Excess burden of antibiotic-resistant bloodstream infections: evidence from a multicentre retrospective cohort study in Chile, 2018–2022

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Summary

Background Antibiotic-resistant bloodstream infections (ARB BSI) cause an enormous disease and economic burden. We assessed the impact of ARB BSI caused by high- and critical-priority pathogens in hospitalised Chilean patients compared to BSI caused by susceptible bacteria.

Methods We conducted a retrospective cohort study from 2018 to 2022 in three Chilean hospitals and measured the association of ARB BSI with in-hospital mortality, length of hospitalisation (LOS), and intensive care unit (ICU) admission. We focused on BSI caused by *Acinetobacter baumannii*, Enterobacterales, *Staphylococcus aureus*, Enterococcus species, and *Pseudomonas aeruginosa*. We addressed confounding using propensity scores, inverse probability weighting, and multivariate regressions. We stratified by community- and hospital-acquired BSI and assessed total hospital and productivity costs.

Findings We studied 1218 adult patients experiencing 1349 BSI episodes, with 47.3% attributed to ARB. Predominant pathogens were *Staphylococcus aureus* (33% Methicillin-resistant 'MRSA'), Enterobacterales (50% Carbapenem-resistant 'CRE'), and *Pseudomonas aeruginosa* (65% Carbapenem-resistant 'CRPA'). Approximately 80% of BSI were hospital-acquired. ARB was associated with extended LOS (incidence risk ratio IRR = 1.14, 95% CI = 1.05–1.24), increased ICU admissions (odds ratio OR = 1.25; 1.07–1.46), and higher mortality (OR = 1.42, 1.20–1.68) following index blood culture across all BSI episodes. In-hospital mortality risk, adjusted for time-varying and fixed confounders, was 1.35-fold higher (1.16–1.58) for ARB patients, with higher hazard ratios for hospital-acquired MRSA and CRE at 1.37 and 1.48, respectively. Using a societal perspective and a 5% discount rate, we estimated excess costs for ARB at $12,600 per patient, with an estimated annual excess burden of 2270 disability-adjusted life years (DALYs) and $9.6 (5.0–16.4) million.

Interpretation It is urgent to develop and implement interventions to reduce the burden of ARB BSIs, particularly from MRSA and CRE.

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Disclaimer: This summary is available in Spanish in the Supplementary Material.

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Research in context

Evidence before this study

Antibiotic-resistant bacteria (ARB) have become a global concern, highlighting the need for robust estimates of the disease and economic burden associated with ARB infections. Such data are crucial for guiding public health decisions, prioritising research efforts, and evaluating intervention programs. However, existing evidence is scarce. We conducted a comprehensive search in PubMed, SCIELO, and WHO's Global Index Medicus from January 1, 2000, to September 14, 2023. We focused on patient-level studies examining ARB's impact on hospitalized adults with bloodstream infections (BSI). We combined terms such as ((burden) OR (mortality) OR (length of hospital stay, 'LOS') OR (intensive care unit, 'ICU') OR (economic costs)) AND (bloodstream infection)). The search yielded recent studies, including global, regional, and country-level estimates from the Global Burden of Disease collaborators. These estimates show that infections associated with ARB impose an enormous disease burden, particularly *Staphylococcus aureus, Escherichia coli, Klebsiella pneumoniae, Streptococcus pneumoniae, Pseudomonas aeruginosa, and Acinetobacter baumannii.* Previous studies have primarily focused on disease burden, are based on pre-pandemic data, lack hospital-level data, and often neglect economic burden. Studies in Argentina, Brazil, Colombia, and Mexico have noted variations in mortality rates among patients with susceptible and resistant BSI. However, these studies have relatively small sample sizes, focus on a single pathogen, do not stratify infection acquisition, and have not adjusted the sociodemographic and clinical characteristics of previous BSI diagnoses. No study, at the patient level, has simultaneously assessed the association of ARB with mortality, LOS, and ICU admission or has examined economic costs associated with ARB BSI.

Added value of this study

We conducted a comprehensive assessment of BSIs caused by critical and high-priority pathogens among adults, as designated by the WHO, including carbapenem-resistant *Acinetobacter baumannii, Pseudomonas aeruginosa* and Enterobacterales, methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant Enterococcus species. We estimated excess mortality, LOS, ICU admission, hospital costs, and productivity losses associated with ARB BSIs compared to antibiotic-susceptible BSIs. We conducted our research at the patient level in three prominent hospitals in Chile, from the north, centre, and south of the country. We stratified our sample into two categories: community-acquired and hospital-acquired BSIs. This stratification aimed to reduce the underestimation of the impact of ABR BSI as some patients may be hospitalised due to bacterial resistance, leading to biased estimates when community-acquired and hospital-acquired infections are grouped. While analysing hospital-acquired infections separately helps avoid this bias, our results for community-acquired infections may still be biased due to conditioning on hospital admission. This variable potentially lies on the causal pathway from ARB BSI to health-economic outcomes and may induce collider stratification bias. By analysing hospital-acquired infections separately, we can consider varying treatment histories and avoid comparing strains exclusively circulating in hospitals with those in community settings. We provide empirical evidence on the substantial influence of ARB BSIs, revealing higher mortality rates, LOS, ICU admission, and economic costs among these patients compared to individually weighted patients with antibiotic-susceptible bacteria BSI. The greatest health and economic burdens were attributed to *S. aureus* and Enterobacterales. Finally, we adjusted the estimates to national ARB BSI death incidence using the Global Burden of Disease data. The research additionally offers pivotal global perspectives on methodological strategies for assessing the burden of ARB. This encompasses economic evaluations from both healthcare and societal perspectives, using patient background data collated before the BSI onset to determine the subsequent health outcomes.

Implications of all the available evidence

Hospital patients with BSIs face life-threatening short and long-term consequences, with an alarming case mortality rate of 38% throughout the study. Most of these infections were hospital-acquired. Interventions to strengthen early detection of BSIs and improve infection measures within hospital settings are crucial to reduce in-hospital transmission of these pathogens. We hope these results will help set priorities in resource allocation, ultimately enhancing the quality of care provided to patients.

Introduction

Infections produced by antibiotic-resistant bacteria (ARB) represent one of the most pressing challenges to global public health and have significant clinical and economic consequences.[1–6] A recent study by Naghavi et al. estimated 1.14 million annual deaths attributable to ARB worldwide in 2021.[6] A substantial burden exists in the Americas, with an estimated annual toll of 141 thousand deaths attributed to ARB.[7] Among these, bloodstream infections (BSI) were responsible for a

substantial portion of ARB-attributed fatalities in the region, with 43 thousand deaths. Hospital infrastructure and infection control, health-system access, and sanitation and hygiene standards remain limited in this region.[8]

ARB BSIs pose a substantial burden to the healthcare system and patients. They often require complex treatment regimens, which can exhibit diminished therapeutic efficacy, resulting in accelerated disease progression.[2] Estimating the disease and subsequent economic burden among BSI patients is critical for optimising resource allocation and utilisation, aiding in setting priorities for national policies.[3] However, most studies are not based on patient-level data and do not adjust for hospital stays before the onset of BSI. Further, they rarely include more than one economic perspective and do not adequately adjust for inflation.[4,5] A recent systematic review and meta-analysis in low- and middle-income countries, including Argentina, Brazil, Colombia, and Mexico, found that ARB BSIs were associated with 1.58-fold higher crude mortality, a seven-day longer length of hospital stay (LOS), and 1.96-fold higher intensive care unit (ICU) admission rate compared to antibiotic-susceptible bacteria (ASB) BSIs.[9] This review underscored the limited availability of data on the disease and economic burden of ARB BSIs in the Americas, with insufficient multi-pathogen evidence and incomplete consideration of health outcomes, particularly LOS and ICU admissions following BSI onset. Previous articles analysed community- and hospital-acquired BSI among hospitalised patients in a single analysis. This approach may have obscured some of the effects of community-acquired ARB BSI by conditioning on hospital admission because hospital admission could be a step in the causal pathway between community-acquired ARB BSI and health and economic outcomes. Importantly, conditioning on hospital admission, a potential consequence of acquiring an ARB antibiotic-resistant infection in the community, may induce collider stratification bias, which may even cause artificial associations where none exist.[10–12]

Herein, we provide estimates of the health and economic burden of ARB BSIs using patient-level data from three major hospitals in Chile. We expect these comprehensive estimates will offer valuable insights to policymakers and health officials and assist in making informed decisions regarding infection prevention and control measures, antibiotic stewardship, and resource allocation in Chile and globally.

Methods

Study design and setting

We conducted a retrospective parallel matched cohort study of adult inpatients over 15 years of age who presented with BSIs in three major tertiary-care healthcare centres from Chile in Iquique (north), Santiago (capital, central area), and Puerto Montt (south) between January 1, 2018, and December 31, 2022. Participating hospitals had an estimated annual discharge rate of about ~20,000–30,000 patients and 400–500 hospital beds each (Supplementary Material S2 and S3). All centres corresponded to public hospitals that had large ICUs, used the same automated susceptibility (BD Phoenix™) and blood culturing systems (BD BACTEC), and followed Clinical Laboratories Standard Institute (CLSI) guidelines for susceptibility interpretation.[13] Enrolment in the study was defined as the date of collecting the index blood culture.

Our analysis focused on WHO's high- or critical-priority ARBs and their susceptible counterparts.[14] Specifically, we included carbapenem-resistant *Acinetobacter baumannii* (CRAB), carbapenem-resistant *Pseudomonas aeruginosa* (CRPA), carbapenem-resistant Enterobacterales (CRE), methicillin-resistant *Staphylococcus aureus* (MRSA), and vancomycin-resistant *Enterococcus* spp. (VRE). Blood cultures that yielded positive results more than seven days apart from the index BSI and reported a different pathogen from the initial observation were categorised as separate BSI episodes.[15] We excluded polymicrobial BSIs from the analysis to maintain consistency in results interpretation; polymicrobial BSIs accounted for <2% of the total infections.

Data sources

Information regarding previous hospitalisation, antibiotic use, and other relevant patient data was gathered from paper-based medical records, securely stored, and accessible to authorised hospital personnel. Data included two sets of variables: baseline information and time-varying attributes. Baseline variables encompassed patient demographics such as age and gender, and pre-existing underlying health conditions assessed using the Charlson Comorbidity Index (CCI). Hospitalisations, antibiotic usage, and surgical procedures were recorded within the three months before admission. Variables related to the BSI episode included the source of the BSI (e.g., primary, catheter, respiratory, gastrointestinal, as defined by the primary team.[16]), hospital- or community-acquired infections (i.e., cultures obtained <48 or >48 h after admission, respectively[16–19]), mechanical ventilation (yes/no), and antibiotic usage measured in daily defined doses (DDD per 1000 hospital bed-days) per antibiotic family adhering to WHO ATC/DDD index standards and adjusted for frequency and dosage.[20] We used antibiotic usage for descriptive statistics and costs. No treatment guidelines, including real-time alert systems for agent susceptibility profiles, were established for managing BSI at any of the included hospitals. Therefore, primary attending teams made decisions regarding the therapeutic regimen. All hospitals strictly follow the Ministry of Health's recommendations for contact precautions.

Clinical outcomes

Primary outcomes included in-hospital mortality, hospital LOS (in days), and ICU admission, all measured after the index culture. We used overall in-hospital mortality and at 30 days following the BSI diagnosis. ICU admission was included as a dichotomous variable. We measured the total hospital's LOS following the index blood culture and ICU LOS based on the admission and discharge dates.

Hospital costs

We used an ingredient approach to estimate hospital costs (Supplementary Material S4). Hospital costs considered hospital bed-day in general wards and the ICU (including the costs of contact precaution), antibiotic usage, infectious disease consultation fees, and diagnostic costs associated with each blood culture bottle in an automated system, including antimicrobial susceptibility testing. Costs per hospital bed-day, consultation with an infectious disease specialist, and diagnostics were extracted from the Fondo Nacional de Salud (FONASA), the national public health insurance program.[21] Antibiotic costs, homologated to DDDs, were extracted from the Central de Abastecimiento (CENABAST),[22] the government unit in charge of acquiring and distributing drugs and medical supplies.

Statistical and health burden analyses

We followed a structured approach based on GLASS methods for estimating the burden of ARB BSIs (Supplementary Material S4 for details).[23] First, we evaluated the incidence of ARB BSIs and their susceptible counterparts, analysing each group's main crude clinical and background characteristics. Second, we computed propensity scores using inverse probability weighting (IPW) to control for potential confounders associated with ARB before hospitalisation or BSI onset.[24] Additionally, we separately estimated IPW and propensity scores for hospital-acquired and community-acquired BSIs to identify the primary risk factors associated with ARB (Supplementary Material S7). This stratified analysis allowed us to relax the assumption that antibiotic susceptibility had no impact on the risk of hospital admission and that treatment history was uniform across community-acquired BSIs and strains that are more prevalent among hospital-acquired BSIs. Third, we performed weighted multivariable regression analyses using the whole hospital population and stratified by community-acquired and hospital-acquired BSIs. We evaluated 30-day and overall in-hospital mortality, ICU admission, and LOS after the index blood culture using logistic and negative binomial models, depending upon the distribution of the variable. We computed both aggregate ARB and pathogen-specific models. Fourth, we used an extended Cox regression for competing events among the entire hospital population with BSI and community- and hospital-acquired BSIs to analyse the association of ARB BSIs and mortality.[25] Using cause-specific hazard models, we generated pathogen-specific cumulative incidence graphs, considering discharge alive and in-hospital mortality as endpoints.[26,27] We added year and pathogen fixed-effects and time-varying covariates (surgery and ICU admissions after culture index). We analysed BSI episodes as independent events and applied clustered standard errors at the individual level. We used predictive mean matching for missing data (15% missingness tolerance) to preserve raw data distributions.

All statistical analyses were performed in stata SE 17 and R version 4.3.1

Economic burden and cost analyses

First, we calculated pathogen-specific excess direct and indirect costs attributed to ARB BSIs from both healthcare system and societal perspectives.[28] Hospital-day costs included all inpatient admissions (i.e., ICU and non-ICU ward costs, adjusted to their respective LOS), antibiotics received, consultation, and microbiological test costs. Using the human capital approach, we also calculated indirect costs, including the excess mortality associated with premature mortality resulting from ARB BSIs, compared to ASB BSIs. All costs were expressed in 2022 USDs, adjusting for inflation using US GDP implicit price deflators and a 0%-time discount (we present results with a 5% discount rate presented in Supplementary Material S10). Second, we estimated disease burden based on disability-adjusted life years (DALYs). Last, we estimated the annual excess burden attributable to ARB BSI deaths in Chile, extrapolating our results to the national level using Monte Carlo simulations (n = 1000 repetitions from a random negative binomial distribution) and using mortality incidence attributed to ARB BSIs obtained from the most recent Global Burden of Disease (GBD) study estimates for the Americas.[7] We present upper and lower-bound uncertainty estimates following mortality incidences CIs. For details, refer to Supplementary Material S5 and S6.

Ethical consideration

The study has been approved by the Pontificia Universidad Católica de Chile Human Research Ethics Committee (Protocol ID: 200706001). The study was considered exempt from informed consent; no human health risks were identified. All patient data were anonymised.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Description of BSI events and incidence

We identified 1218 patients experiencing a BSI, resulting in 1349 BSI episodes (47.3%, 638/1349, of which fulfilled

our definition of an ARB) from 2018 until 2022 in the three hospitals (23.3%, 315/1349; 32.7%, 441/1349; and 44.0%, 593/1391 in each hospital). Supplementary Table S4 shows sample details by pathogen and resistance pattern. A total of 1072 BSI episodes (80%) were categorised as hospital-acquired and only 277 as community-acquired (Supplementary Table S4). Fig. 1 shows the overall incidence of BSI over time, revealing a significant peak in 2021. Gram-negative bacteria (Fig. 1B) reported the highest ARB rate among cultures, with 92% for CRAB/(CRAB + CSAB) = 56/61; 65%, CRPA/(CRPA + CSPA) = 154/238; and 50%, CRE/(CSE + CRE) = 233/468, respectively). *S. aureus* comprised most isolates among Gram-positive species (404/582, MRSA rate 33%).

Patient characteristics

Most patients were men (women = 41.6% and 35.3% among ASB and ARB, p = 0.017, Table 1), aged 62 (33–85) and 59 (31, 84) years among ASB and ARB groups (Mann–Whitney U-test p < 0.001, Table 1 and Supplementary Figure S5).

Table 1 reveals that ARB BSI patients showed higher mortality (37.5%, vs. 29.4%; p < 0.001), total LOS (47.3 (8–125), vs. 34.2 (5–95)) and full ICU admission (62.7% vs. 51.9%) than ASB patients, including LOS and ICU outcomes before BSI diagnostic (Mann–Whitney U-test or χ^2 were <0.001 for both outcomes, respectively). Overall, in-hospital mortality rates were consistently higher across all ARB pathogens (Fig. 2) when compared to ASB BSIs, regardless of BSI acquisition (Supplementary Tables S4, S5). After the BSI diagnostic, more patients were admitted to ICU wards for CRE, CRPA, and MRSA (χ^2 < 0.001, vs. their susceptible counterparts). LOS was higher for CRE and CRPA than their susceptible counterparts (Fig. 2).

In the context of hospital- and community-acquired infections, we found a lower CCI score among hospital-acquired ARB BSIs, compared to ASB (CCI_{mean} = 2.7 and 3.3, respectively, Mann–Whitney U-test p < 0.001). However, we found the opposite trend among community-acquired BSIs (Supplementary Tables S4 and S5). Also, patients with hospital-acquired ARB BSIs had a higher rate of catheter usage before the index culture (61.3 among

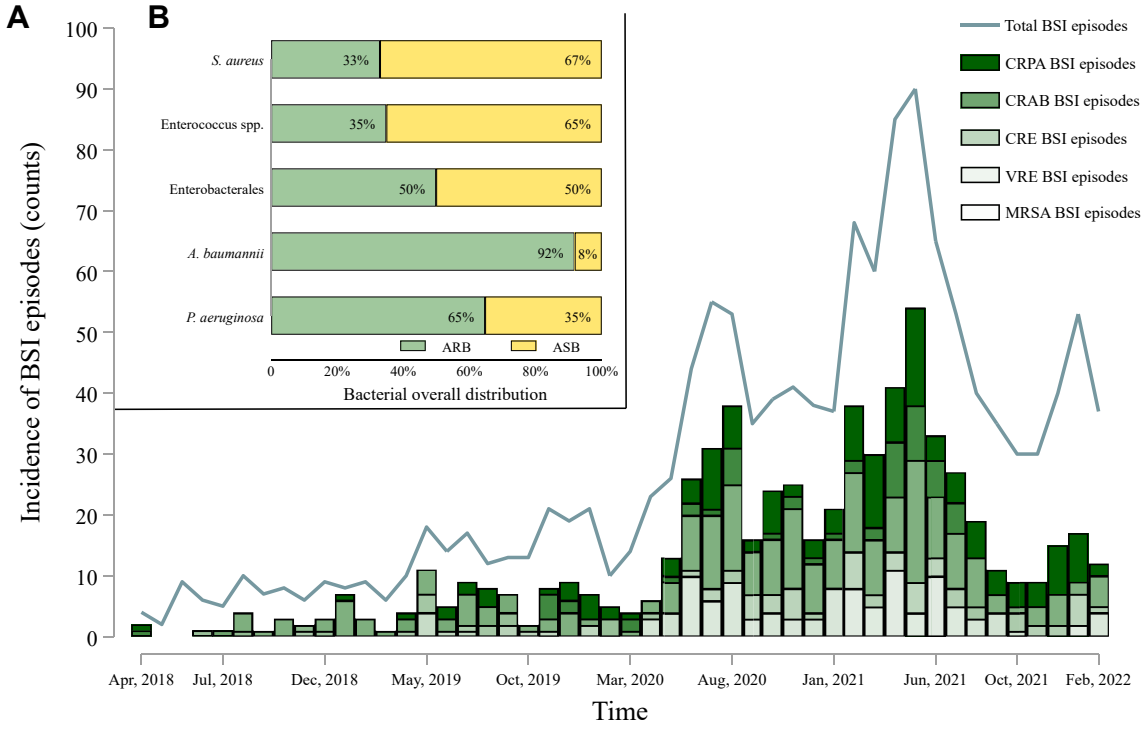

Fig. 1: **Incidence of ARB and ASB BSI episodes and resistance levels over time by pathogen. (A)** Incidence of BSIs and ARB BSIs observed in sampled hospitals (in counts) over time and by pathogen. **(B)** Total proportion of ARB bacteria over time, by pathogen. ARB, Antibiotic-resistant bacteria; ASB, Antibiotic-susceptible bacteria; CRE, Carbapenem/cephalosporin resistant Enterobacterales; MRSA, Methicillin-resistant *Staphylococcus aureus*; CRPA, Carbapenem-resistant *Pseudomonas aeruginosa*; CRAB, Carbapenem-resistant *Acinetobacter baumannii*; VRE, Vancomycin-resistant Enterococcus spp. Total isolates; CRPA = 154, CSPA = 84; CRAB = 56, CSAB = 5, CRE = 233, CSE = 235, VRE = 62, VSE = 116, MRSA = 133, MSSA = 271.

Variables	ASB (N = 711)			ARB (N = 638)			χ^2 or M-WU[a] test
	Median (%)	95% CI	IQR	Median (%)	95% CI	IQR	p
Outcome variables							
Overall mortality (%)	29.40	26–33	–	37.46	34–41	–	0.002
Mortality up until 30-days after BC (%)	25.67	22–29	–	33.02	29–37	–	0.003
Full hospital LOS (days)	34.23	5–95	26	47.34	8–125	38	<0.0001
LOS before BC (days)	11.55	0–36	12	21.28	0–61	21	<0.0001
LOS after BC (days)	23.06	1–71	19	27.75	1–91	26	0.011
Full ICU admission (%)	51.90	48–56	–	62.70	59–66	–	0.0007
ICU admission (%) before BC	6.33	5–8	–	1.88	1–3	–	<0.0001
ICU admission (%) after BC	41.49	38–45	–	55.96	52–60	–	0.0006
Full ICU LOS (days)	10.27	0–42	15	18.87	0–63	30	0.0009
ICU LOS after BC (days)	9.46	0–42	14	18.50	0–63	30	0.0008
Independent variables							
Age (years)	61.53	33–85	21	58.78	31–84	19	0.001
Female (%)	41.63	38–45	–	35.27	32–39	–	0.017
Hospitalisation in last three months (%)	23.98	21–27	–	20.31	17–24	–	0.12
Antibiotic consumption in last three months (%)	12.97	10–16	–	15.05	12–18	–	0.303
CCI (mean)	3.41	0–8	4	2.85	0–8	3	0.0009
Null, CCI = 0 (%)	13.50	11–16	–	19.44	16–23	–	0.003
Mild, CCI = 1 or 2 (%)	28.69	25–32	–	34.33	31–38	–	0.026
Moderate, CCI = 3 or 4 (%)	27.43	24–31	–	22.73	20–26	–	0.047
Severe, CCI ≥5 (%)	30.38	27–34	–	23.51	20–27	–	0.005
Source of the BSI							
Primary (%)	31.67	28–36	–	38.38	34–43	–	0.021
Catheter (%)	16.12	13–20	–	14.23	11–17	–	0.39
Pneumonia/respiratory (%)	23.80	20–28	–	20.00	17–24	–	0.13
Gastrointestinal (%)	9.02	7–12	–	8.65	6–11	–	0.83
Abdomen (%)	13.24	10–16	–	12.97	10–16	–	0.90
Bones and joints (%)	2.88	2–5	–	1.98	1–4	–	0.34
Skin and soft tissue (%)	2.69	1–4	–	3.24	2–5	–	0.59
Meningitis (%)	0.58	0–2	–	0.54	0–2	–	0.94
Community-acquired infection (%)	27.75	24–31	–	12.32	10–15	–	<0.0001
Indwelling catheter (%)	36.43	33–40	–	56.27	52–60	–	<0.0001
Kidney therapy before BC (%)	10.15	8–13	–	4.92	3–7	–	0.001
Transfer from another hospital (%)	19.21	16–22	–	14.06	11–17	–	0.012
ID specialist consultation (%)	26.90	23–31	–	69.09	65–73	–	<0.0001
Mechanical ventilation before BC (%)	4.64	3–6	–	5.33	4–7	–	0.56
Mechanical ventilation after BC (%)	28.83	26–32	–	53.92	50–58	–	<0.0001
Surgery previous BC (%)	0.70	0–2	–	0.63	0–2	–	0.86
Surgery after BC (%)	6.47	5–9	–	15.05	12–18	–	<0.0001
Antibiotic consumption in daily defined doses 'DDDs' per treatment course after BC (in 1000 hospital bed-days)							
Total consumption	196.44	0–645	273.9	260.34	0–765	253.87	0.0002
Carbapenems	1.71	0–10	1.54	3.47	0–11	4.96	0.001
Cephalosporins	7.37	0–29	8.69	6.98	0–25	9.52	0.64
Macrolides	0.32	0–0	0.00	0.80	0–5	0.00	0.006
Fluoroquinolones	0.51	0–3	0.00	0.59	0–4	0.00	0.55
Aminoglycoside	1.19	0–8	0.00	2.22	0–11	2.78	0.006
Tetracyclines	0.04	0–0	0.00	0.22	0–1	0.00	<0.0001
Penicillin	3.43	0–21	1.73	3.08	0–15	3.66	0.47
Glycopeptides	2.75	0–14	3.85	5.15	0–20	6.64	<0.0001

(Table 1 continues on next page)

ARB and 40.7% among ASB; Supplementary Table S4) compared to community-acquired BSIs (19.5% among ARB and 25.5% among ASB; Supplementary Table S5).

Overall, antibiotic consumption was greater among ARB patients than ASB (260.3 and 196.4 DDDs per 1000 hospital bed-days, respectively, Table 1). MRSA, VRE,

Variables	ASB (N = 711)			ARB (N = 638)			χ^2 or M-WU[a] test
	Median (%)	95% CI	IQR	Median (%)	95% CI	IQR	p
(Continued from previous page)							
LOT (days)	16.11	0–64	22	36.26	0–6	2	<0.0001
NOA (number)	2.60	0–9	4	5.18	0–101	39	<0.0001

Notes: ARB, Antibiotic-resistant bacteria; ASB, Antibiotic-susceptible bacteria; BSI, Bloodstream infection; LOT, length of therapy defined as number of days a patient receives any antibiotic; NOA, Number of antibiotics used for treating a patient; CCI, Charlson comorbidity index. 95% CI for proportion variables were estimated. BC, index Blood culture; ID, Infectious disease; ICU, Intensive care unit; LOS, Length of hospital stay. IQR = 75th percentile—25th percentile. [a]χ^2 or Mann–Whitney U-test were used to test differences between independent groups, according to each variable's distribution ($\alpha = 0.05$). Descriptive statistics among community and hospital-acquired infections are shown in Supplementary Material, section 3.

Table 1: **Descriptive statistics among patients presenting with bloodstream infections produced by antibiotic-susceptible bacteria (ASB) or antibiotic-resistant bacteria (ARB).**

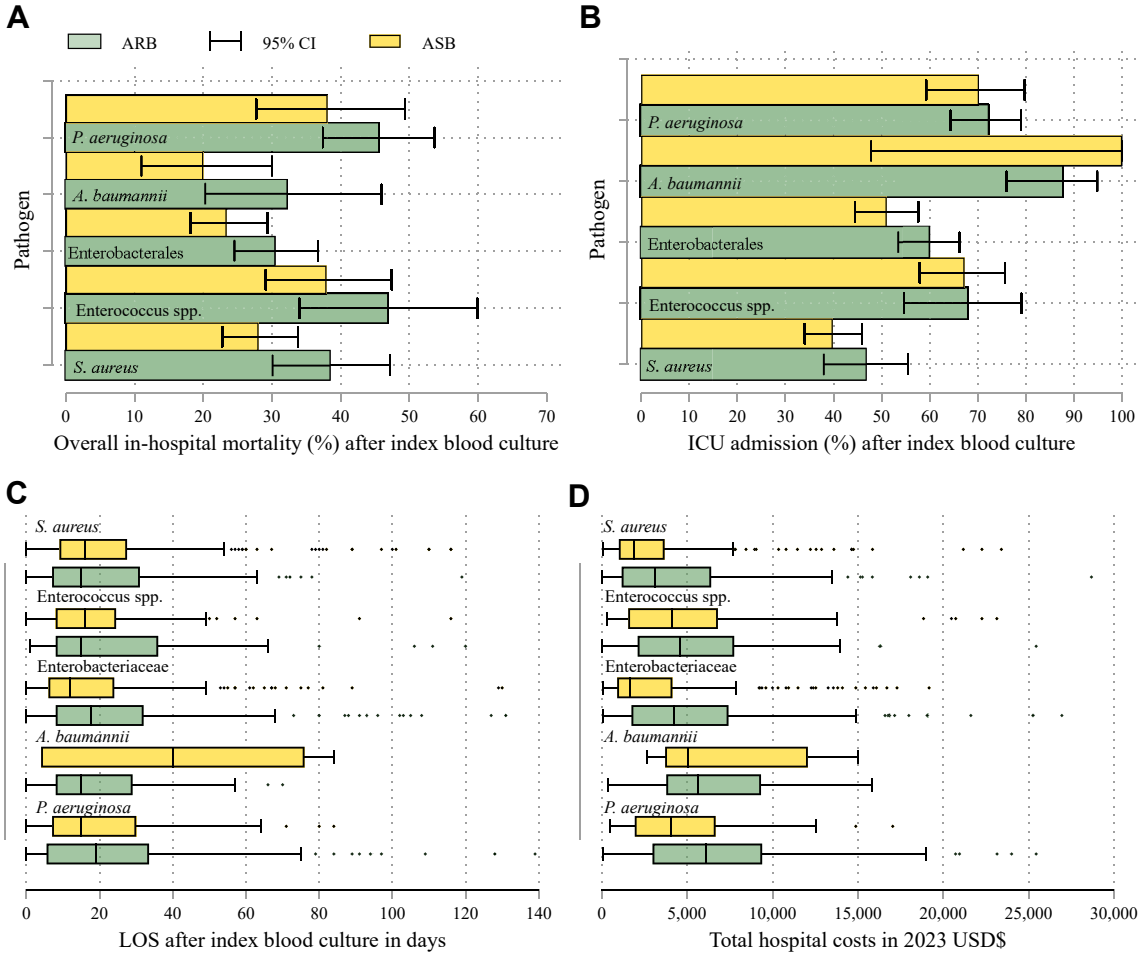

Fig. 2: **Unadjusted distribution of the main outcomes by pathogen and resistance levels. (A)** Mortality proportions by pathogen and resistance level among sampled patients. **(B)** ICU admission proportions by pathogen and resistance level among sampled patients. **(C)** Length of hospital stay by pathogen and resistance level among sampled patients. **(D)** Total hospital economic costs by pathogen and resistance levels. LOS, Length of hospital stay; ICU, Intensive care unit; ARB, Antibiotic-resistant bacteria; ASB, Antibiotic-susceptible bacteria. Pathogen-specific antibiotic resistance and susceptibility included carbapenem/cephalosporin resistant Enterobacterales, methicillin-susceptible or resistant *Staphylococcus aureus*, carbapenem-susceptible or resistant *Pseudomonas aeruginosa*, carbapenem-susceptible or resistant *Acinetobacter baumannii*, and vancomycin-susceptible or resistant Enterococcus spp. Whiskers/error bars present 95% confidence intervals (CI). For proportions, we estimated 95% CIs using Wald's margin of error.

CRE, CRAB, and CRPA patients consumed approximately 1.8, 1.1, 1.2, 3.8, and 1.2 times more antibiotics (especially glycopeptides and carbapenems), respectively, compared to their corresponding susceptible groups (Supplementary Figure S5). Supplementary Tables S4 and S5 show that community-acquired BSIs exhibited greater antibiotic consumption (358.2 vs. 248.8 DDDs per 1000 hospital bed-days) for ARB, compared to hospital-acquired BSIs.

Association between burden variables and ARB BSIs

The IPW-adjusted association of ARB on 30-day in-hospital mortality and overall hospital mortality was OR = 1.42 (1.20–1.69, p < 0.001) among all bacteria, with similar estimates for Gram-positives and Gram-negatives (Table 2). The IPW-adjusted association of hospital-acquired ARB BSIs and mortality was OR = 1.38 (1.14–1.65, p = 0.001), with the most substantial effect among patients harbouring Gram-negative ARB (OR = 1.49, 1.15–1.92, p = 0.002).

ARB BSIs were associated with increased overall ICU admissions (OR = 1.25, 1.07–1.46, p = 0.005) among all patients but greater among those with Gram-negative ARB (OR = 1.41, 1.14–1.75, p < 0.001). The overall association of ARB and LOS after BSI diagnostic showed an incidence rate ratio (IRR) of 1.14 (1.05–1.24, p = 0.001) across all bacteria. It had a greater impact among Gram-positive (IRR = 1.22, 1.09–1.36, p = 0.015). The association of ARB BSIs and LOS suggests a 1.25-fold prolonged stay among patients with community-acquired BSIs (Supplementary Table S20.1).

Pathogen-specific analyses (Supplementary Table S23) revealed MRSA and CRE-associated overall mortality were among the highest (OR = 1.59, 1.2–2.2, p = 0.003;

Outcome	Model[a]	All hospital patients			Hospital-acquired BSIs			Community-acquired BSIs		
		OR/IRR	95% CI	p	OR/IRR	95% CI	p	OR/IRR	95% CI	p
All bacteria[b] (N = 1349 all hospital patients, N = 1072 among hospital-acquired BSIs, N = 277 among community-acquired BSIs)										
30-day mortality after index blood culture	(A) ARB only	1.42	1.20–1.69	0.0001	1.37	1.13–1.66	0.001	1.40	0.87–2.24	0.17
	(B) A + $FE_{H,Y,P}$	1.43	1.20–1.71	0.0001	1.39	1.15–1.69	0.001	1.57	0.95–2.60	0.08
Overall mortality after index blood culture	(A) ARB only	1.42	1.20–1.68	0.0001	1.38	1.14–1.65	0.001	1.27	0.80–2.00	0.31
	(B) A + $FE_{H,Y,P}$	1.44	1.22–1.71	0.0001	1.41	1.17–1.70	0.000	1.38	0.86–2.23	0.19
ICU admission after index blood culture	(A) ARB only	1.25	1.07–1.46	0.005	1.04	0.87–1.24	0.67		Omitted[c]	
	(B) A + $FE_{H,Y,P}$	1.05	0.89–1.25	0.56	0.88	0.73–1.07	0.19		Omitted[c]	
LOS after index blood culture	(A) ARB only	1.14	1.05–1.24	0.001	1.08	0.99–1.19	0.09	1.25	1.03–1.51	0.026
	(B) A + $FE_{H,Y,P}$	1.13	1.04–1.22	0.004	1.05	0.96–1.15	0.33	1.31	1.08–1.59	0.005
Gram-positive[b] (N = 582 all hospital patients, N = 443 among hospital-acquired BSIs, N = 139 among community-acquired BSIs)										
30-day mortality after index blood culture	(A) ARB only	1.45	1.12–1.88	0.005	1.29	0.98–1.71	0.07	1.76	0.87–3.55	0.12
	(B) A + $FE_{H,Y,P}$	1.41	1.07–1.85	0.015	1.31	0.98–1.77	0.07	1.19	0.53–2.67	0.67
Overall mortality after index blood culture	(A) ARB only	1.45	1.13–1.86	0.003	1.30	0.99–1.70	0.06	1.55	0.81–2.95	0.19
	(B) A + $FE_{H,Y,P}$	1.46	1.12–1.91	0.005	1.40	1.04–1.87	0.02	1.00	0.48–2.08	0.99
ICU admission after index blood culture	(A) ARB only	0.96	0.76–1.22	0.74	0.80	0.62–1.04	0.09		Omitted[c]	
	(B) A + $FE_{H,Y,P}$	0.83	0.64–1.09	0.19	0.71	0.53–0.95	0.02		Omitted[c]	
LOS after index blood culture	(A) ARB only	1.22	1.09–1.36	0.015	1.04	0.91–1.19	0.55	1.21	0.91–1.6	0.19
	(B) A + $FE_{H,Y,P}$	1.14	1.01–1.29	0.030	1.07	0.94–1.23	0.30	1.69	1.26–2.25	0.0008
Gram-negative[b] (N = 767 all hospital patients, N = 629 among hospital-acquired BSIs, N = 138 mong community-acquired BSIs)										
30-day mortality after index blood culture	(A) ARB only	1.42	1.12–1.79	0.004	1.46	1.12–1.91	0.005	1.13	0.59–2.16	0.71
	(B) A + $FE_{H,Y,P}$	1.46	1.13–1.87	0.003	1.65	1.24–2.19	0.001	1.17	0.57–2.4	0.67
Overall mortality after index blood culture	(A) ARB only	1.45	1.15–1.82	0.002	1.49	1.15–1.92	0.002	1.07	0.56–2.03	0.84
	(B) A + $FE_{H,Y,P}$	1.45	1.14–1.85	0.003	1.61	1.23–2.12	0.001	1.11	0.54–2.27	0.78
ICU admission after index blood culture	(A) ARB only	1.41	1.14–1.75	0.001	1.20	0.94–1.54	0.14		Omitted[c]	
	(B) A + $FE_{H,Y,P}$	1.46	1.15–1.86	0.002	1.32	0.99–1.75	0.049		Omitted[c]	
LOS after index blood culture	(A) ARB only	1.08	0.95–1.22	0.24	1.11	0.98–1.25	0.12	1.43	1.11–1.84	0.006
	(B) A + $FE_{H,Y,P}$	1.16	1.02–1.32	0.023	1.01	0.87–1.15	0.96	1.41	1.08–1.85	0.012

Notes: Individual-clustered standard errors were estimated, and all models incorporated a constant term. Logistic regression models were computed for mortality and ICU admission outcomes. Poisson regression models were used for LOS. BSI, Bloodstream infection; CI, Confidence interval; FE, Fixed effect; ICU, Intensive care unit; BC, blood culture; LOS, Length of hospital stay; OR, Odds ratio; IRR, Incidence risk ratio. [a]Three (A, B, C) models were performed: (A) only considered ARB, compared to ASB BSI, as an independent variable; (B) considered ARB, compared to ASB BSI, and three variables as fixed effects (hospital, year, and pathogen). [b]Gram-positive bacteria included *Staphylococcus aureus* and Enterococcus spp.; Gram-negative bacteria included *Acinetobacter baumannii*, Enterobacterales, and *Pseudomonas aeruginosa*. See Supplementary Tables S13–S20 for the full models of mortality, LOS, and ICU admission. Supplementary Table S23 summarizes the pathogen-specific analysis. [c]Models were omitted due to a lack of variability in the outcome (only two patients with community-acquired ARB BSIs were admitted to the ICU). ARB, Antibiotic-resistant bacteria.

Table 2: **Results of the adjusted multivariate models for the average treatment effects of antibiotic-resistant bacteria bloodstream infections (ARB BSI), compared to antibiotic-susceptible bacteria (ASB), among all patients, and by hospital- or community-acquired BSI.**

OR = 1.44, 1.1–1.9, p = 0.018, respectively). MRSA and CRE association with overall mortality were OR = 1.44 (1.02–2.03, p = 0.036) and OR = 1.60 (1.12–2.28, p = 0.009) among patients with hospital-acquired BSIs, with estimated effects larger in magnitude among community-acquired MRSA (OR = 2.29, 1.03–4.52, p = 0.040).

Overall, admission to the ICU after BSI diagnostic was 1.58 times higher among all CRE patients (1.2–2.1, p < 0.001), compared to CSE, with consistent estimates among hospital-acquired infections (Supplementary Tables S22.2, S22.5). Contrarily, hospital-acquired VRE BSI episodes were less likely to be admitted into the ICU (OR = 0.34, 0.2–0.6, p = 0.001) compared to VSE (Supplementary Table S22.2). Among all hospital patients, LOS after BSI diagnostic was 1.17-times longer among CRE BSI episodes (1.1–1.3, p = 0.018), compared to CSE, but CRPA presented the most extended (IRR = 1.36, 1.1–1.6, p = 0.003). The association of CRPA and LOS among hospital-acquired BSIs was larger in magnitude (IRR = 1.40, 1.1–1.7, p = 0.003). Patients with community-acquired CRE presented 1.61-fold higher LOS (1.2–2.1, p < 0.001) than CSE.

No substantial ARB associations with mortality, ICU admission, and LOS were found among the remaining pathogens. Models with added fixed effects (i.e., hospital, pathogen, and year) were mainly consistent with the main estimates. (Full model results in Supplementary Material S7 and S8).

Survival analysis using the competing risk model

Table 3 shows the association of ARB and hospital mortality using a COX survival hazard model with competing risks. After accounting for potential time-varying and baseline confounders, the overall IPW-adjusted HR for in-hospital mortality was 1.35 (1.16–1.58, p < 0.001) times higher among ARB BSI episodes, compared to ASB (Table 3, model 1C). The HR was 1.34 (1.08–1.67, p = 0.009) among Gram-negative, whereas similar among Gram-positive pathogens (HR = 1.33, 1.07–1.66, p = 0.008) (Table 3, models 2C and 3C). Fig. 3 illustrates the IPW-adjusted impacts of the pathogen-specific ARB on hospital mortality among hospital-acquired BSIs over time while accounting for hospital discharge as a competing risk. Most patients with hospital-acquired ARB BSIs died in the hospital within the first 30 days after the index blood culture, with significantly different cumulative incidence curves for the ARB and ASB groups (Fig. 3). Cumulative mortality for hospital-acquired MRSA and CRE was 1.37 (1.04–1.79, p = 0.025) and 1.48-times (1.10–2.00, p = 0.013) higher compared to MSSA and CSE, respectively (Fig. 3). Non-significant results were found among community-acquired ARB BSIs. Supplementary Tables S24.1–24.3 and Supplementary Figures S9 and S10 contain the complete results among all stratified models.

Costs and morbidity losses associated with ARB hospitalisation and premature mortality

Average direct hospital costs per patient ranged from $3166 to $7701 among all ARB and ABS BSIs (Supplementary Table S26.1). The highest average excess costs related to ARB BSIs were found among CRPA ($2564 excess), followed by CRE ($2301 excess) and MRSA ($1682 excess). Hospital bed-day costs usually represented 98% of total healthcare spending per patient. We estimated excess hospital costs associated with ARB of about $2282 per patient in our sample.

In our study cohort, the total ARB excess costs associated with premature mortality and hospitalization across pathogens from a societal perspective with a 5% discount rate was estimated at $12,595 per patient (Supplementary Table S26.2). MRSA presented the most significant excess cost per patient, $15,970, followed by CRE and CRPA ($12,233 and $11,912 per patient, respectively). ARB excess costs from a health system perspective (hospitalisation) were estimated at about $2282 per patient.

Excess morbidity and mortality costs derived from DALYs ranged between 1.6 (CRE) and 7.1 (CRAB) DALYs per patient, with an average excess DALYs associated with ARB of 2.96 per patient (Supplementary Table S26.2).

DALYs and economic burden at the national level

The annual societal economic burden attributable to ARB BSI deaths (hospital costs + productivity loss) was projected at about $53.7 million ($27.9–$91.2) with no discount and $9.6 million ($5.0–$16.4) with 5% discount, with hospitalisation costs accounting for about $1.75 million ($0.9–$3.0) (Supplementary Table S26.2). DALYs were projected at 2270 (1179–3853) among national deaths attributed to ARB BSIs.

Discussion

We evaluated the burden associated (and attributed among hospital- and community-acquired BSIs) with ARB infections compared to ASB BSI. We found a substantial health burden associated with ARB BSIs, including a higher number of deaths driven by hospital-acquired BSIs, extended hospital stays, and more admissions to the ICU. MRSA and CRE accounted for substantial health burdens, reiterating the pressing need to reduce these infections, as indicated by the UN's SDG target 3.d. We also report a substantial economic burden associated with BSIs, including hospital spending and productivity losses.

Our findings suggest that, in Chile, hospital patients with ARB BSIs face a 1.42 times higher risk of mortality, with the most substantial mortality attributable burdens produced by hospital-acquired MRSA and CRE (1.60 and 1.44, respectively). These are comparable to those made by a recent global meta-analysis that found 1.52

Pathogen	Model[a]	IPW-adjusted survival model		
		HR	95% CI	p
All hospital patients				
(A) All bacteria (N = 1349)	1.A ARB only	1.34	1.15–1.55	<0.0001
	1.B 1.A + $FE_{H,Y,P}$	1.37	1.18–1.59	0.0006
	1.C 1.B + IV	1.35	1.16–1.58	0.0005
(B) Gram-positive (N = 582)	2.A ARB only	1.35	1.10–1.67	0.004
	2.B 2.A + $FE_{H,Y,P}$	1.34	1.09–1.67	0.007
	2.C 2.B + IV	1.33	1.07–1.66	0.008
(C) Gram-negative(N = 767)	3.A ARB only	1.33	1.09–1.63	0.004
	3.B 3.A + $FE_{H,Y,P}$	1.37	1.10–1.70	0.005
	3.C 3.B + IV	1.34	1.08–1.67	0.009
Hospital-acquired BSIs				
(A) All bacteria (N = 1072)	1.A ARB only	1.30	1.11–1.52	0.001
	1.B 1.A + $FE_{H,Y,P}$	1.32	1.12–1.55	0.0002
	1.C 1.B + IV	1.34	1.14–1.58	0.0002
(B) Gram-positive (N = 443)	2.A ARB only	1.24	0.99–1.54	0.050
	2.B 2.A + $FE_{H,Y,P}$	1.30	1.03–1.63	0.024
	2.C 2.B + IV	1.29	1.03–1.63	0.030
(C) Gram-negative (N = 629)	3.A ARB only	1.38	1.11–1.71	0.004
	3.B 3.A + $FE_{H,Y,P}$	1.50	1.18–1.91	0.0009
	3.C 3.B + IV	1.49	1.17–1.92	0.0009
Community-acquired BSIs				
(A) All bacteria (N = 277)	1.A ARB only	1.21	0.81–1.81	0.35
	1.B 1.A + $FE_{H,Y,P}$	1.28	0.85–1.91	0.24
	1.C 1.B + IV	1.38	0.90–2.10	0.14
(B) Gram-positive (N = 139)	2.A ARB only	1.45	0.83–2.56	0.20
	2.B 2.A + $FE_{H,Y,P}$	1.04	0.61–1.76	0.89
	2.C 2.B + IV	1.12	0.65–1.93	0.69
(C) Gram-negative (N = 138)	3.A ARB only	1.03	0.59–1.81	0.92
	3.B 3.A + $FE_{H,Y,P}$	0.98	0.54–1.80	0.96
	3.C 3.B + IV	1.04	0.55–1.98	0.89

Notes: ARB, Antibiotic-resistant bacteria; ASB, Antibiotic-susceptible bacteria; IPW, Inverse-probability weighting; HR, Hazard ratios. [a]Three (A, B, C) models were performed: (A) only considered ARB as an independent variable, compared to ASB BSIs; (B) considered ARB vs. ASB BSIs, and three variables as fixed effects (hospital, year, and pathogen); (C) considered (B) + additional time-varying independent variables where consistent. CRE, Carbapenem resistant Enterobacterales; MRSA/MRSA, Methicillin-susceptible or resistant *Staphylococcus aureus*; CSPA/CRPA, Carbapenem-susceptible or resistant *Pseudomonas aeruginosa*; CSAB/CRAB, Carbapenem-susceptible or resistant *Acinetobacter baumannii*; VSE/VRE, Vancomycin-susceptible or resistant Enterococcus spp. Supplementary Table S21 contains the full results for all bacteria and Gram-types. BSI, Bloodstream infection; CI, Confidence interval; FE, Fixed effect; IV, independent variables. Supplementary Table S24.4 displays the cumulative number of deaths per model.

Table 3: **Adjusted survival analysis results in the presence of competing risks for antibiotic-resistant bacteria bloodstream infections (ARB BSIs), compared to antibiotic-susceptible bacteria (ASB), among all hospital patients' BSI episodes and those with hospital-acquired infections.**

(0.76–2.28) and 1.49-times (1.09–1.90) greater mortality.[9] We found that 65% of BSI episodes in our study were associated with *S. aureus* and Enterobacterales, an estimate of disease burden consistent with recent findings from GBD 2021.[6]

Our estimates for Chile are lower than those from studies in Europe[26] (OR = 1.80, 1.04–3.2) and Latin America[29] (RR = 1.94, 1.38–2.73) for MRSA BSIs. Research on CRE-infected patients has generally reported approximately twice the mortality rate compared to CSE.[30,31] Several factors may explain these differences. Previous studies often used smaller sample sizes and did not account for selection bias and residual confounding (e.g., errors in subject classification regarding infection acquisition), which could have led to an overestimation of the risk due to mishandled confounding. We stratified our sample based on BSI acquisition, whereas previous studies[9,29] have grouped hospital patients without considering potential cofounders influencing ARB acquisition and development.[10,11] Consistent with previous studies, we found substantial mortality associated with hospital-acquired ARB BSIs compared to community-acquired ARB BSIs.[32] This difference could be explained by the epidemiological characteristics of the pathogens, including limited data for community-acquired BSIs and unobservable accumulated vulnerability (i.e., exposure to complex and toxic treatments and high disease severity) among

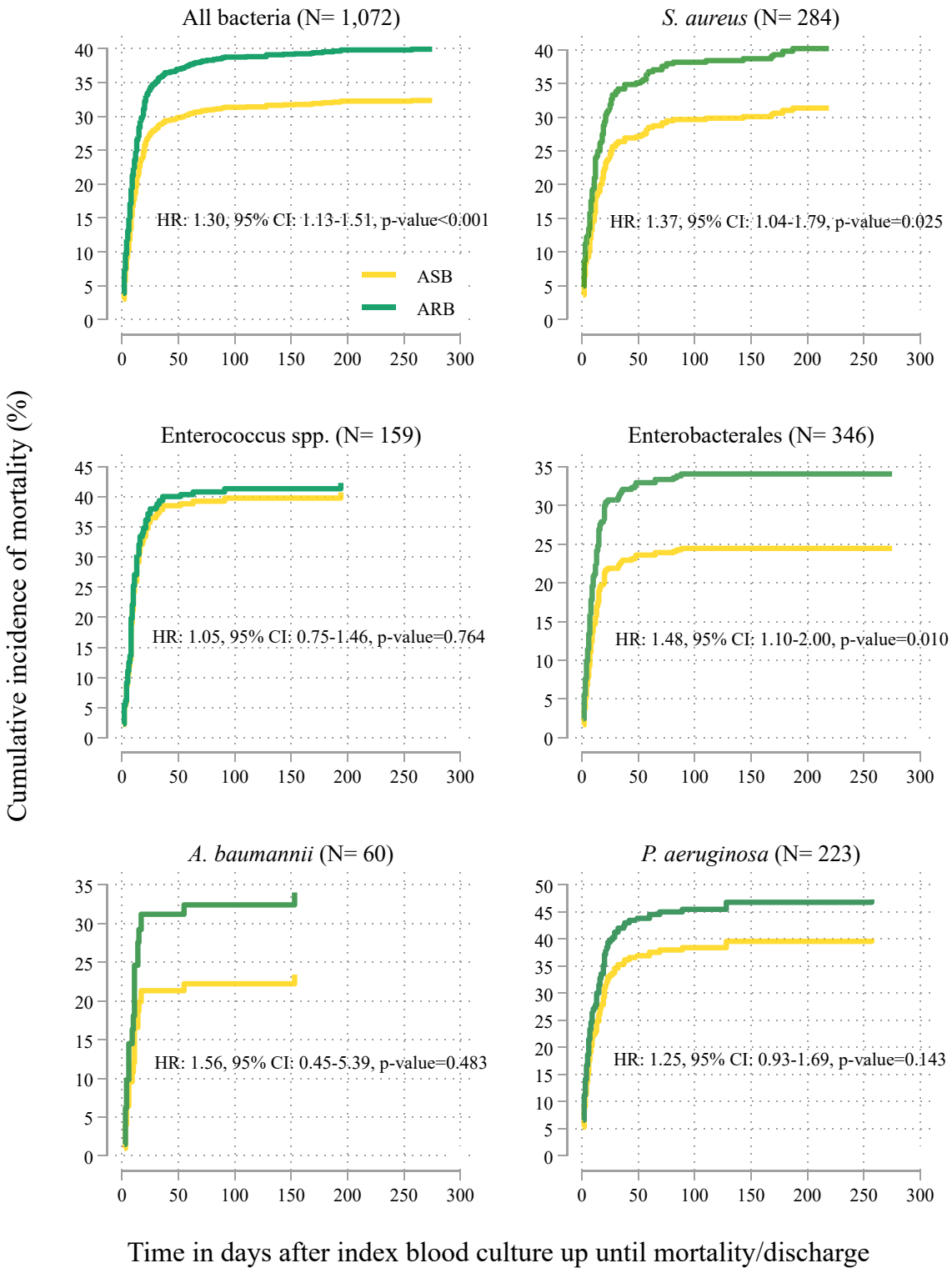

***Fig. 3:* Cumulative incidence of in-hospital mortality over time among hospital-acquired bloodstream infections using an adjusted competing-risk model by pathogen**. ARB, Antibiotic-resistant bacteria; ASB, Antibiotic-susceptible bacteria. Each model was adjusted by resistance level, and individual-clustered standard errors were used. Pathogen-specific antibiotic resistance and susceptibility included carbapenem/cephalosporin resistant Enterobacterales, methicillin-susceptible or resistant *Staphylococcus aureus*, carbapenem-susceptible or resistant

patients with hospital-acquired BSIs.[32] Our estimates for community-acquired infections may be biased due to conditioning on hospital admission. This variable potentially lies on the causal pathway from ARB BSI to health-economic outcomes and simultaneously induces collider stratification bias. Our results for community-acquired infections would be more accurate if ARB had a negligible influence on the probability of hospital admission. For instance, as shown in our data, the role of pathogens such as *A. baumannii* or *P. aeruginosa* in community-acquired infections is minimal, decreasing the relevance of this acquisition in these microorganisms.

ARB infections are complex and often increase the risk of admission to the ICU and hospital's LOS. Recent estimates have suggested a 1.77-times higher risk of ICU admission (1.08–2.89, p = 0.023) for ARB BSI patients from LMICs in the Americas.[9] We found 1.25 and 1.41 higher odds of ICU admission for ARB and CRE species among hospital patients, respectively, with hospital-acquired CRE presenting 1.36 times greater ICU admissions. These disparities can be partly attributed to adjusting estimates for background factors, as crude estimates could potentially overestimate the number of admissions.[9,33]

ARB infections have been associated with longer LOS, typically 2–12 days longer than ASB infections.[9,34] We observed crude median differences in hospital LOS between ARB and ASB BSIs after BSI diagnostic, ranging between 3 and 10 days among CRPA, MRSA, VRE, and CRE. After using IPW-adjusted estimates, we found that ARB, and specifically community-acquired CRE, was associated with significantly longer LOS (IRR = 1.61), with hospital-acquired BSIs presenting 1.36 and 1.40 times higher LOS risk ratios for CRE and CRPA, respectively. Hospital-acquired BSIs often yield worse health outcomes compared to community-acquired BSIs.[35] MRSA was not associated with longer LOS, as in previous research.[26] This null finding may relate to factors such as BSI complications, which can vary across populations.[29] Our analysis of MRSA hospital survival dynamics, using competing risk methods to account for individuals who do not die at the hospital, revealed that the majority of MRSA-infected patients in our study died within the first 30 days of hospitalisation, consistent with previous findings.[36]

Excess hospital (direct) costs attributed to ARB BSIs were estimated at $2282 compared to ASB BSIs, consistent with recent studies.[9] Researchers in Colombia[37] found excess hospitalisation costs of $10,212 associated with MRSA BSIs, and estimates for CRAB in China and CRE in Turkey have been reported at $10,763,[38] and $10,002,[39] respectively. Notably, prior studies did not include costs for therapy, treatment, and professional staff.[4,5] Our estimates based on FONASA and CENABAST are proxies for health-system opportunity costs for BSI treatment. While they reflect centralised national procurement, some might be outdated. Our cost estimates are conservative, as relevant variables such as invasive device replacement, the need for physical therapy, and the use of vasoactive drugs, were not included due to data limitations, which could otherwise increase the estimated economic costs.[40]

Following Daroudi et al.'s[41] approach for monetising DALYs based on GDP per capita (1.2 times GDP per capita times DALYs), our estimate of 2270 excess DALYs attributed to ARB BSIs translates to additional costs of ~$44.3 million. These costs are associated with the increased mortality and morbidity resulting from ARB among BSI patients. Including hospital expenses and productivity losses, we found a total societal cost of $53.7 million attributed to ARB BSI-related mortality (0% discount rate), representing a substantial economic burden. The estimated DALYs attributed to ARB surpass those previously calculated for HIV (n = 149), tuberculosis (n = 65), and lower respiratory infections (n = 375), mounting to ~9% (2270 out of 24,829) of the total estimated DALYs in Chile in 2019.[42]

Heightened host vulnerability, inadequate empirical antibiotic treatment, excessive antibiotic usage following culture results, and reduced efficacy of reserve antibiotics contribute to this ARB burden.[30,43] A meta-analysis reported that CRE patients were consistently less likely to receive appropriate initial antibiotic therapy.[30] We found that ARB patients had more substantial DDDs per 1000 hospital bed-days compared to patients with ASB. This increased burden of ARB pathogens may be associated with delays in administering appropriate treatment. Additionally, conventional treatments for MRSA and Enterobacterales, such as vancomycin or levofloxacin, may not be as rapidly effective as beta-lactam antibiotics against their susceptible counterparts. In an exploratory analysis, we estimated that ~32.0% of all BSI episodes (n = 432) were exposed to antibiotics within 48 h after the index blood culture that did not align with their corresponding treatment. ASB BSI episodes accounted for 26.2% wrong exposure to antibiotic treatment vs. 39.1% among ARB (χ^2 test p < 0.001), with the largest differences among MRSA and CRE, compared to MSSA and CSE, respectively

Pseudomonas aeruginosa, carbapenem-susceptible or resistant *Acinetobacter baumannii*, and vancomycin-susceptible or resistant Enterococcus spp. IPW, Inverse probability weighting; HR, Hazard ratio; CI, Confidence interval. Supplementary Figure S9 displays the entire period, while it was restricted to 100 days in this picture. Models were only weighted using IPW; no additional independent variables were added. Supplementary Table S25.1 shows the number of patients at risk and cumulative deaths by period.

(14.0% vs. 42.9%, χ^2 test $p < 0.001$; and 26.4% vs. 37.8%, χ^2 test $p < 0.001$, Supplementary Table S27). Early identification of BSI pathogens, especially Enterobacterales and *S. aureus*, could improve outcomes in patients with BSIs at a population level.[44]

Consistent with previous studies,[45–47] we found that VRE BSIs are more costly and harder to control than VSE. However, we did not find significant differences in the health burdens caused by VRE. This finding could be explained by the limited sample size or the uniform antibiotic exposures between the VSE and VRE groups in the study period (215.7 and 236.0 DDDs per 1000 hospital bed-days, respectively, χ^2 $p = 0.59$). Factors such as in-hospital mortality and LOS associated with VRE may be more affected by the specific Enterococcus species, concurrent underlying conditions, or the use of invasive medical devices,[12] rather than solely by resistance to vancomycin.[48,49] In contrast, although *A. baumannii* is recognised for its high pathogenicity[50] and is notably prevalent in colonisation in tertiary care hospitals in Chile,[51] the incidence of *A. baumannii* BSI episodes in our study sample was very low. We found significant resistance, consistent with other findings in the region.[7]

This study has some shortcomings. First, we used IPW methods, which may decrease the efficiency of our estimates and rely on observed variables. However, we included various host risk factors, encompassing LOS before the onset of infection, underlying health conditions, and sociodemographic factors, which might mitigate vulnerability following BSI diagnosis in hospital wards. Second, we found large confidence intervals and small sample sizes for pathogen-specific analyses, limiting the certainty of our conclusions. Third, hospitals can exhibit variations in blood culture sampling techniques and clinical management, potentially affecting the comparability of our estimates. We sought to minimise this risk by selecting hospitals with similar equipment and infrastructure (e.g., automated blood culture systems and antimicrobial susceptibility guidelines). Nevertheless, other factors, such as operational staff and day-to-day practices, may have introduced unobserved data variability. Fourth, we did not perform genomic analyses, which could have impacted appropriate treatments, especially considering the emergence of new MRSA clones[52] and carbapenemase prevalence among Enterobacterales[53,54] in Latin America. Fifth, our results show a large increase in BSI during the COVID-19 pandemic. Research suggests that the COVID-19 pandemic increased antibiotic usage and led to less stringent stewardship practices, probably contributing to the emergence and transmission of resistant bacteria.[54,55] Unfortunately, we lacked data to analyse COVID-19 infections and their potential interactions with susceptible and resistant bacterial infections. Sixth, our hospital cost data focused on essential items such as hospital bed-day, consultation fees, and diagnostics,[40] but omitted potentially relevant variables such as invasive device use, physical therapy needs, and vasoactive drugs. Finally, factors such as strain virulence,[56–58] particularly for MSSA, and variations in the definition of community-acquired BSIs,[59] may impact individual health status and prevalence. Colonisation with resistant bacteria may persist undetected in hosts for years,[60–62] potentially leading to transmission to others,[62] and highlighting challenges in distinguishing community-acquired from hospital-acquired infections. We adopted a widely used threshold of 48 h for consistency and comparability with prior research.[16–19]

Our study revealed a substantial health and economic burden associated with ARB BSIs in Chile, highlighting the need for enhanced infection prevention and control measures. Strengthening antibiotic stewardship programs and integrating surveillance systems are crucial in addressing this challenge. Effective strategies encompass a spectrum of approaches, ranging from well-established methods such as promoting hand hygiene and adhering to precautions and isolation measures to expanding the coverage of pneumococcal conjugate vaccines for vulnerable populations and potentially other vaccines currently in the pipeline.[63] Additionally, expanding molecular epidemiology, monitoring selective pressure, and implementing more stringent antimicrobial stewardship programs are essential components of a comprehensive approach to combat ARB BSIs.[64–66] Emphasising these practices is essential to mitigate the severe health and economic consequences associated with ARB in hospital settings.

Contributors

Conceptualisation, KA, PG, JM, EU; methodology, KA, LY, KP, JM, EU; data collation and extraction, AP, MS, JC, JM, EU; formal analysis, KA; writing—original draft preparation, KA; writing—review and editing, AP, HH, MS, PG, KP, LY, JM, EU; supervision, LY, JM, EU. KA, AP, MS, JC, PG, JM, and EU had full access to study data and vouch for the accuracy and completeness of the data. All authors have read and approved the final version of the manuscript, are entirely responsible for study design, data collection, and data analysis, and accept responsibility for publication.

Data sharing statement

Our use of data follows Chilean Law 19.628 on personal data protection. Owing to this data privacy law, the individual-level data used in this study cannot be shared. Aggregate, anonymised data are available from the corresponding author upon request.

Declaration of interests

KP declares to have received grant support from NIHR/HPRU, Wellcome Trust, Ineos Oxford Institute for AMR Research, CEPI, UK Health Security Agency, NIHR, Medical Research Foundation, Waltham Foundation, EU-H2020 IMI-2, and EU-H2020. JM declares to have received research grant support from ANID/FONDECYT, Pfizer, and MSD. EU declares to have received research grant support from ANID/FONDECYT, ANID/FONDAP, CIFAR, and MSD. KA, AP, HP, MS, JC, PG, and LY declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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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.2024.100943.

References

1 Murray CJ, Ikuta KS, Sharara F, et al. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. *Lancet*. 2022;399(10325):629–655.
2 Jee Y, Carlson J, Rafai E, et al. Antimicrobial resistance: a threat to global health. *Lancet Infect Dis*. 2018;18(9):939–940.
3 Roope LS, Smith RD, Pouwels KB, et al. The challenge of antimicrobial resistance: what economics can contribute. *Science*. 2019;364(6435):eaau4679.
4 Naylor NR, Atun R, Zhu N, et al. Estimating the burden of antimicrobial resistance: a systematic literature review. *Antimicrob Resist Infect Control*. 2018;7:1–17.
5 Gandra S, Barter D, Laxminarayan R. Economic burden of antibiotic resistance: how much do we really know? *Clin Microbiol Infect*. 2014;20(10):973–980.
6 Naghavi M, Vollset SE, Ikuta KS, et al. Global burden of bacterial antimicrobial resistance 1990-2021: a systematic analysis with forecasts to 2050. *Lancet*. 2024;404(10459):1199–1226.
7 Aguilar GR, Swetschinski LR, Weaver ND, et al. The burden of antimicrobial resistance in the Americas in 2019: a cross-country systematic analysis. *Lancet Reg Health Am*. 2023;25:100561.
8 Co-operation OfE, Staff D. *Stemming the superbug tide: just a few dollars more*. OECD; 2019.
9 Allel K, Stone J, Undurraga EA, et al. The impact of inpatient bloodstream infections caused by antibiotic-resistant bacteria in low-and middle-income countries: a systematic review and meta-analysis. *PLoS Med*. 2023;20(6):e1004199.
10 Pouwels K, Vansteelandt S, Batra R, Edgeworth J, Smieszek T, Robotham J. Intensive care unit (ICU)-acquired bacteraemia and ICU mortality and discharge: addressing time-varying confounding using appropriate methodology. *J Hosp Infect*. 2018;99(1):42–47.
11 Pouwels KB, Vansteelandt S, Batra R, Edgeworth J, Wordsworth S, Robotham JV. Estimating the effect of healthcare-associated infections on excess length of hospital stay using inverse probability–weighted survival curves. *Clin Infect Dis*. 2020;71(9):e415–e420.
12 López-Luis BA, Sifuentes-Osornio J, Lambraño-Castillo D, et al. Risk factors and outcomes associated with vancomycin-resistant Enterococcus faecium and ampicillin-resistant Enterococcus faecalis bacteraemia: a 10-year study in a tertiary-care centre in Mexico City. *J Glob Antimicrob Resist*. 2021;24:198–204.
13 Clinical and Laboratory Standards Institute. *CLSI Performance standards for antimicrobial susceptibility testing; twenty-fourth informational supplement M100-S24 January*. Wayne, PA: Clinical and Laboratory Standards Institute; 2014.
14 Tacconelli E, Carrara E, Savoldi A, et al. Discovery, research, and development of new antibiotics: the WHO priority list of antibiotic-resistant bacteria and tuberculosis. *Lancet Infect Dis*. 2018;18(3):318–327.
15 Daneman N, Fridman D, Johnstone J, et al. Antimicrobial resistance and mortality following E. coli bacteremia. *eClinicalMedicine*. 2023;56:101781.
16 Rodríguez-Baño J, López-Prieto MD, Portillo MM, et al. Epidemiology and clinical features of community-acquired, healthcare-associated and nosocomial bloodstream infections in tertiary-care and community hospitals. *Clin Microbiol Infect*. 2010;16(9):1408–1413.
17 Friedman ND, Kaye KS, Stout JE, et al. Health care–associated bloodstream infections in adults: a reason to change the accepted definition of community-acquired infections. *Ann Intern Med*. 2002;137(10):791–797.
18 Garner JS, Jarvis WR, Emori TG, Horan TC, Hughes JM. CDC definitions for nosocomial infections, 1988. *Am J Infect Control*. 1988;16(3):128–140.
19 Haque M, Sartelli M, McKimm J, Bakar MA. Health care-associated infections–an overview. *Infect Drug Resist*. 2018;11:2321–2333.
20 World Health Organization. *ATC/DDD index 2023*; 2023. https://www.whocc.no/atc_ddd_index/?code=J01CR01. Accessed July 13, 2023.
21 Fondo Nacional de Salud. *Aranceles mai*; 2023. https://www.fonasa.cl/sites/fonasa/prestadores/modalidad-atencion-institucional#aranceles-mai-2023. Accessed July 13, 2023.
22 Central de abastecemiento (CENABAST) Chile. Reporte de compras historicas de CENABAST. https://www.cenabast.cl/compras-cenabast/; 2023. Accessed July 13, 2023.
23 Organization WH. *GLASS method for estimating attributable mortality of antimicrobial resistant bloodstream infections*. 2020.
24 De Kraker M, Wolkewitz M, Davey P, et al. Burden of antimicrobial resistance in European hospitals: excess mortality and length of hospital stay associated with bloodstream infections due to Escherichia coli resistant to third-generation cephalosporins. *J Antimicrob Chemother*. 2011;66(2):398–407.
25 Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc*. 1999;94(446):496–509.
26 de Kraker ME, Wolkewitz M, Davey PG, Grundmann H, Burden Study Group. Clinical impact of antimicrobial resistance in European hospitals: excess mortality and length of hospital stay related to methicillin-resistant Staphylococcus aureus bloodstream infections. *Antimicrob Agents Chemother*. 2011;55(4):1598–1605.
27 Lau B, Cole SR, Gange SJ. Competing risk regression models for epidemiologic data. *Am J Epidemiol*. 2009;170(2):244–256.
28 Sanders GD, Neumann PJ, Basu A, et al. Recommendations for conduct, methodological practices, and reporting of cost-effectiveness analyses: second panel on cost-effectiveness in health and medicine. *JAMA*. 2016;316(10):1093–1103.
29 Seas C, Garcia C, Salles MJ, et al. Staphylococcus aureus bloodstream infections in Latin America: results of a multinational prospective cohort study. *J Antimicrob Chemother*. 2018;73(1):212–222.
30 Kohler PP, Volling C, Green K, Uleryk EM, Shah PS, McGeer A. Carbapenem resistance, initial antibiotic therapy, and mortality in Klebsiella pneumoniae bacteremia: a systematic review and meta-analysis. *Infect Control Hosp Epidemiol*. 2017;38(11):1319–1328.
31 Xu L, Sun X, Ma X. Systematic review and meta-analysis of mortality of patients infected with carbapenem-resistant Klebsiella pneumoniae. *Ann Clin Microbiol Antimicrob*. 2017;16:1–12.
32 Diekema D, Beekmann S, Chapin K, Morel K, Munson E, Doern G. Epidemiology and outcome of nosocomial and community-onset bloodstream infection. *J Clin Microbiol*. 2003;41(8):3655–3660.
33 Ben-David D, Kordevani R, Keller N, et al. Outcome of carbapenem resistant Klebsiella pneumoniae bloodstream infections. *Clin Microbiol Infect*. 2012;18(1):54–60.
34 Barrasa-Villar JI, Aibar-Remón C, Prieto-Andrés P, Mareca-Doñate R, Moliner-Lahoz J. Impact on morbidity, mortality, and length of stay of hospital-acquired infections by resistant microorganisms. *Clin Infect Dis*. 2017;65(4):644–652.
35 Page DB, Donnelly JP, Wang HE. Community-, healthcare-and hospital-acquired severe sepsis hospitalizations in the University HealthSystem consortium. *Crit Care Med*. 2015;43(9):1945.
36 Bai AD, Lo CK, Komorowski AS, et al. Staphylococcus aureus bacteraemia mortality: a systematic review and meta-analysis. *Clin Microbiol Infect*. 2022;28(8):1076–1084.
37 Barrero LI, Castillo JS, Leal AL, et al. Economic burden of methicillin-resistant Staphylococcus aureus bacteremia in critical care patients in hospitals in Bogotá. *Biomedica*. 2014;34(3):345–353.
38 Huang W, Qiao F, Zhang Y, et al. In-hospital medical costs of infections caused by carbapenem-resistant Klebsiella pneumoniae. *Clin Infect Dis*. 2018;67(suppl_2):S225–S230.

39 Gulen TA, Guner R, Celikbilek N, Keske S, Tasyaran M. Clinical importance and cost of bacteremia caused by nosocomial multi drug resistant Acinetobacter baumannii. *Int J Infect Dis*. 2015;38:32–35.
40 Poudel AN, Zhu S, Cooper N, et al. The economic burden of antibiotic resistance: a systematic review and meta-analysis. *PLoS One*. 2023;18(5):e0285170.
41 Daroudi R, Akbari Sari A, Nahvijou A, Faramarzi A. Cost per DALY averted in low, middle-and high-income countries: evidence from the global burden of disease study to estimate the cost-effectiveness thresholds. *Cost Eff Resour Alloc*. 2021;19(1):1–9.
42 Vos T, Lim SS, Abbafati C, et al. Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the global burden of disease study 2019. *Lancet*. 2020;396(10258):1204–1222.
43 Holland TL, Bayer AS, Fowler VG Jr. Persistent methicillin-resistant Staphylococcus aureus bacteremia: resetting the clock for optimal management. *Clin Infect Dis*. 2022;75(9):1668–1674.
44 Kadri SS, Lai YL, Warner S, et al. Inappropriate empirical antibiotic therapy for bloodstream infections based on discordant in-vitro susceptibilities: a retrospective cohort analysis of prevalence, predictors, and mortality risk in US hospitals. *Lancet Infect Dis*. 2021;21(2):241–251.
45 Shay DK, Maloney SA, Montecalvo M, et al. Epidemiology and mortality risk of vancomycin-resistant enterococcal bloodstream infections. *J Infect Dis*. 1995;172(4):993–1000.
46 Salgado CD, Farr BM. Outcomes associated with vancomycin-resistant enterococci: a meta-analysis. *Infect Control Hosp Epidemiol*. 2003;24(9):690–698.
47 Carmeli Y, Eliopoulos G, Mozaffari E, Samore M. Health and economic outcomes of vancomycin-resistant enterococci. *Arch Intern Med*. 2002;162(19):2223–2228.
48 Kramer TS, Remschmidt C, Werner S, et al. The importance of adjusting for enterococcus species when assessing the burden of vancomycin resistance: a cohort study including over 1000 cases of enterococcal bloodstream infections. *Antimicrob Resist Infect Control*. 2018;7:1–9.
49 Piezzi V, Marschall J, Buetti N. Are vancomycin-resistant enterococcal bloodstream infections associated with decreased survival? *Clin Infect Dis*. 2020;71(6):1586.
50 Brito BP, Koong J, Wozniak A, et al. Genomic analysis of carbapenem-resistant Acinetobacter baumannii strains recovered from Chilean hospitals reveals lineages specific to South America and multiple routes for acquisition of antibiotic resistance genes. *Microbiol Spectr*. 2022;10(5):e0246322.
51 Allel K, Labarca J, Carvajal C, et al. Trends and socioeconomic, demographic, and environmental factors associated with antimicrobial resistance: a longitudinal analysis in 39 hospitals in Chile 2008–2017. *Lancet Reg Health Am*. 2023;21:100484.
52 Arias CA, Reyes J, Carvajal LP, et al. A prospective cohort multicenter study of molecular epidemiology and phylogenomics of Staphylococcus aureus bacteremia in nine Latin American countries. *Antimicrob Agents Chemother*. 2017;61(10). https://doi.org/10.1128/AAC.00816-17.
53 Thomas GR, Corso A, Pasterán F, et al. Increased detection of carbapenemase-producing enterobacterales bacteria in Latin America and the Caribbean during the COVID-19 pandemic. *Emerg Infect Dis*. 2022;28(11):1–8.
54 Allel K, Peters A, Conejeros J, et al. Antibiotic consumption during the coronavirus disease 2019 pandemic and emergence of carbapenemase-producing Klebsiella pneumoniae lineages among inpatients in a Chilean hospital: a time-series study and phylogenomic analysis. *Clin Infect Dis*. 2023;77(Supplement_1):S20–S28.
55 Langford BJ, Soucy J-PR, Leung V, et al. Antibiotic resistance associated with the COVID-19 pandemic: a systematic review and meta-analysis. *Clin Microbiol Infect*. 2023;29(3):302–309.
56 Hekker T, Groeneveld A, Simoons-Smit A, De Man P, Connell H, MacLaren D. Role of bacterial virulence factors and host factors in the outcome of Escherichia coli bacteraemia. *Eur J Clin Microbiol Infect Dis*. 2000;19:312–316.
57 Victor LY, Hansen DS, Ko WC, et al. Virulence characteristics of Klebsiella and clinical manifestations of K. pneumoniae bloodstream infections. *Emerg Infect Dis*. 2007;13(7):986.
58 Cheung GY, Bae JS, Otto M. Pathogenicity and virulence of Staphylococcus aureus. *Virulence*. 2021;12(1):547–569.
59 Folden D, Machayya J, Sahmoun A, et al. Estimating the proportion of community-associated methicillin-resistant Staphylococcus aureus: two definitions used in the USA yield dramatically different estimates. *J Hosp Infect*. 2005;60(4):329–332.
60 Bonten MJ, Slaughter S, Ambergen AW, et al. The role of colonization pressure in the spread of vancomycin-resistant enterococci: an important infection control variable. *Arch Intern Med*. 1998;158(10):1127–1132.
61 Bonten MJ, Hayden MK, Nathan C, Rice TW, Weinstein RA. Stability of vancomycin-resistant enterococcal genotypes isolated from long-term-colonized patients. *J Infect Dis*. 1998;177(2):378–382.
62 Smith DL, Dushoff J, Perencevich EN, Harris AD, Levin SA. Persistent colonization and the spread of antibiotic resistance in nosocomial pathogens: resistance is a regional problem. *Proc Natl Acad Sci U S A*. 2004;101(10):3709–3714.
63 Jansen KU, Knirsch C, Anderson AS. The role of vaccines in preventing bacterial antimicrobial resistance. *Nat Med*. 2018;24(1):10–19.
64 Rice S, Carr K, Sobiesuo P, et al. Economic evaluations of interventions to prevent and control health-care-associated infections: a systematic review. *Lancet Infect Dis*. 2023;23(7):e228–e239.
65 Salvador BC, Lucchetta RC, Sarti FM, et al. Cost-effectiveness of molecular method diagnostic for rapid detection of antibiotic-resistant bacteria. *Value Health Reg Issues*. 2022;27:12–20.
66 Allel K, Hernández-Leal MJ, Naylor NR, et al. Costs-effectiveness and cost components of pharmaceutical and non-pharmaceutical interventions affecting antibiotic resistance outcomes in hospital patients: a systematic literature review. *BMJ Glob Health*. 2024;9(2):e013205.