



# Socioeconomic factors associated with antimicrobial resistance of *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *Escherichia coli* in Chilean hospitals (2008–2017)

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## ABSTRACT

**Objective.** To identify socioeconomic factors associated with antimicrobial resistance of *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *Escherichia coli* in Chilean hospitals (2008–2017).

**Methods.** We reviewed the scientific literature on socioeconomic factors associated with the emergence and dissemination of antimicrobial resistance. Using multivariate regression, we tested findings from the literature drawing from a longitudinal dataset on antimicrobial resistance from 41 major private and public hospitals and a nationally representative household survey in Chile (2008–2017). We estimated resistance rates for three priority antibiotic–bacterium pairs, as defined by the Organisation for Economic Co-operation and Development; i.e., imipenem and meropenem resistant *P. aeruginosa*, cloxacillin resistant *S. aureus*, and cefotaxime and ciprofloxacin resistant *E. coli*.

**Results.** Evidence from the literature review suggests poverty and material deprivation are important risk factors for the emergence and transmission of antimicrobial resistance. Most studies found that worse socioeconomic indicators were associated with higher rates of antimicrobial resistance. Our analysis showed an overall antimicrobial resistance rate of 32.5%, with the highest rates for *S. aureus* (40.6%) and the lowest for *E. coli* (25.7%). We found a small but consistent negative association between socioeconomic factors (income, education, and occupation) and overall antimicrobial resistance in univariate ( $p < 0.01$ ) and multivariate analyses ( $p < 0.01$ ), driven by resistant *P. aeruginosa* and *S. aureus*.

**Conclusion.** Socioeconomic factors beyond health care and hospital settings may affect the emergence and dissemination of antimicrobial resistance. Preventing and controlling antimicrobial resistance requires efforts above and beyond reducing antibiotic consumption.

## Keywords

Drug resistance, microbial; antibacterial agents; social conditions; social determinants of health; Latin America.

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The emergence and spread of antimicrobial resistance is one of the most urgent global public health threats (1, 2). Infections caused by resistant bacteria produce greater morbidity and mortality, complicate treatments, and often result in longer hospitalizations, imposing higher costs to health systems (2, 3). Antimicrobial resistance occurs naturally as an adaptive mechanism of bacteria; global increases in antibiotic use in humans, animals (e.g., food production), and agriculture (e.g., use of copper as a bactericide), have increased the selective pressure that drives the development of resistance, dramatically accelerating this natural phenomenon (4–6). A recent estimate for 76 countries by Klein et al. (7) shows overall antibiotic consumption, in defined daily doses (DDD), increased about 65% and antibiotic consumption rate (DDDs per 1 000 inhabitants per day) increased about 39% between 2000 and 2015. This increase in antibiotic consumption was largely driven by low- and middle-income countries (7).

Although frequently overlooked, the emergence and dissemination of antimicrobial resistance is also affected by socioeconomic and environmental factors, including inadequate water, sanitation, and hygiene (WASH) infrastructure, living conditions, waste management, education and awareness, economic activities, and other factors such as climate, health care quality, and migration (8–12). In addition, the lack of incentives has limited the development of new antibiotics; the process is expensive and expected profits are limited compared to other medications, largely because the clinical benefits of antibiotics decrease in time and their use needs to be restricted to prevent resistance (13).

Recent estimates indicate that antimicrobial resistance in Latin American countries ranges from 21% in Chile to 40% in Brazil, in contrast to an average antimicrobial resistance rate of 17% for countries from the Organisation for Economic Co-operation and Development (OECD) (14). Socioeconomic factors could be important predictors of antimicrobial resistance spread in Latin America, a region with several competing health priorities, limited health resources, deficient WASH infrastructure, uneven health care access, South-South migration, extreme poverty, a large food industry, and ubiquitous economic inequality (15, 16).

The objective of our study was to identify socioeconomic factors associated with imipenem and meropenem resistant *Pseudomonas aeruginosa*, cloxacillin resistant *Staphylococcus aureus*, and cefotaxime and ciprofloxacin resistant *Escherichia coli* in Chilean hospitals (2008–2017).

## MATERIALS AND METHODS

### Literature review

We searched for articles on antimicrobial resistance and socioeconomic factors in PubMed combining the keywords antibiotic resistance OR resistant bacteria with each of the following key-terms: “socioeconomic” OR “poverty” OR “water, sanitation, and hygiene” OR “WASH” OR “slum” for years 2000 through August 2019, in any language. We restricted the search to NOT “HIV” OR “AIDS” OR “tuberculosis” OR “TB” OR “virus” OR “fungus” OR “parasites” OR “malaria” OR “parasitic diseases.” We included all articles with empirical data or literature reviews, full-text available, scientifically valid approach, and external validity. We also looked for additional records in the references of the articles that qualified

for our qualitative synthesis, and included articles from our research on antimicrobial resistance (e.g., not indexed, book chapters, government reports, policy briefs). We excluded editorials, qualitative reports, opinions, and duplicated studies. Last, we only considered articles related to antimicrobial resistance in general, or those that included the following bacteria: *P. aeruginosa*, *S. aureus*, and *E. coli*.

### Empirical analysis: Chile as a case study

We combined two datasets. We used antimicrobial resistance rates from 41 tertiary care hospitals (i.e., high complexity) in Chile, and socioeconomic data from the Encuesta de Caracterización Socioeconómica Nacional (CASEN). More specifically, antimicrobial resistance data were collected annually (2008–2017) by the Grupo Colaborativo de Resistencia Bacteriana (GCRB) from the Chilean Society of Infectious Diseases (17); data include 67% of public and private tertiary hospitals in Chile. The GCRB hospital network began with 19 hospitals in 2008 and has increased in size, to more than 50 hospitals in 2019. We included observations from all hospitals reporting at least one observation (resistance rate) over time for each antibiotic–bacterium pair considered in our analysis ( $n = 41$ ). For comparability, we estimated resistance proportions based on three OECD-defined priority antibiotic–bacterium pairs in 2015, i.e., cefotaxime and ciprofloxacin resistant *E. coli*; cloxacillin resistant *S. aureus*; and imipenem and meropenem resistant *P. aeruginosa* (14). GCRB is an unbalanced panel; on average, hospitals reported 4.6 years of antimicrobial resistance data between 2008 and 2017 ( $n = 190$ ) in 24 municipalities in Chile. GCRB is a collaborative clinical surveillance network; participant hospitals annually report the average susceptibility of a series of antibiotic–bacterium pairs from clinical samples, following Clinical and Laboratory Standards Institute (CLSI) recommendations (17, 18). Antibiotic resistance rates were calculated by dividing the number of laboratory tests that showed bacterial resistance to antibiotics by the total number of tests.

We characterized the population attended by hospitals at the municipality level, based on the CASEN survey for 2008–2017. CASEN is a nationally representative household survey, applied every two or three years since 1985 by the Chilean Ministry of Social Development, to socioeconomically characterize households. With an emphasis on poverty and social vulnerability, CASEN collects data on education, health, housing, work, and income. We standardized sociodemographic variables from CASEN by subtracting the overall mean and dividing by the overall standard deviation (SD) (8). Because we only had a limited number of annual observations for 41 hospitals in 24 municipalities, we reduced the number of covariates in the regressions to avoid overfitting. We created two sociodemographic indexes based on the expected characteristics of the population served by hospitals, aggregated at the municipality level. First, we created a household infrastructure index to characterize people’s living conditions that may affect the spread of resistant bacteria (19–22), based on a household’s poverty rate, sanitation, overcrowding, and material deprivation. Second, we created a socioeconomic status index, which aims to reflect economic activity, behavioral practices, and occupation of the population, composed of education level, income per capita, and occupation at the municipality level. Both indexes were standardized for the analysis (mean = 0, SD = 1). Table 1 shows

**TABLE 1. Descriptive statistics for antibiotic resistance rates and socioeconomic factors associated with its emergence and dissemination in Chile, 2008–2017**

Variables	Mean	SD	IQR	Definition
<b>Antimicrobial resistance</b>				
Overall (%)	32.5	0.09	12.9%	Average of three antibiotic–bacterium pairs, as described below
<i>P. aeruginosa</i> (%)	33.3	0.12	15.4%	Proportion of imipenem and meropenem resistant <i>P. aeruginosa</i>
<i>E. coli</i> (%)	25.7	0.09	11.4%	Proportion of cefotaxime and ciprofloxacin resistant <i>E. coli</i>
<i>S. aureus</i> (%)	40.6	0.18	26.1%	Proportion of cloxacillin resistant <i>S. aureus</i>
<b>Household infrastructure index<sup>a</sup></b>				
Poverty (%)	10.2	0.06	9.8%	Population with income per capita below the poverty line (–US\$ 180 in 2017)
Inadequate sanitation (%)	2.4	0.02	1.6%	Population with inadequate sanitation (House Sanitation Index). Inadequate sanitation (=1) defined as household with no access to drinkable water, or toilet or latrine not connected to the sewer or septic tank
Material deprivation (%)	11.6	0.07	11.7%	Population living in poor quality housing. Material deprivation (=1) defined as housing of reused materials or a hut, tent, mobile home, or similar.
Overcrowding (%)	10.8	0.06	10.1%	People living in an overcrowded household defined as people/rooms >2.4
<b>Socioeconomic index<sup>a</sup></b>				
Income per capita (\$1 000 CLP)	435	289	229	Average income per capita, in 2017 CLP (Chilean pesos; 1 US\$ = –CLP 700)
Years of schooling	12.5	1.7	2.2	Average years of schooling for adult population (≥18 years of age)
Occupation index (ISCO)	5.2	1.0	1.1	Continuous variable (1–9), representing average ISCO codes for occupations classification. Higher scores represent high skilled occupations

**Notes.** SD: standard deviation; IQR: interquartile range. IQR = 75<sup>th</sup> percentile – 25<sup>th</sup> percentile. Hospitals in the sample are located in 26 municipalities, in 11 regions of Chile. <sup>a</sup>: These variables were obtained from the CASEN survey for years 2006, 2009, 2011, 2013, 2015, and 2017. Table prepared by authors.

variable definitions and descriptive statistics (further information is available from the authors by request).

We first examined descriptive statistics in our study sample. We plotted antimicrobial resistance rates for *P. aeruginosa*, *S. aureus*, and *E. coli*, and household infrastructure and socioeconomic status indexes in the regions of Chile for which hospital data were available. We then examined the bivariate correlation between antimicrobial resistance and sociodemographic characteristics of the population both graphically and using Pearson’s test. Last, we ran linear regression models using pooled data to assess the association between antimicrobial resistance rates and socioeconomic status and household infrastructure, using year fixed effects, clustering of standard errors by hospital, and bootstrapping (random sampling with replacement) with 50 repetitions to make inferences about the population.

## RESULTS

### Literature review

We identified 145 published articles related to antimicrobial resistance and socioeconomic variables. Of these, 40 articles satisfied our inclusion and exclusion criteria. The main findings are summarized below.

**Socioeconomic factors affecting antimicrobial resistance globally.** Socioeconomic factors generally reflect people’s living conditions, social status, and economic activities. These living conditions include overcrowded households, material deprivation, and inadequate access to WASH. Other related factors in the literature refer to years of schooling, income per capita, occupation, and various types of wealth. Social and economic disparities are also important because they may determine differential exposure to infectious diseases, including antimicrobial resistance, and differential access to and quality of health care (6, 8, 10–12, 20, 23, 24).

Research suggests poverty and material deprivation are important risk factors for the emergence and transmission of antimicrobial resistance (6, 12, 19, 21, 23). Plausible mechanisms

to explain this association include limited access to professional health care, inadequate hygiene, overcrowded households, deficient management of residuals, a higher burden of malnutrition, and limited access to drinkable water. Compared to high-income countries, antibiotics may also be of lower quality in lower-income countries, possibly because antibiotics are affected by weather conditions, such as humidity and temperature, and storage conditions may not be adequately regulated and supervised, resulting in degraded medications (25). Previous studies have also found substantial disparities on antimicrobial resistance by socioeconomic characteristics within and between countries (12). The development of antimicrobial resistance in low- and middle-income countries has been accelerated by poor regulation, self-medication, inadequate nosocomial infection control, inadequate epidemiological surveillance, clinical misuse, and deficient quality of antibiotics (5, 7, 13, 20). Previous studies (21, 26) suggest that people from deprived areas or low educational background have a higher likelihood of self-medication, favoring the emergence of antimicrobial resistance. The main driver of antimicrobial resistance in high-income countries is excess antibiotic use, including reserve use antibiotics, partly due to inadequate hospital regulation (27). On the other hand, in low- and middle-income countries antimicrobial resistance rates are largely driven by poor governance and sanitation, limited access to professional health care, insufficient WASH infrastructure, and self-medication (8).

Despite suggestive evidence, there is no closure over the association between low socioeconomic status and antimicrobial resistance. For instance, two studies, in Indonesia and India, found that people living in poorer or overcrowded households had a lower probability of having resistant *E. coli*. This finding could be partially explained by limited or null access to antibiotics, and because overcrowding in the south of India may also occur in relatively high-income households (28, 29).

**Socioeconomic status may be driving antimicrobial resistance rates in Latin America.** Only a handful of studies have examined the association between antimicrobial resistance

and socioeconomic factors in Latin America, specifically, in Brazil (22), Argentina (30), Mexico (31), Bolivia (32), and Peru (24). A study in Osasco (Brazil) collected stool samples from 79 children aged 5–10 years in a slum, to analyze the presence of diarrheagenic *E. coli*. Results showed 58% were positive for *E. coli*, of which 65% were resistant to at least one antibiotic (22). Similarly, researchers analyzed 591 clinical isolates of *S. aureus* recovered from 66 different hospitals in Argentina. The study suggested patients infected with drug-resistant *S. aureus* were more likely to come from low-income, overcrowded households, and had less years of schooling (30). A study in Mexico found 75% of the 158 *P. aeruginosa* isolates from three public hospitals in Mexico City were resistant to at least one antibiotic (31). In Bolivia, a study in a rural area with high poverty rates examined 213 isolates, of which 170 were *E. coli* isolates with 74% of the sample resistant to trimethoprim-sulfamethoxazole (32). In contrast, a study in two Amazonian communities in Peru found that children from wealthier families were more likely to have antimicrobial resistant *E. coli* (24). Interestingly, the authors noted that antibiotic consumption was not apparently driving the association of wealth and antimicrobial resistance. Overall, most studies suggest that worse socioeconomic indicators are associated with higher rates of antimicrobial resistance.

### Empirical analysis: the case of Chile

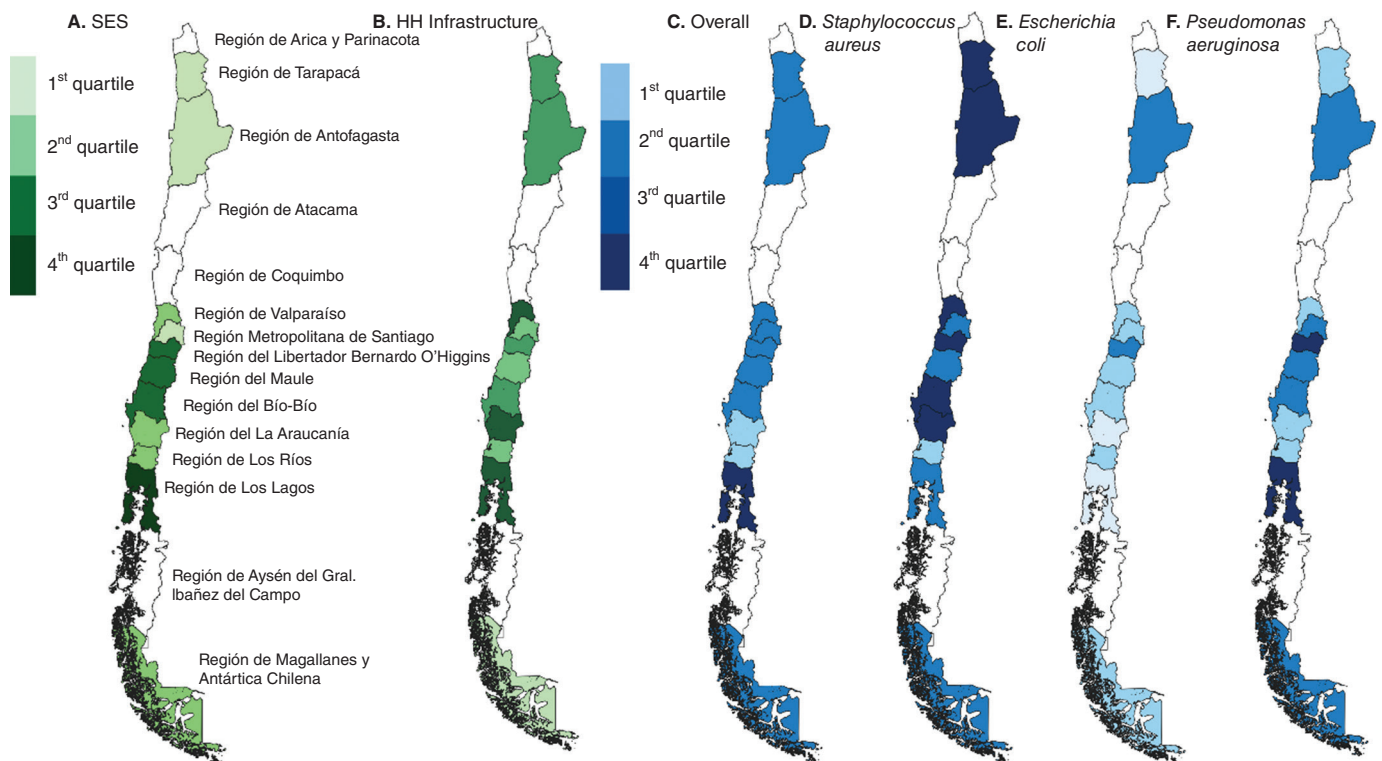
**Descriptive statistics.** Table 1 shows that the overall antimicrobial resistance rate was 32.5% for our sample of hospitals,

with the highest for *S. aureus* (40.6%, SD = 0.18), and the lowest antimicrobial resistance for *E. coli* (25.7%, SD = 0.09). The interquartile ranges (IQR), suggest there was a relatively lower variation in antimicrobial resistance for *E. coli* across hospitals (11.4%), compared to *S. aureus* (26.1%) and *P. aeruginosa* (15.4%). Socioeconomic factors among the population in municipalities with tertiary hospitals included in the sample show relatively low rates of poverty (10.2%, SD = 0.06), few households with inadequate sanitation (2.4%, SD = 0.02), and an average of 12 years of schooling (SD = 1.7).

Fig. 1 shows how socioeconomic status, household infrastructure, and antimicrobial resistance rates are distributed by region in Chile. Colors represent quartiles in the average values for each variable across all years in the sample, with lighter colors representing a more desirable situation. The distribution suggests relatively better socioeconomic indicators (Fig. 1, panels A and B) are found in northern regions, Región Metropolitana, and Región de Magallanes. Interestingly, Fig. 1, panel C, suggests overall antimicrobial resistance rates are higher in Región de Los Lagos, particularly for *P. aeruginosa* (Fig. 1, panel F). Regions in central and southern Chile show a more consistent correlation between worse socioeconomic status and household infrastructure indexes and higher antimicrobial resistance rates. Fig. 1 also shows higher antimicrobial resistance rates in northern regions, particularly for *S. aureus* (panels C and D).

**Univariate analysis.** Fig. 2 shows the Pearson bivariate correlation level (ranging from -1 to 1) between antimicrobial

**FIGURE 1. Distribution of socioeconomic status, household infrastructure index and antimicrobial resistance rates by region in Chile, 2008–2017**



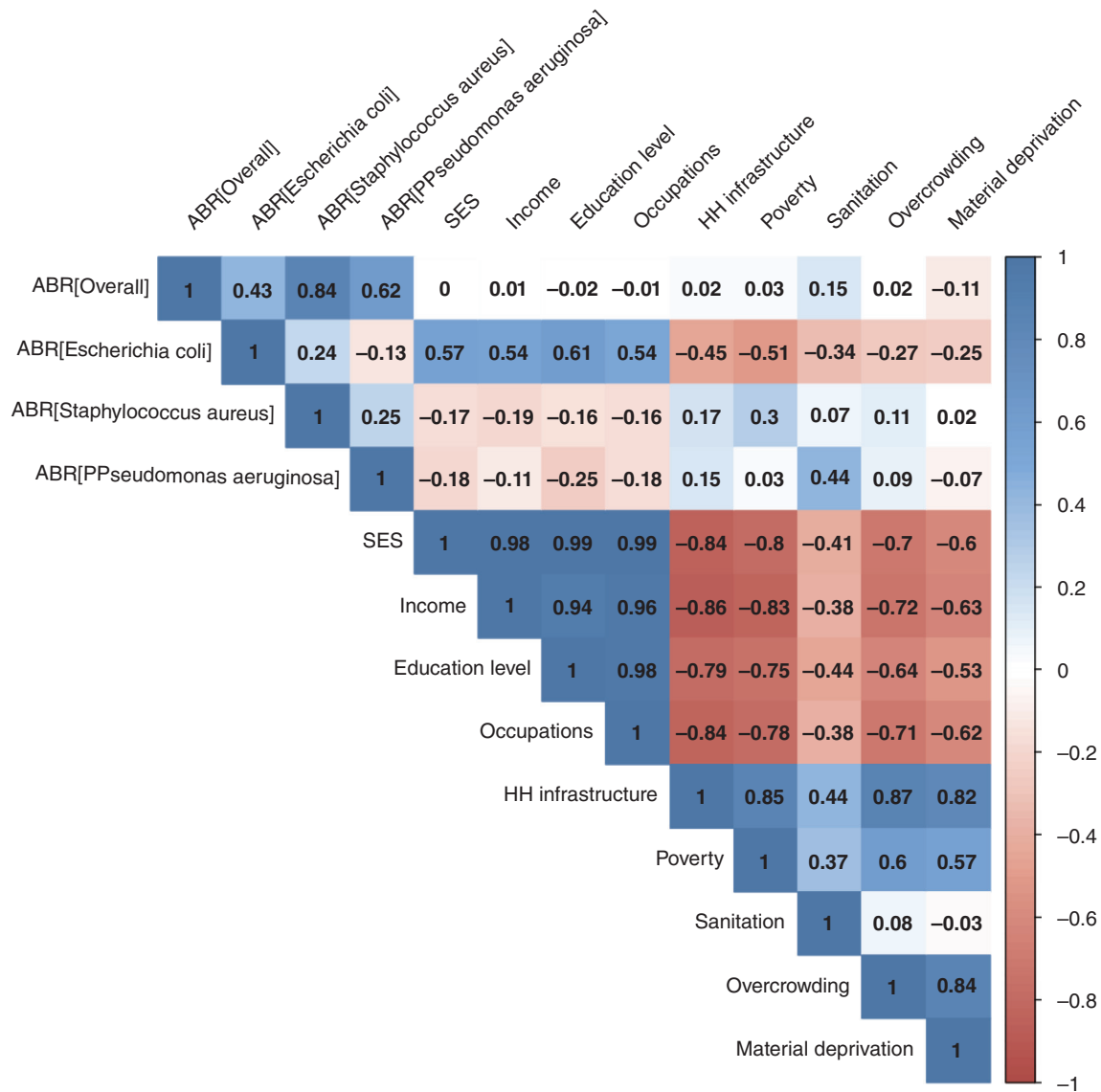
**Notes.** Maps A and B show the distribution of socioeconomic status (SES) and household (HH) infrastructure indexes respectively by quartiles. Maps C, D, E, and F show overall antimicrobial resistance rates for *S. aureus*, *E. coli*, and *P. aeruginosa*, and then for each bacterium separately based on OECD standards and specifications (14). Antimicrobial resistance rates range from 0–18%, 18–28%, 28–40%, and +40% for each quartile, respectively. White areas display regions with no available data. The 1st quartile presents the best socioeconomic and antimicrobial resistance scenario. Figure prepared by authors.

resistance and several social and economic factors included in our data. Negative values are shown in red and positive values in blue. We found a consistent negative association between socioeconomic status factors (income, education, and occupation) and overall antimicrobial resistance rate, with large correlations for *P. aeruginosa* ( $r = 0.62, p < 0.001$ ) and *S. aureus* ( $r = 0.84, p = 0.01$ ). We found a positive correlation between *P. aeruginosa* resistance rates and inadequate sanitation ( $r = 0.44, p = 0.02$ ), and a weaker correlation between *S. aureus* resistance and income ( $r = -0.19, p = 0.1$ ). Last, Fig. 2 suggests an unexpected correlation between *E. coli* resistance and socioeconomic factors (socioeconomic status and household infrastructure) possibly explained by the small observed variation in antimicrobial resistance of *E. coli* within hospitals ( $r = 0.57, p = 0.01$ ;  $r = -0.45, p = 0.01$ , respectively). Values between  $-0.1$  and  $0.1$  were not significant ( $\alpha = 10\%$ ).

Fig. 3 suggests the median overall resistance rate for *E. coli*, *S. aureus*, and *P. aeruginosa* does not show significant variation, with rates around 28% to 38%, and a slight decrease from 2009 to 2017 ( $p < 0.001$ , see Fig. 3, panel A). *E. coli* rates have remained relatively constant across years (Fig. 3, panel B). Resistance rates of *P. aeruginosa* show some variation over the years, but also show the smallest variation across hospitals in the sample. Finally, *S. aureus* resistance rates have substantially decreased from 2009 (~68%) to 2017 (~38%).

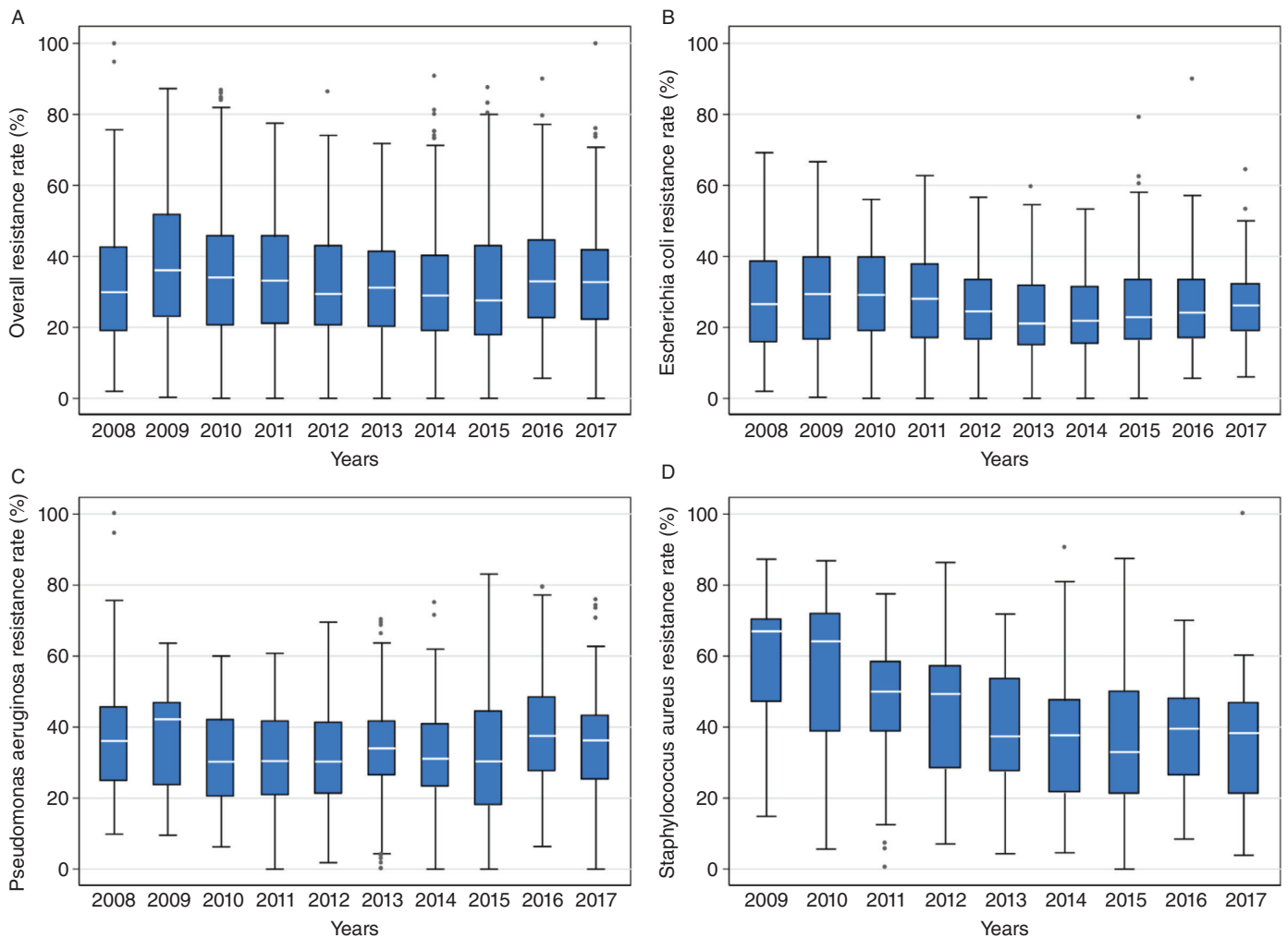
**Multivariate analysis.** Table 2, model 1, shows a negative association of socioeconomic status index and overall antimicrobial resistance rate ( $\beta = -0.01$ , standard error (se) = 0.00,  $p = 0.06$ ), which suggests one SD increase in the socioeconomic status index is associated with a 1% decrease in antimicrobial resistance. This statistically significant association was similar for *P. aeruginosa* (Table 2, model 2,  $\beta = -0.01$ , se = 0.00,  $p < 0.001$ ),

**FIGURE 2. Pearson correlations of antibiotic resistance rates of *E. coli*, *S. aureus*, and *P. aeruginosa* and socioeconomic factors in Chile, 2008–2017**



**Notes.** Red colors represent negative relation, while blue colors display positive relations. Lighter blocks represent no significant correlation ( $p < 0.10$ ). Figure prepared by authors. ABR stands for antibiotic or antimicrobial resistance rates, which were calculated based on OECD standards. Antibiotic–bacterium pairs are cefotaxime and ciprofloxacin resistant *E. coli*, imipenem and meropenem resistant *P. aeruginosa*, and cloxacillin resistant *S. aureus*.

**FIGURE 3. Evolution of the proportion of antimicrobial resistant bacteria for (A) all bacteria in the sample, (B) cefotaxime and ciprofloxacin resistant *E. coli*, (C) imipenem and meropenem resistant *P. aeruginosa*, and (D) cloxacillin resistant *S. aureus* in 41 hospitals in Chile, 2008–2017**



**Notes.** *E. coli*, *S. aureus*, and *P. aeruginosa*. Resistance rates are calculated as 1-Susceptibility rate. White lines indicate the median rate. Circle markers stand for outliers. Figure prepared by authors. Antimicrobial resistance rates were calculated based on OECD standards.

**TABLE 2. Linear regression of antimicrobial resistance rates for *E. coli*, *S. aureus*, and *P. aeruginosa* against household infrastructure and socioeconomic status indexes, pooled data analysis for 41 hospitals in Chile, 2008–2017**

Outcome:	Model 1		Model 2		Model 3		Model 4	
	Overall rate	Overall rate	<i>P. aeruginosa</i>	<i>P. aeruginosa</i>	<i>E. coli</i>	<i>E. coli</i>	<i>S. aureus</i>	<i>S. aureus</i>
	$\beta$	se	$\beta$	se	$\beta$	se	$\beta$	se
Household infrastructure	0.00	0.00	0.00	0.00	0.00	0.00	-0.01**	0.01
Socioeconomic status	-0.01*	0.00	-0.01***	0.00	0.03**	0.00	-0.04***	0.01
Constant	0.40***	0.01	0.39***	0.01	0.30***	0.01	0.60***	0.02
Number of observations	190		190		190		190	
$R^2$	6%		6%		16%		18%	

**Notes.** se = standard error. \*  $p < 0.1$ , \*\*  $p < 0.05$ , and \*\*\*  $p < 0.01$ . Hospitals were observed with an average of 4.6 years between 2008 and 2017. All regressions include year fixed-effects, clustering of standard errors by hospital, and bootstrapping (random sampling with replacement) with 50 repetitions. Table prepared by authors. Antimicrobial resistance rates were calculated based on OECD standards and specifications.

and four times larger for *S. aureus* (Table 2, model 4,  $\beta = -0.04$ , se = 0.01,  $p < 0.001$ ). We found evidence of a positive statistically significant association between *E. coli* and socioeconomic factors ( $\beta = 0.03$ ,  $p = 0.04$ ), and a negative association between the household infrastructure index and *S. aureus* ( $\beta = -0.01$ , se = 0.01,  $p = 0.03$ ).

## DISCUSSION

We have examined the association between social and economic factors and antimicrobial resistance rates for *P. aeruginosa*, *S. aureus*, and *E. coli*, through a literature review in PubMed and an empirical analysis in 41 hospitals in Chile for 2008–2017. Consistent with previous reviews (6, 12, 19, 21, 23), we found that poverty and material deprivation may be important risk factors for antimicrobial resistance transmission. This association is probably explained by limited access to professional health care, inadequate WASH infrastructure, overcrowded

households, and limited education (22). We found a significant partial correlation for an index of socioeconomic status (income, schooling, and occupation) and overall antimicrobial resistance, and *S. aureus* and *P. aeruginosa* resistance, consistent with previous literature (30). We did not find much evidence of a significant association between antimicrobial resistance and an index of household infrastructure, possibly due to the low variation of this index across municipalities and a relatively small sample size. A very large proportion of the population in Chile has access to adequate sanitation infrastructure, and compared to other countries in the region, Chile has relatively low poverty, overcrowding, and material deprivation rates.

Antimicrobial resistance is a relevant public health challenge in many countries of Latin America (1, 3, 7, 14, 19, 22). For instance, the OECD estimates resistance rates  $\geq 30\%$  for eight priority antibiotic–bacterium pairs in Argentina, Brazil, Colombia, Costa Rica, Mexico, and Peru (14). Klein et al. (7) estimated increases in national antibiotic consumption rates between 2002 and 2015 (DDDs per 1 000 inhabitants per day) for all countries in Latin America and the Caribbean where data were available, except for Mexico. But beyond antibiotic consumption, antimicrobial resistance could worsen because of a relatively large proportion of the population living in poverty, many of whom lack adequate WASH infrastructure, and have limited access to professional health care and formal education (6, 8, 15).

The results for our empirical analysis in Chile showed an overall 32.5% antimicrobial resistance rate for all three bacteria analyzed, six percentage points over recent estimates (26.5%) published by the OECD (14). Specifically, we found resistance rates of 33.3% for *P. aeruginosa*, 25.7% for *E. coli*, and 40.6% for *S. aureus*, compared to OECD (14) estimates of 25.1%, 28.1%, and 26.4%, respectively. Our results provide, for the first time, national and subnational estimates of antimicrobial resistance for three clinically relevant antibiotic–bacterium pairs using a large longitudinal dataset of 41 hospitals in Chile, their geographical distribution in Chile, and also the evolution of resistance rates in the past decade (2008–2017). Rigorous and comparable estimates of antimicrobial resistance are essential to inform policy-making, define research and funding priorities, and evaluate stewardship programs and interventions.

Our analysis also showed a consistent negative association between socioeconomic status factors (income, education, and occupation) and overall antimicrobial resistance rate, with large correlations for *P. aeruginosa* and *S. aureus*, consistent with previous literature (6, 8, 10–12, 20, 23, 24). There is sparse literature on this topic globally, and only a handful of studies in Latin America. Our findings in Chile provide external validity to previous studies, and highlight the importance of factors associated with social and material living conditions that may help control this emerging public health crisis.

The multivariate model showed a relatively small but statistically significant association between socioeconomic status and antimicrobial resistance rates (specifically for *P. aeruginosa* and *S. aureus*). Unfortunately, we lack the data to test for setting-specific factors or transmission mechanisms. Resistant *S. aureus*, common in the nose and skin, has been associated with lack of adequate housing or homelessness, with transmission probably occurring in the communities (33). *P. aeruginosa* is ubiquitous in the environment and frequently found in streams and ponds; however, most documented infections are nosocomial. But

there is at least some evidence that environmental conditions may favor *P. aeruginosa* infections in developing countries (34), perhaps related to a lack of running water. We found no evidence of correlation with *E. coli*, which is also frequently linked to inadequate WASH infrastructure. The bivariate analysis showed very consistent associations, and so perhaps the lack of significance is explained by insufficient power. While small, these associations underscore the importance of factors beyond health care and hospital settings that may affect the emergence and dissemination of antimicrobial resistance. These factors have largely been overlooked by decisionmakers and researchers.

Our empirical analysis has at least five limitations. First, we limited the analysis to three antibiotic–bacterium pairs, as defined by the OECD (14), because of their clinical relevance, prevalence in the literature, and because they are considered priority by the World Health Organization (35). But focusing on only three bacteria limits the generalizability of our findings to antimicrobial resistance more broadly. Second, we examined global literature but then empirically tested findings using data from a single country. While our findings are consistent with existing literature, their external validity could be limited if there were some unobserved idiosyncratic characteristics of Chile driving the results. We currently lack data to test this, but are working with colleagues from other countries in Latin America to generate cross-country data. Third, our panel was not balanced, limiting our ability to use longitudinal panel data analysis strategies. We partially addressed this by controlling for time periods and by using bootstrapping and clustering of standard errors. Fourth, GCRB data are anonymized and we were thus not able to characterize the samples based on the sociodemographic characteristics of patients. We addressed this limitation by characterizing the communities attended by the tertiary hospitals in the dataset based on socioeconomic factors at the municipality level from the CASEN survey. Last, our revision of the literature was limited to PubMed, references cited in selected articles, and our own previous work. Hence, our search may have excluded relevant literature, such as national publications not indexed in PubMed.

Our literature review highlighted that poverty and material deprivation are important risk factors for the emergence and transmission of antimicrobial resistance. Our results were consistent with the literature; we found a negative association between socioeconomic factors (income, education, and occupation) and overall antimicrobial resistance, driven by imipenem and meropenem resistant *P. aeruginosa* and cloxacillin resistant *S. aureus*. These results underscore the need to increase efforts to systematically study risk factors for emergence and spread of antibiotic resistance in humans, including setting-specific factors such as WASH infrastructure or specific industries (e.g., animal protein), and to understand transmission dynamics and interactions across domains (e.g., health care settings, demographics, socioeconomic factors, animal contacts, water sources). More detailed longitudinal cohort studies including public and private health care visits, use of medications, interactions with community members, and economic activities, would be particularly useful; more so if they included various centers across countries to increase external validity of findings. Antimicrobial resistance is a multifactorial public health challenge; researchers and policymakers from the public health community urgently need to pay attention to factors beyond

nosocomial induced resistance, including poverty reduction, education, and sanitation improvements.

In conclusion, socioeconomic factors beyond health care and hospital settings may affect the emergence and dissemination of antimicrobial resistance. Preventing and controlling antimicrobial resistance requires efforts above and beyond reducing antibiotic consumption.

**Author contributions.** Study design and analytical methods: KA, PG, JL, JMM, EAU. Data analyses: KA. Manuscript writing (lead): KA, EAU. Data collection (GCRB): PG, JL, JMM, GCRB. Other data collection: KA, MR. Data interpretation, critical manuscript review, edition, final approval: all authors. Secured funding: PG, JL, JMM, EAU. All authors attest they meet the ICMJE criteria for authorship and have reviewed and approved the final manuscript.

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This study is part of a long-term research agenda to study antimicrobial resistance in Chile in close collaboration with the GCRB

network and as participants of the Millennium Nucleus for Collaborative Research in Antimicrobial Resistance (MICROB-R). MICROB-R is an interdisciplinary team – including medical doctors, veterinarians, biologists, epidemiologists, economists, and engineers – doing research to understand the mechanisms driving the emergence and dissemination of antimicrobial resistance, evaluate antimicrobial resistance prevention and control programs, and estimate the economic and disease burden of infections in developing countries, to support evidence-based decisions in public health.

**Conflicts of interest.** The authors declare no conflicts of interest.

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## Factores socioeconómicos relacionados con la resistencia a los antimicrobianos de *Pseudomonas aeruginosa*, *Staphylococcus aureus* y *Escherichia coli* en hospitales chilenos (2008-2017)

### RESUMEN

**Objetivo.** Determinar los factores socioeconómicos relacionados con la resistencia a los antimicrobianos de *Pseudomonas aeruginosa*, *Staphylococcus aureus* y *Escherichia coli* en hospitales chilenos (2008-2017).

**Métodos.** Se revisó la bibliografía científica acerca de los factores socioeconómicos relacionados con la aparición y el incremento de la resistencia a los antimicrobianos. Mediante una regresión con múltiples variables se examinaron los resultados de la bibliografía respecto a un conjunto de datos longitudinales sobre resistencia a los antimicrobianos de 41 importantes hospitales privados y públicos, así como a una encuesta domiciliaria representativa a nivel nacional en Chile (2008-2017). Se estimaron las tasas de resistencia para tres pares de antibióticos y bacterias prioritarios, de conformidad con lo definido por la Organización de Cooperación y Desarrollo Económicos, es decir: *P. aeruginosa*, resistente a imipenem y meropenem; *S. aureus*, resistente a cloxacilina y *E. coli*, resistente a la cefotaxima y ciprofloxacino.

**Resultados.** La evidencia de la revisión bibliográfica es indicativa de que la pobreza y la privación material suponen importantes factores de riesgo para la aparición y transmisión de la resistencia a los antimicrobianos. La mayoría de los estudios ha demostrado que los peores indicadores socioeconómicos están asociados a mayores tasas de resistencia a los antimicrobianos. Este análisis ha indicado una tasa general de resistencia a los antimicrobianos de 32,5 %, con las tasas más elevadas para *S. aureus* (40,6 %) y las más bajas para *E. coli* (25,7 %). Se apreció una asociación negativa mínima, aunque uniforme, entre los factores socioeconómicos (ingresos, educación y ocupación) y la resistencia general a los antimicrobianos en un análisis de variable única ( $p < 0,01$ ) y análisis multifactoriales ( $p < 0,01$ ), impulsadas por las bacterias *P. aeruginosa* y *S. aureus* resistentes.

**Conclusiones.** Los factores socioeconómicos no relacionados con la atención de la salud y los entornos hospitalarios pueden afectar la aparición y la propagación de la resistencia a los antimicrobianos. Su prevención y control precisan esfuerzos adicionales que se sumen a la reducción del consumo de antibióticos.

### Palabras clave

Farmacoresistencia microbiana; antibacterianos; condiciones sociales; determinantes sociales de la salud; América Latina.

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## Fatores socioeconômicos associados à resistência antimicrobiana em *Pseudomonas aeruginosa*, *Staphylococcus aureus* e *Escherichia coli* em hospitais chilenos (2008-2017)

### RESUMO

**Objetivo.** Identificar os fatores socioeconômicos associados à resistência antimicrobiana de *Pseudomonas aeruginosa*, *Staphylococcus aureus* e *Escherichia coli* em hospitais chilenos (2008-2017).

**Métodos.** Fizemos uma revisão da literatura científica sobre os fatores socioeconômicos associados ao surgimento e à disseminação da resistência antimicrobiana. Usando a regressão multivariada, testamos os resultados da literatura baseando-nos em um conjunto de dados longitudinais sobre a resistência antimicrobiana em 41 grandes hospitais privados e públicos e em uma pesquisa domiciliar representativa da realidade nacional no Chile (2008-2017). Estimamos as taxas de resistência em três pares prioritários de bactérias e antibióticos, como definido pela Organização para a Cooperação e o Desenvolvimento Econômico: *P. aeruginosa* resistente a imipenem e meropenem, *S. aureus* resistente a cloxacilina e *E. coli* resistente a cefotaxima e ciprofloxacino.

**Resultados.** As evidências desta revisão da literatura sugerem que a pobreza e a privação material são fatores de risco importantes para o surgimento e a transmissão da resistência antimicrobiana. A maior parte dos estudos constatou que piores indicadores socioeconômicos estão associados a taxas mais altas de resistência antimicrobiana. A nossa análise mostrou uma taxa global de resistência antimicrobiana de 32,5%; *S. aureus* apresentou as taxas mais altas (40,6%) e *E. coli* as mais baixas (25,7%). As análises univariadas ( $p < 0,01$ ) e multivariadas ( $p < 0,01$ ) identificaram uma associação negativa pequena, porém consistente, entre fatores socioeconômicos (renda, educação e ocupação) e a resistência antimicrobiana global em *P. aeruginosa* e *S. aureus*.

**Conclusão.** Fatores socioeconômicos, para além dos cuidados de saúde e dos ambientes hospitalares, podem afetar o surgimento e a disseminação da resistência antimicrobiana. Para prevenir e controlar esta resistência, é preciso fazer esforços que não se limitem à redução do consumo de antibióticos.

**Palavras-chave** Resistência microbiana a medicamentos; antibacterianos; condições sociais; determinantes sociais da saúde; América Latina.

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