Center on Regulation and Markets at BROOKINGS

JUNE 2022

ANTIMICROBIAL RESISTANCE

DESIGNING A COMPREHENSIVE MACROECONOMIC MODELING STRATEGY

Roshen Fernando and Warwick J. McKibbin

ABSTRACT

Antimicrobial resistance (AMR) is a dominant and growing global health threat that led to 1.27 million deaths in 2019. Given the widespread use of antimicrobials in agriculture and industrial applications in addition to healthcare and a range of factors affecting AMR, including climate variability, demographic trends, and plastic and metal pollution, an economy-wide approach is essential to assess its macroeconomic implications. This study summarizes the existing literature on the identified factors driving AMR and reviews the factors that have been considered in existing macroeconomic studies. We highlight the limitations in the available studies and suggest how those could be overcome via an economy-wide modeling approach that integrates the factors behind the evolution of AMR. We present three frameworks to conceptualize the economy-wide use of antimicrobials, the epidemiology of AMR, and how AMR affects the economy in a stylized economy embedded within a more extensive system. We propose how the AMR impacts could be mapped onto economic variables, discuss the significance of these shocks, and outline how AMR evolution scenarios could be designed, particularly with reference to climate change, demographic trends, and associated socioeconomic changes. We also discuss how modeling studies could be improved to increase their utility to policymakers and increase comparability across studies. We conclude with the major policy implications arising from the study which emphasize an economy-wide one-health approach to address AMR; regulation of the antimicrobial supply chain and incentivizing innovations; global cooperation to address AMR, and alleviating uncertainties for policymaking via scaling up the surveillance of AMR, encouraging research collaboration and enabling access to data on AMR and antimicrobial consumption.

ACKNOWLEDGEMENTS

The authors gratefully acknowledge the financial support from the Australian Research Council Centre of Excellence in Population Ageing Research (CEPAR) (CE170100005).

DISCLOSURES

The Brookings Institution is financed through the support of a diverse array of foundations, corporations, governments, individuals, as well as an endowment. A list of donors can be found in our annual reports, published online. The findings, interpretations, and conclusions in this report are solely those of its author(s) and are not influenced by any donation.

CONTENT

I. BACKGROUND

1.1 Economic importance of microorganisms

Microorganisms, including bacteria, fungi, viruses, algae, and protozoa, have played a vital role in the survival and evolution of humans, animals, and plants. One of the most important functions of microorganisms is recycling organic and inorganic matter through their interactions in the carbon, nitrogen, and sulfur cycles via which they contribute to maintaining the stability of the biosphere. Microorganisms are also the initial source of nutrients in many food chains. The chemical reactions of microorganisms on organic and inorganic matter have been utilized in various agriculture (e.g., production of fertilizers) and industrial applications (e.g., fermentation and synthesis of proteins and enzymes). However, microorganisms also have a range of undesirable effects on the survival of humans, animals, and plants, including microbial diseases. The historical plagues such as the "Black Death" and the ongoing COVID-19 pandemic exemplify the negative implications of microorganisms on humans.

With the advancement of science and technology, methodologies to harness the positive implications and reduce the negative impacts of microorganisms have been developed. The discovery and mass production of antimicrobial medicine and chemicals has been an effective response to tame the undesirable implications of microorganisms. The discovery of antimicrobial medicine, such as penicillin and sulfonamides in the early 1900s, revolutionized the treatment of microbial infections and has been vital to medical procedures, such as cesarean sections, chemotherapy, organ transplants, and surgeries. Currently, antimicrobials are used in agriculture and aquaculture for therapeutic, metaphylaxis, and prophylaxis purposes and growth promotion. In industrial applications, antimicrobials are used to control the activity of microorganisms where physical processes (such as irradiation or heat) are ineffective or impractical[1]. Antimicrobial paints, coatings, additives, and preservatives have widespread uses in manufacturing wood, paper, textile and cosmetics, plastic and metal, energy production, construction, transportation, utility sectors, and the healthcare sector.

However, harmful microorganisms, notably the pathogens that cause infections among humans and animals, have developed resistance to antimicrobials (WHO 2021a). In general, the increase in resistance in microorganisms against antimicrobials is called antimicrobial resistance (AMR), and AMR threatens the effective use of antimicrobials.

1.2 AMR: Origins and evolution

Adapting to challenging and changing environments or circumstances is a fundamental driver of the evolution of all living beings, which is also applicable to microorganisms. Accordingly, developing resistance to antimicrobials is an element of the natural evolution of microorganisms. While some microorganisms are intrinsically resistant to antimicrobials, there are two main ways a non-intrinsically resistant microorganism acquires resistance: genetic mutations within the cell to its own chromosomal DNA and acquisition of genetic material from a resistant cell via transformation, transduction, or conjugation. Antimicrobials often target destroying a microorganism or preventing its growth by either disrupting the cell membrane, inhibiting cell wall synthesis, inhibiting protein synthesis, inhibiting nucleic acid (DNA or RNA) synthesis, or inhibiting metabolism (Rani et al. 2021). While intrinsically resistant microorganisms would either have an impermeable cell membrane or lack the target of antimicrobials, acquired resistance could lead to producing enzymes that deactivate antimicrobials, pumping antimicrobials out of the cells, or modifying the target of antimicrobials[2]. When antimicrobials are used to eliminate the susceptible and non-resistant strains to the antimicrobials, the survival advantage for the resistant strains increases. Overuse, misuse, and underuse of antimicrobials for various applications, including therapeutic uses, and continuous exposure of antimicrobials in the environment (such as in healthcare settings, wastewater treatment facilities, and the built environment) further increase the selective pressure and accelerate the resistant acquisition rates among microorganisms. With the exposure to a broader array of antimicrobials, some microorganisms have developed resistance not only to a single antimicrobial targeting them but to multiple antimicrobials. The microorganisms are referred to as "superbugs" (Davies & Davies 2010).

Harmful microorganisms, notably the pathogens that cause infections among humans and animals, have developed resistance to antimicrobials.

1.3 Factors driving AMR

Suboptimal consumption of antimicrobials and selective pressure exerted by such consumption is the uncontested and immediate factor driving AMR. A vast body of literature explores how antimicrobial consumption in different sectors, particularly healthcare and agriculture (including crops, livestock, and aquaculture), has aggravated AMR[3]. In the healthcare sector, a wide range of literature analyzes the suboptimal antimicrobial consumption among individuals (self-prescription or not following the prescription by a healthcare practitioner[4]), within primary care settings (via suboptimal diagnosis and prescription by general practitioners[5]), and within hospital settings (via mismanagement and suboptimal consumption of antimicrobials[6]). The literature also often focuses on different infections and/or antimicrobial-pathogen combinations and illustrates possible interventions to reduce suboptimal diagnosis, prescription, and consumption.

However, as Llor and Bjerrum (2014) suggest, health standards and practices, sociocultural characteristics (such as attitudes, beliefs, perceptions, etc.), and socioeconomic background (such as the healthcare financing structure, economic incentives provided by the pharmaceutical industry, and income distribution) of various countries influence the behavior of patients and healthcare practitioners when consuming antimicrobials. To understand the underlying factors driving antimicrobial consumption in the healthcare sector, the World Health Organization (WHO) (2015) recommends the use of the Knowledge-Attitude-Practice (KAP) framework[7]. Accordingly, a large body of regional, national, and sub-national studies explore the role of sociocultural and socioeconomic factors above in driving antimicrobial diagnosis, prescription, and consumption practices in different parts of the world.

Demography is another crucial factor often highlighted in KAP studies when explaining the variation of antimicrobial consumption across countries. There is also a wide range of studies assessing the demographic characteristics of patients suffering from various infections affected by AMR and the role of demographic factors in the consumption of antimicrobials (e.g., Nugent et al. 2022; Di et al. 2022; Alnasser et al. 2021; Jimah & Ogunseitan 2020; Chen et al. 2019; Schroder et al. 2016). Some of the common demographic factors considered in these studies are age, gender, marital status, educational level, income, occupation, and place of residence. Although limited, existing time-series studies have also explored the implications of broader demographic trends such as changes in population growth and density (e.g., Michael et al. 2014; Bruinsma et al. 2003), population aging (e.g., McKee et al. 2021; Yoshikawa 2002), and migration (e.g., Elisabeth et al. 2021; Peters et al. 2020; Abbas et al. 2018; Nellums et al. 2018). Notably, the studies on population aging point out a two-way relationship with AMR. As the susceptibility to infections increases and with multimorbidity (the co-occurrence of multiple chronic conditions), the elderly populations require more antimicrobial medicine. Accordingly, consuming more antimicrobials by the elderly population increases the selective pressure for microorganisms and aggravates AMR. Polypharmacy, or the reliance on multiple antimicrobials to treat various diseases and conditions among elderly people, enables resistance acquisition among various microorganisms and gives rise to superbugs. Aggravating AMR, in turn, reduces the effectiveness of existing medicine and disproportionately affects the aging population.

An ecological perspective on AMR recognizes the interactions among pathogens and commensal microorganisms and how such interactions would strengthen the acquisition, retention, and increase of AMR (Gonzalez-Zorn & Escuredo 2012; Marshall et al. 2009; Summers 2002). Palecchi et al. (2008) summarize the

Climate variability has recently garnered attention as another critical mechanism affecting AMR.

presence of AMR genes in humans and animals, especially in remote areas of the world, even in the absence of sustained exposure to antimicrobials. They emphasize the role of environmental contamination and environmental ecosystems (such as rivers) in transmitting AMR genes. Preventing both the natural (such as air, soil, and waterways) and built environment (such as sanitation infrastructure) from becoming reservoirs of antimicrobial genes is thus crucial to preventing the spread of AMR (World Economic Forum 2020; Bengtsson-Palme et al. 2017; Prestinaci et al. 2015). The United Nations Environment Programme (UNEP) (2017) discusses the role of not only antimicrobial medicine but also other antimicrobial chemicals, such as biocides. An emerging body of evidence demonstrates how plastic pollution, particularly microplastics in marine ecosystems, increases the surface area for the growth of pathogens and thereby aggravates AMR (Pham et al., 2021; Bank et al., 2021; Moore et al., 2020). A similar strand of studies discusses the role of soil pollution induced by heavy metals (particularly mercury, cadmium, copper, and zinc) in co-selection and thereby aggravating AMR (Seiler & Berendonk 2012; Knapp et al. 2011). UNEP (2022) highlights the importance of effectively managing effluent and waste from pharmaceutical industries, healthcare facilities, crops, livestock, fish processing industries, and other industries extensively using antimicrobials.

With the prevalence of antimicrobial genes in the environment, the movement of humans and live animals, especially across borders, enables the global spread of AMR. In a recent review, Bokhary et al. (2021) found that out of 30,060 resistant isolates evaluated, the most common origin of resistant genes was Asia, accounting for 36 percent of the total isolated genes. High-income countries globally are more likely to be recipients of AMR genes. Plaza-Rodriguez et al. (2021)

present evidence for AMR genes in migrant birds, and Arnold et al. (2016) emphasize the role of aquatic and terrestrial wildlife trade and transfer in the spread of AMR genes. Collignon et al. (2018) also observe the role of governance in explaining the diversity of AMR across countries. These findings point to the importance of empowering health systems and policies worldwide and how AMR has become a 'global wicked problem' that requires collective action.

Climate variability has recently garnered attention as another critical mechanism affecting AMR. Existing studies have found evidence of rising AMR amidst increasing average temperatures (e.g., Kaba et al. 2020 and McGough et al. 2020 in Europe; McFadden et al. 2018 in the US). Rodriguez-Verdugo et al. (2020) illustrate that the increasing temperature could affect the response of pathogens to antimicrobials at three primary levels: physiological, genetic, and community levels. Gudipati et al. (2020) argue that some of the factors contributing to climate change, such as land-use changes via deforestation and intensive agricultural practices, have aggravated AMR from disruptions to animal habitats. In addition to the direct implications on AMR, climate variability could also indirectly affect AMR through its impacts on the incidence of infections and the resulting demand for antimicrobial consumption. Cavicchioli et al. (2019) explain how host-pathogen interactions change amidst climate variability, which could prompt water, air, food, and vector-borne diseases to spread faster. Addressing climate change is also likely to be crucial for taming AMR.

1.4. Implications of AMR: Current understanding

Most existing studies have emphasized the AMR implications on human, animal, and environmental (mostly plant) health. The existence of AMR among pathogens was known even before the discovery of antimicrobial medicine, and the development of resistance was expected even during the early stages of antimicrobial medicine development (Davies & Davies 2010). Since the 1950s, when most of today's antimicrobial drugs were developed, the pharmaceutical industry has continued to learn about pathogens' biochemical reactions and resistance mechanisms and improved the medicine to withstand them. However, with the increase in resistance, the antimicrobial drug administration regulations require using the new antimicrobial medicine sparingly which reduces the exposure of the antimicrobial medicine to pathogens or microorganisms in general. Consequently, this reduces the opportunity for the pharmaceutical industry to recover the underlying significant investment costs in antimicrobial medicine production by selling the medicine widely and for a longer period of time. Accordingly, no new classes of antimicrobial medicine have been discovered since the 1980s (Wellcome Trust 2020; Ventola 2015). About 43 traditional antimicrobial drugs are currently in the clinical development stage, and 292 are in the pre-clinical development stage. Of these, only 26 and 60, respectively, focus on the priority pathogens[8] (some of which are multidrug-resistant) (WHO 2022).

WHO recognizes AMR as one of the top ten global public health threats (WHO 2021a). The declining efficacy of antimicrobial drugs is leading to numerous challenges:

- Infections are taking longer to heal and are costlier to treat,
- Some infections cannot be treated with existing antimicrobial medicine,
- Susceptibility to infections and the risk of death from infections are increasing,
- Infections once eradicated in one part of the world are re-emerging or emerging in a different part of the world,
- New infections are emerging, and
- The effectiveness of medical procedures is reduced.

Increasing mortality and morbidity from infections is the main pathway through which AMR affects humans. In 2014, KPMG and RAND Europe estimated that 700,000 deaths were attributable to AMR related to HIV, Malaria, Tuberculosis, and three priority pathogens (*Staphylococcus aureus*, *Escherichia coli*, and *Klebsiella pneumoniae*), and that the deaths could reach 10 million per annum by 2050 (O'Neil 2016). Cecchini et al. in 2015 illustrated that the likelihood of dying from an infection could increase three-fold in G7 countries if the infection does not respond to antimicrobial medicine. In 2017, the Centre for Disease Control (2019) estimated that two million infections were attributable to AMR in the United States alone, leading to at least 23,000 deaths. The European Centre for Disease Prevention and Control (2017) estimated 25,000 AMR-attributable deaths in Europe in the same year. The latest global estimate on AMR-attributable deaths is provided in the Global Burden of Bacterial Antimicrobial Resistance study (GRAM) for 2019, released in 2022. According to that report, 1.27 million lives lost in 2019 have been attributed to 23 pathogens resistant to existing antimicrobial medicine (Murray et al. 2022).

A one-health framework recognizes human, animal, and plant (environmental) health as interconnected components when achieving optimal planetary health. Within a one-health framework, as Morel et al. (2020) point out, direct and indirect costs of AMR could be identified. The direct costs of AMR encompass out-of-pocket expenditures (from patients or farmers), treatment costs borne by the health services, treatment costs for patients for long-term complications, costs of decontamination in the case of the environment, surveillance of AMR, training for healthcare and other relevant professionals, and legal and insurance costs. The indirect costs include opportunity costs of, morbidity and mortality among the labor force, public healthcare expenditure, healthcare resources, research and development costs, loss of productivity in the livestock sector, and additional burden to consumers from reduced production. Recognizing AMR's direct and indirect costs within a one-health framework demonstrates the relevance of an economy-wide response to AMR and how implications on one component of the triad could spill over to other components.

Alternatively, the burden of AMR could also be evaluated at multiple tiers: patient, healthcare system, and the economy or society (Wozniak et al. 2019; Dadgostar 2019; Shrestha et al. 2018). Health economic approaches have been widely utilized to assess the burden of AMR at the first two levels and the costs considered include hospital occupancy, use of medicine, laboratory services and medical procedures, and human resource utilization. At the societal or economic level, the focus has been on the loss of productivity and healthcare expenditure.

In 2019, 23 pathogens resistant to the existing antimicrobial medicine were responsible for 1.27 million deaths.

Covering HIV, Malaria, Tuberculosis, and three priority pathogens (*Staphylococcus aureus*, *Escherichia coli*, and *Klebsiella pneumoniae*), as well as their effects on morbidity and mortality among employees and government expenditure on healthcare, KPMG (2014) and RAND Europe (2014) expect the cumulative economic burden of AMR to reach $US 100 trillion by 2050. Using a similar methodology, Ahmed et al. (2017) estimate the burden of AMR to reach $US 85 trillion between 2015 to 2050. OCED (2018) estimates that in 33 European countries alone, the direct annual healthcare cost associated with AMR could be as high as $US 3.5 billion. The World Bank (2017), considering implications on livestock in addition to mortality and morbidity among humans due to AMR, estimates that under a low-AMR scenario, global annual GDP losses could exceed $US 1 trillion after 2030 and reach $US 2 trillion by 2050. Under a high-AMR scenario, the yearly GDP losses could reach $US 3.4 trillion by 2030 and $US 6.1 trillion by 2050. WHO (2021b) also demonstrates the disproportionate burden of AMR on developing countries, and how an additional 28.3 million people could be pushed into poverty in these countries. Progress toward achieving at least seven Sustainable Development Goals (SDGs) is directly affected, and about six additional SDGs could be indirectly affected by AMR. Therefore, containing AMR is central to both sustainable economic growth and development.

II. ECONOMIC IMPLICATIONS OF AMR

2.1 Modeling the economic implications of AMR: Current understanding

Early studies assessing the economic implications of AMR extended the fundamental health economic approaches, such as cost minimization, cost-effectiveness, cost-benefit, or cost-utility analyses, to evaluate the additional burden of infections affected by AMR (Coast et al. 1996; Holmberg et al. 1987, and Liss & Batchelor 1987). With the growing appreciation of the significance of AMR as a problem beyond infections, three main strands of literature assessing the economic implications of AMR can be identified in more recent studies. The first strand considers the patient burden of AMR due to mortality and morbidity arising from infections affected by AMR. The second strand assesses the healthcare system burden of AMR due to secondary infections in patients due to AMR and extended hospital care induced by infections affected by AMR. These studies mainly utilize regression analysis and significance tests (Naylor et al. 2016). The third strand assesses the economy-wide implications of AMR. These studies mostly use partial or computable generable equilibrium (CGE) models.

One of the earliest attempts to apply an economy-wide CGE model to AMR was to assess the implications of methicillin-resistant Staphylococcus aureus (MRSA) in Britain (Smith et al. 2005). The closed-economy model featured ten sectors, a representative firm in each sector, a representative consumer, a bank, and a government. AMR has been introduced as a shock on labor supply, sectoral productivity, and a cost to healthcare delivery. The simulations demonstrated the implications of AMR on macroeconomic aggregates such as GDP, investment, savings, consumption, employment, and welfare. The application of the GLOBE model by Keogh-Brown et al. (2009) extended CGE modeling to the global economy. The approach involved evolving antibiotic resistance as a function of prescription and calculating morbidity and mortality estimates due to pathogens developing resistance to the antibiotics. The study explored the implications on savings, trade, and exchange rates and evaluated the potential of interventions to reduce antibiotic consumption and optimize antibiotic prescriptions.

The first systematic review of the economic implications arising from the priority pathogens and infections acquiring resistance to existing antimicrobials against them was commissioned in 2014 by the Prime Minister of the United Kingdom. The review, chaired by Jim O'Neil and completed in 2016, included two economic studies conducted by KPMG and RAND Europe in 2014. KPMG (2014) utilized a partial general equilibrium model where total factor productivity (TFP) was modeled as a function of five factors: macroeconomic stability, the openness of the economy, quality of infrastructure, the strength of public institutions, and human capital. The impacts on TFP were combined with the effects modeled on the labor force due to augmented mortality and morbidity related to AMR and capital-income ratio to derive the implications on the global economy. The study was also supplemented with an analysis of financial impacts at the regional level, emanating from public health expenditure spent on combating AMR. The CGE model used by RAND Europe (2014) had shocks on population growth—due to mortality—and labor efficiency—due to morbidity impacts of AMR.

Ahmed et al. (2017) used the GLOBE-Dyn model, the recursive dynamic version of the GLOBE model, to assess the global macroeconomic impacts of AMR due to the same priority pathogens and infections covered in the AMR Review by O'Neil et al. (2016). Extending the KPMG and RAND Europe (2014) studies, the reduction in livestock production and global restrictions on livestock trade were considered. The World Bank (2017) has also estimated the AMR implications on both the labor force and livestock under two AMR evolution scenarios, although the details provided on the modeling approach are limited. OECD (2018) used the OECD Strategic Public Health Planning for AMR (SPHeP-AMR) model, a health economic model, with an extensive focus on the evolution of AMR and the epidemiology of the infections affected by AMR. The study also covered eight pathogens and considered the implications of AMR on medical procedures in addition to infections.

2.2 Modeling the economic implications of AMR: Limitations and challenges

While the existing studies provide valuable estimates of the economic burden of AMR, Hillock et al. (2022) outline several limitations that future studies should address. Designing reliable future AMR evolution scenarios is fundamental to the modeling. Such efforts should consider the transmission dynamics of AMR within a one-health framework. Furthermore, the non-linear relationships between AMR and antimicrobial consumption need to be better understood. The existing studies also do not demonstrate the role of behavioral and social factors, such as patient compliance with infection prevention and antimicrobial treatment measures. They also emphasize obtaining country-specific estimates to capture the heterogeneity across various parts of the world and increase transparency when reporting modeling methodologies and results.

A major challenge in assessing the economic implications of AMR lies in the lack of antimicrobial consumption and resistance data. There is no comprehensive accounting of the economy-wide production of antimicrobials, particularly antimicrobial medicine. Even the best available data on antimicrobial medicine consumption, which comes from the Global Antibiotic Consumption and Usage in Humans study by the Institute for Health Metrics and Evaluation (IHME), is likely to underestimate actual antimicrobial medicine consumption because of the prevalence of informal antimicrobial production, especially at household levels. Even though proprietary higher quality data on antimicrobial sales are available with pharmaceutical companies and private entities that collect such data, the data are not affordable for most researchers. Although the trade data available from the United Nations Comtrade database could be a useful source for identifying pharmaceutical sales across countries, disaggregating the data for antimicrobial classes remains a challenge. The availability of global granular data on the use of antimicrobial chemicals in agriculture and industries is even lower than that for pharmaceuticals.

Global surveillance of AMR by WHO only commenced in 2015, with the launch of the Global Antimicrobial Resistance and Use Surveillance System (GLASS). GLASS provides a standardized approach to collecting, analyzing, interpreting, and sharing data on AMR. Before that, only a handful of high-income countries (including Europe and the United States) had national or regional extensive surveillance mechanisms. The possibility of conducting global panel studies on historical data is thus limited. Even though the data on AMR rates in the food chain and environment is even more limited than in healthcare, GLASS is expected to incorporate those sectors into surveillance gradually. The GRAM study (Murray et al. 2022) provides the regional AMR rates for 88 drug-pathogen combinations covering 23 pathogens and 12 infections in 2019. The study also provides a consistent framework to map the consumption of antimicrobial medicine to infections, which was a challenge until the study was published.

III. AN INTEGRATED FRAMEWORK FOR ASSESSING THE MACROECONOMIC CONSEQUENCES OF AMR

In the above sections, we have reviewed the existing literature modeling the economic implications of AMR and the areas where modeling can be improved. In this section, we discuss three critical issues for designing an integrated modeling exercise on AMR: (1) Modeling the epidemiology of AMR, (2) Designing AMR evolution scenarios, and (3) Modeling the macroeconomic implications of AMR. The following sections discuss how these issues could be addressed despite the existing challenges, especially regarding data.

3.1 Modeling the epidemiology of AMR

3.1.1. ROLE OF ANTIMICROBIAL CONSUMPTION IN AGGRAVATING AMR

The widely cited framework for the epidemiology of AMR by Linton (1977) illustrates the role of antimicrobials in human consumption, agriculture (crops, livestock, and aquaculture), and industrial applications. It also outlines how antimicrobial consumption in households, agriculture, and industries could interact with environmental ecosystems and contaminate the environment. We extend this framework to highlight industrial applications of antimicrobials that are amenable to economic modeling. Figure 1 presents the modified framework. We illustrate soil, freshwater, and marine ecosystems but do not explicitly present air. We assume the economic sectors and the other ecosystems could interact with air anywhere within the framework. Antimicrobials always reach the ecosystems through an economic sector unless explicitly added.

The agriculture sector consists of crops, aquaculture and fisheries, livestock and companion animals, and forestry and wildlife. Antimicrobials (such as Streptomycin, Oxytetracycline, Gentamicin, etc.) are used to prevent diseases in crops (mainly rice, wheat, cereals, vegetables, and fruits) and as an additive to fertilizers[9]. Animal feed and aquaculture use antimicrobials for therapeutic, metaphylaxis, and prophylaxis purposes, and growth promotion[10].

The main industrial applications of antimicrobials are food production and packaging, textile manufacturing, sanitizers, paints, coatings, additives, preservatives, and petroleum recovery (in the energy sector). The paints, coatings, additives, and preservatives are then used in secondary applications in the manufacturing (such as wood, paper, textiles and cosmetics, plastics, and metal), energy, and services (such as construction, transportation, and utility) sectors, demonstrating the economy-wide consumption of antimicrobials[11].

Antimicrobial residues from agriculture, industries, and services contaminate the ecosystems mainly through solid waste and effluents. The exposure of antimicrobials to air via their industrial applications also increases the selective pressure. Interactions among the forestry and wildlife with soil and water bodies facilitate resistance gene transfer and the discovery of new hosts. Human interactions with the ecosystems and wildlife, mainly via recreational activities and agricultural and industrial applications, also enable resistance gene transfer.

3.1.2 ROLE OF FACTORS OTHER THAN ANTIMICROBIAL CONSUMPTION IN AGGRAVATING AMR

The extended framework for the epidemiology of AMR in Figure 1 assumes antimicrobial consumption to be the sole driver of AMR. While it is the dominant driver, as discussed in Section 1.3, other factors, such as socioeconomic, sociocultural, demographic, and environmental factors, either directly affect AMR or indirectly affect AMR via antimicrobial consumption. The role of these factors cannot be depicted in Figure 1 without substantially increasing its complexity. Figure 2 frames these factors contributing to AMR along with antimicrobial consumption.

Figure 2 illustrates that in addition to antimicrobial consumption in healthcare, agriculture, and industries, contamination of ecosystems with antimicrobials and other AMR promoters, global and national demographic trends, governance, health system resilience to internal and external health threats, climate variability, and openness to travel are important factors that contribute to AMR. As discussed in Section 1.3, there is already evidence for many of these factors. However, there is a general lack of systematic studies exploring the role of governance, health system resilience, and some aspects of demographic trends and climate variability.

The ICRG framework is a helpful starting point for evaluating the implications of AMR's systematic risks. The International Country Risk Guide (ICRG) (The PRS Group 2012) considers 22 indicators across three primary groups: political, economic, and financial. The political indicators include government stability, socioeconomic conditions, investment profile, conflicts, corruption, law and order, military, religious and ethnic tensions, democratic accountability, and bureaucracy. The economic indicators are GDP per capita, real GDP growth, inflation, fiscal balance, and current account balance. The financial indicators account for foreign debt holdings, international liquidity, and exchange rate stability.

Even though the relationship between some indicators of health systems (such as sanitation infrastructure) and AMR has been assessed in the existing studies, we believe there is the potential for a comprehensive evaluation to provide richer insights into the relationship. The Global Health Security Index, devised by the Nuclear Threat Initiative, the Johns Hopkins Center for Health Security, and the Economist Impact (2022), provides a valuable framework to think about the health system's resilience to global threats such as AMR. The Index accounts for the ability of a given country to prevent, detect, and respond to such threats, its health system capacity, compliance with global norms, and the risk environment.

Regarding climate variability, the current studies have only explored the implications of global warming, which indicates a part of the chronic climate risks on AMR. It is possible to incorporate other climate variables, such as precipitation, to identify the role of latent climate drivers in AMR. Furthermore, an investigation of the importance of extreme climate risks, such as droughts, floods, heat and cold waves, wildfires, and storms, could provide a more comprehensive assessment of the implications of climate risks on AMR.

3.2 Designing AMR evolution scenarios

As discussed in Section 2.2, one of the main challenges in modeling the implications of AMR lies in designing AMR evolution scenarios. With the limited observations of historical resistance rates, the existing studies have used hypothetical resistance rates or projected increases in future resistance rates. Economic evaluations, even under those hypothetical resistance rates, would still be helpful to policymakers given the complexity of AMR, lack of historical AMR surveillance, and lack of comprehensive knowledge about the evolution of AMR and uncertainty around the plethora of factors affecting it. We outline three possible approaches to improve the design of AMR evolution scenarios.

Firstly, the evolution of diseases could be incorporated as an intermediary step to derive mortality and morbidity estimates attributable to AMR. The existing studies mainly use mortality and morbidity rates directly attributable to priority pathogens affecting a range of diseases. A more granular approach would be to model the epidemiology of diseases affected by AMR and apply AMR rates to future pathways of disease evolution. The historical data on a wide array of diseases since 1990 is available from the Global Burden of Disease (GBD) studies conducted by IHME. Along with the mapping of diseases to pathogens causing them and antimicrobial medicine used to treat them provided in the 2019 GRAM study (Murray et al. 2022), reliable and more granular scenarios of the evolution of diseases and the burden of the diseases attributable to AMR could be derived. The future burden attributable to AMR from diseases could be analyzed within such scenarios using 2019 resistance rates or historical rates (where available). A range of sensitivity analyses could be conducted to support policymakers to account for the uncertainty. As both the GBD and GRAM studies also include health economic metrics, such as Deaths, Disability-adjusted Life Years (DALYs), Years Lived with Disability (YLDs), and Years of Life Lost (YLLs), the changes in the severity of diseases could also be analyzed. Additional weights for such considerations could be allocated within the design of scenarios.

Secondly, there are widely used scenarios with recognized narratives for other global challenges affecting AMR, such as demographic trends and climate change. The Shared Socioeconomic Pathways (SSPs), which have been used to evaluate climate change scenarios since the Intergovernmental Panel on Climate Change (IPCC) sixth assessment report, are defined with socioeconomic and demographic assumptions. Incorporating such assumptions along with climate pathways would also help integrate the climate implications of AMR (and diseases) into the climate impact literature. Assessing the economic impacts of AMR alongside climate change impacts within similar modeling frameworks would also enable policymakers to compare the scale of AMR burden with climate change.

Thirdly, the effect of antimicrobial consumption on the productivity of agriculture and industrial applications needs to be better understood. Even though the proportion of antimicrobials used among other inputs could be lower, the impact antimicrobials have on the outputs is substantial (e.g., the loss of cattle from a disease would not be preventable without antimicrobials). Such analyses would help reliably derive the implications of aggravating AMR on the productivity of agriculture and industries relying on antimicrobials.

3.3 Modeling the macroeconomic implications of AMR

3.3.1 A STYLIZED ECONOMY WITHIN THE ENVIRONMENT

Figure 3[12] illustrates the interactions among economic agents within a stylized economy that interacts with the broader environment[13]. The environment mainly consists of four ecosystems: air, marine ecosystems, freshwater ecosystems, and soil. Plants, animals, microorganisms, and households are living beings in the environment, and they interact among themselves and the firms. In addition to its interactions with the ecosystems and living beings, firms also rely on the environment for energy. The activities of households and firms generate solid waste, effluents, and emissions which are passed on to the environment.

There are four main economic agents in the domestic economy: households, firms, a government, and asset markets. The domestic economy interacts with the foreign economies via an external sector. Households provide labor to the firms and receive wages in return. Households rely on firms for consumption and pay for goods and services using their income and assets, both physical and financial. Households also pay taxes to the government and receive subsidies and public goods from the government. The excess income is accrued into assets via savings. When constrained for liquidity, households could borrow from the asset markets.

Firms utilize labor from households, capital (debt and equity) from asset markets, and imports from the external sector when producing goods and services for households, the government, and exports. Firms pay wages to households, capital rents to asset markets, and taxes to the government. Firms could also receive investments from the external sector as foreign direct investments and invest in the asset markets or conduct foreign direct investments.

When the effectiveness of antimicrobials used in agriculture and industrial applications declines, the productivity of those sectors falls.

The government provides public goods to households and transfers and subsidies to households and firms. It also purchases goods and services from firms. Government expenditure is financed with taxes from households and firms, public bonds issued to asset markets, and foreign aid from the external sector. When running a fiscal surplus, the government could also invest in the asset markets.

The asset markets combine savings from households, investments from firms and the government, and foreign portfolio investments from the external sector. The asset markets could lend to households and the government and invest in or lend to firms.

The economy is assumed to interact with the ecosystems only through households and firms. The sectors illustrated in Figure 1 are the main channels of antimicrobial consumption by households and firms. Households interact with microorganisms, animals, and plants when consuming goods and services provided by firms. The microorganisms, animals, and plants also interact among themselves and with the ecosystems (although not specifically illustrated in Figure 3 for simplicity). Firms interact with the ecosystems via resource extractions, emissions, and disposal of solid waste and effluents. The ecosystems also interact among themselves.

3.3.2 MACROECONOMIC SHOCKS DUE TO AMR WITHIN THE STYLIZED ECONOMY

Within the stylized economy, there are six possible shocks or pathways via which AMR could impact the economy: reduction in labor productivity, decrease in total factor productivity of firms, increase in government expenditure, changes in consumption patterns, changes in household wealth, and changes in country and sector risk premia. While the first five shocks could be illustrated in Dynamic Stochastic General Equilibrium (DSGE) models and Computable General Equilibrium (CGE) models, substantial characterization of financial markets is necessary for such models to illustrate the changes in country risk premia.

Reduction in labor productivity due to morbidity and mortality is the dominant pathway via which AMR affects the economy. When the effectiveness of antimicrobial medicine and medical procedures relying on antimicrobial drugs reduces, the susceptibility to diseases rises, the diseases take longer to heal, and the probability of death from the diseases increases. Consequently, the quantity and quality of existing and potential labor force available for productive economic activities would reduce. The burden on the dependent population groups (such as children and the elderly) suffering from the diseases affected by AMR could further diminish the productivity of the working-age population group. Various economic sectors would be differently affected depending on how they rely on labor as an input compared to other inputs. All the studies discussed in Section 2.1 have employed shocks on labor productivity, even though they differ in the granularity and formulation approaches. Macroeconomic studies could utilize health economic metrics such as DALYs, YLDs, and YLLs to formulate labor productivity shocks consistently across models, enabling model comparison to be more convenient for policymakers[14].

Reduction in factor productivity is another important pathway for mapping AMR implications onto the economy. When the effectiveness of antimicrobials used in agriculture and industrial applications declines, the productivity of those sectors falls. The sectors that rely on those sectors would subsequently be affected depending on their reliance on the directly affected sectors. A conventional approach would be to derive the productivity shocks based on the proportion of inputs contributed by those affected by AMR. However, traditional approaches may underestimate the broader importance of antimicrobials in the production processes and the substantial changes required in production processes if antimicrobials are not as effective. Therefore, productivity shocks should capture the broader role of antimicrobials in various affected sectors. Formulating productivity shocks at sector levels would be amenable in CGE, DSGE, and hybrid models such as G-Cubed (see Fernando et al. (2021)) with sector disaggregation. For DSGE models without sectoral disaggregation, sector-specific productivity shocks could be aggregated to derive an economy-wide total factor productivity shock.

The fiscal burden of AMR is a significant yet underestimated aspect of current economic studies. While a conveniently justifiable approach would be to assess the incremental expenses borne in treating diseases affected by AMR, a comprehensive approach would also have to account for costs for preventive measures. WHO's (2015) guidance on national action plans for AMR includes strategies, such as strengthening national AMR surveillance, strengthening infection prevention and control, and improving awareness of the development of AMR and rational use of antimicrobials, which could be considered when costing such preventive measures.

The impact of consumer choices in products using antimicrobials, including antimicrobial medicine and particularly food (processed or raw crops, meat, fish, and their derivatives), on AMR is an emerging body of research. Jans et al. (2018) have demonstrated consumer exposure to antimicrobials used in the food chain via both domestic and imported food. Ancillotti et al. (2022) argue that forward-looking consumers would change their food consumption preferences once educated about the consequences of AMR. The ongoing COVID-19 pandemic is also exemplary of the changes in consumer preferences, particularly for service sectors (such as transportation, food and beverage services, etc.), when faced with health risks and their economic consequences (Kohli et al. 2022). Thus, modeling the economic repercussions of changes in consumer preferences once faced with AMR risk is a helpful input for policymakers to understand the burden of AMR.

Household wealth depends on their current assets and the present value of expected future income flows. When faced with survival risks, households tend to increase the risk premium of their subjective discount rate. Increases in the risk premia could result in substantial household wealth, utility, and welfare changes. Even though this pathway is widely adopted in assessing the economic consequences of diseases[15], it has not yet been adopted when evaluating the economic effects of AMR. Adopting this pathway in AMR studies could help compare literature on known diseases with AMR and observe the importance of aggravating AMR.

Asset markets, particularly financial markets, respond to changes in relative systemic risks among countries and unsystematic risks among the sectors. When faced with a global threat that affects different countries and sectors differently, investor preferences tend to change. These changes would be reflected in financial markets via the rebalancing of investments. COVID-19 is exemplary of such changes in financial markets (Jabeen et al. 2022; Bradley & Stumpner 2021). As AMR also affects specific sectors directly due to their reliance on antimicrobials (such as agriculture) and labor (such as services) and other sectors indirectly through production chains relying on directly affected sectors, investor preferences among sectors would change. As the systematic risk of AMR differs across countries depending on the differential exposure of countries to factors driving AMR (discussed in Section 1.3), investor preferences for countries would change. General equilibrium models with an illustration of financial markets would be able to demonstrate the economic consequences of AMR due to changes in country and sector risk premia[16].

3.3.3 MODELING RESULTS, SENSITIVITY ANALYSES, AND POLICY EXPERIMENTS

Section 3.3.2 discusses how AMR impact pathways could be mapped onto a general equilibrium model with the characterization of the stylized economy in Figure 3. The model results would demonstrate the implications of various AMR shocks on economic aggregates, such as real GDP, investment, consumption, fiscal balance, current account balance, trade, employment, and welfare, under different scenario assumptions. Results on interest rates, wages, price levels, and exchange rates could also be produced depending on the model characteristics. Such results would be helpful to policymakers, including governments and central banks.

However, given the enormous uncertainty around factors driving AMR and the lack of comprehensive data on AMR, modeling exercises should be transparent about their assumptions and amenable to sensitivity analyses. Following a coherent framework such as the one suggested in this study and continuous cooperation among modelers could improve the comparability, reliability, and utility of modeling outputs to policymakers. Introducing mitigation policy responses to macroeconomic modeling would also increase the relevance for policymakers. Communicating the modeling approaches and results while appreciating the multidisciplinary audience for AMR research could increase the acceptability and enrich the interdisciplinary dialogues for further improving modeling approaches.

IV. POLICY IMPLICATIONS AND RECOMMENDATIONS

This study alludes to several important policy implications. We discuss the importance of four main implications: (1) An economy-wide one-health approach to address AMR; (2) Regulation of the antimicrobial supply chain and incentivizing innovations; (3) Global cooperation to address AMR, and (4) Alleviating uncertainties for policymaking via scaling up the surveillance of AMR, encouraging research collaboration and enabling access to data on AMR and antimicrobial consumption.

AMR should no longer be perceived as a challenge to the health sector or agriculture sector alone but rather as an economy-wide problem that interacts with the broader environment for two main reasons. On one hand, as illustrated in Figure 1, the consumption of antimicrobials is not limited to healthcare and agriculture but extends to the whole economy via direct or indirect dependencies. Thus, aggravating AMR will not only affect the healthcare and agriculture sectors but also other economic sectors via linkages and spillovers, illustrated in Figure 3. On the other hand, the current understanding of factors affecting AMR itself demonstrates that factors beyond overuse, underuse, and misuse of antimicrobials, such as climate variability, demographic trends, governance, the quality of the natural and built environment, and cross-border mobility also interact with AMR. Thus, adopting an economy-wide approach within a one health framework, which recognizes the interactions between the economy and the broader environment, is essential.

AMR should no longer be perceived as a challenge to the health sector or agriculture sector alone but rather as an economy-wide problem.

The development of new antimicrobials is inhibited by numerous challenges , and thus preserving the existing stock of antimicrobials is essential. Regulating all the elements of the supply chain of antimicrobials is a vital part of this effort. This includes production, evaluation and market authorization, procurement and supply, consumption, and disposal, as illustrated in FAO, OIE, and WHO (2020). In the short to medium term, it is critical to disincentivize the informal production of antimicrobials, prevent further expansion of informal markets (especially in developing countries), and raise awareness of antimicrobial consumption among both firms and households. It is also important to improve diagnosis and prescription standards (particularly in the healthcare sector) and regulate antimicrobial disposal throughout the economy. Incentivizing research and development and innovations to sustain the efficacy of existing antimicrobials and to explore alternatives to antimicrobials[17] are vital in the long term.

Given the transboundary nature of AMR, global cooperation is essential to collectively address the issue.

AMR is a global problem that requires global solutions built on global cooperation. As discussed in Section 1.3, there are factors affecting AMR which are beyond the control of an individual state. Given the transboundary nature of AMR, global cooperation is essential to collectively address the issue. WHO, Food and Agriculture Organization (FAO), The United Nations Environment Programme (UNEP), and the World Organization for Animal Health (OIE) have an active role in promoting and facilitating such cooperation. Empowering nations with limited technical and financial resources to adopt responsible regulations and collectively managing corporate interest is timely. The historical lessons from global actions towards cross-country problems such as ozone depletion, marine plastic pollution, and climate change could provide useful insights to initiate and sustain global cooperation toward AMR.

AMR creates at least two major sources of uncertainties for policy design. Firstly, as illustrated in Section 1.3, the world is still learning the factors driving AMR. Secondly, the AMR rates for different antimicrobial-pathogen combinations are not known for a vast majority of countries, especially Low and Low-middle Income countries. Hence, the global evolution of AMR is not yet completely understood. Given these existing uncertainties, the exact impacts of AMR on humans, the environment, and the economy as well as impact pathways cannot be fully evaluated. While we have suggested a robust pathway to model the macroeconomic consequences of AMR while navigating through these uncertaintie, scaling up AMR surveillance and making data widely available are vital to produce research evidence for policymaking. Furthermore, making the commercial data related to AMR, such as those on antimicrobial consumption and sales, widely publicly available is vital to empowering ongoing

IV. CONCLUSION

AMR is a natural phenomenon where microorganisms acquire resistance to antimicrobials as part of their evolution. However, overuse, misuse, and underuse of antimicrobials in healthcare, agriculture (crops, livestock, and aquaculture), and industrial applications have aggravated AMR. In addition to antimicrobial consumption, socioeconomic, sociocultural, demographic, and environmental factors also contribute to AMR, including climate change, demographic trends such as population aging, population growth, and migration, and plastic and metal pollution. Existing economic studies probably underestimate the burden of AMR in the absence of a comprehensive framework to incorporate the multitude of factors contributing to its evolution.

In this study, we present three frameworks that illustrate: (1) the economy-wide consumption of antimicrobials, (2) factors affecting AMR along with antimicrobial consumption, and (3) a stylized economy within the broader environment indicating the pathways via which AMR could give rise to economic shocks. We also present a comprehensive methodology to formulate economic shocks from AMR within DSGE or CGE models and indicate possible data sources that could be used in economic modeling. We discuss how scenarios amenable to policymakers could be developed also considering AMR interactions with other global challenges. We highlight the importance of sensitivity analyses in the economic modeling of AMR, given the uncertainties. We emphasize that modelers improve the communication of results and cooperate to support policymakers in understanding and addressing the silent pandemic of AMR.

We conclude the study by discussing four main policy implications arising from this exercise of developing a comprehensive macroeconomic modeling strategy for AMR. We reiterate the importance of an economy-wide approach to managing AMR within a one-health framework that recognizes the linkages between the economy and the broader environment. We recognize the importance of regulating the antimicrobial supply chains and incentivizing innovations and novel alternatives to antimicrobials in the long term. We illustrate the transboundary nature of AMR and call for global cooperation in action toward reducing not only the macroeconomic but also the holistic implications of AMR. Lastly, we emphasize the importance of scaling up efforts to monitor AMR and share the data on antimicrobial consumption to facilitate research that could produce evidence for effective policymaking.

Existing economic studies probably underestimate the burden of AMR in the absence of a comprehensive framework to incorporate the multitude of factors contributing to its evolution.

END NOTES

1. The spectrum of industrial applications of antimicrobials includes static (preventing growth of a microorganism), antiseptic (preventing infection), sanitizer (reducing the number of harmful microorganisms to a safe level), cidal (eliminating microorganisms of a particular type), disinfectant (eliminating all infectious bacteria), sporicidal (eliminating spores), and sterilant (completely eliminating all living microorganisms) (McEntee 2000).
1. See Reygaert (2018), Kapoor et al. (2017), and Munita & Arias (2016) for an extensive review of AMR acquisition pathways and mechanisms.
2. See Bell et al. (2014) for a systematic review and meta-analysis of the effect of antibiotic consumption on antibiotic resistance during the previous 50 years and van Boeckel et al. (2015), Rushton et al. (2014), and Acar et al. (2012) for a review of antimicrobial use in food animals.
3. See Zowalaty et al. (2016) and Grosso et al. (2012) for country case studies and Morgan et al. (2011) for a global review of non-prescription antimicrobial use.
4. See Calbo et al. (2013) for a review of factors influencing antimicrobial prescribing.
5. See Schuts et al. (2016) for a review of the role of antimicrobial stewardship in hospitals in AMR and Stein et al. (2018), Ashraf & Cook (2016), Fridkin et al. (2014), and Hecker et al. (2003) for country case studies.
6. Surveys designed following the KAP framework are aimed at collecting information from a specific population group regarding what they know, believe, and do in relation to a particular topic. KAP surveys can identify knowledge gaps, cultural beliefs, or behavioral patterns that could explain the actions of individuals (WHO 2008).
7. See Tacconelli et al. (2018) for the complete list of WHO priority antibiotic-resistant bacteria.
8. See McManus et al. (2002) for a review of antimicrobial use in crops and the implications on human and animal health.
9. See Sibergeld et al. (2008) for a review of antimicrobials used in animal feed production.
10. See McEntee (2000) for a compendium of antimicrobials used in industrial applications.
11. Developed by the authors with reference to WHO (2009) and Woolhouse et al. (2015).
12. The interactions between the economy and environment are much more complex than illustrated. Thus, the illustration is not exhaustive of all plausible interactions. Even the interactions of households, microorganisms, animals, and plants with air, soil, and water are avoided to reduce the complexity of the illustration.
13. Coupled Model Intercomparison Project (CMIP) and Intersectoral Impact Model Intercomparison Project (ISIMIP) are exemplary of the utility of using a consistent framework to evaluate the impacts of climate change.
14. See McKibbin and Fernando (2020b) and Fernando and McKibbin (2021) for the application of changes in household risk premia when modeling the macroeconomic consequences of COVID-19.
15. See McKibbin and Fernando (2020a and 2020b) for the application of changes in country and sector risk premia when modeling the macroeconomic consequences of COVID-19.
16. See Ventola (2015) for a detailed discussion of the economic and regulatory barriers for the pharmaceutical industry when developing new antimicrobials.
17. See Ghosh et al. (2019) for a review of alternatives to antibiotics.

REFERENCES

Abbas, M., Aloudat, T., Bartolomei, J., Carballo, M., Durieux-Paillard, S., Gabus, L., Jablonka, A., Jackson, Y., Kaojaroen, K., Koch, D., Martinez, E., Mendelson, M., Petrova-Benedict, R., Tsiodras, S., Christie, D., Saam, M., Hargreaves, S. & Pittet, D. 2018. A systematic review on the relationship between international migration and antimicrobial resistance. Antimicrobial Resistance and Infection Control, 7, 1-11.

Acar, J. F., Moulin, G., Page, S. W. & Pastoret, P.-P. 2012. Antimicrobial resistance in animal and public health: introduction and classification of antimicrobial agents. Revue Scientifique et Technique-OIE, 31, 15-21.

Ahmed, S. A. A., Baris, E. & Go, D. S. 2017. Assessing the global economic and poverty effects of antimicrobial resistance. The World Bank.

Alnasser, A. H. A., Al-Tawfiq, J. A., Ahmed, H. A. A., Alqithami, S. M. H., Alhaddad, Z. M. A., Rabiah, A. S. M., Albrahim, M. A. A., Al-Kalif, M. S. H., Barry, M., Temsah, M. H., Al-Kalaif, Z. S. H., Shahadah, R. F. B., Alharbi, K. K. S. & Alnasser, A. A. H. P. k., attitude and practice towards antibiotics use and antimicrobial resistance in Saudi Arabia: A web-based cross-sectional survey. Journal of Public Health Research, 10(4). 2021. Public knowledge, attitude and practice towards antibiotics use and antimicrobial resistance in Saudi Arabia: A web-based cross-sectional survey. Journal of Public Health Research, 10, 711-18.

Ancillotti, M., Nilsson, E., Nordvall, A. & Oljans, E. 2022. The status quo problem and the role of consumers against antimicrobial resistance. Frontiers in Sustainable Food Systems, 6, 1-5.

Arnold, K. E., WIlliams, N. J. & Bennett, M. 2016. 'Disperse abroad in the land': the role of wildlife in the dissemination of antimicrobial resistance. Biology Letters, 12, 1-8.

Ashraf, M. S. & Cook, P. P. 2016. Antibiotic misuse in hospital, outpatient, and long-term care settings. North Carolina Medical Journal, 77, 346-49.

Bank, M. S. 2022. Microplastic in the environment: pattern and process, Springer.

Bell, B. G., Schellevis, F., Stobberingh, E., Goossens, H. & Pringle, M. 2014. A systematic review and meta-analysis of the effects of antibiotic consumption on antibiotic resistance. BMC Infectious Diseases, 14, 1-25.

Bengtsson-Palme, J., Kristiansson, E. & Larsson, D. J. 2017. Environmental factors influencing the development and spread of antibiotic resistance. FEMS Microbiology Reviews, 42, 68-80.

Bokhary, H., Rangesti, K. N. A., Rashid, H., Ghany, M. A. E. & Hill-Cawthorne, G. A. 2021. Travel-related antimicrobial resistance: a systematic review. Tropical Medicine and Infectious Diseases, 6, 1-27.

Bradley, C. & Stumpner, P. 2021. The impact of COVID-19 on capital markets, one year in [Online]. McKinsey & Company. Available: https://www.mckinsey.com/business-functions/strategy-and-corporate-finance/our-insights/the-impact-of-covid-19-on-capital-markets-one-year-in [Accessed 13 May 2022 2022].

Bruinsma, N., Hutchinson, J. M., van den Bogaard, A. E., Giamarellou, H., Degener, J. & Stobberingh, E. E. 2003. Influence of population density on antibiotic resistance. Journal of Antimicrobial Chemotherapy, 51, 385-90.

Calbo, E., Álvarez-Rocha, L., Gudiol, F. & Pasquau, J. 2013. A review of the factors influencing antimicrobial prescribing. Infectious Diseases and Clinical Microbiology, 31, 12-15.

Cavicchioli, R., Ripple, W. J., Timmis, K. N., Azam, F., Bakken, L. R., Baylis, M., Behrenfeld, M. J., Boetius, A., Boyd, P. W., Classen, A. T. & Crowther, T. W. 2019. Scientists' warning to humanity: microorganisms and climate change. Nature Reviews Microbiology, 17, 569-86.

Cecchini, M., Langer, J. & Slawomirski, L. 2015. Antimicrobial resistance in G7 countries and beyond: economic issues, policies and options for action. Organization for Economic Cooperation and Development.

Centres for Disease Control and Prevention 2019. Antibiotic resistance threats in the United States. Centres for Disease Control and Prevention.

Chen, Y., Kirk, M. D., Stuart, R., Cheng, A. C., Pearson, S., Hayen, A., Banks, E. & Liu, B. 2019. Socio-demographic and health service factors associated with antibiotic dispensing in older Australian adults. PLoS ONE, 14, 1-10.

Coast, J., Smith, R. D. & Millar, M. R. 1996. Superbugs: should antimicrobial resistance be included as a cost in economic evaluation? Health Economics, 5, 217-26.

Collignon, P., Beggs, J. J., Walsh, T. R., Gandra, S. & Laxminarayan, R. 2018. Anthropological and socioeconomic factors contributing to global antimicrobial resistance: a univariate and multivariable analysis. Lancet Planet Health, 2, 1-8.

Dadgostar, P. 2019. Antimicrobial resistance: implications and costs. Infection and Drug Resistance, 12, 3903-10.

Davies, J. & Davies, D. 2010. Origins and evolution of antibiotic resistance. Microbiology and Molecular Biology Reviews, 74, 417-33.

Di, L. N., Tay, S. T., Ponnampalavanar, S. S. L. S., Pham, D. T. & Wong, L. P. 2022. Socio-Demographic Factors Associated with Antibiotics and Antibiotic Resistance Knowledge and Practices in Vietnam: A Cross-Sectional Survey. Antibiotics, 11, 1-11.

El Zowalaty, M. E., Belkina, T., Bahashwan, S.A.,, El Zowalaty, A. E., Tebbens, J. D., Abdel-Salam, H. A., Khalil, A. I., Daghriry, S. I., Gahtani, M. A., Madkhaly, F. M., Nohi, N. I., Khodari, R. H., Sharahili, R. M., Dagreery, K. A., Khormi, M., Habibah, S. A., Medrba, B. A., Gahtani, A. A., Hifthi, R. Y., Zaid, J. M., Amshan, A. W., Alneami, A. A., Noreddin, A. & Vlcek, J. 2016. Knowledge, awareness, and attitudes toward antibiotic use and antimicrobial resistance among Saudi population. International Journal of Clinical Pharmacy, 38, 1261-68.

Elisabeth, M., Maneesh, P., Katarina, S. F., Slobodan, Z. & Michael, S. 2021. Antimicrobial resistance & migrants in Sweden: Poor living conditions enforced by migration control policies as a risk factor for optimal public health management. Frontiers in Public Health, 9, 1-5.

European Centre for Disease Prevention and Control 2017. Surveillance of antimicrobial resistance in Europe 2017. Stockholm: European Centre for Disease Prevention and Control.

Fernando, R., Liu, W. & McKibbin, W.J. 2021. Global economic impacts of climate shocks, climate policy and changes in climate risk assessment. Climate and Energy Economics Discussion Paper. Washington D.C.: Brookings Institution.

Fernando, R. & McKibbin, W. J. 2021. Macroeconomic policy adjustments due to COVID-19: scenarios to 2025 with a focus on Asia. ADBI Working Paper Series. Tokyo: Asian Development Bank Institute.

Food and Agriculture Organization of the United Nations (FAO), W. O. f. A. H. O., and World Health Organization, 2020. International instruments on the use of antimicrobials across the human, animal and plant sectors. Food and Agriculture Organization of the United Nations (FAO), World Organization for Animal Health (OIE), and World Health Organization.

Fridkin, S., Baggs, J., Fagan, R., Magill, S., Pollack, L. A., Malpiedi, P., Slayton, R., Khader, K., Rubin, M. A., Jones, M., Samore, M. H., Dumyati, G., Dodds-Ashley, E., Meek, J., Yousey-Hindes, K., Jernigan, J., Shehab, N., Herrera, R., McDonald, L. C., Schneider, A. & Sirinivasan, A. 2014. Vital signs: Improving antibiotic use among hospitalized patients. Morbidity and Mortality Weekly Report, 63, 194-200.

Ghosh, C., Sarkar, P., Issa, R. & Haldar, J. 2019. Alternatives to conventional antibiotics in the era of antimicrobial resistance. Trends in Microbiology, 27, 323-38.

González Zorn, B. & Escudero, J. A. 2012. Ecology of antimicrobial resistance: humans, animals, food and environment. International Microbiology, 15, 101-109.

Grosso, G., Marventano, S., Ferranti, R. & Mistretta, A. 2012. Pattern of antibiotic use in the community: Non-adherence and self-prescription rates in an Italian urban population. Molecular Medicine Reports, 5, 1305-10.

Gudipati, S., Zervos, M. & Herc, E. 2020. Can the one health approach save us from the emergence and reemergence of infectious pathogens in the era of climate change: implications for antimicrobial resistance? Antibiotics, 9, 1-7.

Hecker, M. T., Aron, D. C., Patel, N. P., Lehmann, M. K. & Donskey, C. J. 2003. Unnecessary use of antimicrobials in hospitalized patients: Current patterns of misuse with an emphasis on the antianaerobic spectrum of activity. Arch Intern Med, 163, 972-78.

Hillock, N. T., Merlin, T. L., Turnidge, J. & Karnon, J. 2022. Modelling the future clinical and economic burden of antimicrobial resistance: the feasibility and value of models to inform policy. Applied Health Economics and Health Policy, 1-8.

Holmberg, S. D., Solomon, S. L. & Blake, P. A. 1987. Health and economic impacts of antimicrobial resistance. Reviews of Infectious Diseases, 9, 1065-78.

Institute for Health Metrics and Evaluation. 2022. Global antibiotic consumption and usage in humans, 2000–18 [Online]. Institute for Health Metrics and Evaluation. Available: https://www.healthdata.org/research-article/global-antibiotic-consumption-and-usage-humans-2000%E2%80%9318-spatial-modelling-study [Accessed 4 March 2022].

Institute for Health Metrics and Evaluation. 2022. Global Burden of Disease Study 2019 (GBD 2019) Data Resources [Online]. Institute for Health Metrics and Evaluation. Available: http://ghdx.healthdata.org/gbd-2019 [Accessed 4 March 2022].

Jabeen, S., Farhan, M., Zaka, M. A., Fiaz, M. & Farasat, M. 2022. COVID and world stock markets: A comprehensive discussion. Frontiers in Psychology, 12, 1-16.

Jans, C., Sarno, E., Collineau, L., Meile, L., Stark, K. D. C. & Stephan, R. 2018. Consumer exposure to antimicrobial resistant bacteria from food at Swiss retail level. Frontiers in Microbiology, 9, 1-19.

Jimah, T. & Ogunseitan, O. 2020. Socio-demographic characteristics of the association between knowledge of antibiotic therapy and prudent use in Ghana. Journal of Global Health Reports, 4, 1-10.

Kaba, H. E. J., Kuhlmannb, E. & Scheithauer, S. 2020. Thinking outside the box: Association of antimicrobial resistance with climate warming in Europe – A 30 country observational study. International Journal of Hygiene and Environmental Health, 223, 151-158.

Kapoor, G., Saigal, S. & Elongavan, A. 2017. Action and resistance mechanisms of antibiotics: a guide for clinicians. Journal of Anaesthesiology Clinical Pharmacology, 33, 300-305.

Keogh-Brown, M., McDonald, S., Smith, R., Martinez-Alvarez, M. & Coast, J. 2009. Global CGE modelling of antibiotic resistance: An application of the GLOBE model. Journal of Global Economic Analysis, 1-24.

Knapp, C. W., McCluskey, S. M., Singh, B. K., Campbell, C. D., Hudson, G. & Graham, D. W. 2011. Antibiotic resistance gene abundances correlate with metal and geochemical conditions in archived Scottish soils. PLoS ONE, 6, 1-6.

Kohli, S., Timelin, B., Fabius, V. & Veranen, S. M. 2022. How COVID-19 is changing consumer behavior – now and forever.

KPMG 2014. The global economic impact of antimicrobial resistance. United Kingdom: KPMG.

Linton, A. H. 1977. Animal to man transmission of Enterobacteriaceae. Royal Society of Health Journal, 97, 115-18.

Liss, R. H. & Batchelor, F. R. 1987. Economic evaluations of antibiotic use and resistance: a perspective. Reviews of Infectious Diseases, S297-312.

Llor, C. & Bjerrum, L. 2014. Antimicrobial resistance: risk associated with antibiotic overuse and initiatives to reduce the problem. Therapeutic Advances in Drug Safety, 5, 229-41.

MacFadden, D. R., McGough, S. F., Fisman, D., Santillana, M. & Brownstein, J. S. 2018. Antibiotic resistance increases with local temperature. Nature Climate Change, 8, 510-515.

Marshall, B. M., Ochieng, D. J. & Levy, S. B. 2009. Commensals: underappreciated reservoir of antibiotic resistance. Microbe, 45, 231-38.

McEntee, T. 2000. Industrial antimicrobial agents. Kirk-Othmer Encyclopedia of Chemical Technology.

McGough, S. F., MacFadden, D. R., Hattab, M. W., Molbak, K. & Santillana, M. 2020. Rates of increase of antibiotic resistance and ambient temperature in Europe: a cross-national analysis of 28 countries between 2000 and 2016. Euro Surveillance, 25.

McKee, M., Dunnell, K., Anderson, M., Brayne, C., Charlesworth, A., Johnton-Webber, C., Knapp, M., McGuire, A., Newton, J. N., Taylor, D. & Watt, R. G. 2021. The changing health needs of the UK population. Health Policy, 397, 1979-91.

McKibbin, W. & Fernando, R. 2020a. The global macroeconomic impacts of COVID-19: seven scenarios. Asian Economic Papers, 19, 1-55.

McKibbin, W. & Fernando, R. 2020b. Global macroeconomic scenarios of the COVID-19 pandemic. COVID Economics: Vetted and Real Time papers, 1-58.

McManus, P. S., Stockwell, V. O., Sundin, G. W. & Jones, A. L. 2002. Antibiotic use in plant agriculture. Annual Review of Phytopathology, 40, 443-65.

Michael, C. A., Dominey-Howes, D. & Labbate, M., 2, 145. 2014. The antimicrobial resistance crisis: causes, consequences, and management. Frontiers in Public Health, 2, 145-52.

Moore, R. E., Millar, C. & Moore, J. E. 2020. Antimicrobial resistance (AMR) and marine plastics: can food packaging litter act as a dispersal mechanism for AMR in oceanic environments? Marine Pollution Bulletin, 150, 1-7.

Morel, C. M., Alm, R. A., Ardal, C., Bandera, A., Bruno, G. M., Carrara, E., Colombo, G. L., de Kraker, M. E. A., Essack, S., Frost, I., Gonzalez-Zorn, B., Goossens, H., Guardabassi, L., Harbath, S., Jorgenson, P. S., Kanj, S. S., Kostyanev, T., Laxminarayan, R., Leonard, F., Hara, G. L., Mendelson, M., Mikulska, M., Mutters, N. T., Outterson, K., Bano, J. R., Tacconelli, E., Scudeller, L. & GAP-ONE Network 2020. A one health framework to estimate the cost of antimicrobial resistance. Antimicrobial Resistance & Infection Control, 9, 1-14.

Morgan, D. J., Okeke, I. N., Laxminarayan, R., Perencevich, E. N. & Weisenberg, S. 2011. Non-prescription antimicrobial use worldwide: a systematic review. The Lancet Infectious Diseases, 11, 692-701.

Munita, J. M. & Arias, C. A. 2016. Mechanisms of Antibiotic Resistance. Microbiology Spectrum, 4, 1-37.

Murray, C. J. L. C. 2022. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. The Lancet, 399, 629-55.

Naylor, N. R., Atun, R., Zhu, N., Kulasabanathan, K., Silva, S., Chatterjee, A., Knight, G. M. & Robotham, J. V. 2016. Estimating the burden of antimicrobial resistance: a systematic literature review. Antimicrobial Resistance & Infection Control, 1-17.

Nellums, L. B., Thompson, H., Holmes, A., Castro-Sanchez, E., Otter, J. A., Norredam, M., Friedland, J. S. & Hargreaves, S. 2018. Antimicrobial resistance among migrants in Europe: a systematic review and meta-analysis. Lancet Infectious Diseases, 18, 796-811.

Nuclear Threat Initiative, Johns Hopkins Center for Health Security & The Economist Intelligence Unit. 2020. GHS Index [Online]. Nuclear Threat Initiative, Washington DC, Johns Hopkins Center for Health Security, Maryland, and The Economist Intelligence Unit, London. Available: https://www.ghsindex.org/ [Accessed 11 November 2020].

Nugent, C., Verlander, N. Q., Varma, S., Bradley, D. T. & Patterson, L. 2022. Examining the association between socio-demographic factors, catheter use and antibiotic prescribing in Northern Ireland primary care: a cross-sectional multilevel analysis. Epidemiology & Infection, 1-36.

O'Neil, J. C. 2016. Tackling drug-resistant infections globally: Final report and recommendations. United Kingdom.

Organization for Economic Cooperation and Development (OECD) 2018. Stemming the superbug tide: just a few dollars more. OECD Health Policy Studies. Paris: Organization for Economic Cooperation and Development.

Pallecchi, L., Bartoloni, A., Paradisi, F. & Rossolini, G. M. 2008. Antibiotic resistance in the absence of antimicrobial use: mechanisms and implications. Expert Review of Anti-infective Therapy, 6, 725-32.

Peters, A. S., Cabieses, B., Ramirez, O., Uphoff, E., Acuna, M. P., Astorga, S., Araos, R. & Munita, J. M. 2020. A systematic review on the relationship between international migration and antimicrobial resistance. Research Square, 1-21.

Pham, D. N., Clark, L. & Li, M. 2021. Microplastics as hubs enriching antibiotic-resistant bacteria and pathogens in municipal activated sludge. Journal of Hazardous Materials Letters, 2, 1-7.

Plaza-Rodriguez, C., Alt, K., Grobbel, M., Hammerl, J. A., Irrgang, A., Szabo, I., Stingl, K., Schuh, E., Wiehle, L., Pfefferkorn, B., Naumann, S., Kaesbohrer, A. & Tenhagen, B. 2021. Wildlife as sentinels of antimicrobial resistance in Germany? Frontiers in Veterinary Science, 7, 1-15.

Prestinachi, F., Pezzotti, P. & Pantosti, A. 2015. Antimicrobial resistance: a global multifaceted phenomenon.

Pathogens and Global Health, 109, 309-318.

PRS Group. 2012. The International Country Risk Guide Methodology (ICRG) [Online]. PRS Group. Available: https://www.prsgroup.com/wp-content/uploads/2012/11/icrgmethodology.pdf [Accessed 11 November 2020].

Ramsay, D. E., Invik, J., Checkley, S. L., Gow, S. P., Osgood, N. D. & Waldner, C. L. 2018. Application of dynamic modelling techniques to the problem of antibacterial use and resistance: a scoping review. Epidemiology & Infection, 146, 2014-27.

RAND Europe 2014. Estimating the economic costs of antimicrobial resistance. United Kingdom: RAND Europe.

Rani, A., Saini, K. C., Bast, F., Varjani, S., Mehariya, S., Bhatia, S. K., Sharma, N. & Funk, C. 2021. A review on microbial products and their perspective application as antimicrobial agents. Biomolecules, 11, 1-28.

Reygaert, W. C. 2018. An overview of the antimicrobial resistance mechanisms of bacteria. AIMS Microbiology, 4, 482–501.

Rodriguez-Verdugo, A., Lozano-Huntelman, N., Cruz-Loya, M., Savage, V. & Yeh, P. 2020. Compounding effects of climate warming and antibiotic resistance. iScience, 23, 1-16.

Rushton, J., Ferreira, J. P. & Stark, K. D. C. 2014. Antimicrobial resistance: the use of antimicrobials in the livestock sector. OECD Food, Agriculture and Fisheries Papers. Paris: OECD Publishing.

Schroder, W., Sommer, H., Gladstone, B. P., Foschi, F., Hellman, J., Evengard, B. & Tacconelli, E. 2016. Gender differences in antibiotic prescribing in the community: a systematic review and meta-analysis. Journal of Antimicrobial Chemotherapy, 71, 1800-06.

Schuts, E. C., Hulscher, M.E.J.L.,, Mouton, J. W., Verduin, C. M., Stuart, J. W. T. C., Overdiek, H. W. P. M., van der Linden, P. D., Natsch, S., Hertogh, C. M. P. M., Wolfs, T. F. W., Schouten, J. A., Kullberg, B. J. & Prins, J. M. 2016. Current evidence on hospital antimicrobial stewardship objectives: a systematic review and meta-analysis. The Lancet Infectious Diseases, 16, 847-56.

Seiler, C. & Berendonik, T. U. 2012. Heavy metal driven co-selection of antibiotic resistance in soil and water bodies impacted by agriculture and aquaculture. Frontiers in Microbiology, 3, 1-10.

Shrestha, P., Cooper, B. S., Coast, J., Oppong, R., Do Thi Thuy, N., Phodha, T., Celhay, O., Guerin, P. J., Wertheim, H. & Lubell, Y. 2018. Enumerating the economic cost of antimicrobial resistance per antibiotic consumed to inform the evaluation of interventions affecting their use. Antimicrobial Resistance & Infection Control, 7, 1-9.

Silbergeld, E. K., Graham, J. & Price, L. B. 2008. Industrial food animal production, antimicrobial resistance, and human health. Annual Review of Public Health, 29, 151-69.

Smith, R. D., Yago, M., Millar, M. & Coast, J. 2005. Assessing the macroeconomic impact of a healthcare problem: the application of computable general equilibrium analysis to antimicrobial resistance. Journal of Health Economics, 24, 1055-75.

Stein, K., Farmer, J., Singhal, S., Marra, F., Sutherland, S. & Quinonez, C. 2018. The use and misuse of antibiotics in dentistry: A scoping review. The Journal of the American Dental Association, 149, 869-84.e5.

Sumers, A. O. 2002. Generally overlooked fundamentals of bacterial genetics and ecology. Clinical Infectious Diseases, 34, S85-92.

Tacconelli, E., Carrara, E., Savoldi, A., Harbarth, S., Mendelson, M., Monnet, D. L., Pulcini, C., Kahlmeter, G., Kluytmans, J., Carmeli, Y. & Ouellette, M. 2018. Discovery, research, and development of new antibiotics: the WHO priority list of antibiotic-resistant bacteria and tuberculosis. The Lancet Infectious Diseases, 18, 318-327.

United Nations Environment Programme 2017. Antimicrobial resistance: investigating the environmental dimension. United Nations Environment Programme.

United Nations Environment Programme 2022. Environmental dimensions of antimicrobial resistance: summary for policymakers. United Nations Environment Programme.

Van Boeckel, T. P., Brower, C., Gilbert, M., Grenfell, B. T., Levin, S. A., Robinson, T. P., Teilant, A. & Laxminarayan, R. 2015. Global trends in antimicrobial use in food animals. Proceedings of the National Academy of Sciences, 112, 5649-54.

Ventola, C. L. 2015. The antibiotic resistance crisis: part 1: causes and threats. Pharmacy and Therapeutics, 40, 277-83.

Wellcome Trust. 2020. Why is it so hard to develop new antibiotics? [Online]. Wellcome Trust. Available: https://wellcome.org/news/why-is-it-so-hard-develop-new-antibiotics [Accessed 24 May 2021].

Woolhouse, M., Ward, M., van Bunnik, B. & Farrar, J. 2015. Antimicrobial resistance in humans, livestock and the wider environment. Philosophical Transactions Royal Society, 370, 1-7.

World Bank Group 2017. Drug-resistant infections: a threat to our economic future. Washington, DC: World Bank Group.

World Economic Forum 2020. The costs and risks of AMR water pollution. World Economic Forum.

World Health Organization 2008. A guide to developing Knowledge, Attitude and Practice survey. World Health Organization.

World Health Organization 2009. WHO guide to identifying the economic consequences of disease and injury. World Health Organization.

World Health Organization 2015. WHO Costing and Budgeting Tool for National Action Plans on Antimicrobial Resistance: User Guide. World Health Organization.

World Health Organization. 2021a. Antimicrobial resistance [Online]. World Health Organization. Available: https://www.who.int/news-room/fact-sheets/detail/antimicrobial-resistance#:~:text=What%20is%20antimicrobial%20resistance%3F,spread%2C%20severe%20illness%20and%20death [Accessed 13 May 2022 2022].

World Health Organization 2021b. Antimicrobial resistance and the United Nations Sustainable Development Cooperation Framework: Guidance for United Nations country teams. World Health Organization.

World Health Organization 2022. 2021 Antibacterial agents in clinical and preclinical development: An overview and analysis. Geneva: World Health Organization (WHO).

Wozniak, T. M., Barnsbee, L., Lee, X. J. & Pacella, R. E. 2019. Using the best available data to estimate the cost of antimicrobial resistance: a systematic review. Antimicrobial Resistance & Infection Control, 8, 1-12.

Yoshikawa, T. T. 2002. Antimicrobial resistance and aging: beginning of the end of the antibiotic era? Journal of American Geriatrics Society, 50, 226-9.

APPENDIX

Figure 1

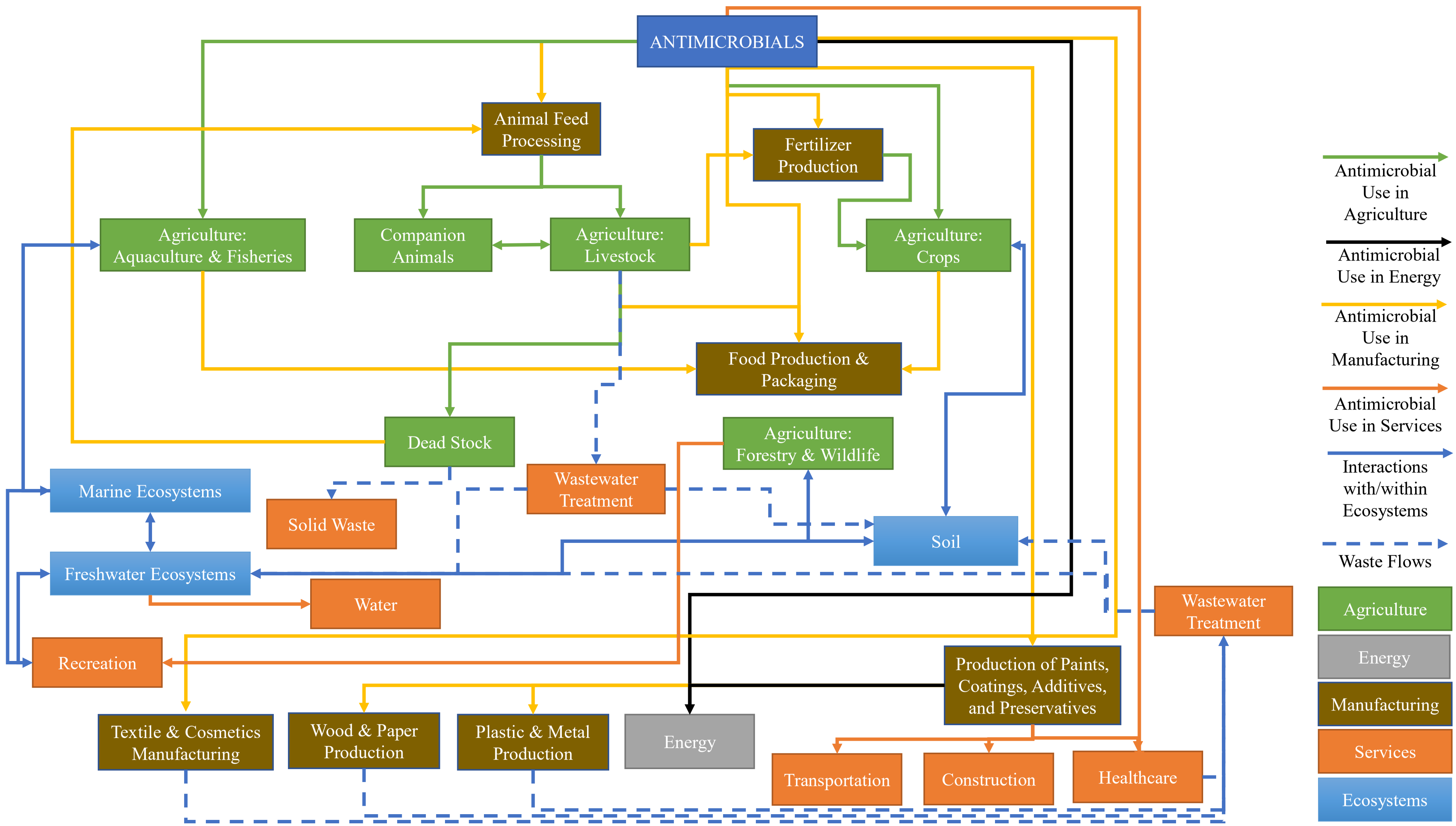
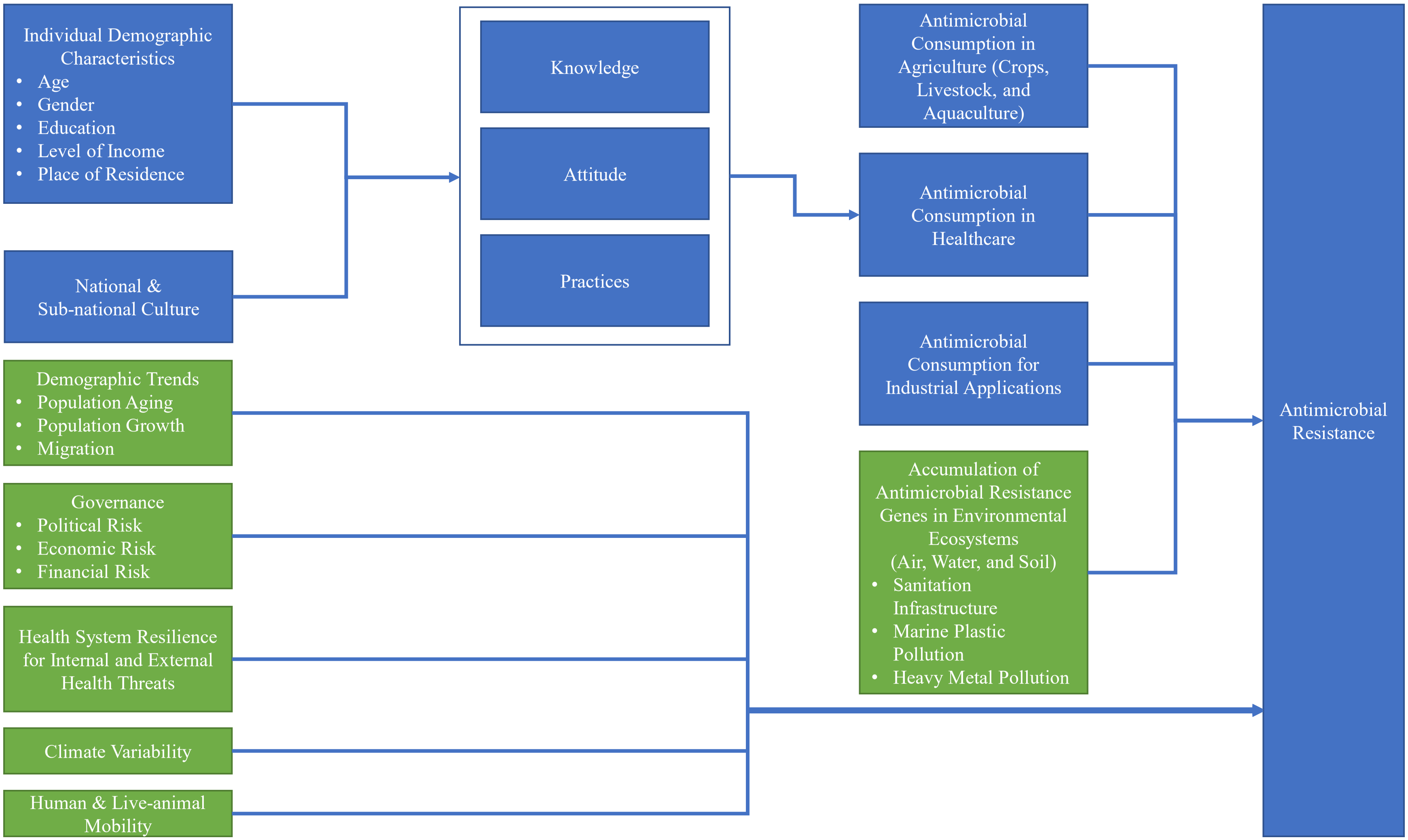
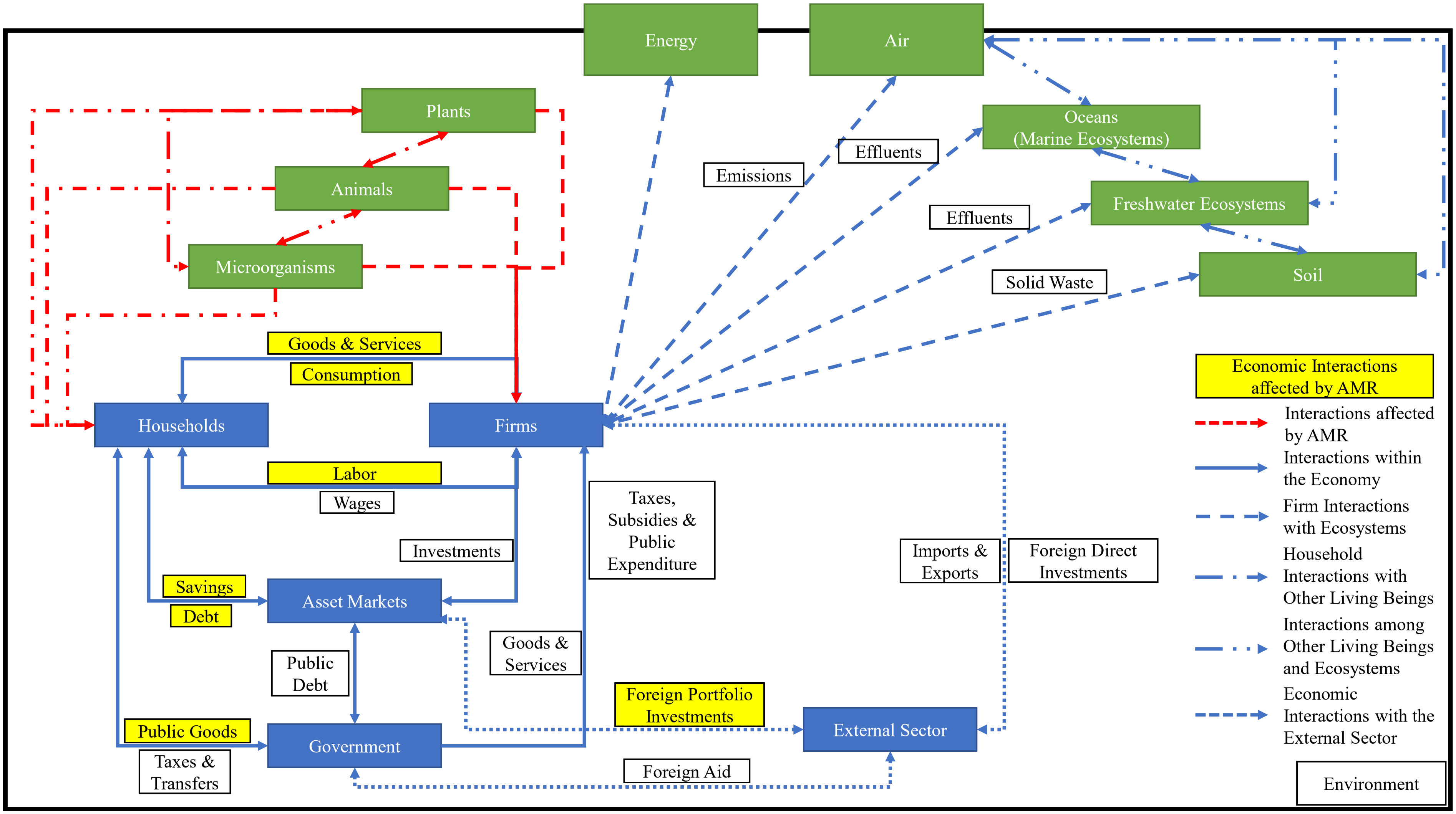


Figure 2



Individual Demographic Characteristics
• Age
• Gender
• Education
• Level of Income
• Place of Residence
National & Sub-national Culture
Demographic Trends
• Population Aging
• Population Growth
• Migration
Governance
• Political Risk
• Economic Risk
• Financial Risk
Health System Resilience for Internal and External Health Threats
Climate Variability
Human & Live-animal Mobility
Knowledge
Attitude
Practices
Antimicrobial Consumption in Agriculture (Crops, Livestock, and Aquaculture)
Antimicrobial Consumption in Healthcare
Antimicrobial Consumption for Industrial Applications
Accumulation of Antimicrobial Resistance Genes in Environmental Ecosystems (Air, Water, and Soil)
• Sanitation Infrastructure
• Marine Plastic Pollution
• Heavy Metal Pollution
Antimicrobial Resistance

Figure 3



Energy
Air
Plants
Animals
Microorganisms
Oceans (Marine Ecosystems)
Freshwater Ecosystems
Soil
Emissions
Effluents
Effluents
Solid Waste
Goods & Services
Consumption
Households
Firms
Labor
Wages
Investments
Taxes, Subsidies & Public Expenditure
Imports & Exports
Foreign Direct Investments
Savings
Debt
Asset Markets
Goods & Services
Public Debt
Foreign Portfolio Investments
Public Goods
Government
External Sector
Taxes & Transfers
Foreign Aid
Economic Interactions affected by AMR
Interactions affected by AMR
Interactions within the Economy
Firm Interactions with Ecosystems
Household Interactions with Other Living Beings
Interactions among Other Living Beings and Ecosystems
Economic Interactions with the External Sector
Environment

BROOKINGS

1775 Massachusetts Ave NW,
Washington, DC 20036
(202) 797-6000
www.brookings.edu