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Determinants of worldwide antibiotic resistance dynamics across drug-bacterium pairs: a multivariable spatial-temporal analysis using ATLAS



Eve Rahbe, Laurence Watier, Didier Guillemot, Philippe Glaser*, Lulla Opatowski*



Summary

Background Antibiotic resistance (ABR) is a major concern for global health. However, factors driving its emergence and dissemination are not fully understood. Identification of such factors is crucial to explain heterogeneity in ABR rates observed across space, time, and species and antibiotics.

Methods We analysed count data of clinical isolates from 51 countries over 2006–19 for thirteen drug-bacterium pairs taken from the ATLAS database. We characterised ABR spatial and temporal patterns and used a mixed-effect negative binomial model, accounting for country-year dependences with random effects, to investigate associations with potential drivers, including antibiotic sales, economic and health indicators, meteorological data, population density, and tourism.

Findings ABR patterns were strongly country and drug–bacterium pair dependent. In 2019, median ABR rates ranged from 6·3% (IQR 19·7% [0·5–20·2]) for carbapenem-resistant *Klebsiella pneumoniae* to 80·7% (41·8% [50·4–92·2]) for fluoroquinolone-resistant *Acinetobacter baumannii*, with heterogeneity across countries. From 2006 to 2019, carbapenem resistance increased in more than 60% of investigated countries; no global trend was observed for other resistances. Multivariable analyses identified significant associations of ABR with country-level selecting antibiotic sales, but only in fluoroquinolone-resistant-*Escherichia coli*, fluoroquinolone-resistant-*Pseudomonas aeruginosa*, and carbapenem-resistant-*A baumannii*. We also found a correlation between temperature and resistance in Enterobacteriaceae and with the health system quality for all drug–bacterium pairs except Enterococci and *Streptococcus pneumoniae* pairs. Despite wide consideration of possible explanatory variables, drug–bacterium pair ABR rates still showed unexplained spatial random effects variance.

Interpretation Our findings reflect the diversity of mechanisms driving global antibiotic resistance across pathogens and stress the need for tailored interventions to tackle bacterial resistance.

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Introduction

Antibiotic resistance (ABR) in clinically relevant bacteria is a major public health threat.¹ Latest estimations show that 1·27 million deaths (95% uncertainty interval 0·91–1·71) were attributable to ABR in 2019 worldwide.^{2,3} Although ABR is a global problem observed in all countries, resistance patterns show important geographical differences and greatly vary depending on the bacterial species and antibiotic resistance considered.³ Factors explaining these variations are not fully understood.

Studies from the past 10 years investigating determinants of country-level ABR suggested that in addition to antibiotic consumption, socioeconomic factors are correlated with ABR rates.^{4,5} Containing ABR spread, rather than only restricting antibiotic consumption, seems crucial to reduce its global burden. But the poor understanding of mechanistic factors driving ABR spread impedes the setup of efficient control measures. Behavioural factors could play a role in ABR

transmission, such as tourism.⁶ In addition, climate warming has been suggested to be associated with ABR dissemination and maintenance, hypothesising that higher temperatures promote bacterial growth and more frequent horizontal gene transfer.^{7–9} More complex mechanisms involving humans and their environment might drive ABR, setting the issue in a One Health perspective.¹⁰

Because pathogens exhibit different resistance mechanisms, thrive in different ecological niches, and can be associated with different epidemiological sources (the environment, hospitals, or the community), understanding ABR dynamics requires studying it at the bacterial species level. Global ABR determinants have been previously analysed using data from one or two selected bacteria or aggregated resistance indices, but no study compared worldwide ABR drivers between species.^{4,5,11}

Data collected by surveillance programmes are needed to analyse and identify determinants of ABR dynamics

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Research in context

Evidence before this study

We searched PubMed for articles in English published between Jan 1, 2000, to Dec 31, 2021. Search terms for titles and abstracts were (“global” OR “worldwide” OR “country” OR “country-level”) AND (“antibiotic resistance” OR “antimicrobial resistance” OR “bacterial resistance” OR “drug resistance”) AND (“factors” OR “determinants” OR “association” OR “correlation”). We excluded studies analysing viruses, parasites, fungi, cancers, cholera, and tuberculosis. The search yielded 100 results. After filtering articles referring to ecological or prevalence studies focusing on only one country, one species or one infection source, articles addressing molecular epidemiology, predicting country-level ABR rates in space or time, or general reviews discussing ABR, we found five relevant studies. Two articles found a link between climate warming and ABR in European countries. The three other articles studied multiple individual socioeconomic and national associated factors, two in Europe, and one in a worldwide dataset. Most studies considered only resistant Enterobacteriaceae or *Staphylococcus aureus*, or used aggregated resistance indices. Reviews retrieved using the search indicated that international travel and tourism could also play a role in ABR spread. No article compared multiple bacterial species and antibiotic resistances using longitudinal data to assess differences in ABR spread factors at the worldwide level.

Added value of this study

ATLAS represents a unique dataset, useful to compare ABR rates worldwide and question their dynamics. We used longitudinal surveillance data of ABR rates from infection samples for 51 countries, not restricted to Europe, and over 14 years

(2006–19). To our knowledge, this is the first study to analyse ABR surveillance data from a large number (thirteen) of different clinically relevant drug–bacterium pairs and to characterise the observed heterogeneity in ABR rates across different countries and years. Our statistical analysis approach included both spatial and temporal dimensions of the ABR phenomenon, with country-year dependent outcome variable and covariables, which were not considered in previous studies. Moreover, the choice of covariables is not restricted to global indices, but rather detailed metrics representing putative mechanistic drivers of ABR, such as meteorological factors (rainfall, relative humidity, temperature, and extreme climatic events—such as flooding) or antibiotic sales described at the antibiotic class level.

Implications of all the available evidence

Analysis of the ATLAS data showed that ABR rates are highly dependent on the country and, most importantly, on the drug–bacterium pair considered. Results from our statistical analysis suggested that factors associated with ABR rates were different across drug–bacterium pairs but more similar within a bacterial species, reflecting different underlying ecological behaviours. Variance between countries was only explained by the proposed factors for *Escherichia coli* where antibiotic sales, temperature, extreme climatic events, and the health system quality could explain most ABR rates differences. For other drug–bacterium pairs, strong spatial variance remained unexplained. Overall, results from this study suggest that ABR should be considered as a plural problem whose control should be tailored regarding the country or the drug–bacterium pair under consideration.

globally in different pathogens. Specifically, the Antimicrobial Testing Leadership and Surveillance (ATLAS) system monitors antibiotics efficacy against a wide range of bacteria.¹² ATLAS gathers clinical isolates from different bacterial infections using a systematic protocol and collects longitudinal data over all continents, including low-income, middle-income, and high-income countries. It uses a standardised and centralised procedure of determining minimal inhibitory concentrations across multiple species and antibiotics combinations, so-called drug–bacterium pairs.

In this study, we aimed to analyse spatial-temporal dynamics of drug–bacterium pairs from worldwide infection ABR surveillance data collected through ATLAS and identify and compare key mechanistic factors—antibiotic sales, meteorological and climatic variables, wealth and health metrics, population density, and tourism—associated with such dynamics.

Methods

Study design

In this study, we analysed count data of clinical isolates from 51 countries between 2006 and 2019 for thirteen

drug–bacterium pairs extracted from the ATLAS database. We first characterised ABR spatial and temporal patterns. Then we ran univariate and multivariable analyses using a mixed-effect negative binomial model to investigate associations with potential drivers, including antibiotic sales, economic, and health indicators; meteorological data; population density; and tourism. We did sensitivity analyses to assess the effect of putative biases on the outcomes of the model. The aim of the study was to identify the main country-year determinants of ABR across different drug–bacterium pairs of clinical interest for human health.

Data sources

Antibiotic resistance (ABR) data were obtained from ATLAS.¹² The ATLAS programme, implemented by Pfizer, collects bacterial isolates from patients in hospital due to bacterial infections within a worldwide hospital network. ATLAS reports minimal inhibitory concentrations in clinical isolates tested against various antibiotics, and associated information on country, year, hospital ward, source of infection, and bacterial species.

Data represent infection isolates, with the bacterial infection being the putative cause of hospitalisation. Isolates came from five distinct bacterial infections, associated with five main sources: blood, sputum, urine, abscess, and wound. ATLAS sampling protocol is detailed in appendix 1 (p 3).

Count data of non-resistant and resistant isolates from 51 countries (appendix 1 p 4) over 14 years (2006–19) were extracted. 13 clinically relevant antibiotic resistance-bacterium pairs (drug–bacterium pairs) were analysed: fluoroquinolone-resistant *Escherichia coli*, aminopenicillin-resistant *E coli*, third generation cephalosporin-resistant *E coli*, fluoroquinolone-resistant *Klebsiella pneumoniae*, third generation cephalosporin-resistant *K pneumoniae*, carbapenem-resistant *K pneumoniae*, fluoroquinolone-resistant *Pseudomonas aeruginosa*, carbapenem-resistant *P aeruginosa*, fluoroquinolone-resistant *Acinetobacter baumannii*, carbapenem-resistant *A baumannii*, vancomycin-resistant *Enterococcus faecalis* and *Enterococcus faecium*, penicillin-non-susceptible *Streptococcus pneumoniae*, and macrolide-resistant *S pneumoniae*. Minimal inhibitory concentrations values were reported in the ATLAS database and isolates were categorised as susceptible, intermediate, or resistant based on the 2019 (v9.0) Minimal Inhibitory Concentrations Breakpoints from the European Committee on Antimicrobial Susceptibility Testing standards.¹⁴ An isolate was considered resistant if it was in the resistant category, except for penicillin-non-susceptible *S pneumoniae*—isolates of which were considered resistant if they were in the intermediate or resistant categories. An isolate was considered resistant to an antibiotic class if it was resistant to at least one of the drugs in the class (appendix 1 p 5).

Covariables were selected and tested as explanatory factors in the statistical analysis based on their hypothetical mechanistic effect on the dynamics and selection of ABR. They include antibiotic sales, meteorological and climatic variables, wealth and health metrics, population density, and tourism (appendix 1 pp 6–7).

Antibiotic sales data were obtained from the IQVIA MIDAS database (appendix 1 p 8).¹⁵ Data from Denmark, Latvia, Lithuania, and the Netherlands were not available through this database and were instead obtained from the ESAC-Net database by converting defined daily doses into grams (appendix 1 p 8). We analysed the five most frequently sold classes of antibiotics in IQVIA MIDAS over all countries and years (broad-spectrum penicillins, cephalosporins, macrolides, quinolones, and trimethoprim and sulfonamides). We also analysed two other classes, carbapenems and glycopeptides, corresponding to resistances in carbapenem-resistant *K pneumoniae*, carbapenem-resistant *P aeruginosa*, carbapenem-resistant *A baumannii*, and vancomycin-resistant

E faecalis and *E faecium* (appendix 1 p 9). Global sales represented the sum of these seven classes. Average temperature, minimum temperature, average rainfall, and average relative humidity per country-year were obtained through the MERRA-2 dataset, using the data for the capital city of each country.¹⁶ Extreme climatic events (droughts, flooding, or extreme temperatures) faced by the population in 2009 was obtained from the World Bank Data.¹⁷ Population size, population density, Gross Domestic Product (GDP) per capita, and international tourism (legal arrivals and departures) data were obtained through the World Bank Data at the country-year level.¹⁷ As a proxy for national health system qualities, the 2019 Global Health Security index (GHS [0–100]) was used.¹⁸

Statistical analysis

ABR rate was defined as the proportion of resistant isolates (Y) divided by the total number of isolates tested (n) for each drug–bacterium–country(c)–year(t) observation from all infection sources:

$$p_{c,t} = \frac{Y_{c,t}}{n_{c,t}}$$

Data filtering was done to ensure ABR data reliability. Only drug–bacterium–country–year observations with more than ten isolates tested were used to compute ABR rates. For each drug–bacterium pair, country-associated time series with less than 5 years of ABR rates data available from 2006 to 2019 were excluded. Data imputation was done when three or fewer consecutive years exhibited missing ABR rates. Imputation was done using a moving average estimate with a time window (k) of 1 year.

Median ABR rates across all countries were estimated for the year 2019, the most recent year of the dataset. Temporal trends of ABR rates were defined as the slope of the regression equation from 2006 to 2019 for each country and pair. Temporal trends were estimated using linear regression minimising weighted least squares, weights being the inverse variance of observations:

$$\frac{n_{c,t}}{p_{c,t} \times (1 - p_{c,t})}$$

Clustering was done on these regression slopes, using complete linkage method on Euclidean distances, and p values associated with slope coefficients' hypothesis test were reported.

A mixed-effect model was used to analyse ABR rates and to identify associated factors by accounting for the dependence of the data between countries and across years.¹⁹ The count of resistant isolates per country-year was considered as the response variable. A negative binomial response distribution was chosen to account for data overdispersion. The model included spatial and

See Online for appendix 1

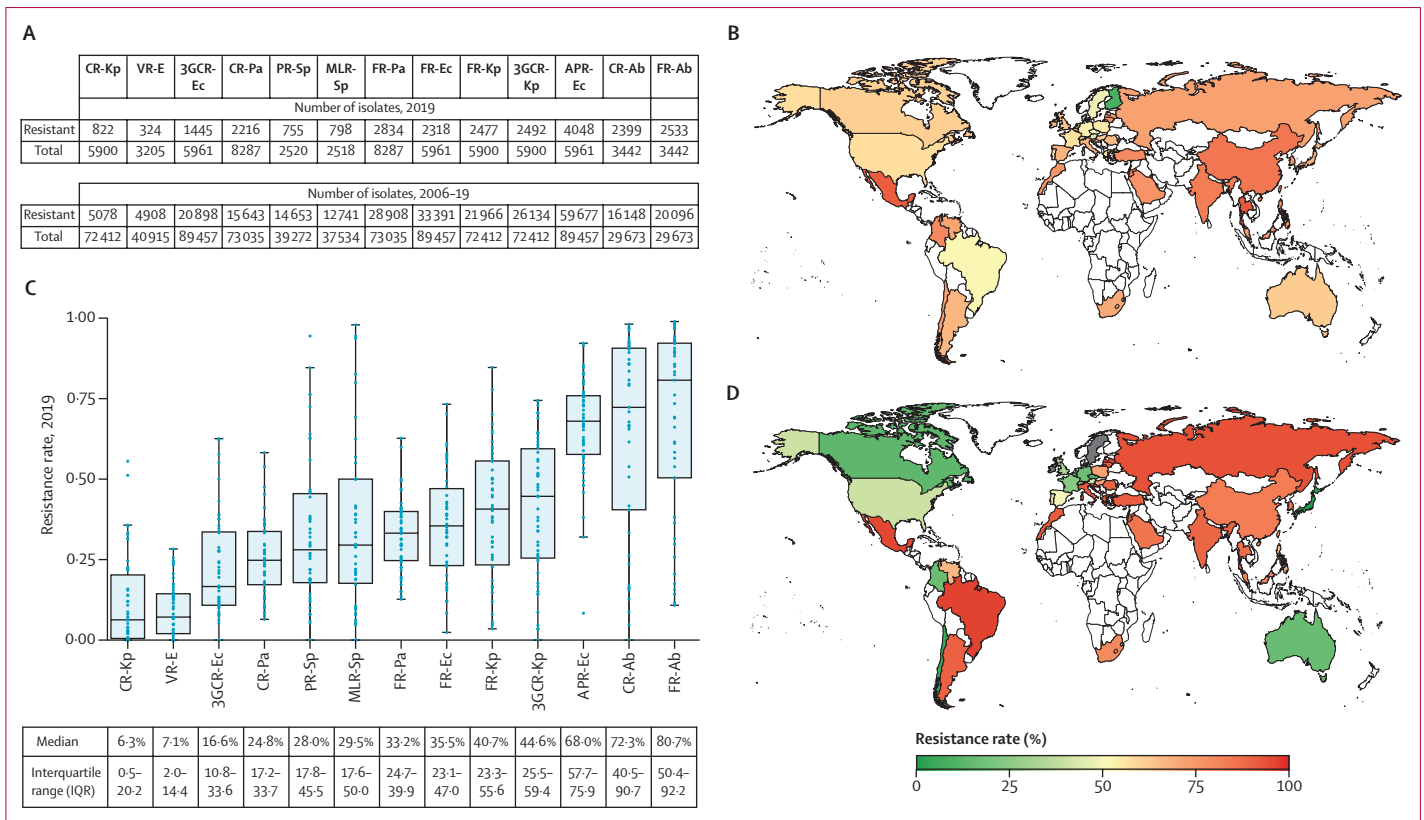


Figure 1: Worldwide ABR rates distribution in 2019 according to ATLAS

ABR rates are reported in proportions or percentages of resistant isolates over total number of tested isolates per country for each drug–bacterium pair. (A) Sample sizes (number of resistant and total isolates) for each drug–bacterium pair, for the year 2019 and for the whole study period (2006–19). (C) Median (IQR) ABR rates across countries for all drug–bacterium pairs. Maps of worldwide ABR rates for APR-Ec (B) and CR-Ab (D), two pairs exhibiting high median rates in 2019; grey countries indicate missing value for 2019. White countries are not included in the analysis. 3GCR-Ec=third generation cephalosporin-resistant *Escherichia coli*. 3GCR-Kp=third generation cephalosporin-resistant *Klebsiella pneumoniae*. ABR=antibiotic resistance. APR-Ec=aminopenicillin-resistant *E. coli*. CR-Ab=carbapenem-resistant *Acinetobacter baumannii*. CR-Kp=carbapenem-resistant *K. pneumoniae*. CR-Pa=carbapenem-resistant *Pseudomonas aeruginosa*. FR-Ab=fluoroquinolone-resistant *A. baumannii*. FR-Ec=fluoroquinolone-resistant *E. coli*. FR-Kp=fluoroquinolone-resistant *K. pneumoniae*. FR-Pa=fluoroquinolone-resistant *P. aeruginosa*. MLR-Sp=macrolide-resistant *Streptococcus pneumoniae*. PR-Sp=penicillin-non-susceptible *S. pneumoniae*. VR-E=vancomycin-resistant Enterococci.

temporal random effects and fixed effects with the covariables data. The model equation used for each drug–bacterium pair was as follows:

$$\begin{aligned}
 Y_{c,t} &\sim NB(\mu_{c,t}, \theta) \\
 \mu_{c,t} &= \pi_{c,t} \times n_{c,t} \\
 \log(\mu_{c,t}) &= \beta_0 + \log(n_{c,t}) + \beta X + b_c + \phi_t + \varepsilon_{c,t} \\
 b_c &\sim N(0, \sigma_b^2) \\
 \phi_t &\sim N(0, \sigma_\phi^2) \\
 \varepsilon_{c,t} &\sim N(0, \sigma_\varepsilon^2)
 \end{aligned}$$

c is the country, t the year, $Y_{c,t}$ the number of resistant isolates per country and year; $\mu_{c,t}$ the expected number of resistant isolates; θ the dispersion parameter of the negative binomial distribution; $n_{c,t}$ the number of isolates tested (offset); $\pi_{c,t}$ the proportion of resistant isolates (ABR rate); β the fixed effects parameter vector of size p (p the number of fixed effects); X the fixed effects model matrix of size $C \times T \times p$ (with C total

number of countries and T total number of years); b_c the country-dependent random intercept; ϕ_t the year-dependent random intercept; and $\varepsilon_{c,t}$ the residuals of the model. Random effects and residuals are assumed to be normally distributed.

Intercept-only (called M-null), univariate, and multivariable models (M-multi) were evaluated independently for all drug–bacterium pairs. Covariables data were standardised (centred with their mean and scaled with their SD). Correlation analysis between each covariable was done using the Pearson coefficient (r), and covariables associated with r of more than 0.7 were excluded from analyses (appendix 1 p 10). For antibiotic sales variables, only global sales and sales of the antibiotic selecting for the specific resistance (antibiotic sales of interest) were tested in the univariate analysis. Covariables associated with a p value less than 20% in the univariate analysis were included in the multivariable analysis. Backward selection was then done using hypothesis testing method (z -test). Every covariable left in the M-multi final multivariable models were

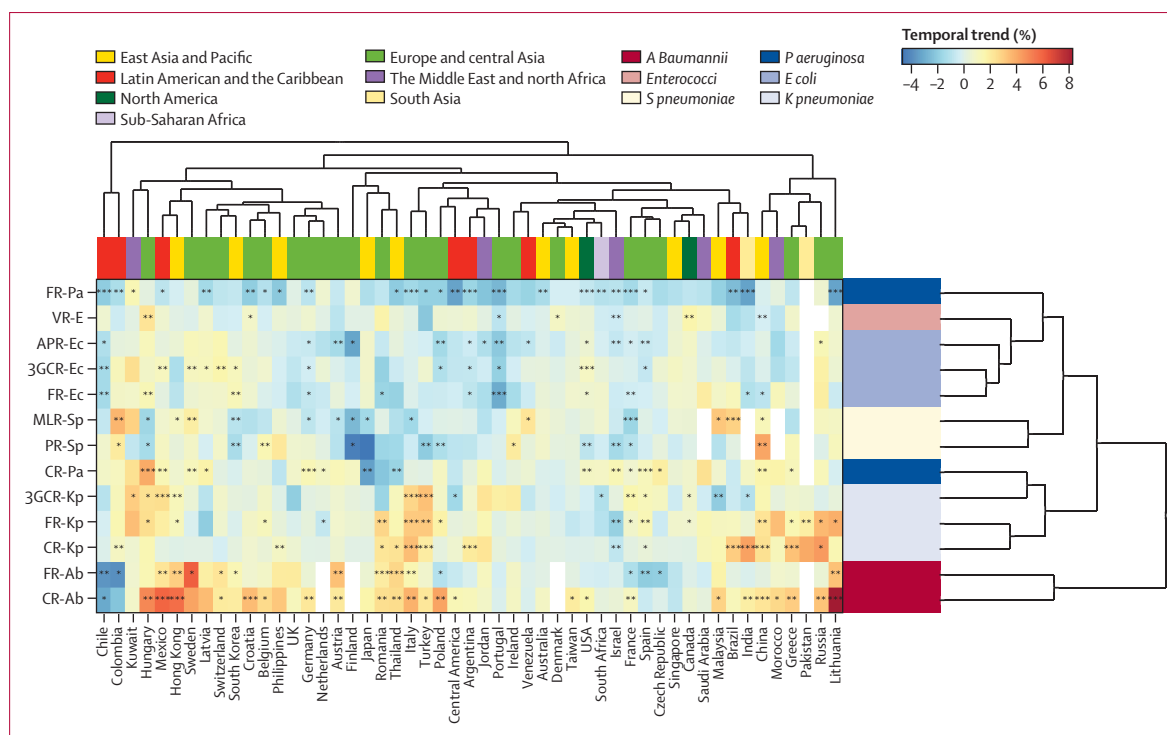


Figure 2: ABR temporal trends (2006–19) by country and drug–bacterium pair

The heat map shows temporal trends, defined as slopes estimated from weighted linear temporal regressions (appendix pp 19–32). Temporal trends represent the ABR rate change per year for each country and drug–bacterium pair. Stars represent p values associated with hypothesis tests on regression slopes (* $p<0.05$; ** $p<0.01$; and *** $p<0.001$). A white cell represents a missing value for a specific country and drug–bacterium pair. Clustering was done on both rows and columns. Possible uncertainty around clustering is reported in the appendix (p 33). Countries were categorised into world's regions based on World Bank indicators and drug–bacterium pairs were categorised into bacterial species, as indicated in the upper legend. 3GCR-Ec=third generation cephalosporin-resistant *Escherichia coli*. 3GCR-Kp=third generation cephalosporin-resistant *Klebsiella pneumoniae*. ABR=antibiotic resistance. APR-Ec=aminopenicillin-resistant *E coli*. CR-Ab=carbapenem-resistant *Acinetobacter baumannii*. CR-Kp=carbapenem-resistant *K pneumoniae*. CR-Pa=carbapenem-resistant *Pseudomonas aeruginosa*. FR-Ab=fluoroquinolone-resistant *A baumannii*. FR-Ec=fluoroquinolone-resistant *E coli*. FR-Kp=fluoroquinolone-resistant *K pneumoniae*. FR-Pa=fluoroquinolone-resistant *P aeruginosa*. MLR-Sp=macrolide-resistant *Streptococcus pneumoniae*. PR-Sp=penicillin-non-susceptible *S pneumoniae*. VR-E=vancomycin-resistant Enterococci.

statistically significant with a p value less than 5%. Akaike Information Criterion (AIC) values were reported to compare M-null and M-multi models for all drug–bacterium pairs. The model parameters were estimated using maximum likelihood by Laplace approximation using the lme4R package (version 1.1.31).²⁰ To test the difference between variances of random effects from M-null and M-multi models, the F-test for equality of two variances was used.

Some drug–bacterium–country–year observations or countries had to be excluded from the statistical model analysis. For carbapenem-resistant *K pneumoniae* and vancomycin-resistant Enterococci, where ABR rates frequently reached zero values, countries with less than two non-zero data points over the full period were excluded. Observations for which some country-year covariables were not available were also excluded (appendix 1 p 11).

Sensitivity analyses were carried out. To assess the potential effect of the filtering threshold related to the minimum number of isolates tested per country-year, we repeated analyses with a filter on 20 isolates instead of ten. To assess whether using ESAC-Net data for

Denmark, Latvia, Lithuania, and the Netherlands had any major effects on the results, we repeated analyses after excluding these countries. To assess whether the infection source might affect ABR rates and associations with covariables, we analysed a subset of the data for which isolates only came from blood. Finally, we evaluated the potential effect of imputing missing ABR rates on given years on the resulting associations between ABR rates and covariables by analysing the dataset without any imputed observations. All analyses were done with R, version 4.0.3.²¹

Role of the funding source

The funder had no role in data analysis, data interpretation or writing of the paper.

Results

808 744 isolates from all infection sources were analysed across the 13 drug–bacterium pairs. Number of tested isolates for each drug–bacterium pair and each year, region, minimal inhibitory concentration distribution, and isolate distribution and ABR rate by infection sources or hospital wards are reported in appendix 1 (pp 13–18).

	FR-Ec	APR-Ec	3GCR-Ec	FR-Kp	3GCR-Kp	CR-Kp	FR-Pa	CR-Pa	FR-Ab	CR-Ab	VR-E	PR-Sp	MLR-Sp
Significant covariables in final multivariable models	<ul style="list-style-type: none"> • Quinolones sales • GHS index • Extreme events • Temperature 	<ul style="list-style-type: none"> • GHS index • Extreme events • Temperature • Tourist departures 	<ul style="list-style-type: none"> • GHS index • Extreme events • Temperature 	<ul style="list-style-type: none"> • GHS index 	<ul style="list-style-type: none"> • GHS index 	<ul style="list-style-type: none"> • GHS index • Temperature 	<ul style="list-style-type: none"> • Quinolones sales • GHS index • GDP 	<ul style="list-style-type: none"> • GHS index • Tourist departures 	<ul style="list-style-type: none"> • GHS index • Rainfall 	<ul style="list-style-type: none"> • Carbapenem sales • Global antibiotic sales • GHS index • GDP 	..	<ul style="list-style-type: none"> • Global antibiotic sales • Relative humidity 	<ul style="list-style-type: none"> • Global antibiotic sales • GDP • Extreme events

Figure 3: Significant covariables associated with each drug–bacterium pair, from final multivariable models
 Summary of significant covariables in multivariable models for each drug–bacterium pair. 3GCR-Kp=third generation cephalosporin-resistant *Klebsiella pneumoniae*. ABR=antibiotic resistance. APR-Ec=aminopenicillin-resistant *E coli*. CR-Ab=carbapenem-resistant *Acinetobacter baumannii*. CR-Kp=carbapenem-resistant *K pneumoniae*. CR-Pa=carbapenem-resistant *Pseudomonas aeruginosa*. FR-Ab=fluoroquinolone-resistant *A baumannii*. FR-Ec=fluoroquinolone-resistant *E coli*. FR-Kp=fluoroquinolone-resistant *K pneumoniae*. FR-Pa=fluoroquinolone-resistant *P aeruginosa*. GDP=Gross Domestic Product. GHS=Global Health Security index. MLR-Sp=macrolide-resistant *Streptococcus pneumoniae*. PR-Sp=penicillin-non-susceptible *S pneumoniae*. VR-E=vancomycin-resistant Enterococci.

Distribution of antibiotic resistance rates across countries in 2019 highlighted strong heterogeneity across drug–bacterium pairs. For 2019 and the whole study period (2006–19), numbers of resistant and total isolates by drug–bacterium pairs are reported in figure 1A. The median ABR ranged from 6.3% (IQR [0.5–20.2]) for carbapenem-resistant *K pneumoniae* to 80.7% [50.4–92.2] for fluoroquinolone-resistant *A baumannii* (figure 1B). Although median ABR rates were similar between carbapenem-resistant *A baumannii* (72.3% [40.5–90.7]) and aminopenicillin-resistant *E coli* (68.0% [57.7–75.9]), the different IQRs indicate different ABR rates distribution across countries (figures 1C and D).

From 2006 to 2019, ABR showed different temporal trends between drug–bacterium pairs (appendix 1 pp 19–32). Figure 2 highlights that ABR temporal trends do not specifically cluster by world’s region, but rather cluster by species or resistances. *E coli* pairs clustered together as did *K pneumoniae* pairs, suggesting similarities in their temporal trends, but no clear worldwide increasing or decreasing temporal pattern was observed. Two pairs showed global worldwide trends. ABR rates for fluoroquinolone-resistant *Pseudomonas aeruginosa* showed decreasing trends over the period, with 24 out of 50 countries exhibiting statistically significant negative slopes. Conversely, ABR rates trends for carbapenem-resistant *A baumannii* globally increased, with 24 of 47 countries exhibiting statistically significant positive slopes. Drug–bacterium pairs associated with carbapenems resistance generally exhibited increasing trends: 31 (61%) of 51 countries had increasing trends for carbapenem-resistant *K pneumoniae* (13 statistically significant positive slopes); 38 (76%) of 50 countries for carbapenem-resistant *P aeruginosa* (14 statistically significant positive slopes); and 39 (83%) of 47 countries for carbapenem-resistant *A baumannii* (24 statistically significant positive slopes; appendix 1 pp 19–32).

From the multivariable analyses, we could assess the association between ABR rates and the proposed covariables (appendix 2; figure 3; appendix 1 pp 35–42).

We found that key factors associated with ABR rates varied greatly between drug–bacterium pairs, but were more similar within same bacterial species. First, antibiotic sales were only significantly associated with

ABR rates in five drug–bacterium pairs: fluoroquinolone-resistant *E coli* and fluoroquinolone-resistant *P aeruginosa* rates were positively associated with quinolones sales; carbapenem-resistant *A baumannii* rates were also positively correlated with carbapenems sales but inversely correlated with global antibiotic sales; penicillin-non-susceptible *S pneumoniae* and macrolide-resistant *S pneumoniae* rates were positively associated with global antibiotic sales. Second, meteorological factors were mostly found to be associated with Enterobacteriaceae and *S pneumoniae* drug–bacterium pairs: all *E coli* resistances were significantly associated with average temperature and extreme climatic events; average temperature was also strongly associated with carbapenem-resistant *K pneumoniae*. Penicillin-non-susceptible *S pneumoniae* rates were inversely associated with average relative humidity and macrolide-resistant *S pneumoniae* rates were positively associated with extreme events. Rainfall was negatively associated to fluoroquinolone-resistant *A baumannii* rates. Third, we found that the GHS index was inversely associated with ABR rates in all *E coli* and *K pneumoniae* associated drug–bacterium pairs, as well as in *P aeruginosa* and *A baumannii* pairs. Carbapenem-resistant *A baumannii* was the only pair positively associated with GDP. Fluoroquinolone-resistant *P aeruginosa* and macrolide-resistant *S pneumoniae* were negatively associated with the GDP. This agrees with the univariate analysis, in which most drug–bacterium pairs were significantly inversely associated with the GDP (appendix 1 pp 44–51). Finally, tourist departures were inversely associated with ABR rates in two pairs, aminopenicillin-resistant *E coli* and carbapenem-resistant *P aeruginosa*. Vancomycin-resistant Enterococci was not significantly associated with any of the proposed factors in the multivariable analysis. Population density and tourism arrivals were not selected for any drug–bacterium pairs. Univariate analyses results and full models results (before backward selection) are summarised in appendix 1 (pp 45–54).

For all drug–bacterium pairs, we found higher heterogeneity in ABR rates between countries than between years (appendix 2): in reference M-null models, spatial random effects variance was high (ranging from 0.03 for aminopenicillin-resistant *E coli* to 1.92 for

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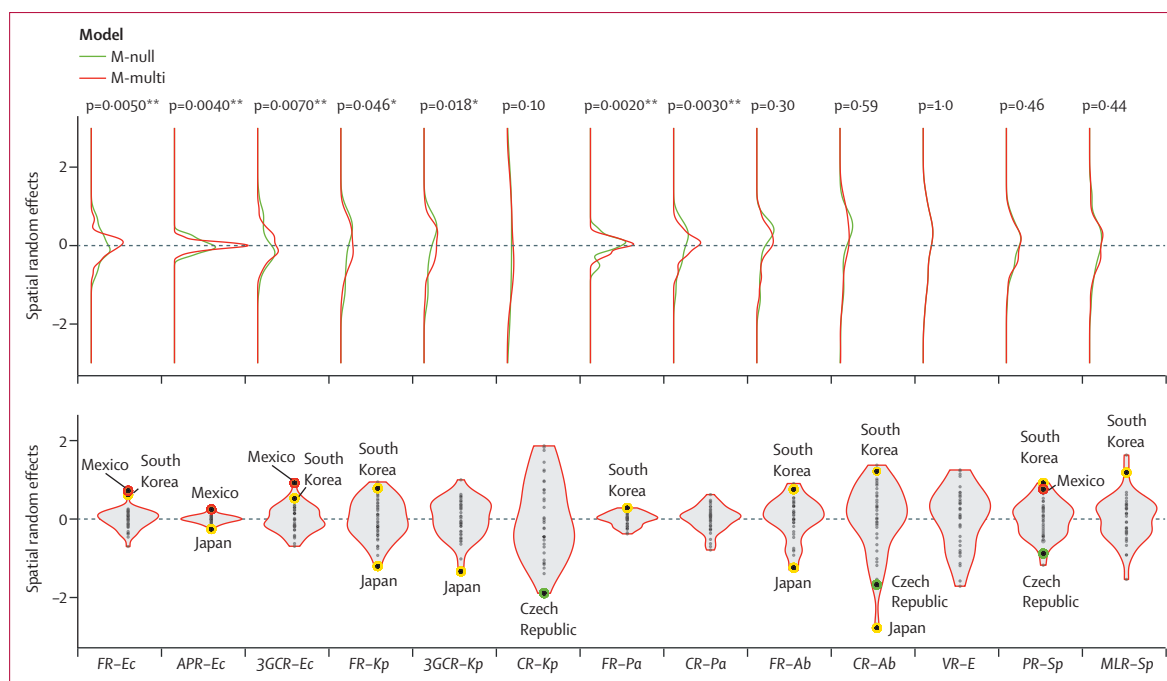


Figure 4: Spatial random effects distribution from final multivariable models for each drug–bacterium pair

(A) Distribution of spatial random effects by drug–bacterium pair. Significance of F-tests to test variance difference between spatial random effects of M-null and M-multi are reported above distributions (* $p < 0.05$; ** $p < 0.01$; and *** $p < 0.001$). (B) Violin plots of spatial random effects resulting from final M_multi by drug–bacterium pair. Random effects' estimates from Czech Republic (Europe and Central Asia), Japan, South Korea (East Asia and Pacific), and Mexico (Latin America and Caribbean) are highlighted. 3GCR-Ec=third generation cephalosporin-resistant *Escherichia coli*. 3GCR-Kp=third generation cephalosporin-resistant *Klebsiella pneumoniae*. APR-Ec=aminopenicillin-resistant *E coli*. CR-Ab=carbapenem-resistant *Acinetobacter baumannii*. CR-Kp=carbapenem-resistant *K pneumoniae*. CR-Pa=carbapenem-resistant *Pseudomonas aeruginosa*. FR-Ab=fluoroquinolone-resistant *A baumannii*. FR-Ec=fluoroquinolone-resistant *E coli*. FR-Kp=fluoroquinolone-resistant *K pneumoniae*. FR-Pa=fluoroquinolone-resistant *P aeruginosa*. MLR-Sp=macrolide-resistant *Streptococcus pneumoniae*. M-multi=final multivariable model. M-null=intercept-only model. PR-Sp=penicillin-non-susceptible *S pneumoniae*. VR-E=vancomycin-resistant Enterococci.

carbapenem-resistant *K pneumoniae*) compared with temporal random effects variance ($< 1 \times 10^{-4}$ for macrolide-resistant *S pneumoniae* to 0.53 for carbapenem-resistant *K pneumoniae*). For all drug–bacterium pairs, the M-multi model had lower AIC compared with M-null (appendix 2) suggesting that multivariable model was better at explaining the data.

In mixed-effect models, the introduction of explanatory factors is expected to decrease variance in random effects if the covariables explain the observed variance between groups of interest. Although temporal random effects variance was reduced in final multivariable models in all pairs except for aminopenicillin-resistant *E coli* and fluoroquinolone-resistant *A baumannii*, the low variance first observed in null models impeded strong interpretations of such reduction. Conversely, spatial random effects variance in null models was relatively high, and reduction of variance in the final multivariable models is presented in figure 4.

As shown from the results of F-tests in figure 4A, the introduction of covariables in the multivariable model led to a significant spatial reduction of random effects variance compared with the null model in *E coli* resistances, fluoroquinolone-resistant *K pneumoniae*,

third generation cephalosporin-resistant *K pneumoniae*, fluoroquinolone-resistant *P aeruginosa*, and carbapenem-resistant *P aeruginosa*. The resulting unexplained spatial random effects variances after the introduction of explanatory variables in the final M-multi models are shown in figure 4B. We observed that some country–drug–bacterium trios systematically exhibited outlying spatial random effects estimates compared with the observed average ABR rate in ATLAS. For example, spatial random effects estimate was systematically high for Mexico (for all *E coli* pairs and penicillin-non-susceptible *S pneumoniae*) and South Korea (for fluoroquinolone-resistant *E coli*, third generation cephalosporin-resistant *E coli*, fluoroquinolone-resistant *K pneumoniae*, fluoroquinolone-resistant *P aeruginosa*, fluoroquinolone-resistant *A baumannii*, carbapenem-resistant *A baumannii*, penicillin-non-susceptible *S pneumoniae*, and macrolide-resistant *S pneumoniae*) and low for Japan (for aminopenicillin-resistant *E coli*, fluoroquinolone-resistant *K pneumoniae*, third generation cephalosporin-resistant *K pneumoniae*, fluoroquinolone-resistant *A baumannii*, and carbapenem-resistant *A baumannii*) and Czech Republic (carbapenem-resistant *K pneumoniae*, carbapenem-resistant *A baumannii*, and penicillin-non-susceptible *S pneumoniae*). This suggests

that the proposed covariables are not sufficient to explain the observed spatial heterogeneity in ABR rates, especially in these countries (appendix 1 pp 55–62).

Sensitivity analyses were used to evaluate the effect of some of our method choices: threshold on the number of isolates below which drug–bacterium–country–year observations were excluded, inclusion of external antibiotic sales data for countries for which IQVIA MIDAS data were not available, and finally imputation of some missing country-year ABR rates. Results leading to similar interpretations to those presented in the main analysis were obtained, suggesting no major effect of our assumptions. We also did a sensitivity analysis on blood isolates only. Restricting analyses to the blood source led to lower sample sizes (appendix 1 p 13). For example, 20 401 (24%) of 48 485 of resistant *E coli* isolates and 8560 (24%) of 36 685 vancomycin-resistant Enterococci isolates came from blood compared with 7752 (11%) of 70 151 resistant *P aeruginosa* isolates. Overall, resulting associations were consistent with the main analysis, with wider 95% CIs but similar coefficient estimations and sign of associations with few exceptions. First, the analysis of blood samples led to negative association of GDP with carbapenem-resistant *A baumannii* and third generation cephalosporin-resistant *K pneumoniae* ABR rates, whereas it was positively associated in the main analysis. Second, the association between temperature and carbapenem-resistant *A baumannii*, penicillin-non-susceptible *S pneumoniae*, and vancomycin-resistant Enterococci showed higher estimated coefficients, suggesting stronger correlation. Lastly, some covariables associations had different signs for *S pneumoniae* associated pairs, such as macrolides and temperature association with macrolide-resistant *S pneumoniae*. The sensitivity analyses are reported in full in appendix 1 (pp 43–52).

Discussion

Using longitudinal data provided by ATLAS, we analysed spatial and temporal patterns of ABR and determinants of ABR for thirteen drug–bacterium pairs of clinical relevance. Our results confirmed that worldwide ABR dynamics were highly drug–bacterium pair dependent, both spatially and temporally. We found that key factors varied greatly between drug–bacterium pairs, but some similarities existed between bacteria of the same species. However, after hypothesis driven investigation of factors, high unexplained country-level variance remained in most of the drug–bacterium pairs.

The ATLAS data exhibited strong heterogeneities in spatial and temporal ABR patterns across drug–bacterium pairs. In 2019, high median ABR rates were observed for aminopenicillin-resistant *E coli* and carbapenem-resistant *A baumannii* but with different spatial heterogeneities. Aminopenicillins are broad-spectrum penicillins, the most used antibiotics class worldwide.²² Between 2000 and 2015, consumption of aminopenicillins in low-income

and middle-income countries (LMICs) doubled, reaching levels observed in high-income countries.²² By contrast, consumption of carbapenems, a last resort antibiotics class, increased in all countries, but levels were still much lower in LMICs compared with high-income countries. This could explain the large inter-country variation observed in carbapenem-resistant *A baumannii* rates compared with aminopenicillin-resistant *E coli* in 2019.²² Moreover, we found that carbapenem-resistant Gram-negative bacteria were on the rise globally in ATLAS, in agreement with previous studies.^{23,24}

The antibiotic consumption-resistance association strongly depended on the considered drug–bacterium pair. We found that fluoroquinolone-resistant *E coli*, fluoroquinolone-resistant *P aeruginosa*, and carbapenem-resistant *A baumannii* ABR rates were significantly associated with sales of their selecting antibiotics in the multivariable analysis (appendix 2; figure 3). ABR rates in *S pneumoniae* pairs were significantly associated with global antibiotic sales. Bystander selection certainly plays a role in this association, especially in commensals, such as *S pneumoniae*, where antibiotics select resistance in off-target bacteria in microbiota.²⁵ Surprisingly, none of the third-generation cephalosporin resistances were associated with any antibiotic sales. This could be because reported third-generation cephalosporin resistances trends are relatively stable and consumption of these antibiotics is decreasing, especially in high-income countries.²² Although antibiotic consumption exerts a selective pressure and favours the emergence of resistant bacteria, our results suggested that dissemination and persistence of such resistant bacteria might contribute more widely to the observed ABR heterogeneities worldwide. Significant signals were found in all drug–bacterium pairs for other factors, including climatic and meteorological factors, the health system quality, wealth, or tourism. Thus, the spread of resistant bacteria could influence ABR rates in populations in which antibiotic use is low. Spillover can happen at large geographical scales, weakening observed global antibiotic consumption-resistance associations.²⁶

Warm temperatures were found to be significantly associated with ABR rates only for Enterobacteriaceae (*E coli* and *K pneumoniae*) in the multivariable analysis (appendix 2; figure 3). This is consistent with previous ecological studies from smaller datasets in the USA and Europe.^{7–9} Our findings suggest that this association is highly drug–bacterium pair dependent because the association does not hold true for other bacterial species. Extreme climatic events were only positively associated in *E coli* and *S pneumoniae* pairs. This association suggests that natural disasters, such as flooding, rather than rainfall itself, potentially contribute to high ABR rates. Increased numbers of infections with ABR bacteria in people exposed to natural disasters or unprecedented levels of ABR genes in water following hurricanes have been reported in the literature.^{27,28} This certainly result

from infrastructures disruption, especially of wastewater treatment plants, which are known reservoirs for antibiotic resistance in urban environments.²⁹ This association might be especially strong in orofecally-transmitted bacteria, such as *E coli*.

High GHS index, used as a proxy for health system quality, was significantly associated with decreased ABR rates in most drug–bacterium pairs. This result highlights the crucial role of hygiene and infection control measures for containing resistance, especially in hospitals. They are consistent with findings from Collignon and colleagues,⁴ who showed that aggregated resistance in *E coli*, *K pneumoniae*, and *S aureus* were significantly inversely correlated with infrastructures and health expenditure.⁴ In our analysis, the GHS index was not associated with vancomycin-resistant Enterococci nor in *S pneumoniae* pairs, the only two investigated Gram-positive bacteria. For vancomycin-resistant Enterococci, this finding could potentially reflect discrepancies in nosocomial infection control approaches regarding this specific pathogen across countries with similar health system quality.³⁰ For *S pneumoniae*, the absence of association with the GHS could be explained by the fact that *S pneumoniae* dissemination is mostly driven by community transmission rather than nosocomial transmission. Overall, these findings highlight the importance of testing the validity of global ABR associations in different clinically relevant bacterial resistances.

Carbapenem-resistant *A baumannii* was the only pair positively associated with the GDP per capita (appendix 2; figure 3). From the univariate analysis, we found a large reduction in temporal random effects variance indicating that the individual contribution of GDP was mostly temporal. This result is consistent with other findings that showed the fastest increase in *A baumannii* resistances in Organisation for Economic Co-operation and Development (OECD) countries compared with other countries, where OECD countries have a higher GDP per capita.²⁴ Conversely, fluoroquinolone-resistant *P aeruginosa*, and macrolide-resistant *S pneumoniae* showed an inverse significant association with the GDP per capita, and such association also led to decreased temporal random effects variance. This finding suggests that economic growth over time is correlated with increase of emerging resistances, such as carbapenem-resistant *A baumannii*, but decrease of some other resistances.

After the introduction of significant explanatory variables in the final models, spatial random effects variance exhibited strong heterogeneity across drug–bacterium pairs. For Enterobacteriaceae pairs, such as fluoroquinolone-resistant *E coli*, random effects variance was low suggesting that the proposed factors (quinolones sales, average temperature, extreme climatic events, and GHS index) explained most ABR heterogeneities between countries. However, for vancomycin-resistant

Enterococci or carbapenem resistances, random effects variances remained high suggesting that the proposed factors could not explain most ABR spatial heterogeneities. This result stresses the scarcity of knowledge about global factors favouring the dissemination of newly emerged resistances. In addition, some countries, such as Mexico, Japan, and South Korea, exhibited high spatial random effects estimates compared with other countries in ATLAS; and this was true across different drug–bacterium pairs (figure 4). In South Korea, it is documented that primary care systems are less well established than in other OECD countries.³¹ Patients thus mostly seek care in secondary and tertiary care system (eg, hospitals), where the per capita antibiotic exposure is higher. Additional factors, such as health-care seeking behaviours, antibiotic use in livestock, and percentage of rural population, might then better explain ABR rates for these outliers. Due to the scarcity of available data, such hypotheses could not be assessed in this study.

Our study had a number of limitations. First, because the sampling protocol was based on clinical isolates from hospitals, ABR rates reported in ATLAS might not be fully representative of true resistance prevalence at the country level. Isolates from severe infections could present more resistance because going to the hospital is the last option after unsuccessful community treatment). This would lead to over-estimations of ABR rates globally in ATLAS. In addition, analysed sample sizes were small for some drug–bacterium–country–year observations, leading to high uncertainty around ABR rates. To evaluate such potential biases, we compared ABR rates estimated from ATLAS with those reported by EARS-Net in 20 European countries from 2006 to 2019. Although ABR rates were higher in ATLAS for some drug–bacterium pairs, our results suggest a global consistency for average ABR rates and trends reported across systems (appendix 1 pp 64–79). Because our statistical analyses focused on relative average ABR rates and trends, such possible over-estimations—if stable over countries and years—should not affect the associations with covariables found in this study. Catalán and colleagues³² did an extensive analysis on the ATLAS data quality, comparing it with other published databases. In concordance with our findings, they showed that although ATLAS presented higher resistance frequencies, the between-country ABR signal might be correctly captured by the programme. They also pointed out that differences in ABR rates between databases were lowered when ATLAS samples sizes were the highest, which is the case for the frequently surveyed bacterial species included in our analysis. Second, although this is a common feature in most ABR surveillance programmes, the number of reported isolates in ATLAS increased from 2006 to 2019 (appendix 1 p 13). To evaluate the potential effect of sampling variations, and because blood isolates collection in ATLAS was more stable over the study period, we ran a sensitivity

analysis on blood source only. Although some associations were reversed, such as association with GDP, temperature, or macrolides consumption in some drug–bacterium pairs, results were mainly consistent with our main analysis that included isolates from all sources. Ultimately, this highlights the need for global efforts, such as the GLASS programme, to evenly collect ABR data across the globe using standardised procedures, and to focus such efforts on still under-sampled regions.³³

Choices in analysed covariables data can also be discussed. First, for the meteorological factors, the capital city was used as a proxy for the country's weather, which could be misleading for large countries and those with large temperature differentials. However, previous studies suggested that using either the capital city's data or the country's weighted temperature mean did not affect associations.⁸ Second, we used the IQVIA MIDAS database, which currently represents one of the only sources of harmonised data on global antibiotic sales.²² However, these data might under-estimate true antibiotic consumption because it does not include over-the-counter drugs. Within a country, distribution of retail versus hospital sales were not available, nor information about heterogeneity in use in different populations. Both phenomena could contribute to resistance selection.³⁴ In addition, antibiotic use in livestock could not be included here due to scarcity of available data. In the future, access to more detailed and finer-grained data on antibiotic use in humans and animals should improve understanding of ABR drivers. Finally, tourism was measured here by the total numbers of tourists entering and leaving a country. This metric possibly missed important information, such as destination country. Yet, travel to some African or Asian countries, rather than travel itself, has been shown to be a significant risk factor for resistant bacteria colonisation.^{35,36} Poor precision in the available data could explain the unexpected inverse association with tourism-associated factors obtained in our statistical analysis.

Overall, our findings show that antibiotic resistance is a plural threat. Associations between antibiotic resistance rates and global factors, found in the two studied Enterobacteriaceae species for example, do not necessarily hold true in other bacterial species. Moreover, these known global factors cannot explain all heterogeneities observed worldwide in ATLAS. Absence of explanation could also be associated with the previously mentioned limitations concerning the specificity of ATLAS data collection, which advocates for the careful design of robust global surveillance systems. Our work highlights the importance to study determinants of worldwide antibiotic resistance in all drug–bacterium pairs of clinical relevance. Despite differences across pathogens, resistances are driven by both individual behaviours and global environmental mechanisms setting ABR in a One Health framework. Therefore, strategies to tackle worldwide antibiotic resistance should be tailored accounting for the species, the resistance, and the epidemiological settings at stake.

Contributors

ER, PG, LO, and LW designed the statistical analyses. ER, PG, and LO interpreted the results. ER analysed the data. ER, PG, and LO wrote the manuscript. LW and DG reviewed the manuscript. ER, LO, and PG verified the data. All authors had access to the data. All authors take responsibility for the decision to submit for publication.

Declaration of interests

ER's reports an independent research Pfizer Global Medical Grant (number 57504809). PG reports consulting fees from Pfizer for an unrelated project. LW reports consulting fees from Pfizer, Heva and IQVIA for unrelated projects.

Data sharing

The antibiotic resistance data can be visualised through the ATLAS website (<https://atlas-surveillance.com>). Covariables data are publicly available through the World Bank Data website (<https://data.worldbank.org>); the Global Health Security index website (<https://www.ghsindex.org>); the Solar Radiation and Meteorological Data services website (<http://www.soda-pro.com>) for the MERRA-2 data; the ECDC websites (<https://www.ecdc.europa.eu/en/all-topics/related-topics>) for the EARS-Net and ESAC-Net data. IQVIA MIDAS data are not publicly available. R codes to describe country-year longitudinal resistance data for an antibiotic–bacterium pair of interest and quantify its association with candidate factors are available online (https://github.com/EveRah/drug_bug_pair_NBMM).

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Editorial note: The Lancet Group takes a neutral position with respect to territorial claims in published maps and institutional affiliations.

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