Poverty and corruption as determinants of global antimicrobial resistance

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ความยากจนและคอร์รัปชันในฐานะปัจจัยกำหนดการดื้อยาต้านจุลชีพในโลก. (Poverty and corruption as determinants of global antimicrobial resistance) อ.ที่ปรึกษาหลัก : นพพล วิทย์วรพงศ์

การดื้อยาต้านจุลชีพนับเป็นภาวะคุกคามที่สำคัญของการสาธารณสุขในระดับโลกและอาจมีผลทำให้เกิดการเสียชีวิตของประชากรกว่า 7 แสนคนต่อปีทั่วโลก ความพยายามในการแก้ไขปัญหาดังกล่าวที่ผ่านมามักจะพิจารณาการลดการบริโภคยาต้านจุลชีพและการสนับสนุนการใช้ยาอย่างถูกวิธีเป็นหลักการศึกษานี้พิจารณาความสำคัญของปัจจัยทางเศรษฐกิจและสังคมที่นอกเหนือไปจากการบริโภคยาต้านจุลชีพ โดยเฉพาะอย่างยิ่ง ภาวะความยากจน (ที่วัดโดยรายได้ประชาชาติต่อหัว) และ คอรัปชั่น (วัดโดยคุณภาพของธรรมาภิบาล) ที่อาจส่งผลต่อการดื้อยาต้านจุลชีพ การศึกษานี้ใช้ข้อมูลพาเนลของประเทศจำนวนทั้งสิ้น 48 ประเทศในช่วงปี ค.ศ. 2008-2017 และใช้วิธีการวิเคราะห์แบบอิทธิพลตรึงหลายตัวแปรนอกจากนี้ ยังใช้การทดสอบ Sobel และการวิเคราะห์อิทธิพลทางอ้อมในการประเมินว่าความยากจนและคอรัปชั่นนั้นมีผลต่อการดื้อยาต้านจุลชีพผ่านตัวแปรอธิบายอธิบายอื่นๆ ในแบบจำลองด้วยหรือไม่ อันรวมถึง ตัวแปรการบริโภคยาต้านจุลชีพในมนุษย์ ตัวแปรค่าใช้จ่ายด้านสุขภาพ ตัวแปรระดับการเข้าถึง สุขอนามัยพื้นฐาน และตัวแปรระดับการเข้าถึงบุคลากรทางการแพทย์ การศึกษานี้พบว่าความยากจนและคอรัปชั่นมีนัยสำคัญทางสถิติในการกำหนดระดับการดื้อยาต้านจุลชีพ ไม่พบว่าการบริโภคยาต้านจุลชีพมีผลต่อการดื้อยาต้านจุลชีพ และพบว่าค่าใช้จ่ายด้านสุขภาพที่เป็นสัดส่วนของค่าใช้จ่ายของรัฐเป็นตัวแปรอธิบายเดียวที่เป็นตัวแปรคั่นกลางและส่งผลต่อการดื้อยาต้านจุลชีพผ่านความยากจน การศึกษานี้เป็นงานแรกที่พิจารณาความสัมพันธ์ระหว่างความยากจนและคอรัปชั่นกับการดื้อยาต้านจุลชีพ โดยใช้ข้อมูลแบบพาเนล ที่รวมประเทศนอกทวีปยุโรปด้วย ผลการศึกษาสนับสนุนสมมติฐานที่ว่าสภาวะธรรมาภิบาลอ่อนแอและความยากจนส่งผลต่อการดื้อยาต้านจุลชีพและสุขภาพของประชาชน

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Antimicrobial resistance is a major threat to global public health and is believed to cause over 700,000 deaths per year. Efforts to tackle this problem have tended to focus on reducing antibiotic consumption and promoting the appropriate use of medicines. This study examines the relative importance of other socio-economic factors, more specifically poverty (Gross National Income per capita) and corruption (measured by quality of governance), in determining antibiotic resistance compared to use of antibiotics. Using panel data of 48 countries in 2008-2017, a fixed-effects multivariate analysis was used. Sobel tests and mediation analyses were also carried out to determine the extent to which the effects of poverty and corruption on antimicrobial resistance were mediated through other explanatory variables in the model, including human antibiotic usage, healthcare expenditure, access to basic sanitation and the availability of medical personnel. Poverty and corruption were found to be significant factors in determining the level of resistance. No significant association was found between antibiotic consumption and resistance, and health expenditure as a proportion of government expenditure was found to be the only variable with a mediating effect (for poverty) in determining the level of antibiotic resistance. This is the first study to examine antimicrobial resistance and its association with poverty and corruption using panel data and including countries outside Europe. The findings support the hypothesis that poor governance and poverty contribute to levels of antibiotic resistance and population health.

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Lyvia Ann Sanders Guerrier De Dumast

TABLE OF CONTENTS

Page

Chapter 1: Introduction

Antimicrobial resistance (AMR) occurs when microorganisms (bacteria, fungi or viruses) are no longer killed by antimicrobial drugs (such as antibiotics, antivirals or antimalarials). Once these drugs become ineffective, any infection will persist in the body and the risk of it spreading to others is increased (World Health Organization, 2015). This global public health problem is already believed to cause over 700,000 deaths every year. In the U.S. alone there are more than 2.8 million infections from bacteria resistant to antibiotics and over 35,000 deaths per year. In Europe in 2015, EARS-Net data showed that over 670,000 people had infections with antibiotic-resistant bacteria, of which 63.5% occurred in hospitals or other healthcare settings (Cassini et al., 2019). These infections resulted in over 33,000 deaths with the burden highest among infants and older people (over 65 years old), suggesting that as the proportion of older people within a population increases, the burden of these antibiotic-resistant infections is also likely to increase. A study from the European Centre for Disease Prevention and Control (ECDC) found that the burden of antibacterial-resistant infections is similar to that of tuberculosis, influenza and HIV/AIDS and that bacteria resistant to "last-resort" antibiotics (such as colistin or carbapenems) caused 39% of this burden (Cassini, 2019).

As new resistance mechanisms continue to emerge, our ability to treat common infectious diseases such as tuberculosis is likely to be severely compromised, resulting in prolonged illness, disability and death. Common treatments that depend on the availability of effective antimicrobial drugs could also be seriously undermined: interventions such as organ transplantation, chemotherapy for cancer treatment or hip replacement surgery would no longer be able to be done safely. Bacterial infections

which are resistant to multiple antimicrobial drugs are already among the main factors influencing negative outcomes in patients undergoing these procedures (Prestinaci et al., 2015).

The World Health Organisation's (WHO) first global report on AMR published in 2014, drawing on resistance-data in 114 countries, noted that resistance levels to first-line antibacterial drugs have reached over fifty percent in at least half of the countries included in the study. The report went on to warn that "a post-antibiotic era—in which common infections and minor injuries can kill—far from being an apocalyptic fantasy, is instead a very real possibility for the 21st century" (WHO, 2014).

The report called for global, coordinated action on antimicrobial resistance, similar in scale to the actions being taken to combat climate change, and recommended that all countries set up basic systems to track and monitor the problem as well as do more to prevent infections occurring in the first place in order to reduce the need for antibiotics. However, these recommendations were actually relatively limited in scope, simply calling for policy makers to "strengthen resistance tracking and laboratory capacity" and "regulate and promote appropriate use of medicines" for example. Health workers and pharmacists were urged to "enhance infection prevention and control" and to "prescribe and dispense the right antibiotic(s) to treat the illness". Following the setting up of WHO monitoring network Global Antimicrobial Resistance Surveillance System (GLASS) in 2015, data on resistance rates is now gathered from 88 countries worldwide, 55 of which are low- or middle-income countries. Since the publication of the WHO report, AMR has become more prominent on the political agenda of national and international organisations although widespread public awareness of the scale of the problem is still limited.

Rates of antimicrobial resistance

Within the OECD, between 2005 and 2014 AMR prevalence increased by an average of 5% in 23 out of 26 countries. In Greece, the prevalence of resistance was approximately 45% in 2014 (OECD, 2016). Recorded prevalence of 3rd generation cephalosporin-resistant E. Coli and carbapenem-resistant Klebsiella pneumoniae infections increased between 3 and 4 times in OECD countries.

Within LMICs, AMR data is more difficult to obtain. Klein et al. (2019) recently developed a new tool for monitoring the effectiveness of antibiotic therapy (the Drug Resistance Index) which indicated that resistance rates are generally higher in low-income and middle-income countries (LMICs) and that the countries with the lowest relative effectiveness were mainly LMICs.

The economic impact of antimicrobial resistance

In 2014 the Review on Antimicrobial Resistance's first report estimated that AMR could cost as many as 10 million lives per year by 2050 if no effective solution is found to reduce current rates of increase (Review on Antimicrobial Resistance, 2014). This alarming forecast would result in a sizeable human cost, making deaths from AMR the leading cause of death, easily surpassing the current number of deaths from cancer (9.0 million) or ischaemic heart disease (9.4 million) (WHO Global Health Estimates, 2016).

Research by KPMG (2014) estimated the cost in terms of reduced global GDP through an increased level of mortality and a rise in morbidity. Focusing on three bacteria with resistance to specific antibiotics and three diseases affected by AMR (HIV/AIDS, TB and

malaria), the report looked at the economic impact on 156 countries under four different scenarios. The report suggests that the economic cost would potentially also be very significant with an estimated reduction of global GDP of between 1.6% and 3.4% depending on the resistance scenario

The financial impact of AMR on global healthcare lies in the increased length of stay in hospital and care required for patients. The report estimates that infections due to the three bacteria selected resulted in approximately four million extra hospital days in 2012 with a cost of approximately $2.2 billion (AMR Review, 2016).

Although the economic burden of AMR is difficult to calculate accurately, many studies point to LMICs being more heavily impacted than high-income countries. This is because within developing countries poor infection, prevention and control programs, poor hygiene conditions, lack of antimicrobial stewardship measures and lax surveillance intensify the threat from resistant bacteria by promoting their spread. Higher levels of endemic diseases such as tuberculosis or diarrheal diseases due to infection also mean that LMICs have a higher disease burden than high-income countries (HICs). Indeed, diarrhea kills approximately 1.8 million people every year, 90% of whom are under five years old living in low- and middle-income countries (Ahs, Tao et al., 2010).

The World Bank estimates that by 2030 over 24 million people could fall into extreme poverty because of antimicrobial resistance. Ahmed and Khan (2019) argue that AMR will have a disproportionate negative GDP impact on low-income countries, through its adverse effects on labour supplies, labour productivity, health care costs and livestock production and trade. For example, health care expenditures in 2050 are projected to be up to 25% higher than they would be without AMR for low-income countries,

compared to up to 6% higher for high-income countries. The larger disease burden experienced by low-income countries will require additional health expenditures which would represent a significant part of the household budget (Allegranzi et al., 2011). Given that lower-income countries typically do not have universal health coverage or financial protection, these additional expenditures will be made out of pocket and thus are more impoverishing and regressive than in the context of high- or middle-income countries. Resources which could have been used to reduce poverty in an LMIC will need to be used to manage a larger disease burden arising from AMR and to finance the higher costs of a larger health sector.

Mechanisms of the spread of antimicrobial resistance

Antibiotic resistance is able to develop throughout bacteria populations through two mechanisms: vertical transmission (when bacteria mutate and pass on their antibiotic resistance genes) or horizontal transfer (when genetic material is exchanged between nearby bacteria). It is believed that the horizontal transfer mechanism is responsible for increasing the prevalence of antibiotic-resistant infections throughout the world (Huddleston, 2014). Following this initial stage, resistant strains of bacteria are spread within the environment by vectors (either human or animal) and vehicles (food, water and soil) (Collignon et al, 2018). Once resistance has developed and spread throughout populations and the environment, it is extremely difficult to subsequently reduce it again. The amount of antibiotics and other pharmaceuticals present in the environment is determined by several factors including the size of the local population, access to healthcare, the size and type of pharmaceutical manufacturing in the area, as well as the sanitation infrastructure of the public system (Kookana, 2014).

The ability of bacteria to become resistant to antibiotics was first predicted by the microbiologist Alexander Fleming during his Nobel Prize acceptance speech in 1945 when he warned about the dangers of misusing penicillin: *"It is not difficult to make microbes resistant to penicillin in the laboratory by exposing them to concentrations not sufficient to kill them, and the same thing has occasionally happened in the body. The time may come when penicillin can be bought by anyone in the shops. Then there is the danger that the ignorant man may easily underdose himself and by exposing his microbes to non-lethal quantities of the drug make them resistant."* Studies earlier this century documented a positive correlation between antibiotic consumption and development of resistance, beginning with Goossens et al in 2005 who found that countries with high antibiotic consumption in southern and eastern Europe had higher rates of AMR than countries in northern Europe which had lower rates of consumption.

More recent evidence suggests that the two variables of consumption and resistance are no longer so closely correlated across countries (European Centre for Disease Prevention and Control 2014). Collignon et al. (2015) finds that, within Europe, "only 28% of the total variation in antibiotic resistance among countries is attributable to variation in antibiotic usage". In LMICs resistance rates are generally higher than in high-resource countries, even though usage rates per capita are actually lower (Klein et al, 2018), suggesting that factors other than usage may also have a significant impact on resistance. In this study, I explore what other factors may be involved. In particular, I examine the contribution of corruption and poverty as possible causes explaining the variations in resistance observed between countries.

Objectives

Primary objective:

- To investigate the impact of poverty and governance on antibiotic resistance globally.

Secondary objectives:

- To determine whether antibiotic usage is a significant driver of resistance levels.
- To determine the relative importance of poverty and governance as factors driving antibiotic resistance globally.
- To examine whether poverty and governance exert mediating effects on antibiotic resistance.

Hypotheses

There is a positive correlation between corruption and rates of AMR.

There is a positive correlation between poverty and rates of AMR.

There is a positive correlation between antibiotic usage and resistance levels.

Policy implications

Identifying which factors have the most influence on levels of resistance is key to controlling its spread within LMICs. In 2015, the WHO introduced its Global Action Plan on antimicrobial resistance, with recommendations that all countries implement antibiotic stewardship programs to promote the appropriate use of antibiotics and animals.

Although over 40 LMICs have already set up stewardship interventions, evidence for their effectiveness is limited (Cox et al., 2017). As well as having weaker systems of surveillance, LMICs also have fewer resources to fight AMR: the human and animal healthcare workforces are smaller and more homogenous than in high-resource countries and there is less strict regulation of antimicrobial drugs. Furthermore, policies tend to focus mainly on controlling the use and misuse of antimicrobials and less on factors involved in the spread of resistance.

Reducing contagion by implementing policies aimed at improving basic sanitation is key to controlling antimicrobial resistance. One of the United Nations Sustainable Development Goals adopted by all member states in 2015 aimed at providing universal access to adequate sanitation and hygiene. However, initial ambitions to achieve this target have weakened and progress has been slow. Without a renewed focus on improving governance and infrastructure, other efforts to reduce levels of resistance in LMICs are unlikely to be truly effective.

Chapter 2: Literature review

A literature review was conducted to construct a conceptual framework to establish the relationships between the drivers of antimicrobial resistance. Information about dependent and independent variables used the models for these articles (where appropriate) are set out in Table A.1 in the appendix at the end of this paper.

The general perception of antibiotic resistance was that it was closely linked to the amount of antibiotics consumed by people. As knowledge has developed about the mechanisms driving the transmission of antimicrobial resistance, it has become clear that there are many other factors (as well as consumption) behind the increase in rates of resistance. For this literature review, I begin with three papers which investigate these other factors and their role in the spread of AMR. Following this, I will discuss those papers which examine the two factors of particular interest in this study: corruption and poverty.

Holmes et al. (2019) distinguish between the emergence of AMR at the individual human level and its emergence and subsequent transmission at a societal level. They identify numerous complex and interlinking factors such as public health issues (e.g. rates of vaccination), differences in healthcare systems as well as effects arising from migration and tourism, population densities, water infrastructure and sanitation. They consider that human and animal antimicrobial misuse or overuse are the most significant potential contributing factors to AMR but believe that the strategy of limiting or suspending the use of antimicrobials will not be effective in reversing the development and spread of AMR. Knight et al. (2018) recognize the importance of the role of the misuse of antimicrobials in the prevalence of AMR, as well as exposure to resistant strains of

bacteria in the soil, wastewater and other environmental reservoirs. They emphasize the need for further analysis and quantification of the sources and transmission routes of AMR in order to establish the relative contribution of each driving factor in settings at a subnational, national and global level. This process should help to identify the most effective combinations of policies and interventions to combat AMR.

Vikesland et al. (2019) discuss how the dissemination of resistant bacteria globally is determined by highly interconnected socioeconomic risk factors. They believe that the development status of a country needs to be taken into consideration when developing strategies to address AMR. In the same way that consumption of antibiotic agents differs in LMICs relative to HICs, they state that various economic, social and economic factors within LMICs promote the spread of AMR primarily because of three conditions which occur more frequently in LMICs than in HICs: high population densities, poor sanitation infrastructure, and inadequate solid waste disposal.

Examining a single driver of AMR in more detail, Collignon (2015)'s paper was the first cross-national study of the determinants of antibiotic resistance, focusing on the quality of governance as the most important driver. His analysis, using a panel data set of 28 European countries from 1998 to 2010, suggested that control of corruption is an even more important determinant of antibiotic resistance than antibiotic usage in people. He uses three methods in his model: Pooled Ordinary Least Squares; the Fixed Effects technique and the system Generalized Method of Moments technique (as a robustness check) and finds that factors other than antibiotic usage are potentially very important in explaining variations in AMR in the 29 European countries studied. He reports that antibiotic usage explains only 28 percent of the total variation in antibiotic resistance.

The pair-wise correlation coefficient between resistance and corruption was -0.71 compared to 0.53 for resistance and usage, indicating that governance is more closely linked to resistance than is usage.

Rönnerstrand and Lapuente (2017) also restrict their analysis of the link between corruption and use of antibiotics to Europe but examine sub-national data from over 100 European regions. Their paper differs from Collignon in its use of two regional measures of corruption – prevalence of corruption in the health sector and prevalence of bribes in the society (data obtained from the European Quality of Government Index). They find that indicators of corruption are strongly and positively correlated with the use of antibiotics and recommend that policy-makers should pay increased attention to the role of governance and corruption when pursuing goals of reducing antibiotic consumption. Indicators of antibiotic resistance are not discussed at all in this analysis.

Collignon et al. (2018) extended their previous analysis of 2015 to 73 countries and examined AMR as an outcome of antibiotic consumption worldwide together with a wide range of other potential contributing factors, including infrastructure, climate and governance. They used three sources of data on AMR levels to create two global resistance indices. The IQVIA MIDAS database was used for antibiotic consumption data. A corruption index was derived from Transparency International data. Using a cross-section logistic regression model, they found a weak inverse relationship between antibiotic consumption and resistance (r=-11%) overall. This finding contrasts with previous studies by other authors, possibly as a result of the inclusion of non-European data in the analysis. Indeed, when the sample included only European countries, there was a strong positive relationship for consumption with resistance (r=62%) which, they suggested, was an indication of different contagion levels in HICs compared to LMICs.

Conversely, better governance and better infrastructure were significantly associated with lower levels of AMR. Even though this analysis was broader in scope than their 2015 study, it used cross-sectional data only and not panel data.

Research on AMR to date has predominately focused on wealthy OECD countries - where there is little variation in the underlying infrastructure to allow us to clearly identify the impact that differences in social, physical and economic environments may have on resistance levels. The dominant contributing factor in Collignon's paper was found to be contagion (the spread of resistant strains and resistant genes), implying that improving sanitation and access to clean water and affordable healthcare are a better approach to reducing AMR than reducing consumption in LMICs.

Three of the papers reviewed concern poverty as a driver of AMR. Planta (2007) examined the role of poverty-driven practices (such as sharing medication or using discounted, poor quality drugs bought online) in the United States as a contributing factor in the development of antimicrobial resistance. She states that efforts to combat AMR will no longer be effective if government authorities within the United States do not study and recognise the influence that socio-economic and behavioural factors have on antibiotic usage and resistance.

Alvarez-Uria et al. (2016) set out to evaluate the link between the income status of a country (in terms of GNI per capita) and the incidence of AMR in three common bacteria (E coli, MRSA and Klebsiella). As before, they used data from the ResistanceMap repository in 2013-14 and carried out a log linear regression, in order to predict the overall prevalence of AMR among 45 lower-middle, upper-middle- and high-income

countries. They found a significant negative relationship between GNI per capita and the prevalence of AMR and conclude by showing that the burden of AMR for LMICs will be greater than that for richer countries because of three factors:

- Infections caused by resistant organisms are associated with higher mortality and health costs.
- Antimicrobials that are effective against resistant bacteria are more expensive and out of reach financially for many of those living in lower income countries
- Increasing the use of effective medicines against superbugs will lead to higher resistance to “last-resort” antibiotics.

The third study on the association between poverty and AMR is a systematic review by Alividza et al. (2018) of 19 papers. They categorize these 19 papers by the following dimensions of poverty a) housing and living conditions, b) income and income inequality, c) education level and d) water and sanitation. Only seven of the articles examined the association between poverty and AMR in LMICs, suggesting a need for further study in this area. None of the articles in this study investigated the association between poverty and AMR on a cross-national basis.

Klein et al. (2019) calculated a Drug Resistance Index (DRI) as a tool which combines use of and resistance to antibiotics into a single measure of the effectiveness of antibiotic therapy. They found a high level of variation in resistance rates across countries with high-income countries generally having lower rates than low- and middle-income countries, reflecting the lower burden of disease in HICs as well as a higher rate of antibiotic effectiveness due to better access to newer, more effective antibiotics. The nine countries with the highest DRIs (and hence the lowest relative effectiveness of

treatment with antibiotics) were all LMICs. The four worst countries out of the 41 countries examined (Venezuela, Ecuador, Thailand and India) actually had relatively low antibiotic use rates compared to many HICs. Not all HICs had low DRIs: Greece, Spain, Italy and Ireland had high values for the DRI, reflecting their relatively higher rates of use and resistance.

Of all the papers reviewed, only four presented a regression model in their analysis of the relationship between AMR and the factors that are believed to drive it (see Appendix Table A.1 for more details). Three papers used cross-sectional data and one (Collignon, 2015) used panel data. The reason for this is primarily due to a previous lack of cross-national data regarding antibiotic usage and resistance rates.

The relatively few studies available which investigate the drivers of AMR from a socio-economic perspective highlight the need for more research in this area. This study builds on Collignon's 2015 paper investigating the link between AMR and corruption but uses a more recent time-series data and has a wider geographical scope. The main contribution of this research is therefore including countries outside Europe in the analysis and by considering poverty as additional driver of AMR.

By underlining the significant contribution of corruption and poverty as determinants of resistance, this study seeks to show that it is important that governments in LMICs address the problem of contagion, as well as the amount of antibiotics consumed in humans and animals, if they are to be successful in combating this major international problem.

Drivers of increasing rates antimicrobial resistance

Based on the preceding literature review, the main factors driving increasing rates of AMR are as follows:

Consumption of antibiotics

Consumption of antibiotics in human medicine increased by nearly 65% from 2000 to 2015, from 21.1 to 34.8 billion DDDs. Data from the IQVIA MIDAS database indicates that high income countries (HICs) had the highest rates of antibiotic consumption but the global increase was primarily driven by increased consumption in low- and middle-income countries, with four of the six countries with the highest antibiotic consumption rates in 2015 being LMICs (Turkey, Tunisia, Algeria, and Romania) (Klein et al., 2018). Increasing use of antibiotics in human medicine has been accompanied by increasing use in other sectors: more than half of all commercially manufactured antibiotics are used as growth promotors or for prophylactic use in animals for food, in aquaculture or in household pets; for pest control or cloning for plants and agriculture or used as antiseptics in personal or household cleaning products. Over 130,000 tonnes of antibiotics were used by the food animal industry in 2013 and consumption levels are expected to keep on rising in order to keep up with the world's growing demand for meat (Van Boeckel et al., 2017).

Increasing consumption of antibiotics also implies increasing production of antibiotics. The global antibiotics market was valued at just over U.S.$45 billion in 2018 (Grand View Research, 2019) and is expected to grow approximately 4% a year to 2026. A large share of the world's supply of antibiotics is manufactured in Chinese and Indian factories: dirty production processes and improper discharge disposal of waste into the

environment are leading to high levels of drug-resistant bacteria in water treatment plants in the vicinity of these plants (European Public Health Alliance, 2019).

Corruption

A country which has a poor quality of governance and in which public sector corruption is widespread is likely to be less effective in monitoring usage of antibiotics (in animals and in people) and in enforcing laws governing medicine, the agriculture industry and the water infrastructure. Corruption in water and sanitation systems in low-income countries is driven by the complexity and the informality of a sector in which incentives for corruption are high and laws intended to protect water sources from encroachment and pollution are frequently not enforced (Jenkins, 2017). Estimates by the World Bank in 2006 suggest that between twenty and forty percent of public finances intended for the water sector are being lost to dishonest practices (Odiwuor, 2013).

Healthcare is a particularly high-risk sector for corruption because of the complexity of health systems themselves which, when combined with information asymmetry and high levels of public spending, provide many opportunities for personal enrichment. It is estimated that between 10% and 25% of global public healthcare spending is lost through corruption every year, the equivalent of $700 billion to $1.75 trillion (Jain et al, 2014). Transparency International categorises healthcare corruption into eight areas: health system governance and regulation, research and development, marketing, procurement, product distribution and storage, financial and workforce management and delivery of healthcare services. Corruption within healthcare at the service delivery level takes many forms and is usually small in scale. However, the high frequency of corruption at this level cumulatively causes much damage, significantly undermining efforts to improve and expand the affordability, accessibility and quality of healthcare.

Poverty

Approximately 84% of the world's population live in LMICs (defined as those with a GNI per capita, calculated using the World Bank Atlas method, of less than $12,376). With increasing rates of urbanisation as people move from rural areas to cities, housing densities also increase as do the chances of catching an infectious disease as a result of overcrowding or poor sanitation. According to the United Nations Population Division, in 2018 almost 30% of the world's urban population lived in slums, that is over 1.2 billion people.

Poverty may lead individuals in LMICs to undertake shorter treatments, share medication or use lower quality (or even counterfeit) medicine (Okeke, 1995). Furthermore, underlying malnutrition or immunodeficiency combined with a greater exposure to infectious diseases may lead to a greater need for antimicrobial treatment (Okeke, 1995).

Poverty is also linked to poor educational status and low awareness about the appropriate use of antibiotics. An example of inappropriate use of antibiotics is the practice of buying a mixture of pills called 'Yaa Chut' in Thailand: a random selection of antibiotics, steroids, anti-inflammatory drugs and antimalarials frequently purchased over-the-counter for self-medication when people feel unwell (Newton et al., 2008).

Poverty and corruption may also have an indirect impact on AMR through the following pathways:

Inadequate public health care resources or spending

The theft of national or donated funds from health systems is a serious problem for many countries, reducing a country's ability to provide healthcare to its people.

Health expenditure as a share of GDP in LMICs is usually lower than that in developed countries. Thirty-two of the 36 OECD member states allocated more than 6 percent of their GDP to health expenditure in 2015-17 (OECD, 2020). The average share for all OECD member countries was over 12%, compared with an average of 3.8% for lower middle-income countries (World Bank). Domestic general government health expenditure in 2015-17 was over $4,400 per capita on average for high income countries compared to just $23 for low income countries. Lower-middle income countries spent $82 per capita on average.

Effective antibiotics to combat resistant strains of bacteria are extremely expensive and unaffordable for many LMICs. Hospitals often have limited access to clinical microbiology laboratories, so physicians are unlikely to have enough information to prescribe the appropriate antibiotic to treat a patient's disease or to decide that antibiotics are unnecessary. This scarcity of diagnostic tools is so acute in resource-poor settings it has been called the 'Achilles Heel' of antibiotic resistance containment (Okeke, 2011).

Widespread vaccination can help reduce AMR by preventing bacterial and viral infections, thereby reducing the use or misuse of antibiotics and by preventing resistant strains from occurring and spreading (Buchy et al., 2020). Low government spending on healthcare may result in lower rates of vaccination coverage. In 2017, approximately

77% of 1-year old children in low-income countries received vaccinations for diphtheria, pertussis and tetanus, compared with over 95% in high-income countries.

Access to healthcare made more difficult or expensive

In poorer countries without universal access to primary healthcare services, appropriate medical care is less affordable or more difficult to obtain, encouraging people to self-medicate or seek treatment from less well-regulated providers (Okeke et al., 2010). The majority of people will finance much of their healthcare out-of-pocket: Alsan et al. (2016) found that 76% of health expenditures were out-of-pocket in their sample of 47 LMICs.

Poor sanitation

Corruption in this sector negatively affects health outcomes of the population, food security and the ability of people to work by increasing the cost of drinking water, by disrupting irrigation or by polluting water sources (Transparency International, 2017). The same study estimates that approximately 80% of health problems in low-income countries are related to inadequate water and sanitation. Access to properly functioning water and sanitation services is important in the prevention of serious infectious diseases. Dirty water and inadequate sanitation are responsible for over 800,000 deaths annually worldwide (WHO, 2014) with contaminated water transmitting diseases such as diarrhoea, cholera, typhoid, polio and dysentery. Untreated wastewater is the perfect environment for bacteria to develop resistance to antibiotics (Di Cesare, 2016). Given that 26% of the world's population do not have access to even basic sanitation and only 45% are able to use "safely managed" sanitation, many of the waterways in LMICs in both urban and rural areas are likely to be vectors of AMR.

The three previous factors are themselves highly influenced by the level of corruption and poverty prevailing in a country. Corruption and poverty therefore may not only have a direct impact on AMR but may also have mediating effects. This study investigates the extent to which AMR is affected by direct and indirect effects by including mediation analysis in the study design.

Other factors

Other factors which may be drivers of AMR include climate, international travel, the level of public awareness related to appropriate antibiotic use or the size of the agricultural sector.

Chapter 3: Conceptual Framework

Any analysis of the drivers of AMR is difficult because of the complex relationships between antibiotic consumption, different systems of health care, public health factors, socioeconomic factors, environmental factors, sanitation, population densities and migration on a macro level together with more micro level factors concerning the pathogens themselves and their different mechanisms of emergence and transmission (Harbarth, 2005).

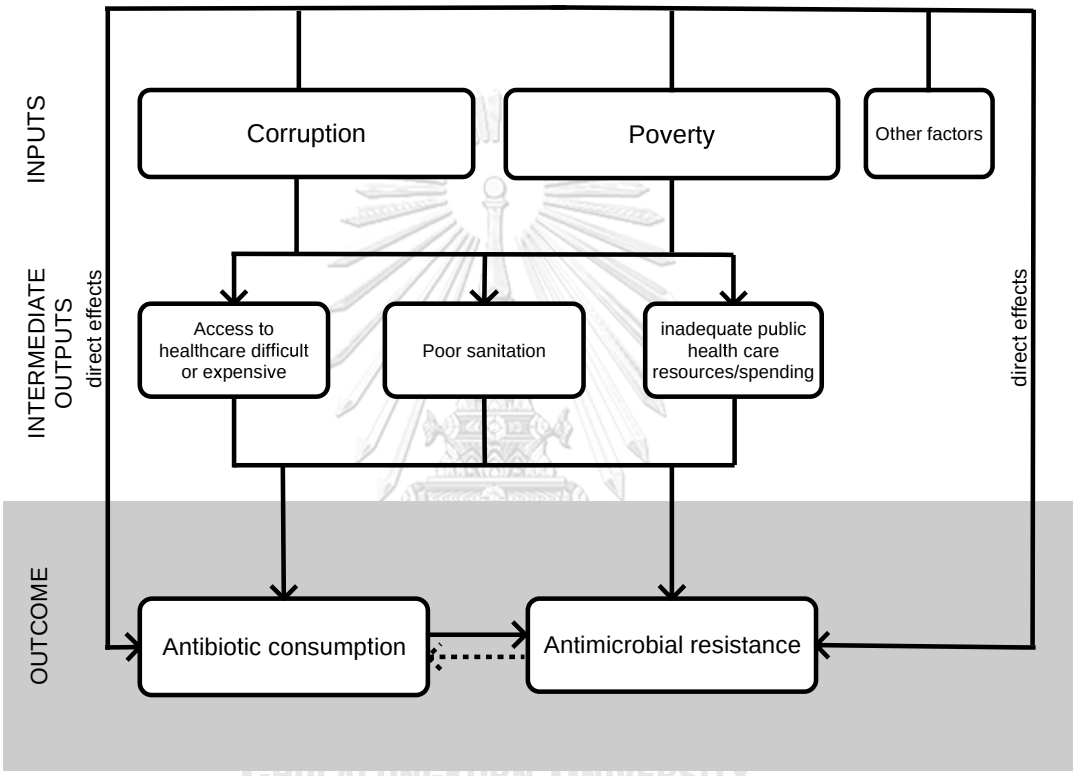
The preceding examination of existing literature revealed that there are six primary drivers of antimicrobial resistance: antibiotic consumption, corruption and poverty together with three socio-economic mediating factors which themselves are affected by corruption and poverty, namely poor sanitation, inadequate public healthcare resources and greater difficulty or cost accessing healthcare.

Figure 1 shows the conceptual framework for this study. The main variables, corruption and poverty, are shown in the top line as inputs. They are assumed to have both a direct effect on antibiotic consumption and resistance, as well as a mediating effect. There are also other social, environmental and economic factors which may contribute to AMR including climate (particularly higher temperatures), population density, urbanisation, global travel or environmental contamination (MacFadden et al, 2018).

Some or all of the impact of these inputs on AMR may be mediated through intermediate outputs which themselves influence the spread of disease at the population level. For the purposes of this study, these intermediate outputs have been identified as poor sanitation, inadequate public healthcare resources or spending and the extent to which

healthcare is difficult to access or expensive. Antibiotic consumption has been modelled as an outcome as well as an input.

Figure 1: Conceptual framework



Chapter 4: Methodology

Having identified the main socioeconomic factors believed to affect AMR, regression analysis was used to determine their significance. The first part of the analysis was conducted using panel data between 2008 and 2017 with a fixed-effects regression model. Data for all variables other than antibiotic consumption and resistance were obtained from online sources, either the World Bank databank or the World Health Organization databank. Resistance and consumption data were obtained from the ResistanceMap database, a repository of national and subnational data set up by the Center for Disease Dynamics, Economics and Policy (CDDEP) in 2010 to enable comparisons in rates of use and resistance between countries.

The second part of the analysis was conducted with annual cross-sectional data over a ten-year period (from 2008 to 2017) using the Ordinary Least Squares estimation method. The sources were identical as for the panel data analysis. The intention here was to use a cross-sectional analysis as a robustness check of the panel data results obtained in this paper as well as with previous research into this subject.

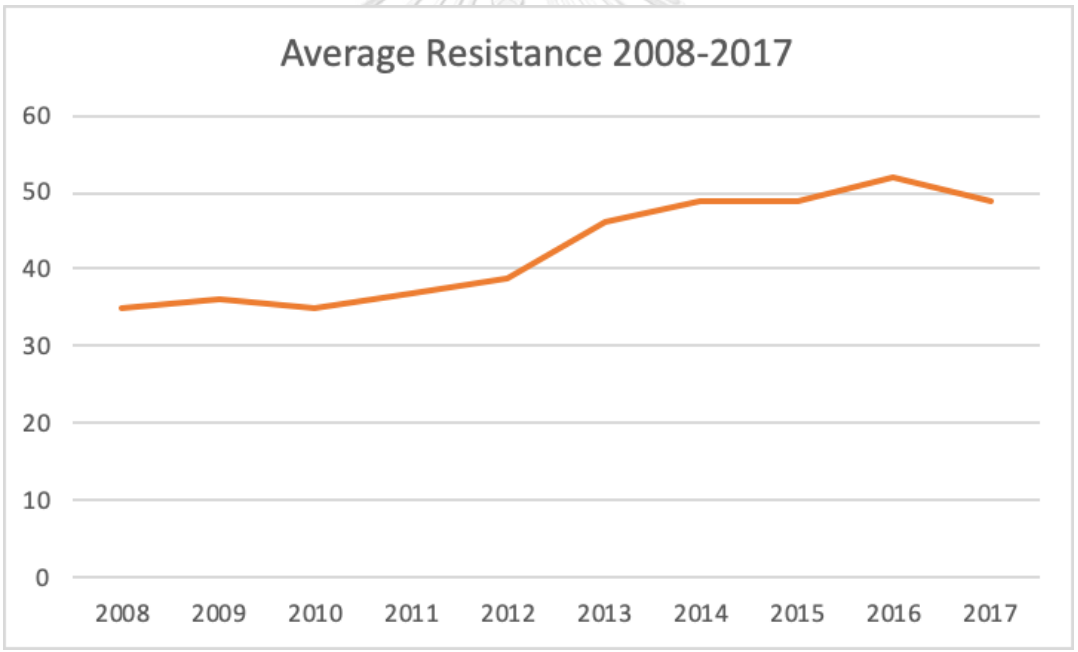
Main Model

For the panel data analysis, the following fixed-effects regression model was used to explain antimicrobial resistance:

$$\mathrm{AMR}_{it} = \beta_0 + \beta_1 \mathrm{CORR}_{it} + \beta_2 \mathrm{GNICAT}_{it} + \beta_3 \mathrm{USE}_{it} + \beta_4 \mathrm{HEGOVEX}_{it} + \beta_5 \mathrm{BASS}_{it} + \beta_6 \mathrm{PHYS}_{it} + \beta_7 \,\mathrm{trend} + \beta_8 \,\mathrm{trend}^2 + \mu_i + \varepsilon_{it}$$

where AMR, the dependent variable, is the rate of resistance to antibiotics, i is the subscript denoting country and t denoting year. Explanatory variables which may have an impact on antibiotic resistance and contagion include corruption, antibiotic usage, GDP per capita and healthcare expenditure. As can be seen from Figure 2 below, the level of average annual AMR for 2008 to 2017 appears to increase slowly over the period, suggesting that linear trend and quadratic terms should also be included in the model.

Figure 2: average rate of resistance to antibiotics



The term μ_i represents country fixed effects and captures time-invariant heterogeneity across countries that may impact AMR. The term ε_{it} is the idiosyncratic error term.

The explanatory variables, with the expected sign of the regression coefficient, are set out in Table 1:

Table1: model variables

Variable	Sign	Unit	Description	Source	Expectation
AMR		%	Average rate of resistance to antibiotics.	ResistanceMap	
CORR	+		Control of corruption index. Values range from 0 (good control of corruption) to 100 (poor control of corruption).	World Bank governance indicators	Better governance is associated with lower levels of resistance (Collignon, 2015)
GNICAT (poverty=1)	+		Variable is binary and indicates whether a country is poor or not. Based on gross national income per capita (constant 2010 US$).	World Health Organization Global Health Expenditure database	A higher income per capita is likely to result in a healthier population and better healthcare (Preston, 1975).
USE	+	Defined daily doses (DDD) per 1,000 people	Annual consumption of antibiotics in humans	ResistanceMap/IQVIA	Increased use of antibiotics leads to higher rates of resistance (Goossens, 2005)

HEGOVEX	-	%	Domestic general government expenditure on health as a percentage of general government expenditure.	World Health Organization	Low health expenditure is associated with higher levels of AMR (Collignon, 2018)
BASS	-	%	% of population using at least basic sanitation services.	WHO/UNICEF	The spread of resistance to antibiotics spreads proportionally to the lack of sanitation (Andremont, Walsh 2015, 2015).
PHYS	-		Number of physicians per 1,000 people.	World Health Organization	Health professionals are key to preventing and controlling the spread of AMR (WHO, 2016)

Robustness Check

A majority of the previous papers which examine the association of socioeconomic factors and AMR used cross-sectional models only. In order to check the findings from this paper with findings carried out by other researchers, a cross-sectional analysis using the OLS model below was used to investigate the association between AMR and its drivers with annual data from 2008 to 2017:

$$\mathrm{AMR_i} = \beta_0 + \beta_1 \mathrm{CORR_i} + \beta_2 \mathrm{GNICAT_i} + \beta_3 \mathrm{USE_i} + \beta_4 \mathrm{HEGOVEX_i} + \beta_5 \mathrm{BASS_i} + \beta_6 \mathrm{PHYS_i} + \varepsilon_i$$

This will also allow results from the cross-sectional analysis to be compared with results from the panel data analysis in this study to determine whether or not they are consistent.

Data Sources and Variable Definitions

Resistance (AMR) and consumption (USE) data were sourced from ResistanceMap. ResistanceMap was developed in 2010 by the CDDEP (The Center for Disease Dynamics Economics & Policy) with national resistance data for the USA, Canada and over 30 countries in Europe and it has gradually expanded its coverage to 81 countries currently. Comprehensive global time-series data for consumption and resistance are not available from any other source.

In total, ResistanceMap provides time-series data for both consumption and resistance for 57 countries, resistance only for 11 countries and consumption only for 13 countries. Resistance data gives resistance rates for eleven different pathogens and twenty-one

different antibiotic classes for isolates from hospital patients of all ages. The time period covered depends on the country. I chose to focus on seven major categories of antibiotics: aminoglycosides, aminopenicillins, cephalosporins (3rd gen), fluoroquinolones, amoxicillin-clavulanate, piperacillin-tazobactam and polymyxins and calculated average aggregate resistance rates for combinations of Escherichia coli and Klebsiella pneumoniae, where available, for 2008 to 2017. This is similar to the methods employed by Collignon et al. (2015) and Alvarez-Uria et al. (2016) who each calculated an average resistance rate from a reduced number of pathogen/antibiotic pairs.

For antibiotic consumption, data is available for eighteen different classes of antibiotics. CORR and GNICAT are the explanatory variables of interest as determinants of AMR. CORR indicates the level of corruption or the level of "abuse of entrusted power for private gain" (Transparency International, www.transparency.org/) which is perceived to be prevalent within a country. Values range from 0 to 100, with a high score indicating a high degree of public sector corruption and a low score indicating very little corruption. GNICAT is derived from country-level data for Gross National Income per person (measured in international dollars at purchasing power parity (PPP) rates). GNI is defined as gross domestic product, plus net receipts from abroad of compensation of employees, property income and net taxes less subsidies on production: it is considered to be representative of the real income gap between richer and poorer countries (Anand and Bärnighausen, 2004). Countries with a GNI per capita in excess of $6650 (in international dollar PPP terms) were assigned a value of 0 for GNICAT whereas countries with a GNI per capita below $6650 were assigned a value of 1 for GNICAT. The cut-off point of $6650 corresponded to approximately the lowest quartile of countries in the dataset in terms of GNI per capita. This variable served as a dummy variable for poverty.

Other variables included in the regression model were chosen as indicators which reflected the healthcare resources available within a country or the basic infrastructure with a potential impact on public health of a population. The sanitation variable (BASS) is sourced from the WHO/UNICEF Joint Monitoring Programme for Water Supply, Sanitation and Hygiene and represents the percentage of a country's population using at least basic sanitation services i.e. improved sanitation facilities that are not shared with other households. HEGOVEX represents public expenditure on health as a share of total public expenditure and was sourced from the WHO Global Health Expenditure database. It is an indicator of the priority of the government to spend on health from its own domestic public resources.

The data for the number of physicians (per 1,000 people) (PHYS) was sourced from the World Health Organization's Global Health Workforce Statistics and includes all generalist and specialist medical practitioners. The WHO estimates that at least 2.5 medical staff (physicians, nurses and midwives) per 1,000 are required in order to provide sufficient primary care coverage (WHO, 2006).

This specification is similar to that used by Collignon et al. in their 2015 paper examining the association of corruption and antimicrobial resistance in Europe from 1998 to 2010, in that the dependent variable is antibiotic resistance and the main independent variable is corruption. However, their paper includes only one measure related to health (private health expenditure as a percentage of total GDP) whereas my specification examines total government healthcare spending and an additional indicator included to represent the ability of people to access healthcare (the number of physicians). Collignon's paper also does not include any variables related to infrastructure which could be relevant in

terms of the spread of resistant bacteria, specifically access to basic sanitation. They do not examine poverty as a driver of AMR, other than including data for GDP per capita.

The model used in this paper is an improvement on Collignon et al. (2015) in that it includes more socio-economic factors believed to be associated with AMR.

Chapter 5: Results

The results of the panel data analysis and of the cross-sectional analyses are set out separately below. Descriptive statistics are given in Table 2 and Table 3 for the panel data and in Table 7 by year for the cross-sectional data. Similarly, mediation effect test results are also given separately (in Table 6 and Table A.4 respectively).

5.1 Results of panel data analyses

Descriptive Statistics

Data were analysed using Stata version 16.1 (IC). Summary statistics for the panel data are displayed below.

Table 2: descriptive statistics for panel data

Variables	Observations	Mean (SD)
Resistance	427	32.70677 (17.9337)
Corruption	1,150	47.25776 (28.8636)
Poverty (=1)	1,150	0.25130 (0.4340)
Antibiotic consumption	593	7935.838 (3511.5340)
Health Expenditure	1,138	11.09695 (4.8373)
Sanitation	1,125	81.96643 (24.0690)
No of physicians	1,140	2.06238 (1.3795)

Note: standard deviations are reported in parentheses

Table 3 Correlation matrix for panel data

	Resistance	Corruption	Poverty	Antibiotic Use	Health Expenditure	Sanitation	No of physicians
Resistance	1						
Corruption	0.878* (0.0000)	1					
Poverty	0.4938* (0.0000)	0.545* (0.0000)	1				
Antibiotic Use	0.1097* (0.0311)	-0.1774* (0.0000)	-0.1321* (0.0013)	1			
Health Expend-iture	-0.6731* (0.0000)	-0.5181* (0.0000)	-0.437* (0.0000)	0.1684* (0.0000)	1		
Sanitation	-0.6124* (0.0000)	-0.5497* (0.0000)	-0.7789* (0.0000)	0.2874* (0.0000)	0.4581* (0.0000)	1	
No of Physicians	-0.3752* (0.0000)	-0.5291* (0.0000)	-0.6181* (0.0000)	0.2255* (0.0000)	0.3558* (0.0000)	0.6941* (0.0000)	1

Note: figures in parentheses are *p* values

A Pearson's correlation was carried out and the results have been set out in Table 3 above. The Pearson correlation coefficient, *r*, is displayed in the top row of each cell in the table. Its value ranges from -1 for a perfect negative linear relationship to +1 for a perfect positive linear relationship. A correlation of 0 indicates that there is no linear association between two variables. The level of statistical significance, *p*, is shown in the bottom row of each cell. An asterisk (*) next to the Pearson's correlation coefficient

indicates that the relationship between the two variables is statistically significant at the 5% level. Using Cohen's (1988) suggested guidelines for interpreting the magnitude of correlation coefficients, r values can be classified into three groups: an absolute value of r of 0.1 represents a small association; an absolute value of 0.3 is classified as moderate and of 0.5 as a strong effect. According to these guidelines, the association between antibiotic use and the other variables in the model is weak on average. Antibiotic use was most strongly associated with the variable for access to sanitation at 0.2874, indicating that access to basic sanitation explained less than 9% of antibiotic use. Antibiotic use showed a weak negative association with corruption (r = -0.1774) and poverty (r = -0.1321). The association between antibiotic use and resistance is examined in more detail below. Resistance is strongly correlated with corruption and poverty (positive correlation) and strongly correlated with factors related to health and spending on health (negative correlation). Corruption and poverty also showed a strong negative correlation with factors related to health and spending on health.

Each of the independent variables has a correlation with each other of less than 0.7, indicating that multicollinearity in the model is unlikely to be severe.

Investigating the importance of antibiotic consumption

The conceptual framework suggests that consumption of antibiotics and AMR may be joint outcomes i.e. that corruption and poverty may determine the quantity of antibiotics consumed in a country as well as the level of antibiotic resistance prevalent in that country. It is therefore important to consider how antibiotic consumption affects AMR in order to correctly design the empirical strategy.

If antimicrobial use affects AMR:

- Antibiotic use could be treated as a dependent variable together with AMR in a joint estimation framework; or
- Antibiotic use could be treated as an endogenous explanatory variable in the AMR regression which would require an instrumental-variable approach.

If antimicrobial use does not affect AMR:

- Antibiotic use may be left out of the empirical specification altogether.

A preliminary analysis was carried out to assess the relationship between antibiotic use and resistance. Using the panel data, there is a very low positive correlation between resistance and use, r (292) = 0.1097, p-value = 0.0311. The coefficient of determination, r^2, is equal to 0.00096721 indicating that use of antibiotics explains less than 1% of the variation in resistance.

Bell et al. (2014) assessed the relationship between the level of AMR in the community and the consumption of antibiotics in the community, examining 243 studies for which a statistical analysis of the connection between consumption and resistance had been carried out. These studies had mainly been conducted in either Europe or the U.S. They found a positive association between antibiotic consumption and the subsequent development of bacterial resistance at both the individual and community level in two-thirds of the studies examined. For the remaining one-third of studies examined, no association between use and resistance was found. As an example of a study where no association was found, Bartoloni et al. (2004) examined AMR in a remote rural community in Bolivia whose use of antimicrobials had been extremely low and found that 67% of subjects were carriers of E.Coli with acquired resistance to one or more antimicrobials. They conclude that the spread of AMR can occur regardless of the

selective pressure generated by the use of antibiotics and that other mechanisms (such as contagion) may be the cause of the high prevalence of resistance observed.

Table 4: Fixed effects estimates of resistance on use

Variable	Coefficient	Coefficient
Use	-0.0005618	-0.000686
	(0.0007103)	(0.0006573)
Corruption		0.1761649*
		(0.1026)
Poverty		13.65067***
		(4.7851)
Health Exp		-0.6396647*
		(0.3718)
Sanitation		0.0761818
		(0.3645)
no of physicians		-1.802605*
		(1.0408)
trend	1.33848***	1.115186**
	(0.45732)	(0.4391)
trend2	-7.486732**	-4.569733
	(3.15014)	(3.2428)
Constant	32.51956***	34.99214
	(7.19741)	(34.9966)
no of observations	386	384
F test for fixed effects	4.10**	10.78***

Note: Robust standard errors in parentheses.

Significance levels: * p < 0.1; ** p < 0.05; *** p < 0.01.

A regression analysis was carried out to examine the association between antibiotic use and AMR. In the first column, use was the sole explanatory variable. In the right hand column, use as well as other explanatory variables was included in the regression model. The results (Table 4) suggest that there is no significant association between antibiotic use and resistance for the data used in this analysis.

Reverse causality

The possibility that antibiotic resistance influenced antibiotic consumption was also considered. Recent research by Pouwels et al (2019) argued that reverse causality (healthcare workers providing antibiotics in response to local resistance rates) was a more important factor in determining antibiotic consumption than forward causality (the biological selection for resistance). In the absence of a suitable instrumental variable for antibiotic consumption, it was not possible to use Stata to control for endogeneity. A regression of consumption on resistance alone using the panel data returned a p-value of 0.35 and a coefficient of determination (R^2) of 0.0120, indicating that AMR is not a good predictor for use of antibiotics. I was unable to find any evidence of reverse causality or indeed of any significant association between antibiotic resistance and consumption. This finding may be a consequence of the fact that the data for antibiotic consumption may not accurately reflect the actual quantity of antibiotics consumed by humans in a country. Furthermore, significant quantities of antibiotics are consumed in animal agriculture (approximately three times the quantities used in human health) and accurate data for non-human use are not available at all. An alternative explanation for this finding could be that antibiotic use can be a positive or a negative predictor of

resistance (Bell et al, 2014) so that the two opposing forces effectively cancel each other out.

Data for the correlation between antibiotic consumption and AMR by year from 2008 to 2017 is set out in the appendix (Table A.2). The relationship seems to change over time from being negative or very close to zero at the beginning of the time period to a stronger positive correlation from 2013 to the end of the period. The correlation coefficients are not significantly different from zero for any year. At most, antibiotic consumption explains only 3.7% of antibiotic resistance.

Further analysis of the data for antibiotic use and the other socioeconomic variables of interest in the main model was carried out. A regression of antibiotic consumption on poverty, corruption, sanitation, number of physicians and health expenditure showed a very low coefficient of determination (R^2 = 0.0736) with sanitation being the only significant explanatory variable (*p*-value = 0.016). When AMR was included as an explanatory variable, the coefficient of variation was even lower (R^2 = 0.0030), with sanitation and number of physicians being significant variables (at *p*-values of 0.042 and 0.000 respectively). This result implies that antibiotic use is itself not determined by other variables which are included in the full regression model for resistance.

Overall, analysis of data for resistance and consumption shows that use is not significant regardless of how the regression is specified. Consequently, antibiotic consumption can be included in the full regression model for AMR without creating a problem of endogeneity.

Main Results: Association of antibiotic resistance with poverty and corruption

The results for the multivariate analysis are presented in Table 5. Results for the full model are shown in the column furthest to the right. Coefficients for all six of the explanatory variables are given, together with their robust standard errors in parentheses. Levels of significance are indicated by asterisks: if a *p*-value is less than 0.10, it is flagged with one star (*). If a *p*-value is less than 0.05, it is flagged with two stars (**). A *p*-value of less than 0.01 is flagged with three stars (***). Two other models are also shown: Model A is a partial model and represents the regression of AMR on corruption and the trend variables only. Model B represents the regression of AMR on poverty and the trend variables only. The use of partial models allows the effect of corruption and poverty on AMR to be seen more clearly. When other variables are added (as in the full model) the coefficients for corruption and poverty decrease by -9.69% and -2.64% respectively.

Model A: All variables in this partial model are significant. The Breusch and Pagan Lagrangian multiplier test for random effects was used to determine whether panel data techniques are necessary. The result indicates that the use of panel data is appropriate. A Hausman test was carried out to test if a random effects or fixed effects model is more appropriate. The result indicates that use of a fixed effects model is preferred. Finally, the F-test for fixed effects was used to determine the significance of the fixed effects in the model. The result indicates that the fixed effects are non-zero.

Model B: All variables in this partial model are significant. The same tests as for Model A above were carried out. The results were also similar indicating that use of a panel data fixed effects model was preferred.

Full model: Using a quadratic trend model, there is a positive relationship between antibiotic resistance and poverty and corruption which is significant at the 10% level and at the 1% level respectively. Other factors which also showed a significant (negative) association with AMR were health expenditure (p-value = 0.091) and the number of physicians per 1,000 people (p-value = 0.089). Antibiotic consumption did not show a significant association with antibiotic resistance (p-value = 0.301). Access to basic sanitation was also not found to be a significant factor in determining AMR. The linear trend variable was significant (p-value = 0.014) whereas the quadratic time trend was not. As for the partial models, other tests indicated that the use of a panel data fixed effects model was preferred.

The coefficient for corruption is 0.1761649, which indicates that for a one unit increase in the level of corruption (while holding other variables in the model constant), the rate of antibiotic resistance will increase by 0.1762%. Similarly, for a one unit of increase in the level of health expenditure, basic sanitation and the number of physicians, the level of AMR will change by -0.6396%, +0.0762% and -1.8026% respectively. AMR in poor countries will be on average 13.65% higher than for countries which are not in the poor category.

Table 5: Panel data - main results

Variables	Partial model A (with corruption only)	Partial model B (with poverty only)	Full model
Corruption	0.1950767* (0.1093155)		0.1761649* (0.1026)
Poverty[1]		14.02021*** (0.5405719)	13.65067*** (4.7851)
Antibiotic consumption			-0.000686 (0.000657)
Health expenditure			-0.6396647* (0.3718)
Basic sanitation			0.0761818 (0.3645)
No of physicians			-1.802605* (1.0408)
Trend	1.242525** (0.4716)	1.270165** (0.4923602)	1.115186** (0.4391)
Trend2	-6.617914** (3.2899)	-6.491956* (3.453571)	-4.569733 (3.2428)
Constant	22.89192*** (3.2415)	27.10459*** (1.513898)	34.99214 (34.9966)
No of observations	427	427	384

Breusch and Pagan Lagrangian multiplier test	471.25***	858.31***	259.67***
Hausman test	30.70***	23.47***	28.64***
F-test for fixed effects	5.63***	8.71***	10.78***

[1] Countries where GNICAT=1 were India, Pakistan, Kenya, Vietnam, Zambia, Bangladesh and the Philippines.

Note: Robust standard errors in parentheses.
Significance levels: * p < 0.1; ** p < 0.05; *** p < 0.01.

Mediation effects of poverty and corruption

As can be seen from Table 5, the size of the estimated coefficients for poverty and corruption decrease in size between the individual partial models A and B, on the one hand, and the full model which includes all the other explanatory variables, on the other. This is possibly evidence that some of the effect of poverty and corruption on antibiotic resistance works through mediating variables such as sanitation or health expenditure.

Sobel tests were carried out in order to ascertain whether these mediating variables significantly carry the influence of the independent variables of interest (corruption and poverty) to the dependent variable. The Sobel test is similar to a t-test and provides a method of examining whether the reduction in the effect of the independent variable, after the inclusion of the mediator in the model, is a significant reduction and hence whether the mediation effect is statistically significant (Sobel, 1982).

The Sobel (1982) test statistic is $t = (a * b)/SE$, where a is the estimated coefficient for poverty or corruption on a mediating variable and b is the coefficient for the mediating variable in the regression model for antimicrobial resistance. SE is the standard error defined as $\sqrt{(aSEb)^2 + (bSEa)^2}$. The resulting statistic can be compared to the normal distribution to determine its significance, with rejection rule of, for example, t < -1.67 or t > +1.67 at the 90% confidence level.

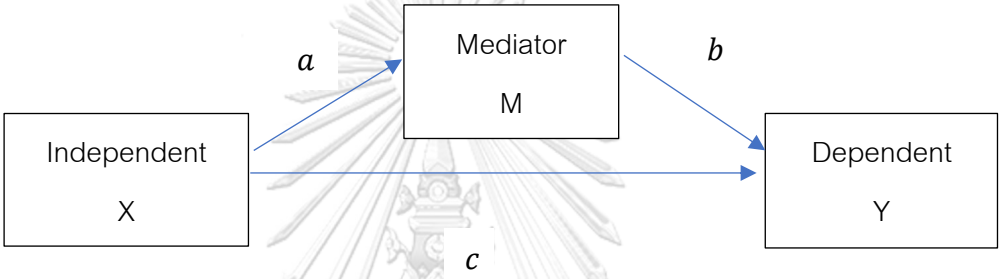


Figure 3: Mediation paths

To establish that an independent variable *X* affects a dependent variable *Y* through a mediating variable M as shown in Figure 3, paths a, b and c are tested by the following regressions:

$$M = i_1 + aX + e_1$$

$$Y = i_3 + cX + bM + e_3$$

A mediated effect is said to occur when ***a x b*** is significant. If ***a x b*** is not significant there may be a direct effect only, if **c** is significant. If ***a x b*** is not significant and **c** is also not significant, then there is no-effect non-mediation.

Three independent variables were investigated as possible mediating variables: health expenditure, access to basic sanitation and the number of physicians per 1,000 people.

Mediation test results

The results of the mediation tests are shown in Table 6. The coefficients for poverty and corruption from the full model are shown in the last column on the right. The columns to the left show the coefficients a (the estimated coefficient for poverty or corruption on a mediating variable) and b (the coefficient for the mediating variable in the full regression model for antimicrobial resistance) for each mediating variable (health expenditure, sanitation and number of physicians). The Sobel test statistic is also shown, together with its significance level where appropriate.

The outcome is given as “Direct only” if the Sobel test $a \times b$ pathway is not significant but c is significant, “Mediating effect” if the $a \times b$ pathway is significant and “No effect” if $a \times b$ is not significant and c is also not significant.

The results for the tests for mediation for corruption indicate that corruption does not appear to have any significant mediation effects (t-value < 1.67 in every case). For poverty, health expenditure as a proportion of government spending was found to be a mediator for poverty in determining the level of antimicrobial resistance. According to the outcome of the mediation tests, poverty does not affect AMR through either the abililty of the population to access basic sanitation or through the density of the healthcare workforce. Some but not all of the impact of poverty on AMR is expressed through the amount of government healthcare expenditure.

In spite of the change in size of both of the coefficients for poverty and corruption between the partial models and the full models which suggested the possibility of the presence of mediation, the outcome of the Sobel tests implies that the mediating

Table 6: Mediation results for Panel data

PANEL DATA	MEDIATION FOR CORRUPTION	Health Expenditure	Sanitation	No of physicians	Corruption
	a	-0.02812 (0.0160)	-0.04801 (0.0429)	0.00033 (0.0019)	
	b	-0.63966* (0.3718)	0.07618 (0.3645)	-1.80261* (1.0408)	
	c				0.176165* (0.1026)
	t value	1.23074	0.20544	0.16888	
	Mediation type	Direct only	Direct only	Direct only	
	MEDIATION FOR POVERTY	Health Expenditure	Sanitation	No of physicians	Poverty
	a	-0.92832** (0.3715)	-2.98702*** (0.9763)	-0.10282 (0.1010)	
	b	-0.63966* (0.3718)	0.07618 (0.3645)	-1.80260* (1.0408)	
	c				13.65067*** (4.7851)
	t value	2.49872***	0.20850	0.87774	
	Mediation type	**Mediating effect**	Direct only	Direct only	

Note: Robust standard errors in parentheses.

Significance levels: * p < 0.1; ** p < 0.05; *** p < 0.01.

variables do not significantly carry the influence of the independent variables of interest, in the case of corruption, to the dependent variable. Healthcare expenditure is the only mediating variable (for poverty) in this model.

Overall, evidence for mediation is weak and inconsistent. Poverty and corruption do not appear to statistically impact AMR indirectly and mostly have only direct effects.

5.2 Results for cross-sectional data analysis

An analysis using cross-sectional data for each year from 2008 to 2017 was carried out as a robustness check for the panel data analysis. Descriptive statistics are set out in Table 7. The results of the cross-sectional regression analysis for each year are shown in the Appendix, Table A.3.

Table 7: descriptive statistics for cross-sectional data by year

Year	Variable	Obs	Mean	Std Dev
2008	Resistance	35	26.0521	(11.9734)
	Corruption	115	47.3027	(29.4336)
	Poverty	115	0.2870	(0.4543)
	Use	36	8638.2220	(3415.7550)
	Health	113	10.4360	(4.7722)
	Sanitation	113	79.8313	(25.3783)
	no of physicians	114	2.0079	(1.3911)
Year				
2009	Resistance	36	27.6169	(12.9536)
	Corruption	115	47.8011	(29.4146)
	Poverty	115	0.2957	(0.4583)
	Use	35	8439.5710	(3238.1710)
	Health	113	10.7221	(4.8265)
	Sanitation	113	80.3279	(25.0599)
	no of physicians	114	1.9900	(1.3682)

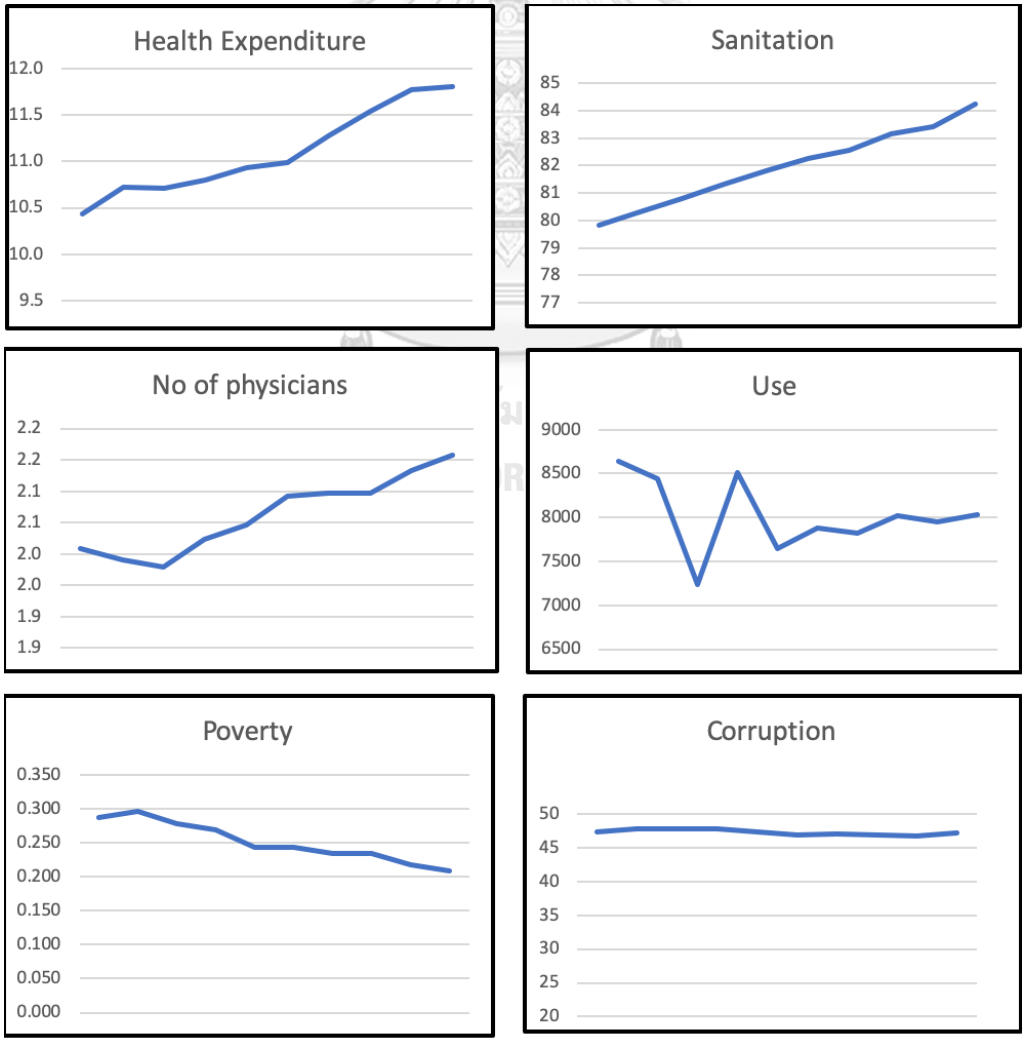
Year				
2010	Resistance	35	28.1033	(12.8703)
	Corruption	115	47.7598	(29.4079)
	Poverty	115	0.2783	(0.4501)
	Use	67	7241.4030	(3274.7890)
	Health	114	10.7082	(4.6588)
	Sanitation	113	80.8204	(24.7551)
	no of physicians	114	1.9800	(1.3272)
Year				
2011	Resistance	37	31.6005	(15.9240)
	Corruption	115	47.7395	(29.3275)
	Poverty	115	0.2696	(0.4457)
	Use	35	8508.5140	(3103.4980)
	Health	114	10.7961	(4.8334)
	Sanitation	113	81.3099	(24.4682)
	no of physicians	114	2.0230	(1.3535)
Year				
2012	Resistance	39	31.8776	(17.4176)
	Corruption	115	47.2986	(29.1686)
	Poverty	115	0.2435	(0.4311)
	Use	70	7642.1430	(3448.4090)
	Health	114	10.9263	(4.7019)
	Sanitation	113	81.7971	(24.1988)
	no of physicians	114	2.0457	(1.3635)
Year				
2013	Resistance	46	32.6062	(18.7089)
	Corruption	115	46.8205	(28.8904)
	Poverty	115	0.2435	(0.4311)
	Use	70	7876.2140	(3568.5640)
	Health	114	10.9827	(4.7751)
	Sanitation	113	82.2708	(23.9596)
	no of physicians	114	2.0915	(1.3778)

Year				
2014	Resistance	49	33.9684	(19.4640)
	Corruption	115	46.9732	(28.7131)
	Poverty	115	0.2348	(0.4257)
	Use	70	7817.8140	(3570.6260)
	Health	114	11.2764	(4.8745)
	Sanitation	112	82.5677	(23.7795)
	no of physicians	114	2.0976	(1.4030)
Year				
2015	Resistance	49	35.9609	(20.8053)
	Corruption	115	46.8646	(28.5161)
	Poverty	115	0.2348	(0.4257)
	Use	70	8318.2214	(3705.2090)
	Health	114	11.5357	(4.9410)
	Sanitation	113	83.1492	(23.4978)
	no of physicians	114	2.0976	(1.4030)
Year				
2016	Resistance	52	37.9492	(20.4046)
	Corruption	115	46.7809	(28.4172)
	Poverty	115	0.2174	(0.4143)
	Use	70	7995.5770	(3705.2090)
	Health	114	11.7751	(4.9979)
	Sanitation	112	83.4388	(23.3443)
	no of physicians	114	2.1330	(1.4121)
Year				
2017	Resistance	49	35.9984	(19.4575)
	Corruption	115	47.2366	(28.4302)
	Poverty	115	0.2087	(0.4082)
	Use	70	8014.7000	(3705.2090)
	Health	114	11.8020	(4.9593)
	Sanitation	110	84.2297	(22.6633)
	no of physicians	114	2.1576	(1.4348)

Data for each year from 2008 to 2017 for each variable are shown in the graphs below in Figure 4. Healthcare expenditure, number of physicians and access to basic sanitation increased over the period by 13.1%, 7.4% and 5.5% respectively. Corruption was very

stable. Aggregate antibiotic consumption data was very volatile, however, particularly in 2010 and 2012. This may be the result of inconsistent methods of data collection between countries or differences in data coverage. The WHO itself advises against cross-country comparisons, reporting in 2018 that “depending on the source(s) selected, data coverage or population coverage may be incomplete in some countries, thus not showing the full picture of antibiotic consumption” (WHO, 2018). Since 2012 the consumption data has been much more stable with a steadily increasing trend, possibly the result of efforts to standardise methods of data collection.

Figure 4: Data by variable by year



A multivariate linear regression with robust standard errors was carried out for each year using the model previously specified. Corruption was highly significant in every year at the $p < 0.01$ level. Poverty was not significant in eight of the ten years examined. The coefficient for poverty was extremely volatile, ranging from a minimum of - 21.71 in 2015 to a maximum of 19.60 in 2011. The significance of the other variables varied considerably over the period: health expenditure was significant in 2012, 2015 and 2016 (at the $p < 0.05$ level) and 2014 (at the $p < 0.01$ level); sanitation was significant at the $p < 0.01$ level in 2008 and 2015 and not significant in the other years; number of physicians was significant every year from 2008 to 2011 and then of no significance subsequently.

Overall, the goodness of fit was nevertheless reasonably high, with a maximum value for R^2 of 0.9245 in 2012.

Comparison of the results from the panel data analysis with the cross-sectional data analysis reveal that generally the explanatory variables which are significant in the former are also significant in the latter (albeit not consistently). However, because of the large variations in the sizes of the coefficients from one year to the next in the cross-sectional data analysis, a comparison with the coefficients in the panel data analysis is not useful.

Mediation test results

As for the panel data results, Sobel tests were carried out in order to ascertain whether the mediating variables (number of physicians, sanitation, health expenditure and poverty/corruption) significantly carry the influence of the independent variables of

interest (corruption and poverty) to the dependent variable. The outcome of the tests for the cross-sectional regressions are set out below in the appendix (Table A.4.).

In the case of cross-sectional analysis, mediation appears to have occurred for each of the chosen mediators, but usually not consistently. Corruption, however, was a mediating variable for poverty every year from 2008 to 2016. Health expenditure was the second most frequent mediating variable for both corruption and poverty. Sanitation had a mediating effect the fewest number of years.

The finding that corruption has a mediating effect for poverty for every year possibly explains why, in the full panel data model, the coefficient for poverty decreases less between the partial model and the full model compared to the coefficient for corruption (-9.69% compared to -2.64%). The coefficient for poverty also is highly significant in the full panel data model ($p < 0.01$), whereas the coefficient for corruption is a little less significant ($p < 0.1$): essentially some of the effect of corruption on AMR is being "diverted" to poverty.

It was not possible to present results for the mediation analysis for poverty for 2017 due to a problem with multicollinearity.

Comparison of regression results between rich and the poor countries

A sub-sample analysis of the effect of corruption on AMR for rich and poor countries was also carried out. The results of the analysis are shown in Table 8 below:

Table 8: subsample analysis of effect of corruption on AMR for rich and poor countries

	Rich countries (GNICAT=0)	Poor countries (GNICAT=1)
Coefficient for corruption	0.1227691 (0.1191991)	0.8492716*** (0.1816056)

Note: Robust standard errors in parentheses.
Significance levels: * p < 0.1; ** p < 0.05; *** p < 0.01.

The results indicate that corruption impacts AMR significantly among low-income countries but not high-income countries. The sub-sample analysis suggests that, since corruption and poverty are positively correlated, the impact of corruption on AMR manifests itself only when the level of corruption is *sufficiently* high. Furthermore, the fact that AMR is differentially impacted by corruption across different country groups suggests that political institutions play an important role in the determination of AMR; in low-income countries, given the absence of accountability mechanisms, corruption is 'allowed' to affect AMR while, in high-income countries, the effect of corruption dissipates, potentially counteracted by the strength of the governance structure.

Mediation analysis of the effect of corruption on AMR for rich and poor countries indicates that there are no mediation effects (results in Table 9 below) and that corruption only has a direct impact on antimicrobial resistance for both rich and poor countries.

Table 9: mediation analysis results of effect of corruption on AMR for rich and poor countries

MEDIATION FOR CORRUPTION	POOR COUNTRIES	Health Expenditure	Sanitation	No of physicians	Corruption
	a	-0.05032*** (0.02112)	-0.082954 (0.06437)	-0.000866 (0.00184)	
	b	-4.76841 (4.6525)	0.42473 (2.2634)	20.34870 (35.2389)	
	c				0.84927*** (0.1816)
	t value	0.941519	0.185692	0.365179	
	Mediation type	Direct only	Direct only	Direct only	
	RICH COUNTRIES	Health Expenditure	Sanitation	No of physicians	Corruption
	a	-0.0153605 (0.0208)	-0.0059485 (0.0559)	0.0000203 (0.0029)	
	b				
	c				0.12228 (0.1192)
	t value	0.675205	0.106303	0.00688	
	Mediation type	**Direct only**	Direct only	Direct only	

Note: Robust standard errors in parentheses.

Significance levels: * p < 0.1; ** p < 0.05; *** p < 0.01.

Chapter 6: Conclusion

This study examined the association of a number of socio-economic factors believed to influence levels of antimicrobial resistance. Data for antibiotic consumption and AMR were obtained for up to 48 countries, including several lower-middle income countries, for 2008 to 2017. Panel data regression analysis as well as cross-section data analysis were conducted to determine the significance of the factors driving AMR. Further tests were run in order to ascertain whether there was any mediation occurring between corruption and poverty and the dependent variable.

This study is important in that it is the first to examine the socio-economic drivers of antimicrobial resistance in a wide range of countries, both in geographical terms and in terms of national income categories. Previous studies have either been limited to Europe (Collignon et al., 2015) and hence have not included any lower middle-income countries, or have been restricted to a cross-sectional analysis only. Country-level time-series data from India, Philippines, Bangladesh, Pakistan, Kenya, Vietnam and Zambia are included here. A fixed effects quadratic trend model was used for the panel data analysis and the results compared with regression results from annual cross-section multivariate linear regression analysis. Mediation analysis was carried out on both the panel data regression and the cross-sectional regressions to investigate the possibility of mediating variables which carry the influence of corruption and poverty to the antibiotic resistance. The results suggest that corruption and poverty have a significant impact on AMR, irrespective of the model used. In the panel data analysis, little mediation appeared to be occurring and the effects of corruption and poverty on AMR were mainly direct. For the cross-sectional regressions, all of the independent variables

included in the analysis showed evidence of acting as mediator variables for at least one year.

The findings for antibiotic consumption and resistance indicate that the poor countries in the dataset have an average rate of resistance which is more than twice that of richer countries (66.75% compared to 30.40%) whilst the average quantity of antibiotics consumed is much lower on average (5,963 DDDs per 1,000 inhabitants compared to 8,045 DDDs). This outcome is also reflected in the regression results which indicate no significant association between antibiotic consumption and resistance.

In this study, higher levels of antimicrobial resistance were consistently associated with poorer governance and poverty. Low health expenditure (as a proportion of government expenditure) was also associated with higher levels of AMR. These results potentially have important implications in terms of national and international policies that seek to address high levels of antibiotic use and resistance. The WHO adopted a global action plan on antimicrobial resistance in 2015 whose goal was to ensure prevention of infectious diseases with effective and safe medicines which were to be used responsibly and to be made available to all who needed them. Members of the WHO were encouraged to develop and implement national action plans on AMR by 2017. Two of the key objectives of the plan were to reduce the incidence of infection and to optimise the use of antibiotics through the use of stewardship programmes (ASP). A paper published in 2018 (Bertollo et al.) which analysed the role of ASPs in reducing the emergence of AMR was unable to find clear evidence that they are effective in reducing the emergence of resistance. The lack of research as to the effectiveness of ASPs in lower-middle and upper-middle income countries makes it difficult to draw conclusions

about the most appropriate way to reduce AMR in low resource environments. However, it seems clear that focussing on reducing antibiotic use alone will not be helpful.

This study highlights the association between poor infrastructure and poor governance with antimicrobial resistance levels. National policies to control AMR should perhaps concentrate their efforts far less on reducing antibiotic use in humans and more on the factors responsible for the spread of resistance. Appropriate use of antibiotics should be enforced through better regulation concerning the manufacturing and dispensing of antibiotics using measures such as the restriction of over-the-counter (OTC) sales of antibiotics without a prescription. Within the animal sector, the use of antibiotics as growth promoters should be prohibited and such legislation enforced. Most action plans and policies ignore the issue of antibiotic and antibiotic resistance gene (ARG) pollution of natural environments. India recently published a draft bill to regulate antibiotic residue in industrial effluents from antibiotic manufacturing plants but the bill is currently the subject of intense lobbying from within a pharmaceutical industry seeking to weaken the rules for commercial reasons (Mohan, 2020). Even if the bill is eventually passed, the success of such a policy depends on robust implementation with regular controls and enforcement measures.

On a national level, governments should concentrate on improving their health systems as well as the ability of people to access affordable healthcare. More resources devoted to health would reduce levels of infectious diseases prevailing in a country thereby reducing contagion. On an international level, binding agreements could be introduced - similar to the United Nations Framework Convention on Climate Change - which would collectively hold the member states to significant reductions in resistance levels and in environmental contamination. Such an agreement would more effectively mitigate AMR-

related problems caused by corruption because it would increase transparency and accountability and would, ideally, be enforceable. AMR-related problems related to poverty are more difficult to mitigate but as poorer countries progress they are able to increase the resources spent on healthcare. As part of the Sustainable Development Goals, Member States of the WHO have agreed to try to achieve universal health coverage (UHC) by 2030. Although UHC is not part of any antibiotic stewardship programme, it would undoubtably be useful in the fight against AMR.

In order to achieve lower rates of resistance, systems should be put in place to assess the existing levels of AMR in a country or region. In the words of the American statistician W. Edwards Deming, “you can’t improve what you can’t measure”. As I have found in the process of this research, accurate data on antibiotic resistance is not consistently measured, not up-to-date and often missing. Improving the availability of good surveillance systems would also be another important part of any future global policy to reduce AMR.

Limitations

This study and model have many limitations, the most significant of which is incomplete or missing data for consumption of and resistance to antimicrobial drugs for many countries and years. In most developing countries there is still little or no surveillance of the development of antibiotic resistance. The situation has improved only slightly since the publication of the first WHO report on AMR in 2015 for which only 129 out of 194 Member States provided data and only 22 had data on all nine of the pathogen-antibiotic resistance pairs considered to be emerging global threats to health. Consequently, only 32 countries had sufficient resistance and consumption data to be included in the multivariate analysis prior to 2013. Developing countries are also under-

represented in this analysis because the majority of the data available is from high-resource countries in Europe and North America. A study with wider scope in geographical and income terms may be possible in the future as more LMICs implement national surveillance systems.

Country resistance data is aggregated by ResistanceMap from several sources and then harmonised to present similar definitions of resistance across countries and regions. Nevertheless, breadth of testing varied between countries making comparison of resistance rates between countries more difficult. Furthermore, country resistance data were not consistently defined in terms of coverage (hospital or community) nor for the numbers of isolates or bacteria reported. Consumption data may have been underestimated in countries where access to antimicrobial drugs is not tightly regulated. Antimicrobial use in food animals was also not included in the model (said to account for more than 70% of total antimicrobial usage) (Van Boeckel et al, 2015).

Another limitation is that of potential omitted variable bias. Other papers which examine socio-economic drivers of AMR have included other explanatory variables such as rainfall, access to electricity, internet penetration, levels of tertiary education, the proportion of the population living in urban areas or the livestock production index. Many alternative variables were tested before the selection of the final model, including all of those previously mentioned, and none of which were significant. There may also have been a time lag between antibiotic consumption and the emergence of antibiotic resistance: this possibility has not been taken into account in my model. The potential for omitted variable bias was minimized by using fixed effects modelling,

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APPENDIX

Table A.1: Independent and dependent variables for papers used in literature review

	Dependent variable		Independent variables																
	Antibiotic usage	Antibiotic resistance	Antibiotic usage	Corruption	Health expenditure	GDP per capita	Education indicator	% of employment in agriculture	Inhabitants per medical doctor	Mortality rates	Poverty indicator	Climate indicator	Urban-isation % of pop	Infra-structure indicator	Nature of data	SCOPE
ABR—Antibiotic Resistance Rate) is the rate of resistance to antibiotics measured in bacteria causing bloodstream infections, i = 1, 2, . . ., N is the subscript representing country, and t = 1, 2, . . ., T represents the time unit in years.		✓ □																	
Antibiotic consumption			✓ □																
ABU quantity of antibiotic usage in people expressed as Defined Daily Doses (DDD) (+)			✓ □																
GOV index of the quality of governance/level of corruption (+)				✓ □															
PHE private health expenditure as a percentage of national income (+)					✓ □														
PGDP per capita gross domestic product in constant (2000) price (in natural logarithms) (-)						✓ □													
TED percentage of tertiary educated people in total population (-)							✓ □				(8)								
AGR percentage of people employed in the agriculture sector out of total employment (+)								✓ □											
									✓ □	✓ □									
											(11)			(2)					
											✓ □	✓ □	✓ □	✓ □					
Average precipitation or average temperature																			
Urban-isation % of pop																			
Adequate sanitation/access to electricity/access to improved water source																			
Nature of data															Panel	Cross-sectional	Cross-sectional	Cross-sectional	N/A
SCOPE															Europe 28 countries 1998-2010	Europe 206 regions	Global n=103 usage n=69	Global n=43	Systematic review LMICs + HICs
CORRUPTION																			
COLLIGNON, P., ATHUKORALA, P. C., SENANAYAKE, S. & KHAN, F. 2015. Antimicrobial resistance: the major contribution of poor governance and corruption to this growing problem. *PLoS One*, 10, e0116746.		✓ □		✓ □	✓ □	✓ □	✓ □	✓ □											
RONNERSTRAND, B. & LAPUENTE, V. 2017. Corruption and use of antibiotics in regions of Europe. *Health Policy*, 121, 250-256.	✓ □								✓ □	✓ □									
COLLIGNON, P., BEGGS, J. J., WALSH, T. R., GANDRA, S. & LAXMINARAYAN, R. 2018. Anthropological and socioeconomic factors contributing to global antimicrobial resistance: a univariate and multivariable analysis. *Lancet Planet Health*, 2, e398-e405.		✓ □		✓ □	✓ □	✓ □	✓ □					✓ □	✓ □	✓ □					
POVERTY																			
ALVAREZ-URIA, G., GANDRA, S. & LAXMINARAYAN, R. 2016. Poverty and prevalence of antimicrobial resistance in invasive isolates. *Int J Infect Dis*, 52, 59-61.		✓ □				✓ □													
ALVIDZA, V., MARIANO, V., AHMAD, R., CHARANI, E., RAWSON, T. M., HOLMES, A. H. & CASTRO-SANCHEZ, E. 2018. Investigating the impact of poverty on colonization and infection with drug-resistant organisms in humans: a systematic review. *Infect Dis Poverty*, 7, 76.		✓ □																	

Table A.2: Antibiotic consumption and antimicrobial resistance - Cross-sectional data:

Year	r	p
2008		0.7972
2009	0.0029	0.9875
2010	0.0127	0.9448
2011	0.0209	0.9096
2012	-0.0401	0.8190
2013	0.1584	0.3164
2014	0.1590	0.2967
2015	0.1700	0.2698
2016	0.1925	0.1900
2017	0.1761	0.2528

Table A.3: Regression results for cross-sectional data by year

2008	coefficient	S.E.	t	Significance
Corruption	0.39415	(0.0709)	5.56	***
Poverty	1.56381	(8.5762)	0.18	
Use	0.00038	(0.0002)	1.73	*
Health Expenditure	-0.27594	(0.4199)	-0.66	
Sanitation	-0.49270	(0.1742)	-2.83	***
No of physician	1.70582	(0.8475)	2.01	*
Constant	58.81892	(16.3096)	3.61	***
no of obs	32			
R2	0.90750			

2009	coefficient	S.E.	t	Significance
Corruption	0.50621	(0.0730)	6.93	***
Poverty	10.19149	(10.4125)	0.98	
Use	0.00039	(0.0003)	1.48	
Health Expenditure	-0.20533	(0.4152)	-0.49	
Sanitation	-0.25619	(0.2133)	-1.20	
No of physician	2.17817	(0.8596)	2.53	**
Constant	32.10843	(20.8293)	1.54	
no of obs	32			
R2	0.91120			

2010	coefficient	S.E.	t	Significance
Corruption	0.54024	(0.0622)	8.69	***
Poverty	13.90647	(11.4442)	1.22	
Use	0.00072	(0.0003)	2.07	**
Health Expenditure	-0.79945	(0.5155)	-1.55	
Sanitation	-0.06317	(0.2447)	-0.26	
No of physician	2.86698	(0.7644)	3.75	***
Constant	17.04790	(20.1903)	0.84	
no of obs	32			
R2	0.90150			

2011	coefficient	S.E.	t	Significance
Corruption	0.57367	(0.0976)	5.88	***
Poverty	19.60233	(11.3695)	1.72	*
Use	0.00071	(0.0003)	2.57	**
Health Expenditure	-1.19023	(0.5113)	-2.33	**
Sanitation	0.17732	(0.2641)	0.67	
No of physician	1.93025	(0.9831)	1.96	*
Constant	3.30723	(26.3105)	0.13	
no of obs	32			
R2	0.77100			

2012	coefficient	S.E.	t	Significance
Corruption	0.56123	(0.0894)	6.27	***
Poverty	8.81603	(6.1434)	1.44	
Use	0.00082	(0.0003)	2.84	***
Health Expenditure	-1.23861	(0.5008)	-2.47	**
Sanitation	-0.00651	(0.1668)	-0.04	
No of physician	1.44872	(1.1139)	1.30	
Constant	22.49028	(17.5148)	1.28	
no of obs	35			
R2	0.92450			

2013	coefficient	S.E.	t	Significance
Corruption	0.66692	(0.1423)	4.69	***
Poverty	-2.92679	(12.5115)	-0.23	
Use	0.00079	(0.0003)	2.40	**
Health Expenditure	-0.39491	(0.4698)	-0.84	
Sanitation	-0.24784	(0.2949)	-0.84	
No of physician	1.54873	(1.1601)	1.34	
Constant	32.12370	(32.2659)	1.00	
no of obs	42			
R2	0.82940			

2014	coefficient	S.E.	t	Significance
Corruption	0.50184	(0.1156)	4.34	***
Poverty	-6.88379	(7.1740)	-0.96	
Use	0.00107	(0.0004)	2.62	**
Health Expenditure	-1.35124	(0.4916)	-2.75	***
Sanitation	-0.22365	(0.2424)	-0.92	
No of physician	1.24210	(1.5815)	0.79	
Constant	45.40879	(23.0961)	1.97	*
no of obs	44			
R2	0.78100			

2015	coefficient	S.E.	t	Significance
Corruption	0.53192	(0.1249)	4.26	***
Poverty	-21.70675	(7.2665)	-2.99	***
Use	0.00119	(0.0004)	2.68	**
Health Expenditure	-1.02139	(0.4883)	-2.09	**
Sanitation	-0.73778	(0.2534)	-2.91	***
No of physician	0.36485	(1.5963)	0.23	
Constant	92.35122	(24.7944)	3.72	***
no of obs	44			
R2	0.79920			

2016	coefficient	S.E.	t	Significance
Corruption	0.62946	(0.1138)	5.53	***
Poverty	-6.08369	(6.0382)	-1.01	
Use	0.00093	(0.0003)	2.71	***
Health Expenditure	-1.03413	(0.4734)	-2.18	**
Sanitation	-0.28059	(0.1970)	-1.42	
No of physician	1.61273	(1.3669)	1.18	
Constant	44.63252	(19.9913)	2.23	**
no of obs	48			
R2	0.82440			

2017	coefficient	S.E.	t	Significance
Corruption	0.73609	(0.1083)	6.80	***
Poverty	0.79785	(3.9382)	0.20	
Use	0.00088	(0.0004)	2.34	**
Health Expenditure	-0.44646	(0.4188)	-1.07	
Sanitation	-0.05320	(0.2030)	-0.26	
No of physician	0.50379	(1.4145)	0.36	
Constant	16.46553	(15.7509)	1.05	
no of obs	43			
R2	0.84340			

Note: Robust standard errors in parentheses.

Significance levels: * p < 0.1; ** p < 0.05; *** p < 0.01.

Table A.4: Mediation results for cross-sectional analysis

MEDIATION FOR CORRUPTION	Health Expenditure	Sanitation	No of physicians	Poverty
2008	Direct only	Mediation	Direct only	Direct only
2009	Direct only	Direct only	Direct only	Direct only
2010	Direct only	Direct only	Direct only	Direct only
2011	Mediation	Direct only	Mediation	Direct only
2012	Mediation	Direct only	Mediation	Direct only
2013	Direct only	Direct only	Direct only	Direct only
2014	Mediation	Direct only	Mediation	Direct only
2015	Mediation	Mediation	Mediation	Mediation
2016	Mediation	Direct only	Mediation	Direct only
2017	Direct only	Direct only	Direct only	Direct only
MEDIATION FOR POVERTY	Health Expenditure	Sanitation	No of physicians	Corruption
2008	No effect	No effect	Mediation	Mediation
2009	No effect	No effect	No effect	Mediation
2010	No effect	No effect	Mediation	Mediation
2011	Mediation	No effect	No effect	Mediation
2012	Mediation	No effect	No effect	Mediation
2013	No effect	No effect	No effect	Mediation
2014	Mediation	No effect	No effect	Mediation
2015	Mediation	Mediation	Direct only	Mediation
2016	Mediation	Direct only	Direct only	Mediation

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