Quality of Governance and Antimicrobial Resistance:

Identifying *socioeconomic and governance-related factors associated with antimicrobial resistance across Europe*

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Abstract

BACKGROUND: For decades, the spread of antimicrobial resistance (AMR) has challenged healthcare professionals, communities, and policymakers. Yet, there is little known about the socioeconomic and governance-related factors contributing to AMR. Recent studies have introduced quality of governance as a potential factor influencing AMR prevalence. This study thus relies on the assumption that good governance is associated with better health outcomes.

OBJECTIVE: The purpose of this research is to better explain the variation in AMR rates across European countries through identifying relevant socioeconomic and governance variables and testing the strength and significance of these relationships in a modern 30-country dataset.

METHOD: After completing a scoping review to discover significant variables and determine the state of knowledge, as well as gaps of knowledge in the literature, bivariate and multivariate models were estimated from a panel dataset of 30 European countries during the time period of 2011-2017. The methodology of pooled least ordinary squares (POLS) and fixed effects (FE) regression were used for analysis. Results from the scoping review and regression analysis are compared in the discussion.

RESULTS: According to the assessed literature in the scoping review, quality of governance (QoG) has a significant and negative relationship to AMR rates. The quantitative study confirms this relationship as QoG explained the majority of variance in the models compared to the other 11 explanatory variables. The factors of human consumption of antimicrobials, education, GDP, and private health expenditure have also been significant in past related studies. While these variables were significant in POLS multivariate regression, only antimicrobial consumption in animals and quality of governance were significant in the FE analysis.

CONCLUSION: This study on socioeconomic and governance-related factors supports the findings of past research on the significant relationship between QoG and AMR. Considering the effects of the current global pandemic, AMR will be a critical issue for health systems and communities for years to come. This research contributes to the understanding of AMR as well as the growing evidence of the positive association between quality of governance and health.

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Abbreviations and Acronyms

A	
AMC	Antimicrobial consumption
AMCanimal	Antimicrobial consumption in animals
AMChuman	Antimicrobial consumption in humans
AMR	Antimicrobial resistance
AMRAvg	Average antimicrobial resistance rate
C	
Campylo	Notification rate of campylobacteriosis
CC	Control of Corruption
D	
DDD	Defined Daily Dose
DID	Defined Daily Dose (DDD)/1000 inhabitants/day
DG SANTE	Directorate-General for Health and Food Safety
E	
EARS-Net	European Antimicrobial Resistance Surveillance Network
ECDC	European Centre for Disease Prevention and Control
EDU	Education variable (percentage of tertiary-education population)
EFSA	European Food Safety Authority
EMA	European Medicines Agency
ENSP	Erythromycin-nonsusceptible S. pneumoniae
ESAC-Net	European Surveillance of Antimicrobial Consumption Network
ESVAC	European Surveillance of Veterinary Antimicrobial Consumption
EU	European Union
F	
FAO	Food and Agriculture Organization of the United Nations
FE	Fixed effects
G	
GE	Government Effectiveness
GDP	Gross Domestic Product
M	
mg	Milligram
N	
NPI	Norwegian Publication Indicator
O	
OECD	Organisation for Economic Co-Operation and Development
OIE	The World Organisation for Animal Health
OLS	Ordinary Least Squares

P

PCA	Partial Correlation Analysis
PCU	Population Correction Unit
PHE	Private Health Expenditure
PNSP	Penicillin-No susceptible Streptococcus Pneumoniae
POLS	Pooled Ordinary Least Squares
PPI	Physicians per 10,000 inhabitants
PS	Political Stability and Absence of Violence

Q

QoG	Quality of Governance
QoGavg	average Quality of Governance measure

R

RL	Rule of Law
RQ	Regulatory Quality

S

Salmon	Notification rate of salmonellosis
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2

T

THE	Total Health Expenditure

V

VA	Voice and Accountability
VIF	Variance Inflation Factor

W

WGI	Worldwide Governance Indicators
WHO	World Health Organization

1 Introduction

In 2010, the European Centre for Disease Prevention and Control (ECDC, 2010) identified antimicrobial resistance as the "most important disease threat in Europe" (p. 3). One decade later, there is still much uncertainty surrounding the variation and spread of antimicrobial resistance while the threat remains urgent. The objective of this study is to contribute to the limited, yet growing literature involving the relationship of antimicrobial resistance (AMR) to socioeconomic and governance-related factors (Collignon et al., 2015; Collignon et al., 2018; Kaba et al., 2020). Relevant variables will be identified through a limited scoping review and used in bivariate and multivariate analyses to determine significant socioeconomic and governance-related variables associated with AMR in European countries. Through the inclusion of antimicrobial consumption in animals and zoonoses prevalence measures, the study will introduce novel variables for analysis in this literature as well as evaluate the robustness of past findings with a more recent dataset and broader sample of countries. With the aim of strengthening the understanding of AMR development, this research will support the timely issue of predicting and controlling the spread of resistant microorganisms.

The challenge of AMR is growing as resistance rates continue to rise and treatments prove to be ineffective against resistant strains. With the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) pandemic influencing the current use of antibiotic therapy and risk of healthcare-associated infections (Rawson et al., 2020), the issue of AMR will likely only become more pressing.

Although the seriousness of AMR development has been known in the medical community and to the public for decades, there is still a wide variation in AMR rates and antimicrobial use across countries and regions in Europe (ECDC, 2018; Masiero et al., 2010). A majority of the research aimed at explaining the variation has focused on linking traditional factors such as access to antibiotics, level of education, healthcare expenditure, and past individual antibiotic use to variation in antibiotic consumption (Blommaert et al., 2014; Čižman, 2003; Goossens et al., 2005). However, much of the variation in AMR is still unexplained by antimicrobial consumption and its related factors. Emerging studies have examined the relationship of quality of governance and antibiotic consumption and therefore indirectly, AMR rates, citing a strong, negative relationship between the two variables (Gaygısız et al., 2017; Rönnerstrand & Lapuente, 2017). The concept of good governance has been viewed as a prerequisite for economic growth, poverty reduction, and social development (Holmberg et al., 2009; United Nations, 2000), so the assumed positive association with health outcomes seems to be reasonable.

The assumption behind this relationship is that a government deemed as of "higher quality" is expected to be more effective in its enactment and enforcement of laws and regulations as well as in the management and quality of its public services (Kaufmann et al., 2005). Relating to AMR, a country with a stronger quality of government will likely exercise increased control over the use of antimicrobials and implement measures to contain the spread of resistance such as establishing surveillance and disease prevention systems (Gaygısız et al., 2017). In a country with a high quality of governance, citizens are more likely to have confidence and trust in the systems and institutions, which will be reflected in the adherence to policy measures and cooperation among many individual actors (Kaufmann et al., 2004). Thus, high quality of governance may also strengthen a country's capacity for ensuring responsible "health behavior" among its citizens.

Direct support for the relationship of AMR and quality of governance is scarce, yet a few recent studies have shown a significant association between the two variables that better explains the variation in AMR compared to levels of antimicrobial consumption (Collignon et al., 2015; Collignon et al., 2018). With this emerging research topic at the intersection of political science and medicine, it is interesting to examine what socioeconomic and governance-related factors may influence AMR rates. Further research in this area can provide important information to better guide policy on controlling the spread of AMR and contribute to broader knowledge about the relationship of quality of governance and health.

The research project is structured in seven chapters and includes two scientific articles. In the following chapter, background information on the research topic is provided and the current study is situated in the literature through the process of a scoping review. Chapter 3 presents the analytical framework of the research by addressing the theoretical literature on governance and empirical findings on the relationship between health and quality of governance. The hypotheses of the study are also stated in this chapter. Chapter 4 discusses the study design and modeling methodology. The results are then displayed in Chapter 5 from the quantitative study through correlation and regression analysis methods. Chapter 6 discusses the main findings and significance of the study as well as offers a reflection on the recommendations and limitations of this research. To conclude, Chapter 7 summarizes the important takeaways from the study and encourages future research on the topic. Two scientific papers are presented at the end of these chapters under the sections titled Article 1 and Article 2. Article 1 involves the scoping review on socioeconomic and governance-related factors linked to AMR. The review was conducted as part of the research process in order to explore the state of knowledge on what appears so far as a relatively limited field of research. The findings from the literature review are used to support the quantitative study design for regression analysis. Article 2 describes the main findings and key ideas from the quantitative study.

2 Background

The World Health Organization (WHO, 2020c) lists AMR as one of the 13 biggest threats to global health for this decade. The organization's global action plan on this threat focuses on improving the understanding of AMR, advocating for increased research and development into the antibiotic pipeline, and promoting the sensible use of antimicrobials (WHO, 2015). The plan also presents the objectives of strengthening surveillance systems and implementing the WHO's recommendations into practice, which relies heavily on a nation's quality of governance as to how these objectives are met.

Among the most pressing threats to global health, the WHO also lists epidemic preparedness as a top global health concern (WHO, 2020c). As new data and studies emerge covering the coronavirus, the underlying burden of AMR can be seen in the variation of cases and mortality rates across countries, especially in Europe. The pandemic provides a sobering example of the importance of addressing the spread of AMR in order to maintain effective treatment options as well as the importance of good governance and institutional guidance to address healthcare challenges. Countries, such as Italy, with known higher rates of antimicrobial resistance have been disproportionally affected by virus (Berild et al., 2020). There is a clear need for identifying factors associated with the spread of AMR and considering these identified factors to improve policy measures and stewardship programs.

2.1 Antimicrobial Resistance

AMR occurs when microorganisms become resistant to antimicrobial substances to which they were previously susceptible (European Commission, 2017). The term microorganisms covers bacteria, fungi, parasites, and viruses (Food and Agriculture Organization of the United Nations [FAO], 2016) and the term antimicrobial substances includes antibiotics, which are "chemical substances naturally produced by various infections species of microorganisms such as bacteria, fungi, actinomycetes and streptomyces that kill or inhibit the growth of other microorganisms" (Bbosa et al., 2014, p. 419). Bacteria can also become resistant to several antimicrobial substances, which is termed as multiple resistance (ECDC, 2018).

AMR results from natural selection and genetic mutation; however, the development of AMR is accelerated by human behaviors including the inappropriate or excessive consumption of antimicrobials in human and animals and poor hygiene environments and practices in healthcare settings or in the food chain (European Commission, 2017). The arising selective pressure on resistance prompts healthcare providers to use more expensive and increased quantities of broad-spectrum antibiotics (Laximinarayan et al., 2013). The serious consequence of AMR is that antimicrobials are becoming less effective and useful for treatment.

This loss of effectiveness can lead to significant economic and societal consequences including higher mortality rates, increased severity of or prolonged sicknesses, and production losses (FAO, 2016). Treatment costs will also increase in response to more expensive and powerful antimicrobial use and longer hospital lengths of stay (Phelps, 1989). The lack of regulation and mismanagement of antimicrobial use, over-the-counter access of antimicrobials, and the rise of poor-quality medicines have also been attributed to the growing AMR rates (FAO, 2016). Resistance to multiple antimicrobials, increased human travel, food trade practices, population density, and environmental exposure are also factors contributing to the challenge of controlling the spread of AMR (Bruinsma et al., 2003; ECDC et al., 2017). However, antibiotic consumption has remained as the focus for interventions in reducing the prevalence of AMR.

2.2 Antibiotic Consumption

Antibiotic consumption is popularly regarded as the primary driver of antimicrobial resistance (Filippini et al., 2013; Goossens et al., 2005; McDonnell et al., 2017). Reducing antibiotic consumption through regulating access and prescription methods are often the interventions taken by national and global authorities to control the spread of AMR. Experts estimate that 20-50% of all antibiotic use could be categorized as of questionable use (Wise et al., 1998). Therefore, the poor management of antimicrobials and inappropriate and unnecessary consumption practices pose a threat to controlling the spread of AMR.

The increase of antibiotic consumption not only creates a risk of resistance at the individual patient level but contributes to the risk of greater resistance at the community, national, and regional levels (Bell et al., 2014). In Europe, The European Surveillance of Antimicrobial

Consumption Network (ESAC-Net) reports large variations in antibiotic consumption across the continent with higher use in Southern Europe and lower use in Northern Europe (ECDC, 2019; Machowska & Stålsby Lundborg, 2018).

Researchers have defined several factors related to antibiotic consumption variation, especially in Europe. The variation may be attributed to different rates of community-acquired infections, culture, and education levels across countries (Goossens et al., 2005). Income, physician density, and reimbursement methods have also been deemed as significant determinants of antibiotic consumption (Masiero et al., 2010). Much of the focus on controlling antibiotic consumption has been placed on the patient-physician relationship and the related prescribing practices in community or primary care settings. Both patient and physician characteristics have been found to influence the prescription and use of antimicrobials (Blommaert et al., 2014; Harbarth et al., 2001).

In a study on antibiotic consumption within ambulatory care in European countries, the use of antibiotics was inversely correlated with respondents' knowledge on antibiotics use (Borg, 2012). Researchers have theorized that variations in consumption patterns may also be explained by differences in drug regulations and the structure of national pharmaceutical markets (Goossens et al., 2005). In a study involving 15 European countries, researchers found a connection between community antibiotic consumption and the number of trade names of oral antibacterial agents; therefore highlighting that access and market competition may influence antimicrobial consumption behaviors (Monnet et al., 2005). While the behavioral and socioeconomic factors related to antimicrobial consumption have been studied since the early 2000s, there is a considerable difference shown in the scarce amount of studies related to the determinants of AMR directly. It could be argued that these factors related to antimicrobial consumption also affect AMR and contribute to national and regional AMR variation due to the widely-supported relationship between antimicrobial consumption and AMR.

2.3 Relationship between Antimicrobial Consumption and Antimicrobial Resistance

The positive relationship between antimicrobial consumption and AMR has been well-documented in literature (Bell et al., 2014; Čižman, 2003). The WHO (2015) supports this relationship stating that the development of AMR is connected to the frequency in which antibiotics are used. Therefore, antimicrobial consumption data have been commonly used to evaluate national and regional antimicrobial stewardship programs and practices.

Countries with higher levels of antimicrobial resistance often have significantly higher levels of per capita antimicrobial use (Čižman, 2003; Masiero et al., 2010); however, this is not a simple association. Consumption of antimicrobials has a complex relationship with resistance as it is both a cause of AMR and also an effect as resistant infections necessitate higher doses or another type of antimicrobial for treatment (Goossens et al., 2005). Although consumption is considered to be the main driver behind the spread of AMR, the correlation is not perfect (Isturiz & Carbon, 2000) and should not be considered as the sole factor for controlling the spread of AMR.

For example, there are higher average rates of AMR in low-to-middle income and middle-income countries compared to high income countries despite a lower per-person consumption of antimicrobials (Klein et al., 2018). Researchers have also found a connection between rising AMR rates to national issues such as poor infrastructure, weak governance, and low income (Collignon et al., 2018; Collignon & Beggs, 2019; Pokharel et al., 2019). This imperfect relationship encourages research into other national or regional factors that could contribute to the variation.

2.4 Quality of Governance and Antimicrobial Resistance

As with antimicrobial consumption and resistance patterns, there is significant variation in quality of governance across countries in Europe (Kaufmann & Kraay, 2018). In a study of 28 European countries, researchers made the first link between AMR rates and corruption levels with a study on governmental, social, and economic drivers of AMR. The study found that only 33% of the total variation in AMR among countries can be attributed to antibiotic consumption; however, when including the quality of governance indicator, 63% of the total variation in AMR rates was explained by the regression model (Collignon et al., 2015). The study results suggest that governance is a more important indicator of AMR than antibiotic consumption.

This connection between governance and antimicrobial resistance was expanded on in later studies by testing additional socioeconomic and cultural variables in relation to antibiotic consumption. Using the World Governance Indicators (WGI Index), researchers concluded that the relationship between governance quality and antibiotic use was very strong and negatively associated (Gaygısız et al., 2017). The authors hypothesized that a well-governed country is more likely to be able to implement effective health policies and disease prevention strategies and, therefore, control antimicrobial use and surveillance the spread within its borders. An additional study confirmed the positive relationship between corruption measures and the consumption of antibiotics in European regions and countries (Rönnerstrand & Lapuente, 2017). These studies involving antimicrobial consumption and its relationship to quality of governance encourage future research to examine the comparison of antimicrobial consumption and quality of governance as drivers of AMR.

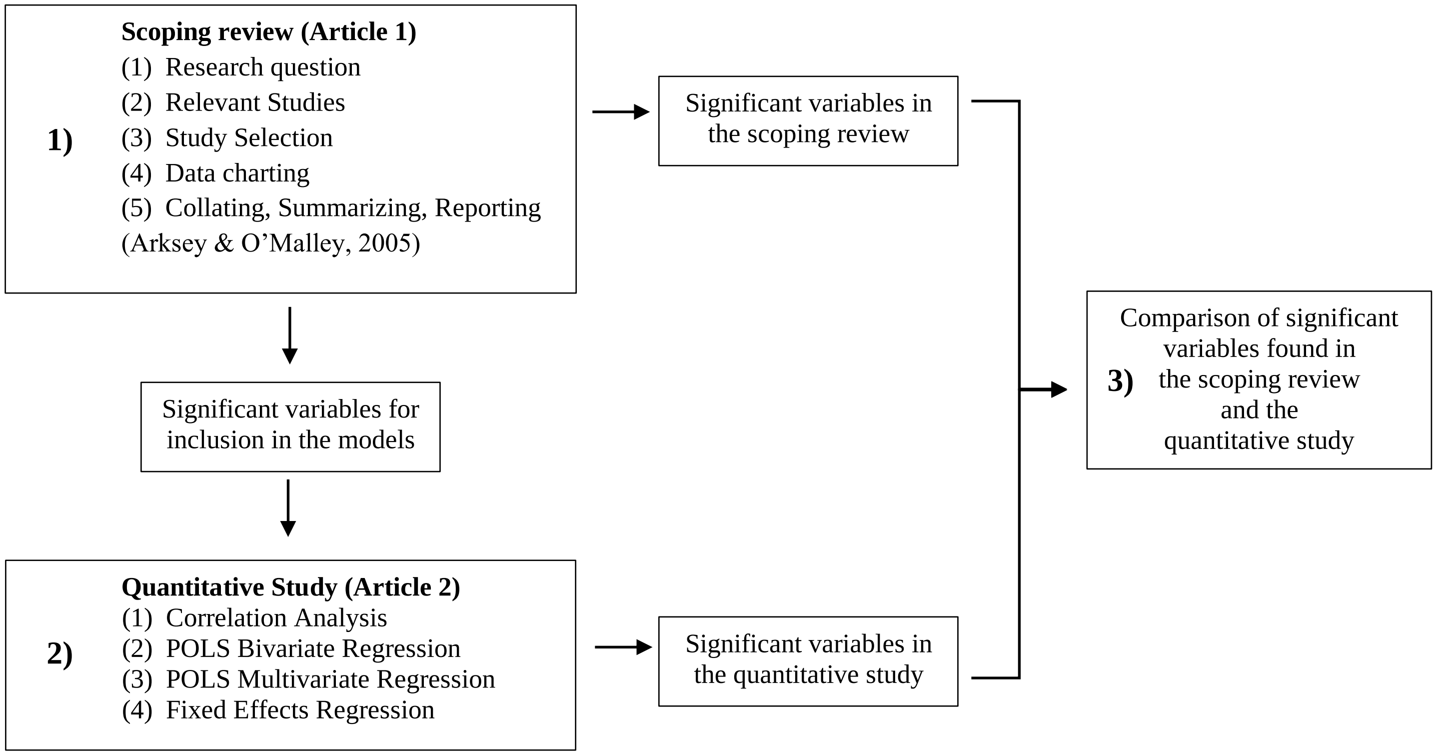
In a 2018 study of 103 countries, researchers explored the connection between AMR and three main variables: governance, infrastructure, and education (Collignon et al., 2018). The results showed a positive relationship between poor governance and AMR thus supporting the findings of previous studies indicating that a government of higher quality is likely to have lower AMR rates. The study also showed an inverse relationship for measures of infrastructure, GDP per capita, public healthcare spending, and antibiotic consumption to AMR (Collignon et al., 2018). The authors conclude that improvements to infrastructure and governance could lower the spread of AMR (Collignon & Beggs, 2019).

While there are several analyses on the socioeconomic, cultural, and political connections to antimicrobial consumption, there is limited research on the influence of political and socioeconomic indicators directly on AMR (Bell et al., 2014; Blommaert et al., 2014). This situation revealed the need for conducting a scoping review to assess the knowledge on socioeconomic and governance-related factors associated with AMR (Article 1). The scoping review was developed for research purposes in order to make an assessment of the state of knowledge and to support the inclusion of diverse variables in the development of the quantitative study design. This research will examine the relationship between quality of governance and AMR rates across European countries and contribute to the literature on this important subject. There is reason to believe interest in this field will grow as the WHO, FAO, and World Organisation of Animal Health (OIE) all include objectives to strengthen governance in their action plans and recommendations for combating antimicrobial resistance (FAO, 2016; WHO, 2015).

2.5 Research Design

To design of this research project involves three main components: (1) a scoping review to assess the state of knowledge and extract variables from the past literature, (2) a quantitative study using the selected variables from the scoping review to create regression models for bivariate and multivariate analyses, and (3) the comparison and discussion of significant variables linked to AMR from both the scoping review (Article 1) and the regression analysis (Article 2). The objective of this framework is to determine which socioeconomic, governance, and health-system related variables are associated with the spread of AMR. Figure 2.1 provides a visual diagram illustrating the process of this research project.

Figure 2.1 Research Design Process



2.6 Scoping Review Findings

A limited scoping review (cf. Article 1 attached) was conducted following the five-stage protocol detailed in Arksey and O'Malley (2005). The objective of the scoping review is to summarize the state of knowledge on socioeconomic and governance factors influencing AMR as well as to identify the shared significant variables among these articles. The research question of the review is: what is known from the existing literature about the association between socioeconomic and government/governance factors, particularly quality of governance, and the prevalence of antimicrobial resistance?

The process included a search of three digital databases for peer-reviewed articles on AMR and socioeconomic and governance-related variables published during the time period between January 2010 and March 2020. The searches resulted in 5782 publications, where 5734 of these articles were excluded based on the irrelevance of their titles and abstracts to the research question or were duplicates generated in the literature search. The remaining 48 articles were subject to a complete review, where a final sample of 13 articles were chosen based on the eligibility criteria and relevance to the research question.

Based on the scoping review analysis, the following variables were extracted for inclusion in the bivariate and multivariate analyses: quality of governance, antimicrobial consumption in humans, antimicrobial consumption in animals, gross domestic product (GDP), education, private health expenditure, and a regional classification variable. The variable of physician density was also included in several studies as a potential confounder. Although not found to be significant in these selected studies, physician density is considered in the multivariate analysis as a control variable. The summary of studies and full process of the scoping review are detailed in Article 1.

2.7 Summary

AMR is an urgent public health issue with serious health, economic, and societal consequences associated with its development. The spread of AMR is facilitated by the overuse of antimicrobials and transmission from person to person or between people and animals. The positive correlation between AMR and consumption of antimicrobials has been long examined in literature; however, additional socioeconomic and governance factors influencing the spread of AMR create a relatively new research focus. A scoping review was conducted (cf. Article 1 attached) to extract variables to be used in the quantitative study. The present study (cf. Article 2 attached) will focus on defining factors associated with AMR and determining the strength and significance of these associations. The study results may have future implications for policy regarding controlling the spread of AMR and prioritizing efforts to address this health challenge. Chapter 3 presents the analytical framework and theoretical foundation for the study design on the relationship between quality of governance and AMR.

3 Analytical framework

The aim of this research is to identify factors associated with the prevalence of AMR in European countries. The scoping review results (cf. Article 1 attached) presented strong support for the inverse association between quality of governance and AMR. The complex nature behind the spread of AMR and the many contributing factors from several sectors including veterinary medicine, human medicine, and agriculture necessitate coordination of governmental and societal institutions to address the public health challenge. The concept of governance and its relationship to health provides the foundational assumption to this study and is examined through the political science definition of governance.

The analytical framework begins with a summary of the theoretical literature on governance. Next, the empirical findings on quality of governance are presented with a focus on the World Bank's Worldwide Governance Indicators (WGI) index. The chapter concludes with the hypotheses for the quantitative study based on the provided theories and past findings.

3.1 Theoretical Literature on Governance

It is important to understand that governance is not simply synonymous with the term government; therefore, the measurement of governance does not solely rely on the actions of the government (Anderson et al., 2019). The concept extends beyond the formal processes of government and focuses more on the organization of society and how it manages its operations (Frenk & Moon, 2013; Legido-Quigley et al., 2018)

While there are many definitions for governance, the World Bank definition is the most commonly used:

> the traditions and institutions by which authority in a country is exercised. This includes: (1) the process by which governments are selected, monitored, and replaced, (2) the capacity of the government to effectively formulate and implement sound policies, and (3) the respect of citizens and the state for the institutions that govern economic and social interactions among them. (Kaufmann et al., 2004, p. 254)

A government that exhibits "good governance" performs well in these three dimensions. Good governance represents an ideal for what governance should be (Barbazza & Tello, 2014). In the

2000 United Nations Millennium Declaration, good governance was emphasized as a crucial factor in meeting the organization's objectives of development and poverty eradication (United Nations, 2000). To strive for good governance, international organizations typically rely on strategies to reduce corruption and improve government effectiveness.

The transition from the term *good governance* to *quality of government* is examined by Rothstein and Teorell (2008). Both of these terms will be used synonymously with the main term of *quality of governance*. The researchers emphasize that quality of government centers on the impartiality of government institutions (Rothstein & Teorell, 2008). Governance is a system-level concept involving the many actors, decisions, and rules of society (Pyone et al., 2017).

Governance literature indicates that a country's quality of governance affects its economic growth (Mo, 2001), public expenditure on education and health (Mauro, 1998), and its population's life expectancy (Besley & Kudamatsu, 2006), well-being, and life satisfaction (Helliwell & Huang, 2008). Countries with higher quality of governance have shown to be able to better perform in economic growth and social development measures (Holmberg et al., 2009). The WGI index supports this claim with findings of associations between its governance indicators and the developmental outcomes of higher per capita incomes, higher adult literacy, and lower infant mortality (Kaufmann et al., 1999).

It is important to acknowledge that governance relies on plans set on a greater level such as a national level, but it must be operationalized by those at lower levels in the system (Pyone et al., 2016). Therefore, the confidence and trust of citizens in a government's policies, institutions, and process is paramount to the effectiveness of these plans (Mattila & Rapeli, 2017). Weak governance can result in oversight in health system operations and can lead to weakened regulations and low accountability in a system (Pokharel et al., 2019). Thus, quality of governance is a likely a significant factor in a country's management of AMR. This assumption is also supported by the findings of the scoping review (cf. Article 1 attached).

3.2 Empirical Findings on Quality of Governance

A country's quality of governance is not a static measure and can experience significant changes over time (Kaufmann et al., 2006). However, researchers have found little support for the idea that quality of governance is improving worldwide (Kaufmann et al., 2008). The values of quality of governance are not randomly distributed across countries, but rather quality of governance requires time and resources for improvement (Kaufmann et al., 1999). Therefore, it is more likely that high income countries have higher measures of quality of governance compared to lower income countries. It is important to also consider that governance has an inherited factor from the country's political and social history, which accounts for variation in the measurement (Kaufmann et al., 1999).

There is an assumption that good governance will ultimately lead to improved health outcomes (Barbazza & Tello, 2014). The assumption has been tested in literature to find positive associations between the health and quality of governance (Wang et al., 2019). In a study involving 19 European countries, citizens in poor health states revealed lower levels of political trust comparatively to those in good health (Mattila & Rapeli, 2017). This finding reflects the importance of quality of governance at all levels of society — from top level decisions regarding laws and policies to the informal perceptions and experiences involving the rules of society and confidence in a country's systems and institutions.

A public health issue such as AMR requires cooperation across many levels to control the spread and adhere to health policy and regulations; therefore, political trust is an important component to a country's measures of quality of governance. Quality of governance can affect many important aspects of the healthcare sector including the creation and implementation of effective policies, the coordination and delivery of services and goods, and the oversight of and accountability to regulations, policies, and laws (Pyone et al., 2016).

In the literature assessed in the scoping review (cf. Article 1 attached), the variable of quality of governance has a significant negative relationship to both AMR and antimicrobial consumption. In a 2015 study, researchers concluded that corruption is the main socioeconomic factor that explains antibiotic resistance (Collignon et al., 2015). Researchers also found corruption levels to be significantly and positively correlated with AMR levels. A later study by Collignon and Beggs (2019) found measures of improved governance, including lower corruption, political stability, rule of law, and absence of violence, were negatively correlated with AMR data.

In regard to antibiotic consumption, a 2017 study found that governance quality had a statistically significant negative relationship to antibiotic use (Gaygısız et al., 2017). Rönnerstrand and Lapuente (2017) echoed this finding in their study which found a significant positive relationship between corruption and antibiotic use.

3.2.1 Corruption

Over the past few decades, there has been an increasing focus on corruption in the healthcare sector. Corruption is defined by Transparency International as “the misuse of entrusted power for private gain” (Vian, 2008, p.84) and the organization has estimated that over 7% of healthcare expenditure is lost to corruption (Bruckner, 2019). The health sector is especially vulnerable to corruption due to the unique features of the industry including the uncertainty in the health market, the many actors and complexity of the system, asymmetric information among the actors (e.g., between physician and patient), and the mix of public money and private actors involved (Vian, 2008). In some areas with high antimicrobial resistance, political corruption is found to be an endemic issue (Ojo et al., 2008).

In a country with weak governance or low control of corruption, this shortcoming is likely to be reflected in its economic growth. Corruption and economic growth have a well-documented negative relationship (Mo, 2001) and corruption has been found to influence the amount that governments invest in education and health (Mauro, 1998). The effects of corruption are often shown in the health status and social welfare of a nation’s citizens. Researchers have found a relationship between national-level corruption and the number of chronic diseases for Europeans under 50 years of age (Ferrari & Salustri, 2020) suggesting that corruption not only affects the delivery and functioning of a health system but affects the individual health of citizens in a country’s population. While corruption is an important component of quality of governance, it is important to note that it is not solely representative of the concept (Rothstein & Teorell, 2008).

3.2.2 Worldwide Governance Indicators Index

In the study design, the concept of quality of governance is measured using the Worldwide Governance Indicators (WGI) Index by the World Bank (Kaufmann & Kraay, 2018). The data are collected on perceptions of governance from survey respondents and business experts from around the world (Kaufmann et al., 2010). The index is comprised of six indicators: Voice and Accountability (VA), Political Stability and Absence of Violence (PV), Government Effectiveness (GE), Regulatory Quality (RQ), Rule of Law (RL), and Control of Corruption (CC). These indicators are broad and based on several hundred variables collected from more than 30 different data sources (Kaufmann et al., 2010). The dataset covers more than 200 countries and has data dating back to 1996. Each indicator relates to one dimension of the World Bank's definition of governance. The descriptions of the six indicators are included below:

The indicators of Voice and Accountability and Political Stability and Absence of Violence and Terrorism are representative of 'the process by which governments are selected, monitored, and replaced.'

1. **Voice and Accountability** is measured by the degree to which a country's citizens are involved in the selection of their government as well as the individual freedoms of expression, association, and a nation's free media (Kaufmann et al., 2009). The concept focuses on holding those in public office accountable and the transparency of governmental processes.

2. **Political Stability and Absence of Violence/Terrorism** is measured as the likelihood of a country's government to be destabilized in a violent manner. This indicator concerns the orderliness of political transitions (Kaufmann et al., 2009).

For the second dimension of the definition involving 'the capacity of the government to effectively formulate and implement sound policies,' Government Effectiveness and Regulatory Quality are measured.

3. **Government Effectiveness** is defined by the perceptions of the quality of public services and policy creation, the civil service capacity, and the extent to which bureaucracy is independent from political pressures (Kaufmann et al., 2009).

4. **Regulatory Quality** captures the ability of the government to provide sound policies and regulations that allow and encourage private sector development (Kaufmann et al., 2009). This indicator considers the barriers to conducting business.

The last dimension of the governance definition involving 'the respect of citizens and the state for the institutions that govern economic and social interactions among them' is captured by the indicators Rule of Law and Control of Corruption.

5. **Rule of Law** involves how citizens respect and abide by the rules of society, including confidence and trust in contract enforcement and property rights, law enforcement, and the judicial system, as well as the likelihood of crime and violence (Kaufmann et al., 2009). A high measure of rule of law should indicate an open and transparent market as well as the political trust of a nation's population.

6. **Control of Corruption** measures the degree to which public power is exercised for private interests (Kaufmann et al., 2009). Corruption is considered in both petty and grand forms.

One measure alone does not capture the concept of governance, so therefore it is best to use multiple indicators. The term *quality of governance* is used as the variable name in the models to encompass these six indicators as it is consistent with the index description.

3.3 Hypotheses

Based on the findings from the studies on quality of governance and health outcomes, it seems reasonable to assume that higher quality of governance is associated with lower levels of AMR in a country. Furthermore, the theories surrounding good governance support its significance in developmental effectiveness such as in economic growth and education measures (Holmberg et al., 2009; Kaufmann et al., 1999). The scoping review provides evidence for significant variables in this literature and justifies the assumptions on the relationships between the included variable (cf. Article 1 attached).

To test the strength and validity of this association in a different dataset with novel variables, the following hypotheses were developed for the quantitative study. The hypotheses included below are the basic overriding assumptions of the study while further assumptions for the individual variables will be discussed in Chapter 4.

H1: Quality of governance is negatively related to antimicrobial resistance prevalence

The main hypothesis concerns an inverse and significant relationship between quality of governance and antimicrobial resistance. Based on the findings of similar studies, the underlying assumption is that a country with a higher quality of governance will likely have better control over AMR spread.

The other hypothesis for the quantitative study involves antimicrobial consumption and AMR. For the animal antimicrobial consumption measure and the human antimicrobial consumption measure, a positive relationship is expected with AMR. It is assumed that increased antibiotic consumption relates to increased AMR as it has been widely considered as the main contributor to AMR prevalence (Goossens et al., 2005).

H2: *Antimicrobial consumption is positively related to antimicrobial resistance prevalence*

Following the scoping review results of significant variables associated with AMR (cf. Article 1 attached), the research will also include additional socioeconomic and health-system control factors to further investigate this relationship such as the national private healthcare expenditures, GDP per capita, physician density, education levels, zoonoses notification rates, health system typology, and regional classification. The expectations of these variables in relation to AMR will be addressed in the following chapter. Chapter 4 explains the selection of panel data and methodology for the quantitative study.

4 Methodology and Data

After reviewing the findings from the scoping review on factors that influence AMR and past literature on the relationship of AMR and quality of governance, variables are selected for inclusion in the bivariate and multivariate analyses. A panel dataset of 30 countries from the years 2011-2017 was created with socioeconomic and health-related variables from seven different data sources. The explanation of the variables and data sources are included in this chapter. Additionally, the statistical methods used for analysis of the data are presented. Methodology and design of the scoping review are detailed in Article 1. The review is instrumental in supporting the study design for explaining the AMR variation among European countries.

In short, the variables of antimicrobial consumption in animals, antimicrobial consumption in humans, private health expenditure, zoonoses notification rates (campylobacteriosis and salmonellosis), and physician density are expected to have a positive relationship with AMR, thus contributing to growing AMR rates. Additionally, health systems with fewer controls such the Etatist Social Health Insurance and Other groups and the regions of Southern and Eastern Europe are expected to have positive associations with AMR. The variables of quality of governance, education, GDP, and total health expenditure are expected to have a negative relationship with AMR. Health systems that are more centralized such the National Health Service, National Health Insurance, and Social Health Insurance groups and the regions of Western and Northern Europe are assumed to be negatively associated with AMR.

4.1 Study Design and Data

While there are many studies on the socioeconomic, cultural, and political connections to antimicrobial consumption, there is a dearth of research on these factors directly related to AMR. This study will examine the relationship between quality of governance and AMR rates across European countries. The objective of this study is to find what factors influence the variation of AMR to contribute to this field of research and suggest areas of consideration in health policy development and implementation relating to AMR.

Building on past studies that link corruption and AMR, the study uses more recent data from the years of 2011 to 2017. Key related studies including Collignon et al. (2015), Rönnerstrand and Lapuente (2017), Gaygısız et al. (2017), and Collignon et al. (2018) used data from 2014 and before. This time period is chosen due to the limited data availability from 2010 and 2018 for AMR rates. This study will seek to validate findings from past studies with the current data.

European countries are a useful sample set for examining these factors due to the high variation in resistance rates and antimicrobial consumption across countries as well as a sophisticated surveillance system on AMR coordinated by the ECDC.

4.1.1 Dataset Description

The research design will focus on country-level data instead of regional subnational data due to the lack of information on AMR rates at the regional level from the ECDC. Other studies have used regional subnational data for the relationship of antimicrobial consumption to quality of governance, which increases the number of observations for the study (Rönnerstrand & Lapuente, 2017). The panel dataset contains 13 national-level variables and 210 observations. The study will include all European countries that have the appropriate data available for the selected variables. These 30 countries include: Austria, Belgium, Bulgaria, Cyprus, Czech Republic, Germany, Denmark, Estonia, Greece, Spain, Finland, France, Croatia, Hungary, Ireland, Iceland, Italy, Lithuania, Luxembourg, Latvia, Malta, Netherlands, Norway, Poland, Portugal, Romania, Sweden, Slovenia, Slovakia, and the United Kingdom.

4.1.2 Antimicrobial Resistance Rates: EARS-Net

The dependent variable is antimicrobial resistance (AMR) rate, which is measured as the rate of resistance to antimicrobials measured in bacteria causing infections in the bloodstream. The antimicrobial resistance data are gathered from the European Antimicrobial Resistance Surveillance Network (EARS-Net) database of the ECDC. EARS-Net annually monitors seven common pathogens (ECDC, 2020a), which represent the idea of general antimicrobial resistance. Of the reported data, 23 pathogen and antimicrobial combinations were chosen based on data availability for the chosen time period.

The dependent variable is calculated as the average of resistance rates from 23 pathogen and antimicrobial combinations. The average is calculated by the number of resistant isolates of the 23 combinations divided by the total number of isolates tested per year per country. The resistance rates are written as decimals and vary from 0 to 1. The combinations sampled are included in a previous study on quality of governance and AMR (Collignon et al., 2015). The 23 combinations are listed in Table 4.1.

Table 4.1 Pathogen and Antimicrobial Combinations

Pathogen	Antimicrobial
1. Escherichia coli	Third-generation cephalosporins
2. Escherichia coli	Aminoglycosides
3. Escherichia coli	Aminopenicillins
4. Escherichia coli	Carbapenems
5. Escherichia coli	Fluroquinolones
6. Klebsiella pneumoniae	Third-generation cephalosporins
7. Klebsiella pneumoniae	Aminoglycosides
8. Klebsiella pneumoniae	Carbapenems
9. Klebsiella pneumoniae	Fluroquinolones
10. Pseudomonas aeruginosa	Aminoglycosides
11. Pseudomonas aeruginosa	Carbapenems
12. Pseudomonas aeruginosa	Ceftazidime
13. Pseudomonas aeruginosa	Fluroquinolones
14. Pseudomonas aeruginosa	Piperacillin/Tazobactam
15. Streptococcus pneumoniae	Penicillins
16. Streptococcus pneumoniae	Macrolides
17. Staphylococcus aureus	Methicillin
18. Enterococcus faecalis	Aminopenicillins
19. Enterococcus faecalis	High-level Gentamicin
20. Enterococcus faecalis	Vancomycin
21. Enterococcus faecium	Aminopenicillins
22. Enterococcus faecium	High-level Gentamicin
23. Enterococcus faecium	Vancomycin

EARS-Net collects data from invasive isolates through human blood and cerebrospinal fluid samples (ECDC, 2018). This measurement was used in similar studies on the relationship of AMR and antibiotic consumption (Bronzwaer et al., 2002; Collignon et al., 2015; McDonnell et al., 2017). The sample data are classified as incomplete and excluded if fewer than 30 isolates were tested per pathogen/antimicrobial combination. From 2011-2017, 411 of the 4830 data samples contained fewer than 30 isolates leaving a viable dataset of 4419 items for 210 observations.

4.1.3 Quality of Governance: WGI Index

Quality of Governance (QoG) is measured using the World Bank's Worldwide Governance Indicators (WGI) Index. The index includes six indicators of governance: Voice and Accountability; Political Stability and Absence of Violence; Government Effectiveness; Regulatory Quality; Rule of Law; and Control of Corruption. These indicators are described in Chapter 3.2.2. The scores are measured on a scale of -2.5 indicating weak governance to a maximum of 2.5 indicating strong governance (Kaufmann & Kraay, 2018). The scale has been recalculated in the study from 0 to 5 to avoid errors from negative values in calculating the average scores. The dataset has been used in similar studies on antimicrobial consumption and resistance for the quality of governance variable (Collignon et al., 2018; Gaygısız et al. , 2017)

The six WGI measures are strongly correlated among themselves (Rothstein & Teorell, 2008) and thus, an average measurement was used that incorporated all six dimensions to avoid errors associated with multicollinearity. The correlation matrix of the six WGI measures is included in the appendix. The QoG dimensions are not tested separately in the models in Chapter 5. For the WGI Index, the dimensions are overlapping and intended to be used only together as a measure of quality of governance (Langbein & Knack, 2008). The authors of the dataset state that the indicators should not be thought of as independent of one another (Kaufmann et al., 2010). A relevant study on quality of governance and antibiotic use created a combined index similar to the created variable of QoGavg, which includes the six dimensions averaged into one measure (Gaygısız et al., 2017).

4.1.4 Antimicrobial Consumption in Humans: ESAC-Net

Antibiotic consumption is used as an independent variable in this study. The data are collected from the European Surveillance of Antimicrobial Consumption (ESAC-Net) which is monitored by the ECDC and consumption is measured by defined daily dose (DDD) per 1000 inhabitants per day (ECDC, 2020a). This is a measure commonly known as DID and has been used in similar studies (Collignon et al., 2015; McDonnell et al., 2017; Mueller et al., 2016). Research has shown a strong correlation between AMR and antibiotic consumption in Europe (Bronzwaer et al., 2002).

Antimicrobial consumption is broken up by ATC group classification and setting (ECDC, 2020b). In this study, antimicrobial consumption will only be considered in the community or primary care sector due to missing data from several countries on hospital sector data. These data are valid to measure consumption in the community as the highest rates of antibiotic prescriptions for systemic use are in primary care sector (Goossens et al., 2005). The decision to only include systemic use antimicrobials for consumption data is justified as more than 90% of antibiotics for medical use in Europe are prescribed to non-hospitalized patients (Bell et al., 2014).

In this analysis, antibiotic use will be measured for ATC class J01, which includes antibacterials for systemic use and excludes antifungals, antibacterials for tuberculosis, and topical antibiotics (ECDC, 2020b). The data from ESAC-Net is based on either distribution or reimbursement data. This dataset is similar to samples used in related studies (Blommaert et al., 2014; Gaygısız et al., 2017; McDonnell et al., 2017).

The term consumption is used for this variable due to the nature of the data, which is an aggregated data source. There is no specific information on the patients who are receiving the antimicrobials or reason for why the antimicrobials are used, thus giving a proxy estimate of the use of antimicrobials classified by the country and setting including community or hospital use (WHO, 2016). Antimicrobial usage data would refer to patient-level data and may allow for the defining of data by patient characteristics or medicine intention.

4.1.5 Antimicrobial Consumption in Animals: ESVAC

Antimicrobial use in animals is an important topic in addressing the challenges of antimicrobial resistance. Antimicrobials are used in food animal production for disease treatment, prevention for common diseases, and animal growth promotion (Landers et al., 2012). In recent years, the EU has banned antimicrobial use for growth purposes in animal production and thus, all antimicrobials used for food production are prescription (Laxminarayan et al., 2013).

Researchers have recognized antibiotic use in livestock as an important topic for future research (Collignon et al., 2015) yet it has not been included in the quality of governance and AMR research.

The data suggest that food animal production is responsible for a significant amount of total antimicrobial use (Landers et al., 2012). In a later report, Collignon and Beggs (2019) state that antimicrobial use in food animals may account for more than 70% of total antimicrobial consumption. This issue is alarming as almost all the classes of antimicrobials for human antimicrobial consumption are also used in livestock (Aarestrup et al., 2008). Food has been traditionally considered the main source of transmission of AMR from animals to humans (Durso & Cook, 2014).

Veterinary antimicrobial consumption will be included in the models to create a more complete picture of antimicrobial consumption in the community. The data are collected from the European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) maintained by the European Medicines Agency (EMA) on veterinary antimicrobial sales.

ESVAC offers data on the population-corrected sales of products used in food-producing animals. It is measured in milligrams (mg) of active ingredient by Population Correction Unit (PCU) (EMA, 2020). The population correction measure considers the differences in size and structure of animal populations. This measurement of consumption data should be comprehensive as most antimicrobial use in livestock requires a veterinary prescription (Landers et al., 2012). As stated earlier, antimicrobial consumption data from humans are reported in DID measurements, defined daily doses (DDD) per 1000 inhabitants and per day. Corresponding data in food-producing animals are typically measured in mg of active substance per kilogram of estimated biomass. It is possible to measure both human and animal consumption of antimicrobials under a common measure; however, data limitations and time constraints have prevented this common measure from being included in these models.

In a joint report on AMR from the ECDC, European Food Safety Authority (EFSA), and EMA, no correlation was observed between antimicrobial consumption in animals and in humans at the national level. However, the report found an overall positive association between antimicrobial consumption and AMR in both humans and food-producing animals (ECDC et al., 2017).) A review of the academic literature addressing antibiotic use in livestock reported that 72% of the studies included in the review found a relationship between antimicrobial consumption in animals and AMR in humans (O'Neill, 2015).

The danger of antimicrobial use in food animals is the potential introduction of resistant organisms into the food chain and the possible spread of these organisms from food products to humans (Cogliani et al., 2011; Landers et al., 2012). The effects of animal antimicrobial consumption are twofold: the causal link between antimicrobial-resistant bacteria from livestock animals and the indirect effect from the resistant organisms spread in the environment resulting from antimicrobial consumption in these animals (Marshall & Levy, 2011; Landers et al., 2012). The World Organisation for Animal Health (OIE) reported findings that antimicrobial use in livestock has an adverse effect on human health (Aguirre, 2017). In a systematic review on the relationship between antibiotic use in livestock and AMR in humans, the authors concluded with a lack of consensus regarding the effect due to the limited findings; however, noted that reducing antimicrobial use in food producing animals appears to be a beneficial strategy for both animal and human populations (Tang et al., 2017). The addition of this variable in our research may be able to spread some light on the topic.

4.1.6 Private Health Expenditure: WHO

Private health expenditure is expected to have a positive relationship with AMR as a more private-based health system is assumed to have fewer controls compared to a public system and increased pharmaceutical and medical provider competition (Collignon et al., 2015). The data are available through the WHO Global Health Expenditure database on health expenditures in European countries and measured as a country's private health expenditure funded from domestic private sources as a percentage of current health expenditures. The private health expenditure measurement includes payments from households, businesses, and organizations as either prepaid health insurance payments or direct payments to healthcare providers (WHO, 2020a).

Researchers have found that the higher the private health expenditure in a country, the higher the levels of AMR (Collignon et al., 2015; Collignon & Beggs, 2019; Hijazi et al., 2019). The assumption behind this relationship is that higher private health expenditures may allow citizens to have greater access to medical services and products as the market may be more competitive.

The relationship between out-of-pocket spending and AMR also followed the private health expenditure trend. Researchers found that larger amounts of out-of-pocket expenditures were connected to higher rates of AMR (Alsan et al., 2015). Pharmaceutical purchases also comprise a large portion of out-of-pocket health expenditures. It has been suggested in previous studies that pharmaceutical expenditures may be influential in antibiotic consumption trends and rising AMR rates (Goossens et al., 2005; Rönnerstrand & Lapuente, 2017).

4.1.7 Education: Eurostat

Level of education is often included as a control indicator of AMR and antimicrobial consumption. The average level of education of a country's inhabitants may also relate to developmental indicators associated with quality of governance (Kaufmann et al., 1999). Education in this model will be measured as the percentage of tertiary-educated people in the total country population. The data are taken from the Eurostat database on the percentage of inhabitants from a country's population from age 15 to 64 years with tertiary education (levels 5-8) (Eurostat, 2020a).

The effects of education on AMR are mixed based on the findings of past research. While the typical assumption would be that increased education would lead to a more educated population that could be expected to display less risk behavior, recent research has found an opposite relationship. Education measures including literacy rates and secondary education completion were found to have a significant and positive association with levels of AMR (Collignon & Beggs, 2019).

In regard to antibiotic consumption, researchers found that the proportion of adults who completed upper secondary education was negatively associated with antibiotic use (Blommaert et al., 2014). Gaygısız et al. (2017) found a similar trend in that the mean years of schooling had a statistically significant negative relationship to antibiotic use. Masiero et al. (2010) also found that educated individuals may use less antibiotics because they are concerned about the risks and consequences of antimicrobial resistance. Research supports the idea that a country with higher education levels seems to consume fewer antibiotics.

4.1.8 GDP per capita: Eurostat

Gross Domestic Product (GDP) per capita is collected from the Eurostat database. The measurement is the ratio of real GDP to the average population of a country (Eurostat, 2020b). GDP per capita measures the total final output of goods and services produced by an economy within a year.

In a study by Rönnerstrand and Lapuente (2017), there was no significant association of GDP per capita to antibiotic consumption. Mueller et al. (2016) also found that GDP per capita was not significantly correlated with antibiotic consumption. However, Klein et. al (2018) found a significant positive association between GDP per capita and changes in antibiotic consumption rate in low- and middle-income countries, but no statistically significant correlation in high income countries. Using gross national income per capita, Masiero et al. (2010) found that richer countries use more outpatient antibiotics compared to poorer countries.

For antimicrobial resistance, GDP per capita was poorly correlated in a study by Collignon et al. (2015). In a later study regarding countries from several continents, Collignon et al. (2018) found that higher GDP per capita had a statistically significant negative relationship to resistance rates. The assumption behind GDP per capita is that high GDP per person would result in higher antibiotic consumption and possibly higher AMR rates.

GDP is a challenging indicator to include in analysis as it is known to have a positive, significant relationship to quality of governance. The authors of the WGI Index state that a simple regression relationship may inflate the true positive impact of income on governance because the effect is strong in both directions (Kaufmann et al., 2005). The inclusion of GDP in multivariate models is therefore interpreted with caution. In Article 2, GDP is omitted from the analysis due to the multicollinearity concern and confounding properties of the variable.

4.1.9 Total Health Expenditure: Eurostat

As an alternative to GDP, total health expenditure was included in the bivariate and multivariate analyses in relation to AMR. The data on total health expenditure (THE) were collected from the Eurostat database and is measured in euro per inhabitant (Eurostat, 2020c). GDP and THE are both tested as control variables in the multivariate models. Like GDP, THE is expected to have an inverse relationship with AMR based on past findings (Collignon et al., 2018).

The two variables are very strongly correlated with the association of .9801 indicating that GDP and THE measure similar factors. Thus, in analysis these two variables are never used together in the same models. THE has a slightly higher correlation with the dependent variable (r= -.7058) compared to GDP (r= -.5828) and both are highly correlated with quality of governance.

4.1.10 Physician Density: WHO

Physician density data are collected from the WHO Global Health Observatory data repository. The variable represents the competition between physicians in a country. The measurement is the number of medical doctors per 10,000 population (WHO, 2020b). The assumption behind physician density is that it would be positively related to AMR as antimicrobial prescribing and competition among doctors are expected to be higher in a country with more physicians.

Physician density was used in connection to antimicrobial consumption in several recent studies. Rönnerstrand and Lapuente (2017) found no significant association of inhabitants per medical doctor to antibiotic consumption and Klein et al. (2018) found similar results. However, in Masiero et al. (2010), physician density had a positive and significant effect on antibiotic use. Thus for completeness of the study, physician density was included as a possible confounder. The variable may be related to the independent variables of quality of governance and antibiotic consumption in the analysis.

4.1.11 Zoonoses: EARS-Net

In evaluating how a country handles its response to the threat of AMR, it may be valuable to consider how the country fares with other outbreaks, for example zoonotic diseases. In the multivariate model, salmonellosis and campylobacteriosis prevalence will be used as control factors. The indicator for these variables is the notification rates by 100,000 persons (ECDC, 2020a). The notification rate is calculated by the number of the reported confirmed cases divided by the Eurostat population year estimate and then multiplied by 100,000.

The data are broken up by country and year and is available through the ECDC EARS-Net database. Salmonella and campylobacter infections are used in this study as they are rarely transferred through human contact in developed countries and likely are transmitted from resistant bacteria developed in livestock production (Garcia-Migura et al., 2014). Therefore, these variables could complement the inclusion of animal antimicrobial consumption in the models.

4.1.12 Health System Typology

Health system classification is also included as a variable in the study to account for differences in healthcare services, availability, and costs. The WHO defined a health system as consisting of "all organizations, people and actions whose primary intent is to promote, restore or maintain heath" (Health Systems 20/20, 2012) The health system typology is divided into six groups classified by the deductive approach used in an analysis of Organisation for Economic Co-operation and Development (OECD) health systems (Böhm et al., 2013). The original six classifications were modified to exclude the Private Healthcare System as it did not fit with any of the countries in the dataset in exchange for the inclusion of an "Other" classification for those health systems that did not fit the other five classifications, including Greece and several Eastern European countries.

The following six classifications were used as a categorical variable in the analysis: (1) National Health Service, (2) National Health Insurance, (3) Social Health Insurance, (4) Etatist Social Health Insurance, (5) Social Based Mixed Type and (6) Other. During analysis, Group 5 (Social Based Mixed Type) and Group 3 (Social Health Insurance) were not statistically significant from the baseline Group 1 (National Health Service), so these two groups were then incorporated into Group 1.

It is assumed that a health system with tighter controls and more government regulation would likely have a lower antimicrobial resistance rate. Additionally, the insurance status of citizens can also affect antimicrobial consumption and therefore, resistance. Antibiotic sales were shown to be higher for individuals with insurance as these patients are likely to not be as price sensitive as someone without insurance (Laxminarayan et al., 2013). In a system with more competition among healthcare providers, antimicrobial prescribing may also be influenced (Laxminarayan et al., 2013). With this supporting literature, more centralized health systems are assumed to be associated with lower levels of AMR due to the expected tighter controls and coordination among its health and government institutions. Therefore, National Health Service, National Health Insurance, and Social Health Insurance are expected to be negatively associated with AMR while the Other group and Etatist Social Health Insurance are assumed to be more likely associated higher rates of AMR.

Table 4.2 Health System Classification

Group	Health System Classification	Countries Included	N=
1	National Health Service	Denmark, Finland, Iceland, Norway, Spain, Portugal, Sweden, United Kingdom	8
2	National Health Insurance	Ireland, Italy	2
3	Social Health Insurance*	Austria, Germany, Luxembourg	3
4	Etatist Social Health Insurance	Belgium, Czech Republic, Estonia, France, Hungary, Netherlands, Poland, Slovakia	8
5	Social Based Mixed Type*	Slovenia	1
6	Other/Not classified	Bulgaria, Croatia, Cyprus, Greece, Latvia, Lithuania, Malta, Romania	8

* Groups 3 and 5 were not statistically significant from the baseline Group 1 and later combined in analysis

A health system variable classified by financing system was also developed and tested with three classifications: social insurance, tax financed, and out-of-pocket. This variable was not significant in bivariate or multivariate analysis.

4.1.13 Region

A regional variable was also added as a categorical variable to account for some of the shared cultural and socioeconomic characteristics among geographic regions in Europe. The regional variable is divided into four groups dependent on where the country is located (1) Northern Europe (2) Southern Europe (3) Western Europe and (4) Eastern Europe. According to literature on AMR trends in Europe, it is expected that the regions of Northern and Western Europe would be associated with lower levels of AMR while the regions of Southern and Eastern Europe would be associated with higher AMR levels (ECDC 2018; Machowska & Stålsby Lundborg, 2018).

These regional trends are often representative of shared cultural and health-system factors among the countries as well as the warmer climate in Southern Europe and traditionally weaker quality of governance measures in Eastern Europe may exaggerate the differences in AMR between the regions.

During analysis, Groups 1 and 3 (Northern and Western Europe) were combined into Group 1 as there was no significant difference between the groups.

Table 4.3 Region Classification

Group	Region	Countries Included	N=
1	Northern Europe	Denmark, Estonia, Finland, Iceland, Ireland, Latvia, Lithuania, Norway, Sweden, United Kingdom	10
2	Southern Europe	Croatia, Cyprus, Greece, Italy, Malta, Portugal, Slovenia, Spain	8
3	Western Europe*	Austria, Belgium, Germany, France, Luxembourg, Netherlands	6
4	Eastern Europe	Bulgaria, Czech Republic, Hungary, Poland, Romania, Slovakia	6

* Group 3 was not statistically significant from the baseline Group 1 and thus combined in analysis

4.2 Statistical Methods

For the analysis, the chosen significance level is 5% as is standard in the social science discipline. The original sample size of 30 countries was quite small, so the panel data cover seven years (2011-2017) to expand the number of observations. As the sample size (n=210) becomes sufficiently large, then the sample mean is approximately normal (Newbold et al., 2013). The data are analyzed using correlation and regression methods. First, associations are analyzed between the dependent variable of AMR and the explanatory variables. Next, bivariate and multivariate linear regression models are used to determine the relationship between the variables and the strength of these associations. Finally, the fixed effects (FE) method is applied for a robustness check to control for individual country-specific factors. The data were initially compiled from multiple sources using Microsoft Excel and analyzed using Stata/IC version 16. Graphs were created in Stata/IC version 16.

4.2.1 Correlation

Correlation analysis identifies the strength and direction of the relationship between variables. The correlation coefficient (Pearson's r) measures the linear relationship between two continuous variables and is the most commonly used correlation measurement (Newbold et al., 2013). This method is used to investigate the correlation between AMR and the explanatory variables.

While correlation analysis is useful for measuring an individual independent variable's relationship to AMR, these associations do not consider the effect of other variables, which can change the final results significantly. Therefore, additional analysis methods are used.

4.2.2 POLS Bivariate Regression

Pooled Ordinary Least Squares (POLS) estimation is used for the initial regression analysis. The panel data are treated then as a pooled dataset and there is no assumption on individual differences in the models (Mućk, 2018). This method was also employed in Collignon et al. (2015).

The bivariate model will examine the relationship of average AMR rates and the independent variables. The main bivariate relationship of this research is between AMR and quality of governance. Other relationships will be investigated in this analysis including the link between antibiotic consumption in humans and AMR as well as antibiotic consumption in animals and AMR. In addition, each independent variable will be tested for its relationship to AMR.

The purpose of a bivariate linear regression (also known as simple regression) analysis is to evaluate the relative impact of the explanatory variable on a particular outcome (Zou et al., 2003). The analysis assesses the strength of the relationships in the dataset and the uncertainty in the model. The bivariate regression contains an independent (also known as explanatory) variable and the dependent variable. The equation of the bivariate model is included below based on models from Newbold et al. (2013) and Mućk (2018):

Equation 4.1 Bivariate Regression Model

$$Y_{it} = \beta_0 + \beta_1 X_{it} + \varepsilon_{it}$$

Y: dependent or outcome variable — the average antimicrobial resistance rate (AMRAvg)

X: independent or explanatory variable — (e.g., average quality of governance score)

β_0: constant intercept, which is constant across groups and time

β_1: coefficient, which is constant across groups and time

ε: error term or residual, which accounts for differences in the model

i: group variable representing country

t: time variable representing year

4.2.3 POLS Multivariate Regression

In the multivariate model, control variables will be introduced to identify other national socioeconomic or health-system factors that could impact AMR rates in a country. The variables that will be tested with the dependent variable of the average AMR rate include: animal antimicrobial consumption (AMCanimal), human antimicrobial consumption (AMChuman), average quality of governance score (QoGavg), percentage of the population who achieved tertiary education (EDU), real GDP per capita (GDP), private health expenditure (PHE), physician density (PPI), total health expenditure (THE), region (Region), OECD health system classification (OECD), campylobacteriosis notification rate (Campylo), and salmonellosis notification rate (Salmon). The data are used in regression analysis to determine any relationship between these variables and AMR rates. The model will be run specific to the year and country of the data.

Due to the high correlation between the variables GDP and THE, only one of these variables will be used at a time in the regression equation. The same logic applies to the categorical variables of region and OECD health system as they share many characteristics. Thus, THE could be included in the model as an alternative to GDP and health system could replace region in the model. If all variables are included, the equation of the multivariate linear regression would be as shown in Equation 4.2.

Equation 4.2 Multivariate Regression Model

$$AMRavg_{it} = \beta_0 + \beta_1 AMCanimal_{it} + \beta_2 AMChuman_{it} + \beta_3 EDU_{it} + \beta_4 GDP_{it} + \beta_5 PHE_{it} + \beta_6 PPI_{it} + \beta_7 Campylo_{it} + \beta_8 Salmon_{it} + \beta_{13} Region_{it} + \varepsilon_{it}$$

β_0 = constant intercept, which is constant across groups and time
$\beta_{1,\ldots,k}$= coefficient, which is constant among groups and times
ε = error term, which accounts for differences in the model
i = group variable representing country
t = time variable representing year

Three methods will be used to determine the final multivariate models: forward selection, backward elimination, and stepwise regression. The different methods will be used and compared for quality control to determine the variables included in the final model.

The forward selection method begins with the independent variables that have the highest correlation to the dependent variable (AMRAvg). When the variables added are no longer significant, the final model is then defined. The method gives priority to variables that have higher correlations, therefore assuming these variables explain most of the variation (Xu & Zhang, 2001).

The backward elimination method includes all independent variables that had a significant relationship (p-value $\leq$ .05) in simple regression to the dependent variable (AMRAvg) to avoid including variables based on coincidence. The variable with the highest p-value is removed each time until only significant variables remain.

A stepwise method combines both the forward and backward methods. The process begins the same as the forward selection with variables with the highest correlation. Each variable added is evaluated on whether it benefits the model (Xu & Zhang, 2001). Subsequent variables are removed if they are no longer significant. Discretion can be used on whether to disregard or include the variable.

To check for issues with heteroscedasticity and multicollinearity, the Breusch-Pagan Test and Variance Inflation Factors will be utilized. To check for goodness of fit of the model, R^2 is used.

R^2 is known as the coefficient of determination and represents the percentage of variability in the dependent variable that is explained by the model (Newbold et al., 2013; Zou et al., 2003). Higher values indicate a better regression; however, R^2 must be interpreted with caution as the measure can be inflated due to issues with the data or model.

4.2.4 Fixed Effects model

The Fixed Effects (FE) model is introduced to address possible omitted variable bias due to country-specific and time-invariant factors that might be associated with both AMR and explanatory variables (Collignon et al., 2015). The Hausman test confirms that the FE model should be used rather than the random effects model for the data. The assumption under the FE model is that the groups share common coefficients on independent variables, but there are group-specific constants. This group constant controls for individual-specific and time-invariant effects (Mućk, 2018). In this model, a dummy variable is generated for each sample unit (i = country). The country variable (i) represents the dependence created by repeated observations and the regression line is moved by a fixed amount for each country.

Equation 4.3 Fixed Effects Model

$$Y_{it} = \beta_{0_i} + \beta_1 X_{1_{it}} + \cdots + \beta_k X_{k_{it}} + \varepsilon_{it}$$

Y: dependent or outcome variable — the average antimicrobial resistance rate (AMRAvg)

X: independent or explanatory variable — (e.g., average quality of governance score)

Both bivariate and multivariate models will be used for fixed effects.

β_0: constant intercept, which differs by group (country)

$\beta_{1,\dots,k}$: coefficient, which is constant across groups and time

ε: error term or residual, which accounts for differences in the model

i: group variable representing country

t: time variable representing year

In the analysis, time dummy variables for the years are also added to the POLS and FE models to test for differences within the time period.

4.3 Added Value of Study

The study adds to the limited research on the associations between socioeconomic and governance-related factors and AMR. By including Romania and Croatia, the study broadens past research to include more European countries in the analysis. The dataset also uses newer data from the years 2011-2017 compared to previous studies as no study has yet to examine the effects in 2017 (Collignon et al., 2015; Gaygısız et al., 2017; Kaba et al., 2020). The variables of zoonoses notification rates of salmonellosis and campylobacteriosis as well as the health system classification add to the novelty of this study. Perhaps the most important addition to this study design is the measurement of antimicrobial consumption in animals. Antimicrobial consumption in animals is significantly larger than consumption in humans (Aguirre, 2017; FAO, 2016) and the inclusion of this variable addresses another important area in the challenge of managing this public health issue. The results of this study may help to better explain the factors influencing the spread and emergence of AMR. The study will give consideration to the many factors associated with AMR and identify patterns across European countries with hopes to encourage further research on the topic.

4.4 Limits in Methodology

While the novelty and expansion of the dataset are the strengths of this study design, there are also several limitations to adds. There have been challenges with data availability, which has resulted in missing values for particular variables due to insufficient reporting numbers. The data availability issue creates a number missing values for the following variables: pathogen and antimicrobial combinations (n=411), animal antimicrobial consumption (n=18), human antimicrobial consumption (n=2), physician density (n=11), campylobacteriosis (n=13), salmonellosis (n=3), and total health expenditure (n=20).

Regarding statistical methods, the POLS method has a weakness due to its exclusion of country-specific factors. While this weakness is addressed in the FE models, there are two possible sources of endogeneity not solved by this method. As discussed in previous studies, it is possible that there is a reverse causal relationship between AMR and antimicrobial consumption (Collignon et al., 2015). In countries with higher AMR rates, it is likely that more antimicrobials are consumed to combat antibiotic-resistant infections.

Additionally, due to the estimated nature of the variables included, there may be possible error in the measurement of these data, particularly quality of governance, antimicrobial consumption, and AMR data. When considering these concerns, the results of this study must be interpreted carefully and not draw statements of causality due to the possible endogeneity of the data and the regression methods used. To address data error issues such as multicollinearity, heteroscedasticity, and autocorrelation, robust standard errors were tested and methods such as the Breusch-Pagan Test and Variance Inflation Factors were used.

5 Results

The full results of the scoping review are presented in Article 1 whereas the main findings of the quantitative study are presented in Article 2. This chapter includes a broader discussion of the results of the quantitative study along with alternative models and methods employed. This chapter thus contextualizes the quantitative study by providing additional information on the process and outcomes of the study.

5.1 Descriptive statistics

In this exploratory study design, there are 11 continuous variables and two categorical variables included in the analyses. These variables are described in Table 5.1. There was one significant outlier in the average AMR data, which was excluded in analysis bringing the total number of observations down to 209. For the observation of Latvia in 2017, the low 3.92% average resistance rate was representative of only one pathogen/antimicrobial combination as this was only combination to meet the 30 isolates tested requirement. Therefore, this outlier is excluded based on a data error. Possible outliers were identified and tested through several measures including Cook's distance measure, leverage vs squared residual plots, and a visual check of the data.

Table 5.1 Description of variables used for statistical analysis

Variable code	Description
AMRAvg	Average antimicrobial resistance rate calculated by the number of resistant isolates divided by the total number of isolates tested for all 23 combinations. Written as a decimal on a scale of 0 to 1
QoGavg	Average score of the six quality of governance dimensions. The score is measured on the scale of 0 to 5
AMCanimal	Sales, in tonnes of active ingredient, of veterinary antimicrobial agents marketed primarily for livestock animals, population correction unit (PCU) and sales in mg/PCU, by country
AMChuman	Consumption of antibacterials for systemic use in the J01 ATC group expressed in defined daily doses (DDD) per 1000 inhabitants and per day (known as the measurement DID)
PHE	Domestic private health expenditure as a percentage of total current health expenditure
GDP	Ratio of real GDP to the average population of a specific year
EDU	Percentage of population aged 15 to 64 years old who have achieved tertiary education (levels 5-8)
PPI	Medical doctors per 10,000 population
Campylo	Notification rates of campylobacteriosis per 100,000 persons: the number of reported confirmed/total cases, divided by the official Eurostat estimate of the population for that year, multiplied by 100,000.
Salmon	Notification rates of salmonellosis per 100,000 persons: the number of reported confirmed/total cases, divided by the official Eurostat estimate of the population for that year, multiplied by 100,000.
THE	Total health expenditure measured in euro per inhabitant
Region	Categorical variable classified by region: 4 groups Northern Europe (group 1); Southern Europe (group 2); Western Europe (group 3); and Eastern Europe (group 4)
OECD	Categorical variable classified by OECD health system classification: 6 groups National Health Service (group 1); National Health Insurance (group 2); Social Health Insurance (group 3); Etatist Social Health Insurance (group 4); Social Based Mixed Type (group 5); and Other/Not classified (group 6)

Table 5.2 Variable summary statistics

Variable	Mean (Std. Dev)	Minimum	Maximum	Countries	Observations
AMRAvg	0.21 (.08)	.0542	.4339	30	209
AMChuman	17.86 (5.15)	8.94	32.15	30	207
AMCanimal	106.10 (105.56)	2.9	453.41	30	191
EDU	26.95 (7.19)	12.9	40.4	30	209
GDP	26900.57 (17305.98)	5300	82880	30	209
PHE	26.28 (9.99)	13.7908	57.1741	30	209
PPI	34.46 (7.37)	19.509	54.789	30	198
QoGavg	3.58 (.50)	2.5704	4.3730	30	209
THE	2652.68 (1748.02)	307.69	7013.51	30	189
Campylo	53.61 (46.63)	0.3374	229.95	29	195
Salmon	24.17 (23.03)	1.5924	126.089	30	206

As seen in Table 5.2, there are large variations among the European countries in the selected variables. The extremes discussed are the country's average for the seven-year time period. Regarding AMR rates, Sweden holds the lowest average AMR rates for the time period with an average of 6.20% and Romania has the highest average AMR rate of 38.67%. This finding is consistent with the expectation that AMR rates are lower in the regions of Northern and Western Europe compared to the regions of Southern and Eastern Europe. Romania also has the lowest average quality of governance score of 2.68 on a scale 0 to 5 whereas Finland has the highest average score of 4.31.

For antimicrobial consumption in humans across the 30 countries, Netherlands had the lowest average consumption for the time period of 9.49 DID and Greece had the highest at 30.16 DID. Animal consumption of antimicrobials is lowest in Norway with an average of 3.3 sales in mg/PCU and highest in Cyprus with an average of 418.9 sales in mg/PCU.

For control variables, the private health expenditure variable follows the same minimum and maximum pattern with Cyprus having the highest percentage of PHE (54.99%) and Norway with the lowest (14.9%). Luxembourg has the highest GDP per capita (€80,114) while Bulgaria has the lowest (€5,570) during this time period. Luxembourg also has the highest average total health expenditure with €5061.84 per inhabitant and Romania has the lowest with €385.74. Tertiary education levels were lowest in Romania with 14.26% of the population who have completed tertiary education and the highest proportion was in Ireland with 37.76%. For physician density, Poland has the lowest number of physicians per 10,000 population with 23 and Austria has the highest with 50 physicians.

The notification rate of campylobacteriosis is highest in the Czech Republic with 197.28 and lowest in Poland with an average 1.53. For salmonellosis, Czech Republic also has the highest notification rate of 104.59 while Portugal has the lowest of 2.65.

Through this brief descriptive analysis, a trend emerges where Southern and Eastern European countries such as Greece, Cyprus, Bulgaria, and Romania have the characteristics hypothesized to be consistent with the spread of AMR while Northern and Western European countries such as Norway, Sweden, the Netherlands, and Finland are likely to have the traits assumed to be associated with lower AMR. This regional trend is consistent to that found in past literature of higher resistance rates in Southern and Eastern Europe and lower resistance rates in Northern and Western Europe (Bell et al., 2014; ECDC, 2019).

5.2 Model Results

In the models presented in the results section, the aggregate AMR rates indicator was used to represent the general resistance which is the focus of the study. This consideration was also given to the quality of governance variable, which used the average score of the six dimensions. The threshold of significance was set at a p-value of less than or equal to 0.05. First, the correlations between the socioeconomic variables and dependent variable were investigated. Bivariate and multivariate regression models were then built to establish overall relationships between AMR and the explanatory variables. Next, the fixed effects (FE) model and robust methods were used to control for data issues.

5.2.1 Correlation Analysis

Correlation analysis is often used in retrospective or observational studies, thus fitting this study design. The purpose of this analysis is to measure and interpret the strength of the relationship between two continuous variables (Zou et al., 2003). For analysis, a correlation coefficient of 1 or -1 indicates that all data lie on an increasing or decreasing straight line while a correlation coefficient of 0 indicates no linear relationship (Newbold et al., 2013). Correlations coefficients were measured on a scale of 0-0.3 (weak), 0.3-0.5 (moderate), and 0.5-1.0 (strong) (Zou et al., 2003). In the analysis, coefficients over 0.6 were noted as concerning for use in regression models due to possible collinearity.

Table 5.3 Pairwise correlation coefficient matrix

Variables	AMRAvg	QoGavg	AMChuman	AMCanimal	EDU	GDP	PHE
AMRAvg	1.000						
QoGavg	-.859***	1.000					
AMChuman	.602***	-.392***	1.000				
AMCanimal	.412***	-.405***	.400***	1.000			
EDU	-.592***	.634***	-.126*	-.182**	1.000		
GDP	-.583***	.789***	-.047	-.283***	.577***	1.000	
PHE	.495***	-.534***	.223***	.475***	-.101	-.530***	1.000

*** p<.01, ** p<.05, * p<.1

As seen in the correlation matrix, the correlations between the independent variables were generally low or moderate in strength. The correlations between the dependent variable and independent variables were quite strong. Quality of governance and AMR (r= -.859) has the strongest association in the sample. Collignon et al. (2015) found a similar high correlation in their study with a correlation coefficient of -.77. Kaba et al. (2020) also found correlations from -.70 to -.822 for individual measures of pathogen resistance and quality of governance. This strong association is expected based on past literature and reveals a negative relationship between quality of governance and AMR.

As mentioned in Chapter 4, GDP and quality of governance also have a high correlation (r=.789). This association is addressed in later models in tests for multicollinearity among the variables. The relationship between GDP and AMR is negative suggesting that richer countries are likely to have lower levels of AMR. This effect is the opposite relative to that of private health expenditure (PHE) in which increased PHE is associated with higher levels of AMR. Both antimicrobial consumption measures (humans and animals) are positively related to AMR rates. It is interesting to note that the correlation between the consumption measures is moderate and similar to the correlation strength of animal consumption to quality of governance and AMR. The negative correlation between education and AMR is as expected based on the hypothesis that a more educated population is likely to have lower AMR. It is also worth noting that QoG and EDU have a strong correlation (r=.634), which is discussed in the WGI index literature (Kaufmann et al., 1999).

Correlation analysis for the individual pathogen/antimicrobial combinations and individual WGI indicators are included in the appendix. Additional independent variables such as total health expenditure, physician density, and zoonoses notification rates were also included in analysis and the results are in the appendix.

5.2.2 Bivariate Regression Analysis

Bivariate (or simple) regression methods were used to expand on the associations discovered in the correlation analysis and evaluate the relative impact of the independent variable on the average AMR rate (Zou et al., 2013). The fit of each model is described using the coefficient of determination, R^2 and AMR is used as the dependent variables in the model.

Table 5.4 Bivariate regression results

Variable	Coefficient	Std. Error	P-value	F test	Adj. R^2
QoGavg	- .1462	.006	0.00***	584.33	.737
AMChuman	.0099	.001	0.00***	116.81	.360
AMCanimal	.0003	.000	0.00***	38.69	.166
PHE	.0042	.001	0.00***	67.18	.241
GDP[1]	- .0030	.000	0.00***	106.47	.337
EDU	- .0070	.001	0.00***	111.58	.347
PPI	.0006	.001	0.44	0.61	-.002
Campylo	- .0003	.000	0.00***	8.39	.037
Salmon	.0004	.000	0.15	2.06	.005
THE[2]	- .0353	.000	0.00***	185.58	.495

*** p<0.01, ** p<0.05, * p<0.1

1 GDP was rescaled by dividing the original value by 1000 to show a more informative coefficient rather than 0.000
2 THE was rescaled by dividing the original value by 1000 to show a more informative coefficient rather than 0.000

The results show a high R^2 of 73.72% and a significant negative relationship based on the low p-value for the main relationship of AMR and quality of governance. With time effects included through the addition of dummy variables for the years, the R^2 lowers slightly to 72.99%. The relationship between antimicrobial consumption for humans and AMR is comparatively much lower with a R^2 of 35.99%. These values are similar to the Collignon et al. study (2015), which found 28% of the total variation explained by antimicrobial consumption alone and 63% of the variation explained between quality of governance and AMR. The simple regression model examining the relationship between average antimicrobial resistance rates and the antimicrobial consumption in animals showed a significant relationship, but a low R-squared of 16.55%. Other significant variables in relation to AMR include private health expenditure (PHE), GDP, population percentage of tertiary educated individuals (EDU), campylobacteriosis notification rate (Campylo), and total health expenditure (THE).

Table 5.5 Bivariate regression results with time effects included

Variables	Coefficient	Std. Error	P-value	F test	Adj. R^2
QoGavg	- .1462	.006	0.00***	81.29	.730
AMChuman	.0100	.001	0.00***	16.34	.343
AMCanimal	.0003	.000	0.00***	5.89	.153
PHE	.0042	.001	0.00***	9.36	.220
GDP[3]	- .0030	.000	0.00***	15.0	.320
EDU	- .0075	.001	0.00***	17.62	.359
PPI	.0006	.001	0.456	0.14	-.031
Campylo	- .0004	.000	0.004***	1.26	.009
Salmon	.0004	.000	0.154	0.32	-.024
THE[4]	- .0354	.003	0.00***	26.13	.483

*** p<0.01, ** p<0.05, * p<0.1

The categorical variables were also analyzed for their relationship to AMR. As mentioned in Chapter 4, region 3 (Western Europe) is not statistically significant from the baseline group of Northern Europe, so it is therefore combined for future analysis. Both regions 2 & 4 are significant after this change. For the OECD variable, Groups 5 and 3 were not significant compared to the base group. Similar to the Region variable, these groups were included in the base group (Group 1- National Health Service).

[3] GDP was rescaled by dividing the original value by 1000 to show a more informative coefficient rather than 0.000
[4] THE was rescaled by dividing the original value by 1000 to show a more informative coefficient rather than 0.000

5.2.3 Multivariate Regression Analysis

The three methods of forward selection, backward elimination, and stepwise regression resulted in one final model for multivariate regression. Multivariate analysis controls for alternative factors that could explain variation in AMR. As only one categorical variable is used at a time due to the complexities in interpretation and similarities in measurement, the variable with the lowest p-value and highest R^2 was selected. This design resulted in the region variable being included as the categorical variable over the OECD health system classification.

The forward selection method began with the quality of governance variable as this variable had the strongest association to AMR. The correlation order followed with the inclusion of education, GDP or total health expenditure, human AMC, private health expenditure, animal AMC, and camplyobacteriosis rates. As some of the variables in the model were no longer significant after the low-correlation variables were introduced, the final model included the variables: QoGavg, AMChuman, EDU, Campylo, PHE and GDP. With these factors included, the model explained an adjusted 84.69% of the variation in AMR.

In using the forward selection model with total health expenditure as an alternative to GDP, the model had a lower R^2 and THE was never a significant variable in the model (p-value >.05). This finding gives additional concern to the variable of GDP being included in the model as THE and GDP are very closely related. GDP could be significant in the model as an effect of confounding. Therefore, in Article 2 GDP is not considered as an independent variable.

In the backward elimination model, variables were removed that fell outside the threshold of 5% significance. The final model included the same variables as in the front selection method. In the stepwise regression method, the model began with those variables which are highly correlated to AMR. Variables were added if they positively contributed to the R^2. The campylobacteriosis variable reduced the coefficient of determination by .51% and was therefore taken out of the final model. The model returned similar results as found in the forward selection method with a high total variance explained of 86.34% with the categorical region variable included as the variable improved the coefficient of determination in the model. It is worth noting that Region 2 (Southern Europe) is not significant against the base group of Northern and Western Europe.

Table 5.6 Multivariate regression results

VARIABLES	(1) POLSM1[5]	(2) POLSM2[6]	(3) POLSM3[7]
QoGavg	-0.123***	-0.0979***	-0.0797***
	(0.0104)	(0.0101)	(0.00848)
AMChuman	0.00493***	0.00486***	0.00561***
	(0.000561)	(0.000542)	(0.000498)
PHE	0.00135***	0.00133***	0.00102***
	(0.000320)	(0.000312)	(0.000303)
GDP	6.55e-07***	7.70e-07***	
	(2.49e-07)	(2.46e-07)	
EDU	-0.00214***	-0.00187***	-0.00161***
	(0.000464)	(0.000497)	(0.000500)
Campylo	0.000278***		
	(6.27e-05)		
2.Region2		0.00304	0.00387
		(0.00823)	(0.00840)
4.Region2		0.0415***	0.0401***
		(0.00973)	(0.00993)
Constant	0.558***	0.463***	0.406***
	(0.0369)	(0.0392)	(0.0355)
Observations	193	207	207
Adj. R-squared	0.847	0.863	0.857

It is noteworthy that there was no significant association between AMR and antimicrobial consumption in animals. Physician density (PPI) and Salmon were not included in the multivariate analysis as these variables did not have a significant relationship to AMR in the simple regression analysis The weak relationship between AMR and physician density is consistent with the findings of past studies (Kaba et al., 2020).

In the multivariate analysis, the quality of governance variable (QoGavg) explained the majority of the variation in AMR (73.72%). The addition of the other socioeconomic and health-system related variables added only a maximum of 12.62%. The inclusion of more variables naturally increases the R^2, so it is important to be skeptical of the inclusion of unnecessary variables. This issue is noted in POLSM2 where the exclusion of campylobacteriosis (Campylo) rates actually

5 POLS multivariate regression from forward selection and backward elimination methods
6 POLS multivariate regression from stepwise method, excluding Campylo variable
7 POLS multivariate regression excluding possible confounder GDP and the Campylo variable

increases R^2 and in POLSM3 where the coefficient of determination was lower when excluding the potential confounder GDP. To control for this issue, several other model types are tested with this dataset.

5.2.4 Variance Inflation Factor

Variance Inflation Factor (VIF) measures the effect of multicollinearity in a set of multiple regression variables (Williams, 2015). A high VIF of over 10 indicates that the independent variable is highly collinear with other variables in the model. A VIF below 2.5 is considered to show a low correlation and usually do not cause concern for the model. In multicollinearity diagnostics, the Variance Inflation Factors were all below the value of 5. However, the moderately high VIF of the quality of governance indicator (4.78) is somewhat concerning because this is the main variable of interest. As noted in Chapter 4 and in the correlation analysis, there is a known high correlation between GDP and quality of governance. GDP also has a moderately high VIF of 3.68.

Table 5.7 Variance Inflation Factors including GDP

Variable	VIF	1/VIF
QoGavg	**4.78**	**0.209369**
GDP	**3.68**	**0.271777**
EDU	**2.10**	**0.477216**
PHE	**1.94**	**0.514798**
Campylo	**1.40**	**0.715232**
AMChuman	**1.35**	**0.741793**
Mean VIF	**2.54**	

If GDP is removed from the regression model and the same variables are used as in POLSM3, the VIF for QoG falls to 3.06. To address issues of multicollinearity, partial correlation analysis of the six quality of governance indicators and the significant multivariate analysis variables were also employed.

Table 5.8 Variance Inflation Factors excluding GDP and Campylo

Variable	VIF	1/VIF
QoGavg	**3.06**	**0.326836**
EDU	**1.98**	**0.504615**
PHE	**1.62**	**0.618158**
AMChuman	**1.22**	**0.819661**
Mean VIF	**1.97**	

Heteroscedasticity was also tested through the Breusch-Pagan test for heteroscedasticity. The test results reveal that heteroscedasticity is present in the data and a correction is needed to solve for this issue. Robust standard errors will be used to correct for this issue.

5.2.5 Partial Correlation Analysis

To address the possible multicollinearity in the model with the QoGavg variable, a partial correlation analysis (PCA) was conducted to create an index of the six indicators to compare with the averaged variable created. This analysis was completed in a related study on antimicrobial consumption and quality of governance (Gaygısız et al., 2017). The Kaiser-Meyer-Olkin measure of sampling adequacy confirmed the appropriateness of the data for the PCA method. The QoG indicator of political stability and the absence of violence/terrorism (PSQoG) was identified as an outlier in the QoGavg variable and thus, a new quality of governance variable was formed for inclusion the multivariate regression models. The inclusion of the partial correlation analysis variable instead of the QoGavg variable results in the same conclusions in the findings of this study. Therefore, the original QoGavg variable remained in analysis as it seemed to be an appropriate measure of the WGI indicators.

The PCA method was also tested using the factors that are significant in multivariate analysis as an index (QoGavg, AMChuman, PHE, GDP, EDU). Two components are created during the analysis, which explained 77.36% of the variance. The R^2 may be a more realistic explanation of the variability and reduces the effects of multicollinearity. One component explains 70.25% of the variance. A second set excluding GDP was tested using PCA, but the Kaiser Meyer-Olkin test proved to be too low for PCA to be useful. The limitations of the partial correlation analysis is that the coefficients are difficult to interpret. These results suggest that the issues of multicollinearity may be resolved by the exclusion of GDP in the multivariate models.

Table 5.9 PCA results with multivariate regression significant factors (QoGavg, AMChuman, PHE, GDP, and EDU)

VARIABLES	(1) PCA1	(2) PCA2
pca1	-0.0431***	-0.0431***
	(0.00195)	(0.00170)
pca2		0.0226***
		(0.00279)
Constant	0.213***	0.213***
	(0.00322)	(0.00281)
Observations	207	207
Adj. R-squared	0.703	0.774

Standard errors in parentheses
*** p<0.01, ** p<0.05, * p<0.1

5.2.6 Robust Standard Errors and Cluster Robust Inference

The inclusion of robust standard errors relaxes the assumption of identically distributed errors and can help fix heteroscedasticity issues (Mućk, 2018). Additionally, the use of a cluster parameter addresses the assumption that error terms are independent.

Table 5.10 Robust standard errors results

VARIABLES	(1) RB1[8]	(2) RM1[9]	(3) RM2[10]
QoGavg	-0.146***	-0.0979***	-0.125***
	(0.00612)	(0.00911)	(0.0109)
EDU		-0.00187***	
		(0.000381)	
GDP		7.70e-07***	
		(1.94e-07)	
AMChuman		0.00486***	0.00519***
		(0.000545)	(0.00101)
PHE		0.00133***	
		(0.000270)	
2.Region2		0.00304	
		(0.00691)	
4.Region2		0.0415***	
		(0.0102)	
Constant	0.738***	0.463***	0.569***
	(0.0231)	(0.0356)	(0.0494)
Observations	209	207	207
R-squared	0.738	0.868	0.822

Robust standard errors in parentheses
*** p<0.01, ** p<0.05, * p<0.1

The bivariate linear regression analysis using robust standard errors presents the same conclusions as the original POLS bivariate model with quality of governance as a significant variable and explains 73.84% of the variation.

For the multiple regression model, the final model explains a slightly higher amount of variation (86.80%) and includes the following variables as significant: QoGavg, EDU, GDP, AMChuman, PHE, and the region variable. Region 2 is not significant in these models as compared to the base group.

When including the cluster parameter which accounts for errors correlated within clusters, the results were drastically different. The clusters are grouped by id, which is country in the dataset.

[8] Robust standard errors included for POLS bivariate model
[9] Robust standard errors included for POLS multivariate model
[10] Cluster robust inference included for POLS multivariate model

GDP, EDU, PHE, and the region variable are no longer significant in the multivariate model and are excluded from the final model. The final model includes only quality of governance (QoG) and antimicrobial consumption in humans as significant factors The model explains a lower amount of the variation than past models, yet the R^2 is still quite high (82.22%).

The VIF analysis of these variables is quite low with both variables reporting a VIF lower than 2.5 (1.18 for both variables). When testing for omitted-variable bias in the model with only quality of governance and human antimicrobial consumption as explanatory variables, the results show that there is no bias in the model and no additional variables are needed. This finding is confirmed by the link test for model specification.

5.2.7 Fixed Effects Analysis

Fixed effects analysis was completed for both bivariate and multivariate models. As mentioned before, the group variable is id which is country in the dataset. Therefore, the dataset has 210 observations and 30 groups in this analysis. The Hausman test results confirm the appropriateness of the fixed effects model over the use of the random effects model.

In the bivariate analysis, only the variables of quality of governance (QoG) and animal antimicrobial consumption (AMCanimal) are significant at the 5% level. Education (EDU) and physicians per inhabitants (PPI) are significant at the 10% level. These variables differ from those found to be significant in the pooled ordinary least squares (POLS) models. The average AMR rate is used as the dependent variable and the results of the bivariate analysis of the fixed effects method are shown in Table 5.11.

Table 5.11 Fixed Effects bivariate results

Variable	Coefficient	Std. Error	P-value	F test	Overall R^2
QoGavg	.0502	.019	0.008***	7.16	.738
AMChuman	.0005	.001	0.517	0.42	.363
AMCanimal	.0001	.000	0.036**	4.49	.170
PHE	.0007	.001	0.920	0.01	.245
GDP[11]	.0009	.001	0.145	2.14	.340
EDU	.0010	.001	0.057*	3.66	.350
PPI	-.0009	.001	0.063*	3.52	.003
Campylo	.0000	.000	0.840	0.04	.042
Salmon	-.0002	.000	0.261	1.27	.010
THE[12]	- .0008	.006	0.893	0.02	.498

*** p<0.01, ** p<0.05, * p<0.1

For the multivariate analysis of the FE model, only the significant variables from the FE bivariate analysis were significant in the multivariate analysis. While EDU is only significant at the 10% level in bivariate analysis, the variance explained by the model increases from 33.32% to 46.44% with its inclusion. However, quality of governance explains 73.84% of the variation by itself. Therefore, the strongest model is with quality of governance alone.

11 In this table, GDP was rescaled by dividing the original value by 1000 to show a more informative coefficient rather than 0.000

12 In this table, THE was rescaled by dividing the original value by 1000 to show a more informative coefficient rather than 0.000

Table 5.12 Fixed Effects multivariate results

VARIABLES	(1) FEB1[13]	(2) FEB2[14]	(3) FEM1[15]	(4) FEM2[16]
QoGavg	0.0502***		0.0292*	0.0350**
	(0.0187)		(0.0169)	(0.0170)
AMCanimal		9.54e-05**	9.68e-05**	0.000105**
		(4.50e-05)	(4.48e-05)	(4.45e-05)
EDU				0.000911**
				(0.000442)
Constant	0.0338	0.197***	0.0915	0.0445
	(0.0672)	(0.00486)	(0.0616)	(0.0651)
Observations	209	191	191	191
Overall R-squared	0.738	0.170	0.333	0.464
Number of id	30	30	30	30

Standard errors in parentheses
*** p<0.01, ** p<0.05, * p<0.1

To control for possible time-wise variation, dummy variables are introduced for the year variable. The first year (2011) serves as the reference category With time effects included in the model, the education variable is no longer significant. The results are shown below in Table 5.13 with FET1 for the bivariate analysis between quality of governance and AMR and FET2 for bivariate analysis between antimicrobial consumption in animals and AMR. The third model, FET3, is the multivariate analysis with both variables, QoG and AMCanimal.

13 FE Bivariate model between QoG and AMR
14 FE Bivariate model between AMCanimal and AMR
15 FE Multivariate model with QoG and AMCanimal
16 FE Multivariate model with QoG and AMCanimal with the addition of EDU

Table 5.13 Fixed Effects results with time effects included

VARIABLES	(1) FET1[17]	(2) FET2[18]	(3) FET3[19]
QoGavg	0.0619***		0.0384**
	(0.0192)		(0.0174)
2012.year	0.00392	0.00387	0.00368
	(0.00371)	(0.00344)	(0.00340)
2013.year	0.00496	0.00431	0.00412
	(0.00371)	(0.00344)	(0.00340)
2014.year	0.00679*	0.00478	0.00493
	(0.00371)	(0.00339)	(0.00335)
2015.year	0.00409	0.00238	0.00266
	(0.00371)	(0.00339)	(0.00335)
2016.year	0.0103***	0.00772**	0.00873**
	(0.00375)	(0.00341)	(0.00340)
2017.year	0.00872**	0.00563	0.00697*
	(0.00380)	(0.00355)	(0.00356)
AMCanimal		0.000114**	0.000123***
		(4.71e-05)	(4.67e-05)
Constant	-0.0139	0.191***	0.0509
	(0.0691)	(0.00584)	(0.0640)
Observations	209	191	191
R-squared	0.728	0.177	.340
Number of id	30	30	30

Standard errors in parentheses
*** p<0.01, ** p<0.05, * p<0.1

When testing the significance of the time value, the results show that the time effect variable is not significant and therefore time-fixed effects do not need to be included in the model. Additionally, the Woolridge test for autocorrelation confirms that there is no first-order autocorrelation in the data.

Article 2 presents the final models and summary of results for the statistical analysis. In the following chapter, the main findings are presented from the overall research process and the interpretations and limitations of these results are discussed.

[17] Fixed Effects bivariate model of QoG with time effects included
[18] Fixed Effects bivariate model of AMCanimal with time effects included
[19] Fixed Effects multivariate model with time effects included

6 Discussion

6.1 Study Objectives

The purpose of this study is to add to the existing body of knowledge on factors associated with antimicrobial resistance and to explain the variation in AMR prevalence across Europe. Through the identification of socioeconomic and governance-related variables related to AMR in the scoping review (cf. Article 1 attached), the strengths and significance of these associations were then measured in regression analysis to test the robustness of past findings.

The main focus of this research is to analyze the strength of the relationship between antimicrobial resistance and quality of governance (QoG) across a diverse set of countries. The study design is based on the hypothesis that QoG holds an inverse relationship to AMR (i.e., a country with stronger measures of QoG will have lower average levels of AMR). This hypothesis is grounded by the assumed positive relationship between quality of governance and improved health outcomes supported by the empirical evidence that good governance is positively related to developmental indicators such as economic growth and education measures (Kaufmann et al., 1999). Novel variables were added in the analysis in an attempt to explain more of the variation in AMR rates in Europe including antimicrobial consumption in animals (AMCanimal) and zoonoses notification rates of campylobacteriosis (Campylo) and salmonellosis (Salmon). Traditional confounders including GDP, physician density (PPI), private health expenditure (PHE), tertiary education level (EDU), and total health expenditure (THE) were considered in the multivariate models as well.

6.2 Main Findings

The associations were examined between AMR and potential contributing factors using simple correlation analysis, POLS methods, and FE models in bivariate and multivariate analyses. The main finding of the study confirmed the hypothesis that quality of governance holds a strong relationship to AMR. As found in similar studies, the relationship between QoG and AMR is negative and explained the majority of the variation in the multivariate models (Collignon et al., 2015; Collignon et al., 2018; Kaba et al., 2020).

Traditionally, human AMC has been considered as the main factor of AMR prevalence at the national level. In bivariate analysis, antimicrobial consumption in humans explained only 33.42% of the variation in AMR whereas QoG explained 73.37%. This finding is consistent to those of past studies with higher measures of R^2 in quality of governance compared to other traditional predictors (Collignon et al., 2015; Collignon et al., 2018). AMC in humans had a positive relationship to AMR which confirms the second hypothesis on a positive association between the two variables.

In the multivariate regression models, QoG continued to explain the bulk of the variance while additional socioeconomic factors such as antimicrobial consumption in humans, education, private health expenditure, GDP, and regional classification contributed only 12.64%. The strength of the quality of governance relationship to AMR is possibly shown best when considering the fixed effects (FE) model. In the FE model which controls for time-invariant country characteristics, QoG, education, and antimicrobial consumption in animals were the only significant variables. QoG explained the majority of the variance in the model as it did in the POLS estimations. By contrast, the dominant AMR-explaining factor of human AMC was notably not significant in this analysis. The exclusion of this variable is surprising as it is popularly considered as the main determinant of antimicrobial resistance. In the Collignon et al. (2015) study, antimicrobial consumption in humans was also not significant in the FE analysis.

Alternatively, antimicrobial consumption in animals was significant in the FE estimations and provides an interesting avenue for further research on this topic. While the results of this study on the effect of animal antimicrobial consumption on AMR are inconclusive, additional research could provide insight on the strength of this explanatory variable. The results of the bivariate analysis confirmed a positive association between antimicrobial consumption in animals and AMR on a national level. Thus, confirming the second hypothesis.

6.2.1 Key variables

The study examined 12 independent variables in relation to the dependent variable of AMR and employed several different regression methods to determine the significance and strength of these relationships. While the results differ between the models, quality of governance remains as a significant factor throughout the methods.

In the multivariate POLS regression, the traditional variables of human antimicrobial consumption, private health expenditure, GDP, and a region categorical variable showed significance in relation to AMR. These variables were all found to be significant in the scoping review results on the topic of antimicrobial resistance and socioeconomic variables. Campylobacterosis notification rate was also a significant variable in the bivariate and multivariate POLS analysis; however, the variable lowered the explanation of variation in the model and should be tested in further research.

In the FE model, animal antimicrobial consumption was significant along with quality of governance and education. This finding should be interpreted with caution as the variable was not strongly associated to AMR in traditional OLS models. The variables of physician density, campylobacterosis notification rates, salmonellosis notification rates, total health expenditure, and OECD health system classification were not found to be significant in multivariate analysis. The results on physician density confirm past findings on a weak association with AMR (Gaygısız et al., 2017; Rönnerstrand & Lapuente, 2017; Kapa et al., 2020). For zoonoses notification rates, additional research should be done to determine their association to AMR. The inclusion of these variables could be influenced by missing values and the unavailability of age-standardized data for this measure. Total health expenditure and health system classification were outperformed by the more traditional variables of GDP and regional classification. These two variables could be tested in further research to determine their relevance.

6.2.2 Contribution to Research

The strengths of the data analyzed in this study include a larger sample group of European countries compared to previous studies (Collignon et al., 2015; Gaygısız et al., 2017; Rönnerstrand & Lapuente, 2017); more recent data from 2011-2017 as past studies focused on the years from 2013 and earlier; the inclusion of new variables (e.g., zoonoses notification rates and animal antimicrobial resistance);the use of different modeling methods and tests; and the combination of diverse indicators in the analysis.

In the study, the reproduction of previously known relationships of variables to AMR was shown through different modeling methods, datasets, and the inclusion of new variables in multivariate analysis. By this process, the findings confirmed past study results and strengthened the validity of the new added variables in the analysis.

To the researcher's best knowledge, antimicrobial consumption in animals is used with quality of governance for the first time in this study. The association between antimicrobial resistance rates and animal antimicrobial consumption is an important finding of this study as it encourages future research as an explanatory factor of AMR.

6.3 Limitations and Further Research

As discussed in Chapter 4, there are possible endogeneity problems within the dataset as antimicrobial consumption rates have been found to influence antimicrobial resistance rates. Data challenges in the form of missing data observations and outliers also presented issues in the collection and analysis of the dataset.

The nature of the data is in the form of estimates as the number of reporting laboratories from each country differs, which can lead to bias in the data source from the ECDC. In an attempt to minimize this issue, the threshold of 30 isolates tested per pathogen/antimicrobial combination was set to only consider samples of a sufficient size. The same testing threshold was used in Collignon et al. (2015). The data involving human antimicrobial consumption also differs in reporting as some countries report both primary care (community) consumption and hospital consumption while some only report one. To control for this discrepancy, only primary care antimicrobial consumption was considered as that was available for the selected 30 countries. Additional research on hospital antimicrobial consumption would be an interesting contribution.

The results of the correlation and regression analyses were significant and interesting; however, the R^2 was quite high in the POLS and FE models as it was consistently 70% or higher. Researchers consider 80% or above to be typical in time-series data (Newbold et al., 2013), so this high coefficient determinant could be heavily influenced by its panel data structure. Even when time effects were included, the model still displayed quite high levels of R^2. These high R^2 levels are found in similar studies, which provides support for these results (Collignon et al., 2015, Gaygısız et al., 2017). Methods such as excluding confounders, the robust standard errors technique, and PCA analysis were introduced to address multicollinearity in the model; however, the measures did not significantly influence the results or decrease the R^2. It may be worthwhile to consider additional methods of analysis or the inclusion of different variables to address the possible multicollinearity issues.

Another limitation of the study is that the geographic boundary. The data were not based on a random sample as the selection of countries within Europe was determined by data availability. New studies in this field have emerged covering regions outside of Europe and particularly in developing countries (Collignon et al., 2018). However, data surveillance is often limited in these regions and thus, analysis is often challenging and involves more estimations. The expansion of this research to new regions and countries could be an important contribution.

There are many topics related to this field that could be explored in future research. For example, the use of antimicrobials companion animals has not been explored in this field and could be included under the umbrella of animal antimicrobial consumption. As this is the first study in quality of governance literature to use animal antimicrobial consumption to predict antimicrobial resistance, there is potential for many new studies examining this relationship and related factors such as food consumption.

Additionally, the combined measure of antimicrobial consumption in humans and animals could be a useful expansion in this research field. As a conversion of antimicrobial consumption in humans in DIDs to the animal antimicrobial consumption measure of consumption in mg/kilogram biomass has been developed in a joint report by the ECDC, EFSA, and EMA. This measurement should be possible to include in future analysis (ECDC et al., 2017). Due to the time and data access constraints during this project, this conversion was not possible for inclusion in this report.

7 Conclusion

Quality of governance is an important factor in the implementation of healthcare policies and regulation as well as in the surveillance and management of its systems and public services. In addressing a public challenge such as AMR, there needs to be cooperation and understanding from a variety of stakeholders including governmental agencies, lawmakers, medical professionals, businesses, and citizens. Therefore, a government and its institutions must have the credibility to set in place the incentives and measures to facilitate and manage interventions to control the spread of AMR.

This study of 30 European countries during the time period of 2011-2017 contributed to the growing literature surrounding the relationship of quality of governance to health-related factors. The results of the study confirmed the negative relationship between quality of governance and antimicrobial resistance found in past studies and introduced new variables for analysis in relation to AMR including antimicrobial consumption in animals and the prevalence of zoonoses diseases.

While the traditional variables associated with AMR including private health expenditure, education, and GDP were significant in multivariate linear regression, these factors lost significance in subsequent, robust estimations of the model. The effect of animal antimicrobial consumption is still subject for debate due to inconclusive results, yet animal antimicrobial consumption remains as an important topic for research due to its disproportionate contribution to total antimicrobial consumption across countries. A common measurement considering both the antimicrobial consumption in humans and animals would be an interesting, and possibly important contribution to this research.

Research involving the association between quality of governance and antimicrobial resistance appears to only be growing as publications have increased in recent years. With the coronavirus pandemic affecting the management of healthcare systems and health policy concerns of the time, the fight against the spread of antimicrobial resistance remains dependent on the quality of governance to prioritize the health issues. As past studies and the current research show, a country's quality of governance has strong implications for the health of its citizens as well as the health systems functioning,

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Article 1

Understanding the variation in antimicrobial resistance prevalence across European countries:

A scoping review of socioeconomic and governance-related factors

Molly Monroe

Abstract

BACKGROUND: Antimicrobial resistance (AMR) is a serious global health issue that imposes a great cost upon communities, health systems, and society. The complex nature of AMR yields a wide variety of studies identifying associated factors. The limited, yet growing literature involving AMR and socioeconomic factors, including quality of governance, seeks to explain this complex public health challenge. Quality of governance relies on the assumption that good governance is associated with better health outcomes and therefore, a country with a higher quality of government would be expected to have lower national AMR prevalence.

OBJECTIVE: The objective of the limited scoping review is to summarize the state of knowledge and gaps in knowledge on socioeconomic and governance factors affecting AMR, as well as to identify the common significant variables found in these publications.

METHOD: The limited scoping review follows a five-stage protocol: (1) identifying the research question, (2) identifying relevant studies, (3) study selection, (4) charting the data, and (5) collating, summarizing, and reporting results. Three databases were searched for peer-reviewed literature on AMR and socioeconomic and governance-related variables published during January 2010 – March 2020.

RESULTS AND DISCUSSION: Through the database searches, 5782 references were generated. 48 of these articles were selected for full-text review based on title and abstract relevance. The final sample includes 13 studies based on the eligibility criteria and the articles were then categorized thematically. Seven of the articles related to quality of governance, whereas six studies were focused on the association between AMR and socioeconomic factors.

CONCLUSION: Identifying associated factors to AMR contributes to the understanding of how it spreads. The results of this review indicate that this is a growing research field with the majority (n=9) of the selected studies published in the last five years. Further investigation on this research could prove to be beneficial particularly including developing or low-income countries as well as identifying the socioeconomic factors related to antimicrobial consumption.

Introduction

The World Health Organization (WHO, 2015) considers antimicrobial resistance as one of the biggest current threats to global public health. Antimicrobial resistance (AMR) is defined as "the ability of a microorganism to resist the action of one or more antimicrobial agents" (European Centre for Disease Prevention and Control [ECDC], 2018, p. 3). This process occurs naturally through genetic mutation; however, the development of AMR is also influenced by human factors such as the excessive or inappropriate use of antimicrobials as well as unsanitary practices in healthcare settings and within the food chain process (European Commission, 2017). AMR is a serious concern as rising resistance rates can impose large costs to health systems and society through increased treatment costs, longer hospital stays for patients, higher mortality rates, and production losses (Food and Agrictulture Organization of the United Nations [FAO], 2016; WHO, 2015).

Although antimicrobial consumption is considered as the main driver behind increasing AMR rates (Filippini et al., 2013; Goossens et al., 2005), there is a complex, imperfect relationship between the two variables (Isturiz & Carbon, 2000). Antimicrobial consumption has a well-established positive association to AMR (Čižman, 2003), but this association is not uniform across all countries (McDonnell et al., 2017) and proportionate to the amount of antimicrobial used (Masiero et al., 2010). Therefore, further research is warranted to identify relevant variables to explain the prevalence of AMR. Understanding factors associated with AMR can allow health systems, countries, and regions to better control its spread and maintain effective treatment options for future use.

Background

In Europe, factors related to socioeconomic characteristics, health systems, and culture have been studied for their associations with AMR since the early 2000s including variables such as gross domestic product (GDP) per capita (Blommaert et al., 2014; Filippini et al., 2013; Masiero et al., 2010), education level (Gaygısız et al., 2017), cultural values (Borg, 2012; Gaygısız et al., 2017; Harbarth et al., 2001), and physician density (Filippini et al., 2013; Masiero et al., 2010). There is a considerable difference in the fewer amount of studies related to these factors of AMR directly. Although it could be argued that factors related to antimicrobial consumption also affect

AMR and contribute to national and regional AMR variation, it is important to examine the effects of these variables on AMR directly as consumption measures do not have a perfect correlation to AMR (Isturiz & Carbon, 2000; McDonnell et al., 2017).

Recent literature has emerged regarding the relationship between quality of governance and health outcomes (Barbazza & Tello, 2014; Ferrari & Salustri, 2020). Governance-related factors pose an interesting contribution to this public health challenge as a government deemed as of "higher quality" would be expected to have more control over the use of antimicrobials, ensure compliance with such policy measures and regulation, and coordinate disease prevention and surveillance systems (Gaygısız et al., 2017; Kaufmann et al., 2005). The concept of governance is defined by the World Bank as:

> the traditions and institutions by which authority in a country is exercised. This includes: (1) the process by which governments are selected, monitored, and replaced, (2) the capacity of the government to effectively formulate and implement sound policies, and (3) the respect of citizens and the state for the institutions that govern economic and social interactions among them(Kaufmann et al., 2004).

Quality of governance influences many important aspects of the healthcare sector including the administration and oversight of health policy measures and the coordination and delivery of public services and goods in the system (Kaufmann et al., 2005). Thus, quality of governance is a likely factor in a country's management of AMR. In the literature, the terms *quality of governance*, *quality of government*, and *control of corruption* are used synonymously to represent this broad concept of measuring good governance.

Socioeconomic factors such as GDP per capita and education often complement and correlate with quality of governance measures (Kaufmann et al., 2005; Mueller et al., 2016). Therefore, when examining the effect of quality of governance it is important to consider related socioeconomic factors. Socioeconomic was defined as a broad term in this review to include significant factors related to the environment, culture, health system, geography, and description of a population. Socioeconomic factors are useful for analysis with AMR to identify factors that could explain variation in AMR prevalence across countries.

As with antimicrobial consumption and resistance patterns, there is significant variation in quality of governance across countries in Europe (Kaufmann & Kraay, 2018). When reviewing the literature on the topic of quality of governance and AMR, it becomes apparent that there is a need for synthesis to address complexity of this global health threat. Therefore, a scoping review was conducted to examine the current state of knowledge on socioeconomic and governance-related factors associated with AMR.

The research in this area is limited with much still unknown about the strength of the relationship between quality of governance and AMR rates as well as identifying and measuring the association of the related factors. This review could be useful for building models to predict or analyze AMR prevalence on a national or regional level.

According to the literature search, this is the first review to address specifically the socioeconomic and governance factors associated with AMR. There have been earlier reviews on factors influencing AMR rates in animals (Murphy et al., 2018), the relationship between antimicrobial consumption and resistance rates (Bell et al., 2014), and drivers of AMR (Chatterjee et al., 2018), but these reviews do not address particular socioeconomic and governance factors potentially linked to AMR.

Based on the framework outlined in Arksey & O'Malley (2005), a limited scoping review was conducted on the socioeconomic and governance factors associated with AMR. The protocol provided five stages:

(1) identifying the research question
(2) identifying relevant studies
(3) study selection
(4) charting the data
(5) collating, summarizing, and reporting results.

The stages are presented as a linear process; however, there was a flexible nature to the review to ensure that literature was comprehensively covered. As new keywords emerged in the literature during the search process, additional searches and keyword alternatives were added. The eligibility criteria were also refined as the process continued to narrow results specific to the research question and purpose of the review.

Research Question

The first step of the Arksey & O'Malley (2005) framework is to identify the research question: what is known from the existing literature about the association between socioeconomic and government/governance factors, particularly quality of governance, and the prevalence of antimicrobial resistance?

The main objective of the scoping review is to determine the state of literature on the association between AMR and quality of governance factors. This review will be useful for identifying gaps in the current literature and generating new study ideas based on the findings. The secondary objective of the scoping review is to identify common socioeconomic variables associated with AMR for use in modeling and analysis to explain the variation in AMR rates across countries.

Data and Methodology

The limited literature on the topic of AMR and quality of governance presents the opportunity to conduct a scoping review to gather information on past relevant studies and possible related factors and trends in this research. While related factors of antimicrobial consumption and corruption expand the literature, there is no review on AMR and governance/socioeconomic factors currently available.

A scoping review incorporates transparent methodology for mapping areas of research and determines the state of knowledge on a specific topic (Arksey & O'Malley, 2005; Baumeister & Leary, 1997). The objective of the scoping review is to systematize, summarize, and present the current knowledge to identify the research gaps in the existing literature.

Identifying relevant studies

The articles were selected from three online electronic databases including the University of Oslo Library in Oria, PubMed, and Web of Science. Alternate keywords were considered to increase the coverage of the literature (e.g., the terms 'antimicrobial resistance' and 'antibiotic resistance' were used interchangeably). This consideration was also given to the term 'quality of governance' with the terms of 'quality of government', 'corruption', and even broader ‘governance.’ For evaluating socioeconomic influences, the terms ‘factors,’ ‘drivers,’ and ‘determinants’ were used interchangeably.

Table 1. Scoping Review Keyword Search Results

Keyword Search	Number of results (n=)		
	UiO-Oria	**PubMed**	**Web of Science**
“Antimicrobial resistance” AND governance	321	459	70
“Antimicrobial resistance” AND quality governance	189	54	9
“Antimicrobial resistance” AND quality government	859	54	28
“Antimicrobial resistance” AND corruption	28	6	7
“Antibiotic resistance” AND governance	415	313	39
“Antibiotic resistance” AND quality governance	192	26	4
“Antibiotic resistance” AND quality government	801	26	15
“Antibiotic resistance” AND corruption	27	9	10
“Antibiotic resistance” AND socioeconomic AND factors	417	94	38
“Antibiotic resistance” AND socioeconomic AND drivers	78	8	5
“Antibiotic resistance” AND socioeconomic AND determinants	168	72	10
“Antimicrobial resistance” AND socioeconomic AND factors	406	101	54
“Antimicrobial resistance” AND socioeconomic AND drivers	89	16	7
“Antimicrobial resistance” AND socioeconomic AND determinants	167	80	11
Total	**4157**	**1318**	**307**

As shown in Table 1, the number of results generated between the databases varies greatly; therefore, it is important to apply eligibility criteria to refine these results to support the objectives of the research. Bibliographies of key studies were also used to guide the search, yet eventually the search yielded no new references. Additionally, the Web of Science Social Sciences Citation Index feature was used for key articles to identify potentially relevant studies.

The inclusion criteria were adjusted to include a ten year time span as a result of the limited amount of research on this topic and the relatively recent introduction of research measuring the association between quality of governance and health outcomes (Barbazza & Tello, 2014; Frenk & Moon, 2013). Foreign language material was excluded due to time and resource constraints in translating articles, so only English language articles were included in the review.

Table 2. Eligibility Criteria

Eligibility Criteria
1. English language publication
2. Publication date from January 2010 to March 2020
3. Literature concerning related socioeconomic and governance factors to AMR
4. Studies of different designs (qualitative, quantitative, reviews)
5. The publication must cover European and/or high-income countries
6. Printed books are excluded from the search
7. Articles must be published in peer-reviewed journals and available online

Greater consideration was given to four key articles that aligned closely with the development of the quality of governance and antimicrobial resistance research field (Collignon et al., 2015; Collignon et al., 2018; Gaygısız et al., 2017; Rönnerstrand & Lapuente, 2017). These articles were analyzed using the backward reference list and forward citation list methods.

The focus of this review involves factors related to AMR rather than only to antimicrobial consumption; therefore, studies focusing solely on socioeconomic factors related to antimicrobial consumption were excluded. Articles focusing on larger governance topics such as global governance or health policy governance were also excluded if they did not address socioeconomic and quality of governance factors related to AMR. Articles mainly covering antimicrobial stewardship programs were also excluded due to the incongruence with the research question. Because the study focuses on European countries which primarily include developed or middle to high-income countries, studies focusing solely on low-income or developing countries were excluded. This process yielded a total of 5,782 references. Of these studies, 48 had titles and abstracts relevant to the research questions and the full articles were reviewed.

Figure 1. Results of the scoping review search strategy and selection process

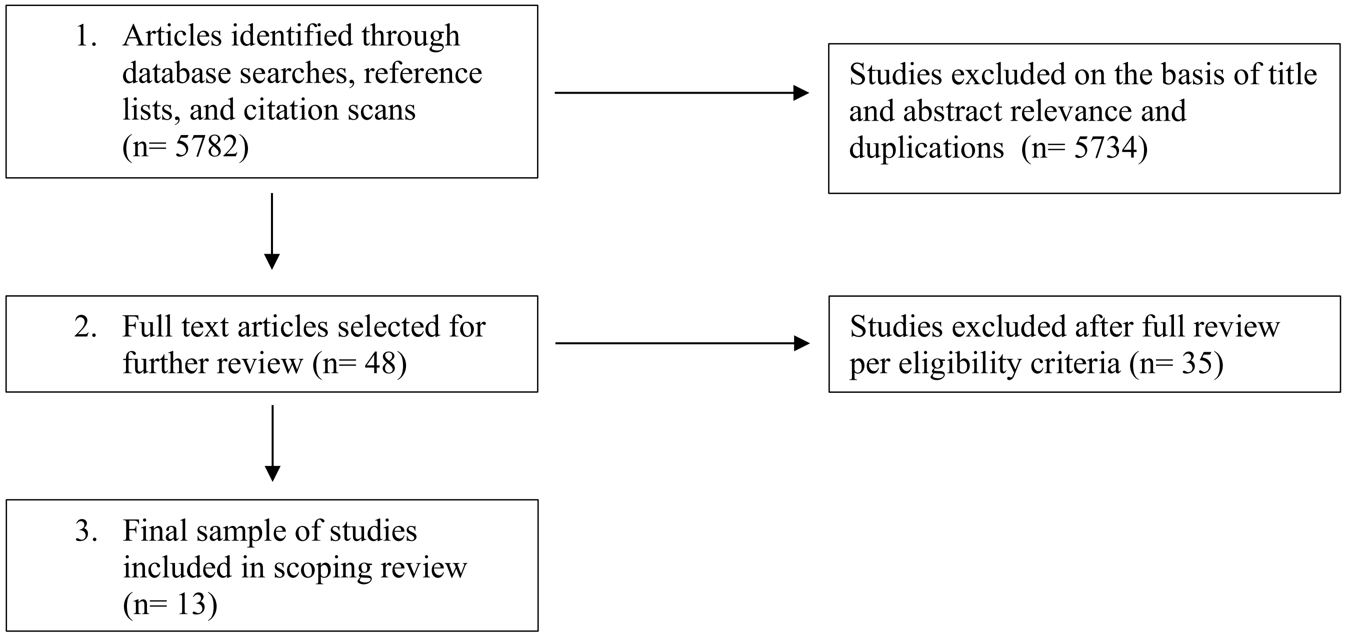

Figure 1 is a flow diagram describing the search and selection process of articles related to AMR and quality of governance to be included in the scoping review.

Study Selection

The search methods generated a large number of duplicates and irrelevant studies, which led to the exclusion of many articles based on title and abstract relevance. The nature of the limited scoping review encourages breadth of a topic rather than depth (Baumeister & Leary, 1997). The diversity of methodology is an important advantage of conducting a scoping review and adds to the value of the process. For this reasons, diversity of methodology was considered in selecting the articles for the final sample. With these eligibility criteria enforced, 48 articles were reviewed. Of these 48 articles, 13 articles were chosen for the final sample due to their connection to the objectives of the review.

Charting the data

The fourth stage involved charting data gathered from the scoping review along a thematic categorization developed during the scoping review process to accommodate for the limited literature on the subject. There are two themes and five sub-themes guiding the charting of the selected studies.

Table 3. Thematic categorization

Primary Theme	Sub-theme
AMR and quality of governance	AMR and Corruption
	AMC and Corruption
AMR and socioeconomic factors	Cultural factors
	Economic factors
	Health-system factors

The primary theme of AMR and quality of governance covers the main objective of the scoping review. There are two sub-themes which allow for increased breadth within the topic. The first sub-theme covers antimicrobial resistance and corruption. The term *quality of governance* encompasses measurements of quality of government, corruption, and individual Worldwide Governance Indicators (WGI) dimensions such as Rule of Law and Regulatory Quality in the literature. Studies included within this sub-theme focus on explaining the variation surrounding AMR by using factors related to quality of governance. This sub-theme could be considered as the direct effects of quality of governance on AMR.

The second sub-theme within AMR and quality of governance is antimicrobial consumption (AMC) and corruption. Studies focusing on AMC as an outcome variable associated with socioeconomic factors were excluded and considered as beyond the scope of this review; however, studies with AMC as the dependent variable were included if they contained quality of governance or corruption-related factors as main components of the study design as this concept is the primary focus in the research. Due to the limited amount of the literature on AMR and quality of governance, these studies were included and considered representative of the indirect effects of quality of governance on antimicrobial resistance as it is well-established that AMC and AMR hold a positive relationship.

The second theme covers AMR and socioeconomic factors with three sub-themes concerning cultural factors, economic factors, and health-system factors. The purpose of this theme was to identify socioeconomic variables used in earlier studies that could impact the relationship of quality of governance and AMR as well as possibly be used as control variables in multivariate analysis. The first sub-theme of cultural factors was regarded as characteristics representative of the ideology and traditions of a society such as religious beliefs, perceptions of trust and confidence in others, antimicrobial consumption practices for animals and humans, household size, and geographic region.

The second sub-theme concerns economic factors at the national level including income inequality, infrastructure quality, and GDP. The third sub-theme of health-system factors considers factors specifically related to the functioning of a nation's health system (e.g., the regulation of health institutions and gatekeeping practices of a system).

The search also yielded many studies covering the socioeconomic and cultural factors related to antimicrobial consumption; however, studies that focused only on antimicrobial consumption as an outcome variable were excluded as this literature does not address to the research question and greatly broadens the topic to include factors such as prescribing practices and individual knowledge regarding antimicrobial resistance.

Results

The final stage of the scoping review is collating, summarizing, and reporting the results. The final sample of 13 articles provided quality of governance and socioeconomic variables which are directly and/or indirectly linked to AMR. The presentation of the results will be divided into six parts to describe the related themes and main findings in this review. The summary of the 13 studies is presented in the appendix.

Scientific Journals

Of the 13 articles included in the final scoping review sample, three articles were published in the *Journal of Antimicrobial Chemotherapy* (Blommaert et al., 2014; Borg & Camilleri, 2019; McDonnell et al., 2017). Two articles were published in *PLOS ONE* (Collignon et al., 2015; Kirby & Herbert, 2013) and the following journals have one article each: *The Lancet Planetary Health* (Collignon et al., 2018); *International Journal of Hygiene and Environmental Health* (Kaba et al., 2020); *Journal of Global Infectious Diseases* (Chokshi et al., 2019); *Accounts of Chemical Research* (Vikesland et al., 2019); *BMC Infectious Diseases* (Bell et al., 2014); *Health Policy* (Rönnerstrand & Lapuente, 2017); *Journal of Infection and Public Health* (Gaygısız et al., 2017); and *Microbial Drug Resistance* (Kenyon & Manoharan-Basil, 2020).

Scientific Field

According to the Norwegian Publication-Indicator (NPI) Scientific Field of the scientific journals for the selected articles, there are six scientific fields covered by this review. Four articles each are included in the fields of Infectious Diseases (Bell et al., 2014; Chokshi et al., 2019; Gaygısız et al., 2017; Kaba et al., 2020) and Pharmacology & Toxicology (Blommaert et al., 2014; Borg & Camilleri, 2019; Kenyon & Manoharan-Basil, 2020; McDonnell et al., 2017). Two articles are classified as Interdisciplinary Natural Sciences (Collignon et al., 2015; Kirby & Herbert, 2013) and one article is included in each of the following fields: Chemistry (Vikesland et al., 2019); Public, Environmental and Occupation Health (Rönnerstrand & Lapuente, 2017); and Interdisciplinary Social Sciences (Collignon et al., 2018). The wide diversity of scientific journals and fields of the sample point to the relevance of this research in many academic disciplines.

Source and Methodology Diversity

Primary sources were the predominant source type in this scoping review accounting for ten of the total 13 studies. The three remaining articles are comprised of two secondary source articles that include systematic and qualitative literature reviews (Bell et al., 2014; Chokshi et al., 2019) and one conceptual paper on the global drivers of AMR (Vikesland et al., 2019). The ten primary research articles used either correlation (n=2) (Kirby & Herbert, 2013; McDonnell et al., 2017) and/or regression methods (n=8) for analysis.

Thematic Categorization

The results are organized thematically by the categorization outlined in Table 3. By applying this approach, these articles yielded variables, which directly or indirectly are linked to AMR. As previously stated, there are two primary themes and five sub-themes guiding the presentation of the scoping review results. The 13 articles are broken up with seven articles in one theme and six in the other, so the research focus is almost equally split between the relationship of AMR and quality of governance and the relationship of AMR and socioeconomic variables.

Under the theme of AMR and quality of governance, seven articles in total were identified (Borg & Camilleri, 2019; Collignon et al., 2015; Collignon et al., 2018; Gaygısız et al., 2017; Kaba et al., 2020; Kenyon & Manoharan-Basil, 2020; Rönnerstrand & Lapuente, 2017). Three articles fit under the sub-theme of AMR and corruption (Collignon et al., 2015; Collignon et al., 2018;

Kaba et al., 2020) and four articles were classified under AMC and corruption (Borg & Camilleri, 2019; Gaygısız et al., 2017; Kenyon & Manoharan-Basil, 2020; Rönnerstrand & Lapuente, 2017). In the AMR and corruption sub-theme, the three articles share the result of a negative relationship between AMR and quality of governance. Thus, supporting the idea that corruption has a positive association to the spread of AMR. In the AMC and corruption sub-theme, all four articles found that quality of governance had a significant negative correlation to AMC. This finding supports the idea that a country with a higher level of quality of governance will likely have more control over the use of antimicrobials within its borders and lower AMC levels, and therefore, likely lower rates of AMR. While this relationship was significant in bivariate analysis for all articles, only five of the articles found quality of governance to be significant in multivariate analysis (Collignon et al., 2015; Collignon et al., 2018; Gaygısız et al., 2017; Kaba et al., 2020; Rönnerstrand & Lapuente, 2017)).

The primary theme of AMR and socioeconomic variables is broken into three sub-themes: cultural, economic and health-system factors. These sub-themes appeared simultaneously in studies as researchers used many variables to test the relationship to AMR. Antimicrobial consumption remained as a significant variable in all five of the studies where it was measured in this theme (Bell et al., 2014; Blommaert et al., 2014; Kirby & Herbert, 2013; McDonnell et al., 2017; Vikesland et al., 2019). Antimicrobial consumption in animals was mentioned as significant in two of the articles (Chokshi et al., 2019; Vikesland et al., 2019) and the other variables regarded as significant in this theme were included in only one of the studies (e.g., life expectancy and income inequality).

Identified Literature Description

The literature included in the scoping review was published between the years of 2013- 2020. From this scoping review, there seems to be a growing trend towards publishing in this field. From the five-year time period of 2010-2015, four articles were published as relevant to the research objective (Bell et al., 2014; Blommaert et al., 2014; Collignon et al., 2015; Kirby & Herbert, 2013). The following time period of 2016-2020 produced nine more articles on the subject with two articles (Kaba et al., 2020; Kenyon & Manoharan-Basil, 2020) already published this year.

Obtained variables
In designing models for the explanation of variation in AMR across countries and regions, the variables used in past studies will be important in framing the research topic and justifying the selection of variables. In total, antimicrobial consumption (AMC) was mentioned as a significant variable in at least one form of analysis in all of the studies where it was used as an independent variable (n=9). In these nine studies, AMC has a positive association to AMR. The variable of quality of governance (QoG) is significant in seven studies and has a negative relationship to AMR.

GDP is included in many of the articles (n=6) as a control variable, yet only significant in the multivariate analysis of two studies (Collignon et al., 2018; Kenyon & Manoharan-Basil, 2020). GDP has a positive association with AMC (Kenyon & Manoharan-Basil, 2020) and a negative relationship to AMR (Collignon et al., 2018) in these studies. The variable of private health expenditure holds a positive significant relationship to AMR in two studies (Collignon et al., 2015; Collignon et al., 2018). Infrastructure is negatively associated with AMR in two studies (Collignon et al., 2018; Vikesland et al., 2019) and warmer temperature is shown to be positively associated to AMR (Collignon et al., 2018; Kaba et al., 2020). Education is a complex variable which has mixed results with studies showing both positive (Collignon et al., 2018) and negative (Collignon et al., 2015) relationships with AMR. The variable of physician density (PPI) was included in several studies as a potential confounder (Gaygısız et al., 2017; Kaba et al., 2020; Rönnerstrand & Lapuente, 2017). Although not found to be significant in these studies, physician density may be useful in future studies as a control variable.

Discussion
The purpose of this review is to assess the current body of knowledge on socioeconomic and governance factors associated with AMR. With the objective of extracting variables for use in future research and analysis, the review can be useful in formulating assumptions around the spread of AMR and investigating characteristics among countries and possibly regions that foster the prevalence of either high or low AMR rates.

While a significant and inverse relationship between quality of governance and antimicrobial resistance has been established in three studies, the topic is still relatively unexplored. There is a need for the introduction of new variables and possible confounders to test the strength of this relationship. It is assumed that quality of governance influences health outcomes as the many processes and institutions involved in this measure set the foundation for successful health interventions; however the high explanatory value of quality of governance found in these studies warrants further research on the robustness of these findings.

The socioeconomic variables identified in the study contribute suggested factors for inclusion in analysis with quality of governance and AMR. Namely, antimicrobial consumption in animals appears to be an important driver of AMR and could be an interesting addition in a study to analyze its connection to quality of governance as well compare its explanatory power to that of antimicrobial consumption in humans.

The sample of literature also points to the multidisciplinary nature of AMR. There are many contributing factors such as antimicrobial consumption in food-producing and companion animals, AMR transmission through the environment in water and sewage systems, unhygienic healthcare institution and food chain conditions, and specific health-system factors such as gatekeeping practices and the level of regulation. These factors relate to the concept of quality of governance in how a system coordinates, manages, and oversees its operations and interventions, yet these variables have not been introduced to the quality of governance and AMR literature.

The added value of this review is that it fills the gap where no current review is available on this growing topic. As seen from the results, in recent years there has been an increase in the publications relating to governance and health outcomes, including AMR. Antimicrobial resistance will continue to be a threat to public health for years to come and the importance of understanding the spread of AMR is shown in the severe consequences to communities and health systems.

Limitations

While this review contributes to the growing literature on socioeconomic and governance factors related to AMR, one limitation of the scoping review methodology is that it is not appropriate for use in recommending policy and practice (Grant & Booth, 2009). Although this is not an objective of the current study, policy recommendations are an important motive for research in this field.

Additionally, scoping reviews do not assess the quality of primary research articles formally. Therefore, the research gaps identified in this scoping review do not reflect whether the presented research is of high or poor quality (Grant & Booth, 2009). In choosing to conduct a systematic review, these limitations would be resolved.

The criteria enforced in the inclusion of publications in the review also lead to potential bias in the results (Grant & Booth, 2009). Due to the specificity of the research question, the review scope is quite narrow and the chosen criteria generate a relatively small number of overall references. Additional scoping or systematic reviews on this subject and related topics could be beneficial in better understanding the many factors influencing variation in AMR across countries.

Further Research

Due to time and resource limitations during this review, the eligibility criteria is quite strict. It is important to note that potentially relevant papers could have been missed. Expanding on this literature to include socioeconomic variables related to antimicrobial consumption or broadening the geographic range to include developing countries or other regions could be an interesting contribution to this research.

Conclusion

AMR is a complex and urgent public health challenge affecting communities, health systems, and society. Explaining the spread of AMR through associated factors is an ambitious task, yet each new finding contributes to better understanding behind the spread of AMR. This review on the state of knowledge between associated socioeconomic and governance factors and AMR establishes a strong support for the negative relationship between quality of governance and AMR as well as the positive association between AMR and antimicrobial consumption in humans. With this foundation, the review reveals a gap in knowledge with regard to studies introducing new and novel variables to test these relationships, such as the introduction of antimicrobial consumption in animals and AMR transmission through the environment. The importance of these findings encourages the need for more research on the impact of quality of governance on AMR as well as the introduction of new variables. With continued focus on the topic of AMR and its linked factors, best practices to fight against AMR can be developed and refined to maintain effective treatment options for the many years to come.

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Appendix Summary of studies

Author(s) (Year)	Study Title	Sample/Methodology	Theme/ Subthemes	Key Findings	Significant Variables
Collignon, Athukorala, Senanayake & Khan (2015)*	Antimicrobial Resistance: The Major Contribution of Poor Governance and Corruption to This Growing Problem	Retrospective multivariate analysis of 28 European countries for the period 1998-2010	AMR and Quality of Governance/ AMR and Corruption	1. Corruption is the main socioeconomic factor explaining AMR 2. PHE[20] is positively associated with AMR 3. QoG correlates better than AMC[21] with AMR	QoG[22] AMC PHE EDU[23] GDP[24]
Collignon, Beggs, Walsh, Gandra, & Laxminarayan (2018)*	Anthropological and socioeconomic factors contributing to global antimicrobial resistance: a univariate and multivariable analysis	Univariate and multivariate regression analyses inclusive of 103 countries for the period of 2008-2014. Study includes 73 countries for multivariate analyses.	AMR and Quality of Governance/ AMR and Corruption	1. All measures of improved governance, THE, GDP, and improved infrastructure were strongly and inversely correlated with AMR 2. All measures of education except completion of primary school, average temperature, and PHE were positively correlated to AMR 3. High AMR rates are more likely attributed to spread through sanitation and water rather than consumption	QoG[25] AMC[26] PHE EDU[27] GDP INFRA[28] THE[29] CLI[30]
Kaba, Kuhlmann, & Scheithauer (2020)	Thinking outside the box: Association of antimicrobial resistance with climate warming in Europe – A 30 country observational study	Cross-sectional observational study of 30 European countries considering the relationship between AMR and climatic variables in the period of 2011-2016	AMR and Quality of Governance/ AMR and Corruption	1. Higher temperature is significantly associated with AMR and explains more variation than AMC 2. Climate change may increase AMR transmission 3. Quality of governance has a strong association with AMR	QoG[31] AMC CLI

*Key articles used for backward reference list and forward citation list methods

20 PHE: Private Health Expenditure
21 AMC: antimicrobial consumption in humans
22 QoG: Quality of Governance includes the control of corruption indicator
23 EDU: tertiary education. Only significant in OLS models
24 GDP: GDP per capita only is significant in OLS models
25 QoG index includes corruption measures and the WGI indicators of Political Stability and Absence of Violence (PS) and Rule of Law (RL)
26 Antimicrobial consumption was strongly and positively correlated in a sample with only European countries
27 EDU referred to an index including literacy rates and completion rates of secondary education and primary school
28 Infrastructure index comprised of urbanization, sanitation, electricity and internet access, and access to quality water source
29 Total health expenditure as a percentage of GDP
30 Climate variable refers to an index comprised of the average temperature and average precipitation. Only average temperature was significantly and positively associated with AMR
31 QoG is measured using the Corruption Perceptions Index (CPI)

Author(s) (Year)	Study Title	Sample/Methodology	Theme/ Subthemes	Key Findings	Significant Variables
Borg & Camilleri (2019)	Broad-spectrum antibiotic use in Europe: More evidence of cultural influences on prescribing behavior.	Correlation and regression analysis for 28 EU countries with Hofstede cultural dimensions and control of corruption (CoC)	AMR and Quality of Governance/ AMC and Corruption	1. CoC had a significant univariate negative correlation to AMC 2. In multiple regression, the CoC variable was no longer significant 3. Uncertainty avoidance is significant in both univariate and multivariate analyses	QoG[32]
Gaygisiz, Lajunen, & Gaygisiz (2017)*	Socio-economic factors, cultural values, national personality and antibiotics use: A cross-cultural study among European countries.	Cross-cultural analysis of 27 European countries from 2013 on the socioeconomic and cultural variables affecting AMC	AMR and Quality of Governance/ AMC and Corruption	1. Governance quality, life expectancy, and the cultural dimensions of masculinity and uncertainty avoidance were significant in explaining AMC 2. Governance quality and education level have a negative correlation with AMC	QoG EDU[33]
Kenyon & Manoharan-Basil (2020)	Cultural Drivers of Antibiotic Consumption in High-Income Countries: A Global Ecological Analysis.	Ecological analysis of 37 countries with separate analysis for 25 European countries on socioeconomic factors influencing AMC from 2013-2015	AMR and Quality of Governance/ AMC and Corruption	1. Univariate analysis shows quality of governance indicators to be negatively correlated to AMC 2. Quality of governance indicators are not significant to AMC in multivariate analysis 3. GDP per capita is significant in multivariate analysis	QoG[34] GDP
Rönnerstrand & Lapuente (2017)*	Corruption and use of antibiotics in regions of Europe.	Multivariate regression analysis of the association between corruption and antibiotic use at the regional level	AMR and Quality of Governance/ AMC and Corruption	1. AMC and corruption hold a significant and strong positive relationship 2. When controlling for GDP and age-standardized mortality rates, corruption and AMC maintain a positive association	QoG

*Key articles used for backward reference list and forward citation list methods

[32] The quality of governance variable (Control of Corruption) was only significant in univariate correlation analysis
[33] Education is measured as mean years of schooling
[34] Quality of Governance is measured by the indicators Control of Corruption and Regulatory Quality. These factors are not significant in multivariate analysis

Author(s) (Year)	Study Title	Sample/Methodology	Theme/ Subthemes	Key Findings	Significant Variables
Bell, Schellevis, Stobberingh, Goossens, & Pringle (2014)	A systematic review and meta-analysis of the effects of antibiotic consumption on antibiotic resistance	Systematic review on the relationship between AMC and AMR in the community setting. Multiple regression analysis was used to determine the relationship	AMR and socioeconomic/ Cultural factors	1. Binomial test revealed a positive relationship between AMC and AMR, but multiple regression models did not produce significant results 2. Countries in southern Europe showed a stronger connection between AMC and AMR than other regions	AMC Region[35]
Blommaert et al. (2014)	Determinants of between-country differences in ambulatory antibiotic use and antibiotic resistance in Europe: a longitudinal observational study	Cross-sectional study identifying key determinants for explaining variation in AMC and AMR in 19 European countries form 1999 to 2007	AMR and socioeconomic/ Cultural and Health-system factors	1. Gatekeeping practices in a health system and THE are negatively associated with a country's AMR levels 2. Larger average household size and higher life expectancy at 65 years was positively associated with AMR 3. AMC is significantly associated with AMR for some drug/organism combinations	AMC[36] GK[37] HS[38] REL[39] LE[40]
Chokshi, Sifri, Cennimo, & Horng (2019)	Global contributors to antibiotic resistance	Qualitative literature review on the contributors to AMR in developed and developing countries from 1963 to 2017	AMR and socioeconomic/ Cultural and Health-system factors	1. In developed countries, poor AMC hospital-level regulation and overuse of antibiotics in livestock are positively related to AMR 2. Lack research of new antimicrobials is also a concerning issue affecting AMR worldwide	AMCA[41] REG[42]
Kirby & Herbert (2013)	Correlations between Income Inequality and Antimicrobial Resistance Problem	Correlation analysis between income inequality and AMR in 15 European countries for the period of 2003-2010	AMR and socioeconomic/ Economic factors	1. Income inequality is positively correlated to AMR in seven pathogens 2. Income inequality is weakly associated with AMC 3. AMC was strongly associated with AMR	AMC IE[43]

35 Regional variable: Northern Europe, Southern Europe, US, and other regional categories
36 AMC was not significant for all pathogen and antimicrobial combinations, namely E. coli and aminopenicillins and combined resistance to PNSP
37 Gatekeeping: refers to the incentive for consulting a GP before seeing a specialist
38 Household size
39 Religiousness: Those who described themselves as atheistic rather than religious had higher average AMR
40 Life expectancy at 65 years for both sexes
41 Antimicrobial use in animals is positively related to AMR
42 Hospital-level regulation: poor regulation is positively related to AMR.
43 Income inequality

Author(s) (Year)	Study Title	Sample/Methodology	Theme/ Subthemes	Key Findings	Significant Variables
McDonnell et al. (2017)	National disparities in the relationship between antimicrobial resistance and antimicrobial consumption in Europe: an observational study in 29 countries.	Observational study using correlation analysis on AMC and AMR in 29 European countries from 2013-2014	AMR and socioeconomic/ Cultural factors	1. Community AMC rates showed strong to moderate correlation with hospital AMR rates per country in 19 bacterial strains 2. This trend was not consistent for all European countries as some showed low AMC and high AMR and vice versa	AMC
Vikesland et al. (2019)	Differential Drivers of Antimicrobial Resistance across the World	Research article framed by the application of a resistance driver model and the differences between high income and low-to middle-income country AMR challenges	AMR and socioeconomic/ Cultural and Economic factors	1. AMC and antimicrobial overuse for animals and humans is the primary selection pressure accelerating the global spread of AMR 2. Changing population density, sanitation infrastructure, and solid-waste disposal influence AMR dissemination, particularly in low- to middle-income countries	AMC AMCA INFRA[44]

[44] Infrastructure was particularly noted for its importance in low- to middle-income countries

Article 2

Quality of Governance and Antimicrobial Resistance:

Explaining the variation in antimicrobial resistance prevalence across Europe

Molly Monroe

Abstract

BACKGROUND: While the positive association between antimicrobial use and resistance is well-known, much of the variation in antimicrobial resistance (AMR) prevalence is still unexplained. Emerging studies have introduced the relationship between quality of governance and AMR based on the assumption that good governance is associated with improved health outcomes; however, there is still limited literature supporting the strength of this relationship.

OBJECTIVE: The study aims to investigate the relationship between quality of governance and AMR rates across European countries with the inclusion of additional socioeconomic and health-system variables to better explain the variation in AMR prevalence.

METHOD: Correlation and regression analyses are employed on a panel dataset of 30 European countries during the time period 2011-2017. Pooled ordinary least squares (POLS) and fixed effects (FE) regression methods are used for bivariate and multivariate analyses. Original variables are introduced in the study including zoonoses notification rates for campylobacteriosis and salmonellosis as well as the measure of antimicrobial consumption in animals.

RESULTS AND DISCUSSION: The quality of governance (QoG) variable confirmed past findings with a significant, negative relationship to antimicrobial resistance. QoG explained the most variation in the models compared to the other eight explanatory variables. Antimicrobial consumption in humans, education level, and private health expenditure were significant in the multivariate POLS model; however, only antimicrobial consumption in animals and quality of governance were significant in the FE models. Due to the mixed results for antimicrobial consumption in animals, further research is needed on this relationship.

CONCLUSION: This retrospective study on socioeconomic and governance-related factors supports the findings of past studies on the significant relationship between quality of governance and AMR. The inclusion of new variables in this study encourages further research on the many factors related to AMR while the study's contribution to the growing literature on the relationship between QoG and health may have implications for future health policy and regulations.

Introduction

In a list of the urgent health challenges for the next decade, the World Health Organization (WHO, 2020) ranks the threat of antimicrobial resistance among the top public health issues. With this threat looming, identifying the factors associated with the spread of AMR are of critical importance in order to better understand and control the spread. While recent studies have found a relationship between quality of governance and antimicrobial resistance (Collignon et al., 2015; Collignon et al., 2018; Kaba et al., 2020), there is a need to test this relationship with a newer dataset and with the inclusion of new variables. In this study, the relationship between quality of governance and antimicrobial resistance will be investigated along with several other control socioeconomic and health-system variables in an attempt to explain the variation of antimicrobial resistance prevalence across European countries.

Antimicrobial resistance (AMR) is defined as "the ability of a microorganism to resist the action of one or more antimicrobial agents" (European Centre for Disease Prevention and Control [ECDC], 2018, p. 3). With the increasing prevalence of AMR, health systems can expect increased treatment costs, longer hospital stays for patients, and higher mortality rates (WHO, 2015). Infections related to AMR cause at least 33,000 deaths in the European Union (EU) per year and create an estimated cost of €1.5 billion worth of healthcare and productivity losses (Directorate-General for Health and Food Safety [DG SANTE], 2018).

The two main drivers behind the spread of AMR are the use of antimicrobial agents and the transmission of resistant microorganisms (ECDC, 2018). In research and policy development, there has been a strong emphasis on the positive relationship between antibiotic usage and resistance (Čižman, 2003; Masiero et al., 2010; McDonnell et al., 2017). Thus, the rise in AMR has been largely attributed to increasing global antibiotic usage (Klein et al., 2018). While policymakers and health professionals have largely focused their efforts on reducing antimicrobial use, research has shown that the relationship between AMR and antibiotic consumption is not perfectly correlated (Isturiz & Carbon, 2000). Therefore, additional factors must be considered in the policies, regulations, and practices to control and reduce the prevalence of antimicrobial resistance.

In Europe, countries with higher resistance levels showed significantly higher levels of per capita antibiotic use; however, the responsiveness of changes in resistance to usage was relatively low (Masiero et al., 2010). A new wave of studies have supported the argument that the spread of AMR is heavily influenced by social and economic factors and the contagion of AMR should be given more priority in policy development and government action (Collignon et al. , 2015; Collignon et al., 2018; Kaba et al., 2020).

Background

In political science literature, the concept of quality of governance has been viewed as essential for economic growth, poverty reduction, and social development (Holmberg et al., 2009). The assumption behind this relationship is that a government deemed as of "higher quality" is expected to have lower corruption rates and likely more control over the use of antibiotics and containing the spread of resistance through sound policy implementation and adherence to these policies (Gaygısız et al., 2017). Recent studies have explored the relationship of quality of governance and antibiotic consumption and therefore, AMR rates, finding a strong, negative relationship between the two variables (Gaygısız et al., 2017; Rönnerstrand & Lapuente, 2017).

While there are several analyses on the socioeconomic, cultural, and political connections to antimicrobial consumption, there is limited research on these variables and their direct associations with AMR (Collignon et al., 2015; Collignon et al., 2018; Kaba et al., 2020). These few studies have shown a significant correlation between the variables that show promising results that better explain the variation in AMR than the traditional measure of antimicrobial consumption (Collignon et al., 2015; Collignon et al., 2018). Despite these interesting new findings, there is still much unknown about the strength of the relationship of quality of governance and antimicrobial resistance rates as well as the associated factors.

The study seeks to explain the variation in antimicrobial resistance rates in Europe while building on past research to include a more comprehensive country set of 30 European nations, including Croatia and Romania, and more recent data from the years 2011-2017. Through retrospective bivariate and multivariate analyses, various health system-related and socioeconomic variables are tested in an attempt to explain the prevalence of AMR across countries. Original variables in this literature including antimicrobial consumption in animals and zoonoses notification rates are explored in the multivariate analysis to further test the primary relationship between quality of governance and antimicrobial resistance. The differences between the explanatory power in antimicrobial consumption in humans and animals is also an original contribution to this literature.

Research Question

Based on the inclusion of variables determined in a scoping review on socioeconomic and governance-related factors (Monroe, 2020)[45], the purpose of the study is to explain the variation of AMR rates across European countries. The primary objective of the study involves the question: what is the strength of the relationship between AMR and quality of governance? The secondary objective encompasses a broader view: what socioeconomic and health-system related factors are associated with the prevalence of AMR?

Analytical framework

In this study, the underlying assumption is that a country's quality of government affects the health and well-being of its population (Barbazza & Tello, 2014; Wang et al., 2019). The terms *quality of* government, *good governance,* and *control of corruption* are used synonymously with the term *quality of governance* in this literature. In this study, governance is explained using the World Bank's definition as:

> the traditions and institutions by which authority in a country is exercised. This includes: (1) the process by which governments are selected, monitored, and replaced, (2) the capacity of the government to effectively formulate and implement sound policies, and (3) the respect of citizens and the state for the institutions that govern economic and social interactions among them (Kaufmann et al., 2004).

Good governance represents an ideal for what governance "ought" to be (Barbazza & Tello, 2014) and is a perception-based measure. Quality of governance can affect many important aspects of the healthcare sector including the implementation and adherence to health policy (Mackenbach & McKee, 2015) and the coordination and delivery of services and goods (Frenk & Moon, 2013). The formal coordination of a government's institutions to enforce compliance as well as the sophistication and capacity of its disease control, prevention, and surveillance

[45] See also Article 1 of this Master Thesis.

systems are essential to the management of a public health issue, such as controlling the spread of AMR.

There is wide variation of quality of governance scores among European countries, which can be explained by the fact that quality of governance is not randomly distributed, but rather requires time and resources for development (Kaufmann et al., 1999). The challenge of AMR requires understanding and coordination from many groups including policymakers, health professionals, and community members. Trust and confidence in government institutions and public policy is also critical for the effectiveness of measures in managing AMR (Mattila & Rapeli, 2018).

The scoping review reports a strong inverse association between quality of governance and AMR rates indicating that a country with a stronger quality of governance is likely more effective in controlling the spread of AMR (Monroe, 2020). The key hypothesis generated from the theoretical foundation and empirical findings is that quality of governance is negatively associated with AMR rates.

H1: *Quality of governance is negatively associated with antimicrobial resistance*

Based on the findings of similar studies (Collignon et al., 2015; Collignon et al., 2018; Kaba et al., 2020), the underlying assumption is that country with a higher quality of governance will likely have better control over AMR spread and a stronger capacity for reducing risk-behavior; therefore, its national AMR rates are expected to be lower.

The other hypothesis related to the study involves antimicrobial consumption and AMR. This relationship has been tested in previous studies, but the inclusion of antimicrobial consumption in animals with quality of governance has not yet been investigated in this literature. For the animal antimicrobial consumption measure and the human antimicrobial consumption measure, it is expected that as consumption increases, resistance rates will also increase.

H2: *Antimicrobial consumption is positively related to antimicrobial resistance*

This assumption is based on past findings relating higher national antimicrobial use to higher AMR rates at a national level (Čižman, 2003; Masiero et al., 2010).

Data and Methodology

The study involves a panel dataset of 30 countries from the years 2011-2017 with socioeconomic and health-related variables from seven different data sources. The sample of countries includes: Austria, Belgium, Bulgaria, Cyprus, Czech Republic, Germany, Denmark, Estonia, Greece, Spain, Finland, France, Croatia, Hungary, Ireland, Iceland, Italy, Lithuania, Luxembourg, Latvia, Malta, Netherlands, Norway, Poland, Portugal, Romania, Sweden, Slovenia, Slovakia, and the United Kingdom. The explanation of the variables and the measurements of the data are included in Table 1.

Table 1. Description of major variables used for statistical analysis

Variable code	Description
AMRAvg	Average antimicrobial resistance rate calculated by the number of resistant isolates, divided by the total number of isolates tested for all 23 combinations. Written as a decimal on a scale of 0 to 1
QoGavg	Average score of 6 quality of governance dimensions: Voice and Accountability, Political Stability and Absence of Violence, Government Effectiveness, Regulatory Quality, Rule of Law, and Control of Corruption. Measured on a scale of 0 to 5
AMCanimal	Sales, in tonnes of active ingredient, of veterinary antimicrobial agents for food-producing animals, Measured in population correction unit (PCU) and sales in mg/PCU, by country
AMChuman	Consumption of antibacterials for systemic use in the J01 ATC group expressed in defined daily doses (DDD) per 1000 inhabitants and per day (known as DID)
PHE	Domestic private health expenditure as a percentage of total current health expenditure. Measured from 0 to 100
EDU	Percentage of population ages 15 to 64 years old who have achieved tertiary education (levels 5-8). Measured from 0 to 100
PPI	Medical doctors per 10,000 population in a country
Campylo	Notification rates of campylobacteriosis are calculated by the number of reported confirmed/total cases, divided by the official Eurostat population estimate for that year, multiplied by 100 000
Salmon	Notification rates of salmonellosis are calculated by the number of reported confirmed/total cases, divided by the official Eurostat population estimate for that year, multiplied by 100 000
Region	Categorical variable that is broken down by geographic region into 4 groups: Northern Europe (group 1); Southern Europe (group 2); Western Europe (group 3); Eastern Europe (group 4)

Antimicrobial Resistance Rates

The dependent variable is antimicrobial resistance rate (AMR), which is the rate of resistance to antibiotics measured in bacteria causing infections in the bloodstream (ECDC, 2020a). The antimicrobial resistance data are gathered from the European Antimicrobial Resistance Surveillance Network (EARS-Net) database of the ECDC. EARS-Net annually monitors seven common pathogens, which are all included in the dataset (ECDC, 2018). Of the reported data, 23 antimicrobial and pathogen combinations were chosen based on data availability for the chosen time period. The combination names are included in Appendix A.

The dependent variable is calculated as the average of antimicrobial resistance rates from 23 antimicrobial and pathogen combinations. The country data are classified as incomplete and excluded if fewer than 30 isolates were tested per pathogen/antibiotic combination. From 2011-2017, 412 of the 4830 data samples contained fewer than 30 isolates leaving a viable dataset of 4418 items for 209 observations. The study time period of 2011-2017 is determined by the availability of data on antimicrobial resistance rates for the selected 30 countries.

Quality of Governance

Quality of Governance is measured using the World Bank's Worldwide Governance Indicators (WGI). The WGI Index is based on more than 30 individual data sources (Kaufmann & Kraay, 2018). The index includes six dimensions of governance: Voice and Accountability; Political Stability and Absence of Violence; Government Effectiveness; Regulatory Quality; Rule of Law; and Control of Corruption. The scores are measured on a scale of -2.5 indicating weak governance to a maximum of 2.5 indicating strong governance. The scale has been recalculated in the study from 0 to 5 to avoid errors from negative values in calculating the average score. The average measure of the six indicators has been used in a related study involving quality of governance and antimicrobial consumption (Gaygısız et al., 2017). The QoG dimensions are not tested separately in the models as the WGI Index dimensions are overlapping and intended to be used only together as an aggregate measure of quality of governance (Langbein & Knack, 2008).

Antimicrobial Consumption in Humans

Antibiotic consumption is included as an independent variable in this model. The data are collected from the European Surveillance of Antimicrobial Consumption (ESAC-Net) which is monitored by the ECDC. Consumption is measured by defined daily dose (DDD) per 1000 inhabitants per day (ECDC, 2020b). In the analysis, only antibiotic use for ATC class J01 in community/ primary care is included, which is comprised of antibacterials for systemic use and excludes antifungals, antibacterials for tuberculosis, and topical antibiotics. This measure has been used in past studies to examine the relationship between consumption and resistance (Blommaert et al., 2014; Gaygısız et al., 2017; McDonnell et al., 2017). The decision to only include primary care estimates of antimicrobial consumption results from the lack of data reporting on hospital consumption. The choice is supported by the fact the overwhelming majority of antibiotics in Europe are prescribed to non-hospitalized patients (Bell et al., 2014).

Antimicrobial Consumption in Animals

Veterinary antimicrobial consumption is included in the models to represent a more complete picture of antimicrobial use at the community and national levels. The data are collected from the European Surveillance of Veterinary Antimicrobial Consumption (ESVAC), which has data on veterinary antimicrobial sales. ESVAC offers population-corrected sales of products used in food-producing animals. The sales are measured in milligrams (mg) of active ingredient by Population Correction Unit (PCU) (European Medicines Agency [EMA], 2020). The population correction measure considers the differences in size and structure of animal populations in countries. Based on the current knowledge, this is the first study to examine both quality of governance and antimicrobial consumption in animals as possible related factors to AMR.

Zoonoses Notification Rate

The inclusion of zoonotic notification rates adds another original contribution to the current literature. The assumption behind its inclusion is based on the idea that a country that poorly manages the use of antimicrobials and controlling the spread of AMR within its borders is likely to also struggle with an increased level of infections as a result of a welcome environment of transmission and ineffective disease controls. In the multivariate model, salmonellosis and campylobacteriosis prevalence are used as control factors. The indicator for these infections is the notification rates by 100,000 persons and the data are collected from the EARS-Net database (ECDC, 2020a).

Control Variables- PHE, EDU, PPI and Region

There are several control variables included in the multivariate models. Data on private health expenditure (PHE) were collected through the World Bank and measured as a country's percentage of private health expenditure of current health expenditures. This measurement has been used in past studies and is assumed to have a positive relationship with AMR based on previous findings (Collignon et al., 2015; Collignon & Beggs, 2019; Hijazi et al., 2019). Education data (EDU) are extracted from the Eurostat database on the percentage of inhabitants from a country's population from age 15 to 64 years with tertiary education (levels 5-8). This variable has shown mixed results based on past findings (Collignon et al., 2018; Gaygısız et al., 2017; Masiero et al., 2010), yet it is assumed that a more educated population understands the serious consequences of AMR and exhibits lower risk behavior. Therefore, education would hold a negative relationship with AMR. Physician density data (PPI) are collected from the WHO Global Health Observatory data repository. The variable serves to represent the competition between physicians in a country and is measured as the number of medical doctors per 10,000 population. It is assumed that a more competitive market among physicians would result in increased antimicrobial consumption and therefore, higher AMR rates. A region variable was also included in the analysis as a categorical variable to account for some of the shared cultural and socioeconomic characteristics among the geographic regions. Traditionally, the regions of Northern and Western Europe have been associated with lower average AMR rates while the regions of Southern and Eastern Europe have been associated with higher AMR rates (ECDC, 2019). However, these regional differences may be exaggerated by unidentified socioeconomic and cultural factors not included in this study. The region classification is included in Table 2.

Table 2. Region Classification

Group	**Region**	**Countries Included**	**N=**
1	Northern Europe	Denmark, Estonia, Finland, Iceland, Ireland, Latvia, Lithuania, Norway, Sweden, United Kingdom	10
2	Southern Europe	Croatia, Cyprus, Greece, Italy, Malta, Portugal, Slovenia, Spain	8
3	Western Europe*	Austria, Belgium, Germany, France, Luxembourg, Netherlands	6
4	Eastern Europe	Bulgaria, Czech Republic, Hungary, Poland, Romania, Slovakia	6
* Group 3 was not statistically significant from the baseline Group 1 and thus combined in analysis			

Statistical Methodology

For the analysis, the chosen significance level is 5%. The sample size of 30 countries is quite small, so the panel data cover seven years (2011-2017) to increase the number of observations. The chosen time period and the use of national-level data are selected due to data availability. The data are analyzed in this study using regression methods. First, associations are explored between the dependent variable of AMR and the explanatory variables. Next, multivariate regression models are used to determine the relationship between the variables and the strength of these associations. Finally, the fixed effects (FE) technique is utilized to adjust for country-specific factors. The data were initially compiled from multiple data sources using Microsoft Excel and analyzed using Stata/IC version 16. Graphs were created in Stata/IC version 16.

Results

As seen in Table 3, there are large variations among the European countries within the selected variables. Regarding AMR rates, Sweden holds the lowest average antimicrobial resistance rates (6.20%) for the time period while Romania has the highest average antimicrobial resistance rate (38.67%). This finding is consistent with the regional expectation that AMR rates are lower in the regions of Northern and Western Europe compared to the regions of Southern and Eastern Europe. Romania also has the lowest average quality of governance score (2.68) and Finland has the highest average score (4.31).

For human antimicrobial consumption among the 30 countries, the Netherlands had the lowest average consumption for the time period (9.49 DID) and Greece had the highest (30.16 DID). Animal consumption of antimicrobials is lowest in Norway (3.3 sales in mg/PCU) and highest in Cyprus (418.9 sales in mg/PCU).

Through this brief descriptive analysis, a trend emerges where Southern and Eastern European countries such as Greece, Cyprus, Bulgaria, and Romania have the characteristics hypothesized to be consistent with the spread of AMR while Northern and Western European countries such as Norway, Sweden, the Netherlands, and Finland are likely to have the traits associated with lower AMR.

Table 3. Variable summary statistics

Variable	Mean (Std. Dev)	Minimum	Maximum	Countries	Observations
AMRAvg	0.21 (.085)	.054	.434	30	209
AMChuman	17.86 (5.147)	8.94	32.15	30	207
AMCanimal	106.10 (105.558)	2.9	453.41	30	191
EDU	26.95 (7.193)	12.9	40.4	30	209
PHE	26.28 (9.990)	13.791	57.174	30	209
PPI	34.46 (7.370)	19.510	54.789	30	198
QoGavg	3.58 (.498)	2.570	4.373	30	209
Campylo	53.61 (46.631)	0.337	229.95	29	195
Salmon	24.17 (23.030)	1.592	126.089	30	206

Scatter diagram plots were constructed to illustrate the association between AMR and the main explanatory variables: QoG, AMChuman, and AMCanimal. Data from 2013 was used as the representative year due to the large amount of total observations for graph visibility and the data availability for the variables included in the plots.

As shown in the scatterplot, there is a negative relationship between quality of governance and AMR (r= -.859). This result is expected based on previous studies between these two variables (Collignon et al., 2015; Collignon et al., 2018). A country code key is found in Appendix B.

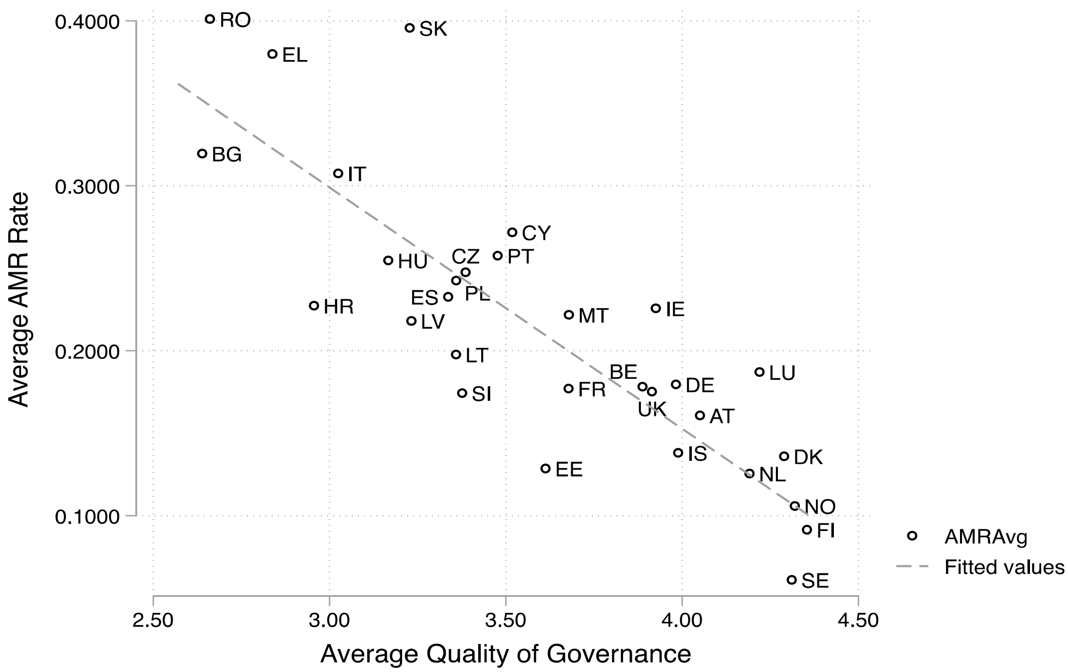

Figure 1. AMR and quality of governance in European Countries
Source: EARS-Net (2013) and WGI Index (2013)

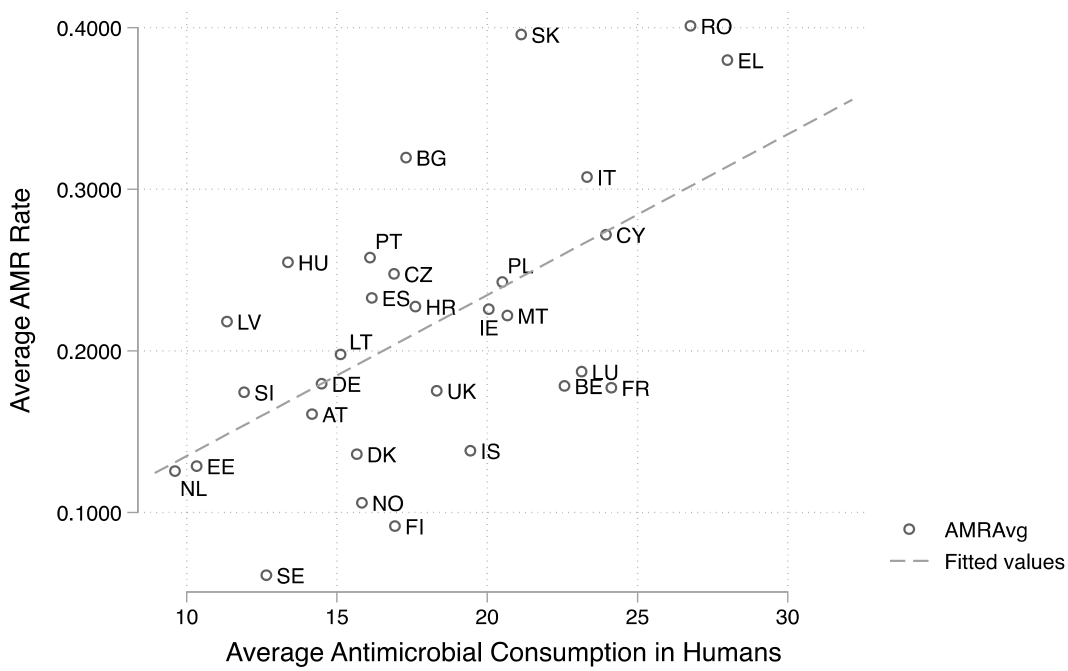

Figure 2. AMR and antimicrobial consumption in humans in European countries
Source: EARS-Net (2013) and ESAC-Net (2013)

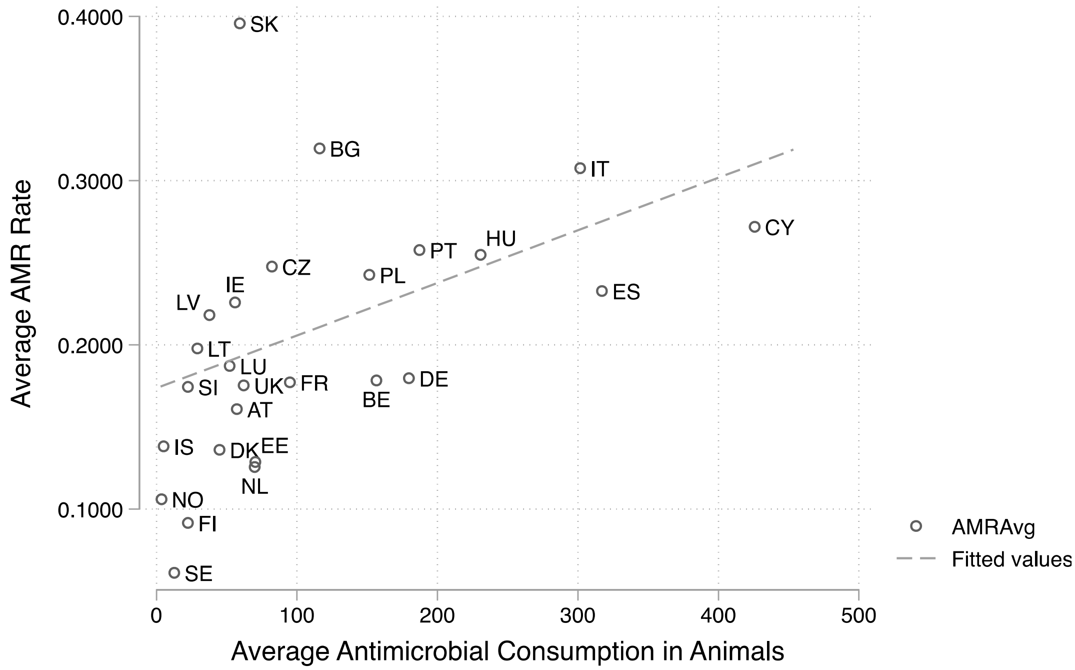

Figure 3. AMR and antimicrobial consumption in animals in European countries
Source: EARS-Net (2013) and ESVAC-Net (2013)

The associations between antimicrobial consumption in humans (r= .602) and animals with AMR (r= .412) are positive and moderately strong based on the relationship in the scatterplots (Figures 2-3). This relationship is consistent with the hypothesis and supports past findings (Collignon et al., 2015; Kaba et al., 2020).

POLS Bivariate Regression Models

Next, regression models were fitted to the data to identify factors that affect AMR across the range of countries. The fit of each model is described using the coefficient of determination, adjusted R^2. The output of the simple regression for average quality of governance (Model POLSB1), antimicrobial consumption in humans (Model POLSB2) and antimicrobial consumption in animals (Model POLSB3) with average antimicrobial resistance rates as the dependent variable are shown below.

Table 4. POLS Bivariate Regression with time effects included

VARIABLES	(1) POLSB1	(2) POLSB2	(3) POLSB3
QoGavg	-0.146***		
	(0.00613)		
AMChuman		0.00998***	
		(0.000934)	
AMCanimal			0.000325***
			(5.20e-05)
Constant	0.734***	0.0280	0.159***
	(0.0235)	(0.0211)	(0.0162)
Observations	209	207	191
Adj. R-squared	0.730	0.343	0.153

Standard errors in parentheses
*** p<0.01, ** p<0.05, * p<0.1

Time effects were included in this model through the addition of dummy variables for the years. While the inclusion of time effects did not change the significance of the variables, the R^2 estimates were lowered slightly. The results show a very high R^2 of 72.99% and a significant negative relationship based on the low p-value for the main relationship of AMR and quality of governance. The relationship between antimicrobial consumption for humans and AMR is comparatively much lower with a R^2 of 34.27%. The simple regression for average antimicrobial resistance rates and antimicrobial consumption in animals showed a significant relationship with a very low p-value , but also a low R^2 of 15.28%. These values are similar to the Collignon et al. study (2015), which found 28% of the total variation explained by antimicrobial consumption alone and 63% of the variation explained when the quality of governance indicator was included. The control variables of private health expenditure, education, and campylobacteriosis notification rates were also significant in simple regression while the values of physicians density and salmonellosis notification rates were not significant.

The categorical variable of region was analyzed for its relationship to AMR. Region 3 (Western Europe) is not statistically significant from the baseline group of Northern Europe, so it is therefore combined for future analysis. Both regions 2 & 4 (Southern and Eastern Europe) are significant after this consolidation.

POLS Multivariate Regression Models

After using the three methods of forward selection, backward elimination, and stepwise regression, one final model was determined for pooled ordinary least squares (POLS) multivariate regression. The forward selection and backward elimination models initially included campylobacterosis notification rates in the model; however, this variable was removed in stepwise regression after it was discovered that the variable negatively affected R^2.

The final model included the variables: QoGavg, EDU, AMChuman, and PHE. The region variable and time effects were also included as it improved the p-values and coefficient of determination in the model. It is worth noting that Region 2 (Southern Europe) is not significant against the base group of Northern and Western Europe. With these factors included, the final multivariate model (POLSM2) explained 85.72% of the variation in AMR.

Table 5. POLS Multivariate Regression with time effects included

	(1)	(2)
VARIABLES	POLSM1	POLSM2
QoGavg	-0.0867***	-0.0760***
	(0.00987)	(0.00867)
AMChuman	0.00551***	0.00577***
	(0.000534)	(0.000504)
PHE	0.00123***	0.00114***
	(0.000333)	(0.000309)
EDU	-0.00205***	-0.00208***
	(0.000546)	(0.000548)
Campylo	0.000172**	
	(6.93e-05)	
2.Region2	-0.00351	0.000613
	(0.00868)	(0.00854)
4.Region2	0.0277**	0.0365***
	(0.0113)	(0.0101)
	(0.00902)	(0.00896)
Constant	0.424***	0.391***
	(0.0385)	(0.0363)
Observations	193	207
Adj. R-squared	0.852	0.857

Standard errors in parentheses

*** p<0.01, ** p<0.05, * p<0.1

It is worth noting that there was no significant association between AMR and antimicrobial consumption in animals in the OLS multivariate analysis. Physician density and salmonellosis notification rates were not included in the multivariate analysis as the variables did not have a significant relationship to AMR in the simple regression models. The weak relationship between physician density and AMR is consistent with the findings of past studies (Kaba et al., 2020).

Fixed Effects Model

The fixed effects method was run for both bivariate and multivariate models. The group variable is characterized by country, so the dataset has 209 observations and 30 groups in this analysis. The Hausman test results confirm the appropriateness of the fixed effects model over the use of the random effects model.

In the bivariate analysis without time effects, only the variable of quality of governance (QoG) and animal antimicrobial consumption (AMCanimal) are significant at the 5% level. Antimicrobial consumption in animals was not significant in the pooled ordinary least squares (POLS) multivariate models yet holds a significant relationship in the FE model. The findings of the fixed effects models with time effects are included below.

Table 4. Fixed Effects Regression with time effects included

	(1)	(2)	(3)
VARIABLES	FE_T1	FE_T2	FE_T3
QoGavg	0.0619***		0.0384**
	(0.0192)		(0.0174)
AMCanimal		0.000114**	0.000123***
		(4.71e-05)	(4.67e-05)
Constant	-0.0139	0.191***	0.0509
	(0.0691)	(0.00584)	(0.0640)
Observations	209	191	191
Overall R-squared	0.728	0.177	0.340
Number of id	30	30	30

Standard errors in parentheses
*** p<0.01, ** p<0.05, * p<0.1

For the multivariate analysis of the FE model, only those significant variables from the FE bivariate analysis were significant in the model. The multivariate model with both QoG and AMCanimal has an overall R^2 of 33.96% while the bivariate model of quality of governance alone explains 72.81%. Therefore, the strongest model is between AMR and quality of governance.

Discussion

The purpose of the study is to add to the existing knowledge on factors associated with antimicrobial resistance by analyzing the relationship between antimicrobial resistance and quality of governance (QoG) as well as other socioeconomic and health-system variables across a diverse range of countries. The study design is based on the hypothesis that QoG holds an inverse relationship to AMR that is, a country with stronger measures of quality of governance will have lower average levels of AMR. Novel variables including antimicrobial consumption in animals and zoonoses notification rates of campylobacteriosis and salmonellosis were added in the analysis in an attempt to explain more of the variation in AMR rates in Europe.

The study examines multiple potential sources of variation in AMR through the associations between AMR and socioeconomic and governance-related factors using POLS and FE methods in bivariate and multivariate analyses. The study findings confirmed the main hypothesis that quality of governance holds a strong relationship to AMR.

The secondary hypothesis of a positive relationship between antimicrobial consumption and AMR was also confirmed. However, this relationship was not significant in all models. Traditionally, antimicrobial consumption has been considered as the main influence of AMR in a country. While human antimicrobial consumption in bivariate analysis explained only 33.42% of the variation in AMR, QoG explained 72.99%. In the multivariate regression models, QoG continued to explain the majority of the variance while additional socioeconomic factors such as antimicrobial consumption in humans, education, private health expenditure, and region classification contributed only 12.73%. Perhaps, the strength of the quality of governance relationship is shown best when considering the fixed effects (FE) model.

In the FE model which controls for time-invariant group (country) characteristics, quality of governance and animal antimicrobial consumption were the only significant variables. QoG explained the majority of the variance in the model as it did in the POLS estimations. By contrast, the popular AMR determinant of antimicrobial consumption in humans was notably not significant in this analysis.

Antimicrobial consumption in animals was significant in the FE estimations and provides an interesting opportunity for further research on this topic. While the results of this study on the effect of antimicrobial consumption in animals on AMR are inconclusive in multivariate analysis, additional research could provide insight on the strength of this explanatory variable. Animal antimicrobial consumption is an important topic as two-thirds of the estimated future growth of antimicrobial consumption is expected to occur within the animal production sector (Food and Agriculture Organization of the United Nations [FAO], 2016).

Added value

The present study adds to the limited research on socioeconomic and governance-related factors to AMR. By including Romania and Croatia and the recent time period of 2011-2017, the study broadens past research on the link between AMR and antimicrobial consumption and governance in Europe. The newly considered variables of zoonoses notification rates of salmonellosis and campylobacteriosis add to the novelty of this study. One of the most important additions to this study design is the variable of animal antimicrobial consumption. Antimicrobial consumption of animals is significantly larger than human consumption and the inclusion of this variable addresses another important topic in the challenge of controlling AMR.

The findings of this study validate past conclusions on the significant explanatory power of quality of governance on antimicrobial resistance. Surprisingly, antimicrobial consumption in humans and animals explained far less of the variation compared to quality of governance. The traditional control factors of private health expenditure and education were significant in multivariate POLS models, but not significant when factoring for country-specific factors. The insignificance of the inclusion of zoonotic notification rates is surprising based on the assumption that high AMR rates would likely coincide with greater incidence of disease and infections; however, these variables should be included in future analysis to conclude on their appropriateness to these types of studies. The results of this study may help to better explain the factors influencing the spread and emergence of AMR and contribute to the greater understanding of how AMR develops across countries.

Limitations

While the study has a number of strengths in the novelty of variables tested and the recent data, the study design and analysis also face several limitations. Due to the many contributing factors affecting antimicrobial resistance, the inclusion of all variables discovered in the scoping review literature is not possible due to limited data sources and time constraints (Monroe, 2020). Additionally, there have been challenges with data availability, which has resulted in missing values for particular variables due to insufficient reporting numbers including pathogen and antimicrobial combination and animal antimicrobial consumption measures.

Due to the nature of the variables measured, there may be possible error in the measurement of the variables as these values are based on estimates, particularly quality of governance, antimicrobial consumption, and AMR data. When considering this concern, causality cannot be inferred from this analysis. This concern also stands when considering how antimicrobial consumption is both a cause and consequence of AMR (Goossens et al., 2005).

In the analysis, the R-squared values are quite high. These high values are consistent with the high explanatory power found in past studies on quality of governance (Collignon et al., 2015; Collignon et al., 2018; Kaba et al., 2020) yet the values create skepticism in whether the explanatory power is overestimated, potentially due to issues of multicollinearity. For instance, quality of governance is likely to have an effect on education (Piergiuseppe & Ugo, 2015). The potential for endogeneity among the variables could overestimate the significance of these variables. While methods were introduced to control for the possible confounding between factors, the values remained quite high through all regression methods.

Another limitation of the study is that the data are only from European countries. New studies in this field have emerged covering regions outside of Europe and particularly in developing countries (Collignon et al., 2018). However, data surveillance is often limited and inconsistent in these regions and thus, analysis may be more challenging and involve more estimations.

Further Research

It is possible to measure both human and animal consumption of antimicrobials under a common measure; however, data limitations and time constraints have prevented this common measure from being included in these models. The inclusion of this common measure could be an important contribution in evaluating a more complete measure of antimicrobial consumption in communities. Additionally, the use of subnational regional data would be interesting in this design as subnational regional variation has shown significant results in past studies involving antimicrobial consumption (Rönnerstrand & Lapuente, 2017) and increases the sample size. However, AMR rates at a subnational level are not currently available for this sample of European countries.

The complexity of AMR involves many academic disciplines and industry sectors including agriculture, government, and human and animal medicine. Therefore, there are many topics related to the spread of AMR that could be explored in future research. As this is the first study to use antimicrobial consumption in animals with quality of governance to predict antimicrobial resistance, there is the potential for many new studies examining this relationship and related factors such as food consumption and usage of antimicrobials in companion animals.

Conclusion

Quality of governance is an important concept relating to the functioning and effectiveness of a government and its institutions as well the processes and systems that surround them. The positive impact of governance on health outcomes deserves more attention in the healthcare community and healthcare-associated research fields. The results of the study confirmed the negative relationship between quality of governance and antimicrobial resistance found in past studies and introduced new variables for analysis in relation to AMR including animal antimicrobial consumption and the prevalence of zoonoses notification rates. This study of 30 European countries during the time period of 2011-2017 contributes to the growing literature surrounding the relationship of quality of governance to health-related outcomes by confirming the significance of governance-related factors for health and encouraging future research to explore and expand on this important topic.

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Appendices

Appendix A

Pathogen and Antimicrobial Combinations

Pathogen	Antimicrobial
Escherichia coli	Third-generation cephalosporins
Escherichia coli	Aminoglycosides
Escherichia coli	Aminopenicillins
Escherichia coli	Carbapenems
Escherichia coli	Fluroquinolones
Klebsiella pneumoniae	Third-generation cephalosporins
Klebsiella pneumoniae	Aminoglycosides
Klebsiella pneumoniae	Carbapenems
Klebsiella pneumoniae	Fluroquinolones
Pseudomonas aeruginosa	Aminoglycosides
Pseudomonas aeruginosa	Carbapenems
Pseudomonas aeruginosa	Ceftazidime
Pseudomonas aeruginosa	Fluroquinolones
Pseudomonas aeruginosa	Piperacillin/Tazobactam
Streptococcus pneumoniae	Penicillins
Streptococcus pneumoniae	Macrolides
Staphylococcus aureus	Methicillin
Enterococcus faecalis	Aminopenicillins
Enterococcus faecalis	High-level Gentamicin
Enterococcus faecalis	Vancomycin
Enterococcus faecium	Aminopenicillins
Enterococcus faecium	High-level Gentamicin
Enterococcus faecium	Vancomycin

Appendix B

Country Code Key

Country	Country Code
Austria	AT
Belgium	BE
Bulgaria	BG
Croatia	HR
Cyprus	CY
Czech Republic	CZ
Denmark	DK
Estonia	EE
Finland	FI
France	FR
Germany	DE
Hungary	HU
Iceland	IS
Ireland	IE
Italy	IT
Latvia	LV
Lithuania	LT
Luxembourg	LU
Netherlands	NL
Norway	NO
Poland	PL
Portugal	PT
Romania	RO
Slovakia	SK
Slovenia	SI
Spain	ES
Sweden	SE
United Kingdom	UK

Appendix C
Regression output without time effects

Bivariate Regression

VARIABLES	(1) POLSB1	(2) POLSB2	(3) POLSB3
QoGavg	-0.146***		
	(0.00605)		
AMChuman		0.00995***	
		(0.000921)	
AMCanimal			0.000320***
			(5.15e-05)
Constant	0.738***	0.0354**	0.174***
	(0.0219)	(0.0171)	(0.00770)
Observations	209	207	191
Adj. R-squared	0.737	0.360	0.166

Fixed Effects Regression

VARIABLES	(1) FE1	(2) FE2	(3) FE3	(4) FE4
QoGavg	0.0502***		0.0594***	0.0350**
	(0.0187)		(0.0188)	(0.0170)
AMCanimal		9.54e-05**		0.000105**
		(4.50e-05)		(4.45e-05)
EDU			0.00125**	0.000911**
			(0.000495)	(0.000442)
Constant	0.0338	0.197***	-0.0332	0.0445
	(0.0672)	(0.00486)	(0.0713)	(0.0651)
Observations	209	191	209	191
Overall R-squared	0.738	0.170	0.731	0.464
Number of id	30	30	30	30

Standard errors in parentheses
*** p<0.01, ** p<0.05, * p<0.1

Appendices

Appendix A
Additional variables key

Variable name	Description
EC3rd	Resistance rate of Escherichia coli and 3rd generation cephalosporins
ECamiglyc	Resistance rate of Escherichia coli and aminoglycosides
ECaminop	Resistance rate of Escherichia coli and aminopenicillins
ECcarba	Resistance rate of Escherichia coli and carbapenems
ECfluro	Resistance rate of Escherichia coli and fluroquinolones
KP3rd	Resistance rate of Klebsiella pneumoniae and 3rd gen cephalosporins
KPcarba	Resistance rate of Klebsiella pneumoniae and carbapenems
KPfluro	Resistance rate of Klebsiella pneumoniae and fluroquinolones
KPamiglyc	Resistance rate of Klebsiella pneumoniae and aminoglycosides
PAcarba	Resistance rate of Pseudomonas aeruginosa and carbapenems
PAaminglyc	Resistance rate of Pseudomonas aeruginosa and aminoglycosides
PAcefta	Resistance rate of Pseudomonas aeruginosa and ceftazidime
PAfluro	Resistance rate of Pseudomonas aeruginosa and fluroquinolones
PApiptaz	Resistance rate of Pseudomonas aeruginosa and piperacillin/tazobactam
SPpeni	Resistance rate of Streptococcus pneumoniae and penicillins
SPmacro	Resistance rate of Streptococcus pneumoniae and macrolides
SAmethi	Resistance rate of Staphylococcus aureus and methicillin
EFlisamino	Resistance rate of Enterococcus faecalis and aminopenicillins
EFlisgenta	Resistance rate of Enterococcus faecalis and high-level gentamicin
EFlisvanco	Resistance rate of Enterococcus faecalis and vancomycin
EFiumamino	Resistance rate of Enterococcus faecium and aminopenicillins
EFiumgenta	Resistance rate of Enterococcus faecium and high-level gentamicin
EFiumvanco	Resistance rate of Enterococcus faecium and vancomycin
QoGcum	Cumulative score of 6 quality of governance dimensions
VAQoG	Estimate of Quality of Governance Dimension Voice and accountability
PSQoG	Estimate of Quality of Governance Dimension Political stability and absence of violence/terrorism
GEQoG	Estimate of Quality of Governance Dimension Government effectiveness
RQQoG	Estimate of Quality of Governance Dimension Regulatory Quality
RLQoG	Estimate of Quality of Governance Dimension Rule of Law
CCQoG	Estimate of Quality of Governance Dimension Control of Corruption

Appendix B
Correlation Matrices

Pairwise correlation coefficient matrix with individual WGI indicators

Variables	AMRAvg	QoGavg	CCQoG	GEQoG	PSQoG	RLQoG	RQQoG	VAQoG
AMRAvg	1.000							
QoGavg	-.859***	1.000						
CCQoG	-.860***	.973***	1.000					
GEQoG	-.845***	.969***	.942***	1.000				
PSQoG	-.572***	.709***	.595***	.633***	1.000			
RLQoG	-.855***	.981***	.959***	.954***	.631***	1.000		
RQQoG	-.778***	.922***	.883***	.866***	.571***	.901***	1.000	
VAQoG	-.795***	.965***	.936***	.931***	.655***	.946***	.870***	1.000

*** p<0.01, ** p<0.05, * p<0.1

Pairwise correlation coefficient matrix with full variable set

Variables	AMRAvg	QoGavg	AMChuman	AMCanimal	EDU	GDP	PHE	THE	PPI	Campylo	Salmon
AMRAv	1.000										
QoGavg	-.859***	1.000									
AMChuman	.602***	-.392***	1.000								
AMCanimal	.412***	-.405***	0.400***	1.000							
EDU	-.592***	.634***	-0.126*	-0.182**	1.000						
GDP	-.583***	.789***	-0.047	-0.283***	0.577***	1.000					
PHE	.495***	-.534***	0.223***	0.475***	-0.101	-0.530***	1.000				
THE	-0.706***	.850***	-0.179**	-0.345***	0.546***	0.925***	-0.600***	1.000			
PPI	0.056	-0.030	-0.116*	-0.149**	-0.138*	-0.058	0.035	-0.027	1.000		
Campylo	-0.204***	.363***	-0.162**	-0.345***	0.053	0.296***	-0.484***	0.284***	0.146**	1.000	
Salmon	0.100	-0.066	-0.145**	-0.183**	-0.251***	-0.190***	-0.186***	-0.209***	0.008	0.692***	1.000

*** p<0.01, ** p<0.05, * p<0.1

Pairwise correlation coefficient matrix with individual pathogen/antimicrobial combinations

Variables	AMRAvg	QoGavg	EC3rd	ECamiglyc	ECaminop	ECcarba	ECfluro	AMChuman	AMCanimal
AMRAvg	1.000								
QoGavg	-0.859***	1.000							
EC3rd	0.789***	-0.686***	1.000						
ECamiglyc	0.809***	-0.736***	0.901***	1.000					
ECaminop	0.755***	-0.629***	0.736***	0.747***	1.000				
ECcarba	0.219***	-0.133*	0.235***	0.234***	0.124*	1.000			
ECfluro	0.791***	-0.637***	0.841***	0.817***	0.789***	0.189***	1.000		
AMChuma	0.602***	-0.392***	0.414***	0.419***	0.487***	0.092	0.520***	1.000	
AMCanima	0.412***	-0.405***	0.496***	0.528***	0.578***	-0.007	0.706***	0.400***	1.000

*** p<0.01, ** p<0.05, * p<0.1

Variables	AMRAvg	QoGavg	AMChuman	AMCanimal	EFiumamino	EFiumgenta	EFiumvanco
AMRAvg	1.000						
QoGavg	-0.859***	1.000					
AMChuman	0.602***	-0.392***	1.000				
AMCanimal	0.412***	-0.405***	0.400***	1.000			
EFiumamino	0.381***	-0.338***	-0.085	-0.028	1.000		
EFiumgenta	0.275***	-0.295***	-0.213***	-0.271***	0.439***	1.000	
EFiumvanco	0.486***	-0.314***	0.399***	0.181**	0.376***	-0.076	1.000

*** p<0.01, ** p<0.05, * p<0.1

Variables	AMRAvg	QoGavg	AMChuman	AMCanimal	EFlisamino	EFlisgenta	EFlisvanco
AMRAvg	1.000						
QoGavg	-0.859***	1.000					
AMChuman	0.602***	-0.392***	1.000				
AMCanimal	0.412***	-0.405***	0.400***	1.000			
EFlisamino	0.156**	-0.259***	-0.043	-0.057	1.000		
EFlisgenta	0.545***	-0.548***	-0.064	0.160**	0.300***	1.000	
EFlisvanco	0.194***	-0.111	0.182**	0.003	0.111	0.236***	1.000

*** p<0.01, ** p<0.05, * p<0.1

Variables	AMRAvg	QoGavg	AMChuman	AMCanimal	KP3rd	KPamiglyc	KPcarba	KPfluro
AMRAvg	1.000							
QoGavg	-0.859***	1.000						
AMChuman	0.602***	-0.392***	1.000					
AMCanimal	0.412***	-0.405***	0.400***	1.000				
KP3rd	0.863***	-0.862***	0.426***	0.202***	1.000			
KPamiglyc	0.847***	-0.832***	0.393***	0.133*	0.973***	1.000		
KPcarba	0.592***	-0.505***	0.618***	0.304***	0.477***	0.391***	1.000	
KPfluro	0.859***	-0.834***	0.447***	0.201***	0.961***	0.954***	0.501***	1.000

*** p<0.01, ** p<0.05, * p<0.1

Variables	AMRAvg	QoGavg	PAaminglyc	PAcarba	PAcefta	PAfluro	PApiptaz	AMChuman	AMCanimal
AMRAvg	1.000								
QoGavg	-0.859***	1.000							
PAaminglyc	0.839***	-0.798***	1.000						
PAcarba	0.829***	-0.809***	0.871***	1.000					
PAcefta	0.847***	-0.787***	0.907***	0.896***	1.000				
PAfluro	0.837***	-0.768***	0.934***	0.863***	0.891***	1.000			
PApiptaz	0.817***	-0.733***	0.904***	0.855***	0.938***	0.904***	1.000		
AMChuman	0.602***	-0.392***	0.476***	0.483***	0.462***	0.480***	0.442***	1.000	
AMCanimal	0.412***	-0.405***	0.145*	0.245***	0.171**	0.169**	0.118	0.400***	1.000

*** p<0.01, ** p<0.05, * p<0.1

Variables	AMRAvg	SAmethi	SPmacro	SPpeni	AMChuman	AMCanimal
AMRAvg	1.000					
SAmethi	0.771***	1.000				
SPmacro	0.657***	0.650***	1.000			
SPpeni	0.543***	0.540***	0.511***	1.000		
AMChuman	0.602***	0.628***	0.687***	0.362***	1.000	
AMCanimal	0.412***	0.606***	0.428***	0.376***	0.400***	1.000

*** p<0.01, ** p<0.05, * p<0.1