Trends and socioeconomic, demographic, and environmental factors associated with antimicrobial resistance: a longitudinal analysis in 39 hospitals in Chile 2008–2017

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Summary

Background Antimicrobial resistance (AMR) is among the most critical global health threats of the 21st century. AMR is primarily driven by the use and misuse of antibiotics but can be affected by socioeconomic and environmental factors. Reliable and comparable estimates of AMR over time are essential to making public health decisions, defining research priorities, and evaluating interventions. However, estimates for developing regions are scant. We describe the evolution of AMR for critical priority antibiotic-bacterium pairs in Chile and examine their association with hospital and community-level characteristics using multivariate rate-adjusted regressions.

Methods Drawing on multiple data sources, we assembled a longitudinal national dataset to analyse AMR levels for critical priority antibiotic-bacterium combinations in 39 private and public hospitals (2008–2017) throughout the country and characterize the population at the municipality level. We first described trends of AMR in Chile. Second, we used multivariate regressions to examine the association of AMR with hospital characteristics and community-level socioeconomic, demographic, and environmental factors. Last, we estimated the expected distribution of AMR by region in Chile.

Findings Our results show that AMR for priority antibiotic-bacterium pairs steadily increased between 2008 and 2017 in Chile, driven primarily by *Klebsiella pneumoniae* resistant to third-generation cephalosporins and carbapenems, and vancomycin-resistant *Enterococcus faecium*. Higher hospital complexity, a proxy for antibiotic use, and poorer local community infrastructure were significantly associated with greater AMR.

Interpretation Consistent with research in other countries in the region, our results show a worrisome increase in clinically relevant AMR in Chile and suggest that hospital complexity and living conditions in the community may affect the emergence and spread of AMR. Our results highlight the importance of understanding AMR in hospitals and their interaction with the community and the environment to curtail this ongoing public health crisis.

Abbreviations: AMR, Antimicrobial resistance; OECD, Organization for Economic Cooperation and Development; LMICs, Low and middle income countries; eCDC, European Centre for Disease Prevention and Control; WHO, World Health Organization; CDC, Centers for Disease Control and Prevention; GDP, Gross domestic product; SES, Socioeconomic status; USD, United States dollars; ICU, Intensive care unit; CASEN, Chilean National Socioeconomic Characterization Survey

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Keywords: Antimicrobial resistance; Antibiotics; Latin America; Socioeconomic; Global health

Research in context

Evidence before this study

There is limited documented evidence of antimicrobial resistance (AMR) outside northern High-Income countries. Reliable and comparable estimates over time of AMR are essential for making public health decisions, defining research priorities, and evaluating the impact of disease prevention and infection control programs. We reviewed articles published in the Web of Science, Medline-PubMed, and SCIELO from 2000 to 2020 on factors associated with AMR and found 109 articles. Antibiotic consumption has substantially increased in the past decades. Evidence suggests antibiotic consumption in low- and middle-income countries is substantially lower than in high-income countries; however, AMR is often higher. Surveillance and laboratory capabilities are inadequate, antibiotics are often available without a prescription, and access to novel compounds is limited. AMR transmission is affected by socioeconomic and environmental factors, including water and sanitation infrastructure, education, living conditions, access to healthcare, human mobility, and contact with other vectors, such as animals. Using country-level data, two recent articles found a statistically significant association between better infrastructure and governance and lower AMR. In Latin American and Caribbean countries, a study in Chile reported an association between socioeconomic factors and AMR, and a study in informal settlements in El Salvador and Peru characterized resistance dissemination networks across interconnected habitats. While limited, evidence suggests that the transmission of resistant bacterial organisms and transferable resistance genes may affect global AMR spread.

Added value of this study

We assembled a longitudinal dataset using multiple sources to analyze AMR in 39 hospitals (2008–2017). We provide updated estimates of the evolution of AMR critical, high, and medium-priority antibiotic-bacterium pairs in Chile. We show a steady AMR increase driven primarily by *Klebsiella pneumoniae* resistant to third-generation cephalosporins, carbapenems, and vancomycin-resistant *Enterococcus faecium*. AMR levels in Chile were more prominent than the Organisation for Economic Cooperation and Development (OECD) estimates. Higher hospital complexity, a proxy for antibiotic use, and poor local community infrastructure were associated with higher AMR. Last, we projected our estimates at the regional level to estimate the geographical distribution of AMR in Chile. Our study undertakes a comprehensive country-level analysis of the trends in AMR resistance over time and their association with sociodemographic factors.

Implications of all the available evidence

Our main results are consistent with previous findings that suggest that frequently overlooked factors associated with the spread of resistant bacteria and genetic determinants of resistance, such as water and sewage infrastructure, overcrowding, and pollution, are probably essential drivers of AMR. Improved spatiotemporal estimates of AMR and a greater understanding of the sociodemographic and environmental factors associated with the emergence and spread of AMR are essential to prevent and control this growing global public health threat. Overall, available evidence suggests that improving sanitation and local infrastructure, as well as known controls on antimicrobial use, are important components of strategies to reduce global AMR levels.

Introduction

Antimicrobial resistance (AMR) is among the most critical global health threats of the 21st century.[1–4] Modern healthcare relies on effective antibiotics to treat and prevent infections. Infections caused by resistant bacteria produce greater morbidity and mortality, complicate treatments, and often result in prolonged hospitalizations, increasing healthcare costs globally.[5–8] A lack of incentives has limited the development of new antibiotics. The process is expensive, and the expected gains are limited compared to other drugs, mainly because antibiotic courses are comparably short, and the clinical activity of antibiotics diminishes over time due to resistance. AMR occurs naturally as an adaptative mechanism of bacteria, wherefore infectious diseases specialists frequently set to restrict the use of novel antimicrobials to prevent AMR.[7,9]

Increases in overall antibiotic consumption, obstacles in the development of antibiotics, and insufficient surveillance, among other factors, are key areas to draw

the government's attention to avoid a global health backlash.[7] Specifically, a global increase in antibiotic use and misuse in humans, animals, and agriculture and insufficient infection control policies have accelerated the emergence and spread of resistance.[10–15] Antibiotic consumption has substantially increased in the past decades, mostly in low- and middle-income countries. While reported antibiotic consumption low- and middle-income countries is substantially lower than in high-income countries, AMR is often higher. However, antibiotics are often sold without prescriptions and over the counter, and surveillance systems have many limitations.[13]

Although often overlooked, AMR is also affected by socioeconomic and environmental factors, including inadequate water, sanitation, and hygiene infrastructure, living conditions, waste management, education and awareness, human mobility, and other factors such as access to healthcare and medicine.[15–20] The relative importance of the spread of resistant strains and genes through human and non-human animals, water, agriculture, and the environment is underscored by the high proportion of resistant bacteria in countries with lower consumption of antibiotics per capita.[13,16,21] Collignon et al.[16] examined factors that affect average resistance prevalence for *Escherichia coli, Klebsiella* spp., and *Staphylococcus aureus* in 73 countries, and found a statistically significant association of better infrastructure and governance with lower AMR. A study in 28 European countries found that a large proportion of the variation in AMR was explained by country-level governance, possibly due to variations in the control of antibiotic use.[22] A study in Chile found an association between socioeconomic factors (income, education, occupation) and AMR profiles of *Pseudomonas aeruginosa* and *S. aureus*.[23] A study in two low-income informal settlements in El Salvador and Peru characterized bacterial communities and resistance dissemination networks across interconnected habitats, highlighting potential routes of spread of resistant bacteria in areas with unregulated access to antibiotics and inadequate water and sewage infrastructure.[24] Additional details in the Supplementary Material (Section 1, Fig. S1 and Table S1).

Previous studies from high-income western countries have estimated the proportion of resistant bacteria at the national level for high-priority antibiotic-bacterium combinations.[1,2,25,26] These reports often rely on data from surveillance networks gathering information from multiple laboratories, which may use different testing standards or guidelines, hampering comparability.[2] Despite their importance, estimates of AMR from developing regions are scant, most likely due to limited epidemiologic surveillance and laboratory resources.[27] Having reliable and comparable estimates of AMR over time is essential to inform public health policy, define research priorities, and evaluate the impact of disease prevention and infection control programs.[3,28,29]

Here we provide a country-wide estimation of the proportion of antibiotic resistance for high-priority antibiotic-bacterium combinations in Chile and use official national data to factor in the socioeconomic, demographic, and environmental factors possibly contributing to AMR dissemination. Our estimates are based on the critical, high, and medium priority bacterium-antibiotic pairs, as classified by the World Health Organization (WHO), aggregated following recent reports by the Organization of Economic Cooperation and Development (OECD) and the European Centre for Disease Prevention and Control (eCDC).[2,26] We draw on multiple data sources, including annual susceptibility reports from a country-wide network of 39 public and private hospitals from 2008 to 2017, official national surveillance reports, and socioeconomic, demographic, and environmental data from administrative records and national surveys.

Chilean context

In 2017, Chile had a GDP per capita of about USD 15,000, high income inequality (GINI index of 44.4), and about 17% of households lived in multidimensional poverty, as defined by the World Bank.[30] About 42% of the Chilean population live in the Región Metropolitana, which includes Santiago, the capital city. Chile has a hybrid public-private health system, including service and insurance, with high coverage (~98% of the population). A global comparison put Chile in the 74th percentile in effective universal healthcare coverage, between other countries in South America, such as Brazil (65th) and Uruguay (69th), and high-income countries, such as Israel (81st) and the United States (82nd).[31] Approximately 80% of the population is affiliated to the Fondo Nacional de Salud (FONASA), a health insurance program that collects, administers, and distributes funds for the public healthcare system. The rest of the population is affiliated to private insurance (~14%) or the armed forces and police subsystems.[32] Health care is available nationwide through a network of primary care centers and referral hospitals.

There were 194 public hospitals in Chile in 2018. Of these, 63 (32%) were classified as high complexity, 30 (15%) of median complexity, including only some medical specialties, and the rest (n = 101, 52%) were classified as low complexity, including primary care services in rural and isolated places. Private hospitals totalled 76. Of these, eight (11%) had more than 200 beds, 13 (17%) had between 100 and 200 beds, and the rest (n = 55, 72%) were smaller hospitals with less than 100 beds.[33] About 70% of beds in the health system correspond to public hospitals; private hospitals and armed forces represent approximately 18% and 8% of beds. Individuals can choose to receive healthcare

services through public or private providers. Outpatient services have the highest demand in the private sector, primarily diagnostic exams (45% of services).[32,33]

Since 1984, antibiotics in Chile have been available to the public in pharmacies only by medical prescription. Recent regulations include control of public and private hospitals for microbial isolation (1999), restrictions of the use of antibiotics in clinical care (1999), critical bacteria included as notifiable communicable diseases (2004), and the launch of a National Plan Against Antimicrobial Resistance,[34] focusing on awareness among people and professionals, surveillance, prevention and control of healthcare associated infections, and scientific research (Supplementary Material, Tables S2 and S3).

Methods

Study design and data

We employed a longitudinal hospital-level ecological study in Chile, drawing on multiple data sources. We assembled a national dataset including the proportion of resistant bacteria for high and critical-priority antibiotic-bacterium combinations in 39 Chilean hospitals (2008–2017), and socioeconomic and demographic characteristics by municipality (the smallest administrative division in Chile). Critical, high, and medium-priority pathogens are those in urgent need of new antibiotics because of the resistance mechanism they might develop, which pose a significant health threat in hospitals, nursing homes, and communities.[35] We estimated the proportion of antibiotic-bacterium combinations using data from a collaborative AMR surveillance network (GCRB) encompassing public (82%) and private (18%) tertiary hospitals (Supplementary Material, Table S4). Hospitals in the GCRB network represent about half of the public tertiary hospitals in Chile. Half of these hospitals were located in Región Metropolitana, and the rest were located in 10 of 15 regions in Chile. Most private hospitals were based in Santiago (N = 6), and one in Valparaiso.

Participant institutions annually report the susceptibility of selected antibiotic-bacterium pairs obtained from clinical samples from patients hospitalized in medical, surgical, and Intensive Care Unit (ICU) services. Susceptibility testing is performed locally at each institution following Clinical and Laboratory Standards Institute recommendations.[36] We focused on eight antibiotic-bacterium combinations included in OECD and eCDC surveillance reports.[2,26] Specifically, *Acinetobacter baumannii, Pseudomonas aeruginosa*, and Enterobacterales (*Klebsiella pneumoniae and Escherichia coli*) resistant to carbapenems, vancomycin-resistant *Enterococcus faecium* and *Enterococcus faecalis*, and methicillin-resistant *Staphylococcus aureus*. Penicillin-resistant *Streptococcus pneumoniae* data were also obtained, at the regional level, from the Chilean Institute of Public Health.

We combined various data sources to characterize the population attended by each hospital at the municipality level. Individuals could receive healthcare from different providers, so characteristics at the municipality level are a proxy. We used data from the National Socioeconomic Characterization Survey (CASEN) (2008–2017),[37] a country-wide representative household survey emphasizing poverty and social vulnerability, which collects data on education, health, housing, work, and income. We used hospital management reports and administrative data from the Department of Statistics and Health Information from the Ministry of Health to characterize hospitals and census data to characterize the hospital catchment population demographically. A description of the variables and datasets used is provided in the Supplementary Material (Table S5).

Analysis

We performed a three-tiered analysis approach. First, we described the trends of AMR for high-priority antibiotic-bacterium combinations throughout Chile between 2008 and 2017, as defined by OECD and eCDC, for comparability with other countries.[2,26]

Second, we used multivariate regression analyses to examine the association between AMR and socioeconomic, demographic, and environmental covariates. We used data from the CASEN survey to characterize the population at the municipality level based on the hospital's location. Because the survey is carried out every two years, we interpolated the variables' values from CASEN using nearest neighbour and natural cubic spline interpolation. To reduce the risk of overfitting and multicollinearity, we reduced the dimensionality of our dataset by creating index variables based on the expected characteristics of the population attended by each of the hospitals. Indexes were computed based on a two-step method: *i)* each variable was standardized by subtracting its overall mean and dividing it by the overall standard deviation (SD), and *ii)* standardised variables were summed correspondingly to quantify each index.

We created five indexes (variable definitions in Table S5, Supplementary Material). First, a *hospital complexity index* that encompassed annual hospital discharges, the average stay of patients, hospital expenditure, percentage of uninsured population, and the number of years since hospital construction. Greater index values suggest higher hospital complexity. Second, we created a *household infrastructure index* to characterize people's living conditions. This index included inadequate sanitation, overcrowding, material deprivation, and the inverse of municipal expenditures per capita. Higher index values indicate a poorer household infrastructure. Third, the *socioeconomic status (SES) index* comprises educational level, primary occupation, and the inverse of poverty and dependency rates. Higher

values show a higher SES. Fourth, the *environmental index* comprises the annual average temperature and humidity. Fifth, the *territorial index* contains the proportion of people living in a rural area and population density.

We estimated the association between the proportion of AMR and our indexes using two linear regression models, including fixed effects by year and municipality and bootstrapping (random sampling with substitution) using hospital-level clustered standard errors. Two linear models were fitted to the data to identify the factors that most affected AMR (M1 and M2), as follows:

Linear model (M1):

$$AMR_{ihmt} = \alpha + \beta H_{ht} + \gamma M_{mt} + \delta_m + \tau_t + \varepsilon_{ihmt}$$

Linear model using a logarithmic function as dependent variable (M2):

$$\log\left(\frac{AMR_{ihmt}}{100 - AMR_{it}}\right) = \alpha + \beta H_{ht} + \gamma M_{mt} + \delta_m + \tau_t + \varepsilon_{ihmt}$$

where AMR_{ihmt} corresponds to the proportion of resistant antibiotic-bacterium pairs i in hospital h, in the municipality m, in year t. AMR_{ihmt} was measured in percentage points and could range between 0 and 100. AMR_{ihmt} was calculated for each of the eight antibiotic–bacteria pairs analyzed and as an altogether measure as per the OECD suggests. M contains four municipality-level variables (household infrastructure, socioeconomic status, territory, environment), H is the hospital complexity index, and δ_m, τ_t are municipality and time fixed-effects. ε_{ihmt} is an error term. The model's coefficients (α, β, δ, τ) are understood as the direct impact of the explanatory variable on AMR proportion points in M1. In M2, these coefficients represent the percentage change in the odds ratio (OR) of AMR proportion for a unit change in the explanatory variable. We did not add antibiotic-bacterium fixed effects because we employed different models to account for subgroup variability (bacterium-specificWe used a significance level of $\alpha = 0.10$.

Third, based on the regression results, we estimated the expected AMR proportion for hospitals not included in the GCRB to obtain an approximate country-wide spatial distribution of AMR based on hospitals and communities' characteristics. All analyses were done using Stata 15.1 (College Station, TX), R 3.6.2 (R Foundation, Vienna), and Excel 16.39 (Microsoft Corporation, WA).

Ethics statement

The research protocol was approved by the Unidad de Ética y Seguridad en Investigación, Pontificia Universidad Católica de Chile, project 181205019. The study was considered exempt from informed consent, no human health risks were identified.

Role of the funding source

The funders of the study had no role in study design, data collection, analysis, or interpretation, in the writing of the report, or in the decision to submit the paper for publication.

Results

Using longitudinal data from a country-wide network of 39 public and private tertiary hospitals, we examined the proportion and trends of AMR in Chile. Table 1 shows the proportion of AMR (%) for priority antibiotic-bacterium combinations in Chile 2008–2017. For comparability, the combinations of antibiotic-bacterium used were based on those used in surveillance reports by the OECD and eCDC.[2,26] Our results showed an average resistance proportion of 28.5% across all antibiotic-bacterium combinations based on eCDC pairs and 27.8% according to OECD pairs (Table 1, bottom panel).

Fig. 1 shows a violin plot representing the overall 10-year AMR trends between 2008 and 2017 following the bacterium-antibiotic combinations used by the OECD.[2] Fig. 2 shows the 10-year trends for each of the studied combinations. Overall, the results suggest there has been a significant increase in the proportion of resistant bacteria in 2008–2017 (Fig. 1). Importantly, this increase appears to be primarily driven by a rise in the proportion of third-generation cephalosporin- and carbapenem-resistant *K. pneumoniae* and vancomycin-resistant *E. faecium*, both of which are among the most worrisome multidrug-resistant organisms worldwide. In contrast, we found stable AMR rates over time using the eCDC classification due to the reduced reported amikacin-resistance among *E. coli*, *K. pneumoniae* and *Pseudomonas aureginosa* (Figs S2 and S3).

Next, we examined the association between AMR and covariates of interest. Table S6 (Supplementary Material) shows the descriptive statistics for the socioeconomic, demographic, hospital, and environmental indexes potentially associated with AMR's emergence and spread and their comparison with national averages. The national distribution of these factors is shown in Fig. S4, the average proportion of resistance for antibiotic-bacterium pairs is shown in Fig. S5 and the distribution densities and range are shown in Fig. S6 (Supplementary Material). Overall, socioeconomic factors in the municipalities served by hospitals in our sample showed relatively low poverty rates (9.0%, SD = 0.06), few households with inadequate sanitation (2.2%, SD = 0.02), and an average of 12 years of schooling (SD = 2.3) over 2008–2017. We observed minor differences from the national averages except for inadequate sanitation (6.2%, SD = 0.24). Figs. S7 and S8 (Supplementary Material) display the number of hospitals included over time and by antibiotic-bacterium pair; and Table S7 shows Pearson's bivariate correlation (ranging from −1 to 1) between AMR rate and

Antibiotic	*Acinetobacter baumannii*	*Escherichia coli*	*Enterococcus faecalis*	*Enterococcus faecium*	*Klebsiella pneumoniae*	*Pseudomonas aeruginosa*	*Staphylococcus aureus*	*Streptococcus pneumoniae*	Total
Amikacin	51.4 (32.6)[a]	2.4 (4.6)[a]			10.8 (11.3)[a]	13.84 (10.73)[a]			
Gentamicin	36.3 (27.9)[a]				40.8 (16.4)[a]	24.48 (13.36)[a]			
Cefotaxime or ceftriaxone		16.8 (11.4)[a,b]			65.2 (17.6)[b]				
Piperacillin/Tazobactam						31.48 (14.44)[a]			
Ciprofloxacin	70.4 (27.6)[a]	28.7 (12.2)[a,b]			57.7 (17.4)[a]	32.78 (15.09)[a]			
Ertapenem		1.4 (6.1)[a]			24.3 (15.9)[a,b]				
Imipenem	50.9 (30.6)[a]	0.6 (4.1)[a]			2.7 (8.8)[a,b]	34.14 (15.73)[b]			
Meropenem	53.9 (31.2)[a]	1.1 (7.1)[a]			8.5 (11.1)[b]	32.59 (15.20)[b]			
Methicillin							39.8 (19.3)[a,b]		
Vancomycin			2.48 (7.6)[a,b]	62.8 (25.9)[a,b]			–		
Penicillin								7.99 (14.99)[a,b]	
[a]**eCDC standard**	**51.23 (31.90)**	**8.6 (13.6)**	**2.48 (7.6)**	**62.8 (25.9)**	**27.71 (26.8)**	**28.29 (15.8)**	**39.8 (19.3)**	**7.99 (14.99)**	**28.49 (19.49)**
[b]**OECD standard**	**-**	**22.8 (11.8)**	**2.48 (7.6)**	**62.8 (25.9)**	**25.17 (13.4)**	**33.37 (15.5)**	**39.9 (19.3)**	**7.99 (14.99)**	**27.79 (15.50)**
Average years of hospital data	5.46	5.64	5.26	5.28	5.64	5.59	5.23	[c]	5.44

Notes. Average proportion of antimicrobial resistant bacteria, standard deviation in parentheses. Average resistance across antibiotic-bacterium combinations between 2008 and 2017, as defined by eCDC and OECD. Bold letters indicate the average resistance rates by bacteria and accross bacterias based on eCDC and OECD estimates. [a]Antibiotic-bacterium combinations considered by eCDC.[26] [b]Antibiotic-bacterium combinations considered by OECD.[2] [c]*Streptococcus pneumoniae* was reported by the Chilean Institute of Public Health aggregated at the regional level, not by hospital. All other antibiotic-bacterium combinations are reported annually by participant hospitals, based on clinical samples of hospitalized patients in medical, surgical, and ICU services following Clinical and Laboratory Standards Institute guidelines.[36]

Table 1: **Proportion of antibiotic resistant bacteria (%) for high-priority antibiotic-bacterium combinations in Chile in 2008–2017, averaged according to eCDC and OECD standards.**

socioeconomic and demographic factors of the community and hospitals. We found a greater positive correlation between the total proportion of AMR and hospital characteristics as compared to the other factors, particularly for the number of discharges of older adults (ρ = 0.29), the average length of stay (ρ = 0.29), and the proportion of the population with public health insurance (ρ = 0.20).

Table 2 shows the results from the multivariate regressions. The rows show OECD antibiotic-bacterium pairs (results using eCDC pairs are comparable; Supplementary Material, Table S8). The coefficient of

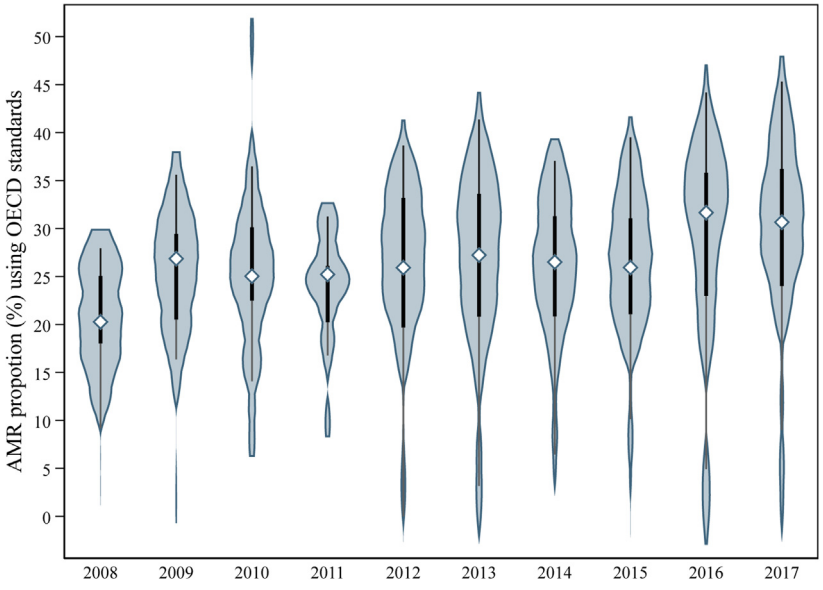

Fig. 1: **Average proportion of resistance across antibiotic-bacterium pairs, based on annual reports from 39 participating hospitals in Chile (2008–2017).** **Notes**: Antibiotic-bacterium pairs as defined by the OECD.[2] Violin plots present the probability density (distribution) of AMR rates at their different values. Density is smoothed by a kernel density estimator. The diamond marker represents the AMR rates' median, while the thick black box shows the interquartile range (the difference between 75th and 25th percentiles). The thin grey line indicates 95% CI.

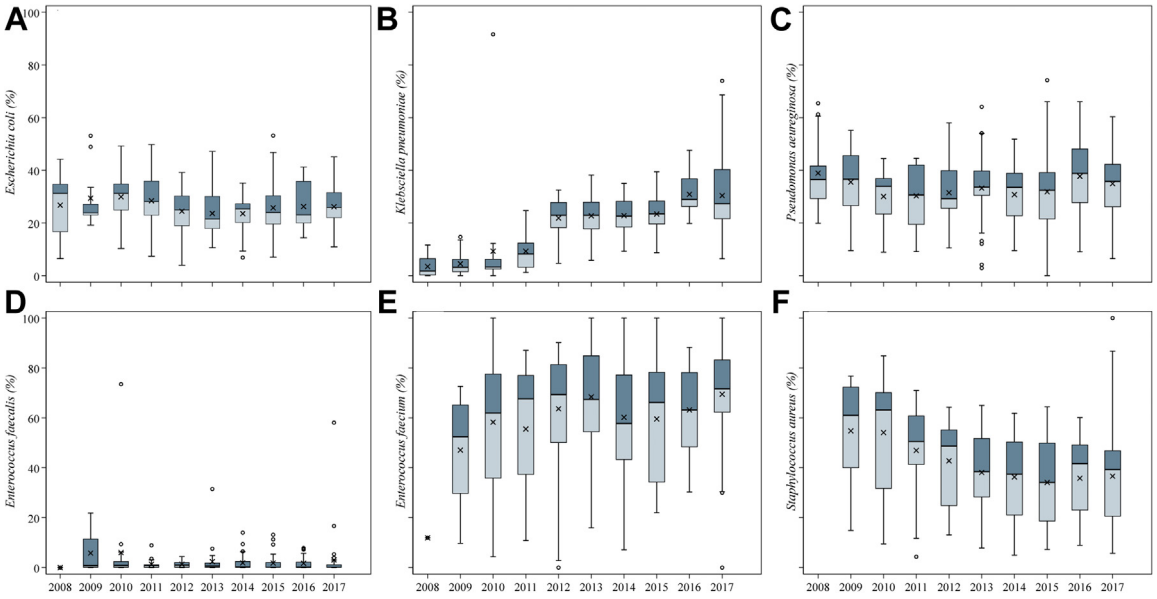

Fig. 2: **Trends in the average proportion of resistance for antibiotic-bacterium pairs (2008–2017)**. Proportion of resistant bacteria for the following antibiotics based on OECD criteria:[2] **(A)** *E. coli* resistant to third-generation cephalosporins and quinolones, **(B)** *K. pneumoniae* resistant to third-generation cephalosporins and carbapenems, **(C)** *P. aeruginosa* resistant to carbapenems, **(D)** *E. faecalis* resistant to vancomycin, **(E)** *E. faecium* resistant to vancomycin, and **(F)** *S. aureus* resistant to oxacillin. X-symbol stands for the average proportion while hollow-circles for outliers.

determination (R^2) suggests that our model explained about half of the variance of AMR. The hospital complexity index had the largest and more consistent association with AMR, most likely because the variables composing such index are probably a proxy of heavy antibiotic use (Supplementary Material, Tables S9 and S10). For the linear model, one standard deviation increase in the hospital complexity index was associated with a 3.81 percentage points in the overall AMR rate (Table 2, upper panel, $\beta = 3.81$, $p < 0.001$). Consistently, for the logistic model, one standard deviation in the hospital complexity index was associated with a 22% increase in the overall AMR rate (Table 2, lower panel, OR = 1.22, $p < 0.001$). An increase in the hospital complexity index was also significantly associated with a higher proportion of *A. baumannii* (Table 2, upper panel, $\beta = 11.85$, $p < 0.001$; lower panel $\beta = 0.55$, $p < 0.001$), *E. coli* (Table 2, upper panel, $\beta = 3.78$, $p < 0.001$; lower panel $OR_\beta = 1.73$, $p < 0.001$), *K. pneumoniae, P. aeruginosa,* and *S. aureus* (Table 2, upper panel, $\beta = 3.33$, $p < 0.001$, $\beta = 2.90$, $p = 0.02$; $\beta = 10.70$, $p < 0.001$, respectively; results in the lower panel were comparable).

Our results also suggest there was a significant association between household infrastructure and fluoroquinolone– and cephalosporin-resistant *E. coli* and methicillin-resistant *S. aureus* and vancomycin-resistant enterococci (Table 2, upper panel, $\gamma = 3.68$, $p < 0.001$; lower panel, $OR_\gamma = 1.17$, $p < 0.001$; and upper panel, $\gamma = 2.58$, $p = 0.03$; lower panel, $OR_\gamma = 1.22$, $p = 0.03$). We tested our estimates for specification error (omitted variables), multicollinearity, and normality of residuals using the Ramsey test, variance inflation factor (VIF), and normal probability plots. Models were adequately specified (Ramsey test $p > 0.10$), had no substantial multicollinearity (VIF<10), and residuals were approximately normally distributed (Supplementary Material, Figs. S9 and S10 and Table S11).

As a robustness check, we predicted estimated changes in AMR for specific and aggregate antibiotic-bacterium pairs adjusting by socioeconomic, demographic, and environmental factors. The results, shown in the Supplementary Material Fig. S11 and Table S12, suggest that, on average, there is an upward overall trend in aggregate AMR estimates and for *A baumanii, E. coli, K. pneumoniae, and E. faecium.* Table S13, Supplementary Material, shows the percentage change in estimated AMR resistance rate compared to baseline (2008) for specific and aggregate antibiotic-bacterium pairs. Most pairs show increases compared to baseline, except for *P. aeruginosa* and *S. aureus* that show consistent decreases over time.

Last, based on the regression results, we estimated the expected AMR for tertiary hospitals not included in the GCRB dataset for 2017 and aggregated these estimates at the regional level to estimate the spatial distribution of AMR in Chile. Fig. 3 shows the expected country-wide spatial distribution of AMR for selected

AMR	Hospital Complexity	Community characteristics				R^2	AIC	BIC	N
		Infrastructure	SES	Environment	Territory				
Linear model 1	**β (SE)**	**γ (SE)**	**γ (SE)**	**γ (SE)**	**γ (SE)**				
All[a]	3.81***	1.58	−1.09	−0.73	−0.80	0.52	1463	1542	225
	(0.64)	(0.96)	(0.99)	(0.54)	(1.05)				
A. baumanii[b]	11.85***	−6.58*	−1.28	2.05	−0.72	0.50	1877	1955	213
	(2.49)	(3.50)	(5.15)	(2.35)	(2.26)				
E. coli[a]	3.78***	3.68***	−2.4	−1.44	1.19	0.50	1491	1569	220
	(0.81)	(1.28)	(1.93)	(1.37)	(1.21)				
E. faecalis[a,b]	−0.34	−1.20	−0.35	−0.67	−0.65	0.35	1357	1430	205
	(0.54)	(1.49)	(1.36)	(0.87)	(1.3)				
E. faecium[a,b]	3.81	2.02	3.87	−0.39	4.93	0.39	1828	1901	206
	(3.26)	(4.07)	(4.56)	(2.99)	(3.6)				
K. pneumoniae[a]	3.33***	−0.55	0.09	−0.86	−1.47	0.63	1582	1659	220
	(0.58)	(1.83)	(2.32)	(1.08)	(2.18)				
P. aeruginosa[a]	2.90**	2.70	−4.22*	0.38	−2.51	0.49	1621	1699	218
	(1.15)	(1.77)	(2.50)	(0.96)	(2.60)				
S. aureus[a,b]	10.70***	2.58**	1.68	−1.20	−1.85	0.64	1597	1670	204
	(1.46)	(2.00)	(3.36)	(1.74)	(1.69)				
S. pneumoniae[a,b]	−0.16	−0.27	0.35	−1.00	−0.59	0.36	1963	2053	301
	(0.20)	(0.44)	(0.53)	(1.51)	(0.69)				
Logistic model 2	**OR_β/(SE)**	**OR_γ/(SE)**	**OR_γ/(SE)**	**OR_γ/(SE)**	**OR_γ/(SE)**				
All[a]	1.22***	1.08	0.95	0.97	0.95	0.52	147	226	225
	(0.04)	(0.05)	(0.06)	(0.03)	(0.06)				
A. baumanii[b]	1.73***	0.74	0.98	1.12	1.06	0.46	574	646	213
	(0.13)	(0.23)	(0.25)	(0.13)	(0.17)				
E. coli[a]	1.22***	1.17***	0.86	0.97	1.07	0.48	239	317	220
	(0.05)	(0.07)	(0.11)	(0.07)	(0.06)				
E. faecalis[a,b]	1.06	0.78	0.96	0.99	1.04	0.31	528	601	205
	(0.10)	(0.19)	(0.27)	(0.15)	(0.21)				
E. faecium[a,b]	1.31**	1.19	1.12	0.90	1.40*	0.50	504	576	206
	(0.11)	(0.18)	(0.21)	(0.14)	(0.17)				
K. pneumoniae[a]	1.27***	0.99	1.15	1.00	0.86	0.67	457	534	220
	(0.06)	(0.13)	(0.23)	(0.16)	(0.14)				
P. aeruginosa[a]	1.14*	0.79	0.79**	0.79	0.79	0.46	343	421	218
	(0.07)	(0.10)	(0.14)	(0.04)	(0.13)				
S. aureus[a,b]	1.67***	1.22**	1.06	0.92	0.96	0.64	363	436	204
	(0.07)	(0.09)	(0.18)	(0.08)	(0.08)				
S. pneumoniae[a,b]	0.99	0.99	1.03	1.11	0.82**	0.38	692	781	301
	(0.02)	(0.04)	(0.05)	(0.19)	(0.10)				

Notes. *$p < 0.1$, **$p < 0.05$, ***$p < 0.01$. Standard errors are shown in parenthesis (SE). OR stands for odds ratio. M1: Linear model, M2: Linear model with logistic ratio as dependent variable. All regressions include fixed effects by municipality and year ($\delta_m + \tau_t$), standard errors were clustered at the hospital-level. Bootstrapping techniques (random sampling with replacement) with 50 replications were used. N stands for number of observations. AIC presents the Akaike fit criterion, BIC the Bayesian information fit criterion, and, R^2 is the coefficient of determination that calculates the overall fit of the model. *S. pneumoniae* models used regional average values for each hospital. SES means socioeconomic status. [a]AMR estimated according to bacterial–antibiotic combinations considered critical by OECD.[2] [b]AMR was estimated according to eCDC.[26] Variable definition in web appendix, Table S2.

Table 2: **Association between AMR and socioeconomic and demographic factors in the 39 hospitals in Chile, 2008–2017.**

antibiotic-bacterium pairs considered critical by the OECD.[2] The numerical results are shown in Supplementary Material, Tables S14 and S15.

Discussion

Drawing from various data sources, including data from 39 hospitals in Chile, we estimated an overall proportion of resistant bacteria (2008–2017) of 27.8% for selected antibiotic-bacterium pairs considered critical by the OECD and 28.5% according to eCDC high priority antibiotic-bacterium pairs. We found a steady increase in overall AMR in 2008–2017 in Chile, which was particularly driven by substantial increases in *K. pneumoniae* resistant to third-generation cephalosporins and carbapenems, and vancomycin-resistant *E. faecium*. Our estimates for Chile are similar to the

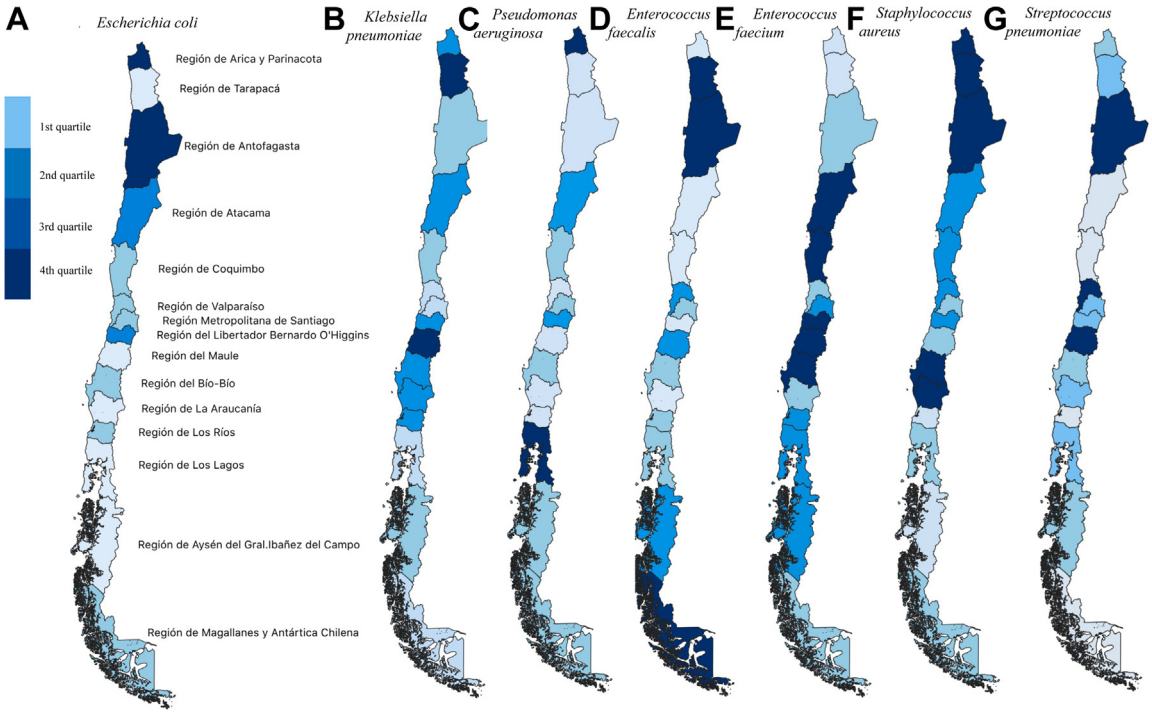

Fig. 3: **Proportion of antibiotic resistant bacteria in 2017 according to bacterial–antibiotic combinations considered critical by OECD.** Data were aggregated by region. Graph includes expected AMR based on the characteristics of the hospitals and the population of the community. Expected values are based on regression results in Table 2.

2013 OECD AMR estimates for countries of similar income in South America, such as Argentina (31.6%), Brazil (33.8%), and Colombia (33.8%), and comparable to the average reported for the G20 countries (29.2%).[2] The OECD estimated an average AMR prevalence of 21% in Chile in 2013.[2] Nonetheless, almost all antibiotic-bacterium pairs presented in that report were missing for Chile except for *E. coli* in 2014, which was not classified as a priority pathogen by the WHO.[35] Interestingly, we observed stable AMR rates after 2009 based on eCDC classification, based upon different antibiotic-susceptibility types, such as aminoglycosides for *E. coli*, *K. pneumoniae*, and *P. aeruginosa*. The WHO has not considered these combinations a critical priority, and their burden is relatively low, compared to 3rd-generation cephalosporins and carbapenems[1,2] Our study is novel in having included eight antibiotic-bacterium pairs, classified as either medium, high, or critical priority by the WHO.[35] Moreover, we included relevant community- and hospital-level characteristics to estimate AMR proportion using a significant sample of hospitals over time. Above all, our results highlight the potential for a regional and global health crisis.[2,7]

AMR occurs because of the development of novel mutations, the horizontal spread of resistance genes, and the successful dissemination of resistant strains in various settings – hospitals, communities, and environments.[16] We reviewed the association between AMR and socioeconomic factors in high-income and low- and middle-income countries. The factors commonly associated with AMR included income inequality, poor housing, low socioeconomic status, being from a marginalized group, inadequate sanitation and hygiene infrastructure, lack of clean water, and lack of strong governance (Supplementary Material). AMR is a particularly relevant public health challenge in Latin America because a substantial proportion of the population lives under such conditions, providing a suitable environment for the development and spread of resistant bacteria.

Our multivariate analysis showed that, in Chile, most of the AMR variation was explained by differences in the hospital complexity index. This is most likely explained because hospital complexity significantly correlates with antibiotic use. In the absence of a direct antibiotic consumption measure, the use of antibiotics is, on average, more prevalent in patients with medical complexities (i.e., higher disease burden, older age, poor functional status) who have been treated at hospitals. We also found evidence to support the association between AMR and deprivation, as measured by our household infrastructure index. Even though previous literature has suggested that climate factors contribute to the spread of AMR,[2] we found no evidence in our data.

These results should be interpreted with caution, as our analysis has limitations. First, despite including about 50% of tertiary hospitals in Chile, our sample is relatively small and presented a reduced number of hospitals providing information during 2008–2011, which resulted in large standard errors. We attempted to address this limitation by creating indexes to summarize the relevant covariates found in the literature and using bootstrapping techniques to estimate the sampling distribution of our standard errors more precisely. Nonetheless, our results are consistent with the international literature suggesting that examining factors that affect the emergence and spread of resistance, beyond the inadequate use of antibiotics and infection control in hospitals, are a fitting complement to help prevent and control AMR locally. Second, we did not use a probabilistic sample of hospitals from Chile but rather a convenience sample based on healthcare centers participating in the GCRB network. These hospitals could, in theory, systematically differ from non-participant hospitals, for example, in their complexity. However, our sample represented about 50% of Chile's high-complexity public hospitals, and included hospitals from 11 of the 16 regions of the country, with about half of the centers from Región Metropolitana, the most populated region in Chile. Our sample included a small number (n = 7, 18%) of private hospitals. While this number is proportional to the share of beds in the private sector at the national level, it is possible that having most private hospitals in Región Metropolitana (n = 6) may have resulted in an underestimation of AMR in that region and an overestimation of AMR in the rest of the country. Third, our aggregate AMR measures include bacteria that occupy different ecological niches, such as *E. coli* and *S. aureus*. While it is safe to assume many factors driving the evolution and spread of resistant bacteria are common, some are likely to be more specific within individual species or ecological niche.[38] Moreover, while most of the antibiotic-bacterium pairs corresponded to combinations usually observed in the hospital environment, it is possible that some cases, such as third-generation cephalosporin-resistant *E. coli* and methicillin-resistant *S. aureus,* could correspond to community-acquired organisms. However, it is worth noting that a large part of our findings were mainly driven by an increase in vancomycin-resistant Enterococci and carbapenem-resistant *K. pneumoniae*, which are typically found within hospitals. Fourth, we lacked data to directly examine antibiotic consumption at the hospital level in every healthcare center included in our study. A cross-country study showed that antibiotic consumption explained about one-third of the variation in AMR.[22] To avoid omitting such a relevant factor, we created an index of hospital complexity which we show had a high correlation with antibiotic consumption in our data using a small sample of 11 hospitals. This proxy probably resulted in less precise estimates than a measure of actual antibiotic consumption. Finally, our estimates should be interpreted as associations and not as causal effects.

Our findings underscore some of the limitations in AMR surveillance in Chile and the urgency to improve surveillance and infection control, at least among high and medium-complexity healthcare centers in the country. Surveillance should continue to focus on high-priority bacteria, as defined by the WHO. It would be essential to include, as suggested by the eCDC, the monitoring of aminoglycosides (amikacin and gentamicin) for *E. coli, K. pneumoniae, P. aeruginosa* and *A. baumannii*. It is also essential to characterize the impact of bacterial resistance in the community. For example, we should include the surveillance of *E. coli* resistance as a causative agent of urinary tract infection for oral antimicrobials such as first-generation cephalosporins, quinolones, cotrimoxazole, nitrofurantoin, and fosfomycin.

Last, there are limitations in the strategies to prevent and control the emergence and spread of AMR in Chile (Supplementary Material, Tables S2 and S3). Strengthening the National Plan Against AMR, particularly by generating cutting-edge research, requires more active collaboration between the government, the private sector, and academia. Furthermore, it is crucial to understand the relation of AMR with antimicrobial consumption at the hospital and community levels. This would improve our understanding of the impact of the policies and regulations to decrease antimicrobial use and its effects on resistance levels. Additionally, incorporating a One Health approach by integrating the human, animal, and environmental medicine sectors is essential to broadly understand the emergence and spread of AMR. It is essential to understand AMR as a phenomenon within the hospital environment while considering its interaction with the community, the environment, and other relevant factors, such as the hospital's complexity and social development.

We expect that improved spatiotemporal AMR estimates and a greater understanding of the socioeconomic factors associated with bacterial resistance will contribute to informing policy decisions and research priorities. More broadly, reliable AMR estimates should contribute to developing an international commitment and public health strategies to address the growing threat of bacterial AMR.

Contributors

Study design and analytical methods: KA, CC, PG, JL, JM, EU. Data analyses: KA. Manuscript writing: KA, EU. Data collection: PG, JL, CC, MC, FS, JM. Other data collection: KA, EU. Data verification: KA, EU. Data interpretation, critical manuscript review, edition, final approval: all authors. Secured funding: PG, JM, EU. All authors attest they meet the ICMJE criteria for authorship and have approved the final article.

Data sharing statement

All data collected for the study, included a data dictionary, are available from the corresponding author upon reasonable request. Socioeconomic data at the municipality level are available at http://observatorio.ministeriodesarrollosocial.gob.cl/encuesta-casen.

Editor note

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

Declaration of interests

The authors declare no conflict of interests.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lana.2023.100484.

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