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Total antibiotic use in a state-wide area and resistance patterns in Brazilian hospitals: an ecologic study

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ABSTRACT

Introduction: Use of antibiotic and bacterial resistance is the result of a complex interaction not completely understood.
Objectives: To evaluate the impact of entire antimicrobial use (community plus hospitals) on the incidence of bloodstream infections in intensive care units adjusted by socioeconomic factors, quality of healthcare, and access to the healthcare system.
Design: Ecologic study using a hierarchical spatial model.
Setting: Data obtained from 309 hospitals located in the state of São Paulo, Brazil from 2008 to 2011.
Participants: Intensive care units located at participant hospitals.
Outcome: Hospital acquired bloodstream infection caused by MDRO in ICU patients was our primary outcome and data were retrieved from São Paulo Health State Department. Socioeconomic and healthcare indexes data were obtained from IBGE (Brazilian Foundation in charge of national decennial census) and SEADE (São Paulo Planning and Development Department). Information on antimicrobial sales were obtained from IMS Brazil. We divided antibiotics into four different groups (1–4).
Results: We observed a direct association between the use of group 1 of antibiotics and the incidences of bloodstream infections caused by MRSA (1.12; 1.04–1.20), and CR-*Acinetobacter* sp. (1.19; 1.10–1.29). Groups 2 and 4 were directly associated to VRE (1.72; 1.13–2.39 and 2.22; 1.62–2.98, respectively). Group 2 was inversely associated to MRSA (0.87; 0.78–0.96) and

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CR-*Acinetobacter* sp. (0.79; 0.62–0.97). Group 3 was inversely associated to *Pseudomonas aeruginosa* (0.69; 0.45–0.98), MRSA (0.85; 0.72–0.97) and VRE (0.48; 0.21–0.84). No association was observed for third generation cephalosporin-resistant *Klebsiella pneumoniae* and *Escherichia coli*.

Conclusions: The association between entire antibiotic use and resistance in ICU was poor and not consistent for all combinations of antimicrobial groups and pathogens even after adjusted by socioeconomic indexes. Selective pressure exerted at the community level seemed not to affect the incidences of MDRO infection observed in intensive care setting.

Introduction

The use of antibiotics has been considered an important driver of bacterial resistance since they were introduced to modern medicine.[1] Given that these drugs are necessary for human and animal care as well as to ensure food safety, their use must meet best practices of consumption and be treated as a common good. Bacterial infections due to resistant microorganisms, like other infectious diseases, have been demonstrated to be associated with socioeconomic status, access and quality of healthcare.[2] Furthermore, the burden of bacterial resistance is different in different areas of the globe.[3] In this sense, understanding the determinants of bacterial resistance in a given area is important to support public policies leading to more efficient control of its spread.

The World Health Organization as well as Infectious Diseases Societies have proposed that governments coordinate actions to minimize and limit the spread of antimicrobial resistance.[4,5] In Brazil, a law restricting over-the-counter sales of antibiotics was passed by the federal government in 2010, which had a variable impact on sales in different geographic areas of the country.[6] Another study, investigating socioeconomic determinants of antibiotic use in the state of São Paulo, Brazil, found an association between higher consumption of antimicrobial drugs and markers of social inclusion such as higher human development index, density of private health establishments, and lower illiteracy.[7] To date, no studies were published investigating the impact of this Brazilian law on the occurrence of multidrug resistant organisms (MDRO) either in the community or in the healthcare setting.

In this study we explored the impact of overall antibiotic use, i.e. the sum of what is consumed at the community and in hospitals, on the incidence of infections caused by MDRO within intensive care units in the same area and adjusted for socioeconomic indexes, quality and access to healthcare.

Objective

The aim of this study was to evaluate the impact of overall antimicrobial use (community plus hospitals) on the incidence of bloodstream infections at intensive care units adjusted by socioeconomic factors, quality of healthcare, and access to the healthcare system.

Methods

Study design, geographic area and study population

An ecologic study aggregating data from 309 hospitals located in the state of São Paulo, Brazil from 2008 to 2011 (Fig. 1) was designed. São Paulo is the wealthiest state of the Brazilian Federation, located in the southeastern of the Country, with approximately 41 million inhabitants and a human development index of 0.78 in 2010 (www.ibge.gov.br). This study was approved by the Research Ethics Committee of the University of São Paulo, protocol number 443/11 in November 9th, 2011.

Data sources

1. *State Health Department* (SHD) — the hospital infection branch of SHD established a Nosocomial Surveillance System in 2004, which included the reporting of central line-associated bloodstream infections as well as secondary bacteremia due to infections at other sites. We included 309 hospitals distributed in 105 municipalities based on their consistent data reporting during the study period (2008 through 2011).
2. *Instituto Brasileiro de Geografia e Estatística* (IBGE) — a Brazilian Federal Foundation responsible for the national decennial census. We extracted São Paulo socioeconomic and healthcare indexes from this database as described below.
3. *Sistema Estadual de Análise da Dados* (SEADE) — this foundation is a branch of São Paulo Planning and Development Department and is responsible for socioeconomic and demographic analyses.
4. *Intercontinental Medical Statistics Brazil* (IMS) — this is a private company that provides information on antimicrobial sales in a given geographic area. We acquired information on antimicrobial sales in the state of São Paulo during the study period. Data on sales were considered as a proxy for antimicrobial use. Antimicrobial data are presented as daily defined doses (DDD) per 1000 inhabitants per year according to the Anatomical Chemical Classification system.[8] This reflects the number of daily defined doses consumed per 1000 inhabitants in one year as follows: (quantity of antimicrobial in a given year (g) × 1000)/(DDD for that drug × population). Bloodstream infection (BSI) rates of a given year were estimated based on the antimi-

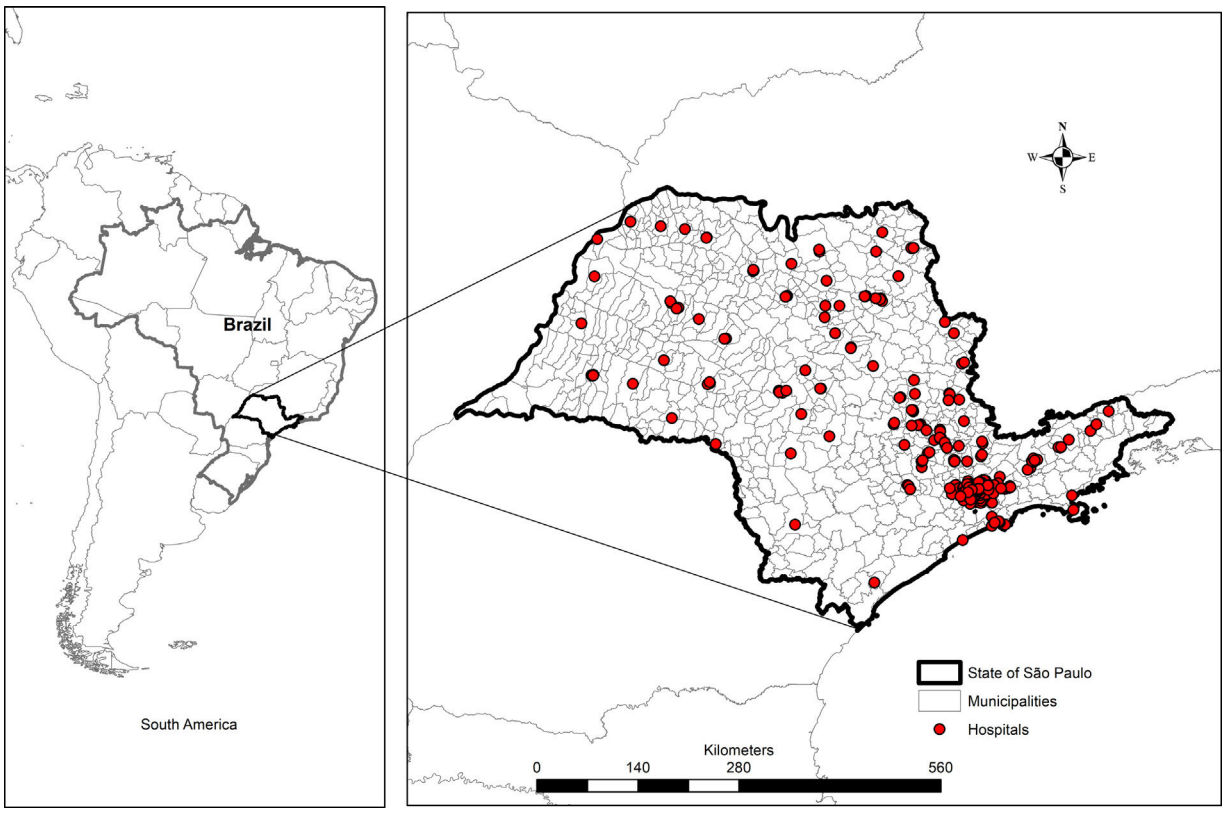

Fig. 1 – Spatial distribution of participant hospitals (n = 309). State of São Paulo, Brazil, 2008–2011. The coordinate system is Datum World Geodesic System (WGS 1984).

crobial use during the previous year as an explanatory variable.

Outcomes and independent covariates

Our primary outcome was the number of BSI caused by MDRO in ICUs reported to São Paulo SHD. The definition of BSI was a composite of the Centers for Disease Control and Prevention (Atlanta, USA) criteria for catheter-associated BSI[9] and bacteremia secondary to infection at other anatomic sites. MDRO were defined as: carbapenem-resistant *Acinetobacter* sp. and *Pseudomonas aeruginosa; Escherichia coli* and *Klebsiella pneumoniae* resistant to third generation cephalosporins; methicillin-resistant *Staphylococcus aureus* (MRSA); and vancomycin-resistant *Enterococcus* spp. (VRE).

We investigated socioeconomic status, quality of healthcare, access to healthcare system and antimicrobial use (overall antibiotic use throughout the state of Sao Paulo i.e., community plus hospital use) as independent covariates associated with BSI caused by MDRO. Initially, the following indicators were evaluated (Table 1):

a) Socioeconomic indexes: proportion of individuals older than 60 years; proportion of homes provided with sewerage; Gini index; municipal human development index; proportion of the population with earnings of half a minimum wage *per capita* or less; and demographic density.
b) Quality of healthcare was evaluated by infant mortality rate defined by the number of deaths of children under one year of age per 1000 live births.
c) Access to the healthcare system was evaluated by the number of hospital beds (public + private)/1000 inhabitants; and the number of hemodialysis equipment/1000 inhabitants.
d) Hospital type — hospitals were divided into four administrative categories: philanthropic, private, public, and catholic hospitals (a subset of hospitals usually managed by the catholic church providing public and private care); and into two size categories: up to 15 intensive care beds; and more than 15 intensive care beds.
e) Overall (community + hospital) antimicrobial use: since there were 42 covariates (single compounds) representing all antibiotic consumption in the state of São Paulo, we used Principal Component Analysis (PCA) to dimensionality reduction. This procedure converts a set of possibly correlated covariates into a set of linearly non-correlated covariates. Thus, each Principal Component (PC) represents a group of antibiotics that would explain part of the variability of our primary outcome.

Data analysis and statistics

We used hierarchical models assuming that some factors have a direct impact on the outcome and others are mediated through other factors. In this study socioeconomic indexes, access to the healthcare system and quality of healthcare

Table 1 – Hierarchical classification of independent covariates and their aggregation levels investigated as potential associated factors with bloodstream infections caused by multidrug resistant organisms in intensive care units in the state of São Paulo, Brazil, 2009–2011.

Independent covariates			
Group	Name	Hierarchical position	Aggregation level
Socioeconomic	Proportion of people >60 y	Distal	Municipality
	Proportion of ≤½ minimum national monthly wage *per capita*	Distal	
	Proportion of houses provided with adequate basic sewage	Distal	
	Demographic density	Distal	
	Gini index	Distal	
	Municipal human development index	Distal	
Quality of health care services	Infant mortality rate	Distal	
Access to the healthcare system	Public beds per 1000 inhabitants	Distal	
	Number of beds (public plus private) per 1000 inhabitants	Distal	
	Hemodialysis equipments per 1000 inhabitants	Distal	
Administrative category of hospitals	Philanthropic Public Private Catholic hospitals	Medial	Hospital
Number of ICU beds per hospitals	≤15 >15	Medial	
Overal (community plus hospital) use of antibiotics	Defined daily dose (for each antibiotic) per 1000 inhabitants per year	Proximal	Municipality and year

delivered were defined as distal covariates. Administrative category of hospitals and number of ICU beds as medial covariates and antimicrobial use during the year preceding the outcome as proximal covariate. Also, these covariates had different aggregation levels (Table 1). The distal and medial covariates were evaluated for collinearity using variance inflation factor (VIF), with a cut point <3.[10]

We built hierarchical models using the number of cases of each BSI as outcomes measured for each hospital once-a-year (2009–2011). To account for the fact that several hospitals were located in the same municipality, a municipality random effect was included; we also specified a random effect for the years. We then considered a more complex model, where in addition to the random effects described above, the spatial dependence of BSI incidence related to geographic localization of the hospitals was accounted for through a combination of unstructured and spatially structured random effect (BYM).[11]

A Poisson distribution was specified on the outcome. In all models, the logarithm of the expected number of cases, calculated by indirect standardization, was used as "offset" to express the cases in terms of relative risk (RR).[11] Given the high proportion of zeros within MDRO BSI incidence among hospitals, varying from 34% to 85% for MRSA and VRE, respectively, we also considered a zero-inflated Poisson distribution on the outcome for the models with and without the spatial component.

The models were run using INLA (Integrated Nested Laplace Approximations) in a Bayesian context.[12] We considered non-informative priors for the fixed effects and for the random effects related to the covariates "municipality" and "year. Analyses were performed using R 3.4.1 software (R Core Team, 2017) and INLA packages 0.0-1432754561 (www.r-inla.org).

Table 2 – Distribution of hospitals based on number of ICU (intensive care beds). São Paulo State nosocomial surveillance system, 2008–2011.

Number of ICU beds	Number of hospitals (%)
5	14 (5%)
6–10	147 (48%)
11–20	95 (31%)
21–30	30 (10%)
31–40	14 (5%)
41–70	6 (2%)
>100	3 (1%)

Results

Descriptive epidemiology

The number of hospitals per municipality categorized by number of beds is shown in Table 2. From 2008 to 2011 14,392 BSI caused by MDRO were reported to the São Paulo State Health Department (SHD). The incidence by species is listed in Table 3. During the study period, there was a significant increase in incidence of BSI caused by carbapenem-resistant *Acinetobacter* sp. and a decrease in incidence of BSI caused by carbapenem-resistant *P. aeruginosa* and by third generation cephalosporin-resistant *K. pneumoniae*. We observed stability in incidences of third generation cephalosporin-resistant *E. coli*, methicillin-resistant *S. aureus* (MRSA), and vancomycin-resistant *Enterococcus* sp. Surveil-

Table 3 – Pooled means (percentile 90) of incidence of laboratory confirmed bloodstream infection per 1000 patients in intensive care units from 309 hospitals stratified by multidrug-resistant organism. State Health Department, São Paulo, Brazil, 2008 to 2011.

Multidrug resistant organism (number of reported isolates)	2008 p90	2009 p90	2010 p90	2011 p90	P-value
Carbapenem-resistant *Acinetobacter* sp. (3065)	1.32	1.22	1.42	1.50	<0.0001 (+)
Carbapenem-resistant *Pseudomonas aeruginosa* (1396)	0.84	0.84	0.70	0.62	0.006 (–)
Third generation cefalosporin-resistant *Escherichia coli* (613)	0.40	0.42	0.35	0.36	0.67
Third generation cefalosporin-resistant *Klebsiella pneumoniae* (2960)	1.57	1.50	1.34	1.19	0.003 (–)
Methicillin-resistant *Staphylococcus aureus* (5708)	3.37	2.86	2.89	2.65	0.73
Vancomycin-resistant *Enterococcus* sp. (650)	0.28	0.25	0.30	0.21	0.08

p90: 90th percentile; + increasing incidence; – decreasing incidence.

lance of carbapenem-resistant *Enterobacteriaceae* was started in 2011, with increasingly high incidences (data shown) and were not analyzed in this study.

Principal components analysis (PCA)

After applying the PCA, we transformed the highly correl 42 antibiotic compounds into four linearly non-correl covariates (Groups 1–4). Using the component varimax tion, these four components presented eigenvalues gr than 1 and explained 91% of the whole data varial (Table 6). Based on these results, we used the four PC to ide four groups of antibiotics, so that, each PC represented of antibiotics that plays the role of one explanatory cova Thus, we used the correlation between consumption of antibiotic and the four PC (Table 4). Each group consisted of antibiotics that presented significant correlation coefficients with the correspondent components (shaded cells in Table 4). Groups 2–4 consisted predominantly of cephalosporins and semi-synthetic penicillins and Group 1 agglutinated predominantly non-beta-lactam antibiotics. Most non-beta-lactam large spectrum antibiotics used in hospitals are represented in group 1. All the groups were associated with BSI caused by MRSA, VRE, carbapenem-resistant *Acinetobacter* sp. and *P. aeruginosa* in different directions. The higher the use of antimicrobials of group 1, the higher was the incidence of BSI caused by MRSA and *Acinetobacter* spp., while the higher the use of group 2 and 4, the higher was the incidence of BSI caused by VRE. On the other hand, group 2 was inversely correlated with incidence of MRSA and *Acinetobacter* spp. and group 3 was inversely correlated with *P. aeruginosa*, MRSA and VRE. No association was observed between antimicrobial use and cephalosporin-resistant *K. pneumoniae* and *E. coli* incidences.

Hierarchical models

First, we conducted the variance inflation factor analysis of the distal and medial covariates (Table 1) and two socioeconomic covariates were not considered in the modelling because of collinearity: demographic density and number of beds (public + private) per 1000 inhabitants.

We present the posterior mean fixed effects and 95% credible intervals (CI) for the models with the spatial component and Poisson distribution inflated with zeros for BSI caused by MDRO in ICU (Table 5). The 11 most used antimicrobials were ranked by their sales (Fig. 2).

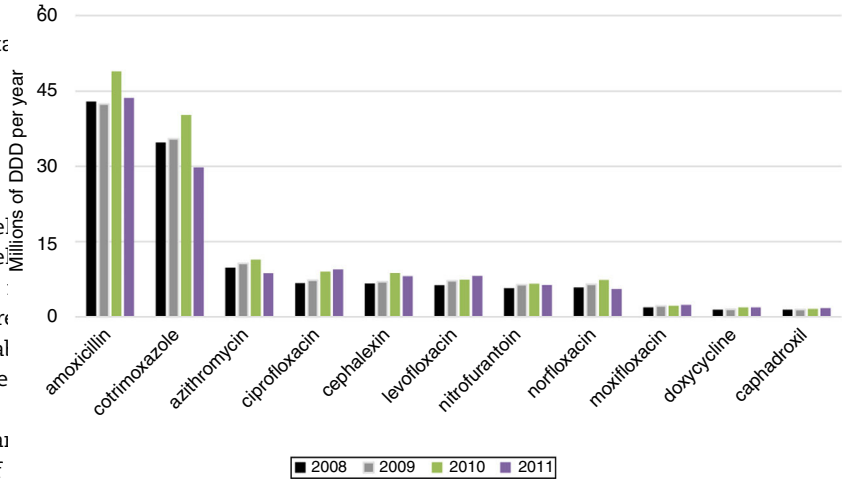

Fig. 2 – Distribution of the eleven most sold antimicrobials in the state of São Paulo, Brazil, between 2008 and 2011 expressed in millions of DDD (defined daily dose).

Discussion

Despite efforts of medical societies and governments, excessive prescription of antimicrobials is still frequent and contributes to expose patients to unnecessary adverse effects, increasing costs and the burden of bacterial resistance.[1,13] This study aimed to explore the association between the burden of total antimicrobial use, mixing community and hospital use, and its impact on bacterial resistance at the hospital level adjusted for socioeconomic indices, access and quality of the healthcare system. Although we found an association between antimicrobial use and resistance, it was not consistent for all combinations of antimicrobial groups and pathogens.

As individual antimicrobial compounds were highly correlated, we used a statistical procedure to cluster them in four groups. This strategy aimed to reduce the mass of data on the use of antibiotics, with a minimum possible loss of information. We examined antibiotic use during the previous year in relation to our primary outcome i.e. incidence of bacteremia caused by MDRO in the intensive care unit. Whether or not

Table 4 – Correlation coefficients between 42 antibiotics sold during 2008–2010 within the state of São Paulo, Brazil and the four principal components named as antimicrobial groups 1–4.

		Group 2	Group 3	Group 4	h2	u2
Nalidixic acid	0.3	0.75	0.14	−0.01	0.67	0.3265
Amikacin	−0.03	0.43	0.83	0.03	0.88	0.1229
Amoxicillin	−0.02	0.95	0.24	0.06	0.96	0.039
Ampicillin	0.06	0.55	0.78	0.09	0.92	0.0838
Azithromycin	−0.01	0.93	0.3	−0.03	0.95	0.0487
Aztreonam	−0.03	0.08	0.24	0.65	0.49	0.5108
Cefaclor	−0.05	0.93	0.16	−0.01	0.89	0.1095
Cefadroxil	−0.03	0.92	0.05	0.06	0.85	0.1504
Cefalexin	−0.02	0.94	0.17	0	0.92	0.0782
Cefalotin	−0.04	0.5	0.68	0.17	0.74	0.2563
Cefepime	−0.02	0.36	0.87	0.12	0.9	0.104
Cefotaxime	0	0.25	0.05	0.66	0.5	0.5014
Cefoxitin	0	0.61	0.01	0.5	0.62	0.3783
Ceftazidime	0	0.09	0.95	0.05	0.92	0.0795
Ceftriaxone	−0.04	0.72	0.55	0.26	0.89	0.112
Cefuroxime	−0.03	0.83	0.08	0.42	0.88	0.1175
Ciprofloxacin	−0.02	0.95	0.24	0.07	0.97	0.0271
Clindamycin	−0.02	0.7	0.68	0.08	0.95	0.0455
Chlortetracycline	−0.02	0.97	0	0.11	0.94	0.0554
Co-trimoxazole	0.01	0.85	0.43	0.08	0.91	0.0895
Doxycycline	1	0.02	0.01	−0.01	1	0.0043
Erythromycin	0.93	0.05	0.02	−0.03	0.86	0.1365
Ertapenem	1	−0.02	−0.01	0.01	1	0.0044
Gatifloxacin	0.94	−0.03	−0.02	0	0.88	0.1192
Gentamicin	0.99	0.02	0	−0.01	0.99	0.0108
Imipenem	1	0	−0.01	0	1	0.0041
Levofloxacin	1	0.02	0	−0.02	1	0.0017
Linezolid	1	−0.01	−0.02	0	1	0.0029
Meropenem	1	−0.01	−0.02	0	1	0.0037
Minocycline	1	0.01	−0.01	0	1	0.0042
Moxifloxacin	1	0	−0.01	0	0.99	0.0052
Nitrofurantoin	1	0.01	0	−0.01	1	0.0024
Norfloxacin	1	0.02	0.01	−0.02	1	0.0028
Ofloxacin	0.99	0	−0.01	0	0.98	0.0171
Penicillin	1	0.01	0.01	−0.01	1	0.0043
Piperacillin	1	−0.02	−0.01	0	1	0.0029
Polymyxin	0.97	0.03	0	−0.01	0.95	0.0497
Roxithromycin	1	0	0	0	0.99	0.0059
Tiamphenicol	0.97	0.03	0	−0.02	0.94	0.0643
Ticarcillin	0.95	−0.05	−0.01	0.02	0.91	0.0888
Tigecycline	0.99	−0.01	−0.02	0	0.99	0.0096
Vancomycin	1	0	−0.01	0	0.99	0.0058

Groups 1–4 — principal component, h2 — proportion of variability explained by the individual antimicrobial; u2 — proportion of the variability not explained by the individual antimicrobial. Shaded cells represent significant correlation (>0.3) and thus, these compounds together (in each column) constitute a group that would explain part of the variability of the incidence of bloodstream infections caused by multidrug-resistant organisms in intensive care units.

a one-year gap is enough to demonstrate such association remains a matter of debate.[1]

Antimicrobials of group 1 were associated with MRSA and carbapenem-resistant *Acinetobacter* spp. interestingly, most group 1 antibiotics had broad spectrum and are predominantly for hospital use only. Broad spectrum hospital use of antimicrobials and incidence of MDRO infection and/or colonization is an association demonstrated in other ecologic studies.[14,15] For all other groups, the associations were inversely proportional. Moreover, no association was observed for third generation cephalosporin-resistant *E. coli* and *Klebsiella* spp. This lack of consistent association between overall use of antibiotics and bacterial resistance in ICUs, led us to hypothesize that community and hospital environments function as two different compartments for selective pressure. Concurring to this idea, selective pressure exerted at community level seems to affect bacterial resistance at this level as already demonstrated in other ecologic studies.[16] On the other hand, selective pressure exerted within hospitals would lead to a greater resistance burden in this scenario[14] with interhospital spread of resistant strains as demonstrated by David et al.[17] Based on our findings, community use of antimicrobials does not seem to have a direct effect on bacterial resistance in critical patients in ICUs, even when adjusted by socioeconomic indices and access and quality of healthcare.

Table 5 – Regression analysis for covariates predicting bloodstream infection caused by multi-drug resistant organisms in 309 intensive care units of São Paulo State, Brazil, 2008-2011.

	Klebsiella pneumoniae (95% CI)	*Pseudomonas aeruginosa* (95% CI)	MRSA	*VRE*	*Acinetobacter* spp. (95% CI)	*E. coli*
	RR (LL;UL)	RR (LL;UL)	RR (LL;UL)	RR (LL;UL)	RR (LL;UL)	RR (LL;UL)
(Intercept)	1.03 (0.91–1.16)	0.90 (0.57–1.32)	1.10 (0.87–1.37)	0.67 (0.36–1.13)	0.62 (0.45–0.83)	1.04 (0.53–1.74)
Antibiotics (Principal components)						
Group 1	1.05 (0.98–1.13)	1.07 (0.93–1.22)	1.12 (1.04–1.20)	1.09 (0.91–1.27)	1.19 (1.10–1.29)	1.10 (0.90–1.31)
Group 2	0.94 (0.86–1.02)	0.93 (0.76–1.11)	0.87 (0.78–0.96)	1.72 (1.13–2.39)	0.79 (0.62–0.97)	0.88 (0.64–1.14)
Group 3	0.96 (0.87–1.05)	0.69 (0.45–0.98)	0.85 (0.72–0.97)	0.48 (0.21–0.84)	0.93 (0.75–1.11)	0.71 (0.40–1.10)
Group 4	0.98 (0.90–1.07)	1.13 (0.93–1.34)	0.98 (0.88–1.08)	2.22 (1.62–2.98)	1.01 (0.83–1.19)	1.23 (0.93–1.58)
Socioeconomic indexes						
Population older than 60y	0.90 (0.81–0.99)	0.91 (0.70–1.14)	0.89 (0.77–1.03)	0.52 (0.36–0.72)	0.76 (0.65–0.89)	0.80 (0.55–1.11)
Proportion of adequate sewerage	1.08 (0.99–1.18)	1.02 (0.85–1.21)	1.14 (1.02–1.27)	1.19 (0.91–1.53)	0.98 (0.87–1.09)	1.27 (0.97–1.66)
Gini index	0.94 (0.85–1.03)	0.89 (0.71–1.09)	0.86 (0.75–0.98)	0.73 (0.58–0.90)	1.00 (0.89–1.12)	0.90 (0.67–1.22)
Human development index	1.07 (0.96–1.18)	1.48 (1.13–1.94)	1.08 (0.92–1.25)	2.27 (1.54–3.28)	1.48 (1.25–1.74)	1.58 (1.09–2.28)
Access and quality of the healthcare system						
Infant mortality rate	0.97 (0.89–1.06)	1.30 (1.06–1.59)	1.09 (0.97–1.21)	1.20 (0.89–1.58)	0.93 (0.82–1.05)	1.04 (0.79–1.37)
Public hospital beds/1000 inhabitants	1.01 (0.93–1.11)	1.09 (0.81–1.38)	0.92 (0.81–1.05)	1.14 (0.83–1.53)	0.94 (0.80–1.10)	1.21 (0.91–1.57)
Hemodialysis equipment/1000 inhabitants	1.09 (1.00–1.20)	0.78 (0.59–0.98)	1.06 (0.93–1.21)	1.15 (0.80–1.60)	1.16 (0.98–1.35)	1.05 (0.78–1.39)
Administrative categories of hospitals						
Private hospitals	0.95 (0.80–1.10)	0.90 (0.58–1.33)	0.80 (0.62–1.01)	1.09 (0.60–1.86)	1.18 (0.86–1.58)	0.89 (0.47–1.54)
Public hospitals	1.37 (1.15–1.61)	1.68 (1.08–2.51)	1.22 (0.94–1.55)	2.08 (1.16–3.52)	2.50 (1.80–3.37)	1.75 (0.90–3.08)
Catholic hospitals	0.82 (0.65–1.02)	0.39 (0.19–0.69)	0.93 (0.68–1.26)	0.34 (0.08–0.89)	0.42 (0.25–0.65)	0.97 (0.43–1.89)
Complexity of hospitals						
Hospital with more than 15 ICU beds	1.01 (0.86–1.17)	1.03 (0.77–1.34)	0.88 (0.74–1.04)	1.17 (0.84–1.59)	1.13 (0.93–1.37)	0.93 (0.63–1.34)

RR — relative risk, LL — lower limit, UL — upper limit, Groups 1–4 — principal (regression) component, ICU — intensive care unit. Shaded variables are statistically significant.

Table 6 – Principal component (PC) analysis considering all antibiotics sold in the state of São Paulo between 2008 and 2010. Data obtained from IMS Health Brazil.

Prinicipal components	PC1	PC2	PC3	PC4
SS loadings	21.54	10.51	4.72	1.45
Proportion of explanied variance	0.51	0.25	0.11	0.03
Cumulative proportion of explained variance	0.51	0.76	0.88	0.91

SS — sum of squares.

Socioeconomic covariates were used for adjustment in this study. The hierarchical model chosen to explain the relationship of the multiple explanatory factors and the outcome requires a conceptual framework for epidemiological analysis that assumes that distal factors can affect the outcome directly or indirectly mediated by other factors (medial and/or proximal).[18] In this logic, the initial model tests distal factors only. A second model tests the medial factor (properly) adjusted for the distal factor. A third model tests the proximal factor (properly) adjusted for the distal and medial factors. In our study, socioeconomic factors were classified as distal factors because, at least in theory, health indexes (medial factors) are not real confounders, rather they are partly determined by them. The same was assumed for the use of antimicrobials in relation to the distal and medial factors.

Interestingly, our findings demonstrated consistently higher incidences of most MDROs among public hospitals and lower incidences among catholic hospitals for all studied pathogens. For public hospitals, we hypothesize cross transmission having an incremental impact on the burden of resistance. Most of public hospitals have overcrowded emergency departments in which identifying patients harboring MDRO and controlling cross-transmission is a huge challenge.[19] The lower incidence of MDRO infections among catholic hospitals are more difficult to explain. Although these hospitals merge care delivery to both private and public sectors, in the state of São Paulo these hospitals are located mostly in small towns. Among the 57 catholic hospitals in the state of São Paulo, 27 (47%) are the only hospital in the city in which they are located (data from Sao Paulo Health Care Department). Most of them are overcrowded as well have financial constraints as recently exposed by the lay media in Brazil.[20] In this way, we would expect to see similar incidences of BSI caused by MDRO in catholic and public hospitals. One possible explanation for their low incidence of MDRO might be poor laboratory diagnostic performance among catholic hospitals due to shortage of financial resources. Costa et al.[21] found an association between laboratories serving hospitals located outside state capitals in Brazil and low laboratory quality. Further investigation is needed to clarify this finding.

Fifty-three percent of ICUs had 10 or less beds. We believe that this distribution reflects the organization of the Brazilian healthcare system. Tertiary health care is concentrated in large and medium-sized cities. Thus, most municipalities have few ICU beds available. Moreover, 146 out of 645 municipalities host all ICUs in the State of São Paulo. In addition, this indicates inequality in access, especially to tertiary care, of the Brazilian population. Although the State of São Paulo State is the wealthiest and the number of ICU beds per inhabitant is above the national rate, there is a huge difference in access for patients from the private and public sectors, namel 29 versus 14.9/100.000 inhabitants.[22] The relationship between the number of ICU beds and the incidence of infections caused by multi-drug resistant organisms is not established in the literature. Even though, Correa et al. found that multi-drug resistance can be a problem even in small hospitals.[23]

Human development index (HDI) is the socioeconomic indicator most positively correlated (i.e. as HDI increases, the incidence of BSI caused by some MDRO also increases, e.g. CR *Acinetobacter* sp. and *P. aeruginosa*, 3rd generation cephalosporin-resistant *E. coli* and vancomycin-resistant *Enterococcus* sp.). HDI is a composite of life expectancy at birth plus average income plus educational level and taken in a wider perspective this indicator is associated to equity within a society. Thus, instead of causality it might function as a marker of risky areas for resistance occurrence. Interestingly, MRSA was not associated with higher HDI. This finding is in line with the report by Auguet et al.[2] that analyzed a potential association between MRSA carriage and markers of social and material deprivation. The indicators of quality and access of healthcare as well as markers of complexity were not correlated to MDRO incidences. It is important to highlight that socioeconomic covariates were used for adjustment in this study and their contribution as independent factors require testing in further studies.

This study has limitations. First, there is always a possibility of ecologic fallacy in such a design. Thus, we cannot assume that associations raised in aggregated data analyses necessarily occur at the individual level. Concerning the impact of antibiotic use on bacterial resistance, it is difficult to establish an ideal timeframe to explore the gap between antibiotic exposure and laboratory identified resistance. A one-year time lag between use and incidence of BSI caused by MDRO was analyzed. Although other studies were based on 1–2-year time lag, the best approach is not clear.[16]

Moreover, we assumed that sales in the region were equal to antibiotic use. Patients' compliance with prescriptions, especially among outpatients, was not evaluated and is indeed hard to achieve since a good surrogate for antibiotic use in large population is lacking. Patient transfers between different hospitals are not formally established on a reference and counter-reference basis in the region. Thus, adjustment for the area-level hospital attendance in order to model potential transmission among facilities was not possible. Furthermore, we have not addressed the antimicrobial stewardship initiatives and policies for preventing HAIs and the spread of MDRO within the studied hospitals. These issues may have had some impact on the outcome, but we could not include these data to adjust for overall antimicrobial use.

Finally, as we did not characterize genotypically the isolates assumptions about transmission between facilities or about a pathway from community to healthcare system were not possible.

Conclusion

We examined a potential association between overall antibiotic use in the state of São Paulo and bacterial resistance within the intensive care setting after adjustment for socioeconomic covariates. The observed association was poor and not consistent for all combinations of antimicrobial groups and pathogens. No association was observed for third generation cephalosporin-resistant *K. pneumoniae* and *E. coli*.

Selective pressure exerted at the community level seemed not to affect the incidences of MDRO infection observed in intensive care setting.

Conflicts of interest

The author declares no conflicts of interest.

CRediT authorship contribution statement

Ícaro Boszczowski: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation. **Francisco Chiaravalloti Neto:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Methodology, Resources, Software, Supervision, Validation. **Marta Blangiardo:** Formal analysis, Methodology. **Oswaldo Santos Baquero:** Formal analysis, Methodology. **Geraldine Madalosso:** Conceptualization, Resources. **Denise Brandão de Assis:** Conceptualization, Resources. **Thais Olitta:** Data curation, Resources. **Anna S. Levin:** Conceptualization, Formal analysis, Funding acquisition, Methodology, Project administration, Resources, Supervision, Validation.

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