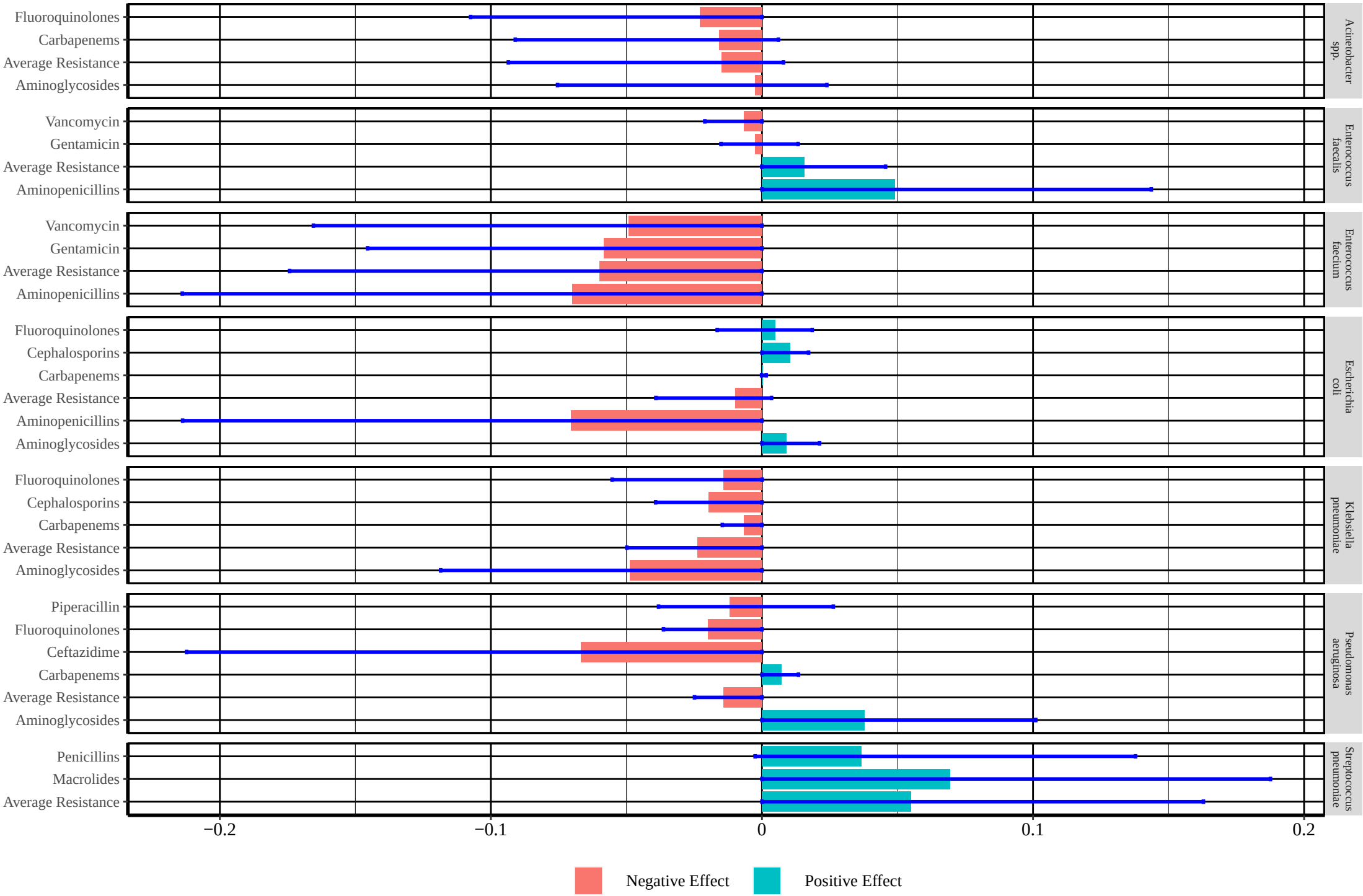
Source: Constructed by the Author.

Figure 02A: Average Responsiveness of AMR Percentage Growth from 2001 to 2020: Growth in Antimicrobial Consumption



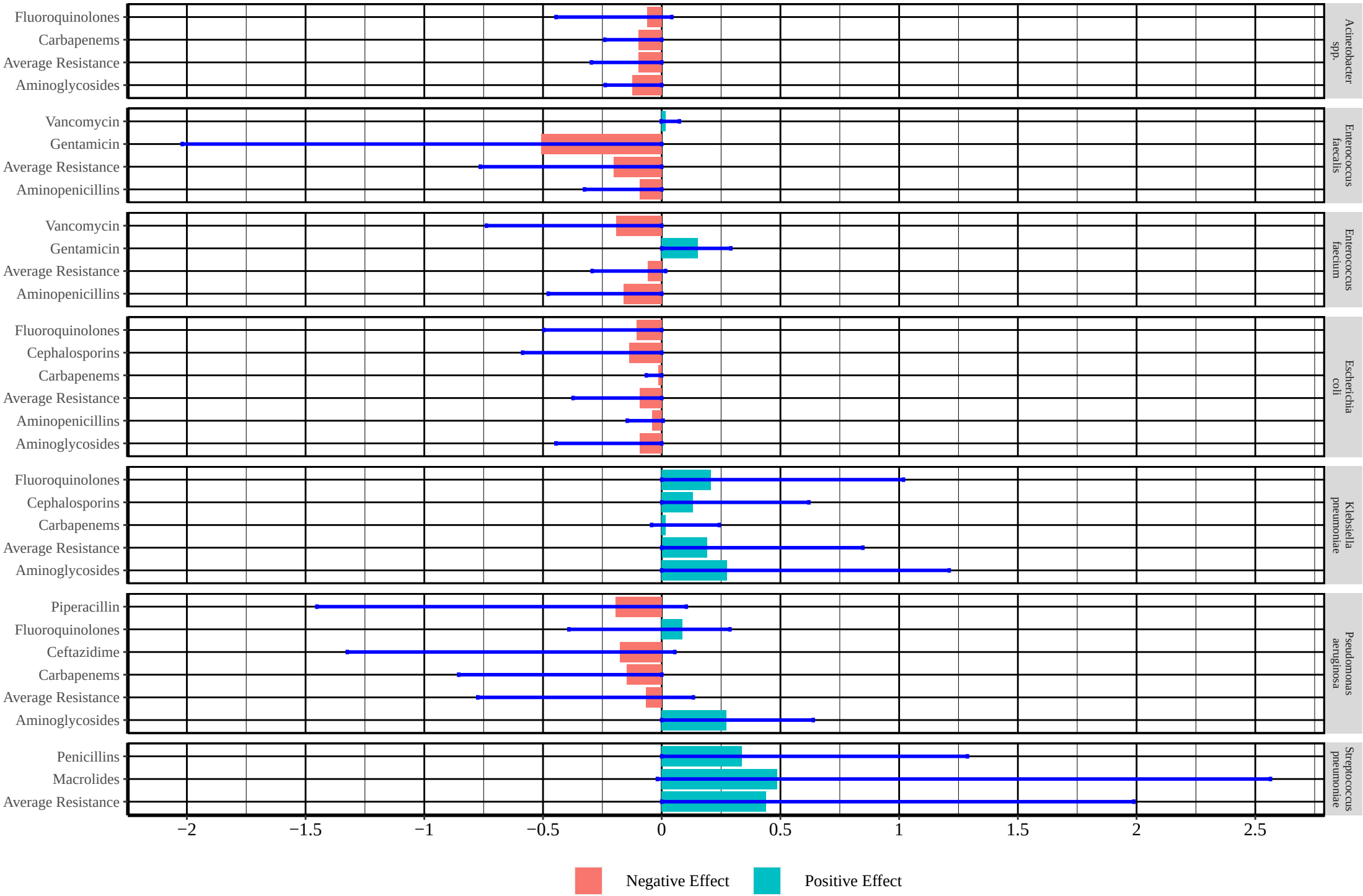
Source: Constructed by the Author.

Figure 02B: Average Responsiveness of AMR Percentage Growth from 2001 to 2020: Growth in GDP per capita



Source: Constructed by the Author.

Figure 02C: Average Responsiveness of AMR Percentage Growth from 2001 to 2020: Growth in Population



Source: Constructed by the Author.

Figure 02D: Average Responsiveness of AMR Percentage Growth from 2001 to 2020: Growth in Old−age Dependency Ratio

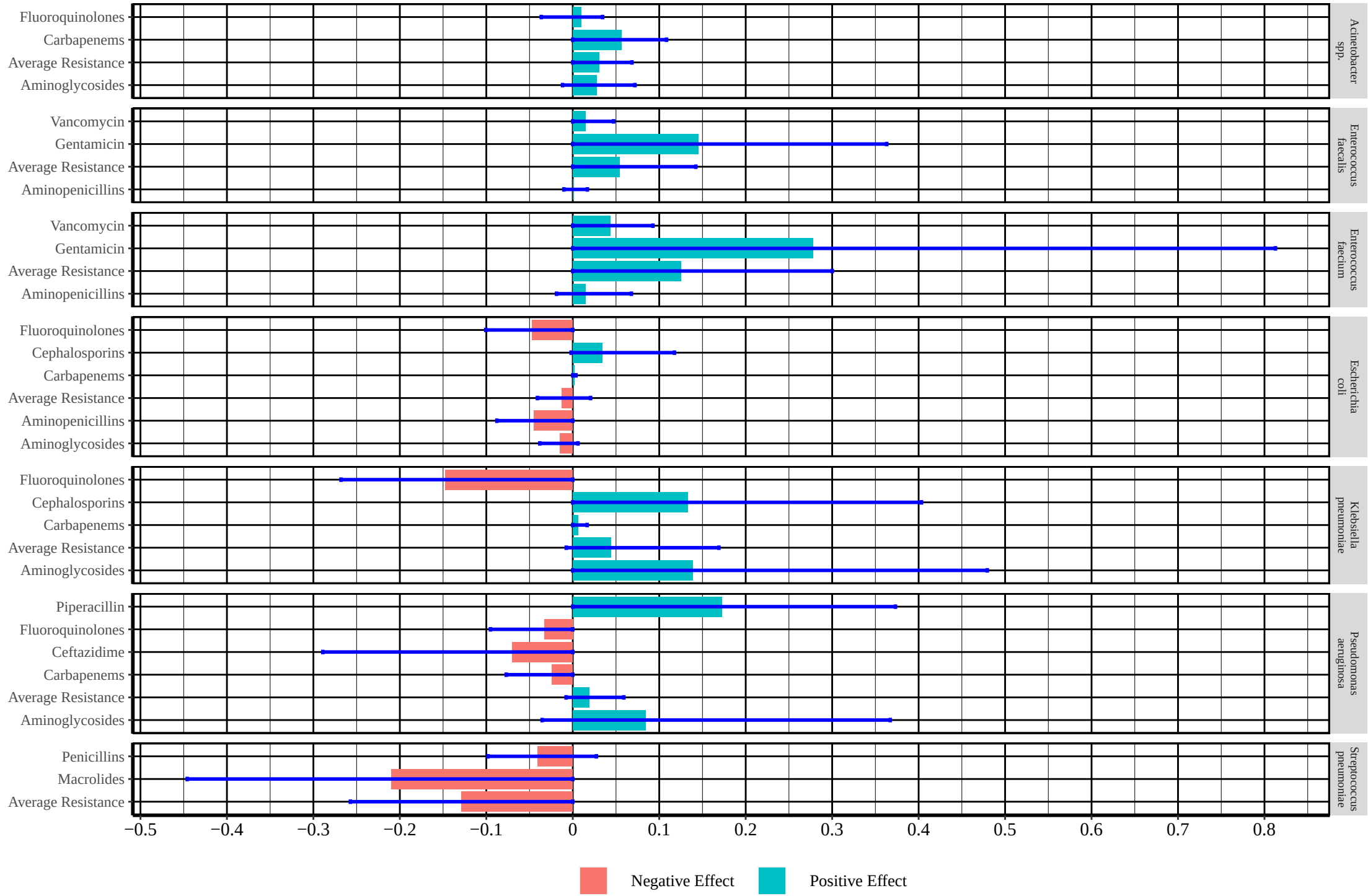


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Figure 02E: Average Responsiveness of AMR Percentage Growth from 2001 to 2020: Growth in Urban Population

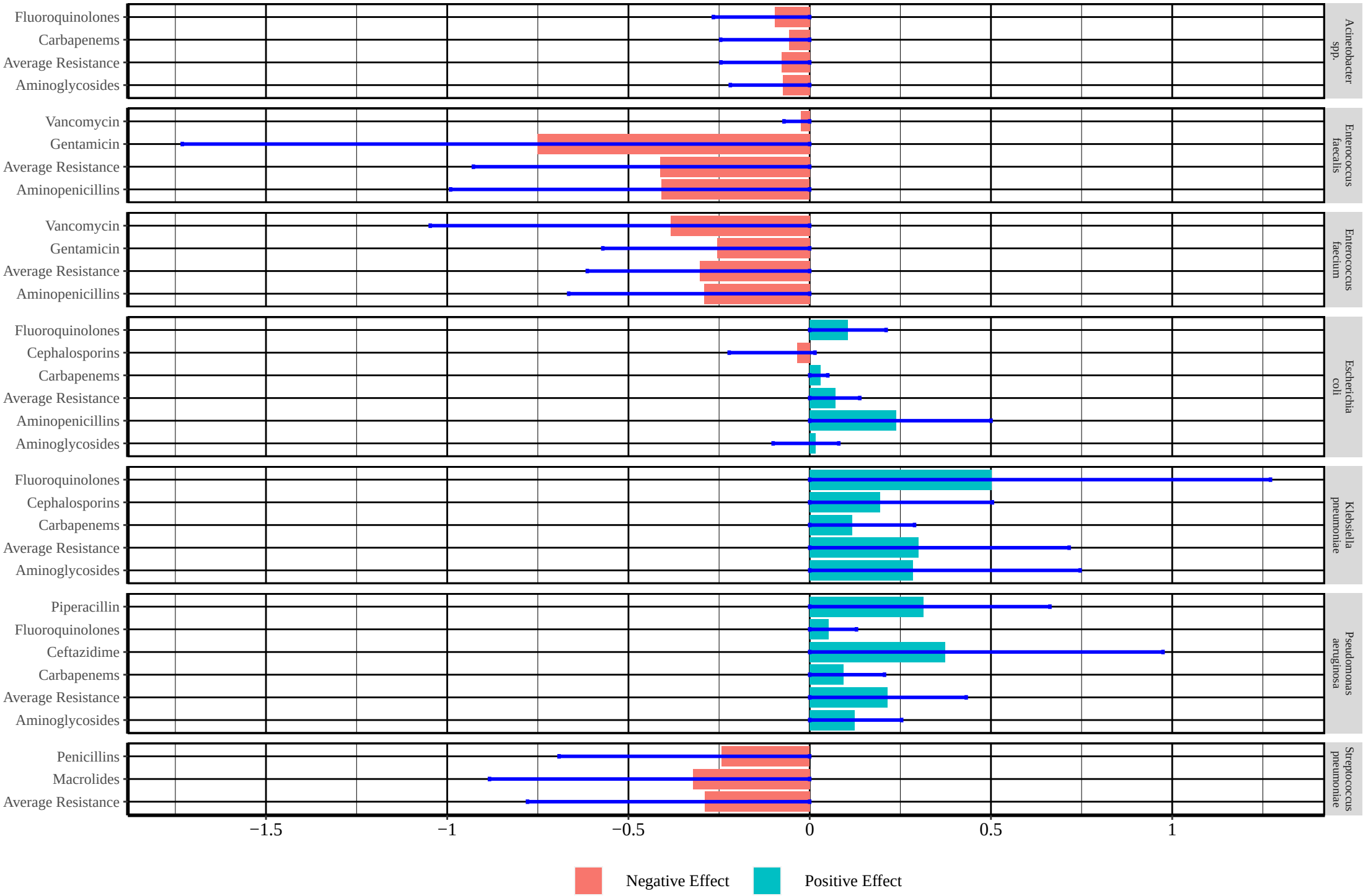

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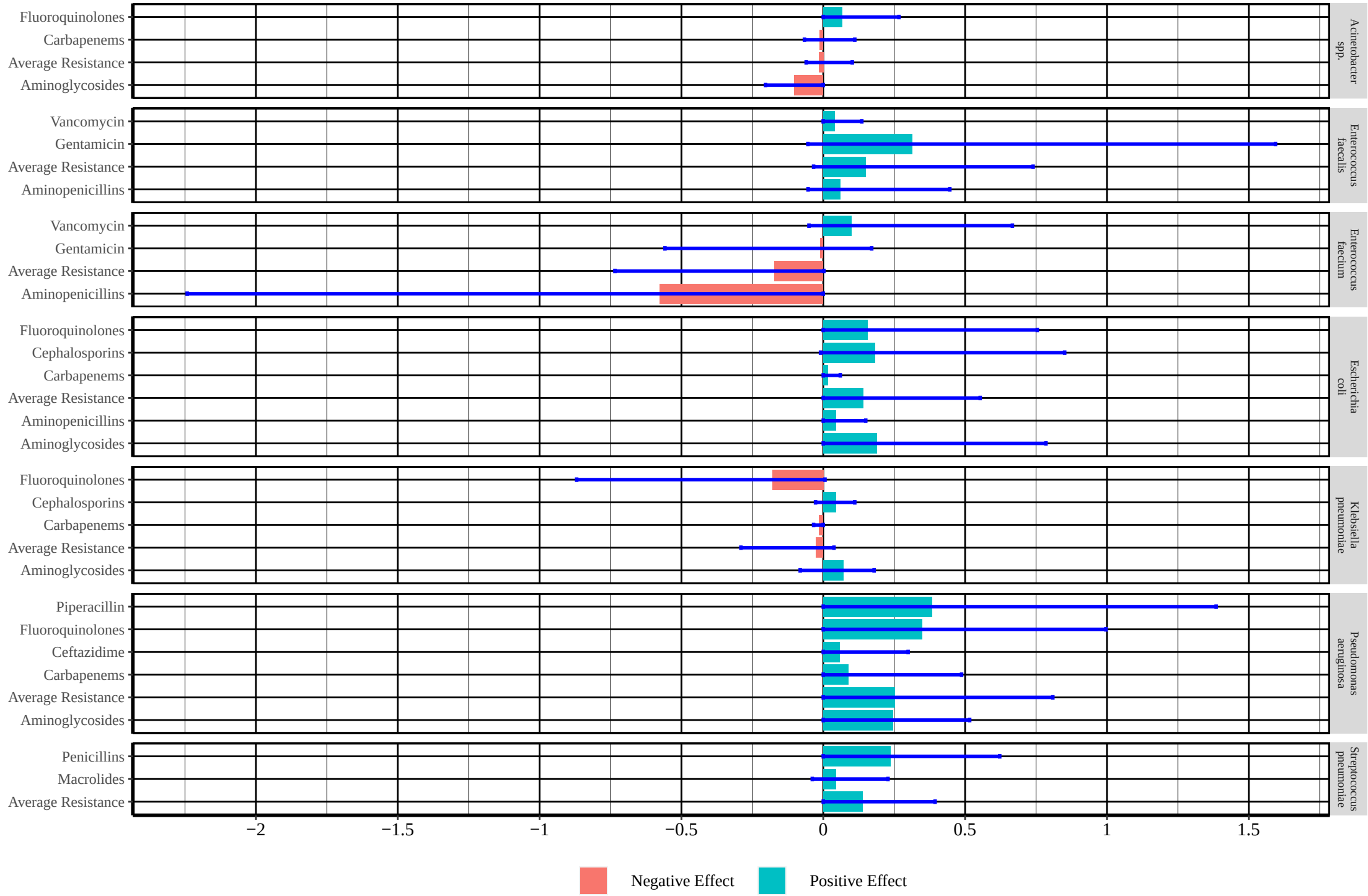
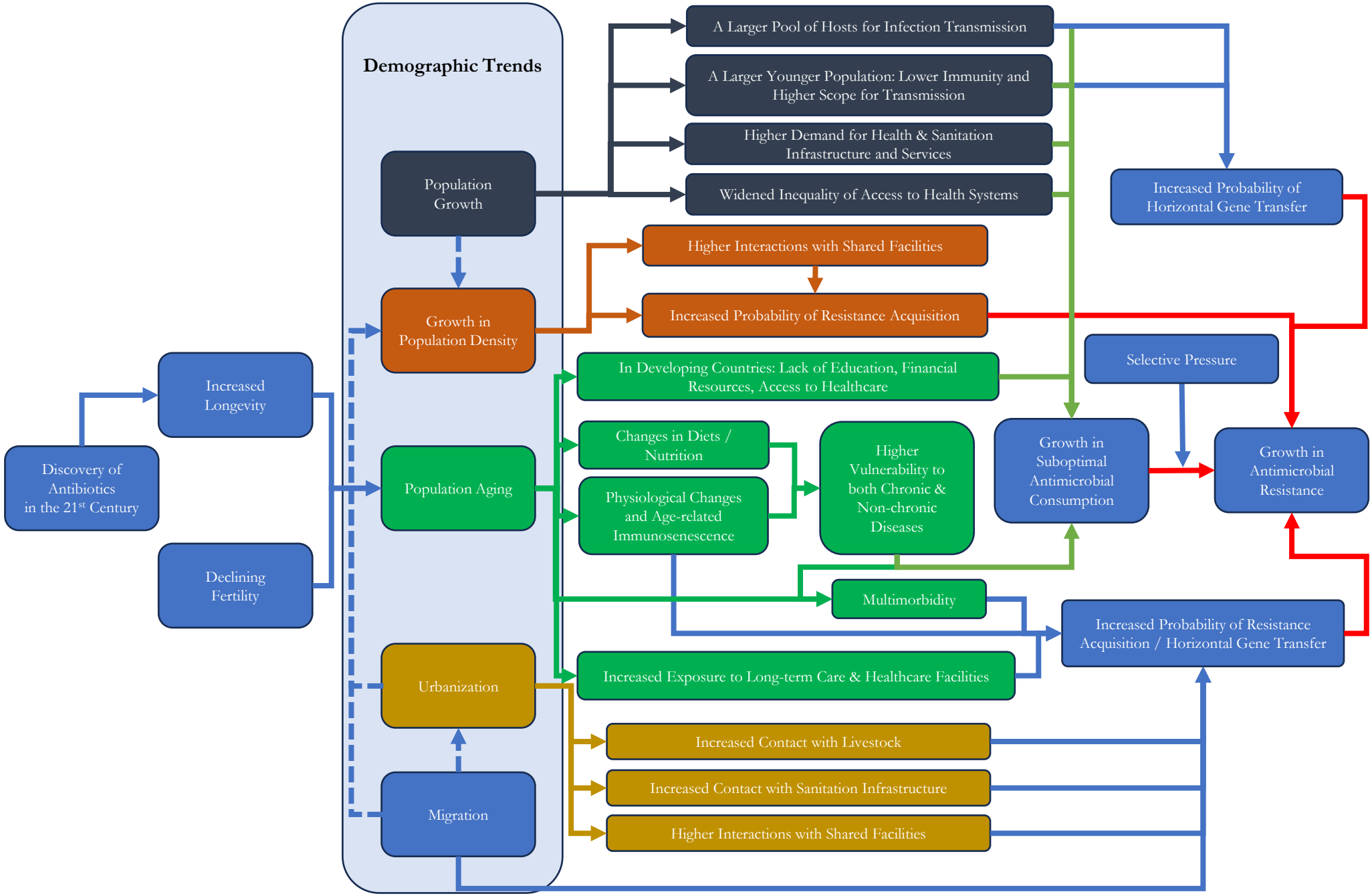
Figure 02F: Average Responsiveness of AMR Percentage Growth from 2001 to 2020: Growth in Population Density



Source: Constructed by the Author.

Figure 3: Linkages between Demographic Indicators and Antimicrobial Resistance



Source: Constructed by the Author.

IMPACT OF DEMOGRAPHIC TRENDS ON ANTIMICROBIAL RESISTANCE

Roshen Fernando

Centre for Applied Macroeconomic Analysis,
Crawford School of Public Policy, The Australian National University

SUPPLEMENTARY ANNEXURES

Supplementary Annexure 1: Countries Considered in the Study and their ISO Codes

	Name	ISO-3	ISO-2	UN Region
1	Austria	AUT	AT	Western Europe
2	Belgium	BEL	BE	Western Europe
3	Bulgaria	BGR	BG	Eastern Europe
4	Croatia	HRV	HR	Southern Europe
5	Cyprus	CYP	CY	Western Asia
6	Czechia	CZE	CZ	Eastern Europe
7	Denmark	DNK	DK	Northern Europe
8	Estonia	EST	EE	Northern Europe
9	Finland	FIN	FI	Northern Europe
10	France	FRA	FR	Western Europe
11	Germany	DEU	DE	Western Europe
12	Greece	GRC	GR	Southern Europe
13	Hungary	HUN	HU	Eastern Europe
14	Iceland	ISL	IS	Northern Europe
15	Ireland	IRL	IE	Northern Europe
16	Italy	ITA	IT	Southern Europe
17	Latvia	LVA	LV	Northern Europe
18	Lithuania	LTU	LT	Northern Europe
19	Luxembourg	LUX	LU	Western Europe
20	Malta	MLT	MT	Southern Europe
21	Netherlands	NLD	NL	Western Europe
22	Norway	NOR	NO	Northern Europe
23	Poland	POL	PL	Eastern Europe
24	Portugal	PRT	PT	Southern Europe
25	Romania	ROU	RO	Eastern Europe
26	Slovakia	SVK	SK	Eastern Europe
27	Slovenia	SVN	SI	Southern Europe
28	Spain	ESP	ES	Southern Europe
29	Sweden	SWE	SE	Northern Europe
30	United Kingdom	GBR	GB	Northern Europe

Source: Constructed by the Authors using data from ECDC (2022).

Supplementary Annexure 2: Antimicrobial Drug–Pathogen Combinations

	Pathogen	Drug
1	*Acinetobacter spp.*	Aminoglycosides
2	*Acinetobacter spp.*	Carbapenems
3	*Acinetobacter spp.*	Fluoroquinolones
4	*Enterococcus faecalis*	Aminopenicillins
5	*Enterococcus faecalis*	Gentamicin
6	*Enterococcus faecalis*	Vancomycin
7	*Enterococcus faecium*	Aminopenicillins
8	*Enterococcus faecium*	Gentamicin
9	*Enterococcus faecium*	Vancomycin
10	*Escherichia coli*	Aminoglycosides
11	*Escherichia coli*	Aminopenicillins
12	*Escherichia coli*	Carbapenems
13	*Escherichia coli*	Cephalosporins
14	*Escherichia coli*	Fluoroquinolones
15	*Klebsiella pneumoniae*	Aminoglycosides
16	*Klebsiella pneumoniae*	Carbapenems
17	*Klebsiella pneumoniae*	Cephalosporins
18	*Klebsiella pneumoniae*	Fluoroquinolones
19	*Pseudomonas aeruginosa*	Aminoglycosides
20	*Pseudomonas aeruginosa*	Carbapenems
21	*Pseudomonas aeruginosa*	Ceftazidime
22	*Pseudomonas aeruginosa*	Fluoroquinolones
23	*Pseudomonas aeruginosa*	Piperacillin
24	*Streptococcus pneumoniae*	Macrolides
25	*Streptococcus pneumoniae*	Penicillins

Source: Constructed by the Authors using data from ECDC (2022).

Supplementary Annexure 3: Descriptive Statistics on Antimicrobial Consumption

	Pathogen	Drug	Mean	SD	Min	Max
1	*Acinetobacter spp.*	Aminoglycosides	1.29	20.21	-99.45	93.75
2	*Acinetobacter spp.*	Carbapenems	1.88	21.49	-97.57	100.00
3	*Acinetobacter spp.*	Fluoroquinolones	-0.26	18.85	-99.64	80.00
4	*Enterococcus faecalis*	Aminopenicillins	-0.28	19.04	-99.61	100.00
5	*Enterococcus faecalis*	Gentamicin	-0.97	24.12	-99.84	100.00
6	*Enterococcus faecalis*	Vancomycin	0.35	23.93	-99.07	100.00
7	*Enterococcus faecium*	Aminopenicillins	-0.28	19.04	-99.61	100.00
8	*Enterococcus faecium*	Gentamicin	-0.97	24.12	-99.84	100.00
9	*Enterococcus faecium*	Vancomycin	0.35	23.93	-99.07	100.00
10	*Escherichia coli*	Aminoglycosides	1.66	20.46	-99.45	100.00
11	*Escherichia coli*	Aminopenicillins	-0.28	19.04	-99.61	100.00
12	*Escherichia coli*	Carbapenems	2.05	21.46	-97.57	100.00
13	*Escherichia coli*	Cephalosporins	0.04	17.90	-99.75	100.00
14	*Escherichia coli*	Fluoroquinolones	-0.18	18.06	-99.64	80.00
15	*Klebsiella pneumoniae*	Aminoglycosides	1.66	20.46	-99.45	100.00
16	*Klebsiella pneumoniae*	Carbapenems	2.05	21.46	-97.57	100.00
17	*Klebsiella pneumoniae*	Cephalosporins	0.04	17.90	-99.75	100.00
18	*Klebsiella pneumoniae*	Fluoroquinolones	-0.18	18.06	-99.64	80.00
19	*Pseudomonas aeruginosa*	Aminoglycosides	1.66	20.46	-99.45	100.00
20	*Pseudomonas aeruginosa*	Carbapenems	2.05	21.46	-97.57	100.00
21	*Pseudomonas aeruginosa*	Ceftazidime	0.79	23.58	-99.92	100.00
22	*Pseudomonas aeruginosa*	Fluoroquinolones	-0.18	18.06	-99.64	80.00
23	*Pseudomonas aeruginosa*	Piperacillin	-0.58	14.70	-99.90	100.00
24	*Streptococcus pneumoniae*	Macrolides	-0.88	16.57	-99.80	81.25
25	*Streptococcus pneumoniae*	Penicillins	-0.17	17.20	-99.66	82.14

Source: Constructed by the Authors using data from ECDC (2022).

Supplementary Annexure 4: Descriptive Statistics on Antimicrobial Resistance

	Pathogen	Drug	Mean	SD	Min	Max
1	*Acinetobacter spp.*	Aminoglycosides	-0.13	5.55	-21.15	22.88
2	*Acinetobacter spp.*	Carbapenems	-0.24	5.32	-31.82	22.08
3	*Acinetobacter spp.*	Fluoroquinolones	-0.42	4.97	-22.75	27.73
4	*Enterococcus faecalis*	Aminopenicillins	0.09	4.63	-26.43	32.25
5	*Enterococcus faecalis*	Gentamicin	-0.55	8.84	-42.27	50.00
6	*Enterococcus faecalis*	Vancomycin	0.02	2.00	-21.97	31.09
7	*Enterococcus faecium*	Aminopenicillins	1.03	9.14	-37.87	39.29
8	*Enterococcus faecium*	Gentamicin	0.38	12.03	-49.23	59.71
9	*Enterococcus faecium*	Vancomycin	0.72	5.61	-27.65	46.60
10	*Escherichia coli*	Aminoglycosides	0.40	2.91	-13.42	25.19
11	*Escherichia coli*	Aminopenicillins	0.45	4.38	-23.34	23.91
12	*Escherichia coli*	Carbapenems	0.00	0.42	-3.03	3.03
13	*Escherichia coli*	Cephalosporins	0.68	2.91	-16.43	24.36
14	*Escherichia coli*	Fluoroquinolones	0.75	3.51	-19.87	32.16
15	*Klebsiella pneumoniae*	Aminoglycosides	0.07	5.66	-20.89	29.06
16	*Klebsiella pneumoniae*	Carbapenems	0.52	2.40	-8.98	19.07
17	*Klebsiella pneumoniae*	Cephalosporins	0.45	6.10	-27.94	30.33
18	*Klebsiella pneumoniae*	Fluoroquinolones	1.29	5.90	-29.26	28.45
19	*Pseudomonas aeruginosa*	Aminoglycosides	-0.60	5.92	-26.67	25.00
20	*Pseudomonas aeruginosa*	Carbapenems	0.17	6.44	-32.86	33.75
21	*Pseudomonas aeruginosa*	Ceftazidime	-0.03	7.38	-32.12	33.12
22	*Pseudomonas aeruginosa*	Fluoroquinolones	-0.65	6.55	-33.69	32.95
23	*Pseudomonas aeruginosa*	Piperacillin	-0.26	6.16	-34.13	36.38
24	*Streptococcus pneumoniae*	Macrolides	0.08	6.80	-37.47	27.60
25	*Streptococcus pneumoniae*	Penicillins	-0.36	6.82	-45.45	31.62

Source: Constructed by the Authors using data from ECDC (2022).

Supplementary Annexure 5: Historical Variation of Antimicrobial Consumption

The online dashboard presents the historical antimicrobial consumption growth variation in the 30 countries this paper focuses on from 2000 to 2020, aggregated for the 12 ATC-4 drug classes and five UN regions. For better presentation and interpretation of the consumption trends, the growth rates have been normalized relative to 2000. Accordingly, a five percent consumption growth rate in a given region should be interpreted as seven percent if the consumption growth rate in that particular region was two percent in 2000. The consumption trends are discussed by ATC-3 drug classes: J01C, J01D, J01F, J01G, J01M, and J01X.

J01C refers to Beta-lactam Antibacterials and Penicillins. J01C encompasses Penicillins with Extended-spectrum (J01CA), Beta-lactamase Sensitive Penicillins (J01CE), Beta-lactamase Resistant Penicillins (J01CF), Beta-lactamase Inhibitors (J01CG), and Combinations of Penicillins, including Beta-lactamase Inhibitors (J01CR). Consumption growth increased in almost all the regions for most of these drugs, except for J01CA. Southern Europe recorded the highest growth among all the regions, except for J01CA, where all the regions had minimal consumption growth changes. Western Europe experienced minimal consumption growth changes across all the drugs, except for J01CF, where the consumption growth almost gained a ten percentage point increase by 2020, compared to 2000. Northern Europe experienced minimal consumption growth changes across all the drugs.

J01D refers to Other Beta-lactam Antibacterials, which mainly include Cephalosporins (J01DB, J01DC, J01DD, and J01DE), Monobactams (J01DF), and Carbapenems (J01DH). Out of these, ECDC data covers J01DD (Third generation Cephalosporins) and J01DH. Eastern Europe experienced an increasing consumption growth of Cephalosporins (J01DD), which reached an increase of about ten percentage points by 2020 compared to 2000. All other regions experienced minimal consumption growth changes compared to 2000. In contrast, all the regions, except Northern Europe, experienced an increasing consumption growth of carbapenems (J01H). Similar to Cephalosporins, Eastern Europe dominated the consumption growth trends, and other regions experienced moderate movements, reaching a 5 to 10 percentage point increase in consumption growth by 2020 compared to 2000.

J01F encompasses Macrolides, Lincosamides, and Streptogramins. ECDC data includes consumption data for J01FA, which refers to Macrolides. All the regions experienced minimal consumption growth changes in Macrolides compared to 2000.

J01G constitutes of Streptomycins (J01GA) and Other Aminoglycosides (J01GB), data for both of which is available from ECDC. Most regions experienced minimal consumption growth changes in Streptomycins compared to 2000. Notably, Eastern Europe experienced a decreasing consumption growth, reaching almost a five percentage point reduction compared to 2000 by 2020. All the regions, except Eastern Europe and Western Asia, experienced minimal consumption growth changes in Other Aminoglycosides. Eastern

Europe and Western Asia reached about a ten percentage point increase in consumption growth by 2020, compared to 2000.

J01M includes Quinolone Antibacterials: Fluoroquinolones (J01MA) and Other Quinolones (J01MB). ECDC data is available for J01MA. Consumption of Fluoroquinolones was similar to Other Aminoglycosides (J01GB), where Eastern Europe and Western Asia experienced the highest consumption growth, while the other regions experienced minimal consumption growth changes compared to 2000.

J01X refers to Antibacterials not covered in other classes, i.e., J01A-G, M, and R. J01X includes Glycopeptide Antibacterials (J01XA), which ECDC data covers. All the regions experienced consumption growth in J01XA, except Northern Europe. Southern Europe experienced almost a 13 percentage point increase in consumption growth compared to 2000. Consumption in other regions grew steadily to reach increments between 9 to 12 percentage points by 2020, compared to 2000.

Overall, we observe that the consumption growth patterns were quite heterogeneous across the regions and the drug classes from 2000 to 2020. Eastern and Southern Europe experienced consumption growth increases, compared to 2000, across most of the drug classes, while Northern Europe experienced the least consumption growth variation.

Supplementary Annexure 6: Historical Variation of Antimicrobial Resistance

The online dashboard presents the historical antimicrobial resistance growth variations in the 30 countries this paper focuses on, aggregated for five UN regions, from 2000 to 2020. The variations cover the resistance of eight pathogens to 12 antimicrobial drugs, totaling 26 antimicrobial drug-pathogen combinations. Similar to antimicrobial consumption growth variations, the resistance growth rates have been normalized to those of 2000 for better presentation and interpretation of the resistance trends.

Acinetobacter spp. mostly cause respiratory diseases, which include bronchiolitis and pneumoniae (especially within healthcare settings). They also cause wound infections, suppurative infections in the lungs, skin, soft tissues, and urinary tract, and rarely meningitis (MSD Manuals 2020a). The data for the resistance growth of *Acinetobacter spp.* towards Aminoglycosides, Carbapenems, and Fluoroquinolones is available. The resistance growth of *Acinetobacter spp.* notably increased in Western Asia across all the drugs, except for Aminoglycosides, where the resistance growth decreased in Western Asia compared to 2000. Western Europe also experienced an increasing resistance growth across all the drugs. The other regions experienced minimal resistance growth changes compared to their respective resistance growth rates in 2000.

Enterococcus faecalis and *Enterococcus faecium* commonly cause skin and wound infections, endocarditis, bacteremia, intra-abdominal infections, and urinary tract infections (MSD Manuals 2020b). Resistance growth variations of *Enterococcus faecalis* to Aminopenicillins, Gentamicin, and Vancomycin were relatively lower than their respective resistance growth in 2000 and other antimicrobial drug-pathogen combinations. Yet, their variations were diverse across the regions and drugs. While the resistance growth of *Enterococcus faecalis* and *Enterococcus faecium* against Gentamicin increased in Western Asia, it decreased in Southern Europe compared to 2000. While Southern Europe also experienced a decreasing resistance growth from both the pathogens against Vancomycin, Western Asia experienced an increasing resistance growth from *Enterococcus faecium*. For Aminopenicillins, Eastern Europe experienced a decreasing resistance growth from both pathogens, while Western Asia experienced an increasing resistance growth from *Enterococcus faecium*. Other regions demonstrated minimal resistance growth changes, compared to 2000, across all the drugs.

Escherichia coli mainly causes diarrheal infections, urinary tract infections, wound infections, and bacteremia (MSD Manuals 2020c). The data for its resistance growth variations towards Aminoglycosides, Aminopenicillins, Carbapenems, Fluoroquinolones, and Third generation Cephalosporins is available. Overall, the resistance growth minimally changed for Carbapenems across all the regions. Resistance growth towards Aminopenicillins, Cephalosporins, and Fluoroquinolones notably increased in Western Asia, which exceeded a three percentage point increase in growth compared to 2000. Resistance growth decreased against Aminopenicillins and Fluoroquinolones in several regions compared to 2000. Eastern and Southern Europe experienced the highest resistance growth declines for Aminopenicillins, while Southern and Western Europe experienced the highest declines for Fluoroquinolones.

Klebsiella pneumoniae causes pneumoniae (especially in healthcare settings), urinary tract infections, wound infections, and various bloodstream infections (MSD Manuals 2020d). The data for its resistance growth variations towards Aminoglycosides, Carbapenems, Fluoroquinolones, and Third-generation Cephalosporins is available. The resistance growth changes were minimal for Carbapenems and Cephalosporins. At the same time, the regions illustrated mixed patterns for Fluoroquinolones, where Eastern and Western Europe experienced increasing resistance growth, and Northern Europe and Western Asia experienced decreasing resistance growth. Notably, in Western Asia, the resistance growth against Fluoroquinolones decreased by six percentage points compared to 2000.

Pseudomonas aeruginosa is responsible for malignant external otitis and most hospital-acquired infections. It also causes urinary tract infections, skin and soft-tissue infections, ear infections, and bacteremia (MSD Manuals 2020e). The data for its resistance growth variations towards Aminoglycosides, Carbapenems, Ceftazidime, Fluoroquinolones, and Piperacillin Tazobactam is available. The resistance growth against Carbapenems did not change noticeably in any regions. The resistance growth against Ceftazidime increased in Western Asia and decreased in Southern Europe. Several regions experienced decreases in resistance growth against Aminoglycosides, with Western Asia reaching a 15 percentage point decrease by 2020 compared to 2000. The resistance growth against Piperacillin Tazobactam decreased in Southern Europe and Western Asia, while the resistance growth against Fluoroquinolones decreased in Western Europe.

Staphylococcus aureus mainly causes complex skin infections (MSD Manuals 2020f). The data for its resistance growth variations against Methicillin is available. All the regions did not experience any resistance growth changes, compared to their respective growth in 2000.

Streptococcus pneumoniae mainly causes pneumoniae (both within the community and healthcare settings), sinusitis, meningitis, bacterial conjunctivitis, and skin infections (MSD Manuals 2020g). The data for its resistance growth variations against Macrolides and Penicillins is available. The resistant growth against Macrolides and Penicillins did not noticeably change from its growth in 2000 across all the regions except Western Asia, where it experienced a decreasing resistance growth against both Macrolides and Penicillins.

Similar to antimicrobial consumption growth variations, the resistance growth against different drug classes illustrated quite heterogeneous patterns across the regions from 2000 to 2020. Eastern and Southern Europe and Western Asia generally experienced notable resistance growth changes compared to 2000. Similar to antimicrobial consumption growth patterns, Northern Europe experienced minimal resistance growth changes compared to its resistance growth in 2000.

Supplementary Annexure 7: Historical Variation in Demographic Indicators

The online dashboard presents the historical variation in demographic indicators in the 30 countries this paper focuses on, aggregated for five UN regions, from 2000 to 2020. Population growth remained constant in all the regions, except for Northern and Western Europe, where the population growth mildly increased between 2000 and 2020. The growth in the old-age dependency ratio, in contrast, increased notably across all regions except for Southern Europe, where it remained almost constant throughout the period. Eastern Europe observed the highest growth, reaching nearly a four percent growth in the old-age dependency ratio by 2020. Growth in population density and urban population remained constant from 2000 to 2020 across most regions. However, while Western Europe experienced a decline in population density growth, Eastern Europe experienced an increase in proportional urban population growth. Overall, population aging is the only demographic indicator that considerably varied across most regions.

Supplementary Annexure 8: Regularized Regression Methods

Linear regression and its variants are widely used in estimating the empirical relationships between variables. Linear regression, in general, attempts to find the magnitudes of the coefficients that minimize the residual error between the actual observations and their predicted counterparts. The general representation of a linear regression model is presented in Equation 1, and the objective function is presented in Equation 2[1].

Equation 1: General Form of a Linear Regression Model

$$Y_i = \beta_0 + \sum_{j=1}^{n} \beta_j X_{ij} + \varepsilon$$

Equation 2: Objective Function of a Linear Regression Problem

$$\text{argmin}\left(\sum_{i=1}^{N} (Y_i - \widehat{Y}_i)^2 = \sum_{i=1}^{N}\left[Y_i - \beta_0 - \sum_{j=1}^{n} \beta_j X_{ij}\right]^2\right)$$

However, when using linear regression models for predictions, two significant problems could occur: overfitting and underfitting. Overfitting happens when the regression model performs well on the training data but poorly on the testing data. Underfitting occurs when the regression model does not perform well on either data. Regularization prevents overfitting in regression models without changing the number of features or predictor variables. LASSO (Least Absolute Shrinkage and Selection Operator) and Ridge are two widely used regularization algorithms. The objective functions of LASSO and Ridge are presented in Equations 3 and 4[2].

Equation 3: Objective Function of a LASSO Regression Problem

$$\text{argmin}\left(\sum_{i=1}^{N}\left[Y_i - \beta_0 - \sum_{j=1}^{n} \beta_j X_{ij}\right]^2 + \alpha \sum_{j=1}^{n} |\beta_j|\right)$$

Equation 4: Objective Function of a Ridge Regression Problem

$$\text{argmin}\left(\sum_{i=1}^{N}\left[Y_i - \beta_0 - \sum_{j=1}^{n} \beta_j X_{ij}\right]^2 + \alpha \sum_{j=1}^{n} {\beta_j}^2\right)$$

[1] The notation in the equations follows the standard interpretation of an OLS regression problem, where Y_i is the dependent variable and X_{ij} is an independent variable with β_j as its coefficient. β_0 is the intercept of the regression equation.

[2] The notation in the equations follows the standard interpretation of an OLS regression problem, where Y_i is the dependent variable and X_{ij} is an independent variable with β_j as its coefficient. β_0 is the intercept of the regression equation, and α is the regularization parameter.

As illustrated in Equations 3 and 4, both LASSO and Ridge regressions start with the conventional objective function of linear regression and impose a non-negative penalty on the coefficients of the predictors. The penalty prevents the coefficients from being too large when optimizing the conventional objective function. The penalty in LASSO regression works with the linear summation of coefficients and, thus, could shrink some coefficients to zero. However, Ridge regression works with the squared summation of the coefficients and does not necessarily reduce the coefficients to zero. This characteristic qualifies LASSO as a feature selection algorithm that could identify the optimum set of predictors from a large group of predictors.

The two algorithms also behave differently when there are correlated predictors. While LASSO would shrink some of the coefficients of correlated variables to zero, Ridge regression would treat all the correlated variables the same. Given these differences across LASSO and Ridge, a generalized form of regularized regression combining both approaches could also be used. Equation 5[3] presents the objective function of the generalized form[4].

Equation 5: Objective Function of a General Regularized Regression Problem

$$\text{argmin}\left(\sum_{i=1}^{N}\left[Y_i - \beta_0 - \sum_{j=1}^{n}\beta_j X_{ij}\right]^2 + \alpha\sum_{j=1}^{n}\left((1-\theta)\,{\beta_j}^2 + \theta\,|\beta_j|\right)\right)$$

[3] The notation in the equations follows the standard interpretation of an OLS regression problem, where Y_i is the dependent variable and X_{ij} is an independent variable with β_j as its coefficient. β_0 is the intercept of the regression equation, α is the regularization parameter, and θ is the weight.

[4] See Hastie et al. (2017) for a detailed discussion on linear, LASSO, and Ridge regression models.

Supplementary Annexure 9: Diagnostics for Empirical Models

Pathogen	Drug	Lambda	Variance	Bias	MSE	F Statistic	R-Squared	Adjusted R-Squared	DF	Residual Effective DF	Effective-ness Index	AIC	BIC
		0.00	2676.03	0.00	2676.03	6.54	0.41	0.35	49.99	470.00	4213.08	1607.07	5071.70
		0.11	900.41	270.19	1170.60	6.52	0.33	0.26	42.60	472.43	6.61	1596.58	5029.77
		0.22	671.26	533.00	1204.26	6.45	0.28	0.20	38.37	474.30	3.80	1596.41	5011.63
		0.33	550.37	786.57	1336.94	6.35	0.24	0.16	35.09	476.04	2.73	1599.72	5000.98
Acinetobacter spp.	Aminogly-cosides	0.44	468.24	1030.33	1498.57	6.24	0.21	0.12	32.39	477.71	2.17	1604.70	4994.47
		0.56	406.79	1262.67	1669.46	6.14	0.18	0.09	30.11	479.33	1.82	1610.45	4990.50
		0.67	358.44	1482.62	1841.06	6.04	0.16	0.07	28.14	480.86	1.59	1616.48	4988.16
		0.78	319.19	1689.91	2009.10	5.95	0.14	0.05	26.42	482.33	1.42	1622.52	4986.91
		0.89	286.62	1884.71	2171.33	5.87	0.13	0.03	24.91	483.71	1.29	1628.42	4986.37
		1.00	259.15	2067.52	2326.67	5.79	0.11	0.02	23.57	485.01	1.19	1634.09	4986.33
		0.00	2184.68	0.00	2184.68	8.12	0.46	0.40	50.99	489.00	4513.65	1574.28	5190.55
		0.11	773.67	222.81	996.48	8.08	0.37	0.31	43.56	491.37	6.38	1564.52	5148.89
		0.22	580.26	462.57	1042.83	7.96	0.31	0.24	39.24	493.27	3.51	1566.20	5132.04
		0.33	477.99	707.96	1185.94	7.80	0.26	0.19	35.88	495.04	2.45	1571.98	5123.41
Acinetobacter spp.	Car-bapenems	0.44	408.51	952.47	1360.98	7.64	0.23	0.15	33.11	496.76	1.90	1579.67	5119.22
		0.56	356.47	1190.84	1547.31	7.48	0.20	0.11	30.77	498.41	1.56	1588.13	5117.64
		0.67	315.42	1419.91	1735.33	7.33	0.17	0.09	28.76	499.98	1.34	1596.77	5117.64
		0.78	281.99	1638.02	1920.00	7.19	0.15	0.06	27.00	501.48	1.19	1605.27	5118.60
		0.89	254.13	1844.52	2098.65	7.06	0.14	0.05	25.46	502.89	1.07	1613.44	5120.13
		1.00	230.54	2039.36	2269.90	6.94	0.12	0.03	24.08	504.23	0.98	1621.21	5122.00
		0.00	2144.42	0.17	2144.59	6.51	0.41	0.35	49.99	470.00	40.35	1492.28	4956.90
		0.11	768.24	13311.02	14079.26	6.10	0.28	0.20	42.60	472.43	0.11	1514.08	4947.28
		0.22	582.01	17584.72	18166.73	5.93	0.23	0.15	38.38	474.30	0.09	1522.23	4937.47
		0.33	479.28	19566.77	20046.05	5.82	0.19	0.11	35.09	476.04	0.09	1527.78	4929.06
Acinetobacter spp.	Fluoroquin-olones	0.44	407.91	20749.05	21156.96	5.72	0.16	0.08	32.39	477.71	0.09	1532.94	4922.72
		0.56	353.91	21557.86	21911.78	5.64	0.14	0.05	30.11	479.32	0.09	1538.01	4918.07
		0.67	311.21	22159.91	22471.12	5.56	0.12	0.03	28.14	480.86	0.09	1542.97	4914.66
		0.78	276.47	22633.82	22910.29	5.49	0.11	0.02	26.42	482.32	0.08	1547.77	4912.16
		0.89	247.65	23021.63	23269.28	5.42	0.10	0.00	24.91	483.70	0.08	1552.37	4910.33
		1.00	223.35	23348.05	23571.41	5.36	0.09	-0.01	23.57	485.01	0.08	1556.75	4908.99
		0.00	2995.70	0.01	2995.71	0.73	0.07	-0.02	53.99	546.00	1756.49	1903.27	5978.80
		0.11	1047.43	495.93	1543.35	0.73	0.05	-0.04	46.22	548.45	3.94	1889.50	5930.90
		0.22	778.62	718.15	1496.77	0.73	0.04	-0.05	41.67	550.41	3.10	1882.11	5903.50
Enterococcus faecalis	Aminopeni-cillins	0.33	630.46	850.42	1480.88	0.74	0.04	-0.06	38.12	552.26	2.79	1876.61	5882.36
		0.44	528.05	944.36	1472.41	0.74	0.03	-0.06	35.18	554.06	2.62	1872.26	5865.11
		0.56	451.25	1017.26	1468.51	0.74	0.03	-0.07	32.70	555.81	2.51	1868.73	5850.65
		0.67	391.17	1076.86	1468.03	0.74	0.02	-0.07	30.55	557.48	2.43	1865.80	5838.30
		0.78	342.89	1127.25	1470.13	0.74	0.02	-0.07	28.69	559.06	2.36	1863.33	5827.62

		0.89	303.32	1170.84	1474.16	0.74	0.02	-0.08	27.04	560.57	2.31	1861.23	5818.28
		1.00	270.41	1209.17	1479.58	0.74	0.02	-0.08	25.58	561.99	2.26	1859.42	5810.04
Enterococcus faecalis	Gentamicin	0.00	10629.61	0.04	10629.65	1.05	0.09	0.01	53.99	546.00	894.29	2663.21	6738.74
		0.11	3722.49	3458.53	7181.02	1.05	0.07	-0.02	46.22	548.45	2.01	2650.36	6691.76
		0.22	2769.25	4751.96	7521.21	1.05	0.06	-0.03	41.67	550.41	1.66	2643.39	6664.78
		0.33	2244.05	5428.70	7672.74	1.05	0.05	-0.04	38.12	552.26	1.55	2638.34	6644.10
		0.44	1881.20	5882.11	7763.31	1.05	0.04	-0.05	35.18	554.06	1.49	2634.52	6627.37
		0.56	1609.08	6226.29	7835.37	1.05	0.04	-0.06	32.70	555.81	1.45	2631.54	6613.46
		0.67	1396.13	6506.22	7902.36	1.05	0.03	-0.06	30.55	557.47	1.42	2629.17	6601.68
		0.78	1224.91	6743.43	7968.34	1.05	0.03	-0.07	28.69	559.06	1.40	2627.25	6591.55
		0.89	1084.53	6949.74	8034.27	1.05	0.03	-0.07	27.04	560.57	1.38	2625.68	6582.73
		1.00	967.67	7132.35	8100.02	1.05	0.02	-0.07	25.58	561.98	1.36	2624.37	6574.99
Enterococcus faecalis	Vancomycin	0.00	574.92	0.00	574.92	0.46	0.04	-0.05	53.99	546.00	6330.05	912.77	4988.30
		0.11	200.65	36.87	237.52	0.46	0.03	-0.06	46.22	548.45	10.18	898.12	4939.52
		0.22	148.99	56.85	205.84	0.46	0.03	-0.07	41.67	550.40	7.51	889.97	4911.37
		0.33	120.51	69.30	189.81	0.46	0.02	-0.07	38.12	552.26	6.57	883.80	4889.56
		0.44	100.84	78.40	179.25	0.46	0.02	-0.08	35.18	554.06	6.06	878.86	4871.72
		0.56	86.10	85.66	171.76	0.46	0.02	-0.08	32.70	555.80	5.72	874.79	4856.72
		0.67	74.58	91.73	166.31	0.47	0.01	-0.08	30.56	557.47	5.46	871.37	4843.88
		0.78	65.32	96.97	162.29	0.47	0.01	-0.08	28.69	559.06	5.26	868.45	4832.74
		0.89	57.75	101.58	159.33	0.47	0.01	-0.08	27.04	560.56	5.10	865.93	4822.99
		1.00	51.45	105.71	157.15	0.47	0.01	-0.09	25.58	561.98	4.96	863.73	4814.35
Enterococcus faecium	Aminopeni-cillins	0.00	9966.04	0.01	9966.05	2.60	0.20	0.13	53.99	546.00	3249.55	2624.47	6700.01
		0.11	3499.87	1922.16	5422.03	2.59	0.16	0.07	46.22	548.45	3.39	2613.34	6654.73
		0.22	2619.04	3490.62	6109.66	2.57	0.13	0.04	41.67	550.41	2.12	2609.94	6631.32
		0.33	2134.87	4620.38	6755.26	2.56	0.11	0.02	38.12	552.26	1.71	2608.44	6614.19
		0.44	1799.71	5497.59	7297.30	2.54	0.09	0.00	35.18	554.06	1.50	2607.97	6600.82
		0.56	1547.46	6216.32	7763.77	2.53	0.08	-0.01	32.70	555.81	1.37	2608.13	6590.05
		0.67	1349.23	6826.34	8175.57	2.52	0.07	-0.02	30.55	557.48	1.27	2608.69	6581.19
		0.78	1189.13	7356.48	8545.61	2.50	0.06	-0.03	28.69	559.06	1.20	2609.48	6573.77
		0.89	1057.28	7824.85	8882.13	2.49	0.05	-0.04	27.04	560.57	1.15	2610.43	6567.48
		1.00	947.03	8243.66	9190.69	2.48	0.05	-0.04	25.58	561.99	1.10	2611.46	6562.08
Enterococcus faecium	Gentamicin	0.00	17247.15	0.01	17247.16	2.62	0.21	0.13	53.99	546.00	4488.82	2953.61	7029.14
		0.11	6035.71	1629.96	7665.67	2.62	0.17	0.09	46.22	548.45	6.91	2940.34	6981.74
		0.22	4502.24	2729.06	7231.31	2.61	0.14	0.06	41.67	550.41	4.69	2934.99	6956.38
		0.33	3662.52	3598.51	7261.03	2.60	0.12	0.03	38.12	552.26	3.80	2932.27	6938.02
		0.44	3083.61	4363.21	7446.83	2.59	0.10	0.01	35.18	554.06	3.27	2931.04	6923.89
		0.56	2649.30	5059.97	7709.27	2.58	0.09	0.00	32.70	555.81	2.90	2930.72	6912.64
		0.67	2308.81	5702.98	8011.79	2.57	0.08	-0.01	30.55	557.47	2.64	2930.99	6903.49
		0.78	2034.28	6299.52	8333.80	2.55	0.07	-0.02	28.69	559.06	2.43	2931.62	6895.91
		0.89	1808.46	6854.36	8662.83	2.54	0.06	-0.03	27.04	560.57	2.27	2932.48	6889.53
		1.00	1619.82	7371.29	8991.10	2.53	0.06	-0.04	25.58	561.98	2.13	2933.48	6884.10
Enterococcus faecium	Vancomycin	0.00	4152.58	0.01	4152.58	1.40	0.12	0.04	53.99	546.00	1582.81	2099.13	6174.66
		0.11	1453.13	793.20	2246.34	1.41	0.09	0.01	46.22	548.45	3.42	2086.06	6127.46

		0.22	1082.41	1184.69	2267.10	1.40	0.08	-0.01	41.67	550.40	2.60	2079.81	6101.20
		0.33	878.34	1437.90	2316.24	1.40	0.07	-0.02	38.12	552.26	2.29	2075.56	6081.32
		0.44	737.27	1628.87	2366.13	1.40	0.06	-0.03	35.18	554.06	2.11	2072.49	6065.34
		0.56	631.36	1783.77	2415.12	1.40	0.05	-0.04	32.70	555.80	1.98	2070.20	6052.12
		0.67	548.39	1914.69	2463.07	1.40	0.04	-0.05	30.56	557.47	1.89	2068.46	6040.97
		0.78	481.61	2028.22	2509.83	1.39	0.04	-0.05	28.69	559.06	1.82	2067.12	6031.42
		0.89	426.80	2128.42	2555.22	1.39	0.03	-0.06	27.04	560.56	1.76	2066.08	6023.14
		1.00	381.12	2217.96	2599.08	1.39	0.03	-0.06	25.58	561.98	1.71	2065.27	6015.90
		0.00	1168.34	0.00	1168.34	0.89	0.08	-0.01	53.99	546.00	891.51	1338.19	5413.73
		0.11	409.47	421.71	831.18	0.89	0.06	-0.03	46.22	548.45	1.81	1325.86	5367.25
		0.22	304.67	597.52	902.19	0.89	0.05	-0.04	41.67	550.41	1.45	1319.06	5340.44
		0.33	246.81	690.55	937.36	0.89	0.04	-0.05	38.11	552.26	1.34	1313.89	5319.63
Escherichia coli	Aminogly-cosides	0.44	206.80	750.99	957.79	0.89	0.04	-0.06	35.18	554.06	1.29	1309.81	5302.64
		0.56	176.79	794.99	971.78	0.89	0.03	-0.06	32.69	555.81	1.25	1306.51	5288.42
		0.67	153.30	829.33	982.63	0.89	0.03	-0.07	30.55	557.48	1.23	1303.81	5276.30
		0.78	134.43	857.38	991.81	0.89	0.02	-0.07	28.68	559.07	1.21	1301.55	5265.83
		0.89	118.96	881.04	1000.00	0.89	0.02	-0.07	27.04	560.57	1.20	1299.66	5256.70
		1.00	106.08	901.45	1007.53	0.89	0.02	-0.08	25.58	561.99	1.18	1298.04	5248.65
		0.00	2624.44	0.00	2624.45	1.00	0.09	0.00	53.99	546.00	3219.40	1823.89	5899.42
		0.11	918.53	357.53	1276.07	1.00	0.07	-0.02	46.22	548.45	4.79	1810.72	5852.11
		0.22	684.01	595.33	1279.35	1.00	0.05	-0.04	41.67	550.41	3.27	1804.38	5825.77
		0.33	554.72	759.66	1314.39	1.00	0.04	-0.05	38.12	552.26	2.74	1799.82	5805.57
Escherichia coli	Aminopeni-cillins	0.44	465.24	883.46	1348.70	1.00	0.04	-0.06	35.18	554.06	2.45	1796.28	5789.12
		0.56	398.03	981.80	1379.83	0.99	0.03	-0.06	32.70	555.81	2.28	1793.43	5775.35
		0.67	345.38	1062.80	1408.18	0.99	0.03	-0.07	30.55	557.48	2.15	1791.10	5763.61
		0.78	303.02	1131.28	1434.29	0.99	0.03	-0.07	28.69	559.06	2.06	1789.17	5753.46
		0.89	268.26	1190.31	1458.57	0.99	0.02	-0.07	27.04	560.57	1.99	1787.54	5744.59
		1.00	239.33	1241.98	1481.30	0.99	0.02	-0.07	25.58	561.99	1.93	1786.15	5736.77
		0.00	25.01	0.00	25.01	0.51	0.05	-0.04	53.99	546.00	2345.19	-968.61	3106.92
		0.11	8.73	2.70	11.44	0.51	0.04	-0.06	46.22	548.45	6.04	-983.28	3058.09
		0.22	6.48	3.64	10.12	0.51	0.03	-0.06	41.66	550.41	5.10	-991.57	3029.78
		0.33	5.24	4.14	9.38	0.51	0.03	-0.07	38.10	552.27	4.78	-997.81	3007.89
Escherichia coli	Car-bapenems	0.44	4.38	4.49	8.88	0.51	0.02	-0.07	35.17	554.07	4.60	-1002.76	2990.03
		0.56	3.74	4.77	8.51	0.51	0.02	-0.08	32.68	555.82	4.47	-1006.81	2975.05
		0.67	3.24	5.01	8.25	0.51	0.02	-0.08	30.54	557.49	4.36	-1010.19	2962.26
		0.78	2.84	5.21	8.05	0.51	0.02	-0.08	28.68	559.08	4.26	-1013.06	2951.19
		0.89	2.51	5.40	7.91	0.51	0.01	-0.08	27.03	560.58	4.18	-1015.51	2941.49
		1.00	2.24	5.57	7.80	0.51	0.01	-0.08	25.57	562.00	4.10	-1017.64	2932.93
		0.00	1162.27	0.00	1162.27	0.91	0.08	-0.01	53.99	546.00	804.69	1335.26	5410.79
		0.11	407.68	444.24	851.91	0.91	0.06	-0.03	46.22	548.45	1.71	1323.16	5364.54
Escherichia coli	Cephalo-sporins	0.22	303.45	631.03	934.48	0.91	0.05	-0.04	41.67	550.41	1.37	1316.58	5337.96
		0.33	245.89	731.67	977.56	0.91	0.04	-0.05	38.11	552.26	1.26	1311.57	5317.30
		0.44	206.06	797.61	1003.67	0.91	0.04	-0.06	35.18	554.06	1.20	1307.58	5300.41
		0.56	176.16	845.67	1021.84	0.91	0.03	-0.06	32.69	555.81	1.17	1304.34	5286.24

		0.67	152.77	883.11	1035.87	0.91	0.03	-0.07	30.55	557.48	1.15	1301.66	5274.15
		0.78	133.95	913.56	1047.52	0.91	0.02	-0.07	28.68	559.07	1.13	1299.42	5263.70
		0.89	118.54	939.12	1057.66	0.91	0.02	-0.07	27.04	560.57	1.12	1297.53	5254.56
		1.00	105.70	961.05	1066.76	0.91	0.02	-0.08	25.57	561.99	1.10	1295.91	5246.51
		0.00	1594.53	0.01	1594.53	1.65	0.14	0.06	53.99	546.00	678.01	1524.87	5600.40
		0.11	559.97	788.56	1348.53	1.64	0.11	0.02	46.22	548.45	1.32	1513.78	5555.18
		0.22	417.44	1115.98	1533.42	1.64	0.09	0.00	41.67	550.41	1.06	1508.06	5529.44
		0.33	338.81	1289.27	1628.08	1.63	0.08	-0.01	38.12	552.26	0.98	1503.98	5509.73
Escherichia coli	Fluoroquin-olones	0.44	284.44	1403.23	1687.67	1.63	0.07	-0.02	35.18	554.06	0.94	1501.03	5493.87
		0.56	243.62	1487.59	1731.21	1.63	0.06	-0.03	32.70	555.81	0.91	1498.86	5480.78
		0.67	211.65	1554.59	1766.24	1.63	0.05	-0.04	30.55	557.48	0.89	1497.26	5469.76
		0.78	185.92	1610.27	1796.19	1.63	0.05	-0.05	28.69	559.06	0.88	1496.09	5460.38
		0.89	164.81	1657.94	1822.75	1.62	0.04	-0.05	27.04	560.57	0.87	1495.23	5452.28
		1.00	147.22	1699.63	1846.85	1.62	0.04	-0.06	25.58	561.99	0.86	1494.60	5445.22
		0.00	4091.07	0.01	4091.08	1.79	0.15	0.07	53.99	546.00	1289.19	2090.13	6165.66
		0.11	1432.33	887.76	2320.10	1.79	0.12	0.03	46.22	548.45	3.01	2077.18	6118.56
		0.22	1067.19	1279.78	2346.97	1.79	0.10	0.01	41.67	550.41	2.37	2071.20	6092.58
		0.33	866.61	1528.43	2395.05	1.78	0.08	-0.01	38.11	552.26	2.12	2067.47	6073.21
Klebsiella pneumoniae	Aminogly-cosides	0.44	728.14	1719.97	2448.11	1.78	0.07	-0.02	35.18	554.06	1.97	2065.04	6057.87
		0.56	624.23	1880.07	2504.30	1.77	0.06	-0.03	32.69	555.81	1.85	2063.44	6045.35
		0.67	542.82	2019.32	2562.13	1.77	0.05	-0.04	30.55	557.48	1.77	2062.41	6034.91
		0.78	477.26	2143.09	2620.34	1.77	0.05	-0.04	28.68	559.07	1.70	2061.77	6026.05
		0.89	423.41	2254.57	2677.98	1.76	0.04	-0.05	27.04	560.57	1.64	2061.41	6018.45
		1.00	378.49	2355.90	2734.39	1.76	0.04	-0.06	25.58	561.99	1.58	2061.24	6011.85
		0.00	711.98	0.00	711.98	2.19	0.18	0.10	53.99	546.00	767.68	1040.54	5116.07
		0.11	249.35	208.18	457.54	2.19	0.14	0.06	46.22	548.45	2.23	1027.88	5069.24
		0.22	185.83	285.71	471.53	2.18	0.12	0.03	41.66	550.41	1.85	1022.16	5043.50
		0.33	150.97	332.38	483.35	2.18	0.10	0.01	38.10	552.27	1.70	1018.81	5024.51
Klebsiella pneumoniae	Car-bapenems	0.44	126.93	367.91	494.84	2.17	0.09	0.00	35.17	554.07	1.60	1016.87	5009.66
		0.56	108.90	397.71	506.62	2.16	0.08	-0.01	32.68	555.82	1.53	1015.82	4997.69
		0.67	94.78	423.86	518.64	2.16	0.07	-0.02	30.54	557.49	1.46	1015.36	4987.82
		0.78	83.41	447.34	530.74	2.15	0.06	-0.03	28.68	559.08	1.41	1015.30	4979.54
		0.89	74.06	468.68	542.74	2.14	0.05	-0.04	27.03	560.58	1.37	1015.49	4972.50
		1.00	66.26	488.23	554.49	2.14	0.05	-0.05	25.57	562.00	1.33	1015.87	4966.44
		0.00	4796.64	0.00	4796.64	1.66	0.14	0.06	53.99	546.00	3967.82	2185.78	6261.31
		0.11	1676.96	353.13	2030.09	1.66	0.11	0.03	46.22	548.45	8.87	2171.72	6213.10
		0.22	1248.07	550.50	1798.56	1.66	0.09	0.01	41.67	550.41	6.47	2165.05	6186.43
		0.33	1012.64	706.15	1718.79	1.66	0.08	-0.01	38.11	552.26	5.38	2160.83	6166.56
Klebsiella pneumoniae	Cephalo-sporins	0.44	850.26	844.34	1694.59	1.66	0.07	-0.02	35.18	554.06	4.69	2158.00	6150.84
		0.56	728.51	970.93	1699.45	1.65	0.06	-0.03	32.69	555.81	4.21	2156.09	6137.99
		0.67	633.20	1088.02	1721.23	1.65	0.05	-0.04	30.55	557.48	3.84	2154.79	6127.28
		0.78	556.50	1196.70	1753.20	1.65	0.05	-0.05	28.68	559.07	3.56	2153.93	6118.20
		0.89	493.54	1297.75	1791.28	1.65	0.04	-0.05	27.04	560.57	3.33	2153.36	6110.40
		1.00	441.05	1391.81	1832.87	1.64	0.04	-0.06	25.57	561.99	3.14	2153.02	6103.62

		0.00	4648.11	0.04	4648.14	1.25	0.11	0.02	53.99	546.00	378.29	2166.80	6242.33
		0.11	1629.64	2570.60	4200.24	1.25	0.08	0.00	46.22	548.45	1.18	2154.72	6196.12
		0.22	1212.70	3334.34	4547.05	1.25	0.07	-0.02	41.67	550.41	1.04	2147.94	6169.33
		0.33	983.03	3704.14	4687.17	1.25	0.06	-0.03	38.12	552.26	0.99	2143.10	6148.85
Klebsiella pneumoniae	Fluoroquinolones	0.44	824.41	3942.08	4766.49	1.25	0.05	-0.04	35.18	554.06	0.97	2139.52	6132.37
		0.56	705.46	4118.70	4824.16	1.25	0.04	-0.05	32.70	555.81	0.96	2136.81	6118.72
		0.67	612.38	4260.59	4872.97	1.25	0.04	-0.05	30.55	557.48	0.95	2134.71	6107.21
		0.78	537.53	4380.05	4917.58	1.25	0.03	-0.06	28.69	559.06	0.94	2133.07	6097.36
		0.89	476.14	4483.62	4959.76	1.25	0.03	-0.06	27.04	560.57	0.93	2131.77	6088.82
		1.00	425.02	4575.17	5000.19	1.25	0.03	-0.07	25.58	561.99	0.93	2130.73	6081.35
		0.00	4424.87	0.01	4424.88	1.90	0.16	0.08	53.99	546.00	2272.52	2137.19	6212.72
		0.11	1547.67	570.33	2118.00	1.90	0.13	0.04	46.22	548.45	5.07	2123.64	6165.03
		0.22	1152.60	856.76	2009.36	1.90	0.11	0.02	41.67	550.41	3.84	2117.40	6138.78
		0.33	935.72	1059.76	1995.48	1.89	0.09	0.00	38.11	552.26	3.31	2113.51	6119.25
Pseudomonas aeruginosa	Aminoglycosides	0.44	786.06	1227.70	2013.76	1.89	0.08	-0.01	35.18	554.06	2.98	2110.96	6103.80
		0.56	673.79	1374.48	2048.27	1.88	0.07	-0.02	32.69	555.81	2.74	2109.29	6091.19
		0.67	585.86	1505.86	2091.72	1.88	0.06	-0.03	30.55	557.48	2.56	2108.20	6080.69
		0.78	515.06	1624.95	2140.01	1.87	0.06	-0.04	28.68	559.07	2.42	2107.51	6071.79
		0.89	456.92	1733.72	2190.64	1.87	0.05	-0.04	27.04	560.57	2.30	2107.11	6064.16
		1.00	408.44	1833.61	2242.05	1.87	0.05	-0.05	25.58	561.99	2.20	2106.92	6057.54
		0.00	5269.31	0.01	5269.32	1.83	0.15	0.07	53.99	546.00	1589.04	2241.50	6317.03
		0.11	1842.01	791.56	2633.57	1.83	0.12	0.04	46.22	548.45	4.35	2227.72	6269.09
		0.22	1370.70	1096.39	2467.08	1.83	0.10	0.02	41.66	550.41	3.57	2221.12	6242.46
		0.33	1112.14	1295.10	2407.24	1.83	0.09	0.00	38.10	552.27	3.22	2216.99	6222.69
Pseudomonas aeruginosa	Carbapenems	0.44	933.94	1459.39	2393.34	1.82	0.08	-0.01	35.17	554.07	2.98	2214.35	6207.14
		0.56	800.43	1606.25	2406.68	1.82	0.07	-0.03	32.68	555.82	2.80	2212.65	6194.52
		0.67	695.94	1741.14	2437.08	1.82	0.06	-0.03	30.54	557.49	2.64	2211.59	6184.04
		0.78	611.86	1866.31	2478.18	1.81	0.05	-0.04	28.68	559.08	2.51	2210.97	6175.21
		0.89	542.84	1982.97	2525.81	1.81	0.05	-0.05	27.03	560.58	2.40	2210.66	6167.67
		1.00	485.31	2091.91	2577.21	1.80	0.04	-0.05	25.57	562.00	2.30	2210.56	6161.14
		0.00	6368.04	0.02	6368.06	2.85	0.22	0.14	53.99	546.00	867.81	2355.71	6431.24
		0.11	2234.93	2017.90	4252.83	2.85	0.17	0.09	46.22	548.45	2.06	2344.06	6385.45
		0.22	1669.86	2923.81	4593.67	2.83	0.14	0.06	41.67	550.41	1.62	2339.79	6361.16
Pseudomonas aeruginosa		0.33	1360.22	3504.94	4865.16	2.82	0.12	0.04	38.11	552.26	1.44	2337.93	6343.66
Pseudomonas aeruginosa	Ceftazidime	0.44	1146.53	3955.72	5102.25	2.80	0.10	0.02	35.18	554.07	1.33	2337.43	6330.26
		0.56	986.04	4334.84	5320.88	2.79	0.09	0.00	32.69	555.81	1.25	2337.75	6319.65
		0.67	860.08	4666.47	5526.55	2.77	0.08	-0.01	30.55	557.48	1.19	2338.57	6311.05
		0.78	758.42	4962.79	5721.20	2.76	0.07	-0.02	28.68	559.07	1.14	2339.69	6303.97
		0.89	674.71	5230.92	5905.63	2.74	0.06	-0.03	27.04	560.57	1.10	2340.99	6298.03
		1.00	604.71	5475.60	6080.31	2.73	0.06	-0.04	25.57	561.99	1.06	2342.38	6292.99
		0.00	5531.14	0.01	5531.15	1.64	0.14	0.06	53.99	546.00	1448.59	2271.16	6346.70
Pseudomonas aeruginosa	Fluoroquinolones	0.11	1933.90	987.72	2921.62	1.65	0.11	0.03	46.22	548.45	3.66	2257.43	6298.82
		0.22	1438.66	1359.75	2798.41	1.65	0.10	0.01	41.67	550.41	3.02	2250.46	6271.84
		0.33	1166.52	1579.44	2745.96	1.64	0.08	0.00	38.12	552.26	2.77	2245.79	6251.54

		0.44	978.80	1747.21	2726.01	1.64	0.07	-0.02	35.18	554.06	2.62	2242.52	6235.36
		0.56	838.10	1889.42	2727.53	1.64	0.07	-0.03	32.70	555.81	2.49	2240.18	6222.09
		0.67	728.01	2015.53	2743.54	1.64	0.06	-0.03	30.55	557.48	2.39	2238.49	6210.99
		0.78	639.46	2129.79	2769.24	1.64	0.05	-0.04	28.69	559.06	2.31	2237.26	6201.55
		0.89	566.82	2234.48	2801.30	1.63	0.05	-0.04	27.04	560.57	2.23	2236.37	6193.42
		1.00	506.30	2331.07	2837.37	1.63	0.04	-0.05	25.58	561.99	2.16	2235.73	6186.35
Pseudomonas aeruginosa	Piperacillin	0.00	4816.18	0.03	4816.21	1.67	0.14	0.06	52.99	527.00	594.14	2122.97	6044.71
		0.11	1681.55	2058.33	3739.87	1.67	0.11	0.03	45.33	529.43	1.53	2111.00	5999.31
		0.22	1249.81	2781.43	4031.24	1.67	0.09	0.01	40.85	531.37	1.29	2104.90	5973.70
		0.33	1013.31	3163.42	4176.74	1.67	0.08	-0.01	37.36	533.19	1.21	2100.80	5954.38
		0.44	850.36	3424.48	4274.84	1.67	0.07	-0.02	34.49	534.97	1.16	2097.95	5938.97
		0.56	728.28	3626.44	4354.72	1.66	0.06	-0.03	32.05	536.68	1.13	2095.93	5926.32
		0.67	632.76	3793.36	4426.12	1.66	0.05	-0.04	29.95	538.32	1.11	2094.50	5915.73
		0.78	555.93	3936.68	4492.61	1.66	0.05	-0.05	28.12	539.88	1.09	2093.48	5906.73
		0.89	492.89	4062.69	4555.58	1.65	0.04	-0.05	26.51	541.35	1.07	2092.76	5898.97
		1.00	440.36	4175.25	4615.61	1.65	0.04	-0.06	25.07	542.74	1.05	2092.27	5892.22
Streptococcus pneumoniae	Macrolides	0.00	5692.30	0.06	5692.36	2.09	0.17	0.09	52.99	527.00	309.21	2218.73	6140.47
		0.11	2001.12	4994.44	6995.55	2.07	0.12	0.04	45.31	529.45	0.75	2211.37	6099.61
		0.22	1494.81	7104.31	8599.12	2.05	0.10	0.01	40.84	531.39	0.60	2208.68	6077.40
		0.33	1216.38	8280.74	9497.12	2.04	0.08	-0.01	37.35	533.21	0.55	2206.87	6060.37
		0.44	1023.55	9067.57	10091.12	2.03	0.07	-0.02	34.47	534.99	0.52	2205.68	6046.63
		0.56	878.45	9647.81	10526.25	2.03	0.06	-0.03	32.03	536.70	0.50	2204.92	6035.24
		0.67	764.50	10102.37	10866.87	2.02	0.05	-0.04	29.94	538.34	0.49	2204.48	6025.65
		0.78	672.59	10473.20	11145.79	2.01	0.05	-0.05	28.11	539.90	0.48	2204.27	6017.46
		0.89	596.99	10784.55	11381.54	2.01	0.04	-0.05	26.49	541.37	0.48	2204.23	6010.38
		1.00	533.88	11051.56	11585.44	2.00	0.04	-0.06	25.06	542.76	0.47	2204.29	6004.20
Streptococcus pneumoniae	Penicillins	0.00	6298.24	0.01	6298.24	0.98	0.09	0.00	52.99	527.00	3829.22	2277.59	6199.33
		0.11	2191.01	748.92	2939.93	0.98	0.07	-0.02	45.31	529.45	5.51	2264.33	6152.58
		0.22	1626.05	1266.38	2892.43	0.98	0.06	-0.04	40.84	531.38	3.70	2257.76	6126.51
		0.33	1316.66	1613.93	2930.59	0.98	0.05	-0.05	37.35	533.21	3.10	2252.98	6106.51
		0.44	1103.33	1870.68	2974.01	0.98	0.04	-0.05	34.48	534.98	2.79	2249.27	6090.25
		0.56	943.45	2073.04	3016.49	0.98	0.03	-0.06	32.04	536.69	2.59	2246.32	6076.67
		0.67	818.38	2239.62	3058.01	0.98	0.03	-0.07	29.94	538.33	2.46	2243.92	6065.12
		0.78	717.85	2380.91	3098.76	0.98	0.03	-0.07	28.11	539.89	2.35	2241.94	6055.16
		0.89	635.44	2503.34	3138.77	0.98	0.02	-0.07	26.50	541.36	2.27	2240.28	6046.47
		1.00	566.85	2611.11	3177.95	0.98	0.02	-0.08	25.07	542.75	2.20	2238.88	6038.82

Source: Constructed by the Author.

Supplementary Annexure 10: Variance Inflation Factors for Confounders

Pathogen	Drug	Lambda	Growth in Antimicrobial Consumption	Growth in Population	Growth in Population Ageing	Growth in Population Density	Growth in Urbanization	Growth in GDP per Capita
Acinetobacter spp.	Aminoglycosides	0.00	1.11	18.09	2.05	11.86	1.47	3.03
		0.11	0.86	1.23	1.12	1.42	0.86	1.32
		0.22	0.69	0.48	0.78	0.64	0.68	0.79
		0.33	0.57	0.29	0.59	0.39	0.56	0.55
		0.44	0.48	0.20	0.47	0.27	0.47	0.42
		0.56	0.41	0.16	0.38	0.21	0.40	0.33
		0.67	0.36	0.13	0.32	0.17	0.35	0.28
		0.78	0.31	0.11	0.27	0.14	0.31	0.23
		0.89	0.27	0.10	0.24	0.12	0.27	0.20
		1.00	0.24	0.09	0.21	0.11	0.24	0.18
Acinetobacter spp.	Carbapenems	0.00	1.13	15.29	2.03	9.11	1.36	2.96
		0.11	0.87	1.32	1.12	1.49	0.87	1.31
		0.22	0.70	0.52	0.78	0.70	0.68	0.79
		0.33	0.57	0.31	0.59	0.43	0.56	0.55
		0.44	0.48	0.22	0.47	0.30	0.47	0.42
		0.56	0.41	0.17	0.38	0.23	0.40	0.34
		0.67	0.35	0.14	0.32	0.19	0.35	0.28
		0.78	0.31	0.12	0.27	0.16	0.31	0.24
		0.89	0.27	0.10	0.24	0.14	0.27	0.20
		1.00	0.24	0.09	0.21	0.12	0.24	0.18
Acinetobacter spp.	Fluoroquinolones	0.00	1.09	18.02	2.04	11.85	1.47	3.03
		0.11	0.86	1.23	1.12	1.42	0.87	1.32
		0.22	0.69	0.48	0.78	0.64	0.68	0.79
		0.33	0.57	0.29	0.59	0.39	0.56	0.55
		0.44	0.48	0.20	0.47	0.27	0.47	0.42
		0.56	0.41	0.16	0.38	0.21	0.40	0.33
		0.67	0.36	0.13	0.32	0.17	0.35	0.28
		0.78	0.31	0.11	0.27	0.14	0.31	0.23
		0.89	0.27	0.10	0.24	0.12	0.27	0.20
		1.00	0.24	0.09	0.21	0.11	0.24	0.18
Enterococcus faecalis	Aminopenicillins	0.00	1.08	16.42	2.19	11.45	1.33	2.90
		0.11	0.85	1.28	1.15	1.43	0.86	1.31
		0.22	0.69	0.51	0.79	0.65	0.68	0.80
		0.33	0.57	0.30	0.59	0.39	0.56	0.56
		0.44	0.48	0.21	0.46	0.28	0.47	0.42
		0.56	0.41	0.17	0.38	0.21	0.41	0.34
		0.67	0.36	0.14	0.32	0.17	0.35	0.28
		0.78	0.31	0.12	0.27	0.14	0.31	0.24
		0.89	0.28	0.10	0.23	0.12	0.27	0.21
		1.00	0.25	0.09	0.21	0.11	0.24	0.18

Enterococcus faecalis	Gentamicin	0.00	1.08	16.42	2.19	11.46	1.33	2.89
		0.11	0.85	1.28	1.15	1.43	0.86	1.31
		0.22	0.69	0.51	0.79	0.65	0.68	0.80
		0.33	0.57	0.30	0.59	0.39	0.56	0.56
		0.44	0.48	0.21	0.46	0.28	0.47	0.42
		0.56	0.41	0.17	0.38	0.21	0.40	0.34
		0.67	0.36	0.14	0.32	0.17	0.35	0.28
		0.78	0.31	0.12	0.27	0.14	0.31	0.24
		0.89	0.28	0.10	0.23	0.12	0.27	0.21
		1.00	0.25	0.09	0.21	0.11	0.24	0.18
Enterococcus faecalis	Vancomycin	0.00	1.08	16.42	2.19	11.45	1.33	2.88
		0.11	0.85	1.28	1.15	1.43	0.87	1.30
		0.22	0.69	0.51	0.79	0.65	0.68	0.80
		0.33	0.57	0.30	0.59	0.39	0.56	0.56
		0.44	0.48	0.21	0.46	0.28	0.47	0.42
		0.56	0.41	0.17	0.38	0.21	0.41	0.34
		0.67	0.36	0.14	0.32	0.17	0.35	0.28
		0.78	0.31	0.12	0.27	0.14	0.31	0.24
		0.89	0.28	0.10	0.23	0.12	0.27	0.21
		1.00	0.25	0.09	0.21	0.11	0.24	0.18
Enterococcus faecium	Aminopenicillins	0.00	1.08	16.42	2.19	11.45	1.33	2.90
		0.11	0.85	1.28	1.15	1.43	0.86	1.31
		0.22	0.69	0.51	0.79	0.65	0.68	0.80
		0.33	0.57	0.30	0.59	0.39	0.56	0.56
		0.44	0.48	0.21	0.46	0.28	0.47	0.42
		0.56	0.41	0.17	0.38	0.21	0.41	0.34
		0.67	0.36	0.14	0.32	0.17	0.35	0.28
		0.78	0.31	0.12	0.27	0.14	0.31	0.24
		0.89	0.28	0.10	0.23	0.12	0.27	0.21
		1.00	0.25	0.09	0.21	0.11	0.24	0.18
Enterococcus faecium	Gentamicin	0.00	1.08	16.42	2.19	11.46	1.33	2.89
		0.11	0.85	1.28	1.15	1.43	0.86	1.31
		0.22	0.69	0.51	0.79	0.65	0.68	0.80
		0.33	0.57	0.30	0.59	0.39	0.56	0.56
		0.44	0.48	0.21	0.46	0.28	0.47	0.42
		0.56	0.41	0.17	0.38	0.21	0.40	0.34
		0.67	0.36	0.14	0.32	0.17	0.35	0.28
		0.78	0.31	0.12	0.27	0.14	0.31	0.24
		0.89	0.28	0.10	0.23	0.12	0.27	0.21
		1.00	0.25	0.09	0.21	0.11	0.24	0.18
Enterococcus faecium	Vancomycin	0.00	1.08	16.42	2.19	11.45	1.33	2.88
		0.11	0.85	1.28	1.15	1.43	0.87	1.30
		0.22	0.69	0.51	0.79	0.65	0.68	0.80
		0.33	0.57	0.30	0.59	0.39	0.56	0.56
		0.44	0.48	0.21	0.46	0.28	0.47	0.42
		0.56	0.41	0.17	0.38	0.21	0.41	0.34

		0.67	0.36	0.14	0.32	0.17	0.35	0.28
		0.78	0.31	0.12	0.27	0.14	0.31	0.24
		0.89	0.28	0.10	0.23	0.12	0.27	0.21
		1.00	0.25	0.09	0.21	0.11	0.24	0.18
Escherichia coli	Aminoglycosides	0.00	1.09	16.43	2.20	11.45	1.33	2.89
		0.11	0.85	1.28	1.15	1.43	0.86	1.30
		0.22	0.69	0.51	0.79	0.65	0.68	0.80
		0.33	0.57	0.30	0.59	0.39	0.56	0.56
		0.44	0.48	0.21	0.46	0.28	0.47	0.42
		0.56	0.41	0.17	0.38	0.21	0.41	0.34
		0.67	0.36	0.14	0.32	0.17	0.35	0.28
		0.78	0.31	0.12	0.27	0.14	0.31	0.24
		0.89	0.27	0.10	0.23	0.12	0.27	0.21
		1.00	0.24	0.09	0.21	0.11	0.24	0.18
Escherichia coli	Aminopenicillins	0.00	1.08	16.42	2.19	11.45	1.33	2.90
		0.11	0.85	1.28	1.15	1.43	0.86	1.31
		0.22	0.69	0.51	0.79	0.65	0.68	0.80
		0.33	0.57	0.30	0.59	0.39	0.56	0.56
		0.44	0.48	0.21	0.46	0.28	0.47	0.42
		0.56	0.41	0.17	0.38	0.21	0.41	0.34
		0.67	0.36	0.14	0.32	0.17	0.35	0.28
		0.78	0.31	0.12	0.27	0.14	0.31	0.24
		0.89	0.28	0.10	0.23	0.12	0.27	0.21
		1.00	0.25	0.09	0.21	0.11	0.24	0.18
Escherichia coli	Carbapenems	0.00	1.13	16.41	2.19	11.45	1.33	2.88
		0.11	0.87	1.28	1.15	1.43	0.87	1.30
		0.22	0.70	0.51	0.79	0.64	0.68	0.80
		0.33	0.57	0.30	0.59	0.39	0.56	0.56
		0.44	0.48	0.21	0.46	0.28	0.47	0.42
		0.56	0.41	0.17	0.38	0.21	0.40	0.34
		0.67	0.35	0.14	0.32	0.17	0.35	0.28
		0.78	0.31	0.12	0.27	0.14	0.31	0.24
		0.89	0.27	0.10	0.23	0.12	0.27	0.21
		1.00	0.24	0.09	0.21	0.11	0.24	0.18
Escherichia coli	Cephalosporins	0.00	1.10	16.41	2.19	11.44	1.33	2.87
		0.11	0.86	1.28	1.15	1.43	0.86	1.30
		0.22	0.69	0.51	0.79	0.65	0.68	0.80
		0.33	0.57	0.30	0.59	0.39	0.56	0.56
		0.44	0.48	0.21	0.46	0.28	0.47	0.42
		0.56	0.41	0.17	0.38	0.21	0.41	0.34
		0.67	0.36	0.14	0.32	0.17	0.35	0.28
		0.78	0.31	0.12	0.27	0.14	0.31	0.24
		0.89	0.27	0.10	0.23	0.12	0.27	0.21
		1.00	0.24	0.09	0.21	0.11	0.24	0.18
Escherichia coli	Fluoroquinolones	0.00	1.08	16.41	2.19	11.45	1.33	2.89
		0.11	0.85	1.28	1.15	1.43	0.86	1.30

		0.22	0.69	0.51	0.79	0.65	0.68	0.80
		0.33	0.57	0.30	0.59	0.39	0.56	0.56
		0.44	0.48	0.21	0.46	0.28	0.47	0.42
		0.56	0.41	0.17	0.38	0.21	0.41	0.34
		0.67	0.36	0.14	0.32	0.17	0.35	0.28
		0.78	0.31	0.12	0.27	0.14	0.31	0.24
		0.89	0.28	0.10	0.23	0.12	0.27	0.21
		1.00	0.25	0.09	0.21	0.11	0.24	0.18
Klebsiella pneumoniae	Aminoglycosides	0.00	1.09	16.43	2.20	11.45	1.33	2.89
		0.11	0.85	1.28	1.15	1.43	0.86	1.30
		0.22	0.69	0.51	0.79	0.65	0.68	0.80
		0.33	0.57	0.30	0.59	0.39	0.56	0.56
		0.44	0.48	0.21	0.46	0.28	0.47	0.42
		0.56	0.41	0.17	0.38	0.21	0.41	0.34
		0.67	0.36	0.14	0.32	0.17	0.35	0.28
		0.78	0.31	0.12	0.27	0.14	0.31	0.24
		0.89	0.27	0.10	0.23	0.12	0.27	0.21
		1.00	0.24	0.09	0.21	0.11	0.24	0.18
Klebsiella pneumoniae	Carbapenems	0.00	1.13	16.41	2.19	11.45	1.33	2.88
		0.11	0.87	1.28	1.15	1.43	0.87	1.30
		0.22	0.70	0.51	0.79	0.64	0.68	0.80
		0.33	0.57	0.30	0.59	0.39	0.56	0.56
		0.44	0.48	0.21	0.46	0.28	0.47	0.42
		0.56	0.41	0.17	0.38	0.21	0.40	0.34
		0.67	0.35	0.14	0.32	0.17	0.35	0.28
		0.78	0.31	0.12	0.27	0.14	0.31	0.24
		0.89	0.27	0.10	0.23	0.12	0.27	0.21
		1.00	0.24	0.09	0.21	0.11	0.24	0.18
Klebsiella pneumoniae	Cephalosporins	0.00	1.10	16.41	2.19	11.44	1.33	2.87
		0.11	0.86	1.28	1.15	1.43	0.86	1.30
		0.22	0.69	0.51	0.79	0.65	0.68	0.80
		0.33	0.57	0.30	0.59	0.39	0.56	0.56
		0.44	0.48	0.21	0.46	0.28	0.47	0.42
		0.56	0.41	0.17	0.38	0.21	0.41	0.34
		0.67	0.36	0.14	0.32	0.17	0.35	0.28
		0.78	0.31	0.12	0.27	0.14	0.31	0.24
		0.89	0.27	0.10	0.23	0.12	0.27	0.21
		1.00	0.24	0.09	0.21	0.11	0.24	0.18
Klebsiella pneumoniae	Fluoroquinolones	0.00	1.08	16.41	2.19	11.45	1.33	2.89
		0.11	0.85	1.28	1.15	1.43	0.86	1.30
		0.22	0.69	0.51	0.79	0.65	0.68	0.80
		0.33	0.57	0.30	0.59	0.39	0.56	0.56
		0.44	0.48	0.21	0.46	0.28	0.47	0.42
		0.56	0.41	0.17	0.38	0.21	0.41	0.34
		0.67	0.36	0.14	0.32	0.17	0.35	0.28
		0.78	0.31	0.12	0.27	0.14	0.31	0.24

		0.89	0.28	0.10	0.23	0.12	0.27	0.21
		1.00	0.25	0.09	0.21	0.11	0.24	0.18
Pseudomonas aeruginosa	Aminoglycosides	0.00	1.09	16.43	2.20	11.45	1.33	2.89
		0.11	0.85	1.28	1.15	1.43	0.86	1.30
		0.22	0.69	0.51	0.79	0.65	0.68	0.80
		0.33	0.57	0.30	0.59	0.39	0.56	0.56
		0.44	0.48	0.21	0.46	0.28	0.47	0.42
		0.56	0.41	0.17	0.38	0.21	0.41	0.34
		0.67	0.36	0.14	0.32	0.17	0.35	0.28
		0.78	0.31	0.12	0.27	0.14	0.31	0.24
		0.89	0.27	0.10	0.23	0.12	0.27	0.21
		1.00	0.24	0.09	0.21	0.11	0.24	0.18
Pseudomonas aeruginosa	Carbapenems	0.00	1.13	16.41	2.19	11.45	1.33	2.88
		0.11	0.87	1.28	1.15	1.43	0.87	1.30
		0.22	0.70	0.51	0.79	0.64	0.68	0.80
		0.33	0.57	0.30	0.59	0.39	0.56	0.56
		0.44	0.48	0.21	0.46	0.28	0.47	0.42
		0.56	0.41	0.17	0.38	0.21	0.40	0.34
		0.67	0.35	0.14	0.32	0.17	0.35	0.28
		0.78	0.31	0.12	0.27	0.14	0.31	0.24
		0.89	0.27	0.10	0.23	0.12	0.27	0.21
		1.00	0.24	0.09	0.21	0.11	0.24	0.18
Pseudomonas aeruginosa	Ceftazidime	0.00	1.10	16.41	2.19	11.47	1.33	2.89
		0.11	0.86	1.28	1.15	1.43	0.86	1.30
		0.22	0.69	0.51	0.79	0.64	0.68	0.80
		0.33	0.57	0.30	0.59	0.39	0.56	0.56
		0.44	0.48	0.21	0.46	0.28	0.47	0.42
		0.56	0.41	0.17	0.38	0.21	0.41	0.34
		0.67	0.36	0.14	0.32	0.17	0.35	0.28
		0.78	0.31	0.12	0.27	0.14	0.31	0.24
		0.89	0.27	0.10	0.23	0.12	0.27	0.21
		1.00	0.24	0.09	0.21	0.11	0.24	0.18
Pseudomonas aeruginosa	Fluoroquinolones	0.00	1.08	16.41	2.19	11.45	1.33	2.89
		0.11	0.85	1.28	1.15	1.43	0.86	1.30
		0.22	0.69	0.51	0.79	0.65	0.68	0.80
		0.33	0.57	0.30	0.59	0.39	0.56	0.56
		0.44	0.48	0.21	0.46	0.28	0.47	0.42
		0.56	0.41	0.17	0.38	0.21	0.41	0.34
		0.67	0.36	0.14	0.32	0.17	0.35	0.28
		0.78	0.31	0.12	0.27	0.14	0.31	0.24
		0.89	0.28	0.10	0.23	0.12	0.27	0.21
		1.00	0.25	0.09	0.21	0.11	0.24	0.18
Pseudomonas aeruginosa	Piperacillin	0.00	1.12	16.72	2.11	10.96	1.34	2.85
		0.11	0.87	1.27	1.14	1.44	0.86	1.30
		0.22	0.70	0.50	0.79	0.66	0.68	0.80
		0.33	0.57	0.30	0.59	0.40	0.56	0.56

		0.44	0.48	0.21	0.46	0.28	0.47	0.42
		0.56	0.41	0.16	0.38	0.22	0.40	0.34
		0.67	0.35	0.13	0.32	0.18	0.35	0.28
		0.78	0.31	0.12	0.27	0.15	0.31	0.24
		0.89	0.27	0.10	0.24	0.13	0.27	0.21
		1.00	0.24	0.09	0.21	0.11	0.24	0.18
Streptococcus pneumoniae	Macrolides	0.00	1.12	16.51	2.27	11.52	1.33	2.93
		0.11	0.87	1.28	1.16	1.44	0.87	1.31
		0.22	0.70	0.51	0.79	0.64	0.68	0.80
		0.33	0.57	0.30	0.59	0.39	0.56	0.56
		0.44	0.48	0.21	0.46	0.27	0.47	0.42
		0.56	0.41	0.16	0.37	0.21	0.40	0.34
		0.67	0.36	0.14	0.31	0.17	0.35	0.28
		0.78	0.31	0.12	0.27	0.14	0.31	0.24
		0.89	0.27	0.10	0.23	0.12	0.27	0.21
		1.00	0.24	0.09	0.20	0.11	0.24	0.18
Streptococcus pneumoniae	Penicillins	0.00	1.09	16.50	2.27	11.52	1.33	2.94
		0.11	0.85	1.29	1.16	1.44	0.87	1.31
		0.22	0.69	0.51	0.79	0.64	0.68	0.80
		0.33	0.57	0.30	0.59	0.39	0.56	0.56
		0.44	0.48	0.21	0.46	0.27	0.47	0.42
		0.56	0.41	0.16	0.37	0.21	0.40	0.34
		0.67	0.36	0.14	0.31	0.17	0.35	0.28
		0.78	0.31	0.12	0.27	0.14	0.31	0.24
		0.89	0.28	0.10	0.23	0.12	0.27	0.21
		1.00	0.25	0.09	0.20	0.11	0.24	0.18

Source: Constructed by the Authors.

Supplementary Annexure 11: Projected Demographic Indicators

The online dashboard presents the projected demographic indicators under the demographic scenarios. All the regions illustrate comparable patterns of population growth under the scenarios. Western Asia and Western Europe observe the lowest growth variations under the Zero-migration scenario, while Northern and Southern Europe experience those under the Low-fertility scenario. The highest population growth variations are attained under either the Instant replacement or High-fertility scenarios. Between 2025 and 2030, all the regions under all the scenarios observe very low population growth, which then recovers.

The population growth trajectories tend to stabilize starting from the mid-2030s. After that, notably, almost all the regions, except for Eastern Europe, experience a decreasing trend in population growth rates. The scenarios also tend to move together for most regions, while Eastern and Northern Europe illustrate apparent clustering among the regions. Notably, under the Instant-replacement and High-fertility scenarios, either the population growth rates are higher (e.g., in Northern Europe) or the population decline rate slows down (e.g., in Eastern Europe). Overall, the range of variations remains between -1 to +1 percent across all the regions and scenarios.

Population ageing growth changes vary within a higher range compared to population growth. The variation patterns are also not similar across all the regions, as with population growth patterns. In the short run, until the late 2020s, Eastern and Northern Europe experience a reducing trend in population aging growth, while Western Asia and Western Europe experience an increasing trend in population aging growth.

The projections under the scenarios start to diverge starting from 2030. All the regions, except for Eastern Europe, experience a peak in population aging growth in the early 2030s, and the growth rates reduce after that. Population aging growth rates start increasing again from 2045 for Northern and Western Europe and after 2040 for Western Asia. Eastern and Southern Europe experience declining population ageing growth rates after 2045. Overall, Western Asia experience higher population aging growth rates by 2050 compared to 2020 under all the scenarios, while the other regions experience a range of results under the scenarios. The Low-fertility and Zero-migration scenarios yield the highest population aging growth rates in all the regions except for Western Asia.