Global antimicrobial-resistance drivers: an ecological country-level study at the human–animal interface

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Summary

Background Antimicrobial resistance (AMR) is a pressing, holistic, and multisectoral challenge facing contemporary global health. In this study we assessed the associations between socioeconomic, anthropogenic, and environmental indicators and country-level rates of AMR in humans and food-producing animals.

Methods In this modelling study, we obtained data on Carbapenem-resistant *Acinetobacter baumanii* and *Pseudomonas aeruginosa*, third generation cephalosporins-resistant *Escherichia coli* and *Klebsiella pneumoniae*, oxacillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus faecium* AMR in humans and food-producing animals from publicly available sources, including WHO, World Bank, and Center for Disease Dynamics Economics and Policy. AMR in food-producing animals presented a combined prevalence of AMR exposure in cattle, pigs, and chickens. We used multivariable β regression models to determine the adjusted association between human and food-producing animal AMR rates and an array of ecological country-level indicators. Human AMR rates were classified according to the WHO priority pathogens list and antibiotic–bacterium pairs.

Findings Significant associations were identified between animal antimicrobial consumption and AMR in food-producing animals (OR 1·05 [95% CI 1·01–1·10]; p=0·013), and between human antimicrobial consumption and AMR specifically in WHO critical priority (1·06 [1·00–1·12]; p=0·035) and high priority (1·22 [1·09–1·37]; p<0·0001) pathogens. Bidirectional associations were also found: animal antibiotic consumption was positively linked with resistance in critical priority human pathogens (1·07 [1·01–1·13]; p=0·020) and human antibiotic consumption was positively linked with animal AMR (1·05 [1·01–1·09]; p=0·010). Carbapenem-resistant *Acinetobacter baumanii*, third generation cephalosporins-resistant *Escherichia coli*, and oxacillin-resistant *Staphylococcus aureus* all had significant associations with animal antibiotic consumption. Analyses also suggested significant roles of socioeconomics, including governance on AMR rates in humans and animals.

Interpretation Reduced rates of antibiotic consumption alone will not be sufficient to combat the rising worldwide prevalence of AMR. Control methods should focus on poverty reduction and aim to prevent AMR transmission across different One Health domains while accounting for domain-specific risk factors. The levelling up of livestock surveillance systems to better match those reporting on human AMR, and, strengthening all surveillance efforts, particularly in low-income and middle-income countries, are pressing priorities.

Funding None.

Lancet Planet Health 2023; 7: e291–303

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Introduction

Rising antimicrobial resistance (AMR) presents a major threat to global health.[1,2] An estimated 1·27 million deaths attributable to bacterial AMR occurred globally in 2019.[3] AMR contributes to an increased number of deaths, health complications, and increased health expenditure in all countries, irrespective of socioeconomic status.[2,4] Bacterial AMR is a natural phenomenon that can arise through de-novo mutations or the transfer of genetic material encoding resistant phenotypes through processes, such as horizontal gene transfer.[5] Exposure of pathogens to antimicrobials is known to encourage selective proliferation of resistant bacteria.[6] Hence, indiscriminate use of antimicrobials is a primary driver of the global spread of AMR.[7] Misuse and excessive use of antimicrobials is not exclusive to human consumption. In 2017, an estimated 93 309 tonnes of antibiotics were sold for use in food-producing animals globally. This figure is projected to reach 104 079 tonnes by 2030.[8] This increase in antibiotic use is a consequence of the rising demand for meat-products and over-the-counter sales, particularly in low-income and middle-income countries (LMICs), in which populations are continuing to grow and become more economically developed.

Complex and interlinked socioeconomic and environmental factors also have a significant role on the contagion and spread of resistance genes. The quality of health-care systems, water sanitation and hygiene (WASH) infrastructure, gross domestic product (GDP) per capita, and climate have been identified as fundamental risk

Research in context

Evidence before this study

To identify which factors were associated with AMR levels in humans and food-producing animals, we searched PubMed and the grey literature for published studies that either quantified the magnitude of, or reviewed the potential association between, different sociodemographic, environmental, and anthropogenic variables, and global AMR levels in humans or food-producing animals. We searched the evidence between Jan 1, 2000, and Nov 1, 2022. We used keywords related to "global antimicrobial resistance" OR "antibiotic resistance" combined with any of the following MeSH terms: "infrastructure" OR "socioeconomic" OR "sanitation and hygiene" OR "governance" OR "environment" OR "monitoring and surveillance" OR "antibiotic/antimicrobial consumption". Articles containing keywords such as "HIV/AIDS", "tuberculosis", "virus", "fungus", and "parasites" were excluded. After assessing the articles, we found that variables pertaining to climatic, demographic, epidemiological, governmental, and industrial features have all been shown to have associations with resistance. However, no existing study has employed a global ecological analysis looking at AMR levels at the human–animal interface using a One Health approach.

Added value of this study

We collated AMR data from the Centre for Disease Dynamics, Economics and Policy (CDDEP), Global Antimicrobial Resistance and Use Surveillance System, Pan American Health Organisation, ResistanceBank, and published articles, providing the most holistic AMR database to date. Independent variables included antibiotic consumption data (from CDDEP), socioeconomic, environmental, and anthropological data obtained from the World Bank, WHO, and UN databases. β regression models examined country-level univariate and multivariable associations between rates of resistance in humans and animals and the independent variables. For the first time, we identified global bidirectional associations of antibiotic consumption and AMR between humans and animals, crystallising the necessity for a multisectorial framing of this problem to inform optimal interventions. Even after adjusting for other covariates, significant associations with both animal and human AMR were shown for factors pertaining to socioeconomics, including governance.

Implications of all the available evidence

Our results show the necessity for an integrated approach to tackling the spread of AMR that spans across different One Health domains and focuses on social development and poverty reduction as well as more stringent antibiotic consumption practices in humans and animals.

factors for the emergence and transmission of AMR.[9,10] Behavioural factors, such as unnecessary antibiotic use for the treatment of viral infections, and patient-related factors, including underlying health conditions (eg, obesity, smoking, and alcohol consumption), might also affect the spread of AMR by predisposing individuals to infection or reducing the effectiveness of antimicrobial drugs.[11,12] AMR spreads rapidly between environments, driven by a multitude of factors, including human and animal movement, surface water run-off, and exchange of agricultural products.[13] The magnitude of the influence that these diverse multisectoral drivers have on AMR globally is poorly understood, but evidence for a strong link between humans and food-producing animals is burgeoning.[14] A study across 11 European countries found strong, between-species, positive correlations (r coefficient between 0·68 and 0·94) of resistance to numerous antimicrobials (ampicillin, aminoglycosides, third-generation cephalosporins, and fluoroquinolones) in *Escherichia coli* isolated from food-producing animals and from humans.[15] A subsequent systematic review substantiated this link by showing that interventions targeting drug consumption in food-producing animals affected resistance rates in humans and animals.[16] Through increased demand for animal-based food and products, several anthropogenic factors, such as population growth (urban density) and rising incomes, have been reported to contribute to AMR at the human–animal interface.[17,18]

See Online for appendix

We sought to analyse the associations between different socioeconomic, environmental, and anthropogenic indicators and country-level AMR rates in humans and food-producing animals.

Methods

Study design

In this global multivariable β regression modelling study we used country-level data from as close to 2018 as available to examine the associations between global rates of AMR in human and food-producing animals (dependent variables) and an array of independent variables, including antibiotic consumption, and sociodemographic, health-related, and environmental risk factors. Variable definitions and data sources are listed in the appendix (pp 4–11). The countries included in our analyses represented every WHO region (appendix pp 12–15) and World Bank income class (appendix p 17). The aim of the study is to identify the main global determinants of AMR in humans and food-producing animals.

Procedures

We searched existing literature from PubMed to identify the main global risk factors associated with AMR. We extracted country-level data of the risk factors, if available, using global data repositories. We then computed univariate and multivariable β regression models to identify the association between human or food-producing

	Countries with data available	Median (IQR)	Minimum	Maximum	Definition	Expected association with AMR
Antimicrobial resistance (dependent variables)						
Critical priority human pathogens (%)	98	39·89 (23·09–45·68)	6·00	98·00	Average resistance observed in pathogen-antibiotic pairs defined as of critical importance to human health by WHO (carbapenem-resistant *Acinetobacter baumannii*, carbapenem-resistant *Escherichia coli*, third generation cephalosporins-resistant *E coli*, carbapenem-resistant *Klebsiella pneumoniae*, third generation cephalosporins-resistant *K pneumoniae*, and carbapenem-resistant *Pseudomonas aeruginosa*), all of which are Gram-negative bacteria	NA
Carbapenem-resistant *A baumanii* (%)	66	54·68 (28·00–82·00)	1·00	98·00	Average resistance to carbapenems observed for *A baumanii* isolates	NA
Third generation cephalosporins-resistant *E coli* (%)	89	38·31 (17·00–58·00)	6·00	89·00	Average resistance to third generation cephalosporins observed for *E coli* isolates	NA
Third generation cephalosporins-resistant *K pneumoniae* (%)	92	53·11 (27·00–77·00)	6·00	98·00	Average resistance to third generation cephalosporins observed for *K pneumoniae* isolates	NA
Carbapenem-resistant *P aeruginosa* (%)	41	27·00 (13·00–39·00)	4·00	87·00	Average resistance to carbapenems observed for *P aeruginosa* isolates	NA
High priority human pathogens (%)	80	24·00 (15·00–41·00)	1·00	94·26	Average resistance observed in pathogen-antibiotic pairs defined as of high importance to human health by WHO (oxacillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus faecium*)	NA
Oxacillin-resistant *S aureus* (%)	80	22·50 (11·50–40·00)	1·00	88·00	Average resistance to oxacillin observed for *S aureus* isolates	NA
Vancomycin-resistant *E faecium* (%)	37	22·00 (4·00–37·00)	1·00	69·00	Average resistance to vancomycin observed for *E faecium* isolates	NA
Medium priority human pathogens (%)	50	16·00 (6·00–29·00)	1·00	82·35	Average resistance observed in pathogen-antibiotic pairs defined as of medium importance to human health by WHO (penicillin-resistant *Streptococcus pneumoniae*)	NA
Food-producing animals (%)	164	24·80 (21·45–30·30)	5·35	48·36	Average resistance observed in isolates obtained from food-producing animals	NA
Antibiotic consumption (main independent variables)						
Third generation cephalosporins consumption in humans (in DDDs)	73	807·92 (440·52–1365·27)	83·34	5280·11	Annual third generation cephalosporins consumption, DDD per 1000 individuals	Positive associations with AMR
Carbapenems consumption in humans (in DDDs)	71	15·41 (3·69–30·62)	0·50	90·85	Annual third generation cephalosporins consumption, DDD per 1000 individuals	Positive associations with AMR
Oxacillins consumption in humans (in DDDs)	65	1·86 (0·48–3·11)	1·90	24·68	Annual oxacillin consumption, DDD per 1000 individuals	Positive associations with AMR
Glycopeptides consumption in humans (in DDDs)	72	4·81 (0·63–12·20)	0·25	72·51	Annual glycopeptide consumption, DDD per 1000 individuals	Positive associations with AMR
Penicillins consumption in humans (in DDDs)	72	137·88 (43·64–357·63)	0·86	3281·86	Annual penicillin consumption, DDD per 1000 individuals	Positive associations with AMR
Antibiotic consumption in animals (mg per PCU)	166	45·13 (39·57–61·53)	7·05	318·59	Estimated antibiotic consumption in livestock, 2013. Expressed in mg per PCU*	Positive associations with AMR

Positive association caused an increase in AMR. A full description of the variables used and country details and their classification by WHO region and World Bank income group is included in the appendix (pp 4–17). The full descriptive statistics for our raw, analytical, and imputed samples are reported in the appendix (pp 33–35). Longitudinal global rates of resistance and antibiotic consumption are shown in the appendix (pp 60–61). The crude relationship between GDP and AMR among humans and animals are reported in the appendix (p 62). AMR=Antimicrobial resistance. DDD=defined daily dose. GDP=gross domestic product. NA=not applicable. PCU=population correction unit. *PCU represents the total number of food-producing animals in a country (alive or slaughtered) that considers the differences between countries regarding animal weight and number of production cycles annually.

Table 1: **Raw descriptive statistics of the dependent and main independent variables included in the final regression models**

animal AMR with antibiotic consumption in humans and animals, accounting for identified, additional risk factors.

We searched PubMed from Jan 1, 2000, until Dec 1, 2022, for articles using keywords related to "global antimicrobial resistance" OR "antibiotic resistance" AND ("infrastructure" OR "socioeconomic" OR "sanitation and hygiene" OR "governance" OR "environment" OR "monitoring and surveillance" OR

"antibiotic/antimicrobial consumption"). Our search was restricted to articles written in English. Articles containing keywords "HIV/AIDS", "tuberculosis", "virus", "fungus", and "parasites" were excluded because we focused on WHO's bacterial priority pathogens list.[19] From the search, we extracted main global variables associated with AMR, detailed in the appendix (pp 4–11).

We included human and food-producing animal AMR rates as dependent variables. Human AMR rate comprised three different sublevels created based on average country-level resistance rates of pathogen and antibiotic combinations described by WHO as requiring urgent action due to the threat they pose to human health (table 1).[19] We also present a subanalysis by antibiotic–bacterium specific pairs, including carbapenem-resistant *Acinetobacter baumanii*, carbapenem-resistant *Pseudomonas aeruginosa*, third generation cephalosporins-resistant *Escherichia coli*, third generation cephalosporins-resistant *Klebsiella pneumoniae*, oxacillin-resistant *Staphylococcus aureus*, and vancomycin-resistant *Enterococcus faecium* rates in humans. Human AMR data were obtained from the Centre for Disease Dynamics, Economics and Policy's ResistanceMap.[20] When possible, missing human AMR rates were imported from the WHO's Global Antimicrobial Resistance and Surveillance System (GLASS)[21] and the Pan American Health Organisation (PAHO).[22] Countries that had data imported from GLASS and PAHO are listed in the appendix (p 11).

Animal AMR rates were generated based on average country-level resistance rates in food-producing animals. Animal AMR data were obtained from ResistanceBank.[23] Missing animal AMR rates were imported from the European Food Safety Authority (EFSA) national zoonoses country reports[24] and other published reports.[25–33] Missing animal AMR data were extracted from sources following the inclusion criteria used to create ResistanceBank.[23,34] Details regarding the inclusion criteria for animal AMR data are reported in the appendix (p 11). Kernel density figures for the distribution of animal AMR data by species (cattle, chicken, and pig) are available in the appendix (p 18).

Human data were available from 1998 to 2017 and animal data were available from 2000 to 2019. Data from the most recent year provided by each country with available data were used to create the human and animal AMR variables.

For more on the **human and AMR variables** see http://www.resistancemap.cddep.org

The main independent variable was antibiotic consumption data for humans and animals; data obtained from ResistanceMap.[20,35] Human antibiotic consumption data were available from 2000 to 2015, depending on country, and were expressed in defined daily doses per 1000 individuals. Data from the most recent year provided by each country were used for all analyses. Animal antibiotic consumption data were from 2013 only and were modelled estimates measured in mg per population correction units.

Additional independent variables were on socioeconomic, environmental, antibiotic policy and regulation in humans and animals, and health-related indicators, extracted from the World Bank, UN, WHO, Global Burden of Disease, and National Centres for Environmental Information databases (table 2).[53–61]

Statistical analysis

First, we estimated the crude associations between AMR rates in humans and animals and our main independent variables with multiple β regressions. We tested different link functions for the conditional mean (eg, logit, probit, loglog, and cloglog) and determined that the best fit was given by the cloglog function based on the models' Akaike information criterion values.[62] Second, we employed univariate analyses by calculating Pearson's correlation between our dependent variables and all the additional independent variables (appendix pp 25–32); variables with statistically significant Pearson's values (p value less than 0·1) were included in subsequent analyses. Third, we tested the remaining explanatory variables for multicollinearity by using all remaining socioeconomic factors that had been significantly associated with at least one of the animal or human AMR variables (critical, high, or medium priority, and antibiotic–bacterium pairs). Highly correlated variables displaying a variance inflation factor of more than five were removed from the analysis. Fourth, a forward stepwise selection regression approach determined which of the remaining independent variables should be included in each of the final models. Beginning with each null model, independent variables were added one at a time, with the aim of improving the fit until the best performance ratio was found according to the models' Akaike information criterion values. We calculated global descriptive statistics of the dependent and independent variables that were included in the models (sample-restricted) and generated subgroup boxplots by WHO region and World Bank income groups for AMR rates. Finally, we set a multivariable β regression model for each dependent variable. The full multivariable model followed the structure detailed in the equation.

$$g(u_t) = \sum_{i=1}^{k} x_{ti}\beta_i$$

β equals $(\beta_{i=1},\ldots,\beta_{i=k})^T$ and is a vector of unknown regression parameters for each independent variable (κ; $\beta \in IR+$), and $x_{t,i=1},\ldots,x_{t,i=k}$ are observations on κ for each country (t). u_t represents the mean of our AMR rate variables (falling between 0 and 1) whereby conditional variance (dispersion parameter) follows the β density function (to model the mean of the response variable). The $g(u_t)$ term is monotonic and twice differentiable link function that maps variables whose values fall between 0 and 1 into IR. More details on multivariable β regression models and their specifications have been reported by Ferrari and Cribari-Neto.[63]

	Definition	Expected association with AMR
Socioeconomic and demographic indicators		
GDP based on purchasing power parity	GDP purchasing power parity by country; continuous variable presented in 2018 US$	Negative associations with AMR[9]
GINI index	The extent to which the distribution of income between individuals or households within an economy deviates from a perfectly equal distribution	Positive associations with AMR[36]
Current health expenditure	Percentage of gross domestic product spent on health care by country in 2016	Negative associations with AMR[9]
Hospital beds per 10 000 people	Number of hospital beds per 10 000 people by country	Negative associations with AMR[36]
Mortality rate attributable to unsafe WASH	Deaths attributable to unsafe WASH focusing on inadequate WASH services, expressed per 100 000 population	Positive associations with AMR[37]
Population density	Number of people divided by land area measured in km², most recent year available	Positive associations with AMR[38]
Net migration rate	Annual difference in number of immigrants and emigrants, most recent year available around 2018	Positive associations with AMR[39]
Median age of population	Median age of the population, UN projections for 2020	Positive associations with AMR[40]
Homeless people	Annual average number of homeless people due to natural disasters per 1 000 000 people, 2008–18	Positive associations with AMR[41]
Population in work	Percentage of population aged 15 years or older in the labour force, 2018	Negative associations with AMR[42]
Environmental indicators		
$PM_{2·5}$	Annual mean concentration of $PM_{2·5}$ (micrograms of gaseous pollutant per cubic meter of ambient air μg/m³) in urban areas (2016)	Positive associations with AMR[43]
Average temperature (°C)	Average 12 monthly temperature in Celsius, 2016	Positive associations with AMR[10]
Health-related indicators		
Cardiovascular death rate per 100 000	Annual number of deaths per 100 000 people due to cardiovascular disease in 2017	Positive associations with AMR[44]
Obesity prevalence	Crude prevalence of obesity in adults (BMI ≥30 kg/m²), 2016	Positive associations with AMR[45]
Governance indicators		
Control of corruption	Control of corruption captures perceptions of the extent to which public power is exercised for private gain, including both petty and grand forms of corruption, as well as capture of the state by elites and private interests*	Negative associations with AMR[46]
Voice and accountability	Voice and accountability captures perceptions of the extent to which a country's citizens are able to participate in selecting their government, as well as freedom of expression, freedom of association, and a free media*	Negative associations with AMR[46]
Rule of law	Rule of law captures perceptions of the extent to which agents have confidence in and abide by the rules of society, and in particular the quality of contract enforcement, property rights, the police, and the courts, as well as the likelihood of crime and violence*	Negative associations with AMR[46]
Regulatory quality	Regulatory quality captures perceptions of the ability of the government to formulate and implement sound policies and regulations that permit and promote private sector development*	Negative associations with AMR[46]
Antibiotic policy and regulation in humans and animals		
National monitoring systems for sales, prescription, and consumption of antibiotics in humans	Dummy variable indicating whether the country has a national monitoring system for the control of any of the following areas: antibiotic sales, antibiotic consumption, and antibiotic prescribing in humans in 2018 from the Tripartite AMR Country Self-Assessment Survey, 2018	Negative associations with AMR[47]
Country policies and regulation on antimicrobial use in humans	Country has policies and regulation on antimicrobial use (laws or regulations on prescription and sale of antimicrobials, for human use); it is a binary (yes *vs* no) question from the Tripartite AMR Country Self-Assessment Survey, 2018	Negative associations with AMR[48]
Country policies and regulation on antimicrobial use for growth promotion in animals	Country has laws or regulations that prohibits the use of antibiotics for growth promotion in the absence of risk analysis (binary [yes *vs* no] outcome) from the Tripartite AMR Country Self-Assessment Survey, 2018	Negative associations with AMR[47]
Arable land (percentage of land area)	Percentage of land area that is under temporary crops, temporary meadows for mowing or for pasture, land under market or kitchen gardens, and land temporarily fallow, 2018	Positive associations with AMR[49]
Cattle density	Global distribution of cattle expressed in total number of cattle per pixel (5 minute of arc), 2010[50,51]	Positive associations with AMR[52]

Positive association caused an increase in AMR; negative associations caused a decrease in AMR. Definitions and sources for the final independent variables used and all auxiliary independent variables tested but not included in multivariable analyses are reported in the appendix (p 4). Descriptive statistics of the independent variables by model analysed (per dependent variable) and sample (non-imputed raw model, analytical sample considering all raw independent variables, and model with imputed data) are included in the appendix (pp 33–53). AMR=Antimicrobial resistance. GDP=gross domestic product. WASH= water, sanitation, and hygiene. *Estimate gives the country's score on the aggregate indicator, in units of a standard normal distribution (ie, ranging from approximately −2·5 to 2·5), 2018.

Table 2: **Definition of the independent variables included in any of the final multivariable models**

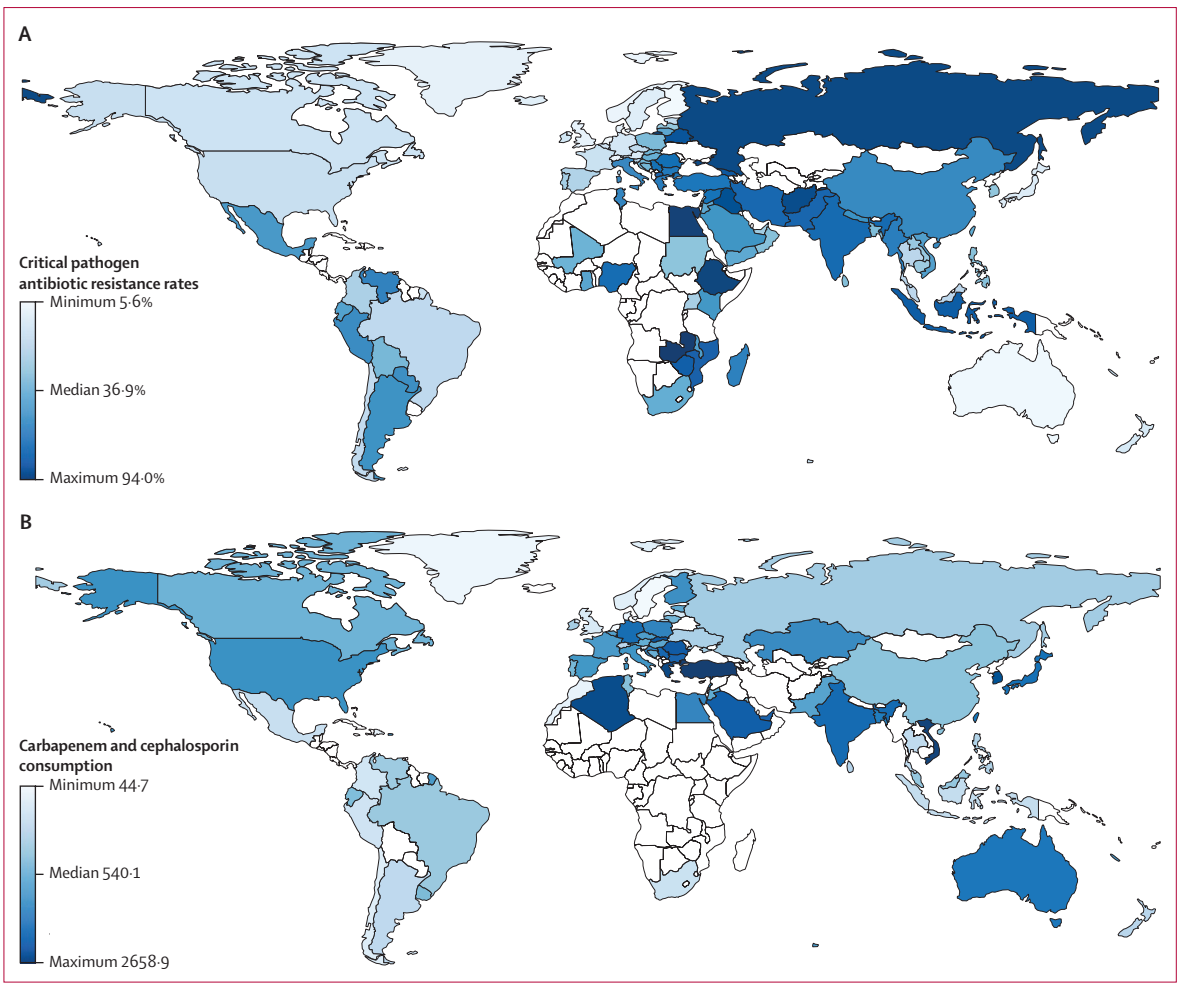

Figure 1: **Critical pathogen antibiotic resistance rates and carbapenem and cephalosporin consumption by country**
(A) Antibiotic-resistance rate in humans for the critical pathogens in humans (96 observations). (B) Antibiotic consumption (in DDDs) in humans for carbapenems and cephalosporins (73 observations). Countries in white represent those with missing data. Pearson's correlation between antibiotic resistance and consumption in humans was 0·30 (p=0·021). DDD=defined daily doses per 1000 individuals.

Each multivariable model included its respective antibiotic consumption data as a forced variable because it has been shown to be the main predictor of AMR rates in previous studies.[7,64] GDP was also incorporated for cross-country comparisons. Continuous variables were standardised (ie, mean subtracted and divided by the variable's SD) for better interpretability and comparability of the estimates in multivariable analyses. Pseudo R^2 is reported as goodness-of-fit for every model.

We assessed the validity of our findings by employing a leave-one-out cross-validation approach to determine the R^2, root mean squared errors, and mean absolute errors of our models after eliminating the i−1th observation from the model. We did a separate analyses for observed data only (excluding imputed observations) and eliminating highly influential countries as determined by their Cook's Distance values.[65] To ensure our model was consistent with recent estimates for antimicrobial sales volume in animals, we tested our model adding countries' amount of sales per kg obtained from Tiseo and colleagues.[8] This dataset provides the most recent data; however, it is restricted to only 41 countries, most of which were high income. We reran our animal model including species-specific AMR data as the dependent variable to assess whether there are differences by food-producing animal group. Finally, to retain statistical power in the multivariable analysis, all remaining independent variables were imputed to restrict the number of missing observations and to compare fully imputed with non-imputed models. We used a multivariable linear regression imputing approach for independent variables and with bootstrap sampling (n=1000 repetitions) using income class, urban population (%), life expectancy, mean years of schooling, population using at least basic sanitation services (%), population (total number), and human development index, as reference variables. All statistical analyses were done in Stata 17 and R studio (version 1.4.1106).

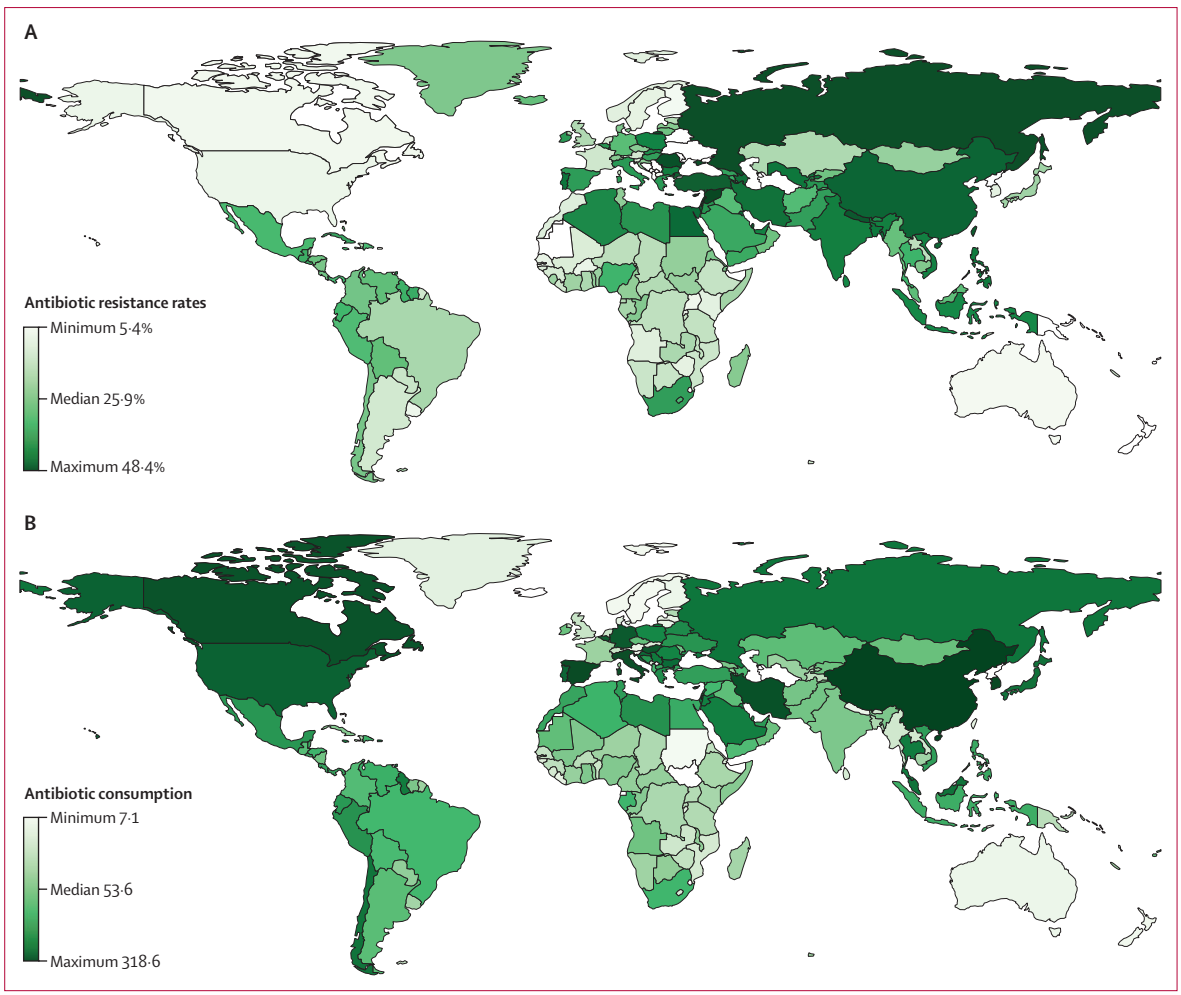

Figure 2: **Antibiotic resistance rates and antibiotic consumption in food-producing animals by country**
(A) Antibiotic resistance rate in animals (166 observations). (B) Estimated antibiotic consumption (mg per PCU) in animals (164 observations). Countries in white represent those with missing data. Pearson's correlation between antibiotic resistance and consumption in food-producing animals was 0·28 (p<0·0001). PCU=population correction unit.

Role of the funding source

There was no funding source for this study.

Results

Table 1 shows the raw descriptive statistics of the dependent and main independent variables included in the final regression models. The median prevalence of human pathogen resistance was 39·89% (IQR 23·09–45·68) for critical pathogens, 24·00% (15·00–41·00) for high priority pathogen, and 16·00% (6·00–29·00) for medium priority pathogens (penicillin-resistant *Streptococcus pneumoniae*) across all countries. For food-producing animals' median resistance prevalence was 24·80% (21·34–30·30). Carbapenem-resistant *A baumanii* (55·68%) and third generation cephalosporins-resistant *K pneumoniae* (53·11%) were the two highest prevalence antibiotic–bacterium combination pairs, whereas oxacillin-resistant *S aureus* (22·50%) and vancomycin-resistant *E faecium* (22·00%) were the two lowest. Figure 1 shows the levels of critical priority pathogen's AMR and carbapenem and cephalosporin consumption in humans. Figure 2 shows AMR and carbapenem and cephalosporin consumption in food-producing animals. Detailed AMR rates and antibiotic consumption levels for humans and animals by World Bank income class and WHO region are shown in the appendix (pp 19–24). The highest rates of resistance for all human pathogens were observed in LMICs, whereas the lowest rates of resistance were found in HICs. Yet, HICs reported the greatest proportion of AMR in food-producing animals, and LMICs the lowest (appendix p 22). The European region consistently reported the lowest average human AMR rates compared with other regions (appendix p 21). Charts per specific antibiotic–bacterium combinations showed large differences in human AMR levels for LMICs among oxacillin-resistant *S aureus* and penicillin-resistant *S pneumoniae* from the Eastern Mediterranean

	OR (95% CI)	p value
WHO critical human pathogen AMR (n=60; R^2 86·4%)		
Consumption of carbapenems and cephalosporins in humans (DDDs)*	1·06 (1·00–1·12)	0·035
Antibiotic consumption in animals (mg per PCU)*	1·07 (1·01–1·13)	0·020
GDP (ppp)*	0·88 (0·76–1·02)	0·081
Control of corruption*	0·65 (0·54–0·79)	<0·0001
Cardiovascular death rate per 100 000 people*	1·18 (1·08–1·28)	<0·0001
Current health expenditure (percentage of GDP)*	0·96 (0·88–1·04)	0·34
GINI index*	1·13 (1·07–1·19)	<0·0001
$PM_{2·5}$*	1·11 (1·04–1·18)	<0·0001
National monitoring systems for sales, prescription, and consumption of antibiotics in humans	0·89 (0·78–1·00)	0·043
Constant term	0·01 (0·01–0·01)	<0·0001
WHO high priority human pathogen AMR (n=56; R^2 58·4%)		
Consumption of oxacillin and glycopeptides in humans (DDDs)*	1·22 (1·09–1·37)	<0·0001
Antibiotic consumption in animals (total sales in kg)*	1·15 (1·00–1·32)	0·049
Median age of population*	0·96 (0·93–0·99)	0·0071
Average temperature (°C)*	1·20 (1·03–1·39)	0·017
GDP (ppp)*	0·72 (0·63–0·82)	<0·0001
Voice and accountability*	0·83 (0·73–0·95)	0·0062
National monitoring systems for sales, prescription, and consumption of antibiotics in humans	0·78 (0·80–1·03)	0·080
Population density*	1·11 (1·06–1·16)	<0.0001
Constant term	0·05 (0·02–0·14)	<0·0001
WHO medium priority human pathogen AMR† (N=40; R^2 70·8%)		
Consumption of penicillin in humans (DDDs)*	0·96 (0·80–1·15)	0·65
Antibiotic consumption in animals (mg per PCU)*	1·05 (0·87–1·26)	0·60
GDP (ppp)*	1·32 (0·94–1·84)	0·11
$PM_{2·5}$*	1·30 (1·01–1·67)	0·040
Regulatory quality*	0·42 (0·28–0·63)	<0·0001
Mortality rate attributable to unsafe WASH*	1·17 (1·02–1·36)	0·029
Constant term	0·01 (0·00–0·01)	<0·0001
AMR in food-producing animals (n=63; R^2 49·6%)		
Antibiotic consumption in animals (mg per PCU)*	1·05 (1·01–1·10)	0·013
Consumption of carbapenems and cephalosporins in humans (DDDs)*	1·05 (1·01–1·09)	0·010
GDP (ppp)*	1·04 (0·93–1·16)	0·49
Average temperature (°C)*	0·97 (0·89–1·06)	0·54
Current health expenditure (percentage of GDP)*	0·91 (0·83–0·99)	0·037
Rule of law*	0·82 (0·69–0·98)	0·027
Cattle density*	1·02 (0·97–1·08)	0·38
Country policies and regulation on antimicrobial use for growth promotion in animals	0·83 (0·69–1·02)	0·078
Arable land (percentage of land area)*	1·04 (0·96–1·12)	0·31
GINI index*	1·01 (0·94–1·10)	0·74
Constant term	0·01 (0·01–0·01)	<0·0001

Data are OR (95% CI). n is the number of countries. p values were derived from the Wald test. Pseudo R^2 were calculated. An illustrative explanation of the marginal association between $PM_{2·5}$ and GDP ppp with AMR critical priority levels is reported in the appendix (p 67). Same models containing imputed data are included in the appendix (p 71). DDD=defined daily doses per 1000 individuals. GDP=gross domestic product. OR=odds ratio. PCU=population correction units. ppp=purchasing power parity. *Variables were standardised (ie, mean subtracted and divided by their SD). †WHO medium priority human pathogen classification only included penicillin-resistant *Streptococcus pneumoniae*.

Table 3: **Multivariable β regression model results for the association between AMR in human pathogens and associated risk factors, and AMR in food-producing animals and associated risk factors**

region (appendix pp 23–24). Rates of Enterobacteriaceae resistant to third generation cephalosporins or carbapenems were between 2-times and 2·5-times higher for LMICs compared with HICs. Carbapenem-resistant *P aeruginosa* and *A baumanii* were highly prevalent in upper-middle-income countries from the European region, compared with the other World Bank income groups and WHO regions. Descriptive statistics of the additional independent variables are included in the appendix (pp 33–55). A full list of the countries included in final analyses (analytical sample) by independent variable is included in the appendix (p 56).

Consumption of carbapenems and cephalosporins was significantly associated with increased AMR in critical human pathogens (appendix p 59). Similarly, antibiotic consumption and AMR levels in food-producing animals were positively associated. AMR levels in high and medium priority pathogens were not associated with oxacillin and glycopeptide consumption and penicillin consumption. Third generation cephalosporins and oxacillin consumption were significantly associated with higher AMR levels in *K pneumoniae*, *E coli*, and *S aureus* (appendix p 59).

Table 3 shows the final β regression model outputs by WHO priority pathogens list and table 4 shows the final β regression by specific antibiotic–bacterium pairs. In the critical human pathogen model, carbapenem and cephalosporin consumption in humans (OR 1·06 [95% CI 1·00–1·12]; p=0·035), antibiotic consumption in food-producing animals (1·07 [1·01–1·13]; p=0·020), cardiovascular death rate, GINI index, and $PM_{2·5}$ were associated with an increase in AMR (positively associated with AMR; R^2 86·4%). For instance, a change of one standard deviation in $PM_{2·5}$ resulted in a 1·11 SD increase in critical human pathogen AMR (appendix p 67).

In the high priority human pathogens model, AMR was positively associated with oxacillin and glycopeptides consumption in humans (OR 1·22 [95% CI 1·09–1·37]; p<0·0001), average temperature, and population density, but inversely associated with GDP (purchasing power parity), countries' voice and accountability, and median age of the population (R^2 58·4%). In the medium priority pathogens model, countries' regulatory quality was associated with a decrease in AMR (negatively associated), but mortality rate attributable to unsafe WASH and $PM_{2·5}$ was positively associated with AMR (R^2 70·8%). Antibiotic consumption in animals (OR 1·05 [95% CI 1·01–1·10]; p=0·013), carbapenems and third generation cephalosporins consumption in humans (1·05 [1·01–1·09]; p=0·010), countries' percentage of arable land, and GINI index were positively associated with resistance in food-producing animals, whereas rule of law was negatively associated with AMR (R^2 49·6%).

The results of the predictive analysis that compared rates of AMR in food-producing animals and critical human pathogens after adjusting for the independent variables are reported in the appendix (p 77). LMICs,

particularly from the Eastern Mediterranean and South-East Asia regions, were predicted to have the highest AMR rates in humans and animals.

Higher antibiotic consumption in humans was associated with greater resistance in almost every antibiotic–bacterium respective pair (table 4). Antibiotic consumption in animals was positively associated with rates of third generation cephalosporins-resistant *E coli* (OR 1·09 [95% CI 1·01–1·19]; p=0·041), oxacillin-resistant *S aureus* (1·11 [1·01–1·21]; p=0·023), and carbapenem-resistant *A baumanii* (1·24 [1·12–1·37]; p<0·0001). Governance indicators (eg, rule of law, voice and accountability, regulatory quality, and control of corruption) and countries policies to monitor and control AMR were consistently associated with lower AMR.

We did not find significant changes in our estimates after using the leave-one-out approach (appendix p 68). The results of our analysis that restricted the dependent variable of the animal model by food-producing animal species are detailed in the appendix (p 69); no substantial change was observed. Our models were consistent with Tiseo and colleagues[8] after using antimicrobial sales as a proxy of antibiotic consumption (appendix p 70). Additionally, most estimates were consistent with our study results after the sensitivity analyses with fully imputed data and by removing highly influential data points (appendix pp 71–76).

Discussion

AMR is crucial to a complex network of stakeholders with different priorities, which restricts the means with which to frame the challenge and drive a response.[66] For instance, important gaps remain in our knowledge of similarities and differences between risk factors for AMR in humans and in animals. We collated data for variables that had identified associations with either human or animal AMR. Analysing these together for country-level associations has provided an important step in elucidating these knowledge gaps.

Antimicrobial consumption is routinely implicated as the key driver for AMR, with compelling evidence for dose dependence in populations of animals and humans.[7,67] We showed that, even after adjusting for other covariates as identified from reviewing the literature, there were significant associations between animal antimicrobial consumption and AMR in food-producing animals, and between human antimicrobial consumption and AMR specifically in WHO critical and high priority pathogens. The WHO global priority list of antibiotic-resistant bacteria was formulated in 2017 with the intention of guiding research, discovery, and development of new drugs,[19] but it has also informed intervention policies targeting these priorities.[68] The human drug–pathogen pairings with the most increased odds of resistance were carbapenem (and cephalosporins) and *P aeruginosa* and carbapenem (and cephalosporins) and *A baumanii*; both of which feature in the 2022 Global Burden of Disease report's leading pathogens for deaths associated with resistance.[3] Data were too scarce to specify equivalently prominent

	OR (95% CI)	p value
Carbapenem-resistant *Acinetobacter baumanii* (n=50; R^2 84·0%)		
Consumption of carbapenems and cephalosporins in humans (in DDDs)*	1·14 (1·06–1·24)	<0·0001
Antibiotic consumption in animals (mg per PCU)*	1·24 (1·12–1·37)	<0·0001
GDP (ppp)*	1·13 (0·95–1·35)	0·17
Control of corruption*	0·48 (0·38–0·60)	<0·0001
Net migration rate*	0·76 (0·68–0·84)	<0·0001
Labour force participation rate*	0·87 (0·80–0·95)	0·011
National monitoring systems for sales, prescription, and consumption of antibiotics in humans	0·67 (0·56–0·81)	<0·0001
Obesity prevalence*	1·01 (0·89–1·14)	0·89
Average temperature (°C)*	1·23 (1·08–1·39)	<0·0001
Hospital beds per 10 000 people*	1·01 (0·88–1·15)	0·89
Population density*	0·96 (0·84–1·09)	0·70
Constant term	0·02 (0·02–0·02)	<0·0001
Carbapenem-resistant *Pseudomonas aeruginosa* (n=35; R^2 60·3%)		
Consumption of carbapenems and cephalosporins in humans (in DDDs)*	1·29 (1·09–1·53)	0·0039
Antibiotic consumption in animals (mg per PCU)*	1·10 (0·88–1·38)	0·39
GDP (ppp)*	1·04 (0·81–1·34)	0·74
Median age of population*	1·06 (0·78–1·44)	0·71
Hospital beds per 10 000 people*	1·05 (0·85–1·30)	0·64
Cardiovascular death rate per 100 000 people*	1·43 (1·00–2·06)	0·042
Mortality rate attributable to unsafe WASH*	1·09 (0·90–1·33)	0·37
National monitoring systems for sales, prescription, and consumption of antibiotics in humans	1·42 (0·84–2·39)	0·19
Voice and accountability*	0·55 (0·35–0·85)	0·0083
Constant term	0·01 (0·00–0·01)	<0·0001
Third generation cephalosporins-resistant *Escherichia coli* (n=57; R^2 85·6%)		
Consumption of cephalosporins in humans (in DDDs)*	1·10 (1·00–1·21)	0·061
Antibiotic consumption in animals (mg per PCU)*	1·09 (1·01–1·19)	0·041
GDP (ppp)*	1·02 (0·88–1·18)	0·83
Regulatory quality*	0·50 (0·44–0·58)	<0·0001
Mortality rate attributable to unsafe WASH*	1·10 (1·03–1·17)	0·0049
Country policies and regulation on antimicrobial use in humans	0·90 (0·87–0·92)	<0·0001
Population density*	1·17 (1·12–1·23)	<0·0001
GINI index*	1·09 (0·99–1·20)	0·074
National monitoring systems for sales, prescription, and consumption of antibiotics in humans	0·66 (0·50–0·85)	0·0048
Constant term	0·01 (0·01–0·01)	<0·0001
Third generation cephalosporins-resistant *Klebsiella pneumoniae* (n=59; R^2 79·1%)		
Consumption of cephalosporins in humans (in DDDs)*	1·07 (0·98–1·18)	0·13
Antibiotic consumption in animals (mg per PCU)*	1·08 (0·96–1·20)	0·19
GDP (ppp)*	0·83 (0·69–1·01)	0·058
Regulatory quality*	0·69 (0·58–0·82)	<0·0001
Cardiovascular death rate per 100 000 people*	1·27 (1·13–1·43)	<0·0001
GINI index*	1·17 (1·05–1·31)	0·0051
National monitoring systems for sales, prescription, and consumption of antibiotics in humans	0·86 (0·71–1·04)	0·13
Hospital beds per 10 000 people*	1·00 (0·91–1·09)	0·92
Constant term	0·01 (0·01–0·02)	<0·0001

(Table 4 continues on next page)

	OR (95% CI)	p value
(Continued from previous page)		
Oxacillin-resistant *Staphylococcus aureus* (n=48; R^2 79·9%)		
Consumption of oxacillin in humans (in DDDs)*	1·17 (1·03–1·28)	0·040
Antibiotic consumption in animals (mg per PCU)*	1·11 (1·01–1·21)	0·023
GDP (ppp)*	0·73 (0·59–0·91)	0·0047
National surveillance system for AMR in humans	0·70 (0·60–0·82)	<0·0001
Homeless people*	1·16 (1·10–1·22)	<0·0001
$PM_{2·5}$*	1·10 (0·93–1·29)	0·26
Average temperature (°C)*	1·30 (1·08–1·57)	<0·0001
Population density*	1·12 (1·01–1·25)	0·040
Constant term	0·01 (0·01–0·01)	<0·0001
Vancomycin-resistant *Enterococcus faecium* (n=33; R^2 54·3%)		
Consumption of glycopeptides in humans (in DDDs)*	1·52 (1·15–2·01)	0·0059
Antibiotic consumption in animals (mg per PCU)*	0·91 (0·72–1·15)	0·43
GDP (ppp)*	0·66 (0·34–1·28)	0·22
National surveillance system for AMR in humans	0·58 (0·43–0·78)	<0·0001
Voice and accountability*	1·03 (0·68–1·57)	0·88
$PM_{2·5}$ (scale ×10)*	1·41 (1·01–1·98)	0·043
Hospital beds per 10 000 people*	1·21 (0·89–1·63)	0·22
Constant term	0·01 (0·01–0·01)	<0·0001

Data are OR (95% CI). n is the number of countries. Pseudo R^2 were calculated. Same models containing imputed data are reported in the appendix (p 72). p value derived from the Wald test. Robust standard errors were used. DDD=defined daily doses per 1000 individuals. GDP=gross domestic product. n=number of countries. OR=odds ratio. PCU=population correction units. ppp=purchasing power parity. *Variables were standardised (ie, mean subtracted and divided by their standard deviation).

Table 4: **Multivariable β regression model results for the association between AMR in human pathogens and associated risk factors, by specific bacterium–antibiotic pairs**

drug–pathogen pairings for animals, highlighting a reconcilable disparity in routine AMR reporting between these One Health sectors.

Antimicrobial consumption in animals was significantly associated with resistance in WHO critical priority human pathogens, and antimicrobial consumption in humans was significantly associated with animal AMR rates. A joint interagency report on integrated analysis of antimicrobial consumption and occurrence of AMR in bacteria from humans and food-producing animals sought to establish associations between data from Europe,[69] but did not find a link between antimicrobial consumption in humans and AMR in animals. Whereas their univariate analysis did find an association between consumption in animals and AMR in humans, statistical significance was not retained following multivariable analysis. To the best our knowledge, our study is the first to identify these bidirectional animal–human associations globally. Retained significance of bidirectionality at this scale, and after adjusting for other covariates, contributes important evidence to the One Health paradigm. Not all implications are necessarily pessimistic. Tang and colleagues[16] describe the benefits to human health of livestock-based stewardship programmes, highlighting the potential for targeting single One Health components with interventions but having system-wide effects.

We found significant associations between AMR and several socioeconomic factors. Results from the multivariable analysis showed significant positive associations between human AMR and the GINI index (WHO critical priority), and increased mortality rate attributable to either unsafe WASH (WHO medium priority) or to cardiovascular complications (WHO critical priority). Significant negative associations were found with GDP (WHO high priority), and national monitoring systems for sales, prescription, and consumption of antibiotics in humans (WHO critical priority). Therefore, our models are consistent with previous literature, showing that factors indicative of lower socioeconomic status are associated with higher levels of AMR in humans.[9] These associations are probably explained by the uncontrolled dissemination of resistant bacteria that can occur in settings in which sanitation services are inadequate and access to health care is reduced.

Governance indicators were closely, and intuitively, linked with AMR in animals and humans. Significant negative associations were found with rule of law (animal), regulatory quality (WHO medium priority), voice and accountability (WHO high priority), and control of corruption (WHO critical priority). The order of magnitude of effect was considerable, with halved odds of carbapenem-resistant *A baumanii*, carbapenem-resistant *P aeruginosa*, and third generation cephalosporins-resistant *E coli*, all associated with more reliable governance. This corroborates earlier reports describing the contributions of poor governance and corruption to human AMR,[46] but our results expand their importance to the One Health context.

This study had some limitations. Crucially, there were a lot of missing data: the small number of AMR datasets available for LMICs might have biased our results. Data paucity was worse for the components of animal health meaning that potentially important risk factors, such as wild animal AMR reservoirs, could not be included. It also meant we used modelled estimates of antibiotic consumption in animals, which potentially risked biasing our results. Country-level data on rates of AMR in food-producing animals were also scarce, and the data available for different animal species and zoonotic pathogens differed by country. Data on food-producing animals were all grouped together in our analysis. When these data become more refined, a more species-specific analysis will provide improved granularity to our understanding.

Even though we used the best available data, there remained inconsistencies in the exact year of data collection, the numbers of included countries by WHO region and World Bank income groups, and bacteria reported. There were also limitations in the analytical component of this work. The effectiveness of stepwise

regression as a method of variable selection can sometimes be compromised when a large number of predictor variables are considered.[70] Additionally, β regression models do not correct estimates for skewed data.[63] For example, β-binomial regression accounts for the difference in the availability of testing between countries, particularly between HICs and LMICs.[71] However, for most countries, the isolate-level data required for this alternative approach was unavailable. Finally, because this was an ecological country-level study, any interpretation should be taken with caution because the results might be affected by the absence of variation over aggregated data usage (ie, ecological fallacy).

Our findings suggest that socioeconomic factors play an underappreciated role in the spread of AMR, and antibiotic consumption is potentially only a secondary risk factor in certain regions of the world in which antimicrobial drug consumption is low and resistance rates are high. Preventing spread of AMR will require national action plans beyond the reduction in antibiotic misuse and must involve efforts to improve governance and sanitation infrastructure. Bidirectionality between animals and humans in antimicrobial consumption and resistance emphasises the need for integrated control methods that aim to prevent transmission across different One Health domains. LMICs, particularly in Asia (eg, Bangladesh, China, and India), were shown to have the highest AMR rates in food-producing animals after adjusting for other variables in this study. This finding highlights the pressing need for better AMR surveillance and control efforts in LMICs.

Contributors

KA and LY conceptualised the study and designed the methods and data provision. KA and LD collated and extracted the data. All authors had access and verified the data. AH, KA, and LD collected, extracted, and verified the data. All authors had access to the data. KA and LD did the formal analysis. KA and LD wrote the original draft. KA, LD, LY, AH, CEM, RL, TVB, and LF-K reviewed and edited the manuscript. KA and LY supervised the study. All authors have read and approved the final version of the manuscript and take responsibility for the decision to submit for publication.

Declaration of interests

We declare no competing interests.

Data sharing

Most data are publicly available. CDDEP data are available upon formal request (https://resistancemap.cddep.org).

Acknowledgments

KA was supported by Asociación Nacional de Investigación y Desarrollo (Santiago, Chile). LL was supported by AIR@InnoHK administered by Innovation and Technology Commission. All authors attest they meet the ICMJE criteria for authorship and have reviewed and approved the final Article. This research was supported by a full scholarship provided by the Asociación Nacional de Investigación y Desarrollo through the Beca de Doctorado en el Extranjero Becas Chile (grant 73200098). RL was supported by the US National Science Foundation (CCF1918628) and support from US Centers for Disease Control and Prevention IPA (21IPA2113462).

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