Anthropological and socioeconomic factors contributing to global antimicrobial resistance: a univariate and multivariable analysis

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Summary

Background Understanding of the factors driving global antimicrobial resistance is limited. We analysed antimicrobial resistance and antibiotic consumption worldwide versus many potential contributing factors.

Methods Using three sources of data (ResistanceMap, the WHO 2014 report on antimicrobial resistance, and contemporary publications), we created two global indices of antimicrobial resistance for 103 countries using data from 2008 to 2014: *Escherichia coli* resistance—the global average prevalence of *E coli* bacteria that were resistant to third-generation cephalosporins and fluoroquinolones, and aggregate resistance—the combined average prevalence of *E coli* and *Klebsiella* spp resistant to third-generation cephalosporins, fluoroquinolones, and carbapenems, and meticillin-resistant *Staphylococcus aureus*. Antibiotic consumption data were obtained from the IQVIA MIDAS database. The World Bank DataBank was used to obtain data for governance, education, gross domestic product (GDP) per capita, health-care spending, and community infrastructure (eg, sanitation). A corruption index was derived using data from Transparency International. We examined associations between antimicrobial resistance and potential contributing factors using simple correlation for a univariate analysis and a logistic regression model for a multivariable analysis.

Findings In the univariate analysis, GDP per capita, education, infrastructure, public health-care spending, and antibiotic consumption were all inversely correlated with the two antimicrobial resistance indices, whereas higher temperatures, poorer governance, and the ratio of private to public health expenditure were positively correlated. In the multivariable regression analysis (confined to the 73 countries for which antibiotic consumption data were available) considering the effect of changes in indices on *E coli* resistance (R^2 0·54) and aggregate resistance (R^2 0·75), better infrastructure (p=0·014 and p=0·0052) and better governance (p=0·025 and p<0·0001) were associated with lower antimicrobial resistance indices. Antibiotic consumption was not significantly associated with either antimicrobial resistance index in the multivariable analysis (p=0·64 and p=0·070).

Interpretation Reduction of antibiotic consumption will not be sufficient to control antimicrobial resistance because contagion—the spread of resistant strains and resistance genes—seems to be the dominant contributing factor. Improving sanitation, increasing access to clean water, and ensuring good governance, as well as increasing public health-care expenditure and better regulating the private health sector are all necessary to reduce global antimicrobial resistance.

Funding None.

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Introduction

Antimicrobial resistance is a substantial global problem across countries regardless of income level and imposes a large clinical and financial burden.[1–3] Multidrug-resistant bacteria that develop in any country or region have been shown to spread rapidly,[4,5] and antimicrobial resistance is recognised as a so-called One Health problem.[6,7] Although the use and overuse of antibiotics are primary drivers of the emergence and maintenance of antimicrobial resistance, other factors contribute to its increased prevalence.[4,5,7–9] The observation of higher antimicrobial resistance rates in several low-income countries and middle-income countries (LMICs), in which per-person consumption of antibiotics is much lower than in high-income countries, supports this idea.[8,10,11] Quality of governance, public spending on health, poverty (ie, gross domestic product [GDP] per person), education, and community infrastructure are known to affect health outcomes.[12–14] However, previous studies have been limited in their assessment of antimicrobial resistance and have not been extrapolated to a global scale. Similarly, little is known about the effect of climate on the prevalence of antimicrobial resistance.

The dissemination of antimicrobial resistance can be described as a two-step process. First, de-novo mutations

Research in context

Evidence before this study
Although the use and overuse of antibiotics are primary drivers for the emergence and maintenance of antimicrobial resistance, many other factors also probably contribute to this problem. Quality of governance, public spending on health, poverty, education, and community infrastructure are known to affect health outcomes and therefore will also likely affect antimicrobial resistance. We searched PubMed for articles published from Jan 1, 2000, to Aug 1, 2018, and restricted our search to articles published in English. We excluded all articles relating to tuberculosis, HIV, malaria, and other parasitic diseases. Using the following combination of terms, we found the following number of articles: "global antimicrobial resistance and corruption" (n=1), "global antimicrobial resistance and sanitation" (n=49), "global antimicrobial resistance and governance" (n=27), "global antimicrobial resistance and infrastructure" (n=29), "global antimicrobial resistance and poverty" (n=23), "global antimicrobial resistance and consumption" (n=389), "global antimicrobial resistance and univariate analysis" (n=9), and "global antimicrobial resistance and multivariate analysis" (n=61). Assessing these positive hits, none have undertaken a global analysis on the above risk factors using univariate and multivariate analysis.

Added value of this study
We used three different sources (ResistanceMap, WHO 2014 report on antimicrobial resistance, and contemporary publications) to find global data on reported antimicrobial resistance levels. We created two global antimicrobial resistance measures: *Escherichia coli* resistance and aggregate resistance. Antibiotic consumption data were obtained from the IQVIA MIDAS database (Danbury, CT, USA). The World Bank DataBank was used for data for governance, education, gross domestic product per person, health-care spending, and community infrastructure (eg, sanitation). We derived a corruption index using data from Transparency International (Berlin, Germany). Associations were examined using simple correlations for univariate analysis and a logistic regression model for multivariable analysis.

Implications of all the available evidence
Multivariate analysis showed that better infrastructure and governance were significantly associated with lower measures of antimicrobial resistance, but that antibiotic consumption was not significantly associated with higher antimicrobial resistance. Reducing antibiotic consumption will not be sufficient to control antimicrobial resistance because contagion—the spread of resistant strains—seems to be the dominant factor. Improving sanitation, increasing access to clean water, ensuring good governance, plus increasing public health-care expenditure all need to be addressed to reduce global antimicrobial resistance.

or acquisition of resistance genes, or both, occurs via mobile genetic elements, such as plasmids mediating an antimicrobial-resistance phenotype. Second, antimicrobial resistance contagion—the spread of resistant strains—proceeds via several vectors (eg, human beings, insects, birds, agriculture, and water).[4,5,9] Selection pressure caused by antibiotic consumption is an important primary factor not only for the de-novo emergence of antimicrobial resistance but also for the selective multiplication of resistant bacteria.[15–19] Reducing inappropriate antibiotic consumption is a recognised policy priority, and substantial efforts are focused on controlling antibiotic usage volumes in hospitals, the community, and the agricultural sector.[1–3,16,18–20] Although antibiotic usage has been shown to be an important driver for increasing antimicrobial resistance levels, the spread of resistant bacteria or the genes that encode for resistance are likely to be much more important in the dissemination and prevalence of antimicrobial resistance.[4,5,9,16,21] The environment (including transmission via water, insects, animals, and birds) plays an underappreciated part in the development and spread of resistant bacteria.[4] Another driver associated with increased resistance levels is poor governance (or corruption). In Europe, poor governance and corruption have been shown to be as closely associated with differences in antimicrobial resistance levels between countries as are antibiotic consumption patterns.[22]

Most research on antimicrobial resistance has focused on data-rich, high-income countries. However, the quality of the physical infrastructure and health systems in high-income countries has converged to such an extent that there is insufficient contrast in data to identify easily how variations in social, physical, and economic environments affect antimicrobial resistance. The variations across countries in a global antimicrobial resistance dataset provide an opportunity to estimate the importance of contagion for variations in antimicrobial resistance levels because low income is typically associated with poor water quality and sanitation, overcrowded housing, and inadequate practices to prevent infection.

The One Health multifaceted nature of antimicrobial resistance suggests the need to understand the relative importance of antibiotic consumption as the driver for the evolution of resistance versus the many other contributing factors that favour contagion. In this study, we examined antimicrobial resistance levels against countries' quality of governance, public spending on health, education, income, community infrastructure, climate, and antibiotic usage volumes with specific antimicrobial-resistance indicators across the world.

Methods

Study design and data sources

We created a dataset on antimicrobial resistance for 103 countries using data from 2008 to 2013 and a second dataset on antibiotic consumption for 69 of those countries using data from 2014 (see appendix for a complete list of countries and associated data and sources). Antimicrobial resistance data were obtained from three sources: ResistanceMap, a global repository of antibiotic resistance data from quality-assured and accredited hospitals and laboratory networks for 2014;[1] the WHO 2014 global report on antimicrobial resistance;[17] and contemporary publications on studies of fluoroquinolone resistance in *Escherichia coli* (appendix).

Antibiotic consumption data were obtained from the IQVIA MIDAS database (Danbury, CT, USA) for 2014 for 73 countries[10] and used for our correlations. Global data from 2004 for 63 countries were available to be used for a separate analysis replicating the regression analysis (appendix).[23] We used the World Bank's DataBank for data on governance, education, GDP per person, health-care spending, community infrastructure, and climate indicators for all included countries.[24] Data from Transparency International (Berlin, Germany) were used for variables on corruption.[25]

Because there are many possible contributing factors affecting antimicrobial resistance and international data coverage of all factors is incomplete, we summarised the data using indices that capture the main probable influences. Six indices were created from the available measures (ie, the raw data)—ie, governance, education, GDP per person, health expenditure, infrastructure, and climate (table 1)—and these were compared with levels of antimicrobial resistance and consumption.

The index covariates each have a mean of 0 and an SD of 1 when taken across available data from the 103 countries considered for this study (appendix). These indices were formed in three steps. First, each measure (or raw data variable) for each country was standardised by subtracting its overall mean and then dividing by the overall SD. Second, for each country, an average of the standardised variables within each index was calculated. For example, the governance (corruption) index was the average of the standardised variables for the 2012 and 2015 corruption indices, the political stability and absence of violence index, and the rule of law index. Data were not uniformly available for all countries for all variables. The SD of the variables formed in the second step was not 1, therefore the final step was to divide the variables created in step 2 for each country by their own SDs.

Statistical analysis

To study the association between antimicrobial resistance and the covariates, we created two country-level measures of antimicrobial resistance: the average prevalence of resistance of *E coli* to third-generation cephalosporins and fluoroquinolones, termed *E coli* resistance, based on

	Countries with available data	Mean (SD)	Maximum	Minimum
Governance				
Corruption, 2012	103	47·5 (20·1)	90·0	13·0
Corruption, 2015	103	48·0 (20·5)	91·0	12·0
Political stability and absence of violence	103	–0·1 (1·0)	1·5	–2·9
Rule of law (World Justice Project)	73	0·6 (0·2)	0·9	0·3
Education				
Literacy (Nationmaster data, 2003)	103	87·2% (16·6)	100·0%	21·8%
Literacy (average of male and female rates)	103	89·3% (15·1)	100·0%	29·9%
Ratio of female to male literacy	103	0·9 (0·1)	1·3	0·5
Female literacy	103	87·2% (18·1)	100·0%	21·8%
Male literacy	103	91·4% (12·5)	100·0%	38·0%
Percentage finishing secondary education (2014)	79	78·4% (19·9)	99·6%	13·6%
Primary school completion rate	97	95·3% (10·6)	100·0%	44·4%
GDP per capita, 2015 (purchasing power parity in 2011, US$)	103	23 903 (19 897)	93 900	581
Health				
Health expenditure, total (percentage of GDP)	103	7·2% (2·7)	17·1%	2·3%
Ratio of public to private public health expenditure	103	0·8 (0·7)	3·7	0·0
Climate				
Average temperature (°C)	103	16·2 (8·5)	28·3	–5·4
Average precipitation (mm per year)	103	1125·3 (768·9)	3240·0	51·0
Infrastructure				
Urbanisation (percentage of population)	103	63·3% (23·5)	100·0%	8·8%
Adequate sanitation, 2015 (percentage of population)	103	82·4% (23·2)	100·0%	18·9%
Access to electricity (percentage of population)	103	88·7% (24·1)	100·0%	7·0%
Access to improved water source (percentage of population)	103	92·7% (11·6)	100·0%	40·0%
Internet penetration (percentage of population)	103	54·9% (27·8)	98·2%	1·4%

GDP=gross domestic product.

Table 1: Indices and measures

WHO resistance data, ResistanceMap data, and additional data from other published sources (appendix); and the average resistance prevalence of *E coli*, *Klebsiella* spp, and *Staphylococcus aureus*, collectively termed aggregate resistance, based on WHO data, ResistanceMap data, and other data (appendix). Aggregate resistance included data on *E coli* and *Klebsiella* spp resistance to third-generation cephalosporins, fluoroquinolones, and carbapenems, and meticillin-resistant *S aureus*. Univariate analyses were reported with the correlation coefficient *r*.

Regression models were fitted to the data to identify the factors that most affected antibiotic resistance across a range of countries. We describe the fit of each model using the coefficient of determination R^2. The explanatory variables are the indices described earlier, along with available data on antibiotic usage. Explanatory variables are

	Effect on resistance rate of 1 SD increase in each explanatory variable (logit)	p value
Usage (standardised)	−0·88	0·64
Governance index	−7·89	0·025
Health expenditure index	−5·54	0·093
GDP per capita (standardised)	6·62	0·030
Education index	7·93	0·058
Infrastructure index	−16·84	0·014
Climate index	2·01	0·33
R^2	0·54	..

GDP=gross domestic product. R^2=coefficient of determination.

Table 2: Effect of changes in indices on the resistance of *Escherichia coli* to third-generation cephalosporins and fluoroquinolones

	Effect on resistance rate of 1 SD increase in each explanatory variable (logit)	p value
Usage (standardised)	2·36	0·070
Governance index	−11·18	<0·0001
Health expenditure index	−6·34	0·0065
GDP per capita index (standardised)	3·36	0·11
Education index	8·59	0·0035
Infrastructure index	−13·24	0·0052
Climate index	−0·25	0·86
R^2	0·75	..

GDP=gross domestic product. R^2=coefficient of determination.

Table 3: Effect of changes in indices on the aggregate resistance rate

denoted by an x in the equation below. Resistance was measured in percentage points and could vary from 0 to 100. In the regression model, the dependent variable was defined as the logarithm of the odds ratio (OR) of the resistance rate to the non-resistance rate. This equation form is often referred to as a logit model, and it ensured that the modelled predicted resistance rates fell between 0 and 100:

$$\log \left(\frac{\text{resistance}_i}{100 - \text{resistance}_i}\right) = \beta_0 + \beta_1 x_{1i} + \cdots.. + \beta_k x_{ki} + u_i$$

In this form the βs are interpreted as the percentage change in the OR for a unit change in the explanatory variable. To express the results of the regression in more familiar terminology, we used the partial derivative with respect to each explanatory variable to show the effect on resistance of a unit increase in the explanatory variable:

$$\frac{\partial \text{resistance}}{\partial x_j} = \beta_{j.} \frac{\text{resistance} \times (100 - \text{resistance})}{100}$$

Modelled in this manner, the effect of a change in any of the explanatory variables was non-linear, and the effect depended on the rate of resistance at the point the calculation was made. The usual practice is to report the effect at the mean of the data.

Although the logit formulation is conceptually preferred, the statistical results are similar when the dependent variable is modelled as simply resistance (linear). This finding increased our confidence in the robustness of the findings. Both regression model results are in the appendix. Models were estimated using Epi InfoTM, English language version 7.2.2.1.
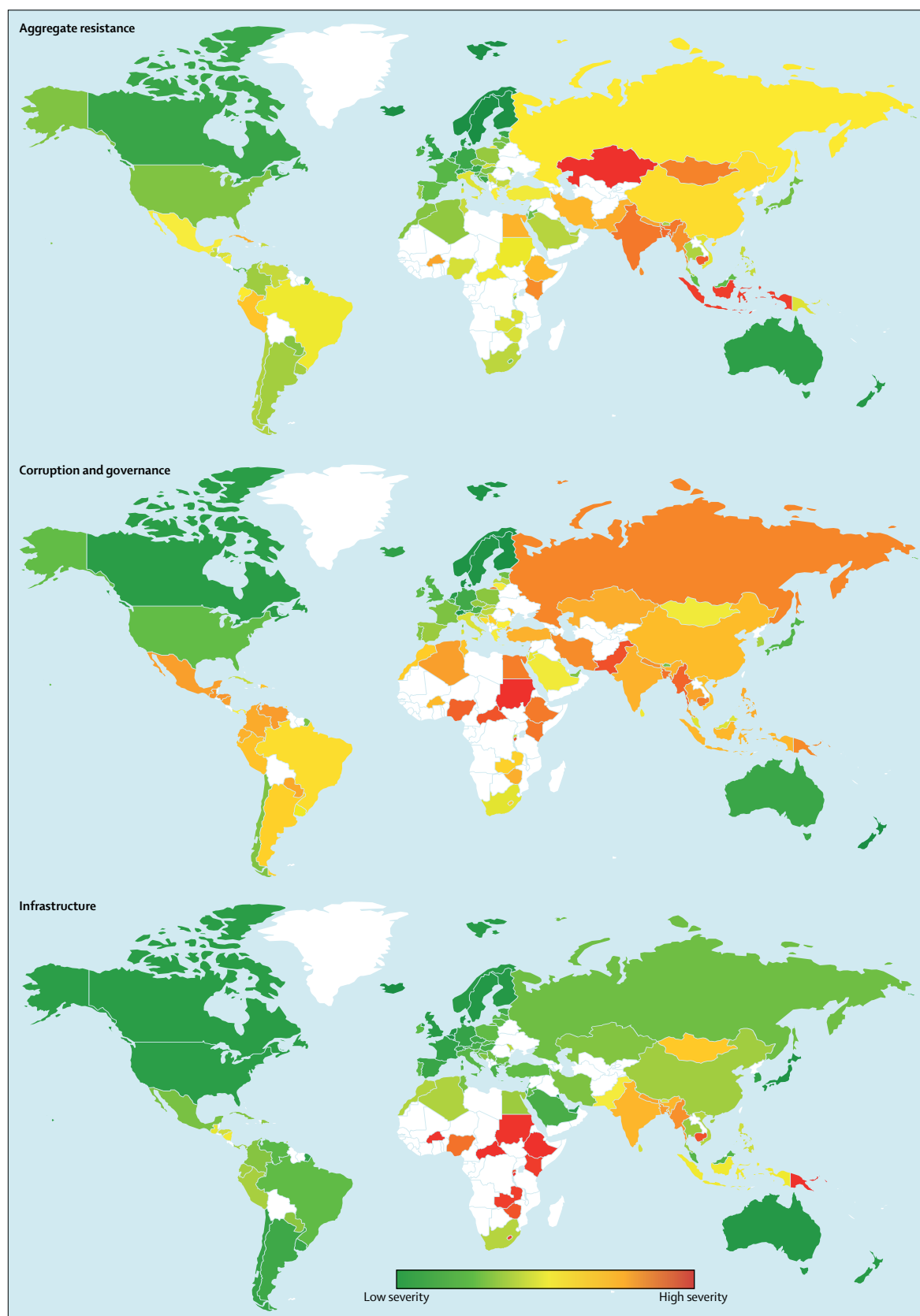
Role of the funding source

Results

The mean prevalence of antimicrobial resistance for the dependent variable *E coli* resistance was 29·4% (SD 18·7) and for aggregate resistance was 29·6% (15·0). Data for *E coli* resistance were available for 103 countries, whereas data for aggregate resistance were available for 73 countries (appendix 1). Data for most measures were available for 103 countries except for rule of law (available for 73 countries), percentage of population finishing secondary education (79 countries), and percentage of population completing primary school (97 countries). Multivariable regression analysis was confined to the 73 countries for which antibiotic consumption data were available.

All measures of improved governance (lower corruption, political stability, rule of law, and absence of violence) and all measures of improved infrastructure (sanitation, safe water, internet accessibility, urbanisation, and access to electricity) were strongly and inversely correlated with both antimicrobial resistance datasets, as was higher GDP per person (appendix). By contrast, all measures of education (national literacy, average of male and female literacy, ratio of female to male literacy, male literacy, female literacy, and secondary education) except for completion of primary education were positively correlated with both antimicrobial-resistance datasets (appendix).

Total health-care expenditure was strongly and inversely correlated with both antimicrobial resistance indices; by contrast, the ratio of private to public health expenditure was strongly and positively correlated. Among measures of climate, average temperature was strongly and positively correlated with both antimicrobial resistance indices, whereas there was a poor correlation with precipitation (appendix). For global antibiotic consumption we showed

Figure 1: Global aggregate resistance versus infrastructure and governance
Figure shows levels of aggregate resistance, corruption and governance, and infrastructure in orders of severity, from low (ie, low resistance, little corruption, and good infrastructure) to high (ie, high resistance, high levels of corruption, and poor infrastructure). The raw data are available in the appendix.
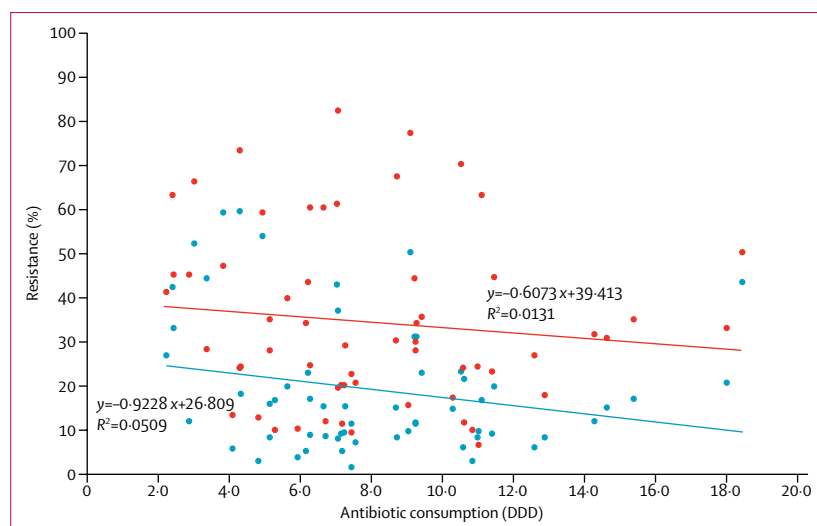
Aggregate resistance

Corruption and governance

Infrastructure

Low severity ████████████ High severity

Figure 2: ***Escherichia coli*** **resistance levels for fluoroquinolones and third-generation cephalosporins compared with antibiotic consumption**
Figure shows data for percentage of resistance versus defined daily dose (DDD) of antibiotic, plotted only for countries with data for DDD and both measures of resistance. Blue circles indicate *Escherichia coli* resistance to third-generation cephalosporins (%). Red circles indicate *E coli* resistance to fluoroquinolones (%). The blue line shows the linear measure of *E coli* resistance to third-generation cephalosporins. The red line shows the linear measure of *E coli* resistance to third-generation fluoroquinolones. R^2=coefficient of determination.

a weak inverse relationship with aggregate resistance (r=−11%) and a moderate inverse correlation with *E coli* resistance (r=−28%). When the sample included only European countries, antibiotic consumption had a strong positive correlation with both antimicrobial resistance indices (r=49% for *E coli* resistance, r=62% for aggregate resistance), reflecting different contagion levels between high-income countries and LMICs.

In multivariable regression analysis, an increase of 1 SD in the infrastructure index, governance index, and health expenditure resulted in significant decreases in *E coli* resistance and aggregate resistance (tables 2, 3). An increase of 1 SD in education and GDP per person resulted in an increase in *E coli* resistance and aggregate resistance (figure 1, appendix).

We found no significant association between the climate index and antimicrobial resistance indices. An increase of 1 SD in the climate index resulted in a non-significant increase in *E coli* resistance but a non-significant decrease in aggregate resistance (table 3). Antibiotic consumption was also not significantly associated with either antimicrobial resistance index (figure 2). Considering all covariates, the variation in aggregate resistance was better explained by the model than was *E coli* resistance (R^2 values 0·75 *vs* 0·54).

Discussion

Our results indicated that poorer infrastructure (eg, poor sanitation) and poorer governance (eg, corruption) were consistently associated with higher levels of antimicrobial resistance. Low health expenditure was also associated with higher levels of antimicrobial resistance. Surprisingly,

after adjusting for these three measures, high GDP per person and high education levels were also associated with higher antimicrobial resistance levels. Also surprising was that antibiotic consumption was not strongly associated with antimicrobial resistance levels.

Our model allowed us to quantify the effects of improving the indices with the most potential for reducing antimicrobial resistance. For example, we would see *E coli* resistance levels fall by 18·6% for every 1 SD improvement in the infrastructure index. Additionally, we would see a 5·5% decrease in *E coli* resistance levels if the governance index were improved by 1 SD. Undeniably, selection pressure due to antibiotic exposure is an important factor in the emergence and selection of antimicrobial resistance bacterial clones.[15,16,18,22] However, our data suggest that globally, a high prevalence of antimicrobial resistance can be more likely attributed to the dissemination of antimicrobial resistance, especially via poor sanitation and contaminated potable water. This expectation is supported by the strong association between the infrastructure index and *E coli* resistance because *E coli* are faecal bacteria and their presence in water indicates human or animal faecal contamination. Aggregate resistance, however, includes *Klebsiella* spp and *S aureus*, which occupy different ecological niches. Aggregate resistance results might have more accurate associations with the covariates considered in our study, because it is supported by better explanation of the variation in antimicrobial resistance (with a high R^2 value of 0·75 *vs* 0·54). However, the measure of aggregate resistance had more data gaps and will need to be reassessed when more information, particularly from LMICs, becomes available. Poor water quality and sanitation have been linked with many poor health outcomes, so seeing their association with high levels of antimicrobial resistance is no surprise.[26,27]

Other infrastructure measures, such as urbanisation, internet accessibility, and access to electricity, were all strongly associated with lower antimicrobial resistance rates. However, these factors might be not directly linked to lower antimicrobial resistance levels but rather indicative of better sanitation, access to clean water, and access to refrigeration. It is notable that the higher the public health-care expenditure, the lower the aggregate resistance. Conversely, a higher proportion of private health-care spending was associated with higher levels of antimicrobial resistance, as was also shown in a previous study comparing only data across Europe.[22] In Brazil, the density of private health clinics was associated with higher antibiotic consumption,[28] an effect that might reflect the regulatory environment—ie, private clinics might follow public health rules and guidelines less often, or regulators with oversight might not restrict the types and quantities of antibiotics used in these clinics. These data have substantial ramifications for public health spending in regions like Africa and south Asia.

Counterintuitively, higher education was significantly associated with increased levels of antimicrobial resistance.

In certain LMICs, more affluent and better educated people have better access to antibiotics and use more antibiotics.[28] Our data also indicated that higher education was correlated with high antibiotic consumption. Thus, perversely, although higher levels of education have many associated benefits, educated people in LMICs might be contributing more to the burden of antimicrobial resistance. Unsurprisingly, therefore, higher GDP per person was associated with higher antimicrobial resistance; however, this was not significant with aggregate resistance in the multivariable analysis. Countries with high GDP per person are known to have high antibiotic usage.[11] Any beneficial effects of higher GDP on antimicrobial resistance might already be captured by more directly relevant variables such as infrastructure and health expenditure. Poverty itself might not have a direct effect on levels of antimicrobial resistance, but this will be affected by factors such as access to sanitation, clean water, and electricity.

There was a univariate correlation with temperature and antimicrobial resistance: the warmer the country, the higher its antimicrobial resistance levels. This correlation might, however, be biased; some cold countries with very good governance and social support (eg, Scandinavian countries and Canada) have low antimicrobial resistance levels, whereas Russia is similarly cold but has antimicrobial resistance levels higher than most other countries (perhaps correlating with poor governance and corruption). The correlation with temperature is an interesting finding, but whether this is a socioeconomic factor (poorer infrastructure in hotter areas) or has to do with temperature per se remains unclear. However, in some environments (eg, waterways), warm temperatures offer more potential for bacteria to multiply and transfer antimicrobial resistance genes at high frequencies. Warmer temperatures are also associated with higher insect populations, which have played a part in disseminating resistant bacteria.[6,29] Data on national climate (average temperature and rainfall) did not have a significant correlation with antimicrobial resistance but might not capture climatic variations that occur within even some reasonably small countries. More detailed analysis examining the effect of climate will require subnational data. Precipitation had a weaker correlation than did temperature; however, precipitation might not be a reliable indicator of flooding, which can spread antimicrobial resistance bacteria throughout communities.

Corruption levels in countries are strongly correlated with high levels of antimicrobial resistance, a result that confirms previous findings in Europe.[22] Rule of law was better correlated with antimicrobial resistance levels than corruption levels, but in our dataset, available data were predominantly from European and developed countries. Accordingly, in view of these data gaps, rule of law is currently a less reliable global indicator of governance than corruption indexes. The effects of corruption on antimicrobial resistance levels are however likely to be indirect.[22]

Surprisingly, we found that antibiotic consumption was poorly correlated with antimicrobial resistance levels. This was also true when we analysed our resistance indices against older published consumption data.[23] Whereas developed regions, such as Europe, showed a correlation between antimicrobial resistance levels and antibiotic usage, this was not evident from the global data. A possible explanation is that antibiotic volumes are not a factor until a country reaches a medium or high level of social and economic development. More importantly, other factors such as water quality and sanitation levels are likely to have a greater effect than antibiotic consumption volumes. This is an important issue for countries where large groups of people have trouble accessing antibiotics. Our data suggest that the relationship between antibiotic consumption and population resistance levels varies across the world.

Our study and our model have several limitations, many of which are also acknowledged in greater detail in other studies.[11,15,17] First, many countries still have incomplete or missing data (especially data for antibiotic consumption), which limited the number of countries included in the multivariable analysis. Second, some additional factors that might correlate with antimicrobial resistance levels could not be measured—eg, insects, even though they are affected by temperature and precipitation. Third, our aggregate resistance measure included *E coli*, *Klebsiella* spp, and *S aureus*, which occupy different environmental niches and will be affected by different demographic factors. Fourth, although we used the best global resistance data available, country data were not consistently defined with regard to community and hospital coverage, nor for the numbers of samples or bacteria reported. The resistance data might be an underestimation or overestimation in the absence of robust, representative surveillance systems, particularly in LMICs. We also might not have captured data from all contemporary publications on *E coli*. Fifth, our data did not capture the number of antibiotics purchased through the internet; such sales are rapidly growing and volumes remain unknown, and consumption data might be an underestimation because they might not have included data about antibiotic donations or exposure as a result of mass antibiotic-administration campaigns in LMICs. Sixth, there might have been a lag period between antibiotic consumption and emergence of antibiotic resistance. Finally, we did not obtain comprehensive data on antimicrobial use in food animals, which might account for more than 70% of total antimicrobial usage and is especially high in LMIC countries.[30]

To our knowledge, this was the first study to examine how several factors affect antimicrobial resistance at the global level. We used a more comprehensive dataset than have previously published studies,[10,11,15,17,18,22,23,28] and

analysed several socioeconomic factors in addition to antibiotic consumption and antimicrobial resistance levels. Our findings have major policy implications. In developed countries, where the focus has been on antibiotic consumption as the most identifiable factor contributing to antimicrobial resistance, we showed that consumption explains only a portion of the observed antimicrobial resistance levels. Moreover, intervention measures to decrease antibiotic consumption alone are not likely to be sufficient, especially in LMICs, because contagion is probably the main factor affecting antimicrobial resistance levels. Simultaneous measures to improve sanitation, infection control and prevention, access to clean water, governance, and public expenditure on health-care need to be implemented to tackle antimicrobial resistance on a global scale.

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