Impacts of antimicrobial resistance bloodstream infections among hospital patients and potential interventions: a case study in Chile

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I, Kasim Allel Henriquez, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

"…..No caigas en el error de que sólo se hace mérito con los grandes trabajos; hay pequeños servicios que son buenos servicios: adornar una mesa, ordenar unos libros, peinar a un niño….."

Gabriela Mistral, El placer de Servir.

Abstract

The rise of antimicrobial resistance (AMR) poses a critical global health challenge. Bloodstream infections contribute significantly to global morbidity and mortality, exacerbated in low- and middle-income countries (LMICs) by insufficient healthcare access and quality. Recognising this, the United Nations has prioritised combating AMR and bloodstream infections within its Sustainable Development Goals, aiming to bolster LMICs' healthcare capacities by 2050. Despite their significance, studies on the disease burden in LMICs remain limited, and there is an urgent need to update in-hospital AMR management guidelines.

My PhD project focused on enhancing the epidemiological understanding of AMR-related bloodstream infections in LMICs, with a particular case study in Chile utilising patient-level data. Starting with a comprehensive global analysis of AMR, I examined its association with various factors through a One Health lens. A meta-analysis was performed to quantify the disease's burden in terms of mortality, hospital stay lengths, ICU admissions, and economic impacts.

In Chile, an epidemiological analysis of in-hospital AMR trends over time was conducted, identifying key pathogens and risk factors relevant across different settings and regions. By analysing patient-level data on bloodstream infections, the additional health and economic burdens posed by AMR from a national cohort of 1,218 patients with bloodstream infections was estimated. Through mathematical modelling, I assessed potential intervention strategies, reviewing their financial implications and projected their cost-effectiveness. These findings culminated in recommendations for improving infection control practices. Focusing on Chile provided a precedent for healthcare improvements in regions where data remains scarce and AMR a growing threat.

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Being an immigrant presents its unique challenges, but with resilience and gratitude, these hurdles can be overcome.

List of abbreviations

ABR	Antibiotic resistance/resistant
ABS	Antibiotic susceptible
AMR	Antimicrobial resistance/resistant
AMS	Antimicrobial susceptible
ATB	Antibiotic
BSI	Bloodstream infections
CDC	Centre for Disease Control
CDDEP	Centre for disease dynamics, economics, and policy
DALYs	Disability-adjusted life years
eCDC	European Centre for Disease Control and Prevention
ESBL	Extended spectrum beta-lactamase
GDP	Gross domestic product
GLASS	Global Antimicrobial Resistance and Surveillance System
GNI	Gross National Income
HICs	High income countries
ICER	Incremental cost-effectiveness ratio
ICU	Intensive Care Units
LOS	Length of Stay
LMICs	Low- and middle-income countries
MDR	Multi-drug resistance
MRSA	Methicillin resistant Staphylococcus aureus
MSSA	Methicillin susceptible Staphylococcus aureus
OECD	Organization for Economic Cooperation and Development
OR	Odds Ratio
PPS	Point Prevalence Study
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QALYs	Quality-adjusted life years
SDG	Sustainable Development Goals
SDR	Single-drug resistance
UN	United Nations
WB	World Bank
WHO	World Health Organization
WTP	Willingness-to-pay
XDR	Extensive-drug resistance

Document structure

Chapter 1 introduces the antimicrobial-resistance issue, setting the stage for the research conducted in this PhD study. **Chapter 2** outlines the aims and objectives of my PhD. **Chapter 3** explores the main One-health factors related to global antimicrobial-resistance in humans and animals. **Chapter 4** describes a systematic literature review and meta-analysis of the excess health and economic burden of bloodstream infections produced by antimicrobial-resistant bacteria in low- and middle-income countries. **Chapter 5** displays a systematic literature review of the cost-effectiveness of pharmaceutical and non-pharmaceutical interventions to reduce antimicrobial-resistance in hospitals. **Chapter 6** displays our hospital-level study analysing antimicrobial-resistance trends in Chile over time. **Chapter 7** presents a case-study in Chile utilising primary data collection to delve into the health and economic effects of antimicrobial-resistant bacteria in hospital patients with bloodstream infections. **Chapter 8** describes a proposed mathematical model of antimicrobial-resistance transmission dynamics calibrated to Chilean data and evaluates cost-effectiveness of national-scale interventions. **Chapter 9** compiles a discussion that includes all the previously analysed chapters. **Chapter 10** summarises the main conclusions and takeaway message.

Chapter 1:

Introduction

The emergence and spread of antimicrobial resistance (AMR) are among the most urgent global public health threats in the 21st century.[1-5] These pathogens are increasingly ubiquitous among animals, humans, food and the environment.[6-8] Infections caused by resistant bacteria produce greater morbidity and mortality, complicate treatments, and often result in longer hospitalisations, imposing high costs to the health system and society as a whole [5,9]. Global estimates suggest that about 700,000 people die annually from infections by resistant bacteria; without preventive actions, 10 million annual deaths are projected by 2050, with accumulated global costs of US$100 trillion.[10] A recent report from the US Centres for Disease Control and Prevention (CDC) estimated that antibiotic resistance underlie at least two million illnesses and 23,000 deaths annually in the United States.[11]

Inadequate antimicrobial use and insufficient infection control have accelerated the emergence and spread of AMR.[12] Global increases in antibiotic use in humans, animals (e.g., food production), and agriculture (e.g., bactericides), have increased selective pressures that drive the development of resistance.[13,14] Estimates show that the consumption of antibiotics (in defined daily doses, DDD) increased by approximately 65% between 2000 and 2015, an increase largely driven by low- and middle-income countries.[15]

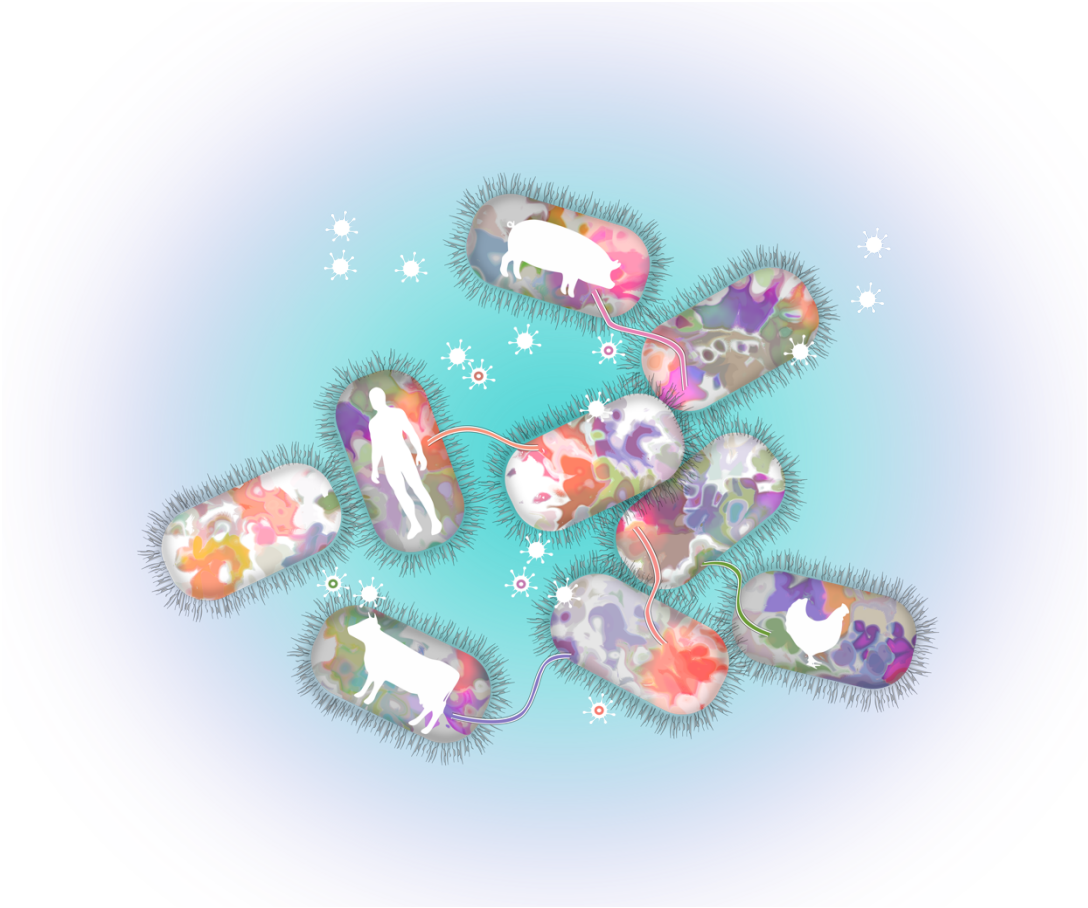
A lack of incentives has limited the development of new antibiotics; the process is expensive, and the expected gains are limited compared to other drugs, largely because the clinical benefits of antibiotics has diminished over time and the use of new drugs would be restricted to prevent resistance.[16,17]

Antimicrobial-resistance drivers: a wicked problem

The global escalation of AMR is a multifaceted issue, deeply intertwined with governance, politics, anthropogenic actions, geographical and sociodemographic factors. Ineffective regulatory frameworks and insufficient enforcement lead to rampant overuse and misuse of antibiotics in humans, animals, and agriculture.[18-20] For instance, countries with weak healthcare systems lack the necessary infrastructure for monitoring and controlling antibiotic use and surveillance of AMR pathogens.[21] Institutional-political commitment and international cooperation are often inconsistent, with variations in policy implementation and resource allocation, which hampers these contexts further.[22] Additionally, human activities, notably in agriculture and aquaculture,[23,24] contribute significantly to AMR through excessive and inappropriate use of antimicrobials. Pollution from pharmaceutical manufacturing and healthcare waste exacerbates the problem by releasing antimicrobials into the environment.[25] Finally, population density, urbanization, and migration affect the spread of AMR. High-density living conditions, particularly in low-resource settings, facilitate the

transmission of these pathogens.[26] That is why AMR is often considered as a 'wicked'[27] problem requiring a holistic, One Health approach for effective management (Figure 1).[7]

Figure 1. Illustration of the interconnectedness among human, animal, and environmental factors in reducing antimicrobial resistance



Source: Made by Laith Yakob.

The burden of antimicrobial-resistant bacteria: overview and measurement

Compared with antibiotic-susceptible infections, infections with resistant bacteria not only produce greater morbidity and mortality in patients, but result in longer hospitalizations, increase the cost of treatment, and compromise clinical procedures that depend on the use of ineffective antibiotics, generating higher costs for the hospital and the health system as a whole.[28,29] Cost increases are mostly related to three phenomena. First, AMR increases patient hospitalization duration, particularly in ICUs.[29,30] Second, patients typically require more resources at higher cost e.g., second-line antibiotics, invasive procedures.[16,31,32]

Finally, AMR can make medical interventions, such as chemotherapy or transplants, more complex or risky to perform.[28]

Quantifying the effects of AMR in the clinical outcomes of patients is a crucial step for assessing its disease and economic burden.[29,30] Recent reviews have highlighted several challenges in estimating the disease burden attributable to AMR, including important adjustments for the severity of illness, hospital stay with antibiotic-susceptible infections, presence of comorbidities, or specific antibiotic therapy.[30,33] Other challenges relate to heterogeneity in the study population and controls, which can require using matching techniques[34,35], or time-dependent bias corrections.[36,37]

Economic burden studies have primarily focused on high-income countries, mainly Europe and the United States.[30,34-36,38] Compared to susceptible infections, the economic burden associated with AMR is usually defined as excess costs incurred by hospitals and/or patients, depending on the economic perspective used.[39] Direct costs include excess costs related to longer lengths of stay (LOS), differential treatment, infection control, diagnostics, and healthcare personnel. So far, the studies have typically not considered societal (total health care costs and benefits), health system (hospital morbidity, mortality, and costs), and patient (illness, productivity) perspectives, as recent recommendations and guidelines for economic evaluations suggest.[40] Therefore, these studies have underestimated the effects of AMR by, for example, overlooking productivity losses from premature death or absenteeism, or lifetime costs following hospital discharge.[32]

Reliable estimates of the disease and economic burden associated with AMR in hospitals is essential for making public health decisions, defining research and funding priorities, and evaluating the impact of disease prevention and control programs.[2] Disease burden studies are essential for decision-making and are promoted by the World Health Organization (WHO) through the Global Burden of Disease (GBD) studies.[41] The GBD studies are important in defining global and local priorities in public health and scientific research, including quantifying the morbidity and mortality associated with different diseases and the ability of health systems to reduce preventable deaths.[42] Nevertheless, these studies on disease burden should be complemented by economic and financial component analyses.[43] Economic analyses allow us to quantify spending, compare alternative interventions using cost-effectiveness analyses, and prioritise research and program funding [39], in addition to supporting a systematic evaluation of disease control and prevention progress.

Epidemiology and burden of bloodstream infections caused by antimicrobial-resistant bacteria

Bloodstream infections (BSI), meaning the presence of bacteria in the bloodstream that is tested through a blood culture, and related organ dysfunctions (named as sepsis shock or severe sepsis), constitute a significant cause of morbidity and mortality worldwide.[44-47] BSI is amongst one of the deadliest health conditions with mortality rates of about 30%, surpassing other primary sources of infection (urine, wound, etc.).[47] The patterns of pathogens causing BSIs have changed during recent years. Gram-negative bacteria are currently the most critical AMR priorities.[48] Pathogens producing enzymes called extended spectrum beta-lactamase (ESBLs), which inhibit the effect of 3rd generation cephalosporins, are extremely difficult to control, especially among hospital inpatients.[48] Additionally, the production of enzymes of the metallo-beta-lactamase or carbapenems types that confer the bacterium the ability to hydrolyse antibiotics including penicillin, cephalosporins, monobactams, and carbapenems are of increasing concern to clinicians. For instance, BSIs due to carbapenem- or colistin-resistant *Klebsiella pneumonia* are extremely restrictive in the drugs which remain effective, resulting in a crude mortality rate of between 30-60% (even as high as 80% among patients with comorbidities).[44,48]

Generally, BSIs occur in three different groups of people that should be targeted for prevention and surveillance control.

(1) In immunologically normal hosts who have intact defences but who develop BSIs, commonly as community-onset infections, through different types of bacterial exposures. Bacterial exposures could be defined as any infected wound in the skin and infections produced in the respiratory/urinary/gastrointestinal tracts whose causative bacterium might spread into the lymphatic system gaining access to the bloodstream. For instance, *N. meningitidis* (affecting the respiratory and central nervous system), *S. pyogenes* diseases (caused by respiratory and skin infections), streptococcus species (occurring at the respiratory tract as primary source) causing BSI endocarditis involving heart valves, post-influenza *S. pneumoniae* (compromised respiratory system), *S. aureus* bacteraemia (wound infection), and Salmonella typhi bacteraemia (contaminated food causing gastrointestinal diseases) in some LMICs, tend to be commonly acquired in the community [48]. Most of these infections are defined as secondary source or extravascular types.
(2) In patients with impaired immunological defences (new-borns and the elderly). These individuals are more susceptible to infections if exposed to bacterial diseases through

different vectors/reservoirs, such as streptococcal and pneumococcal infections, *Escherichia coli*, *Klebsiella* spp. and *Candida* species typically found in contaminated food or water within the community settings.

(3) In patients who have pathological or pharmacological predisposition. Patients with immunodeficiencies due to underlying health conditions (e.g., diabetes, cancer, transplants) and those undergoing highly invasive surgeries (indwelling devices and the use of catheters, or any operation involving the mucus membranes) are at significantly increased risk of BSIs. For those infections occurring directly into the blood vessels or bacterial endocarditis (affecting heart valves), the source of infection is primary because it is originated within the cardiovascular system. This is highly prevalent in individuals experiencing intravenous drug use, heart valve or rheumatic diseases, kidney failure, heart transplants, among other conditions that generally weaken the immune system.

The dynamics, symptoms, and consequences of bloodstream infections

Bacteria can enter the bloodstream through primary (cardiovascular) or secondary sources (extravascular). Once in the bloodstream, also known as bacteraemia (simple presence of bacteria in the blood), it could be transient (the immune system destroys bacterium), or they can be multiplied, causing the systemic manifestation of infection and potentially causing life-threatening damages (commonly understood as blood poisoning and septicaemia/sepsis).[49] While bacteraemia produces null or only mild symptoms (e.g., slight fever), sepsis might produce inflammation, chills, prostration, fever, rapid heart, and respiration rates, falling blood pressure, etc. If sepsis is not rapidly treated, it can present severe consequences due to the organ damage and inflammatory response including organ dysfunction, hypotension, among others, leading to septic shocks (strokes and heart attacks), and therefore, mortality.[47] These patients are usually treated at the Intensive Care Units and represent the sickest patients within the hospital settings. Sepsis kills 11 million people worldwide each year (1 in 5 deaths), and it disproportionately affects vulnerable populations: pregnant women, new-borns, and people living in low-resource settings (e.g., LMICs).[47,50] Approximately 85% of sepsis-related cases and deaths occur in these settings, of which 50% are hospital-acquired.[50] Thus, AMR constitutes a major threat to public health, complicating the treatment of infections and posing a significant challenge, particularly in LMICs where access to preventive measures and treatments is limited.[50,51]

Interventions to reduce antimicrobial-resistance levels in hospitals

Effective interventions to control AMR in hospital settings have included stringent infection control practices such as hand hygiene and use of personal protective equipment, alongside comprehensive antimicrobial stewardship programs to ensure judicious use of antibiotics.[52-55] Routine surveillance for AMR pathogens, coupled with rapid diagnostic testing (e.g., polymerase chain reaction, whole-genome sequencing, etc), enables timely and targeted treatments, reducing unnecessary antibiotic use.[56] Educating healthcare workers and patients about AMR and promoting a culture of safety and responsibility are also crucial. Finally, environmental cleaning and disinfection, along with isolation procedures for infected or colonised patients, help prevent the spread of resistant bacteria within healthcare facilities.[57] Integrating these strategies, coupled with decolonisation treatments,[58] can significantly reduce the prevalence and impact of AMR in hospitals.

Antimicrobial resistance in Chile

Chile has a nominal gross-domestic product (GDP) per capita of ≈$16,000, with poverty rates (less than US$6.9 a day) equal to 4.8% in 2022. Chile is classified as a high-income country by the World Bank based on the GDP's lower bound equal to $13,846 per capita.[59] However, the country has the second highest level of income inequality in the OECD, as measured by the Gini index,[60] suggesting that the classification of income is misleading when considering the country's internal economic disparities. Chile's healthcare system is mixed, with both public and private sectors. The public system, known as FONASA, provides coverage for most of the population (≈70%).[61] The health system provides universal coverage, but challenges remain in ensuring equal access to quality care for all socioeconomic groups.[62] Since 1999, Chile has regulated antimicrobial prescriptions to reduce the escalating threat of AMR, with current OECD estimates revealing a concerning 21% resistance rate (i.e., average proportion of resistance for eight priority antibiotic-bacterium pairs),[1] comparable to regional figures in Argentina (31.6%), Brazil (33.8%), Colombia (33.8%), Costa Rica (29.7%), Peru (39.2%), and Mexico (34.1%) in 2013. Despite launching the National Plan Against Antimicrobial Resistance in 2015,[63] aiming for inter-sectoral coordination and control, significant gaps persist. Coordination among key stakeholders remains fragmented, and detailed impact assessments of AMR on the national health framework are lacking, perpetuating the AMR surge. Although the Public Health Institute mandates biennial AMR surveillance focusing on prevalent hospital bacteria (*Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, *Enterococcus faecium* and *Enterococcus faecalis*), compliance with prevention and control standards varies across hospitals, undermining effective AMR management.[64]

Chapter 2:

Research Objectives

This PhD by publication aims to understand and investigate the burden of BSIs caused by AMR bacteria in LMICs, and the cost-effectiveness of intervention strategies to reduce its burden using Chile as a case study. The research aims/objectives and specific sub-objectives are listed below (in bold and bullet points, respectively). Table 1 presents the status of each research chapter (i.e., publication status).

1. **To understand the global drivers of antibiotic resistant bacteria considering the intersectionality between One Health components**
    - To evidence ecological relationships between sociodemographic, anthropological, political, and environmental factors with AMR levels globally in humans and animals
    - To evaluate regional variations and WHO-defined pathogen severity impacts

2. **To evaluate, quantify and critically review the excess burden of bloodstream infections caused by antibiotic resistant bacteria in LMIC hospital inpatients**
    - To quantify the burden by different burden outcomes (mortality, ICU admission, costs, and length of stays)
    - To assess whether the burden of BSIs caused by AMR bacteria vary by pathogens, antibiotic type, or geographical region

3. **To understand the cost-effectiveness of different interventions to reduce antimicrobial resistance in hospital patients globally**
    - To characterise and classify interventions as pharmaceutical or non-pharmaceutical and outline advanced technologies mitigating AMR in hospital contexts and pathogens
    - To quantify the excess costs and health gains per interventions while assessing setting's willingness-to-pay (WTP) thresholds

4. **To estimate the trends of antimicrobial resistance rates in Chile and main drivers associated**
    - To assess the prevalence of critical and high-priority antibiotic-resistant bacteria across Chile and its administrative divisions.

- To analyse the main sociodemographic, anthropological, and environmental factors moderating AMR rates in the country over time

5. **To estimate the burden of bloodstream infections in Chile attributable to AMR using observational patient-level data**
    - To quantify the excess morbidity, mortality, and economic costs attributable to BSIs caused by AMR, compared to antibiotic susceptible bacteria, in Chilean representative hospitals
    - To identify the main risk factors (previous underlying conditions, sociodemographic characteristics, among others) affecting BSIs caused by AMR

6. **To model cost-effectiveness of different interventions for reducing AMR burden in Chile**
    - To stratify risk factors underlying critical AMR pathogen transmission and estimate the burden among these different groups with BSIs
    - To estimate cost-effectiveness of alternative simulated interventions in reducing the burden of infections caused by AMR in Chile while exploring feasibility in net benefits at a national scale

Table 1. Overview of data collection, methods, and anticipated outputs for each research objective

Aims/ objectives	Data source	Methods	Output	Report chapter
1	Global data from One Health Trust, United Nations, WHO, among other sources	Cross-sectional regression analyses to understand main risk factors towards human and animal AMR, while exploring intersectionality	Published. *Lancet Planetary Health* LINK here	3
2	Published literature	Literature review and estimates of the burden using meta-analytical techniques by comparing BSIs caused by AMR and antimicrobial-susceptible bacteria. Mapping the burden of BSIs attributed to AMR identified in literature.	Published. *PloS Medicine* LINK here	4
3	Published literature	Literature review and estimates of cost-effectiveness including incremental health gains and economic costs per pharmaceutical and non-pharmaceutical interventions.	Published. *BMJ Global Health* LINK here	5
4	National hospital-level data per year including 39 hospitals between 2008-2017	National estimates of the prevalence of AMR in Chile utilising regression methods including time-variations and geographical components	Published *Lancet Regional Health Americas* LINK here	6
5	Case study for the burden of BSIs caused by AMR bacteria in Chilean hospitals using patient-level data	Retrospective analysis utilising a parallel matched cohort design to estimate the adjusted burden of BSIs caused by AMR bacteria in patients	Under review Pre-print available LINK here	7
6	Published literature and previous PhD chapters informing the model schematic, including sex-stratified patient-level data for AMR-infected patients	Mathematical modelling of AMR in Chile with risk stratification informed from the literature review and patient data. Recommendations of cost-effective policies to be taken.	Not yet submitted Draft available in the present thesis	8

Chapter 3:

Global antimicrobial-resistance drivers: an ecological country-level study at the human–animal interface

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Where was the work published?	Lancet Planetary Health		
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Global antimicrobial-resistance drivers: an ecological country-level study at the human–animal interface

Kasim Allel, Lucy Day, Alisa Hamilton, Leesa Lin, Luis Furuya-Kanamori, Catrin E Moore, Thomas Van Boeckel, Ramanan Laxminarayan, Laith Yakob

Summary

Background Antimicrobial resistance (AMR) is a pressing, holistic, and multisectoral challenge facing contemporary global health. In this study we assessed the associations between socioeconomic, anthropogenic, and environmental indicators and country-level rates of AMR in humans and food-producing animals.

Methods In this modelling study, we obtained data on Carbapenem-resistant *Acinetobacter baumanii* and *Pseudomonas aeruginosa*, third generation cephalosporins-resistant *Escherichia coli* and *Klebsiella pneumoniae*, oxacillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus faecium* AMR in humans and food-producing animals from publicly available sources, including WHO, World Bank, and Center for Disease Dynamics Economics and Policy. AMR in food-producing animals presented a combined prevalence of AMR exposure in cattle, pigs, and chickens. We used multivariable β regression models to determine the adjusted association between human and food-producing animal AMR rates and an array of ecological country-level indicators. Human AMR rates were classified according to the WHO priority pathogens list and antibiotic–bacterium pairs.

Findings Significant associations were identified between animal antimicrobial consumption and AMR in food-producing animals (OR 1·05 [95% CI 1·01–1·10]; p=0·013), and between human antimicrobial consumption and AMR specifically in WHO critical priority (1·06 [1·00–1·12]; p=0·035) and high priority (1·22 [1·09–1·37]; p<0·0001) pathogens. Bidirectional associations were also found: animal antibiotic consumption was positively linked with resistance in critical priority human pathogens (1·07 [1·01–1·13]; p=0·020) and human antibiotic consumption was positively linked with animal AMR (1·05 [1·01–1·09]; p=0·010). Carbapenem-resistant *Acinetobacter baumanii*, third generation cephalosporins-resistant *Escherichia coli*, and oxacillin-resistant *Staphylococcus aureus* all had significant associations with animal antibiotic consumption. Analyses also suggested significant roles of socioeconomics, including governance on AMR rates in humans and animals.

Interpretation Reduced rates of antibiotic consumption alone will not be sufficient to combat the rising worldwide prevalence of AMR. Control methods should focus on poverty reduction and aim to prevent AMR transmission across different One Health domains while accounting for domain-specific risk factors. The levelling up of livestock surveillance systems to better match those reporting on human AMR, and, strengthening all surveillance efforts, particularly in low-income and middle-income countries, are pressing priorities.

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Introduction

Rising antimicrobial resistance (AMR) presents a major threat to global health.[1,2] An estimated 1·27 million deaths attributable to bacterial AMR occurred globally in 2019.[3] AMR contributes to an increased number of deaths, health complications, and increased health expenditure in all countries, irrespective of socioeconomic status.[2,4] Bacterial AMR is a natural phenomenon that can arise through de-novo mutations or the transfer of genetic material encoding resistant phenotypes through processes, such as horizontal gene transfer.[5] Exposure of pathogens to antimicrobials is known to encourage selective proliferation of resistant bacteria.[6] Hence, indiscriminate use of antimicrobials is a primary driver of the global spread of AMR.[7] Misuse and excessive use of antimicrobials is not exclusive to human consumption. In 2017, an estimated 93 309 tonnes of antibiotics were sold for use in food-producing animals globally. This figure is projected to reach 104 079 tonnes by 2030.[8] This increase in antibiotic use is a consequence of the rising demand for meat-products and over-the-counter sales, particularly in low-income and middle-income countries (LMICs), in which populations are continuing to grow and become more economically developed.

Complex and interlinked socioeconomic and environmental factors also have a significant role on the contagion and spread of resistance genes. The quality of health-care systems, water sanitation and hygiene (WASH) infrastructure, gross domestic product (GDP) per capita, and climate have been identified as fundamental risk

Research in context

Evidence before this study

To identify which factors were associated with AMR levels in humans and food-producing animals, we searched PubMed and the grey literature for published studies that either quantified the magnitude of, or reviewed the potential association between, different sociodemographic, environmental, and anthropogenic variables, and global AMR levels in humans or food-producing animals. We searched the evidence between Jan 1, 2000, and Nov 1, 2022. We used keywords related to "global antimicrobial resistance" OR "antibiotic resistance" combined with any of the following MeSH terms: "infrastructure" OR "socioeconomic" OR "sanitation and hygiene" OR "governance" OR "environment" OR "monitoring and surveillance" OR "antibiotic/antimicrobial consumption". Articles containing keywords such as "HIV/AIDS", "tuberculosis", "virus", "fungus", and "parasites" were excluded. After assessing the articles, we found that variables pertaining to climatic, demographic, epidemiological, governmental, and industrial features have all been shown to have associations with resistance. However, no existing study has employed a global ecological analysis looking at AMR levels at the human–animal interface using a One Health approach.

Added value of this study

We collated AMR data from the Centre for Disease Dynamics, Economics and Policy (CDDEP), Global Antimicrobial Resistance and Use Surveillance System, Pan American Health Organisation, ResistanceBank, and published articles, providing the most holistic AMR database to date. Independent variables included antibiotic consumption data (from CDDEP), socioeconomic, environmental, and anthropological data obtained from the World Bank, WHO, and UN databases. β regression models examined country-level univariate and multivariable associations between rates of resistance in humans and animals and the independent variables. For the first time, we identified global bidirectional associations of antibiotic consumption and AMR between humans and animals, crystallising the necessity for a multisectorial framing of this problem to inform optimal interventions. Even after adjusting for other covariates, significant associations with both animal and human AMR were shown for factors pertaining to socioeconomics, including governance.

Implications of all the available evidence

Our results show the necessity for an integrated approach to tackling the spread of AMR that spans across different One Health domains and focuses on social development and poverty reduction as well as more stringent antibiotic consumption practices in humans and animals.

factors for the emergence and transmission of AMR.[9,10] Behavioural factors, such as unnecessary antibiotic use for the treatment of viral infections, and patient-related factors, including underlying health conditions (eg, obesity, smoking, and alcohol consumption), might also affect the spread of AMR by predisposing individuals to infection or reducing the effectiveness of antimicrobial drugs.[11,12] AMR spreads rapidly between environments, driven by a multitude of factors, including human and animal movement, surface water run-off, and exchange of agricultural products.[13] The magnitude of the influence that these diverse multisectoral drivers have on AMR globally is poorly understood, but evidence for a strong link between humans and food-producing animals is burgeoning.[14] A study across 11 European countries found strong, between-species, positive correlations (r coefficient between 0·68 and 0·94) of resistance to numerous antimicrobials (ampicillin, aminoglycosides, third-generation cephalosporins, and fluoroquinolones) in *Escherichia coli* isolated from food-producing animals and from humans.[15] A subsequent systematic review substantiated this link by showing that interventions targeting drug consumption in food-producing animals affected resistance rates in humans and animals.[16] Through increased demand for animal-based food and products, several anthropogenic factors, such as population growth (urban density) and rising incomes, have been reported to contribute to AMR at the human–animal interface.[17,18]

See Online for appendix

We sought to analyse the associations between different socioeconomic, environmental, and anthropogenic indicators and country-level AMR rates in humans and food-producing animals.

Methods

Study design

In this global multivariable β regression modelling study we used country-level data from as close to 2018 as available to examine the associations between global rates of AMR in human and food-producing animals (dependent variables) and an array of independent variables, including antibiotic consumption, and sociodemographic, health-related, and environmental risk factors. Variable definitions and data sources are listed in the appendix (pp 4–11). The countries included in our analyses represented every WHO region (appendix pp 12–15) and World Bank income class (appendix p 17). The aim of the study is to identify the main global determinants of AMR in humans and food-producing animals.

Procedures

We searched existing literature from PubMed to identify the main global risk factors associated with AMR. We extracted country-level data of the risk factors, if available, using global data repositories. We then computed univariate and multivariable β regression models to identify the association between human or food-producing

	Countries with data available	Median (IQR)	Minimum	Maximum	Definition	Expected association with AMR
Antimicrobial resistance (dependent variables)						
Critical priority human pathogens (%)	98	39·89 (23·09–45·68)	6·00	98·00	Average resistance observed in pathogen-antibiotic pairs defined as of critical importance to human health by WHO (carbapenem-resistant *Acinetobacter baumannii*, carbapenem-resistant *Escherichia coli*, third generation cephalosporins-resistant *E coli*, carbapenem-resistant *Klebsiella pneumoniae*, third generation cephalosporins-resistant *K pneumoniae*, and carbapenem-resistant *Pseudomonas aeruginosa*), all of which are Gram-negative bacteria	NA
Carbapenem-resistant *A baumanii* (%)	66	54·68 (28·00–82·00)	1·00	98·00	Average resistance to carbapenems observed for *A baumanii* isolates	NA
Third generation cephalosporins-resistant *E coli* (%)	89	38·31 (17·00–58·00)	6·00	89·00	Average resistance to third generation cephalosporins observed for *E coli* isolates	NA
Third generation cephalosporins-resistant *K pneumoniae* (%)	92	53·11 (27·00–77·00)	6·00	98·00	Average resistance to third generation cephalosporins observed for *K pneumoniae* isolates	NA
Carbapenem-resistant *P aeruginosa* (%)	41	27·00 (13·00–39·00)	4·00	87·00	Average resistance to carbapenems observed for *P aeruginosa* isolates	NA
High priority human pathogens (%)	80	24·00 (15·00–41·00)	1·00	94·26	Average resistance observed in pathogen-antibiotic pairs defined as of high importance to human health by WHO (oxacillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus faecium*)	NA
Oxacillin-resistant *S aureus* (%)	80	22·50 (11·50–40·00)	1·00	88·00	Average resistance to oxacillin observed for *S aureus* isolates	NA
Vancomycin-resistant *E faecium* (%)	37	22·00 (4·00–37·00)	1·00	69·00	Average resistance to vancomycin observed for *E faecium* isolates	NA
Medium priority human pathogens (%)	50	16·00 (6·00–29·00)	1·00	82·35	Average resistance observed in pathogen-antibiotic pairs defined as of medium importance to human health by WHO (penicillin-resistant *Streptococcus pneumoniae*)	NA
Food-producing animals (%)	164	24·80 (21·45–30·30)	5·35	48·36	Average resistance observed in isolates obtained from food-producing animals	NA
Antibiotic consumption (main independent variables)						
Third generation cephalosporins consumption in humans (in DDDs)	73	807·92 (440·52–1365·27)	83·34	5280·11	Annual third generation cephalosporins consumption, DDD per 1000 individuals	Positive associations with AMR
Carbapenems consumption in humans (in DDDs)	71	15·41 (3·69–30·62)	0·50	90·85	Annual third generation cephalosporins consumption, DDD per 1000 individuals	Positive associations with AMR
Oxacillins consumption in humans (in DDDs)	65	1·86 (0·48–3·11)	1·90	24·68	Annual oxacillin consumption, DDD per 1000 individuals	Positive associations with AMR
Glycopeptides consumption in humans (in DDDs)	72	4·81 (0·63–12·20)	0·25	72·51	Annual glycopeptide consumption, DDD per 1000 individuals	Positive associations with AMR
Penicillins consumption in humans (in DDDs)	72	137·88 (43·64–357·63)	0·86	3281·86	Annual penicillin consumption, DDD per 1000 individuals	Positive associations with AMR
Antibiotic consumption in animals (mg per PCU)	166	45·13 (39·57–61·53)	7·05	318·59	Estimated antibiotic consumption in livestock, 2013. Expressed in mg per PCU*	Positive associations with AMR

Positive association caused an increase in AMR. A full description of the variables used and country details and their classification by WHO region and World Bank income group is included in the appendix (pp 4–17). The full descriptive statistics for our raw, analytical, and imputed samples are reported in the appendix (pp 33–35). Longitudinal global rates of resistance and antibiotic consumption are shown in the appendix (pp 60–61). The crude relationship between GDP and AMR among humans and animals are reported in the appendix (p 62). AMR=Antimicrobial resistance. DDD=defined daily dose. GDP=gross domestic product. NA=not applicable. PCU=population correction unit. *PCU represents the total number of food-producing animals in a country (alive or slaughtered) that considers the differences between countries regarding animal weight and number of production cycles annually.

Table 1: **Raw descriptive statistics of the dependent and main independent variables included in the final regression models**

animal AMR with antibiotic consumption in humans and animals, accounting for identified, additional risk factors.

We searched PubMed from Jan 1, 2000, until Dec 1, 2022, for articles using keywords related to "global antimicrobial resistance" OR "antibiotic resistance" AND ("infrastructure" OR "socioeconomic" OR "sanitation and hygiene" OR "governance" OR "environment" OR "monitoring and surveillance" OR

"antibiotic/antimicrobial consumption"). Our search was restricted to articles written in English. Articles containing keywords "HIV/AIDS", "tuberculosis", "virus", "fungus", and "parasites" were excluded because we focused on WHO's bacterial priority pathogens list.[19] From the search, we extracted main global variables associated with AMR, detailed in the appendix (pp 4–11).

We included human and food-producing animal AMR rates as dependent variables. Human AMR rate comprised three different sublevels created based on average country-level resistance rates of pathogen and antibiotic combinations described by WHO as requiring urgent action due to the threat they pose to human health (table 1).[19] We also present a subanalysis by antibiotic–bacterium specific pairs, including carbapenem-resistant *Acinetobacter baumanii,* carbapenem-resistant *Pseudomonas aeruginosa*, third generation cephalosporins-resistant *Escherichia coli*, third generation cephalosporins-resistant *Klebsiella pneumoniae,* oxacillin-resistant *Staphylococcus aureus,* and vancomycin-resistant *Enterococcus faecium* rates in humans. Human AMR data were obtained from the Centre for Disease Dynamics, Economics and Policy's ResistanceMap.[20] When possible, missing human AMR rates were imported from the WHO's Global Antimicrobial Resistance and Surveillance System (GLASS)[21] and the Pan American Health Organisation (PAHO).[22] Countries that had data imported from GLASS and PAHO are listed in the appendix (p 11).

Animal AMR rates were generated based on average country-level resistance rates in food-producing animals. Animal AMR data were obtained from ResistanceBank.[23] Missing animal AMR rates were imported from the European Food Safety Authority (EFSA) national zoonoses country reports[24] and other published reports.[25–33] Missing animal AMR data were extracted from sources following the inclusion criteria used to create ResistanceBank.[23,34] Details regarding the inclusion criteria for animal AMR data are reported in the appendix (p 11). Kernel density figures for the distribution of animal AMR data by species (cattle, chicken, and pig) are available in the appendix (p 18).

Human data were available from 1998 to 2017 and animal data were available from 2000 to 2019. Data from the most recent year provided by each country with available data were used to create the human and animal AMR variables.

For more on the **human and AMR variables** see http://www.resistancemap.cddep.org

The main independent variable was antibiotic consumption data for humans and animals; data obtained from ResistanceMap.[20,35] Human antibiotic consumption data were available from 2000 to 2015, depending on country, and were expressed in defined daily doses per 1000 individuals. Data from the most recent year provided by each country were used for all analyses. Animal antibiotic consumption data were from 2013 only and were modelled estimates measured in mg per population correction units.

Additional independent variables were on socioeconomic, environmental, antibiotic policy and regulation in humans and animals, and health-related indicators, extracted from the World Bank, UN, WHO, Global Burden of Disease, and National Centres for Environmental Information databases (table 2).[53–61]

Statistical analysis

First, we estimated the crude associations between AMR rates in humans and animals and our main independent variables with multiple β regressions. We tested different link functions for the conditional mean (eg, logit, probit, loglog, and cloglog) and determined that the best fit was given by the cloglog function based on the models' Akaike information criterion values.[62] Second, we employed univariate analyses by calculating Pearson's correlation between our dependent variables and all the additional independent variables (appendix pp 25–32); variables with statistically significant Pearson's values (p value less than 0·1) were included in subsequent analyses. Third, we tested the remaining explanatory variables for multicollinearity by using all remaining socioeconomic factors that had been significantly associated with at least one of the animal or human AMR variables (critical, high, or medium priority, and antibiotic–bacterium pairs). Highly correlated variables displaying a variance inflation factor of more than five were removed from the analysis. Fourth, a forward stepwise selection regression approach determined which of the remaining independent variables should be included in each of the final models. Beginning with each null model, independent variables were added one at a time, with the aim of improving the fit until the best performance ratio was found according to the models' Akaike information criterion values. We calculated global descriptive statistics of the dependent and independent variables that were included in the models (sample-restricted) and generated subgroup boxplots by WHO region and World Bank income groups for AMR rates. Finally, we set a multivariable β regression model for each dependent variable. The full multivariable model followed the structure detailed in the equation.

$$g(u_t) = \sum_{i=1}^{k} x_{ti}\beta_i$$

β equals $(\beta_{i=1},\ldots,\beta_{i=k})^T$ and is a vector of unknown regression parameters for each independent variable (κ; $\beta \in IR+$), and $x_{t,i=1},\ldots,x_{t,i=k}$ are observations on κ for each country (t). u_t represents the mean of our AMR rate variables (falling between 0 and 1) whereby conditional variance (dispersion parameter) follows the β density function (to model the mean of the response variable). The $g(u_t)$ term is monotonic and twice differentiable link function that maps variables whose values fall between 0 and 1 into IR. More details on multivariable β regression models and their specifications have been reported by Ferrari and Cribari-Neto.[63]

	Definition	Expected association with AMR
Socioeconomic and demographic indicators		
GDP based on purchasing power parity	GDP purchasing power parity by country; continuous variable presented in 2018 US$	Negative associations with AMR[9]
GINI index	The extent to which the distribution of income between individuals or households within an economy deviates from a perfectly equal distribution	Positive associations with AMR[36]
Current health expenditure	Percentage of gross domestic product spent on health care by country in 2016	Negative associations with AMR[9]
Hospital beds per 10 000 people	Number of hospital beds per 10 000 people by country	Negative associations with AMR[36]
Mortality rate attributable to unsafe WASH	Deaths attributable to unsafe WASH focusing on inadequate WASH services, expressed per 100 000 population	Positive associations with AMR[37]
Population density	Number of people divided by land area measured in km^2, most recent year available	Positive associations with AMR[38]
Net migration rate	Annual difference in number of immigrants and emigrants, most recent year available around 2018	Positive associations with AMR[39]
Median age of population	Median age of the population, UN projections for 2020	Positive associations with AMR[40]
Homeless people	Annual average number of homeless people due to natural disasters per 1 000 000 people, 2008–18	Positive associations with AMR[41]
Population in work	Percentage of population aged 15 years or older in the labour force, 2018	Negative associations with AMR[42]
Environmental indicators		
$PM_{2·5}$	Annual mean concentration of $PM_{2·5}$ (micrograms of gaseous pollutant per cubic meter of ambient air $\mu g/m^3$) in urban areas (2016)	Positive associations with AMR[43]
Average temperature (°C)	Average 12 monthly temperature in Celsius, 2016	Positive associations with AMR[10]
Health-related indicators		
Cardiovascular death rate per 100 000	Annual number of deaths per 100 000 people due to cardiovascular disease in 2017	Positive associations with AMR[44]
Obesity prevalence	Crude prevalence of obesity in adults (BMI ≥30 kg/m^2), 2016	Positive associations with AMR[45]
Governance indicators		
Control of corruption	Control of corruption captures perceptions of the extent to which public power is exercised for private gain, including both petty and grand forms of corruption, as well as capture of the state by elites and private interests*	Negative associations with AMR[46]
Voice and accountability	Voice and accountability captures perceptions of the extent to which a country's citizens are able to participate in selecting their government, as well as freedom of expression, freedom of association, and a free media*	Negative associations with AMR[46]
Rule of law	Rule of law captures perceptions of the extent to which agents have confidence in and abide by the rules of society, and in particular the quality of contract enforcement, property rights, the police, and the courts, as well as the likelihood of crime and violence*	Negative associations with AMR[46]
Regulatory quality	Regulatory quality captures perceptions of the ability of the government to formulate and implement sound policies and regulations that permit and promote private sector development*	Negative associations with AMR[46]
Antibiotic policy and regulation in humans and animals		
National monitoring systems for sales, prescription, and consumption of antibiotics in humans	Dummy variable indicating whether the country has a national monitoring system for the control of any of the following areas: antibiotic sales, antibiotic consumption, and antibiotic prescribing in humans in 2018 from the Tripartite AMR Country Self-Assessment Survey, 2018	Negative associations with AMR[47]
Country policies and regulation on antimicrobial use in humans	Country has policies and regulation on antimicrobial use (laws or regulations on prescription and sale of antimicrobials, for human use); it is a binary (yes *vs* no) question from the Tripartite AMR Country Self-Assessment Survey, 2018	Negative associations with AMR[48]
Country policies and regulation on antimicrobial use for growth promotion in animals	Country has laws or regulations that prohibits the use of antibiotics for growth promotion in the absence of risk analysis (binary [yes *vs* no] outcome) from the Tripartite AMR Country Self-Assessment Survey, 2018	Negative associations with AMR[47]
Arable land (percentage of land area)	Percentage of land area that is under temporary crops, temporary meadows for mowing or for pasture, land under market or kitchen gardens, and land temporarily fallow, 2018	Positive associations with AMR[49]
Cattle density	Global distribution of cattle expressed in total number of cattle per pixel (5 minute of arc), 2010[50,51]	Positive associations with AMR[52]

Positive association caused an increase in AMR; negative associations caused a decrease in AMR. Definitions and sources for the final independent variables used and all auxiliary independent variables tested but not included in multivariable analyses are reported in the appendix (p 4). Descriptive statistics of the independent variables by model analysed (per dependent variable) and sample (non-imputed raw model, analytical sample considering all raw independent variables, and model with imputed data) are included in the appendix (pp 33–53). AMR=Antimicrobial resistance. GDP=gross domestic product. WASH= water, sanitation, and hygiene. *Estimate gives the country's score on the aggregate indicator, in units of a standard normal distribution (ie, ranging from approximately −2·5 to 2·5), 2018.

Table 2: **Definition of the independent variables included in any of the final multivariable models**

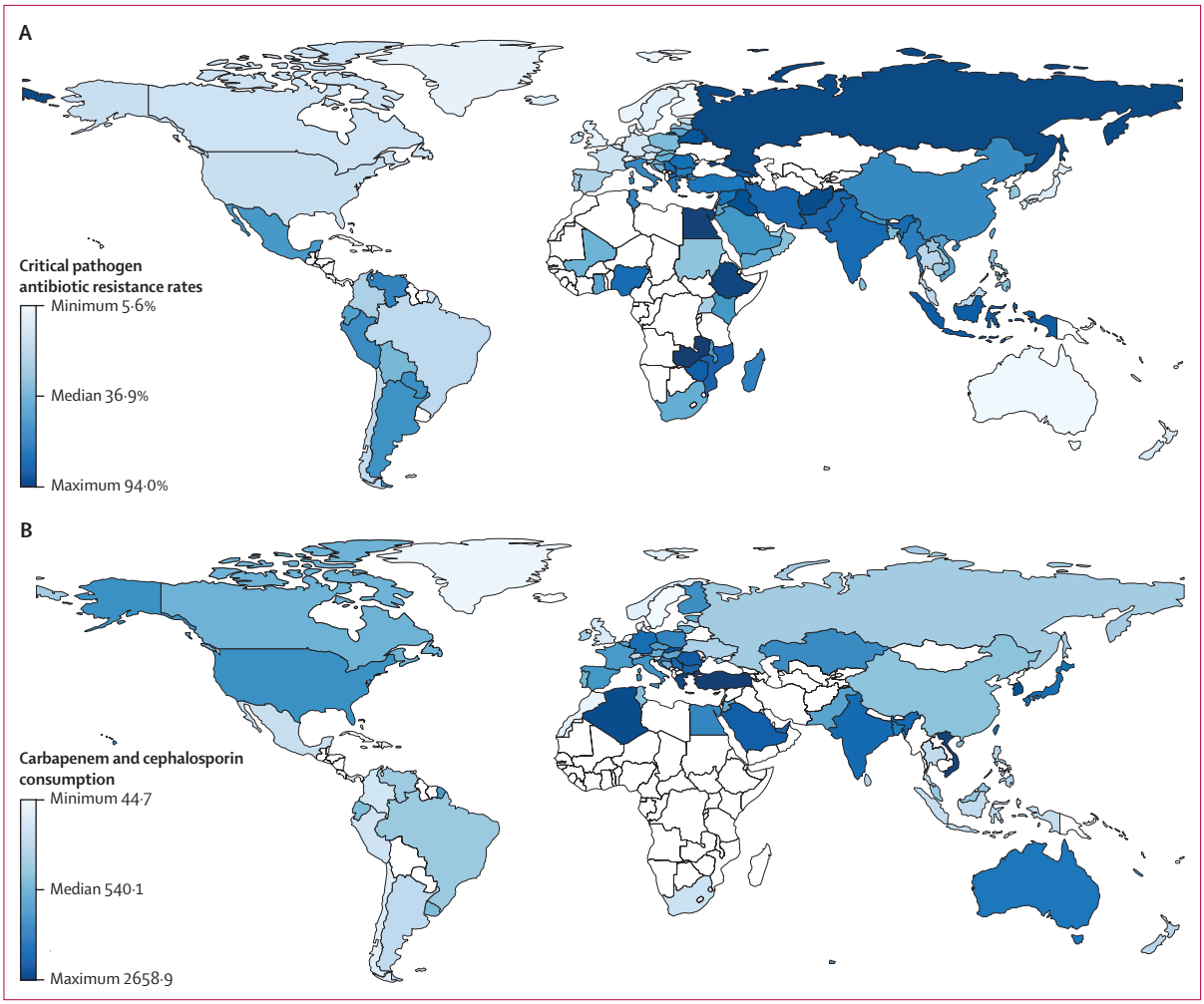

Figure 1: **Critical pathogen antibiotic resistance rates and carbapenem and cephalosporin consumption by country**
(A) Antibiotic-resistance rate in humans for the critical pathogens in humans (96 observations). (B) Antibiotic consumption (in DDDs) in humans for carbapenems and cephalosporins (73 observations). Countries in white represent those with missing data. Pearson's correlation between antibiotic resistance and consumption in humans was 0·30 (p=0·021). DDD=defined daily doses per 1000 individuals.

Each multivariable model included its respective antibiotic consumption data as a forced variable because it has been shown to be the main predictor of AMR rates in previous studies.[7,64] GDP was also incorporated for cross-country comparisons. Continuous variables were standardised (ie, mean subtracted and divided by the variable's SD) for better interpretability and comparability of the estimates in multivariable analyses. Pseudo R^2 is reported as goodness-of-fit for every model.

We assessed the validity of our findings by employing a leave-one-out cross-validation approach to determine the R^2, root mean squared errors, and mean absolute errors of our models after eliminating the i−1th observation from the model. We did a separate analyses for observed data only (excluding imputed observations) and eliminating highly influential countries as determined by their Cook's Distance values.[65] To ensure our model was consistent with recent estimates for antimicrobial sales volume in animals, we tested our model adding countries' amount of sales per kg obtained from Tiseo and colleagues.[8] This dataset provides the most recent data; however, it is restricted to only 41 countries, most of which were high income. We reran our animal model including species-specific AMR data as the dependent variable to assess whether there are differences by food-producing animal group. Finally, to retain statistical power in the multivariable analysis, all remaining independent variables were imputed to restrict the number of missing observations and to compare fully imputed with non-imputed models. We used a multivariable linear regression imputing approach for independent variables and with bootstrap sampling (n=1000 repetitions) using income class, urban population (%), life expectancy, mean years of schooling, population using at least basic sanitation services (%), population (total number), and human development index, as reference variables. All statistical analyses were done in Stata 17 and R studio (version 1.4.1106).

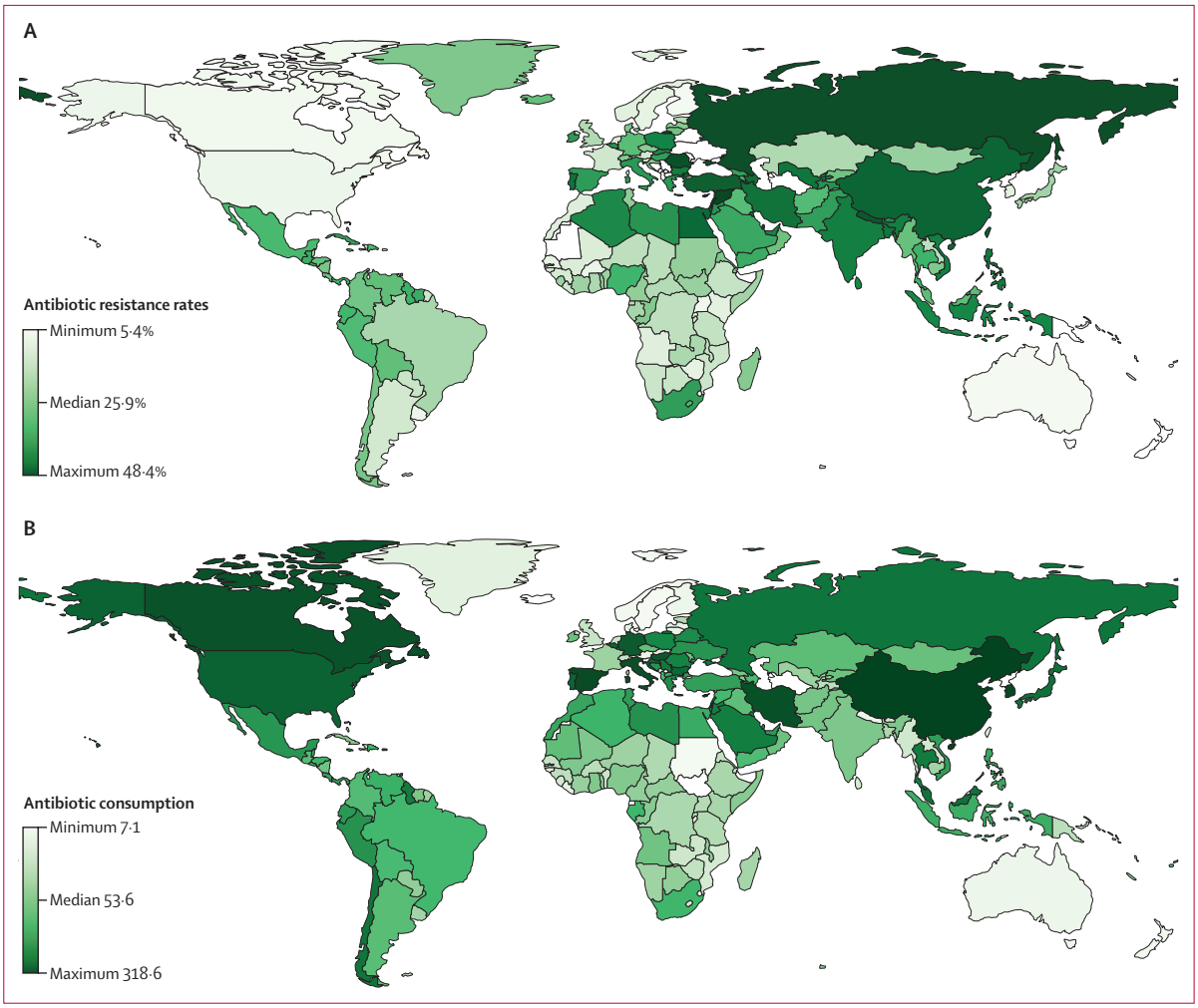

Figure 2: **Antibiotic resistance rates and antibiotic consumption in food-producing animals by country**
(A) Antibiotic resistance rate in animals (166 observations). (B) Estimated antibiotic consumption (mg per PCU) in animals (164 observations). Countries in white represent those with missing data. Pearson's correlation between antibiotic resistance and consumption in food-producing animals was 0·28 (p<0·0001). PCU=population correction unit.

Role of the funding source
There was no funding source for this study.

Results
Table 1 shows the raw descriptive statistics of the dependent and main independent variables included in the final regression models. The median prevalence of human pathogen resistance was 39·89% (IQR 23·09–45·68) for critical pathogens, 24·00% (15·00–41·00) for high priority pathogen, and 16·00% (6·00–29·00) for medium priority pathogens (penicillin-resistant *Streptococcus pneumoniae*) across all countries. For food-producing animals' median resistance prevalence was 24·80% (21·34–30·30). Carbapenem-resistant *A baumanii* (55·68%) and third generation cephalosporins-resistant *K pneumoniae* (53·11%) were the two highest prevalence antibiotic–bacterium combination pairs, whereas oxacillin-resistant *S aureus* (22·50%) and vancomycin-resistant *E faecium* (22·00%) were the two lowest. Figure 1 shows the levels of critical priority pathogen's AMR and carbapenem and cephalosporin consumption in humans. Figure 2 shows AMR and carbapenem and cephalosporin consumption in food-producing animals. Detailed AMR rates and antibiotic consumption levels for humans and animals by World Bank income class and WHO region are shown in the appendix (pp 19–24). The highest rates of resistance for all human pathogens were observed in LMICs, whereas the lowest rates of resistance were found in HICs. Yet, HICs reported the greatest proportion of AMR in food-producing animals, and LMICs the lowest (appendix p 22). The European region consistently reported the lowest average human AMR rates compared with other regions (appendix p 21). Charts per specific antibiotic–bacterium combinations showed large differences in human AMR levels for LMICs among oxacillin-resistant *S aureus* and penicillin-resistant *S pneumoniae* from the Eastern Mediterranean

	OR (95% CI)	p value
WHO critical human pathogen AMR (n=60; R^2 86·4%)		
Consumption of carbapenems and cephalosporins in humans (DDDs)*	1·06 (1·00–1·12)	0·035
Antibiotic consumption in animals (mg per PCU)*	1·07 (1·01–1·13)	0·020
GDP (ppp)*	0·88 (0·76–1·02)	0·081
Control of corruption*	0·65 (0·54–0·79)	<0·0001
Cardiovascular death rate per 100 000 people*	1·18 (1·08–1·28)	<0·0001
Current health expenditure (percentage of GDP)*	0·96 (0·88–1·04)	0·34
GINI index*	1·13 (1·07–1·19)	<0·0001
$PM_{2·5}$*	1·11 (1·04–1·18)	<0·0001
National monitoring systems for sales, prescription, and consumption of antibiotics in humans	0·89 (0·78–1·00)	0·043
Constant term	0·01 (0·01–0·01)	<0·0001
WHO high priority human pathogen AMR (n=56; R^2 58·4%)		
Consumption of oxacillin and glycopeptides in humans (DDDs)*	1·22 (1·09–1·37)	<0·0001
Antibiotic consumption in animals (total sales in kg)*	1·15 (1·00–1·32)	0·049
Median age of population*	0·96 (0·93–0·99)	0·0071
Average temperature (°C)*	1·20 (1·03–1·39)	0·017
GDP (ppp)*	0·72 (0·63–0·82)	<0·0001
Voice and accountability*	0·83 (0·73–0·95)	0·0062
National monitoring systems for sales, prescription, and consumption of antibiotics in humans	0·78 (0·80–1·03)	0·080
Population density*	1·11 (1·06–1·16)	<0.0001
Constant term	0·05 (0·02–0·14)	<0·0001
WHO medium priority human pathogen AMR† (N=40; R^2 70·8%)		
Consumption of penicillin in humans (DDDs)*	0·96 (0·80–1·15)	0·65
Antibiotic consumption in animals (mg per PCU)*	1·05 (0·87–1·26)	0·60
GDP (ppp)*	1·32 (0·94–1·84)	0·11
$PM_{2·5}$*	1·30 (1·01–1·67)	0·040
Regulatory quality*	0·42 (0·28–0·63)	<0·0001
Mortality rate attributable to unsafe WASH*	1·17 (1·02–1·36)	0·029
Constant term	0·01 (0·00–0·01)	<0·0001
AMR in food-producing animals (n=63; R^2 49·6%)		
Antibiotic consumption in animals (mg per PCU)*	1·05 (1·01–1·10)	0·013
Consumption of carbapenems and cephalosporins in humans (DDDs)*	1·05 (1·01–1·09)	0·010
GDP (ppp)*	1·04 (0·93–1·16)	0·49
Average temperature (°C)*	0·97 (0·89–1·06)	0·54
Current health expenditure (percentage of GDP)*	0·91 (0·83–0·99)	0·037
Rule of law*	0·82 (0·69–0·98)	0·027
Cattle density*	1·02 (0·97–1·08)	0·38
Country policies and regulation on antimicrobial use for growth promotion in animals	0·83 (0·69–1·02)	0·078
Arable land (percentage of land area)*	1·04 (0·96–1·12)	0·31
GINI index*	1·01 (0·94–1·10)	0·74
Constant term	0·01 (0·01–0·01)	<0·0001

Data are OR (95% CI). n is the number of countries. p values were derived from the Wald test. Pseudo R^2 were calculated. An illustrative explanation of the marginal association between $PM_{2·5}$ and GDP ppp with AMR critical priority levels is reported in the appendix (p 67). Same models containing imputed data are included in the appendix (p 71). DDD=defined daily doses per 1000 individuals. GDP=gross domestic product. OR=odds ratio. PCU=population correction units. ppp=purchasing power parity. *Variables were standardised (ie, mean subtracted and divided by their SD). †WHO medium priority human pathogen classification only included penicillin-resistant *Streptococcus pneumoniae*.

Table 3: **Multivariable β regression model results for the association between AMR in human pathogens and associated risk factors, and AMR in food-producing animals and associated risk factors**

region (appendix pp 23–24). Rates of Enterobacteriaceae resistant to third generation cephalosporins or carbapenems were between 2-times and 2·5-times higher for LMICs compared with HICs. Carbapenem-resistant *P aeruginosa* and *A baumanii* were highly prevalent in upper-middle-income countries from the European region, compared with the other World Bank income groups and WHO regions. Descriptive statistics of the additional independent variables are included in the appendix (pp 33–55). A full list of the countries included in final analyses (analytical sample) by independent variable is included in the appendix (p 56).

Consumption of carbapenems and cephalosporins was significantly associated with increased AMR in critical human pathogens (appendix p 59). Similarly, antibiotic consumption and AMR levels in food-producing animals were positively associated. AMR levels in high and medium priority pathogens were not associated with oxacillin and glycopeptide consumption and penicillin consumption. Third generation cephalosporins and oxacillin consumption were significantly associated with higher AMR levels in *K pneumoniae*, *E coli*, and *S aureus* (appendix p 59).

Table 3 shows the final β regression model outputs by WHO priority pathogens list and table 4 shows the final β regression by specific antibiotic–bacterium pairs. In the critical human pathogen model, carbapenem and cephalosporin consumption in humans (OR 1·06 [95% CI 1·00–1·12]; p=0·035), antibiotic consumption in food-producing animals (1·07 [1·01–1·13]; p=0·020), cardiovascular death rate, GINI index, and $PM_{2·5}$ were associated with an increase in AMR (positively associated with AMR; R^2 86·4%). For instance, a change of one standard deviation in $PM_{2·5}$ resulted in a 1·11 SD increase in critical human pathogen AMR (appendix p 67).

In the high priority human pathogens model, AMR was positively associated with oxacillin and glycopeptides consumption in humans (OR 1·22 [95% CI 1·09–1·37]; p<0·0001), average temperature, and population density, but inversely associated with GDP (purchasing power parity), countries' voice and accountability, and median age of the population (R^2 58·4%). In the medium priority pathogens model, countries' regulatory quality was associated with a decrease in AMR (negatively associated), but mortality rate attributable to unsafe WASH and $PM_{2·5}$ was positively associated with AMR (R^2 70·8%). Antibiotic consumption in animals (OR 1·05 [95% CI 1·01–1·10]; p=0·013), carbapenems and third generation cephalosporins consumption in humans (1·05 [1·01–1·09]; p=0·010), countries' percentage of arable land, and GINI index were positively associated with resistance in food-producing animals, whereas rule of law was negatively associated with AMR (R^2 49·6%).

The results of the predictive analysis that compared rates of AMR in food-producing animals and critical human pathogens after adjusting for the independent variables are reported in the appendix (p 77). LMICs,

particularly from the Eastern Mediterranean and South-East Asia regions, were predicted to have the highest AMR rates in humans and animals.

Higher antibiotic consumption in humans was associated with greater resistance in almost every antibiotic–bacterium respective pair (table 4). Antibiotic consumption in animals was positively associated with rates of third generation cephalosporins-resistant *E coli* (OR 1·09 [95% CI 1·01–1·19]; p=0·041), oxacillin-resistant *S aureus* (1·11 [1·01–1·21]; p=0·023), and carbapenem-resistant *A baumanii* (1·24 [1·12–1·37]; p<0·0001). Governance indicators (eg, rule of law, voice and accountability, regulatory quality, and control of corruption) and countries policies to monitor and control AMR were consistently associated with lower AMR.

We did not find significant changes in our estimates after using the leave-one-out approach (appendix p 68). The results of our analysis that restricted the dependent variable of the animal model by food-producing animal species are detailed in the appendix (p 69); no substantial change was observed. Our models were consistent with Tiseo and colleagues[8] after using antimicrobial sales as a proxy of antibiotic consumption (appendix p 70). Additionally, most estimates were consistent with our study results after the sensitivity analyses with fully imputed data and by removing highly influential data points (appendix pp 71–76).

Discussion

AMR is crucial to a complex network of stakeholders with different priorities, which restricts the means with which to frame the challenge and drive a response.[66] For instance, important gaps remain in our knowledge of similarities and differences between risk factors for AMR in humans and in animals. We collated data for variables that had identified associations with either human or animal AMR. Analysing these together for country-level associations has provided an important step in elucidating these knowledge gaps.

Antimicrobial consumption is routinely implicated as the key driver for AMR, with compelling evidence for dose dependence in populations of animals and humans.[7,67] We showed that, even after adjusting for other covariates as identified from reviewing the literature, there were significant associations between animal antimicrobial consumption and AMR in food-producing animals, and between human antimicrobial consumption and AMR specifically in WHO critical and high priority pathogens. The WHO global priority list of antibiotic-resistant bacteria was formulated in 2017 with the intention of guiding research, discovery, and development of new drugs,[19] but it has also informed intervention policies targeting these priorities.[68] The human drug–pathogen pairings with the most increased odds of resistance were carbapenem (and cephalosporins) and *P aeruginosa* and carbapenem (and cephalosporins) and *A baumanii*; both of which feature in the 2022 Global Burden of Disease report's leading pathogens for deaths associated with resistance.[3] Data were too scarce to specify equivalently prominent

	OR (95% CI)	p value
Carbapenem-resistant *Acinetobacter baumanii* (n=50; R^2 84·0%)		
Consumption of carbapenems and cephalosporins in humans (in DDDs)*	1·14 (1·06–1·24)	<0·0001
Antibiotic consumption in animals (mg per PCU)*	1·24 (1·12–1·37)	<0·0001
GDP (ppp)*	1·13 (0·95–1·35)	0·17
Control of corruption*	0·48 (0·38–0·60)	<0·0001
Net migration rate*	0·76 (0·68–0·84)	<0·0001
Labour force participation rate*	0·87 (0·80–0·95)	0·011
National monitoring systems for sales, prescription, and consumption of antibiotics in humans	0·67 (0·56–0·81)	<0·0001
Obesity prevalence*	1·01 (0·89–1·14)	0·89
Average temperature (°C)*	1·23 (1·08–1·39)	<0·0001
Hospital beds per 10 000 people*	1·01 (0·88–1·15)	0·89
Population density*	0·96 (0·84–1·09)	0·70
Constant term	0·02 (0·02–0·02)	<0·0001
Carbapenem-resistant *Pseudomonas aeruginosa* (n=35; R^2 60·3%)		
Consumption of carbapenems and cephalosporins in humans (in DDDs)*	1·29 (1·09–1·53)	0·0039
Antibiotic consumption in animals (mg per PCU)*	1·10 (0·88–1·38)	0·39
GDP (ppp)*	1·04 (0·81–1·34)	0·74
Median age of population*	1·06 (0·78–1·44)	0·71
Hospital beds per 10 000 people*	1·05 (0·85–1·30)	0·64
Cardiovascular death rate per 100 000 people*	1·43 (1·00–2·06)	0·042
Mortality rate attributable to unsafe WASH*	1·09 (0·90–1·33)	0·37
National monitoring systems for sales, prescription, and consumption of antibiotics in humans	1·42 (0·84–2·39)	0·19
Voice and accountability*	0·55 (0·35–0·85)	0·0083
Constant term	0·01 (0·00–0·01)	<0·0001
Third generation cephalosporins-resistant *Escherichia coli* (n=57; R^2 85·6%)		
Consumption of cephalosporins in humans (in DDDs)*	1·10 (1·00–1·21)	0·061
Antibiotic consumption in animals (mg per PCU)*	1·09 (1·01–1·19)	0·041
GDP (ppp)*	1·02 (0·88–1·18)	0·83
Regulatory quality*	0·50 (0·44–0·58)	<0·0001
Mortality rate attributable to unsafe WASH*	1·10 (1·03–1·17)	0·0049
Country policies and regulation on antimicrobial use in humans	0·90 (0·87–0·92)	<0·0001
Population density*	1·17 (1·12–1·23)	<0·0001
GINI index*	1·09 (0·99–1·20)	0·074
National monitoring systems for sales, prescription, and consumption of antibiotics in humans	0·66 (0·50–0·85)	0·0048
Constant term	0·01 (0·01–0·01)	<0·0001
Third generation cephalosporins-resistant *Klebsiella pneumoniae* (n=59; R^2 79·1%)		
Consumption of cephalosporins in humans (in DDDs)*	1·07 (0·98–1·18)	0·13
Antibiotic consumption in animals (mg per PCU)*	1·08 (0·96–1·20)	0·19
GDP (ppp)*	0·83 (0·69–1·01)	0·058
Regulatory quality*	0·69 (0·58–0·82)	<0·0001
Cardiovascular death rate per 100 000 people*	1·27 (1·13–1·43)	<0·0001
GINI index*	1·17 (1·05–1·31)	0·0051
National monitoring systems for sales, prescription, and consumption of antibiotics in humans	0·86 (0·71–1·04)	0·13
Hospital beds per 10 000 people*	1·00 (0·91–1·09)	0·92
Constant term	0·01 (0·01–0·02)	<0·0001

(Table 4 continues on next page)

	OR (95% CI)	p value
(Continued from previous page)		
Oxacillin-resistant *Staphylococcus aureus* (n=48; R^2 79·9%)		
Consumption of oxacillin in humans (in DDDs)*	1·17 (1·03–1·28)	0·040
Antibiotic consumption in animals (mg per PCU)*	1·11 (1·01–1·21)	0·023
GDP (ppp)*	0·73 (0·59–0·91)	0·0047
National surveillance system for AMR in humans	0·70 (0·60–0·82)	<0·0001
Homeless people*	1·16 (1·10–1·22)	<0·0001
$PM_{2·5}$*	1·10 (0·93–1·29)	0·26
Average temperature (°C)*	1·30 (1·08–1·57)	<0·0001
Population density*	1·12 (1·01–1·25)	0·040
Constant term	0·01 (0·01–0·01)	<0·0001
Vancomycin-resistant *Enterococcus faecium* (n=33; R^2 54·3%)		
Consumption of glycopeptides in humans (in DDDs)*	1·52 (1·15–2·01)	0·0059
Antibiotic consumption in animals (mg per PCU)*	0·91 (0·72–1·15)	0·43
GDP (ppp)*	0·66 (0·34–1·28)	0·22
National surveillance system for AMR in humans	0·58 (0·43–0·78)	<0·0001
Voice and accountability*	1·03 (0·68–1·57)	0·88
$PM_{2·5}$ (scale ×10)*	1·41 (1·01–1·98)	0·043
Hospital beds per 10 000 people*	1·21 (0·89–1·63)	0·22
Constant term	0·01 (0·01–0·01)	<0·0001

Data are OR (95% CI). n is the number of countries. Pseudo R^2 were calculated. Same models containing imputed data are reported in the appendix (p 72). p value derived from the Wald test. Robust standard errors were used. DDD=defined daily doses per 1000 individuals. GDP=gross domestic product. n=number of countries. OR=odds ratio. PCU=population correction units. ppp=purchasing power parity. *Variables were standardised (ie, mean subtracted and divided by their standard deviation).

Table 4: **Multivariable β regression model results for the association between AMR in human pathogens and associated risk factors, by specific bacterium–antibiotic pairs**

drug–pathogen pairings for animals, highlighting a reconcilable disparity in routine AMR reporting between these One Health sectors.

Antimicrobial consumption in animals was significantly associated with resistance in WHO critical priority human pathogens, and antimicrobial consumption in humans was significantly associated with animal AMR rates. A joint interagency report on integrated analysis of antimicrobial consumption and occurrence of AMR in bacteria from humans and food-producing animals sought to establish associations between data from Europe,[69] but did not find a link between antimicrobial consumption in humans and AMR in animals. Whereas their univariate analysis did find an association between consumption in animals and AMR in humans, statistical significance was not retained following multivariable analysis. To the best our knowledge, our study is the first to identify these bidirectional animal–human associations globally. Retained significance of bidirectionality at this scale, and after adjusting for other covariates, contributes important evidence to the One Health paradigm. Not all implications are necessarily pessimistic. Tang and colleagues[16] describe the benefits to human health of livestock-based stewardship programmes, highlighting the potential for targeting single One Health components with interventions but having system-wide effects.

We found significant associations between AMR and several socioeconomic factors. Results from the multivariable analysis showed significant positive associations between human AMR and the GINI index (WHO critical priority), and increased mortality rate attributable to either unsafe WASH (WHO medium priority) or to cardiovascular complications (WHO critical priority). Significant negative associations were found with GDP (WHO high priority), and national monitoring systems for sales, prescription, and consumption of antibiotics in humans (WHO critical priority). Therefore, our models are consistent with previous literature, showing that factors indicative of lower socioeconomic status are associated with higher levels of AMR in humans.[9] These associations are probably explained by the uncontrolled dissemination of resistant bacteria that can occur in settings in which sanitation services are inadequate and access to health care is reduced.

Governance indicators were closely, and intuitively, linked with AMR in animals and humans. Significant negative associations were found with rule of law (animal), regulatory quality (WHO medium priority), voice and accountability (WHO high priority), and control of corruption (WHO critical priority). The order of magnitude of effect was considerable, with halved odds of carbapenem-resistant *A baumanii*, carbapenem-resistant *P aeruginosa*, and third generation cephalosporins-resistant *E coli*, all associated with more reliable governance. This corroborates earlier reports describing the contributions of poor governance and corruption to human AMR,[46] but our results expand their importance to the One Health context.

This study had some limitations. Crucially, there were a lot of missing data: the small number of AMR datasets available for LMICs might have biased our results. Data paucity was worse for the components of animal health meaning that potentially important risk factors, such as wild animal AMR reservoirs, could not be included. It also meant we used modelled estimates of antibiotic consumption in animals, which potentially risked biasing our results. Country-level data on rates of AMR in food-producing animals were also scarce, and the data available for different animal species and zoonotic pathogens differed by country. Data on food-producing animals were all grouped together in our analysis. When these data become more refined, a more species-specific analysis will provide improved granularity to our understanding.

Even though we used the best available data, there remained inconsistencies in the exact year of data collection, the numbers of included countries by WHO region and World Bank income groups, and bacteria reported. There were also limitations in the analytical component of this work. The effectiveness of stepwise

regression as a method of variable selection can sometimes be compromised when a large number of predictor variables are considered.[70] Additionally, β regression models do not correct estimates for skewed data.[63] For example, β-binomial regression accounts for the difference in the availability of testing between countries, particularly between HICs and LMICs.[71] However, for most countries, the isolate-level data required for this alternative approach was unavailable. Finally, because this was an ecological country-level study, any interpretation should be taken with caution because the results might be affected by the absence of variation over aggregated data usage (ie, ecological fallacy).

Our findings suggest that socioeconomic factors play an underappreciated role in the spread of AMR, and antibiotic consumption is potentially only a secondary risk factor in certain regions of the world in which antimicrobial drug consumption is low and resistance rates are high. Preventing spread of AMR will require national action plans beyond the reduction in antibiotic misuse and must involve efforts to improve governance and sanitation infrastructure. Bidirectionality between animals and humans in antimicrobial consumption and resistance emphasises the need for integrated control methods that aim to prevent transmission across different One Health domains. LMICs, particularly in Asia (eg, Bangladesh, China, and India), were shown to have the highest AMR rates in food-producing animals after adjusting for other variables in this study. This finding highlights the pressing need for better AMR surveillance and control efforts in LMICs.

Contributors

KA and LY conceptualised the study and designed the methods and data provision. KA and LD collated and extracted the data. All authors had access and verified the data. AH, KA, and LD collected, extracted, and verified the data. All authors had access to the data. KA and LD did the formal analysis. KA and LD wrote the original draft. KA, LD, LY, AH, CEM, RL, TVB, and LF-K reviewed and edited the manuscript. KA and LY supervised the study. All authors have read and approved the final version of the manuscript and take responsibility for the decision to submit for publication.

Declaration of interests

We declare no competing interests.

Data sharing

Most data are publicly available. CDDEP data are available upon formal request (https://resistancemap.cddep.org).

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References

1 Mestrovic T, Aguilar GR, Swetschinski LR, et al. The burden of bacterial antimicrobial resistance in the WHO European region in 2019: a cross-country systematic analysis. *Lancet Public Health* 2022; **7:** e897–913.

2 Ikuta KS, Swetschinski LR, Aguilar GR, et al. Global mortality associated with 33 bacterial pathogens in 2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet* 2022; **400:** 2221–48.

3 Murray CJL, Ikuta KS, Sharara F, et al. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. *Lancet* 2022; **399:** 629–55.

4 The Center for Disease Dynamics, Economics & Policy. State of the world's antibiotics 2021: a global analysis of antimicrobial resistance and its drivers. Washington, DC: Center for Disease Dynamics, Economics & Policy, 2021.

5 Burmeister AR. Horizontal gene transfer. *Evol Med Public Health* 2015; **2015:** 193–94.

6 Holmes AH, Moore LSP, Sundsfjord A, et al. Understanding the mechanisms and drivers of antimicrobial resistance. *Lancet* 2016; **387:** 176–87.

7 Bell BG, Schellevis F, Stobberingh E, Goossens H, Pringle M. A systematic review and meta-analysis of the effects of antibiotic consumption on antibiotic resistance. *BMC Infect Dis* 2014; **14:** 13.

8 Tiseo K, Huber L, Gilbert M, Robinson TP, Van Boeckel TP. Global trends in antimicrobial use in food animals from 2017 to 2030. *Antibiotics* 2020; **9:** 918.

9 Collignon P, Beggs JJ, Walsh TR, Gandra S, Laxminarayan R. Anthropological and socioeconomic factors contributing to global antimicrobial resistance: a univariate and multivariable analysis. *Lancet Planet Health* 2018; **2:** e398–405.

10 Reverter M, Sarter S, Caruso D, et al. Aquaculture at the crossroads of global warming and antimicrobial resistance. *Nat Commun* 2020; **11:** 1870.

11 Sun R, Yao T, Zhou X, Harbarth S, Lin L. Non-biomedical factors affecting antibiotic use in the community: a mixed-methods systematic review and meta-analysis. *Clin Microbiol Infect* 2022; **28:** 345–54.

12 Chatterjee A, Modarai M, Naylor NR, et al. Quantifying drivers of antibiotic resistance in humans: a systematic review. *Lancet Infect Dis* 2018; **18:** e368–78.

13 Okeke IN, Edelman R. Dissemination of antibiotic-resistant bacteria across geographic borders. *Clin Infect Dis* 2001; **33:** 364–69.

14 Lazarus B, Paterson DL, Mollinger JL, Rogers BA. Do human extraintestinal *Escherichia coli* infections resistant to expanded-spectrum cephalosporins originate from food-producing animals? A systematic review. *Clin Infect Dis* 2015; **60:** 439–52.

15 Vieira AR, Collignon P, Aarestrup FM, et al. Association between antimicrobial resistance in *Escherichia coli* isolates from food animals and blood stream isolates from humans in Europe: an ecological study. *Foodborne Pathog Dis* 2011; **8:** 1295–301.

16 Tang KL, Caffrey NP, Nóbrega DB, et al. Restricting the use of antibiotics in food-producing animals and its associations with antibiotic resistance in food-producing animals and human beings: a systematic review and meta-analysis. *Lancet Planet Health* 2017; **1:** e316–27.

17 Woolhouse M, Ward M, Van Bunnik B, Farrar J. Antimicrobial resistance in humans, livestock and the wider environment. *Philos Trans R Soc Lond B Biol Sci* 2015; **370:** 20140083.

18 Skurnik D, Ruimy R, Andremont A, et al. Effect of human vicinity on antimicrobial resistance and integrons in animal faecal *Escherichia coli*. *J Antimicrob Chemother* 2006; **57:** 1215–19.

19 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:** 318–27.

20 The Centre for Disease Dynamics Economics and Policy. ResistanceMap. 2021. https://resistancemap.cddep.org/ (accessed Aug 20, 2021).

21 WHO. Global antimicrobial resistance surveillance system (GLASS) report: early implementation 2020. Geneva: World Health Organization, 2020.

22 Pan American Health Organisation. Antimicrobial Resistance. 2019. https://www.paho.org/en/topics/antimicrobial-resistance (accessed Aug 20, 2021).

23 Criscuolo NG, Pires J, Zhao C, Van Boeckel TP. Resistancebank.org, an open-access repository for surveys of antimicrobial resistance in animals. *Sci Data* 2021; **8:** 189.

24 European Food Safety Authority. Biological Hazards Reports. 2021. https://www.efsa.europa.eu/en/data-report/biological-hazards-reports (accessed Dec 26, 2022).

25 European Food Safety Authority & European Centre for Disease Prevention and Control. The European Union summary report on antimicrobial resistance in zoonotic and indicator bacteria from humans, animals and food in 2018/2019. 2021. https://www.ecdc.europa.eu/en/publications-data/EU-summary-report-antimicrobial-resistance-zoonoses-2018-2019 (accessed Feb 20, 2022).

26 Abraham S, Jordan D, Wong HS, et al. First detection of extended-spectrum cephalosporin- and fluoroquinolone-resistant Escherichia coli in Australian food-producing animals. *J Glob Antimicrob Resist* 2015; **3:** 273–77.

27 Shurgold J, Avery B, Volling C, et al. Canadian antimicrobial resistance surveillance system report. Public Health Agency of Canada, 2020. 2020. https://www.canada.ca/en/public-health/services/publications/drugs-health-products/canadian-antimicrobial-resistance-surveillance-system-2020-report.html (accessed Sept 15, 2022).

28 Shimazaki Y, Ozawa M, Matsuda M, et al. Report on the Japanese veterinary antimicrobial resistance monitoring system 2016–2017. 2020. https://www.maff.go.jp/nval/yakuzai/pdf/200731_JVARMReport_2016-2017.pdf (accessed Feb 27, 2023).

29 Makarov DA, Ivanova OE, Karabanov SY, Gergel MA, Pomazkova AV. Antimicrobial resistance of commensal *Escherichia coli* from food-producing animals in Russia. *Vet World* 2020; **13:** 2053–61.

30 Kim S-J, Moon DC, Mechesso AF, et al. Nationwide surveillance on antimicrobial resistance profiles of *Staphylococcus aureus* isolated from major food animal carcasses in South Korea during 2010-2018. *Foodborne Pathog Dis* 2021; **18:** 388–97.

31 US FDA. NARMS Now: integrated data. https://www.fda.gov/animal-veterinary/national-antimicrobial-resistance-monitoring-system/narms-now-integrated-data (accessed Dec 12, 2021).

32 NORM/NORM-VET. 2020. Usage of antimicrobial agents and occurrence of antimicrobial resistance in Norway. Oslo: Norwegian Institute of Public Health, 2021.

33 Technical University of Denmark. DANMAP 2020. 2020. https://www.ssi.dk/-/media/arkiv/subsites/antibiotikaresistens/danmap_2020_07102021_version-2_low.pdf (accessed Sept 20, 2022).

34 Van Boeckel TP, Pires J, Silvester R, et al. Global trends in antimicrobial resistance in animals in low- and middle-income countries. *Science* 2019; **365:** eaaw1944.

35 Van Boeckel TP, Glennon EE, Chen D, et al. Reducing antimicrobial use in food animals. *Science* 2017; **357:** 1350–52.

36 Alvarez-Uria G, Gandra S, Laxminarayan R. Poverty and prevalence of antimicrobial resistance in invasive isolates. *Int J Infect Dis* 2016; **52:** 59–61.

37 Musoke D, Namata C, Lubega GB, et al. The role of environmental health in preventing antimicrobial resistance in low- and middle-income countries. *Environ Health Prev Med* 2021; **26:** 100.

38 Bruinsma N, Hutchinson JM, van den Bogaard AE, Giamarellou H, Degener J, Stobberingh EE. Influence of population density on antibiotic resistance. *J Antimicrob Chemother* 2003; **51:** 385–90.

39 Desai AN, Mohareb AM, Hauser N, Abbara A. Antimicrobial resistance and human mobility. *Infect Drug Resist* 2022; **15:** 127–33.

40 Cassini A, Högberg LD, Plachouras D, et al. Attributable deaths and disability-adjusted life-years caused by infections with antibiotic-resistant bacteria in the EU and the European Economic Area in 2015: a population-level modelling analysis. *Lancet Infect Dis* 2019; **19:** 56–66.

41 Gyarmathy VA, Neaigus A, Ujhelyi E. Vulnerability to drug-related infections and co-infections among injecting drug users in Budapest, Hungary. *Eur J Public Health* 2009; **19:** 260–65.

42 Pulingam T, Parumasivam T, Gazzali AM, et al. Antimicrobial resistance: prevalence, economic burden, mechanisms of resistance and strategies to overcome. *Eur J Pharm Sci* 2022; **170:** 106103.

43 Xie J, Jin L, He T, et al. Bacteria and antibiotic resistance genes (ARGs) in $PM_{2.5}$ from China: implications for human exposure. *Environ Sci Technol* 2019; **53:** 963–72.

44 Harbarth S, Samore MH, Lichtenberg D, Carmeli Y. Prolonged antibiotic prophylaxis after cardiovascular surgery and its effect on surgical site infections and antimicrobial resistance. *Circulation* 2000; **101:** 2916–21.

45 Sarmiento MRA, de Paula TO, Borges FM, et al. Obesity, xenobiotic intake and antimicrobial-resistance genes in the human gastrointestinal tract: a comparative study of eutrophic, overweight and obese individuals. *Genes* 2019; **10:** 349.

46 Collignon P, Athukorala PC, Senanayake S, Khan F. Antimicrobial resistance: the major contribution of poor governance and corruption to this growing problem. *PLoS One* 2015; **10:** e0116746.

47 WHO. Global antimicrobial resistance and use surveillance system (GLASS) report: 2021. 2021. https://www.who.int/publications/i/item/9789240027336 (accessed Jan 10, 2022).

48 Rogers Van Katwyk S, Grimshaw JM, Nkangu M, et al. Government policy interventions to reduce human antimicrobial use: a systematic review and evidence map. *PLoS Med* 2019; **16:** e1002819.

49 Ramos B, Rosalino LM, Palmeira JD, Torres RT, Cunha MV. Antimicrobial resistance in commensal *Staphylococcus aureus* from wild ungulates is driven by agricultural land cover and livestock farming. *Environ Pollut* 2022; **303:** 119116.

50 Gilbert M, Nicolas G, Cinardi G, et al. Global distribution data for cattle, buffaloes, horses, sheep, goats, pigs, chickens and ducks in 2010. *Sci Data* 2018; **5:** 180227.

51 Gilbert M, Nicolas G, Cinardi G, Van Boeckel T, Vanwambeke S, Wint W. Global cattle distribution in 2010 (5 minutes of arc). 2018. https://dataverse.harvard.edu/dataset.xhtml?persistentId=doi:10.7910/DVN/GIVQ75 (Sept 25, 2022).

52 Van Boeckel TP, Brower C, Gilbert M, et al. Global trends in antimicrobial use in food animals. *Proc Natl Acad Sci USA* 2015; **112:** 5649–54.

53 Population Division UN Department of Economic and Social Affairs. World Population Prospects 2019. 2019. https://population.un.org/wpp/ (accessed Aug 20, 2021).

54 The World Bank. World development indicators. 2021. https://data.worldbank.org/indicator (accessed Aug 20, 2021).

55 Population Division UN Department of Economic and Social Affairs. World population prospects: the 2017 revision. Key Findings and Advance Tables, 2017. https://population.un.org/wpp/publications/files/wpp2017_keyfindings.pdf (accessed Feb 27, 2023).

56 Statistics Division UN. UNdata. 2021. http://data.un.org/ (Aug 20, 2021).

57 UN Development Program. Human development data centre. 2021. https://hdr.undp.org/data-center (accessed Feb 27, 2023).

58 WHO. The global health observatory, indicator metadata registry list. 2021. https://www.who.int/data/gho/indicator-metadata-registry (accessed Aug 20, 2021).

59 NOAA National Centres for Environmental Information. Climate at a glance: global time series. 2020. https://www.ncdc.noaa.gov/ (accessed Aug 20, 2021).

60 WHO. Global health observatory data repository. 2021. https://apps.who.int/gho/data/node.main (accessed Aug 20, 2021).

61 Institute for Health Metrics and Evaluation. GBD compare data visualization. Seattle, WA: IHME, University of Washington. 2020. http://www.healthdata.org/data-visualization/gbd-compare (accessed Aug 20, 2021).

65 Sakamoto Y, Ishiguro M, Kitagawa G. Akaike information criterion statistics. Dordrecht: D Reidel, 1986.

63 Ferrari S, Cribari-Neto F. Beta regression for modelling rates and proportions. *J Appl Stat* 2004; **31:** 799–815.

64 Meyer E, Gastmeier P, Deja M, Schwab F. Antibiotic consumption and resistance: data from Europe and Germany. *Int J Med Microbiol* 2013; **303:** 388–95.

65 Cook RD. Cook's distance. In: Lovric M, ed. International encyclopedia of statistical science. Berlin: Springer, 2011: 301–02.

66 Legido-Quigley H, Khan MS, Durrance-Bagale A, Hanefeld J. Something borrowed, something new: a governance and social construction framework to investigate power relations and responses of diverse stakeholders to policies addressing antimicrobial resistance. *Antibiotics* 2018; **8:** 3.

67 Tang KL, Caffrey NP, Nóbrega DB, et al. Comparison of different approaches to antibiotic restriction in food-producing animals: stratified results from a systematic review and meta-analysis. *BMJ Glob Health* 2019; **4:** e001710.

68 Courtenay M, Castro-Sanchez E, Fitzpatrick M, Gallagher R, Lim R, Morris G. Tackling antimicrobial resistance 2019-2024—the UK's five-year national action plan. *J Hosp Infect* 2019; **101:** 426–27.

69 European Centre for Disease Prevention and Control, European Food Safety Authority, European Medicines Agency. Third joint inter-agency report on integrated analysis of consumption of antimicrobial agents and occurrence of antimicrobial resistance in bacteria from humans and food-producing animals in the EU/EEA: JIACRA III 2016-2018. *EFSA J* 2021; **19:** e06712.

70 Smith G. Step away from stepwise. *J Big Data* 2018; **5:** 32.

71 Liu CF, Burgess JF Jr, Manning WG, Maciejewski ML. Beta-binomial regression and bimodal utilization. *Health Serv Res* 2013; **48:** 1769–78.

Chapter 4:

The impact of inpatient bloodstream infections caused by antibiotic-resistant bacteria in low-and middle-income countries: A systematic review and meta-analysis

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Student ID Number	1807578	**Title**	Mr
First Name(s)	Kasim		
Surname/Family Name	Allel Henriquez		
Thesis Title	Impacts of antimicrobial resistance bloodstream infections among hospital patients and potential interventions: a case study in Chile		
Primary Supervisor	Laith Yakob, Dphil		

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SECTION E

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Date	25/March/2024

PLOS MEDICINE

RESEARCH ARTICLE

The impact of inpatient bloodstream infections caused by antibiotic-resistant bacteria in low- and middle-income countries: A systematic review and meta-analysis

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Abstract

Background

Bloodstream infections (BSIs) produced by antibiotic-resistant bacteria (ARB) cause a substantial disease burden worldwide. However, most estimates come from high-income settings and thus are not globally representative. This study quantifies the excess mortality, length of hospital stay (LOS), intensive care unit (ICU) admission, and economic costs associated with ARB BSIs, compared to antibiotic-sensitive bacteria (ASB), among adult inpatients in low- and middle-income countries (LMICs).

Methods and findings

We conducted a systematic review by searching 4 medical databases (PubMed, SCIELO, Scopus, and WHO's Global Index Medicus; initial search $n = 13{,}012$ from their inception to August 1, 2022). We only included quantitative studies. Our final sample consisted of $n = 109$ articles, excluding studies from high-income countries, without our outcomes of interest, or without a clear source of bloodstream infection. Crude mortality, ICU admission, and LOS were meta-analysed using the inverse variance heterogeneity model for the general and subgroup analyses including bacterial Gram type, family, and resistance type. For economic costs, direct medical costs per bed-day were sourced from WHO-CHOICE. Mortality costs

data collection and analysis, decision to publish, or manuscript preparation.

Competing interests: The authors have declared that no competing interests exist.

Abbreviations: AIM, African Index Medicus; ARB, antibiotic-resistant bacteria; ASB, antibiotic-sensitive bacteria; BSI, bloodstream infection; GLASS, Global Antimicrobial Resistance and Surveillance System; GNI, gross national income; ICU, intensive care unit; LMIC, low- and middle-income country; LOS, length of hospital stay; MRSA, methicillin-resistant Staphylococcus aureus; OR, odds ratio; SMD, standardised mean difference; WHO, World Health Organization.

were estimated based on productivity loss from years of potential life lost due to premature mortality. All costs were in 2020 USD. We assessed studies' quality and risk of publication bias using the MASTER framework. Multivariable meta-regressions were employed for the mortality and ICU admission outcomes only. Most included studies showed a significant increase in crude mortality (odds ratio (OR) 1.58, 95% CI [1.35 to 1.80], $p < 0.001$), total LOS (standardised mean difference "SMD" 0.49, 95% CI [0.20 to 0.78], $p < 0.001$), and ICU admission (OR 1.96, 95% CI [1.56 to 2.47], $p < 0.001$) for ARB versus ASB BSIs. Studies analysing Enterobacteriaceae, *Acinetobacter baumanii*, and *Staphylococcus aureus* in upper-middle-income countries from the African and Western Pacific regions showed the highest excess mortality, LOS, and ICU admission for ARB versus ASB BSIs per patient. Multivariable meta-regressions indicated that patients with resistant *Acinetobacter baumanii* BSIs had higher mortality odds when comparing ARB versus ASB BSI patients (OR 1.67, 95% CI [1.18 to 2.36], p 0.004). Excess direct medical costs were estimated at $12,442 (95% CI [$6,693 to $18,191]) for ARB versus ASB BSI per patient, with an average cost of $41,103 (95% CI [$30,931 to $51,274]) due to premature mortality. Limitations included the poor quality of some of the reviewed studies regarding the high risk of selective sampling or failure to adequately account for relevant confounders.

Conclusions

We provide an overview of the impact ARB BSIs in limited resource settings derived from the existing literature. Drug resistance was associated with a substantial disease and economic burden in LMICs. Although, our results show wide heterogeneity between WHO regions, income groups, and pathogen–drug combinations. Overall, there is a paucity of BSI data from LMICs, which hinders implementation of country-specific policies and tracking of health progress.

Author summary

Why was this study done?

- Bloodstream infections (BSIs) caused by antibiotic-resistant bacteria (ARB) have multifaceted impacts, including higher admission to intensive care units (ICUs), prolonged hospitalisations, and high economic and societal costs worldwide.
- Despite the global burden, most evidence on the excess burden of ARB BSIs has been derived from high-income countries; comparatively, there are limited data from low- and middle-income countries (LMICs).

What did the researchers do and find?

- We employed a systematic literature review and subsequent meta-analysis of 109 individual studies to quantify the impact of ARB BSIs in hospitalised patients from LMICs.
- Based mostly on crude data comparisons ignoring the possible influence of confounding factors, we found that ARB BSIs, compared to BSIs caused by antibiotic-sensitive

bacteria (ASB), were associated with substantially longer stays in hospitals and ICUs, higher mortality, and increased direct medical and productivity costs.

What do these findings mean?

- Our findings highlight the excess morbidity, mortality, and costs associated with ARB BSIs and the sparsity of data from LMICs.
- Targeted strategies to improve the prevention, detection, and treatment of resistant BSIs in LMICs are required to reduce the economic and disease burden.

Introduction

Antibiotic-resistant bacteria (ARB) constitute a global health priority, particularly where resistance proportion is highest in low- and middle-income countries (LMICs) [1]. Resource-limited hospital infrastructure, poor health system capacity, and inadequate sanitation and hygiene infrastructure partly explain the spread and impact of ARB in LMICs [1,2]. Ameliorating health inequities is hampered by the feedback caused by ARB infections resulting in increased morbidity and mortality, more complicated treatments due to the use of reserved antibiotics, and prolonged hospitalisations, all of which exacerbate costs to countries' health systems and society [1,3]. Recent figures from the World Health Organization (WHO) Global Antimicrobial Resistance and Surveillance System (GLASS) report show that the proportion of *Escherichia coli* bloodstream infections (BSIs) caused by third-generation cephalosporins resistant *E. coli* was more than triple in LMICs compared to high-income countries, (58.3% and 17.53%, respectively) [4]. A similar trend was observed for other WHO critical- and high-priority BSI pathogens, including *Klebsiella pneumoniae* and *Staphylococcus aureus* [4,5].

BSIs are one of the most lethal infections, having an estimated overall crude mortality of 15% to 30% [4,6]. BSIs are intrinsically more deadly as pathogens can spread quickly via blood, producing multiple infections and leading to organ damage and dysfunction. Extensive literature has examined the excess burden of ARB BSIs in specific locations [7–13]. For example, compared to their sensitive counterparts, carbapenem-resistant *Klebsiella* spp. [12] and methicillin-resistant *Staphylococcus aureus* (MRSA) [11] BSIs are associated with 9.08 (95% CI [1.17 to 70.51]) and 2.23 (95% CI [1.14 to 4.37]) times greater mortality, respectively. Higher admission to the intensive care units (ICUs), (OR 8.57; 95% CI [3.99 to 18.38]), greater length of hospital stay (LOS), (4.89 additional days; 95% CI [0.56 to 11.52]) and sizeable hospital costs ($23,318, 95% CI [$858 to $57,090]) have been linked to vancomycin-resistant versus -sensitive *Enterococci* BSIs [13]. Studies conducted in high-income countries contribute disproportionately to these estimates [14–16]; data from LMICs are scant. This comprises a critical gap in our understanding of the impact of drug-resistant BSI in countries with higher underlying health risks (e.g., cancer, neutropenia and haematological malignancies, pneumonia, and diabetes) [17].

Here, we present a systematic review and meta-analysis of the literature on the impact (i.e., LOS, mortality, and ICU admission) and excess economic costs per patient associated with ARB BSI compared with antibiotic-sensitive (ASB) BSI among hospitalised patients in LMICs.

Methods

This study is reported as per the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline (S1 Checklist) [18] and was prospectively registered with PROSPERO (id number: CRD42021264056).

Search strategy

We searched the literature for studies examining the burden of ARB BSIs compared with ASB BSIs among inpatients from LMICs. PubMed, SCIELO, Scopus, and WHO's Global Index Medicus (Latin American and Caribbean Health Sciences Literature "LILACs" and African Index Medicus "AIM") were searched without restrictions to language or year of publication using a family of keywords related to antibiotic/drug-resistance, bloodstream infections/bacteraemia, and burden measures among inpatients. We searched articles published through August 1, 2022. The complete list of terms, abbreviations, and Boolean connectors used by search engine can be found in the Supporting information (S1 Text, section 1).

Study selection

We selected articles according to a step-guided protocol. First, articles were excluded if carried out in high-income countries; these were defined according to the 2021 World Bank classification list (i.e., gross national income "GNI" per capita > $12,696) [19]. Second, studies were only included if BSIs were presented based on laboratory-confirmed positive blood cultures. Either primary or secondary BSIs were included. Articles that analysed patients with different culture types (e.g., blood, urine, wound, nasal) were removed unless BSI episodes were clearly detailed. Third, articles were included if the ASB and ARB groups were identified among adult patients presenting BSIs in the hospital. Fourth, participants with chronic or severe diseases (e.g., HIV, cancer) were removed unless they were present in the ARB and ASB groups (e.g., studies were withdrawn if HIV–positive patients having ARB BSIs were compared with HIV–negative patients having ASB BSIs). Finally, studies were removed if they did not present our selected outcomes (i.e., mortality, ICU admission, LOS, or costs). Experimental and observational articles were included. We removed correspondence letters or opinions, short reports without data analysis, literature reviews, and single-case studies.

Studies were analysed only when the number of patients was reported. We only included the adult population (average ≥18 years of age) because (i) the number of studies focusing on children was limited ($n = 4$) after looking at the provisional results; and (ii) children's inherent behaviour and exposure level differ from adults [3]. Only data on WHO-priority pathogens were retained [20]. The Results section (PRISMA chart) and Table A in S1 Text present the complete list of search criteria used.

To avoid our study hinging only on published articles' results, we systematically reviewed the grey literature and other current literature reviews analysing similar topics. Four referees resolved any disagreement presented at any stage of study selection through scholarly discussion. Two native Spanish speakers fluent in Portuguese and English, a native English speaker, and a native Chinese speaker fluent in English conducted the screening and consecutive data extraction. Papers written in any other language were translated to English using Google Translate PDF (<1% of the included articles). We used the Rayyan free online tool (https://rayyan.ai/) to screen, select, and decide which articles were included. Double article screening for eligibility was employed, and discrepancies were resolved via scholarly dialogue.

Data extraction

We extracted data including authors, publication year, country, study setting, population characteristics, bacterium type, resistance type, and sample sizes (for cases and control groups). We classified pathogen resistance based on the specific pathogen-resistance profiles evaluated in each study (e.g., cephalosporin-resistant *Acinetobacter baumanii*). For completeness, we also collated data on ESBL+ and non-ESBL (ESBL-) groups for gram-negative pathogens. For the analysis, the case group comprised infections with resistant strains (ARB), whereas the

control group comprised sensitive-strain infections (ASB). Selected studies were organised using unique identifiers (e.g., 1, 2, 3), and sub-studies within the primary articles were classified using consecutive numbers separated by a dot (e.g., 1.1, 1.2, 1.3) if they presented bacterium- or resistance type-specific information (S1 Data).

We extracted the following outcomes by case/control group: mortality (crude 30-day mortality, whenever available, or overall crude mortality if timing was not reported), LOS (average total days and standard deviation), and ICU admission (patients admitted). We also collected data on demographics and underlying conditions: average age, previous surgery and hospitalisation, community- or hospital-acquired BSI, any underlying condition (diabetes, hypertension, cardiovascular or heart diseases, solid tumour or malignancy, liver or kidney disease, pulmonary/respiratory diseases, and any hematologic disease), and BSI source (urinary tract, intravenous or catheter, pulmonary, and intrabdominal or gastrointestinal). Pitt bacteraemia score, APACHE II, and CHARLSON scores were collected if presented. We compared ARB and ASB groups by comparing variables' proportion or mean using McNemar's χ^2 or T-tests for binary and continuous data, respectively. Additionally, we classified the studies by World Bank income level, WHO region, WHO Global Priority Pathogens List, bacterium family and antibiotic class, pathogen strain, and bacterium Gram type. We used Microsoft Excel 2022 to compile and extract included articles' data. We used double data extraction reviewing, and inconsistencies (14% disagreement) were resolved through scholarly discussion.

Study quality and risk assessment

We used a unified framework to evaluate the methodological quality of analytic study designs (MASTER scale) [21]. This framework comprises 36 questions classified into 7 domains concerning equal recruitment, retention, implementation, prognosis, ascertainment, sufficient analysis, and temporal precedence. Each question was scored independently by 2 reviewers as 1 if the study complied with the domain or 0 if it did not. Therefore, a higher score indicates higher study quality. Two independent reviewers performed a risk of bias assessment. Conflicts were addressed through scholarly discussion.

Statistical analysis

Firstly, we employed population-weighted descriptive statistics of the health and demographic characteristics collated by studies' patients having ARB and ASB BSIs to contrast both groups and check whether mean differences across patient features existed. Secondly, the overall estimates for excess mortality, ICU admission, and LOS associated with resistant strains compared to their sensitive counterparts were meta-analysed using the inverse variance heterogeneity model [22]. The heterogeneity was calculated using the I^2 statistics; I^2 values were classified as high (>75%), moderate (50% to 75%), and low (<50%) heterogeneity. All results were computed using odds ratios (ORs) for mortality and ICU admission rates, and the standardised mean difference (SMD) for LOS. We estimated ORs based on studies' crude numbers or unadjusted ORs provided. Forest plots and meta-analyses were computed by outcome and subgroups of variables, including bacterial family, Gram type, reported resistance type, most common antibiotic-resistant microbial strains, World Bank income group, and WHO region. *P*-values (p) were reported using a two-tailed *t* test ($p < 0.05$) for the ORs for mortality and ICU admissions and LOS's standardised mean difference. We also analysed and compared, whenever reported, the unadjusted and confounder-adjusted ORs, for studies reporting univariate and multivariable regression analyses.

As a secondary analysis, we used univariate and multivariable meta-regressions to explore the main determinants of mortality and ICU admission (LOS was not included because of a

small sample size). We included the bacterial family and resistance profile, demographics, and underlying health condition variables in the univariate regression. Variables were transformed to odds between ARB and ASB groups. We evaluated the associations with the original and fully imputed observations. Multiple imputations were performed using fully completed data as factors and with 1,000 repetitions following a multivariable normal regression design. Variables associated with our outcomes in the univariate analysis with $p < 0.05$ using non-imputed data were included in the fully imputed multivariable model.

Excess economic costs per patient (i.e., costs associated with ARB BSI minus costs associated with ASB BSI) were computed only for excess length of stay, separated by ICU and non-ICU wards. Hospital-day costs included all the inpatient hospitality costs per patient stay for primary and secondary level and teaching hospitals and were calculated based on WHO--CHOICE costs [23]. ICU costs were calculated per patient stay for tertiary/teaching hospitals and were retrieved from the literature for countries with available information [24–36], or by using an approximation ratio between hospital and ICU costs [37–39]. Direct medical costs comprised hospital-day and ICU admission costs per patient, adjusted to their respective patients' LOS in the hospitalised or ICU services. We also calculated excess productivity losses per patient associated with premature mortality from ARB BSIs (compared to ASB BSIs) using the life expectancy at death and human capital approaches [40]. Excess productivity losses associated with premature mortality costs were computed by multiplying the years of life lost, based on the reference standard life expectancy at the average age of death [41] from ARB BSI (i.e., costs associated with ARB BSI minus costs associated with ASB BSI), using the study-weighted average age for all patients over all studies, without age-weights and a 5% time discount [42]. All costs were expressed in 2020 USDs, adjusting for inflation using US GDP implicit price deflators. Due to a lack of data, we excluded direct and indirect nonmedical costs (e.g., travel). Cost computations and methods are detailed in S1 Text, section 4.

Small-study effects

The Doi [43] plots and the LFK index were used to evaluate small-study effects when there were at least 5 studies in the meta-analysis. Leave-one-out cross-validation [44] was used to estimate the generalisation performance of our main meta-analyses to cross-validate the results' sensitivity.

Sensitivity analyses

We evaluated whether our main meta-analysis results varied by location. Due to the large proportion of studies from China ($N = 41$), we assessed our meta-analyses by separating our sampled studies into those performed in China and other LMICs.

All statistical analyses included studies and sub-studies according to their specific population features and were performed in Stata 17, College Station, TX: StataCorp LLC.

Results

Yield of the search strategy

Our search strategy identified 13,012 articles: 4,720 through PubMed, 8,193 in Scopus, 55 in SCIELO, and 44 in AIM and LILACs (Fig 1). Of these, 1,076 were duplicated (8.3%; 1,076/13,012), and 10,948 were performed in high-income countries (84.1%; 10,948/13,012) and hence removed. In total, 988 articles were full-text screened, resulting in the inclusion of 109 studies ($N = 22,756$ patients).

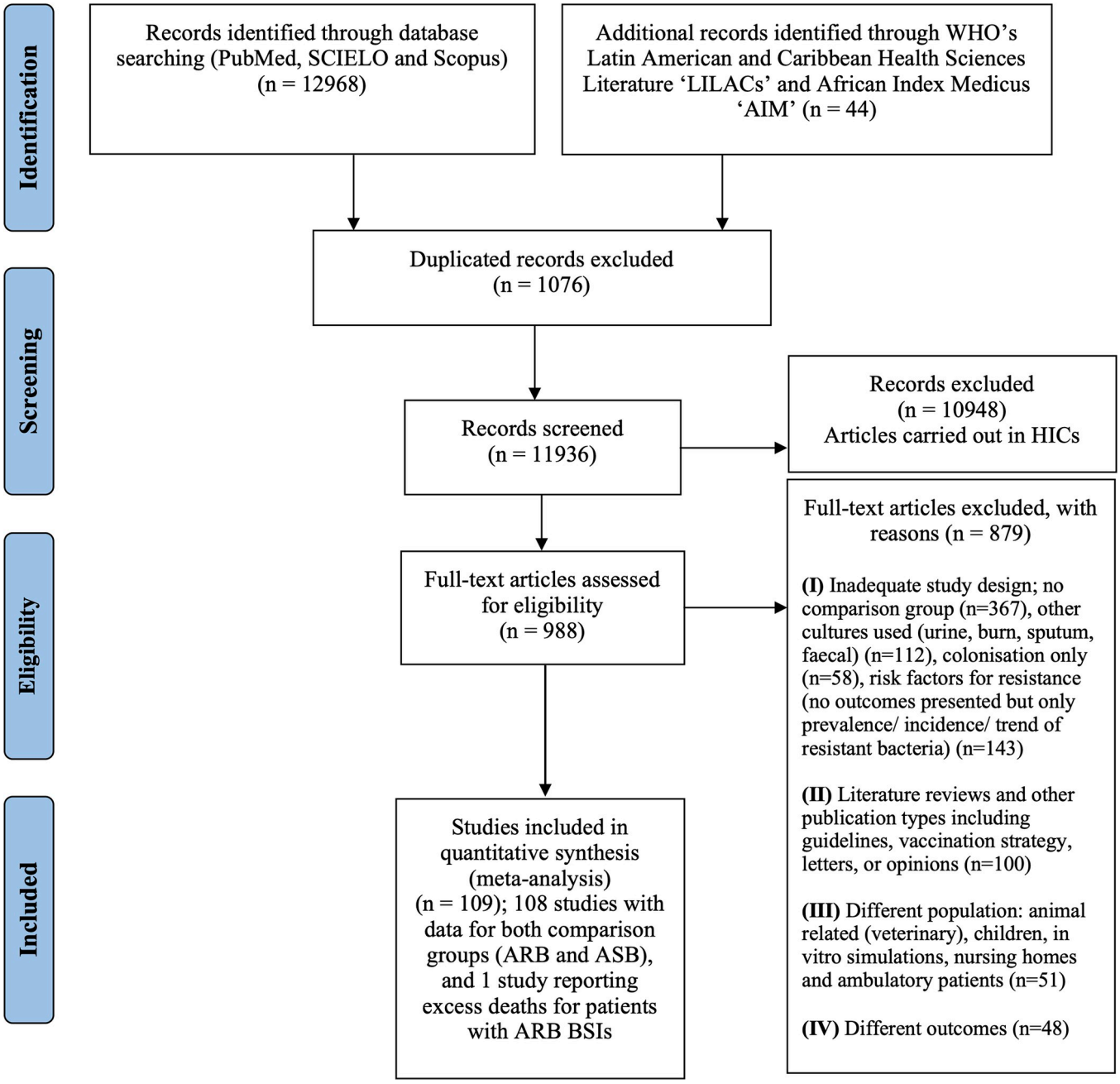

Fig 1. Flowchart detailing systematic review according to PRISMA guidelines. PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines [18]. HICs: High-income countries. PRISMA checklist is provided in S1 Text. ARB, antibiotic-resistant bacteria; ASB, antibiotic-sensitive bacteria; BSI, bloodstream infections; WHO, World Health Organization.

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Characteristics of included studies

Of the 109 articles, 100 (91.7%; 100/109) studies reported the impacts of ARB BSIs on mortality, 42 on hospital LOS, but only 18 displayed the average LOS with its standard deviation (16.5%; 18/109) and 52 (47.7%; 52/109) reported on ICU admission (Table 1). Studies were primarily conducted in China (44.9%; 49/109, $N = 12,092$ patients), Brazil (11.9%; 13/109, $N = 1,559$ patients), and Turkey (8.3%; 9/109, $N = 2,190$ patients) (Fig 2). Most studies

Table 1. Details of all studies included in the systematic literature review (*N* = 109).

ID**	Author/year	Country setting	Bacterium family	Group comparison		Group *N* of obs.		Mortality, *n* (%)		LOS (mean)		ICU admission, *n* (%)	
				Case	Control	Case	Control	Case	Control	Case	Control	Case	Control
1	Abhilash, 2010 [46]	India	Enterobacteriaceae	ESBL+	ESBL-	96	35	24(25)	9(26)				
2	Abolghasemi, 2018 [47]	Iran	Moraxellaceae	XDR	non-XDR	16	14	13(81)	1(7)			8(50)	0(0)
3	Akhtar, 2016 [48]	Pakistan	Enterococcus spp.	VRE	VSE	46	65	29(63)	28(43)	28.5	13.2	23(50)	9(14)
4	Anggraini, 2022 [49]	Indonesia	Moraxellaceae	CRAB	CSAB	72	72	41(57)	35(49)	17	13	60(83)	49(68)
5	Anunnatsiri, 2011 [50]	Thailand	Moraxellaceae	MDR	non-MDR	24	25	22(92)	12(48)	21.5	14	9(38)	3(12)
6	Arias-Ortiz, 2016 [51]	Colombia	Staphylococcaceae	MRSA	MSSA	186	186					105 (56)	89(48)
7	Atmaca, 2014 [52]	Turkey	Staphylococcaceae	MRSA	MSSA	99	99			70.84	14	25(25)	6(6)
8	Barrero, 2014 [53]	Colombia	Staphylococcaceae	MRSA	MSSA	102	102	62(61)	46(45)	30	21	64(63)	54(53)
9.1	Braga, 2013 [54]	Brazil	Staphylococcacea	MRSA	MSSA	12	44	7(58)	25(57)				
9.2	Braga, 2013 [54]	Brazil	Pseudomonadaceae	CRPA	CSPA	14	42	13(93)	19(45)				
9.3	Braga, 2013 [54]	Brazil	Enterobacteriaceae	CREN	CSEN	3	53	2(67)	30(57)				
9.4	Braga, 2013 [54]	Brazil	Enterobacteriaceae	CERKP	CESKP	5	51	4(80)	28(55)				
10	Castillo 2012 [55]	Colombia	Staphylococcaceae	MRSA	MSSA	186	186	62(33)	48(26)			105 (56)	90(48)
11	Carena, 2020 [56]	Argentina	Multiple	MDR	non-MDR	168	226	58(35)	36(16)			54(32)	43(19)
12	Cetin, 2021 [57]	Turkey	Multiple gram-negative	CRGN	CSGN	54	157	29(54)	31(20)	45	20		
13	Chang, 2020 [58]	China	Enterobacteriaceae	CRKP	CSKP	46	239	27(59)	37(15)			26(57)	33(14)
14	Chen, 2022 [59]	China	Enterobacteriaceae	CRKP	CSKP	29	223	14(48)	13(6)			21(72)	38(17)
15	Chen, 2012 [60]	China	Staphylococcaceae	MRSA	MSSA	75	43	25(33)	8(19)	55	38.7		
16	Chusri 2019 [61]	Thailand	Moraxellaceae	CRAB	CSAB	31	11	20(65)	2(18)	89	57	20(65)	6(55)
17	Conterno 1998 [62]	Brazil	Staphylococcaceae	MRSA	MSSA	90	46	44(49)	9(20)			54(60)	13(28)
18	Dantas 2017 [63]	Brazil	Pseudomonadaceae	MDR	non-MDR	67	90					39(58)	35(39)
19	Deodhar 2015 [64]	India	Staphylococcaceae	MRSA	MSSA	40	61	8(20)	13(21)				
20	De-Oliveira 2002 [65]	Brazil	Staphylococcaceae	MRSA	MSSA	159	92	73(46)	19(21)				
21	Deris, 2011 [66]	Malaysia	Moraxellaceae	IRAB	ISAB	15	41	6(40)	9(22)	32.3	32.8	11(73)	20(49)
22	Dramowski, 2022 [67]	South Africa	Enterobacteriaceae	CEREN	CESEN	62	115	27(44)	33(29)	10.5	9		
23	Durdu, 2016 [68]	Turkey	Enterobacteriaceae	CRKP	CRSKP	46	63	23(50)	23(37)				
24	Ergönül, 2016 [69]	Turkey	Multiple	CRGN	CSGN	379	452	236 (62)	135(30)				
25	Ferreira, 2018 [70]	Brazil	Multiple	MDR	non-MDR	25	37	10(40)	3(8)				
26	Fu, 2015 [71]	China	Moraxellaceae	XDR	non-XDR	39	86	31(79)	38(44)	36.7	36.1	31(79)	45(52)
27	Furtado, 2006 [72]	Brazil	Enterococcus spp.	VRE	VSE	34	55			57.7	29	13(38)	18(33)
28	Garnica, 2009 [73]	Brazil	Multiple	MDR	non-MDR	10	44	4(40)	4(9)				
29	Gaytán, 2006 [74]	Mexico	Enterobacteriaceae	CiREC	CiSEC	26	24	4(15)	3(13)				
30	Ghafur, 2014 [75]	India	Multiple	MDR	non-MDR	44	97	28(64)	37(38)				
31.1	Goda, 2022 [76]	India	Multiple	MDR	non-MDR	8	22	1(13)	8(36)				
31.2	Goda, 2022 [76]	India	Multiple	XDR	non-XDR	20	10	8(40)	1(10)				
32	González, 2014 [77]	Colombia	Pseudomonadaceae	MDR	non-MDR	92	141						
33	Guo, 2016 [78]	China	Moraxellaceae	MDR	non-MDR	64	23	38(59)	1(4)			51(80)	5(22)
34	Hincapié, 2020 [45]	Colombia	Staphylococcaceae	MRSA	MSSA	292	909	219 (75)	71(8)			239 (82)	84(9)

(*Continued*)

Table 1. (Continued)

ID**	Author/year	Country setting	Bacterium family	Group comparison		Group *N* of obs.		Mortality, *n* (%)		LOS (mean)		ICU admission, *n* (%)	
				Case	Control	Case	Control	Case	Control	Case	Control	Case	Control
35.1	Islas-Muñoz, 2018 [79]	Mexico	Enterobacteriaceae	ESBL+	ESBL-	123	148	37(30)	35(24)				
35.2	Islas-Muñoz, 2018 [79]	Mexico	Multiple gram-negative	MDR	non-MDR	9	34	6(67)	5(15)				
35.3	Islas-Muñoz, 2018 [79]	Mexico	Multiple gram-positive	MDR	non-MDR	6	43	2(33)	4(9)				
36	Jafari, 2020 [80]	Iran	Enterococcus spp.	VRE	VSE	52	21	30(57)	6(29)	36.6	22.32	30(58)	5(24)
37	Jamulitrat, 2009 [81]	Thailand	Moraxellaceae	IRAB	ISAB	67	131	35(52)	26(20)	37	27		
38	Kalam, 2014 [82]	Pakistan	Multiple	MDR	non-MDR	117	126	54(46)	34(27)			32(27)	36(29)
39	Li, 2019 [83]	China	Enterobacteriaceae	CRKP	CSKP	19	21	8(42)	2(10)	21	18	11(58)	5(24)
40	Li, 2017 [84]	China	Enterobacteriaceae	MDR	non-MDR	76	28	23(30)	3(11)				
41	Li, 2018 [85]	China	Pseudomonadaceae	CRPA	CSPA	63	63	17(27)	8(13)	30	21		
42	Li, 2017 [86]	China	Enterobacteriaceae	CREN	CSEN	26	122	17(65)	21(17)	25.4	21	20(77)	10(8)
43	Li, 2020 [87]	China	Enterobacteriaceae	CRKP	CSKP	164	328	72(44)	49(15)	31	19	116 (71)	58(18)
44	Liang, 2021	China	Enterobacteriaceae	CRKP	CSKP	56	47	22(39)	9(19)	28.5	28	20(36)	13(28)
45.1	Lim, 2016 [88]	Thailand	Staphylococcaceae	MDR	non-MDR	2017		299*					
45.2	Lim, 2016 [88]	Thailand	Enterobacteriaceae	MDR	non-MDR	144		20*					
45.3	Lim, 2016 [88]	Thailand	Enterobacteriaceae	MDR	non-MDR	288		7*					
45.4	Lim, 2016 [88]	Thailand	Pseudomonadaceae	MDR	non-MDR	94		4*					
45.5	Lim, 2016 [88]	Thailand	Moraxellaceae	MDR	non-MDR	864		351*					
46	Lima, 2020 [89]	Brazil	Multiple	CR	CS	60	30	30(50)	12(40)	26.5	15		
47	Lipari, 2020 [90]	Argentina	Enterobacteriaceae	CREN	CSEN	42	42	22(52)	7(17)			32(76)	12(29)
48	Liu, 2019 [91]	China	Enterobacteriaceae	CRKP	CSKP	20	69	11(55)	11(16)				
49	Liu, 2015 [92]	China	Moraxellaceae	MDR	non-MDR	182	59	50(27)	3(5)			109 (60)	7(12)
50	Liu, 2019 [93]	China	Enterobacteriaceae	CRKP	CSKP	70	28	30(43)	12(43)				
51	Liu, 2020 [94]	China	Moraxellaceae	CRAB	CSAB	229	88	60(26)	4(5)			129 (56)	26(30)
52	Loftus, 2022 [95]	Fiji	Enterobacteriaceae	CREN	CSEN	66	96	20(30)	16(17)	13	8		
53.1	Lopez-Luis, 2020 [96]	Mexico	Enterococcus spp	VRE	VSE	107	85	34(32)	11(13)			41(38)	11(13)
53.2	Lopez-Luis, 2020 [96]	Mexico	Enterococcus spp	ARE	ASE	18	129	5(28)	23(18)			4(22)	22(17)
54	Ma, 2017 [97]	China	Enterobacteriaceae	ESBL+	ESBL-	70	43	15(21)	6(14)				
55	Marra, 2006 [98]	Brazil	Enterobacteriaceae	ESBL+	ESBL-	56	52	18(32)	8(15)			31(55)	18(35)
56	Meneküe 2019 [99]	Turkey	Enterobacteriaceae	CRKP	CSKP	111	99	77(69)	44(44)				
57	Metan, 2009 [100]	Turkey	Moraxellaceae	CRAB	CSAB	54	46	41(76)	22(48)				
58	Moghnieh, 2015 [101]	Lebanon	Multiple	MDR	non-MDR	7	68	4(57)	3(4)				
59	Moreira, 1998 [102]	Brazil	Staphylococcaceae	ORSA	OSSA	71	71	40(56)	8(11)	32.7	29.7		
60	Najmi, 2019 [103]	India	Enterobacteriaceae	ESBL+	ESBL-	101	81	29(29)	19(24)				
61	Niu, 2018 [104]	China	Moraxellaceae	CRAB	CSAB	242	51	84(35)	2(4)				
62.1	Palavutitotai, 2018 [105]	Thailand	Pseudomonadaceae	MDR	non-MDR	32	167	12(38)	38(23)				
62.2	Palavutitotai, 2018 [105]	Thailand	Pseudomonadaceae	XDR	non-XDR	56	199	23(41)	50(25)	53.5	45.5	8(14)	42(21)

(*Continued*)

Table 1. (Continued)

ID**	Author/year	Country setting	Bacterium family	Group comparison		Group *N* of obs.		Mortality, *n* (%)		LOS (mean)		ICU admission, *n* (%)	
				Case	Control	Case	Control	Case	Control	Case	Control	Case	Control
63	Porto, 2013 [106]	Brazil	Staphylococcaceae	MRSA	MSSA	61	169	44(71)	36(21)	43.2	20.5		
64	Rao 2020 [107]	India	Enterococcus spp.	VRE	VSE	73	100	27(37)	33(33)	34.47	26.25	21(29)	41(41)
65	Seboxa, 2015 [108]	Ethiopia	Enterobacteriaceae	CEREC	CESEC	10	6	10 (100)	0(0)				
66	Serefhanoglu 2009 [109]	Turkey	Enterobacteriaceae	MDR	non-MDR	30	64	7(23)	12(19)				
67	Shi, 2009 [110]	China	Multiple	MDR	non-MDR	70	82	27(39)	12(15)				
68.1	Shi, 2022 [111]	China	Multiple	CRGN	CSGN	65	953	29(45)	79(8)				
68.2	Shi, 2022 [111]	China	Multiple	ESBL+	ESBL-	347	671	33(10)	75(11)				
68.3	Shi, 2022 [111]	China	Multiple	MDR	non-MDR	412	606	56(14)	52(9)				
69.1	Sirijatuphat, 2018 [112]	Thailand	Enterobacteriaceae	CREC	CSEC	106	100	23(22)	18(18)				
69.2	Sirijatuphat, 2018 [112]	Thailand	Enterobacteriaceae	CRKP	CSKP	45	65	23(51)	22(34)				
69.3	Sirijatuphat, 2018 [112]	Thailand	Pseudomonadaceae	CRPA	CSPA	21	47	10(48)	19(40)				
69.4	Sirijatuphat, 2018 [112]	Thailand	Moraxellaceae	CRAB	CSAB	57	24	38(67)	3(13)				
69.5	Sirijatuphat, 2018 [112]	Thailand	Enterobacteriaceae	FRS	FSS	2	2	0(0)	1(50)				
69.6	Sirijatuphat, 2018 [112]	Thailand	Staphylococcaceae	MRSA	MSSA	16	47	9(56)	13(28)				
69.7	Sirijatuphat, 2018 [112]	Thailand	Enterococcus spp.	VRE	VSE	9	20	6(67)	12(60)				
70	Soares, 2022 [113] ρ	Brazil	Enterobacteriaceae	CRKP	CSKP	28	79						
71	Steinhaus, 2018 [114] a	South Africa	Staphylococcaceae	MRSA	MSSA	23	75						
72	Stewardson, 2019 [115]	Multiple LMICs †	Enterobacteriaceae	CREN	CSEN	123	174	43(35)	35(20)	3.7*		54(44)	51(29)
73.1	Stoma, 2016 [116]	Belarus	Multiple	CR	CS	23	112	17(74)	25(22)				
73.2	Stoma, 2016 [116]	Belarus	Enterobacteriaceae	ESBL+	ESBL-	24	111	6(25)	36(32)				
73.3	Stoma, 2016 [116]	Belarus	Staphylococcaceae	MRSA	MSSA	15	120	4(27)	38(32)				
74	Tang, 2021 [117]	China	Multiple	CRGN	CSGN	78	757	27(35)	79(10)				
75	Tian, 2016 [118]	China	Enterobacteriaceae	CRKP	CSKP	33	81	14(42)	16(20)	50	24		
76	Topeli, 2000 [119]	Turkey	Staphylococcaceae	MRSA	MSSA	46	55	27(59)	17(31)	50.3	32.7	20(43)	13(24)
77	Traverso, 2010 [120]	Argentina	Staphylococcaceae	MRSA	MSSA	17	22	12(71)	8(36)				
78	Tu, 2018 [121]	China	Enterobacteriaceae	MDR	non-MDR	55	145	9(16)	19(13)			16(29)	18(12)
79	Tuon, 2012 [122]	Brazil	Pseudomonadaceae	CRPA	CSPA	29	48	13(45)	26(54)	43	43.1	24(83)	25(52)
80	Valderrama, 2016 [123]	Colombia	Pseudomonadaceae	CRPA	CSPA	42	126	24(57)	45(36)	26	16	26(62)	73(58)
81	Wang, 2016 [124]	China	Enterobacteriaceae	CREN	CSEN	94	93	33(35)	11(12)	40	26	49(52)	33(35)
82	Wang, 2018 [125]	China	Enterobacteriaceae	CRKP	CSKP	48	48	23(48)	2(4)	84	33	25(52)	3(6)
83	Wei, 2020 [126]	China	Pseudomonadaceae	CRPA	CSPA	23	58	14(61)	10(17)				
84.1	Wu, 2021 [127]	China	Enterobacteriaceae	CRKP	CSKP	24	55	10(42)	12(22)				
84.2	Wu, 2021 [127]	China	Enterobacteriaceae	ESBL+	ESBL-	24	55	9(38)	15(27)				
84.3	Wu, 2021 [127]	China	Enterobacteriaceae	MDR	non-MDR	36	43	12(33)	12(28)				
85	Xiao, 2018 [128]	China	Enterobacteriaceae	CRKP	CSKP	135	293	52(39)	26(9)				

(*Continued*)

Table 1. (Continued)

ID**	Author/year	Country setting	Bacterium family	Group comparison		Group *N* of obs.		Mortality, *n* (%)		LOS (mean)		ICU admission, *n* (%)	
				Case	Control	Case	Control	Case	Control	Case	Control	Case	Control
86	Xiao, 2020 [129]	China	Enterobacteriaceae	CRKP	CSKP	104	267	58(56)	37(14)	35	23		
87	Xie, 2018 [130]	China	Multiple	MDR	non-MDR	186	322	59(32)	72(22)			42(23)	40(12)
88	Xu, 2015 [131]	China	Enterococcus spp.	VRE	VSE	31	54					21(68)	24(44)
89	Yang, 2018 [132]	China	Moraxellaceae	CRAB	CSAB	84	34	23(27)	2(6)			55(65)	6(18)
90	Yang, 2021 [133]	China	Pseudomonadaceae	CRPA	CSPA	65	155	17(26)	29(19)	38	24	34(52)	46(30)
91	Ye, 2014 [134]	China	Multiple	rESKAPE	sESKAPE	39	32	22(56)	12(38)				
92	Yilmaz, 2016 [135]	Turkey	Staphylococcaceae	MRSA	MSSA	100	145	22(22)	7(5)				
93	Yuan, 2020 [136]	China	Enterobacteriaceae	CRKP	CSKP	98	141	7(7)	2(1)	55	51	82(84)	44(31)
94	Zhang, 2020 [137]	China	Enterobacteriaceae	CRKP	CSKP	108	388	41(38)	34(9)	24.5	26	85(79)	155(40)
95	Zhang, 2019 [138]	China	Enterobacteriaceae	ESBL+	ESBL-	160	164	39(24)	32(20)				
96	Zhang, 2017 [139]	China	Enterobacteriaceae	CEREC	CESEC	51	197	13(25)	24(12)	29.88	30.98	4(8)	23(12)
97	Zhang, 2017 [140]	China	Enterococcus spp.	VRE	VSE	7	217	2(29)	52(24)				
98	Zhang, 2020 [141]	China	Pseudomonadaceae	CRPA	CSPA	40	29	30(75)	12(41)				
99	Zhao, 2022 [142]	China	Enterobacteriaceae	ESBL+	ESBL-	159	205	29(18)	24(12)				
100.1	Zhao, 2020 [143]	China	Pseudomonadaceae	CRPA	CSPA	55	238	11(20)	14(6)	29	26		
100.2	Zhao, 2020 [143]	China	Pseudomonadaceae	MDR	non-MDR	38	255	11(29)	14(5)	27	26		
101	Zheng, 2018 [144]	China	Enterobacteriaceae	CRKP	CSKP	59	230	32(54)	45(20)			28(47)	47(20)
102	Zheng, 2017 [145]	China	Enterobacteriaceae	CRKP	CSKP	31	17	19(61)	8(47)	31.74	21.47		
103	Zhou, 2019 [146]	China	Moraxellaceae	MDR	non-MDR	274	64	161 (59)	8(13)	29	22.5	184 (67)	12(19)
104	Zhu, 2016 [147]	China	Staphylococcaceae	MRSA	MSSA	22	42	6(27)	6(14)	25.7	15.3		
105	Zhu, 2021 [148]	China	Enterobacteriaceae	CREN	CSEN	152	727	87(57)	133(18)	35	20	98(64)	135(19)
106	Zlatian, 2018 [149]	Romania	Staphylococcaceae	MRSA	MSSA	23	40					14(61)	19(48)
107	Zou, 2020 [150]	China	Enterobacteriaceae	CREC	CSEC	31	367	17(55)	39(11)			20(65)	61(17)
108	Zhang, 2018 [151]	China	Enterobacteriaceae	MDR	non-MDR	77	33	10(13)	10(30)				
109	Zhang, 2017 [152]	China	Moraxellaceae	CRAB	CSAB	49	29	40(82)	6(21)			10(20)	12(41)

Full information can be found in S1 Data.

*Reported as excess mortality or length of stay. Empty cells did not reported values for the outcomes.

[a]This study reported unadjusted and adjusted ORs rather than raw values for outcome variables.

**Studies ID comprised the main articles and articles' sub-studies if information on the outcomes by comparison group was reported separately for more than 1 bacterium or resistance-type according to their specific populations.

†LMICs included in the study were India, Egypt, Nigeria, Colombia, Ghana, Pakistan, Lebanon, Vietnam, and Bangladesh.

[p]Odds ratios were reported only.

MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-sensitive *Staphylococcus aureus*; MDR, multi-drug resistance; CRKP, carbapenem-resistant *Klebsiella pneumoniae*; CSKP, carbapenem-sensitive *Klebsiella pneumoniae*; CRPA, carbapenem-resistant *Pseudomonas aeruginosa*; CSPA, carbapenem-sensitive *Pseudomonas aeruginosa*; CRAB, carbapenem-resistant *Acinetobacter baumannii*; CSAB, carbapenem-sensitive *Acinetobacter baumannii*; CREC, carbapenem-resistant *Escherichia coli*; CSEC, carbapenem-sensitive *Escherichia coli*; IRAB, imipenem-resistant *Acinetobacter baumannii*; ISAB, imipenem-sensitive *Acinetobacter baumannii*; ESBL, extended-spectrum β-lactamases; VRE, Vancomycin-resistant *Enterococcus spp*; VRE, Vancomycin-sensitive *Enterococcus* spp.; CERKP, Cephalosporins-resistant *Klebsiella pneumoniae;* CESKP, Cephalosporins-sensitive *Klebsiella pneumoniae; CiREC*, Ciprofloxacin-resistant *Escherichia coli; CiSEC*, Ciprofloxacin-sensitive *Escherichia coli;* CRGN, Carbapenem-resistant gram-negative bacteria; CSGN, Carbapenem sensitive gram-negative bacteria; CR, Carbapenem resistance; CS, Carbapenem sensitive; CREN, Carbapenem-resistant *Enterobacteriaceae;* CSEN, Carbapenem-sensitive *Enterobacteriaceae;* ARE, Ampicillin-resistant *Enterococcus* spp.; ASE, Ampicillin-sensitive *Enterococcus* spp.; ORSA, Oxacillin-resistant *Staphylococcus aureus;* OSSA, Oxacillin-sensitive *Staphylococcus aureus;* CEREC, Cephalosporins-resistant *Escherichia coli;* CESEC, Cephalosporins-sensitive *Escherichia coli; FRS*, Fluoroquinolone-resistant *Salmonella* spp.; *FSS*, Fluoroquinolone-sensitive *Salmonella* spp.; XDR, Extensive drug-resistance. rESKAPE: Vancomycin-resistant *E. faecium*, methicillin-resistant *S. aureus* (MRSA), extended-spectrum β-lactamase (ESBL)-producing *K. pneumoniae*, carbapenem-resistant *A. baumannii*, carbapenem- and quinolone-resistant P. aeruginosa, and de-repressed chromosomal β-lactam and ESBL-producing Enterobacter species. sESKAPE: sensitive ESKAPE; ICU: intensive care unit; LOS: length of stay.

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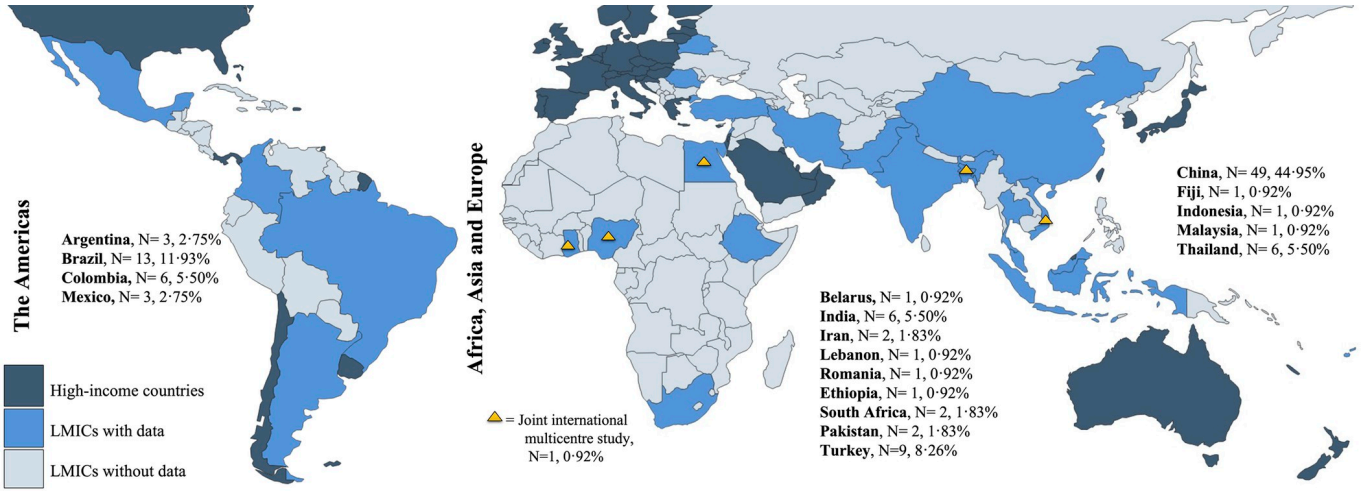

Fig 2. Distribution of the included studies according to country (*N* = 109 articles). Maps indicate the country where studies came from with their respective number (*N*) of studies included and the percentage of studies per country of the total studies analysed. Joint studies used cross-country designs (i.e., analysed ARB BSIs in more than 1 country). White areas represent high-income countries or missing LMICs. Maps were computed in QGIS Development Team (2020), Geographic Information System, version 3.16: Open-Source Geospatial Foundation Project. http://qgis.osgeo.org. ARB, antibiotic-resistant bacteria; BSI, bloodstream infection; LMIC, low- and middle-income country; QGIS, Quantum Geographic Information System.

https://doi.org/10.1371/journal.pmed.1004199.g002

collected data from the Western Pacific region according to the WHO classification (46.8%; 51/109) and 88% (96/109) were from upper-middle-income countries (S1 Text, section 2). The majority of the studies reported on gram-negative bacteria, mainly Enterobacteriaceae (41.3%; 45/109), Moraxellaceae or *Acinetobacter baumanii* (15.6%; 17/109), and *Pseudomonas aeruginosa* (11.9%, 13/109) (Fig 3). The main gram-positive pathogens reported were *Staphylococcus aureus* (19.3%; 21/109) and *Enterococcus* spp. (7.3%; 8/109); 75.2% (82/109) of the pathogens reported were classified as a critical priority following the WHO criteria (Fig 3). β-lactam antibiotics were among the most tested antibiotic class within the studies (67.9%; 74/109), 71.6% (53/74) of which were carbapenems or cephalosporins (Fig 3). The total number of patients and most prevalent features per country's studies are reported in Table E in S1 Text. Table F in S1 Text presents the weighted unadjusted differences for sociodemographic and health variables among ARB and ASB groups. We found no statistically significant difference between ARB and ASB groups for most of these variables (χ^2 test $p > 0.05$). S1 Text section 2 describes the distribution of our studies by WHO region, World Bank income group, year, and outcomes densities per ARB/ASB group.

Quantitative results

The odds of health outcomes. The crude OR for mortality of ARB versus ASB BSIs was 1.58 (95% CI [1.35 to 1.80], $p < 0.001$); we obtained similar values for gram-negative or WHO critical priority pathogens (OR 1.59, 95% CI [1.34 to 1.83], $p < 0.001$) (Table 2, section I). The highest OR of crude mortality for resistant pathogens was for carbapenem-resistant Enterobacteriaceae (OR 1.97, 95% CI [1.37 to 2.56], $p < 0.001$) (Table 3). The impact seemed to be lower among gram-positive bacteria, with an OR of 1.51 (95% CI [0.76 to 2.26], p 0.13) for MRSA and an OR of 1.31 (95% CI [1.01 to 1.60], p 0.02) for vancomycin-resistant Enterococcus species. Compared to ASB BSIs, ARB BSIs in upper-middle-income countries (OR 1.64, 95% CI [1.36 to 1.92], $p < 0.001$) from Europe and Western Pacific WHO regions (OR 1.79, 95% CI [1.49 to 2.11], $p < 0.001$, and OR 1.66, 95% CI [1.18 to 2.14], $p < 0.001$, respectively) had the highest excess mortality (Table G in S1 Text). Among priority pathogens defined by

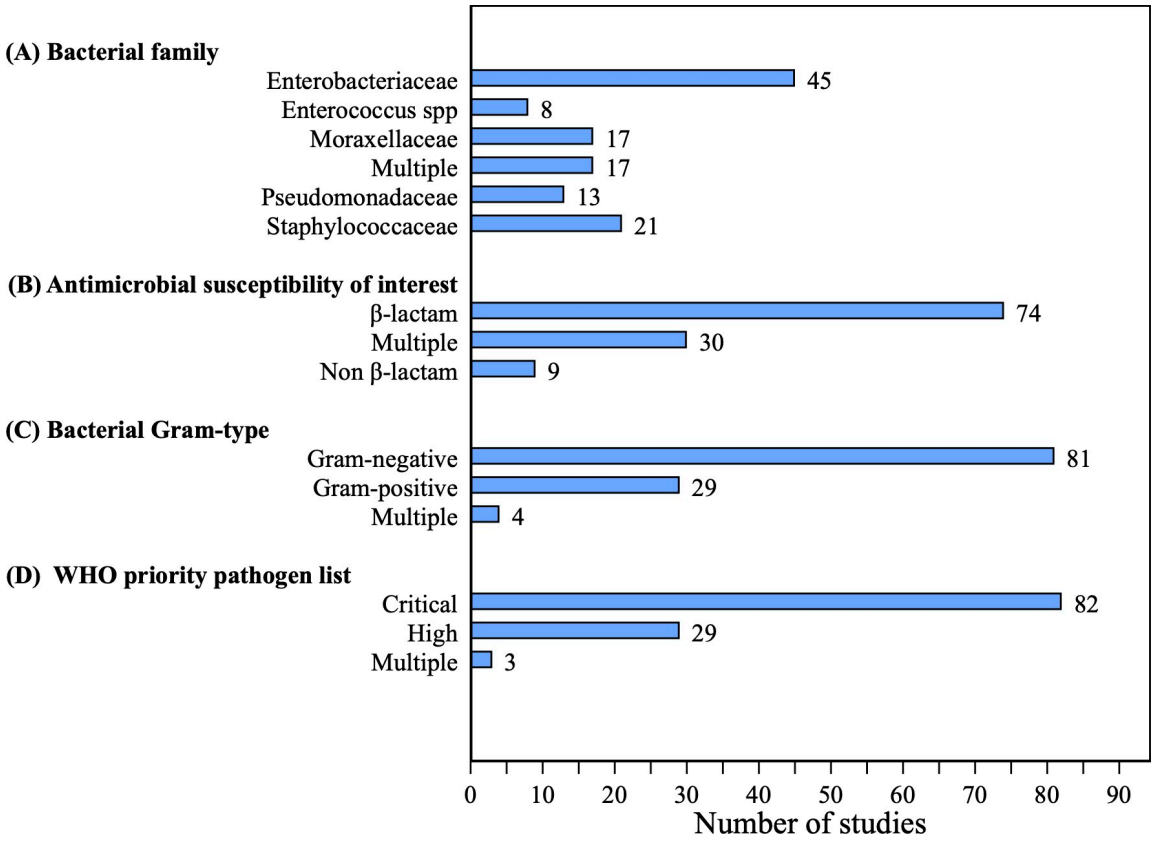

Fig 3. Number of included studies categorised by microbiological features †. (A) Number of included studies by bacterial family (B) Number of included studies by antimicrobial susceptibility of interest (C) Number of included studies by bacterial Gram-type (D) Number of included studies by WHO priority pathogen list. Enterobacteriaceae included *Escherichia coli* and *Klebsiella pneumoniae*. Enterococcus spp. stands for Enterococcus species pluralis (multiple species), which included *Enterococcus faecalis* and *faecium*. The multiple categories stand for either multiple bacteria or antibiotics analysed throughout our selected studies, which were not reported disaggregated by bacterial family, biological strain, gram type, or WHO priority pathogen list. † Studies could include more than 1 subcategory per biological feature (i.e., a study might report Enterobacteriaceae and Pseudomonadaceae species separately in their analyses, or altogether, in which case it was classified as "Multiple," meaning no clear distinction between subcategories). Categories might not be exclusive per study. WHO, World Health Organization.

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the WHO, crude excess mortality from carbapenem-resistant *K. pneumoniae* was substantially higher than for other pathogens (OR 1.79, 95% CI [1.15 to 2.43], p 0.002; Table 3), compared to sensitive counterparts. Among studies reporting both adjusted and unadjusted ORs for mortality ($N = 12$), we found 1.35 and 1.57 times higher unadjusted and adjusted mortality figures, respectively, for patients having BSIs caused by ARB versus ASB (Fig AJ in S1 Text). We found lower mortality estimates among studies reporting adjusted ORs for gram-negative ARB BSIs (OR = 1.88), specifically for Enterobacteriaceae and Moraxellaceae species (OR 1.91 and OR 1.73, respectively), compared to the same unadjusted estimates (OR 2.95 and OR 3.28, respectively) (Figs AK and AL in S1 Text). However, and surprisingly for the most part, adjusted ORs for mortality among ARB versus ASB BSI patients reflected greater odds compared to unadjusted ORs. This is explained by a single, highly influential study [45] among unadjusted estimates displaying a smaller OR (although confidence intervals overlap between unadjusted and adjusted ORs, and study's weight is lower among adjusted estimates).

Overall, the crude odds of ICU admission were 1.96 times higher for ARB compared to ASB BSIs (95% CI [1.56 to 2.47], $p < 0.001$) (Table 2, section II). Patients with WHO critical priority pathogens resistant to antibiotics were twice as likely to be admitted to ICU (OR 2.02,

Table 2. Main results of the meta-analysis comparing outcomes between patients with drug-resistant and drug-sensitive infections, overall and per bacterial family and WHO priority list classification (*N* = 109 studies[‡]).

Outcome variables	OR/SMD	95% CI	*P*-value	tau^2	*N* of patients	*N* of studies
I. Mortality[a]	**OR**					
Overall	1.58	1.35, 1.80	<0.001	0.39	19,597	93
WHO classification						
Critical priority pathogens (gram-negative)	1.59	1.34, 1.83	<0.001	0.36	15,206	72
High-priority pathogens (gram-positive)	1.47	0.94, 2.00	0.045	0.48	4,472	22
Bacterial family						
Enterobacteriaceae	1.49	1.09, 1.90	0.005	0.61	8,646	40
Enterococcus spp.	1.32	1.02, 1.61	0.017	0.00	949	6
Moraxellaceae	1.59	1.16, 2.02	<0.001	0.12	2,297	16
Pseudomonadaceae	1.37	1.04, 1.69	0.011	0.10	1,353	10
Staphylococcaceae	1.52	0.76, 2.28	0.135	0.80	3,566	17
II. ICU admission[b]	**OR**					
Overall	1.96	1.56, 2.47	<0.001	0.33	12,005	52
WHO classification						
Critical priority pathogens (gram-negative)	2.02	1.62, 2.52	<0.001	0.21	8,488	38
High-priority pathogens (gram-positive)	1.82	0.99, 3.37	0.055	0.68	3,517	14
Bacterial family						
Enterobacteriaceae	2.59	1.95, 3.45	<0.001	0.16	4,841	18
Enterococcus spp.	1.48	0.90, 2.41	0.119	0.27	870	6
Moraxellaceae	1.57	1.02, 2.41	0.039	0.20	1,625	12
Pseudomonadaceae	1.37	1.05, 1.77	0.018	0.05	877	5
Staphylococcaceae	1.91	0.86, 4.25	0.112	0.82	2,647	8
III. LOS[c]	**SMD**					
Overall	0.49	0.20, 0.78	<0.001	0.27	3,185	18
WHO classification						
Critical priority pathogens (gram-negative)	0.37	0.17, 0.57	<0.001	0.06	2,097	11
High-priority pathogens (gram-positive)	0.71	0.03, 1.39	0.040	0.66	1,088	7
Bacterial family						
Enterobacteriaceae	0.43	0.14, 0.73	0.004	0.06	1,175	5
Enterococcus spp.	0.25	−0.05, 0.55	0.102	-	173	1
Moraxellaceae	0.16	−0.06, 0.38	0.155	0.00	379	3
Pseudomonadaceae	0.14	−0.11, 0.39	0.276	0.00	332	2
Staphylococcaceae	0.82	0.01, 1.63	0.047	0.78	915	6

WHO, World Health Organization. Where the numbers of studies seem inconsistent, this is attributable to several studies reporting on multiple categories (WHO) or combined pathogens simultaneously. ICU stands for intensive care unit. Fully disaggregated results, including their respective forest plots, are shown in S1 Text, section 3. OR, odds ratio; SMD, standardised mean difference; CI, Confidence interval; N, number.

[a]From the total 109 studies included in the systematic review, 9 were excluded as they had missing data; one study was excluded as it only reported excess deaths for ARB BSIs at the country level [88]; and, 6 studies evaluated mortality by comparison group but reported different bacteria for the sample of individuals and therefore were excluded from the overall analysis but had sufficient information to be retained for the subgroup analyses.

[b]One study [96] reported data on demographics and ARB BSI for 2 different pathogens and with non-duplicate episodes, which were included as separate sub-studies.

[c]The number of studies/sub-studies differs from Table F in S1 Text because some studies did not report the standard deviation of LOS, so the SMD could not be computed.

[‡]One study was excluded from the *N* = 109 initial sample because it only reported excess mortality. *P*-values (p) were reported using a two-sided z-test (α = 5%) for the log-transformed mortality and ICU admission ratios and LOS's SMD.

ARB, antibiotic-resistant bacteria; BSI, bloodstream infection; LOS, length of hospital stay.

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Table 3. Meta-analysis subgroup results by the most common antibiotic-resistant microbial strains according to the WHO global priority list of antibiotic-resistant bacteria.

Outcome	Most common antibiotic-resistant microbial strains*	OR/SMD	95% CI	*P*-value	*N* of studies
I. Mortality		**OR**			
	CRAB	1.46	0.80, 2.11	0.120	10
	CREN	1.97	1.37, 2.56	<0.001	26
	CREC	1.54	0.00, 6.37	0.857	2
	CRKP	1.79	1.15, 2.43	0.002	19
	CRPA	1.36	0.89, 1.82	0.088	9
	MRSA	1.51	0.76, 2.26	0.132	16
	VRE	1.31	1.01, 1.60	0.021	6
II. ICU admission		**OR**			
	CRAB	1.36	0.85, 2.16	0.198	6
	CREN	2.66	1.98, 3.57	<0.001	15
	CREC‡	3.88	2.74, 5.49	<0.001	1
	CRKP	2.60	1.81, 3.75	<0.001	9
	CRPA	1.39	1.02, 1.90	<0.001	3
	MRSA	1.91	0.86, 4.25	0.112	8
	VRE	1.48	0.87, 2.54	0.152	6
III. LOS		**SMD**			
	CRAB	0.22	−0.04, 0.49	0.104	2
	CREN	0.53	0.39, 0.67	<0.001	4
	CREC‡	-	-	-	-
	CRKP	0.56	0.41, 0.71	<0.001	3
	CRPA‡	0.00	−0.46, 0.46	1.000	1
	MRSA	0.82	0.00, 1.63	0.048	6
	VRE‡	0.25	−0.05, 0.55	0.102	1

*All comparisons and ORs/SMD computations were made concerning their sensitive-specific counterpart. CRAB, Carbapenem-resistant *Acinetobacter baumanii*; CREN, Carbapenem-resistant *Enterobacteriaceae*; CREC, Carbapenem-resistant *Escherichia coli*; CRKP, Carbapenem-resistant *Klebsiella pneumoniae*; CRPA, Carbapenem-resistant *Pseudomonas aeruginosa*; MRSA, Methicillin-resistant *Staphylococcus aureus*; VRE, Vancomycin-resistant *Enterococcus faecium/faecalis*.

‡Either non or only study-reported estimates for the specific antibiotic-bacterium pair. Full charts, including the studies, can be found in S1 Text, section 7. *P*-values (p) were reported using a two-sided z-test ($\alpha = 5\%$) for the log-transformed mortality and ICU admission ratios and LOS's SMD.

ARB, antibiotic-resistant bacteria; CI, confidence interval; ICU, intensive care unit; LOS, length of hospital stay; OR, odds ratio; SMD, standardised mean difference; WHO, World Health Organization.

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95% CI [1.62 to 2.52], $p < 0.001$), with the highest observed ratio for gram-negative BSIs caused by antibiotic-resistant Enterobacteriaceae (OR 2.59, 95% CI [1.95 to 3.45], $p < 0.001$). Carbapenem-resistant Enterobacteriaceae in general (OR 2.66, 95% CI [1.98 to 3.57], $p < 0.001$), and specifically *Escherichia coli* (OR 3.88, 95% CI [2.74 to 5.49], $p < 0.001$), accounted for the highest figures (Table 3). Among gram-positive bacteria, Methicillin-resistant *Staphylococcus aureus* had an OR of 1.91 for ICU admission rate (95% CI [0.86 to 4.25], *p* 0.11), and vancomycin-resistant *Enterococcus faecium/faecalis* had an OR of 1.48 (95% CI [0.87 to 2.54], *p* 0.15) (Table 3). The Western Pacific region had the highest increase in ICU odds (OR 2.42, 95% CI [1.88 to 3.12], $p < 0.001$), followed by the Americas (OR 1.77, 95% CI [1.08 to 2.89], *p* 0.02), whereas the Southeast Asia region had the lowest odds of ICU admission of ARB BSIs compared to ASB BSIs (Table G in S1 Text).

The crude SMD for LOS was 0.49 (95% CI [0.20 to 0.78], $p < 0.001$; Table 2, section III). In other words, the curve representing the distribution of LOS times was shifted to the right by 0.49 standard deviations for the ARB BSIs group (i.e., LOS is approximately 7 days longer for

the ARB group; derived from multiplying SMD by LOS's standard deviation among all patients [0.49*13.91]). The SMD was higher for resistant pathogens classified as WHO high-priority pathogens (or gram-positive, SMD 0.71, 95% CI [0.03 to 1.39], *p* 0.04) compared with WHO critical priority pathogens (or gram-negative, SMD 0.37, 95% CI [0.17 to 0.57], *p* 0.13). Studies reporting MRSA accounted for the greatest excess LOS estimated (SMD 0.82; Table 3), compared to methicillin-sensitive *S. aureus*. The highest excess LOS was observed in studies from Turkey (SMD 1.29). Studies from Europe (SMD 1.29) and Brazil (SMD 0.43) contributed substantially to the greater LOS in ARB BSI patients (Table G in S1 Text).

Full details on the meta-analysis main and subgroup results, including their respective forest plots, can be found in S1 Text, section 3.

Tables W and X in S1 Text show the results of the univariate and multivariable meta-regressions for mortality and ICU admission, respectively. Among the variables selected from the univariate analyses, our multivariable meta-regression showed that patients with resistant Moraxellaceae BSIs and hypertension had higher mortality odds when ARB versus ASB BSI patients were compared (OR 1.67, 95% CI [1.18 to 2.36], *p* 0.004; OR 1.13, 95% CI [1.00 to 1.28], *p* 0.035, respectively). Yet, countries from the Southeast Asia WHO region displayed lower mortality odds (OR 0.62, 95% CI [0.46 to 0.85], *p* 0.004). For the ICU admission multivariable meta-regression, we found a weak negative association between BSIs originating as a secondary infection from the urinary tract and the odds of mortality between patients having ARB and ASB BSIs (OR 0.72, 95% CI [0.51 to 1.02], *p* 0.06).

Estimated excess costs

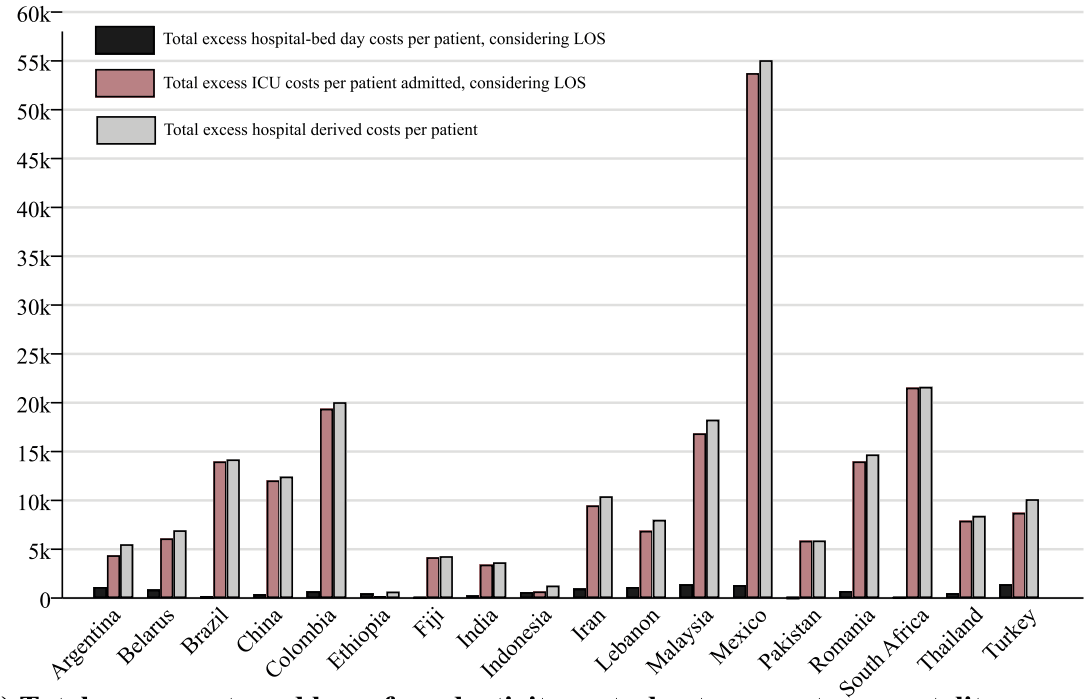
The average excess hospital bed-days cost per ARB BSI patient in tertiary/teaching hospitals, adjusted by the calculated excess LOS from Table 2 and excluding drugs and tests costs, was $812.5 (95% CI [$331.6 to $1,293.3]) (Table J in S1 Text). The excess costs per patient varied considerably between countries, ranging from $30.9, $95.9, and $131.7 (Ethiopia, Pakistan, and India, respectively) to $1,681.7 and $1,683.2 (Mexico and Turkey) (Fig 4, panel A).

We estimated an average excess of productivity loss (indirect costs associated with ARB BSI for an average patient) from years of potential life lost due to premature mortality of $41,102 (95% CI = $30,931 to $51,274) for all bacteria combined (Table L in S1 Text). Romania presented the highest excess producitivity lossess attributed to years of potential life-lost costs per patient, while Ethiopia had the lowest ($86,217 and $6,070, respectively). Mortality costs due to premature mortality using the life expectancy approach had an observed average of $132,560 per patient (95% CI [$99,753 to $165,363]) among all sampled countries (Table L in S1 Text).

The average excess ICU admission costs per patient, multiplied by the calculated ICU LOS, was $11,629 (95% CI [$6,016 to $17,243]) (Table O in S1 Text) for all bacteria combined. The estimates varied, with a middle data dispersion of $5,669 (i.e., third quartile–second quartile). Mexico had the highest costs per patient ($53,747), and Ethiopia had the lowest ($188) (Table O in S1 Text).

Fig 4 displays the direct medical and productivity loss due to premature mortality costs per patient by country (panel B). Direct medical costs (i.e., hospital bed-day costs and bed-day ICU costs per day multiplied by the average hospital and ICU respective LOS) were estimated at $12,442 (95% CI [$6,693 to $18,191]). The average total excess costs for a patient with ARB compared to ASB BSI, comprising direct medical and years of potential life lost, were $53,545 (95% CI [$39,838 to $67,251]). Excess costs for ICU adjusted to ICU's length of stay were 14 times higher compared with hospital-bed LOS-adjusted among patients with ARB BSIs. Lower middle-income countries had the lowest economic burdens per patient; however, we found substantial between-country differences.

(A) Direct (excess) medical costs per patient with a drug-resistant versus a drug-susceptible bloodstream infection, disaggregated and by country



(B) Total excess costs and loss of productivity costs due to premature mortality per patient with a drug-resistant versus a drug-susceptible bloodstream infection, by country

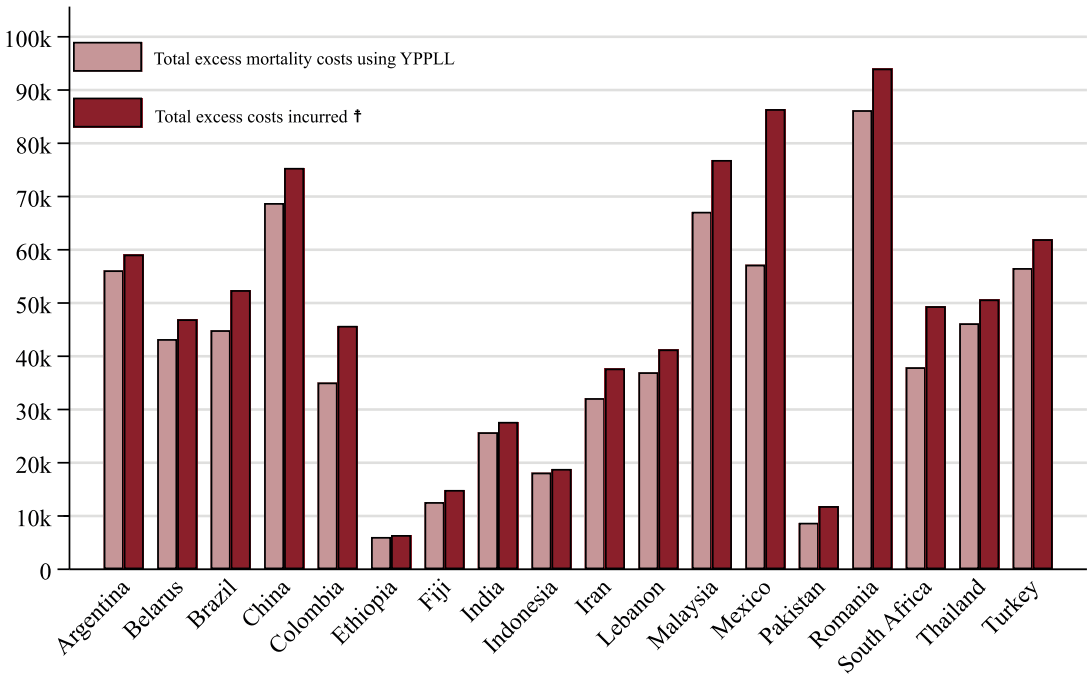


Fig 4. Excess costs (in 2020 USD) associated with productivity loss or excess length of stay per patient with a drug-resistant versus a drug-sensitive bloodstream infection. (A) Direct excess medical costs dissagreggated by ICU and hospital-bed days and by country (B) Total excess costs and productivity lossess due to premature mortality by country. ARB, antibiotic-resistant bacteria; BSI, bloodstream infection; YPLL, years of potential life lost from premature mortality; LOS, length of stay; USD, United States dollars. Full information and data are provided in S1 Text, section 4. † Total excess costs incurred including YPLL and hospital-derived costs per patient with ARB BSI. "k" = thousands. Costs of productivity loss are found in Table L in S1 Text.

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Full details on cost calculation can be found in S1 Text, section 4.

Quality and risk assessment

Using the MASTER scale for methodological assessment, we calculated, on average, 25.1, 23.7, and 23.6 points (out of 36) for the mortality, ICU admission, and length of hospital stay outcomes, respectively (Table 4). Our scores reflect that few studies addressed key confounders (e.g., using statistical methods to control for other correlated risk factors) to account for different prognoses and equal ascertainment (especially for participants, analysts, and caregivers' blindness towards evaluation; <2% of included studies). Only 37%, 11%, and 13% of the studies incorporated statistical techniques (e.g., regression analyses, stratification, matching, among others) for an equal prognosis for the mortality, ICU admission, and LOS outcomes, respectively (Table 4, equal prognosis scores). Most studies achieved equal retention (e.g., low missing data and null attrition) and sufficient analyses safeguards (e.g., absence of numerical contradictions and data dredging), regardless of the outcome analysed. Full results are found in S1 Text sections 8 and 9 and S1 Data, Master Scale spreadsheet.

Small-study effects

We found a medium level of heterogeneity between studies for the mortality outcome (I^2 69%, 95% CI [52% to 78%]), and high variation for ICU admission (I^2 91%, 95% CI [83% to 94%]) and LOS (I^2 90%, 95% CI [75%, 95%]) for the meta-analysis run by specific groups (S1 Text, section 5). Studies reporting ICU admission and LOS were either symmetrical (LFK index $\leq$1) or slightly asymmetrical (LFK index <3) (Figs AM and AN in S1 Text).

Sensitivity analyses

General mortality estimates from studies in China were not different from studies conducted elsewhere. However, we found larger disaggregated estimates for subgroup meta-analyses, such as Enterobacteriaceae, Moraxellaceae, Pseudomonaceae, and Staphylococcaceae species (8%, 25%, 26%, and 20%, respectively) compared to the average mortality estimates reported in Table 2 for the same subgroups. General LOS SMD was 16% higher among countries other than China, compared to the estimates reported in Table 2, specifically driven by Moraxellaceae and Staphylococcaceae species. Finally, the odds for excess ICU admission were 25% greater in China, with respect to average ICU admission found in all included studies, driven by 27% elevated odds among patients having BSIs caused by gram-negative bacteria. Full results in Tables U and V in S1 Text.

When applying the leave-one-out method to our meta-analyses, we observed that after assessing the effect of every single study on the overall estimates, the numbers presented a relative variation with respect to overall estimates ranging between −2% and 4% for mortality (OR 95% CI [1.57 to 1.58]), −8% and 4% for ICU admission (OR 95% CI [1.95 to 1.97]), and −10% and 4% for LOS (SMD 95% CI [0.48 to 0.50]) (S1 Text, section 6). These results suggest a moderate influence of our studies in the overall estimates if relative variations are compared, especially for ICU admission and LOS.

Discussion

Antibiotic resistance imposes substantial morbidity, mortality, and societal costs in LMICs [153]. Bloodstream infections with ARB are among the most lethal, imposing a large disease burden. Examining all available data for hospitalised patients in LMICs, we found that ARB BSIs with WHO critical- and high-priority pathogens were associated with increased mortality

Table 4. Assessment of study quality and risk of bias using the MASTER scale.

Safeguard items and sub-items	Outcomes		
	Mortality	ICU admission	LOS
Equal recruitment	60.4%	58.9%	60.6%
1. Data collected after the start of the study was not used to exclude participants or to select them for the analysis	38.8%	39.6%	40.0%
2. Participants in all comparison groups met the same eligibility requirements and were from the same population and timeframe	100.0%	100.0%	100.0%
3. Determination of eligibility and assignment to treatment group/exposure strategy were synchronised	17.5%	11.3%	12.5%
4. None of the eligibility criteria were common effects of exposure and outcome	85.4%	84.9%	90.0%
Equal retention	96.9%	97.4%	96.5%
5. Any attrition (or exclusions after entry) was less than 20% of total participant numbers	92.2%	94.3%	87.5%
6. Missing data was less than 20%	97.1%	96.2%	97.5%
7. Analysis accounted for missing data	96.1%	96.2%	97.5%
8. Exposure variations/treatment deviations were less than 20%	100.0%	100.0%	100.0%
9. The analysis addressed variations in exposure or withdrawals after start of the study	99.0%	100.0%	100.0%
Equal ascertainment	57.1%	57.4%	57.1%
10. Procedures for data collection of covariates were reliable and the same for all participants	100.0%	100.0%	100.0%
11. The outcome was objective and/or reliably measured	100.0%	100.0%	100.0%
12. Exposures/interventions were objectively and/or reliably measured	100.0%	100.0%	100.0%
13. Outcome assessor(s) were blinded	100.0%	100.0%	100.0%
14. Participants were blinded	0.0%	0.0%	0.0%
15. Caregivers were blinded	0.0%	0.0%	0.0%
16. Analyst(s) were blinded	0.0%	1.9%	0.0%
Equal implementation	64.6%	66.4%	66.3%
17. Care was delivered equally to all participants	0.0%	0.0%	0.0%
18. Cointerventions that could impact the outcome were comparable between groups or avoided	0.9%	0.0%	0.0%
19. Control and active interventions/exposures were sufficiently distinct	100.0%	100.0%	100.0%
20. Exposure/intervention definition was consistently applied to all participants	87.4%	98.1%	97.5%
21. Outcome definition was consistently applied to all participants	100.0%	100.0%	100.0%
22. The period between exposure and outcome was similar across patients and between groups or the analyses adjusted for different lengths of follow-up of patients	99.0%	100.0%	100.0%
Equal prognosis	37.6%	11.0%	12.5%
23. Design and/or analysis strategies were in place that addressed potential confounding	84.5%	0.0%	0.0%
24. Key confounders addressed through design or analysis were not common effects of exposure and outcome	69.9%	0.0%	0.0%
25. Key baseline characteristics/prognostic indicators for the study were comparable across groups	3.9%	0.0%	2.6%
26. Participants were randomly allocated to groups with an adequate randomisation process	4.9%	9.4%	10.0%
27. Allocation procedure was adequately concealed	0.0%	0.0%	0.0%
28. Conflict of interests were declared and absent	62.1%	56.6%	62.5%
Sufficient analysis	89.9%	92.3%	92.5%
29. Analytic method was justified by study design or data requirements	84.2%	88.5%	90.0%
30. Computation errors or contradictions were absent	93.2%	94.3%	90.0%
31. There was no discernible data dredging or selective reporting of the outcomes	92.2%	94.2%	97.4%
Temporal precedence	100.0%	100.0%	100.0%
32. All subjects were selected prior to intervention/exposure and evaluated prospectively	100.0%	100.0%	100.0%
33. Carry-over or refractory effects were avoided or considered in the design of the study or were not relevant	100.0%	100.0%	100.0%
34. The intervention/exposure period was long enough to have influenced the study outcome	100.0%	100.0%	100.0%
35. Dose of intervention/exposure was sufficient to influence the outcome	100.0%	100.0%	100.0%
36. Length of follow-up was not too long or too short in relation to the outcome assessment	100.0%	100.0%	100.0%
Average count of safeguard items (raw score out of 36 items)	25.1	23.6	23.7

(*Continued*)

Table 4. (Continued)

Safeguard items and sub-items	Outcomes		
	Mortality	ICU admission	LOS
Average percentage of sufficiency considering all 36 items (i.e., average raw score/36)	69.6%	65.6%	65.9%

Percentage of fulfilment among all included studies, and per outcome, is presented by MASTER's scale safeguard and items [21].
ICU, intensive care unit; LOS, length of hospital stay. Full results are reported in S1 Data, Master Scale spreadsheet. See S1 Text, section 9, for a subgroup meta-analysis according to quality scores.

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(OR 1.58, 95% CI [1.35 to 1.80]), overall length of stay (SMD 0.49, 95% CI [0.20 to 0.78]), and ICU admission (OR 1.96, 95% CI [1.56 to 2.47]).

Our findings on mortality are consistent with the recent estimates by the Global Burden of Disease study [154]. The largest mortality impact was associated with resistant *A. baumannii* and Enterobacteriaceae. Both bacteria featured in the global top 5 contributors to resistance-associated and -attributable deaths in 2019 [154]. Between a quarter and half of the patients with ARB BSIs caused by Enterobacteriaceae, *A. baumannii* or *P. aureginosa* die, corroborating findings from different country settings for Enterobacteriaceae [8,67], *P. aeruginosa* [155], and large university hospitals in Israel and the US for *A. baumanii* [156,157].

Our results suggest that patients who acquired ARB BSIs during their hospital stay had an overall hospital stay that is about a week longer than patients that acquired ASB BSIs. However, in our study, we could not distinguish between excess length of stay before or after BSI, and as such this is likely an overestimation. Depending on the pathogen, resistant infections have previously been shown to increase LOS typically by 2.0 to 12.7 days [158]. Longer hospital stay, especially before BSI onset, is a primary risk factor for acquiring a resistant infection due to the cumulative risk of hospital transmission of ARBs [158,159]. We found that MRSA had the greatest impact on LOS (extending stay by 14 days relative to sensitive *S. aureus*). Others have also shown considerably increased LOS as a result of MRSA compared with sensitive *S. aureus*: Tsuzuki and colleagues [160] showed an excess overall LOS and LOS after BSI onset of 20 and 7 days, respectively; similarly, Graffunder and colleagues [161] showed MRSA patients presented an overall LOS of 3 weeks longer. Resistant infections are more difficult to treat and increase the rate of ICU admissions. Our analysis showed that resistant Enterobacteriaceae infections more than doubled the odds of ICU admission. This finding is comparable with the 2.69 higher odds of ICU admission previously shown among patients with carbapenem-resistant *K. pneumoniae* BSIs [162]. Our exploratory analysis for studies performed in China and LMICs other than China exhibited divergent results. We found that China's patients with antibiotic-resistant gram-negative BSIs (*A. baumanii*, Enterobacteriaceae, and *P. aeruginosa*) displayed higher excess mortality, ICU admission, and LOS, compared to the other LMICs with reported data. Large increases in antibiotic consumption and resistance levels over the last 20 years and the rapid development or acquisition of drug resistance among gram-negative pathogens might explain the greater excess mortality and morbidity for ARB BSIs in China [1,163,164]. Correspondingly, inappropriate administration of empirical treatments and low testing rates could increase the burden outcomes for patients with ARB BSIs in these settings [165].

Despite being fundamental to resource allocation for healthcare provision, we found very little data on excess costs associated with ARB BSIs among the reviewed studies. One study conducted in Thailand, reported excess costs associated with hospital-acquired carbapenem-resistant *A. baumannii* of $5,682 [61]. A study conducted in Colombia, reported excess

hospitalisation costs associated with MRSA BSI of $10,212, compared to sensitive *S. aureus* [53]. We estimated costs associated with mortality, LOS, and ICU admissions from the provider and societal perspective following the WHO-CHOICE standards and human capital approach. We found that the average hospital-related 2020 USD excess costs were $12,442 (95% CI [$6,693 to $18,190]) per ARB BSI patient, compared to ASB, ranging between Ethiopia, with the lowest figures, to Mexico, with the highest. These differences are partly explained by the countries' disparate economies (Pearson correlation = 0.27 between GDP and hospital costs). Several LMIC-setting studies detailing excess costs of resistant infections were excluded from our review because they did not meet specific inclusion criteria. Cost estimates from these studies include 1 from Turkey in which excess hospital stay and treatment costs were $10,002 [166]. Our estimate for Turkey of $10,403 is similar; however, our estimates did not include therapy/treatment costs. Our estimate for China ($12,516) was higher than a previous study including BSI treatment costs for carbapenem-resistant *K. pneumoniae* ($10,763) [167]. The average excess total costs comprising direct medical costs and years of potential life lost associated with premature mortality were $53,545 (95% CI [$39,838 to $67,251]) per patient with ARB BSI. WHO [168] recently reported that 58.3% of 22,371 isolates were identified as ARB *E. coli*, while 33.3% of 23,031 isolates were ARB *S. aureus* in LMICs, indicating the high relevance of these costs.

This study has limitations. First, the most important limitation is consistent with conclusions from the Global Burden of Diseases study [154]: there is a sparsity of data on ARB from LMICs. Only 18 of the 137 (13%) LMICs published any AMR outcome study. Consistent antibiotic resistance surveillance puts demands on clinical bacteriology, quality control, and data linkage between culture test results and clinical outcomes, which is beyond the capabilities of many LMICs. Applying the leave-one-out method to our meta-analyses (S1 Text, section 6) showed a minor-to-moderate influence of individual studies likely due to the heterogeneity in clinical settings, indicating that our model's results are robust (assuming countries' missing information and selection biases are heterogeneously distributed). Future efforts to improve coverage should prioritise WHO's Africa region, where data were remarkably absent, with no estimates for resistance-associated LOS or ICU admissions. Our results indicate that the studies from the Western Pacific and European areas show the highest excess mortality from ARB BSIs. Studies from Africa show among the lowest but this region has limited data and substantial uncertainty; it is essential to improve epidemiological surveillance of ARB BSIs in this region in particular [169]. Second, some articles were of low quality or reported limited data. Studies often failed to account for confounding factors; hence our analyses relied upon crude estimates. ARB surveillance networks vary in blood culture sampling, potentially overestimating the number of severe cases if selective sampling among patients fulfilling the case definition is present. Third, we did not estimate the total relative harm of ARB BSIs relative to where such infections were prevented (compared to non-infected patients) [170], primarily because of the limited number of studies [171]. While we accounted for some key risk factors when comparing antibiotic-sensitive and antibiotic-resistant groups in the metaregression, others were unavailable. We could not match comparison groups by factors known to impact patients' underlying health conditions, such as illness severity, prolonged previous hospital stays, or the use of invasive devices. The reported LOS does not distinguish between total LOS and LOS following BSI infection, thus risking reverse causality [172]. This ecological study was designed to identify associations; consequently, our results should be interpreted cautiously. Also, we adjusted WHO-CHOICE country estimates using US GPD implicit price deflators, which may not necessarily reflect price changes in some LMICs, particularly for non-tradable cost components of healthcare. Finally, we may have overestimated the true effect size of the association between ARB BSIs and mortality as indicated by the exploratory analysis of studies'

adjusted—compared to unadjusted—ORs reporting both estimates, specifically among gram-negative species.

Here, we described an updated evaluation of the health impact and excess economic costs of resistant BSIs in low-resourced settings. Our results highlight regions where improved surveillance, expanding microbiology laboratory capacity, and data collection systems are most needed and where the current evidence indicates WHO critical and high-priority drug-resistant pathogens exert the greatest toll on morbidity and mortality.

Supporting information

S1 Text. Supporting text, tables, and figures. Text A. Search criteria used by search engine. **Table A.** Studies inclusion and exclusion criteria. **Table B.** Years of the studies included. **Table C.** Number of studies included by WHO region and WB income group. **Table D.** Correlation between main outcomes and demographic variables. **Table E.** Most prevalent bacterium family, Gram type, resistance type, and antibiotic-bacterium pair by country among the included studies. **Table F.** Descriptive statistics of the studies included in the meta-analysis. **Table G.** Summary of the subgroup meta-analysis results for income level and WHO region by outcome variable. **Table H.** Costs of hospital bed-day per patient and by country and hospital level (in 2008 USDs). **Table I.** Costs of total excess hospital bed-days per patient by country and hospital level using estimated SMD and their respective 95% CIs (in 2008 USDs). **Table J.** Costs of total excess hospital bed-days per patient and by country and hospital level using estimated SMD and their respective 95% CIs (inflated to 2020 USDs). **Table K.** Calculation of YPLL, YPPLL, and CPL, by country. **Table L.** Total productivity losses due to premature mortality costs by country using the LE at the age of death and productivity cost approach (age of retirement), discounted. **Table M.** Intensive care unit costs per patient (daily). **Table N.** Intensive care unit costs (per patient and daily) adjusted to 2020 USDs (inflated accordingly). **Table O.** Intensive care unit costs (per day/patient) adjusted to ICU LOS and reported in 2020 USDs (inflated accordingly). **Table P.** Total excess costs incurred for bloodstream infections caused by antibiotic-resistant bacteria, per patient. **Table Q.** Statistics calculated for meta-analysis using mortality as an outcome, by model. **Table R.** Statistics calculated for meta-analysis using ICU admission as an outcome, by model. **Table S.** Statistics calculated for meta-analysis using the length of stay at hospital as an outcome, by model. **Table T.** Summary of the subgroup meta-analysis results for specific antibiotic-bacterium combinations declared important by the WHO, by outcome variable. **Table U.** Meta-analysis subgroup results for bacterium family, and Gram type for those studies carried out in China and other than China, by outcome. **Table V.** Summary results of meta-analysis results for critical antibiotic-bacterium pathogens for those studies in China and other than China, by outcome. **Table W.** Meta-regression results for the mortality outcome (univariate and multivariable). **Table X.** Meta-regression results for the ICU admission outcome (univariate and multivariate). **Table Y.** Summary results of the meta-analysis for the main outcome variables by separating the studies for low- [LS] and high-scores [HS] obtained from the MASTER scale. **Table Z.** Checklist of information that should be included in new reports of global health estimates. **Table AA.** PRISMA Checklist. **Fig A.** Density of the studies over time. **Fig B.** Violin and kernel density estimate plots for the main outcomes and by ARB susceptibility. **Fig C.** Relationship between the main outcomes. **Fig D.** Meta-analysis using all the studies reporting mortality rates. **Fig E**. Subgroup meta-analysis using all the studies reporting mortality rates/odds for critical ($N = 72$) and high-priority ($N = 22$) pathogens according to the WHO criteria. **Fig F.** Subgroup meta-analysis using all the studies reporting mortality rates by bacterium's family name. **Fig G.** Subgroup meta-analysis using all the studies reporting mortality rates by WHO Region. **Fig H.** Subgroup

meta-analysis using all the studies reporting mortality rates by income level. **Fig I.** Meta-analysis results using all the studies reporting the mean and SD for the length of stay at the hospital. **Fig J**. Subgroup meta-analysis using all the studies reporting the mean and SD for the length of stay at the hospital for critical and high-priority pathogens according to the WHO. **Fig K.** Subgroup meta-analysis using all the studies reporting the mean and SD for the length of stay at the hospital for Enterococcus spp., Enterobacteriaceae, Moraxellaceae, Pseudomonadaceae, and Staphyloccocaceae. **Fig L.** Subgroup meta-analysis using all the studies reporting the mean and SD for the length of stay at the hospital by income level. **Fig M.** Subgroup meta-analysis using all the studies reporting the mean and SD for the length of stay at the hospital by WHO region. **Fig N.** Meta-analysis results using all the studies reporting ICU admission rates. **Fig O.** Subgroup meta-analysis using all the studies reporting ICU admission rates for critical pathogens according to the WHO criteria. **Fig P.** Subgroup meta-analysis using all the studies reporting ICU admission rates for high-priority pathogens according to the WHO criteria. **Fig Q.** Subgroup meta-analysis using all the studies reporting ICU admission rates for Enterobacteriaceae. **Fig R.** Subgroup meta-analysis using all the studies reporting ICU admission rates for Enterobacteriaceae. **Fig S.** Subgroup meta-analysis using all the studies reporting ICU admission rates for Moraxellaceae. **Fig T.** Subgroup meta-analysis using all the studies reporting ICU admission rates for Pseudomonadaceae. **Fig U.** Subgroup meta-analysis using all the studies reporting ICU admission rates for Staphylococcaceae. **Fig V.** Subgroup meta-analysis using all the studies reporting ICU admission rates by resistance type (ESBL+). **Fig W.** Subgroup meta-analysis using all the studies reporting ICU admission rates by WHO region: Americas. **Fig X.** Subgroup meta-analysis using all the studies reporting ICU admission rates by WHO region: Eastern Mediterranean. **Fig Y.** Subgroup meta-analysis using all the studies reporting ICU admission rates by WHO region: Europe. **Fig Z.** Subgroup meta-analysis using all the studies reporting ICU admission rates by WHO region: Southeast Asia. **Fig AA**. Subgroup meta-analysis using all the studies reporting ICU admission rates by WHO region: Western Pacific region. **Fig AB.** Subgroup meta-analysis using all the studies reporting ICU admission rates by income level: Low and lower-middle income countries. **Fig AC.** Subgroup meta-analysis using all the studies reporting ICU admission rates by income level: Upper-middle income countries. **Fig AD.** Subgroup analysis for studies reporting unadjusted ORs. **Fig AE.** Subgroup analysis for studies reporting unadjusted ORs, by bacteria's gram type or WHO criticality category (critical = gram-negative, high-priority = gram-positive in this study). **Fig AF.** Subgroup analysis for studies reporting unadjusted ORs, by specific bacterium. **Fig AG.** Subgroup analysis for studies reporting adjusted ORs. **Fig AH.** Subgroup analysis for studies reporting adjusted ORs, by bacteria's gram type (critical = gram-negative, high-priority = gram-positive in this study). **Fig AI.** Subgroup analysis for studies reporting adjusted ORs, by specific bacterium. **Fig AJ.** Subgroup analysis for studies reporting adjusted and unadjusted ORs simultaneously, general mortality estimates. **Fig AK.** Subgroup analysis for studies reporting adjusted and unadjusted ORs simultaneously, mortality rates by Gram type or WHO criticality list classification (high = gram-positive, critical = gram-negative). **Fig AL.** Subgroup analysis for studies reporting adjusted and unadjusted ORs simultaneously, mortality rates by bacterium family. **Fig AM.** Doi plots for Model 1 (general) and by outcome based on Tables Q, R, and S. **Fig AN.** Funnel plots for Model 1 (general) and by outcome based on Tables Q, R, and S. **Fig AO.** Influence analysis for Model 1 using the mortality outcome compared to the general estimates and without subgroup analyses. **Fig AP.** Influence analysis for Model 1 using the ICU admission outcome compared to the general estimates and without subgroup analyses. **Fig AQ.** Influence analysis for Model 1 using the length of hospital stay outcome compared to the general estimates and without subgroup analyses. **Fig AR.** Meta-analysis results disaggregated by specific and prioritised antibiotic-bacterium pairs for

mortality. **Fig AS**. Meta-analysis results disaggregated by carbapenem-resistant Enterobacteriaceae for mortality. **Fig AT.** Meta-analysis results disaggregated by specific and prioritised antibiotic-bacterium pairs for LOS. **Fig AU.** Meta-analysis results disaggregated by carbapenem-resistant Enterobacteriaceae for LOS. **Fig AV.** Meta-analysis results disaggregated by specific and prioritised antibiotic-bacterium pairs for ICU admission. **Fig AW.** Meta-analysis results disaggregated by carbapenem-resistant Enterobacteriaceae for ICU admission. **Fig AX.** Graphical results of Table V. **Fig AY.** Distribution of the Master scale scores by outcome. **Fig AZ.** Kernel density estimate of the Master scale scores by outcome. **Fig BA.** Percentage of full completion by MASTER scale main safeguard and outcome.
(PDF)

S1 Data. Supporting dataset of the included studies and results of the application of the MASTER scale. MasterData spreadsheet. Description and data extracted from each included study. **MasterScale spreadsheet.** Application of the MASTER scale by outcome and study. **Summary MasterScale spreadsheet**. Summary statistics per safeguard/item of the application of the MASTER scale.
(XLSX)

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References

1. Organisation for Economic Cooperation and Development. Stemming the Superbug Tide: Just a Few Dollars More: OECD; 2019.

2. Okeke IN, Laxminarayan R, Bhutta ZA, Duse AG, Jenkins P, O'Brien TF, et al. Antimicrobial resistance in developing countries. Part I: recent trends and current status. Lancet Infect Dis. 2005; 5 (8):481–493. https://doi.org/10.1016/S1473-3099(05)70189-4 PMID: 16048717

3. Cassini A, Högberg LD, Plachouras D, Quattrocchi A, Hoxha A, Simonsen GS, et al. Attributable deaths and disability-adjusted life-years caused by infections with antibiotic-resistant bacteria in the EU and the European Economic Area in 2015: a population-level modelling analysis. Lancet Infect Dis. 2019; 19(1):56–66. https://doi.org/10.1016/S1473-3099(18)30605-4 PMID: 30409683

4. World Health Organization. Global antimicrobial resistance and use surveillance system (GLASS) report: 2021. 2021.

5. Tacconelli E, Carrara E, Savoldi A, Harbarth S, Mendelson M, Monnet DL, 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. https://doi.org/10.1016/S1473-3099(17)30753-3 PMID: 29276051

6. Hattori H, Maeda M, Nagatomo Y, Takuma T, Niki Y, Naito Y, et al. Epidemiology and risk factors for mortality in bloodstream infections: A single-center retrospective study in Japan. Am J Infect Control. 2018; 46(12):e75–e79. https://doi.org/10.1016/j.ajic.2018.06.019 PMID: 30172607

7. de Kraker ME, Wolkewitz M, Davey PG, Grundmann H. 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. https://doi.org/10.1128/AAC.01157-10 PMID: 21220533

8. De Kraker M, Wolkewitz M, Davey P, Koller W, Berger J, Nagler J, 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. https://doi.org/10.1093/jac/dkq412 PMID: 21106563

9. Thaden JT, Li Y, Ruffin F, Maskarinec SA, Hill-Rorie JM, Wanda LC, et al. Increased costs associated with bloodstream infections caused by multidrug-resistant gram-negative bacteria are due primarily to patients with hospital-acquired infections. Antimicrob Agents Chemother. 2017; 61(3):e01709–e01716. https://doi.org/10.1128/AAC.01709-16 PMID: 27993852

10. Wozniak TM, Barnsbee L, Lee XJ, Pacella RE. Using the best available data to estimate the cost of antimicrobial resistance: a systematic review. Antimicrob Resist Infect Control. 2019; 8(1):1–12.

11. Lee H-Y, Chen C-L, Liu S-Y, Yan Y-S, Chang C-J, Chiu C-H. Impact of molecular epidemiology and reduced susceptibility to glycopeptides and daptomycin on outcomes of patients with methicillin-resistant Staphylococcus aureus bacteremia. PLoS ONE. 2015; 10(8):e0136171. https://doi.org/10.1371/journal.pone.0136171 PMID: 26295150

12. Biehle LR, Cottreau JM, Thompson DJ, Filipek RL, O'Donnell JN, Lasco TM, et al. Outcomes and risk factors for mortality among patients treated with carbapenems for Klebsiella spp. bacteremia. PLoS ONE. 2015; 10(11):e0143845.

13. Cheah A, Spelman T, Liew D, Peel T, Howden B, Spelman D, et al. Enterococcal bacteraemia: factors influencing mortality, length of stay and costs of hospitalization. Clin Microbiol Infect. 2013; 19(4): E181–E189. https://doi.org/10.1111/1469-0691.12132 PMID: 23398607

14. Naylor NR, Atun R, Zhu N, Kulasabanathan K, Silva S, Chatterjee A, et al. Estimating the burden of antimicrobial resistance: a systematic literature review. Antimicrob Resist Infect Control. 2018; 7(1):1–17.

15. Ang H, Sun X. Risk factors for multidrug-resistant Gram-negative bacteria infection in intensive care units: A meta-analysis. Int J Nurs Pract. 2018; 24(4):e12644. https://doi.org/10.1111/ijn.12644 PMID: 29575345

16. Saharman YR, Karuniawati A, Severin JA, Verbrugh HA. Infections and antimicrobial resistance in intensive care units in lower-middle income countries: a scoping review. Antimicrob Resist Infect Control. 2021; 10(1):1–19.

17. Akova M. Epidemiology of antimicrobial resistance in bloodstream infections. Virulence. 2016; 7 (3):252–266.

18. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009; 6(7):e1000097. https://doi.org/10.1371/journal.pmed.1000097 PMID: 19621072

19. World Bank. World Bank Country and Lending Groups 2021 [cited 2021 Aug 31]. Available from: https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-country-and-lending-groups.

20. World Health Organization. Antimicrobial resistance: global report on surveillance: World Health Organization. 2014.

21. Stone JC, Glass K, Clark J, Ritskes-Hoitinga M, Munn Z, Tugwell P, et al. The MethodologicAl STandards for Epidemiological Research (MASTER) scale demonstrated a unified framework for bias assessment. J Clin Epidemiol. 2021. https://doi.org/10.1016/j.jclinepi.2021.01.012 PMID: 33485928

22. Doi SA, Barendregt JJ, Khan S, Thalib L, Williams GM. Advances in the meta-analysis of heterogeneous clinical trials I: the inverse variance heterogeneity model. Contemp Clin Trials. 2015; 45:130–138. https://doi.org/10.1016/j.cct.2015.05.009 PMID: 26003435

23. World Health Organization. Choosing interventions that are cost effective (WHO—CHOICE). Cost effectiveness and strategic planning. Available at: http://www.who.int/choice/costs/en/. Accessed March, 2020. 2021.

24. Khwannimit B, Bhurayanontachai R. The direct costs of intensive care management and risk factors for financial burden of patients with severe sepsis and septic shock. J Crit Care. 2015; 30(5):929–934. https://doi.org/10.1016/j.jcrc.2015.05.011 PMID: 26051981

25. Kockaya PD, Kavuncubasi S, Kockaya G. Cost of Intensive Care Stay in Turkey: In the View of Payer and Health Care Provider. Value Health. 2013; 16(7):A466.

26. Mahomed S, Mahomed O. Cost of intensive care services at a central hospital in South Africa. S Afr Med J. 2019; 109(1):35–39.

27. Lorenzovici L, Székely A, Csanádi M, Gaál P. Cost assessment of inpatient care episodes of stroke in Romania. Front Public Health. 2020;8.

28. Haque A, Naveed-ur-Rehman Siddiqui RK, Hoda M, Lakahni G, Hooda K. Cost of care in a paediatric intensive care unit of a tertiary-care university hospital of Pakistan. Trauma. 2015; 21:14.1.

29. Velázquez LDS. Análisis de costos en las Unidades de Terapia Intensiva mexicanas. Estudio multicéntrico. Medicina Crítica. 2010; 24(4):159–166.

30. Aung YN, Nur AM, Ismail A, Aljunid SM. Determining the cost and length of stay at intensive care units and the factors influencing them in a teaching hospital in Malaysia. Value Health Reg Issues. 2020; 21:149–156. https://doi.org/10.1016/j.vhri.2019.09.006 PMID: 31958748

31. Soleymani F. Costs of hospital-acquired infection for patients hospitalized in intensive care unit of an Iranian referral hospital. Med J Islam Repub Iran. 2018; 32:67. https://doi.org/10.14196/mjiri.32.67 PMID: 30643742

32. Peter JV, Thomas K, Jeyaseelan L, Yadav B, Sudarsan TI, Christina J, et al. Cost of intensive care in India. Int J Technol Assess Health Care. 2016; 32(4):241–245. https://doi.org/10.1017/S0266462316000398 PMID: 27608529

33. Olivera COE, Urrego KAG, Duque MG, Góngora EM. Costos de atención en UCI de un Hospital universitario de Bogotá DC. Revista Repertorio de Medicina y Cirugía. 2006; 15(3):133–142.

34. Cong Y. Ethical challenges in critical care medicine: a Chinese perspective. J Med Philos. 1998; 23 (6):581–600. https://doi.org/10.1076/jmep.23.6.581.2558 PMID: 10190842

35. Sogayar AM, Machado FR, Rea-Neto A, Dornas A, Grion CM, Lobo SM, et al. A multicentre, prospective study to evaluate costs of septic patients in Brazilian intensive care units. Pharmacoeconomics. 2008; 26(5):425–434. https://doi.org/10.2165/00019053-200826050-00006 PMID: 18429658

36. Rosenthal VD, Guzman S, Migone O, Crnich CJ. The attributable cost, length of hospital stay, and mortality of central line-associated bloodstream infection in intensive care departments in Argentina: a prospective, matched analysis. Am J Infect Control. 2003; 31(8):475–480. https://doi.org/10.1016/j.ajic.2003.03.002 PMID: 14647110

37. Tan SS, Bakker J, Hoogendoorn ME, Kapila A, Martin J, Pezzi A, et al. Direct cost analysis of intensive care unit stay in four European countries: applying a standardized costing methodology. Value Health. 2012; 15(1):81–86. https://doi.org/10.1016/j.jval.2011.09.007 PMID: 22264975

38. Evans J, Kobewka D, Thavorn K, D'Egidio G, Rosenberg E, Kyeremanteng K. The impact of reducing intensive care unit length of stay on hospital costs: evidence from a tertiary care hospital in Canada. Can J Anesth. 2018; 65(6):627–635.

39. Oostenbrink JB. Buijs-Van der Woude T, van Agthoven M, Koopmanschap MA, Rutten FF. Unit costs of inpatient hospital days. Pharmacoeconomics. 2003; 21(4):263–271. https://doi.org/10.2165/00019053-200321040-00004 PMID: 12600221

40. Springer. Human Capital Approach. In: Kirch W, editor. Encyclopedia of Public Health. Dordrecht: Springer Netherlands; 2008. p. 697–8.

41. Murray CJ. Comprehensive systematic analysis of global epidemiology: definitions, methods, simplification of DALYs, and comparative results from the Global Burden of Disease Study 2010. Supplement to: Murray CJL, Ezzati M, Flaxman AD, Lim S, Lozano R, Michaud C, et al. GBD 2010: design, definitions, and metrics. Lancet. 2012; 380:2063–2066.

42. Haacker M, Hallett TB, Atun R. On discount rates for economic evaluations in global health. Health Policy Plan. 2020; 35(1):107–114. https://doi.org/10.1093/heapol/czz127 PMID: 31625564

43. Furuya-Kanamori L, Barendregt JJ, Doi SA. A new improved graphical and quantitative method for detecting bias in meta-analysis. Int J Evid Based Halthc. 2018; 16(4):195–203. https://doi.org/10.1097/XEB.0000000000000141 PMID: 29621038

44. Hastie T, Tibshirani R, Friedman JH, Friedman JH. The elements of statistical learning: data mining, inference, and prediction: Springer; 2009.

45. Hincapié C, Galeano JA, Tibaduiza MF, Restrepo CA, Garcés D, Caraballo C, et al. Staphylococcemia mortality: Influence of methicillin resistance and site of infection acquisition in a patient's cohort from Medellin. Colombia. Enferm Infecc Microbiol. 2020; 40(1):8–15.

46. Abhilash K, Veeraraghavan B, Abraham O. Epidemiology and outcome of bacteremia caused by extended spectrum beta-lactamase (ESBL)-producing Escherichia coli and Klebsiella spp. in a tertiary care teaching hospital in south India. J Assoc Physicians India. 2010; 58(Suppl):13–17.

47. Abolghasemi S, Madadi Z, Mardani M. Risk Factors for Resistance and Mortality in Patients with Extensively Resistant Acinetobacter Bacteremia in Taleghani Hospital in Tehran, Iran. Arch Pediatr Infect Dis. 2018; 6(3).

48. Akhtar N, Sultan F, Nizamuddin S, Zafar W. Risk factors and clinical outcomes for vancomycin-resistant enterococcus bacteraemia in hospitalised cancer patients in Pakistan: A case-control study. J Pak Med Assoc. 2016; 66(7):829–36. Epub 2016/07/19. PMID: 27427131.

49. Anggraini D, Santosaningsih D, Endraswari PD, Jasmin N, Siregar FM, Hadi U, et al. Multicenter Study of the Risk Factors and Outcomes of Bloodstream Infections Caused by Carbapenem-Non-Susceptible Acinetobacter baumannii in Indonesia. Trop Med Infect Dis. 2022; 7(8):161. https://doi.org/10.3390/tropicalmed7080161 PMID: 36006253

50. Anunnatsiri S, Tonsawan P. Risk factors and clinical outcomes of multidrug-resistant Acinetobacter baumannii bacteremia at a university hospital in Thailand. Southeast Asian J Trop Med Public Health. 2011; 42(3):693–703. Epub 2011/06/29. PMID: 21706949.

51. Arias-Ortiz PM, Calderón LP, Castillo JS, Moreno J, Leal AL, Cortés JA, et al. Risk factors for methicillin-resistant Staphylococcus aureus bacteremia: A multicenter matched case-control study. Biomedica. 2016; 36(4):612–9. https://doi.org/10.7705/biomedica.v36i4.3193 PubMed Central PMCID: PMC27992988. PMID: 27992988

52. Atmaca Ö, Köşker PZ, Karahan C, Çakir B, Ünal S. Risk factors and antibiotic use in methicillin-resistant Staphylococcus aureus Bacteremia in hospitalized patients at Hacettepe University Adult and Oncology Hospitals (2004–2011) and antimicrobial susceptibilities of the isolates: A nested case-control study. Mikrobiyol Bulteni. 2014; 48(4):523–37. https://doi.org/10.5578/mb.8280 PubMed Central PMCID: PMC25492648. PMID: 25492648

53. Barrero LI, Castillo JS, Leal AL, Sánchez R, Cortés JA, Álvarez CA, et al. Economic burden of methicillin-resistant Staphylococcus aureus bacteremia in critical care patients in hospitals in Bogotá. Biomedica. 2014; 34(3):345–53. https://doi.org/10.7705/biomedica.v34i3.1692 PubMed Central PMCID: PMC25504122.

54. Braga IA, Pirett CC, Ribas RM, Gontijo Filho PP, Diogo Filho A. Bacterial colonization of pressure ulcers: assessment of risk for bloodstream infection and impact on patient outcomes. J Hosp Infect. 2013; 83(4):314–20. Epub 2013/01/15. https://doi.org/10.1016/j.jhin.2012.11.008 PMID: 23313027.

55. Castillo Londoño JS, Leal AL, Cortes JA, Alvarez CA, Sanchez R, Buitrago G, et al. Mortality among critically ill patients with methicillin-resistant Staphylococcus aureus bacteremia: A multicenter cohort study in Colombia. Rev Panam Salud Publica Pan Am J Public Health. 2012; 32(5):343–50. https://doi.org/10.1590/S1020-49892012001100004 PubMed Central PMCID: PMC23338691. PMID: 23338691

56. Carena AA, Laborde A, Roccia-Rossi I, Palacios CJ, Jordán R, Valledor A, et al. Proposal of a clinical score to stratify the risk of multidrug-resistant gram-negative rods bacteremia in cancer patients. Braz J Infect Dis. 2020; 24(1):34–43. https://doi.org/10.1016/j.bjid.2019.11.001 PubMed Central PMCID: PMC31851901. PMID: 31851901

57. Cetin S, Dokmetas I, Hamidi AA, Bayraktar B, Gunduz A, Sevgi DY. Comparison of risk factors and outcomes in carbapenem-resistant and carbapenem-susceptible Gram-negative bacteremia. Med Bull Sisli Etfal Hospital. 2021; 55(3):398. https://doi.org/10.14744/SEMB.2020.49002 PMID: 34712083

58. Chang H, Wei J, Zhou W, Yan X, Cao X, Zuo L, et al. Risk factors and mortality for patients with Bloodstream infections of Klebsiella pneumoniae during 2014–2018: Clinical impact of carbapenem resistance in a large tertiary hospital of China. J Infect Public Health. 2020; 13(5):784–90. Epub 2019/12/18. https://doi.org/10.1016/j.jiph.2019.11.014 PMID: 31843651.

59. Chen Y, Chen Y, Liu P, Guo P, Wu Z, Peng Y, et al. Risk factors and mortality for elderly patients with Bloodstream infection of Carbapenem resistance Klebsiella pneumoniae: a 10-year longitudinal study in China. 2022.

60. Chen R, Yan ZQ, Feng D, Luo YP, Wang LL, Shen DX. Nosocomial bloodstream infection in patients caused by Staphylococcus aureus: drug susceptibility, outcome, and risk factors for hospital mortality. Chin Med J (Engl). 2012; 125(2):226–9. Epub 2012/02/22. PMID: 22340550.

61. Chusri S, Chongsuvivatwong V, Silpapojakul K, Singkhamanan K, Hortiwakul T, Charernmak B, et al. Clinical characteristics and outcomes of community and hospital-acquired Acinetobacter baumannii bacteremia. J Microbiol Immunol Infect. 2019; 52(5):796–806. Epub 2019/04/30. https://doi.org/10.1016/j.jmii.2019.03.004 PMID: 31031096.

62. Conterno LO, Wey SB, Castelo A. Risk factors for mortality in Staphylococcus aureus bacteremia. Infect Control Hosp Epidemiol. 1998; 19(1):32–7. Epub 1998/02/25. https://doi.org/10.1086/647704 PMID: 9475347.

63. Dantas RCC, Silva RTE, Ferreira ML, Gonçalves IR, Araújo BF, De Campos PA, et al. Molecular epidemiological survey of bacteremia by multidrug resistant Pseudomonas aeruginosa: The relevance of intrinsic resistance mechanisms. PLoS ONE. 2017; 12(5). https://doi.org/10.1371/journal.pone.0176774 PubMed Central PMCID: PMC28481953. PMID: 28481953

64. Deodhar D, Varghese G, Balaji V, John J, Rebekah G, Janardhanan J, et al. Prevalence of Toxin Genes among the Clinical Isolates of Staphylococcus aureus and its Clinical Impact. J Glob Infect Dis. 2015; 7(3):97–102. Epub 2015/09/24. https://doi.org/10.4103/0974-777X.162234 PMID: 26392716; PubMed Central PMCID: PMC4557147.

65. de Oliveira Conterno L, Wey SB, Castelo A. Staphylococcus aureus bacteremia: comparison of two periods and a predictive model of mortality. Braz J Infect Dis. 2002; 6(6):288–97. Epub 2003/02/15. https://doi.org/10.1590/s1413-86702002000600004 PMID: 12585972.

66. Deris ZZ, Shafei MN, Harun A. Risk factors and outcomes of imipenem-resistant Acinetobacter bloodstream infection in North-Eastern Malaysia. Asian Pac J Trop Biomed. 2011; 1(4):313–5. Epub 2011/08/01. https://doi.org/10.1016/S2221-1691(11)60050-6 PMID: 23569782; PubMed Central PMCID: PMC3614228.

67. Dramowski A, Aiken AM, Rehman AM, Snyman Y, Reuter S, Grundmann H, et al. Mortality associated with third-generation cephalosporin resistance in Enterobacteriaceae bloodstream infections at one South African hospital. J Glob Antimicrob Resist. 2022; 29:176–184. https://doi.org/10.1016/j.jgar.2022.03.001 PMID: 35283332

68. Durdu B, Hakyemez IN, Bolukcu S, Okay G, Gultepe B, Aslan T. Mortality markers in nosocomial Klebsiella pneumoniae bloodstream infection. Springerplus. 2016; 5(1):1892. Epub 2016/11/16. https://doi.org/10.1186/s40064-016-3580-8 PMID: 27843749; PubMed Central PMCID: PMC5084144.

69. Ergönül Ö, Aydin M, Azap A, Başaran S, Tekin S, Kaya Ş, et al. Healthcare-associated Gram-negative bloodstream infections: antibiotic resistance and predictors of mortality. J Hosp Infect. 2016; 94(4):381–5. Epub 2016/11/03. https://doi.org/10.1016/j.jhin.2016.08.012 PMID: 27717604.

70. Ferreira AM, Moreira F, Guimaraes T, Spadão F, Ramos JF, Batista MV, et al. Epidemiology, risk factors and outcomes of multi-drug-resistant bloodstream infections in haematopoietic stem cell transplant recipients: importance of previous gut colonization. J Hosp Infect. 2018; 100(1):83–91. Epub 2018/03/14. https://doi.org/10.1016/j.jhin.2018.03.004 PMID: 29530743.

71. Fu Q, Ye H, Liu S. Risk factors for extensive drug-resistance and mortality in geriatric inpatients with bacteremia caused by Acinetobacter baumannii. Am J Infect Control. 2015; 43(8):857–60. Epub 2015/05/12. https://doi.org/10.1016/j.ajic.2015.03.033 PMID: 25960385.

72. Furtado GHC, Mendes RE, Campos Pignatari AC, Wey SB, Medeiros EAS. Risk factors for vancomycin-resistant Enterococcus faecalis bacteremia in hospitalized patients: An analysis of two case-control studies. Am J Infect Control. 2006; 34(7):447–51. https://doi.org/10.1016/j.ajic.2005.08.015 PubMed Central PMCID: PMC16945692. PMID: 16945692

73. Garnica M, Maiolino A, Nucci M. Factors associated with bacteremia due to multidrug-resistant Gram-negative bacilli in hematopoietic stem cell transplant recipients. Braz J Med Biol Res. 2009; 42(3):289–93. https://doi.org/10.1590/s0100-879x2009000300010 PubMed Central PMCID: PMC19287908. PMID: 19287908

74. Gaytán JJA, Mancilla GC, Meza HAR, Padilla PAV, González CYA, Lara CEG. Tendency of resistance to ciprofloxacin in bacteriemias due to Escherichia coli. Med Interna Mex. 2006; 22(5):386–390.

75. Ghafur AK, Vidyalakshmi PR, Kannaian P, Balasubramaniam R. Clinical study of carbapenem sensitive and resistant Gram-negative bacteremia in neutropenic and nonneutropenic patients: The first series from India. Indian J Cancer. 2014; 51(4):453–5. https://doi.org/10.4103/0019-509X.175362 PubMed Central PMCID: PMC26842159. PMID: 26842159

76. Goda R, Sharma R, Borkar SA, Katiyar V, Narwal P, Ganeshkumar A, et al. Frailty and Neutrophil Lymphocyte Ratio as Predictors of Mortality in Patients with Catheter-Associated Urinary Tract Infections or Central Line–Associated Bloodstream Infections in the Neurosurgical Intensive Care Unit:

Insights from a Retrospective Study in a Developing Country. World Neurosurgery. 2022; 162:e187–e197. https://doi.org/10.1016/j.wneu.2022.02.115 PMID: 35248769

77. González AL, Leal AL, Cortés JA, Sánchez R, Barrero LI, Castillo JS, et al. [Effect of adequate initial antimicrobial therapy on mortality in critical patients with Pseudomonas aeruginosa bacteremia]. Biomedica. 2014; 34(Suppl 1):58–66. Epub 2014/06/27. https://doi.org/10.1590/s0120-41572014000500008 PMID: 24968037.

78. Guo N, Xue W, Tang D, Ding J, Zhao B. Risk factors and outcomes of hospitalized patients with blood infections caused by multidrug-resistant Acinetobacter baumannii complex in a hospital of Northern China. Am J Infect Control. 2016; 44(4):e37–9. Epub 2016/01/26. https://doi.org/10.1016/j.ajic.2015.11.019 PMID: 26804303.

79. Islas-Muñoz B, Volkow-Fernández P, Ibanes-Gutiérrez C, Villamar-Ramírez A, Vilar-Compte D, Cornejo-Juárez P. Bloodstream infections in cancer patients. Risk factors associated with mortality. Int J Infect Dis. 2018; 71:59–64. Epub 2018/04/13. https://doi.org/10.1016/j.ijid.2018.03.022 PMID: 29649549.

80. Jafari S, Abdollahi A, Sabahi M, Salehi M, Asadollahi-Amin A, Hasannezhad M, et al. An Update to Enterococcal Bacteremia: Epidemiology, Resistance, and Outcome. Infect Disord Drug Targets. 2020.

81. Jamulitrat S, Pranee Arunpan RN, Parichart Phainuphong RN. Attributable mortality of imipenem-resistant nosocomial Acinetobacter baumannii bloodstream infection. J Med Assoc Thailand. 2009; 92 (3):413–9. PubMed Central PMCID: PMC19301737. PMID: 19301737

82. Kalam K, Qamar F, Kumar S, Ali S, Baqi S. Risk factors for carbapenem resistant bacteraemia and mortality due to gram negative bacteraemia in a developing country. J Pak Med Assoc. 2014; 64 (5):530–6. Epub 2014/10/03. PMID: 25272538.

83. Li H, Zheng Y, Yang X, Zhang P, Xiao W, Yang M. Clinical characteristics and prognosis of carbapenem-resistant klebsiella pneumoniae infection of critical patients. Chin J Evid Based Med. 2019; 19 (2):129–134. https://doi.org/10.7507/1672-2531.201809113

84. Li L, Huang H. Risk factors of mortality in bloodstream infections caused by Klebsiella pneumonia: A single-center retrospective study in China. Medicine (Baltimore). 2017; 96(35):e7924. Epub 2017/09/01. https://doi.org/10.1097/MD.0000000000007924 PMID: 28858116; PubMed Central PMCID: PMC5585510.

85. Li S, Jia X, Li C, Zou H, Liu H, Guo Y, et al. Carbapenem-resistant and cephalosporin-susceptible pseudomonas aeruginosa: A notable phenotype in patients with bacteremia. Infect Drug Resist. 2018; 11:1225–1235. https://doi.org/10.2147/IDR.S174876 PMID: 30154669

86. Li X, Ye H. Clinical and Mortality Risk Factors in Bloodstream Infections with Carbapenem-Resistant Enterobacteriaceae. Can J Infect Dis Med Microbiol. 2017; 2017:6212910. Epub 2018/01/31. https://doi.org/10.1155/2017/6212910 PMID: 29379527; PubMed Central PMCID: PMC5742906.

87. Li Y, Li J, Hu T, Hu J, Song N, Zhang Y, et al. Five-year change of prevalence and risk factors for infection and mortality of carbapenem-resistant Klebsiella pneumoniae bloodstream infection in a tertiary hospital in North China. Antimicrob Resist Infect Control. 2020; 9(1):79. Epub 2020/06/04. https://doi.org/10.1186/s13756-020-00728-3 PMID: 32487221; PubMed Central PMCID: PMC7268443.

88. Lim C, Takahashi E, Hongsuwan M, Wuthiekanun V, Thamlikitkul V, Hinjoy S, et al. Epidemiology and burden of multidrug-resistant bacterial infection in a developing country. eLife. 2016; 5(September). https://doi.org/10.7554/eLife.18082 PubMed Central PMCID: PMC27599374. PMID: 27599374

89. Lima EM, Cid PA, Beck DS, Pinheiro LHZ, Tonhá JPS, Alves MZO, et al. Predictive factors for sepsis by carbapenem resistant Gram-negative bacilli in adult critical patients in Rio de Janeiro: A case-case-control design in a prospective cohort study. Antimicrob Resist Infect Control. 2020; 9(1). https://doi.org/10.1186/s13756-020-00791-w PubMed Central PMCID: PMC32795380. PMID: 32795380

90. Lipari FG, Hernández D, Vilaró M, Caeiro JP, Saka HA. Clinical, epidemiological and microbiological characterization of bacteremia produced by carbapenem-resistant enterobacteria in a university hospital in Córdoba, Argentina. Rev Chil Infectol. 2020; 37(4):362–70. https://doi.org/10.4067/S0716-10182020000400362 PubMed Central PMCID: PMC33399656. PMID: 33399656

91. Liu J, Wang H, Huang Z, Tao X, Li J, Hu Y, et al. Risk factors and outcomes for carbapenem-resistant Klebsiella pneumoniae bacteremia in onco-hematological patients. J Infect Dev Ctries. 2019; 13 (5):357–64. Epub 2020/02/14. https://doi.org/10.3855/jidc.11189 PMID: 32053504.

92. Liu Q, Li W, Du X, Li W, Zhong T, Tang Y, et al. Risk and prognostic factors for multidrug-resistant Acinetobacter baumannii complex bacteremia: A retrospective study in a tertiary hospital of West China. PLoS ONE. 2015; 10(6). https://doi.org/10.1371/journal.pone.0130701 PubMed Central PMCID: PMC26083415. PMID: 26083415

93. Liu Q, Wu J, Wang Z, Wu X, Wang G, Ren J. Polymicrobial Bacteremia Involving Klebsiella pneumoniae in Patients with Complicated Intra-Abdominal Infections: Frequency, Co-Pathogens, Risk

Factors, and Clinical Outcomes. Surg Infect (Larchmt). 2019; 20(4):317–25. Epub 2019/02/09. https://doi.org/10.1089/sur.2018.207 PMID: 30735082.

94. Liu Y, Wang Q, Zhao C, Chen H, Li H, Wang H, et al. Prospective multi-center evaluation on risk factors, clinical characteristics and outcomes due to carbapenem resistance in Acinetobacter baumannii complex bacteraemia: experience from the Chinese Antimicrobial Resistance Surveillance of Nosocomial Infections (CARES) Network. J Med Microbiol. 2020; 69(7):949–59. Epub 2020/06/26. https://doi.org/10.1099/jmm.0.001222 PMID: 32584215.

95. Loftus MJ, Young-Sharma TE, Lee SJ, Wati S, Badoordeen GZ, Blakeway LV, et al. Attributable mortality and excess length of stay associated with third-generation cephalosporin-resistant Enterobacterales bloodstream infections: a prospective cohort study in Suva, Fiji. J Glob Antimicrob Resist. 2022; 30:286–293. https://doi.org/10.1016/j.jgar.2022.06.016 PMID: 35738385

96. López-Luis BA, Sifuentes-Osornio J, Lambraño-Castillo D, Ortiz-Brizuela E, Ramírez-Fontes A, Tovar-Calderón YE, 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. 2020; 24:198–204. Epub 2020/12/29. https://doi.org/10.1016/j.jgar.2020.12.005 PMID: 33359937.

97. Ma J, Li N, Liu Y, Wang C, Liu X, Chen S, et al. Antimicrobial resistance patterns, clinical features, and risk factors for septic shock and death of nosocomial e coli bacteremia in adult patients with hematological disease. Medicine. 2017; 96(21). https://doi.org/10.1097/MD.0000000000006959 PubMed Central PMCID: PMC28538389. PMID: 28538389

98. Marra AR, Wey SB, Castelo A, Gales AC, Cal RG, Filho JR, et al. Nosocomial bloodstream infections caused by Klebsiella pneumoniae: impact of extended-spectrum beta-lactamase (ESBL) production on clinical outcome in a hospital with high ESBL prevalence. BMC Infect Dis. 2006; 6:24. Epub 2006/02/16. https://doi.org/10.1186/1471-2334-6-24 PMID: 16478537; PubMed Central PMCID: PMC1382232.

99. Menekşe Ş, Çağ Y, Işık ME, Şahin S, Hacıseyitoğlu D, Can F, et al. The effect of colistin resistance and other predictors on fatality among patients with bloodstream infections due to Klebsiella pneumoniae in an OXA-48 dominant region. Int J Infect Dis. 2019; 86:208–11. https://doi.org/10.1016/j.ijid.2019.06.008 PubMed Central PMCID: PMC31402295. PMID: 31402295

100. Metan G, Sariguzel F, Sumerkan B. Factors influencing survival in patients with multi-drug-resistant Acinetobacter bacteraemia. Eur J Intern Med. 2009; 20(5):540–4. https://doi.org/10.1016/j.ejim.2009.05.005 PubMed Central PMCID: PMC19712862. PMID: 19712862

101. Moghnieh R, Estaitieh N, Mugharbil A, Jisr T, Abdallah DI, Ziade F, et al. Third generation cephalosporin resistant Enterobacteriaceae and multidrug resistant gram-negative bacteria causing bacteremia in febrile neutropenia adult cancer patients in Lebanon, broad spectrum antibiotics use as a major risk factor, and correlation with poor prognosis. Front Cell Infect Microbiol. 2015; 5(FEB). https://doi.org/10.3389/fcimb.2015.00011 PMID: 25729741

102. Moreira M, Medeiros EA, Pignatari AC, Wey SB, Cardo DM. [Effect of nosocomial bacteremia caused by oxacillin-resistant Staphylococcus aureus on mortality and length of hospitalization]. Rev Assoc Med Bras (1992). 1998; 44(4):263–8. Epub 1998/12/16. https://doi.org/10.1590/s0104-42301998000400002 PMID: 9852643.

103. Najmi A, Karimi F, Kunhikatta V, Varma M, Nair S. Resistance Trend, Antibiotic Utilization and Mortality in Patients with E. coli Bacteraemia. Open Access Maced J Med Sci. 2019; 7(7):1119–23. Epub 2019/05/03. https://doi.org/10.3889/oamjms.2019.223 PMID: 31049092; PubMed Central PMCID: PMC6490482.

104. Niu T, Xiao T, Guo L, Yu W, Chen Y, Zheng B, et al. Retrospective comparative analysis of risk factors and outcomes in patients with carbapenem-resistant Acinetobacter baumannii bloodstream infections: Cefoperazone–sulbactam associated with resistance and tigecycline increased the mortality. Infect Drug Resist. 2018; 11:2021–2030. https://doi.org/10.2147/IDR.S169432 PMID: 30464544

105. Palavutitotai N, Jitmuang A, Tongsai S, Kiratisin P, Angkasekwinai N. Epidemiology and risk factors of extensively drug-resistant Pseudomonas aeruginosa infections. PLoS ONE. 2018; 13(2). https://doi.org/10.1371/journal.pone.0193431 PubMed Central PMCID: PMC29470531. PMID: 29470531

106. Porto JP, Santos RO, Gontijo Filho PP, Ribas RM. Active surveillance to determine the impact of methicillin resistance on mortality in patients with bacteremia and influences of the use of antibiotics on the development of MRSA infection. Rev Soc Bras Med Trop. 2013; 46(6):713–8. Epub 2014/01/30. https://doi.org/10.1590/0037-8682-0199-2013 PMID: 24474012.

107. Rao C, Dhawan B, Vishnubhatla S, Kapil A, Das B, Sood S. Clinical and molecular epidemiology of vancomycin-resistant Enterococcus faecium bacteremia from an Indian tertiary hospital. Eur J Clin Microbiol Infect Dis. 2021; 40(2):303–14. https://doi.org/10.1007/s10096-020-04030-3 PubMed Central PMCID: PMC32909085. PMID: 32909085

108. Seboxa T, Amogne W, Abebe W, Tsegaye T, Azazh A, Hailu W, et al. High Mortality from Blood Stream Infection in Addis Ababa, Ethiopia, Is Due to Antimicrobial Resistance. PLoS ONE. 2015; 10 (12):e0144944. Epub 2015/12/17. https://doi.org/10.1371/journal.pone.0144944 PMID: 26670718; PubMed Central PMCID: PMC4682922.

109. Serefhanoglu K, Turan H, Timurkaynak FE, Arslan H. Bloodstream infections caused by ESBL-producing E. coli and K. pneumoniae: Risk factors for multidrug-resistance. Braz J Infect Dis. 2009; 13 (6):403–7. https://doi.org/10.1590/s1413-86702009000600003 PubMed Central PMCID: PMC20464329. PMID: 20464329

110. Shi SH, Kong HS, Xu J, Zhang WJ, Jia CK, Wang WL, et al. Multidrug resistant gram-negative bacilli as predominant bacteremic pathogens in liver transplant recipients. Transplant Infect Dis. 2009; 11 (5):405–12. https://doi.org/10.1111/j.1399-3062.2009.00421.x PubMed Central PMCID: PMC19638006. PMID: 19638006

111. Shi N, Kang J, Wang S, Song Y, Yin D, Li X, et al. Bacteriological Profile and Antimicrobial Susceptibility Patterns of Gram-Negative Bloodstream Infection and Risk Factors Associated with Mortality and Drug Resistance: A Retrospective Study from Shanxi, China. Infect Drug Resist. 2022; 15:3561. https://doi.org/10.2147/IDR.S370326 PMID: 35833010

112. Sirijatuphat R, Sripanidkulchai K, Boonyasiri A, Rattanaumpawan P, Supapueng O, Kiratisin P, et al. Implementation of global antimicrobial resistance surveillance system (GLASS) in patients with bacteremia. PLoS ONE. 2018; 13(1). https://doi.org/10.1371/journal.pone.0190132 PubMed Central PMCID: PMC29298323. PMID: 29298323

113. de Moraes LS, Magalhaes GLG, Soncini JGM, Pelisson M, Perugini MRE, Vespero EC. High mortality from carbapenem-resistant Klebsiella pneumoniae bloodstream infection. Microb Pathog. 2022; 167:105519. https://doi.org/10.1016/j.micpath.2022.105519 PMID: 35483557

114. Steinhaus N, Al-Talib M, Ive P, Boyles T, Bamford C, Davies MA, et al. The management and outcomes of Staphylococcus aureus bacteraemia at a South African referral hospital: A prospective observational study. Int J Infect Dis. 2018; 73:78–84. Epub 2018/06/17. https://doi.org/10.1016/j.ijid.2018.06.004 PMID: 29908251.

115. Stewardson AJ, Marimuthu K, Sengupta S, Allignol A, El-Bouseary M, Carvalho MJ, et al. Effect of carbapenem resistance on outcomes of bloodstream infection caused by Enterobacteriaceae in low-income and middle-income countries (PANORAMA): a multinational prospective cohort study. Lancet Infect Dis. 2019; 19(6):601–10. Epub 2019/05/03. https://doi.org/10.1016/S1473-3099(18)30792-8 PMID: 31047852.

116. Stoma I, Karpov I, Milanovich N, Uss A, Iskrov I. Risk factors for mortality in patients with bloodstream infections during the pre-engraftment period after hematopoietic stem cell transplantation. Blood Res. 2016; 51(2):102–6. Epub 2016/07/07. https://doi.org/10.5045/br.2016.51.2.102 PMID: 27382554; PubMed Central PMCID: PMC4931927.

117. Tang Y, Xu C, Xiao H, Wang L, Cheng Q, Li X. Gram-negative bacteria bloodstream infections in patients with hematological malignancies–the impact of pathogen type and patterns of antibiotic resistance: a Retrospective Cohort Study. Infect Drug Resist. 2021; 14:3115. https://doi.org/10.2147/IDR.S322812 PMID: 34413656

118. Tian L, Tan R, Chen Y, Sun J, Liu J, Qu H, et al. Epidemiology of Klebsiella pneumoniae bloodstream infections in a teaching hospital: factors related to the carbapenem resistance and patient mortality. Antimicrob Resist Infect Control. 2016; 5:48. Epub 2016/11/29. https://doi.org/10.1186/s13756-016-0145-0 PMID: 27891222; PubMed Central PMCID: PMC5114729.

119. Topeli A, Unal S, Akalin HE. Risk factors influencing clinical outcome in Staphylococcus aureus bacteraemia in a Turkish University Hospital. Int J Antimicrob Agents. 2000; 14(1):57–63. Epub 2000/03/16. https://doi.org/10.1016/s0924-8579(99)00147-8 PMID: 10717502.

120. Traverso F, Peluffo M, Louge M, Funaro F, Suasnabar R, Cepeda R. [Impact of methicillin resistance on mortality and surveillance of vancomycin susceptibility in bacteremias caused by Staphylococcus aureus]. Rev Argent Microbiol. 2010; 42(4):274–8. Epub 2011/01/14. https://doi.org/10.1590/s0325-75412010000400007 PMID: 21229197.

121. Tu B, Bi J, Wu D, Zhao P, Shi L, Xie Y, et al. Bloodstream infection due to Escherichia coli in liver cirrhosis patients: clinical features and outcomes. Oncotarget. 2018; 9(87):35780–9. Epub 2018/12/06. https://doi.org/10.18632/oncotarget.23200 PMID: 30515269; PubMed Central PMCID: PMC6254670.

122. Tuon FF, Gortz LW, Rocha JL. Risk factors for pan-resistant Pseudomonas aeruginosa bacteremia and the adequacy of antibiotic therapy. Braz J Infect Dis. 2012; 16(4):351–6. https://doi.org/10.1016/j.bjid.2012.06.009 PubMed Central PMCID: PMC22846123. PMID: 22846123

123. Valderrama SL, González PF, Caro MA, Ardila N, Ariza B, Gil F, et al. Risk factors for hospital-acquired bacteremia due to carbapenem-resistant Pseudomonas aeruginosa in a Colombian hospital. Biomedica. 2016; 36:69–77. https://doi.org/10.7705/biomedica.v36i2.2784 PubMed Central PMCID: PMC27622627. PMID: 27622627

124. Wang Q, Zhang Y, Yao X, Xian H, Liu Y, Li H, et al. Risk factors and clinical outcomes for carbapenem-resistant Enterobacteriaceae nosocomial infections. Eur J Clin Microbiol Infect Dis. 2016; 35 (10):1679–89. Epub 2016/07/13. https://doi.org/10.1007/s10096-016-2710-0 PMID: 27401905.

125. Wang Z, Qin RR, Huang L, Sun LY. Risk Factors for Carbapenem-resistant Klebsiella pneumoniae Infection and Mortality of Klebsiella pneumoniae Infection. Chin Med J (Engl). 2018; 131(1):56–62. Epub 2017/12/23. https://doi.org/10.4103/0366-6999.221267 PMID: 29271381; PubMed Central PMCID: PMC5754959.

126. Wei J, Zhu QL, Sun Z, Wang C. [The impact of carbapenem-resistance Pseudomonas aeruginosa infections on mortality of patients with hematological disorders]. Zhonghua Nei Ke Za Zhi. 2020; 59 (5):353–9. Epub 2020/05/07. https://doi.org/10.3760/cma.j.cn112138-20191104-00728 PMID: 32370463.

127. Wu X, Shi Q, Shen S, Huang C, Wu H. Clinical and bacterial characteristics of Klebsiella pneumoniae affecting 30-day mortality in patients with bloodstream infection. Front Cell Infect Microbiol. 2021;11. https://doi.org/10.3389/fcimb.2021.688989 PMID: 34604103

128. Xiao T, Yu W, Niu T, Huang C, Xiao Y. A retrospective, comparative analysis of risk factors and outcomes in carbapenem-susceptible and carbapenem-nonsusceptible Klebsiella pneumoniae bloodstream infections: tigecycline significantly increases the mortality. Infect Drug Resist. 2018; 11:595–606. Epub 2018/05/08. https://doi.org/10.2147/IDR.S153246 PMID: 29731648; PubMed Central PMCID: PMC5926074.

129. Xiao T, Zhu Y, Zhang S, Wang Y, Shen P, Zhou Y, et al. A Retrospective Analysis of Risk Factors and Outcomes of Carbapenem-Resistant Klebsiella pneumoniae Bacteremia in Nontransplant Patients. J Infect Dis. 2020; 221(Suppl 2):S174–s83. Epub 2020/03/17. https://doi.org/10.1093/infdis/jiz559 PMID: 32176799.

130. Xie Y, Tu B, Zhang X, Bi J, Shi L, Zhao P, et al. Investigation on outcomes and bacterial distributions of liver cirrhosis patients with gram-negative bacterial bloodstream infection. Oncotarget. 2018; 9 (3):3980–95. Epub 2018/02/10. https://doi.org/10.18632/oncotarget.23582 PMID: 29423099; PubMed Central PMCID: PMC5790516.

131. Xu X, Wu S, Xie Y, Chen Z, Ma Y, He C, et al. Risk factors of bloodstream infections caused by vancomycin-resistant Enterococcus. Chin J Infect Chemother. 2015; 15(5):447–451.

132. Yang S, Sun J, Wu X, Zhang L. Determinants of Mortality in Patients with Nosocomial Acinetobacter baumannii Bacteremia in Southwest China: A Five-Year Case-Control Study. Can J Infect Dis Med Microbiol. 2018; 2018:3150965. Epub 2018/07/06. https://doi.org/10.1155/2018/3150965 PMID: 29973964; PubMed Central PMCID: PMC6008754.

133. Yang K, Xiao T, Shi Q, Zhu Y, Ye J, Zhou Y, et al. Socioeconomic burden of bloodstream infections caused by carbapenem-resistant and carbapenem-susceptible Pseudomonas aeruginosa in China. J Glob Antimicrob Resist. 2021; 26:101–107. https://doi.org/10.1016/j.jgar.2021.03.032 PMID: 34023532

134. Ye QF, Zhao J, Wan QQ, Qiao BB, Zhou JD. Frequency and clinical outcomes of ESKAPE bacteremia in solid organ transplantation and the risk factors for mortality. Transpl Infect Dis. 2014; 16(5):767–74. Epub 2014/08/16. https://doi.org/10.1111/tid.12278 PMID: 25124187.

135. Yilmaz M, Elaldi N, Balkan İ, Arslan F, Batırel AA, Bakıcı MZ, et al. Mortality predictors of Staphylococcus aureus bacteremia: a prospective multicenter study. Ann Clin Microbiol Antimicrob. 2016; 15:7. Epub 2016/02/11. https://doi.org/10.1186/s12941-016-0122-8 PMID: 26860463; PubMed Central PMCID: PMC4748515.

136. Yuan Y, Wang J, Yao Z, Ma B, Li Y, Yan W, et al. Risk Factors for Carbapenem-Resistant Klebsiella pneumoniae Bloodstream Infections and Outcomes. Infect Drug Resist. 2020; 13:207–15. Epub 2020/03/12. https://doi.org/10.2147/IDR.S223243 PMID: 32158236; PubMed Central PMCID: PMC6985980.

137. Zhang G, Zhang M, Sun F, Zhou J, Wang Y, Zhu D, et al. Epidemiology, mortality and risk factors for patients with K. pneumoniae bloodstream infections: Clinical impact of carbapenem resistance in a tertiary university teaching hospital of Beijing. J Infect Public Health. 2020; 13(11):1710–4. Epub 2020/10/22. https://doi.org/10.1016/j.jiph.2020.09.012 PMID: 33082112.

138. Zhang Q, Gao HY, Li D, Li Z, Qi SS, Zheng S, et al. Clinical outcome of Escherichia coli bloodstream infection in cancer patients with/without biofilm formation: a single-center retrospective study. Infect Drug Resist. 2019; 12:359–71. Epub 2019/02/28. https://doi.org/10.2147/IDR.S192072 PMID: 30809097; PubMed Central PMCID: PMC6377049.

139. Zhang Q, Zhang W, Li Z, Bai C, Li D, Zheng S, et al. Bacteraemia due to AmpC β-lactamase-producing Escherichia coli in hospitalized cancer patients: risk factors, antibiotic therapy, and outcomes. Diagn Microbiol Infect Dis. 2017; 88(3):247–51. Epub 2017/04/25. https://doi.org/10.1016/j.diagmicrobio.2017.04.006 PMID: 28434898.

140. Zhang Y, Du M, Chang Y, Chen LA, Zhang Q. Incidence, clinical characteristics, and outcomes of nosocomial Enterococcus spp. bloodstream infections in a tertiary-care hospital in Beijing, China: a four-year retrospective study. Antimicrob Resist Infect Control. 2017; 6:73. Epub 2017/07/07. https://doi.org/10.1186/s13756-017-0231-y PMID: 28680588; PubMed Central PMCID: PMC5496248.

141. Zhang Y, Li Y, Zeng J, Chang Y, Han S, Zhao J, et al. Risk Factors for Mortality of Inpatients with Pseudomonas aeruginosa Bacteremia in China: Impact of Resistance Profile in the Mortality. Infect Drug Resist. 2020; 13:4115–23. Epub 2020/11/20. https://doi.org/10.2147/IDR.S268744 PMID: 33209041; PubMed Central PMCID: PMC7669529.

142. Zhao S, Wu Y, Dai Z, Chen Y, Zhou X, Zhao J. Risk factors for antibiotic resistance and mortality in patients with bloodstream infection of Escherichia coli. Eur J Clin Microbiol Infect Dis. 2022; 41 (5):713–721. https://doi.org/10.1007/s10096-022-04423-6 PMID: 35190911

143. Zhao Y, Lin Q, Liu L, Ma R, Chen J, Shen Y, et al. Risk Factors and Outcomes of Antibiotic-resistant Pseudomonas aeruginosa Bloodstream Infection in Adult Patients With Acute Leukemia. Clin Infect Dis. 2020; 71(Supplement_4):S386–s93. Epub 2020/12/29. https://doi.org/10.1093/cid/ciaa1522 PMID: 33367574.

144. Zheng SH, Cao SJ, Xu H, Feng D, Wan LP, Wang GJ, et al. Risk factors, outcomes and genotypes of carbapenem-nonsusceptible Klebsiella pneumoniae bloodstream infection: a three-year retrospective study in a large tertiary hospital in Northern China. Infect Dis (Lond). 2018; 50(6):443–51. Epub 2018/01/06. https://doi.org/10.1080/23744235.2017.1421772 PMID: 29303020.

145. Zheng X, Wang JF, Xu WL, Xu J, Hu J. Clinical and molecular characteristics, risk factors and outcomes of Carbapenem-resistant Klebsiella pneumoniae bloodstream infections in the intensive care unit. Antimicrob Resist Infect Control. 2017; 6:102. Epub 2017/10/14. https://doi.org/10.1186/s13756-017-0256-2 PMID: 29026535; PubMed Central PMCID: PMC5625719 Institutional Review Board of the First Affiliated Hospital, College of Medicine, Zhejiang University. This research was conducted in compliance with the tenets of the Helsinki Declaration. CONSENT FOR PUBLICATION: Not applicable. COMPETING INTERESTS: The authors declare that they have no competing interests. PUBLISHER'S NOTE: Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

146. Zhou H, Yao Y, Zhu B, Ren D, Yang Q, Fu Y, et al. Risk factors for acquisition and mortality of multidrug-resistant Acinetobacter baumannii bacteremia: A retrospective study from a Chinese hospital. Medicine (Baltimore). 2019; 98(13):e14937. Epub 2019/03/29. https://doi.org/10.1097/MD.0000000000014937 PMID: 30921191; PubMed Central PMCID: PMC6456023.

147. Zhu C, Liu C, Wu B, Wu Q, Huang D. Analysis of antibiotic resistance in the staphylococcus aureus strains isolated from bloodstream infections and associated patient outcome. Chin J Infect Chemother. 2016; 16 (1):1–4. https://doi.org/10.16718/j.1009-7708.2016.01.001

148. Zhu Y, Xiao T, Wang Y, Yang K, Zhou Y, Luo Q, et al. Socioeconomic Burden of Bloodstream Infections Caused by Carbapenem-Resistant Enterobacteriaceae. Infect Drug Resist. 2021; 14:5385. https://doi.org/10.2147/IDR.S341664 PMID: 34938086

149. Zlatian O, Balasoiu AT, Balasoiu M, Cristea O, Docea AO, Mitrut R, et al. Antimicrobial resistance in bacterial pathogens among hospitalised patients with severe invasive infections. Exp Ther Med. 2018; 16(6):4499–4510. https://doi.org/10.3892/etm.2018.6737 PMID: 30542398

150. Zou XL, Feng DY, Wu WB, Yang HL, Zhang TT. Blood urea nitrogen to serum albumin ratio independently predicts 30-day mortality and severity in patients with Escherichia coli bacteraemia. Med Clin (Barc). 2020. Epub 2020/10/17. https://doi.org/10.1016/j.medcli.2020.06.060 PMID: 33059940.

151. Zhang WL, Huang J, Wu SY, Liu Y, Long F, Xiao YL, et al. [Antibiotic Resistance and Risk Factors for Mortality of Blood Stream Infections (BSIs) with Escherichia coli in Patients with Hematological Malignancies]. Sichuan Da Xue Xue Bao Yi Xue Ban. 2018; 49(1):133–5. Epub 2018/05/08. PMID: 29737104.

152. Zhang Y, Zhu W, Zhang J, Chen B. The risk factors associated with bloodstream infections caused by multi-drug resistant acinetobacter baumannii. Chin J Infect Chemother. 2017; 17(2):134–139. https://doi.org/10.16718/j.1009-7708.2017.02.003

153. Jit M, Ng DHL, Luangasanatip N, Sandmann F, Atkins KE, Robotham JV, et al. Quantifying the economic cost of antibiotic resistance and the impact of related interventions: rapid methodological review, conceptual framework and recommendations for future studies. BMC Med. 2020; 18(1):1–14.

154. Murray CJ, Ikuta KS, Sharara F, Swetschinski L, Aguilar GR, Gray A, et al. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. Lancet. 2022.

155. Zhang Y, Chen X-L, Huang A-W, Liu S-L, Liu W-J, Zhang N, et al. Mortality attributable to carbapenem-resistant Pseudomonas aeruginosa bacteremia: a meta-analysis of cohort studies. Emerg Microbes Infect. 2016; 5(1):1–6. https://doi.org/10.1038/emi.2016.22 PMID: 27004762

156. Paul M, Weinberger M, Siegman-Igra Y, Lazarovitch T, Ostfeld I, Boldur I, et al. Acinetobacter baumannii: emergence and spread in Israeli hospitals 1997–2002. J Hosp Infect. 2005; 60(3):256–260. https://doi.org/10.1016/j.jhin.2005.01.007 PMID: 15893851

157. Chopra T, Marchaim D, Awali RA, Krishna A, Johnson P, Tansek R, et al. Epidemiology of bloodstream infections caused by Acinetobacter baumannii and impact of drug resistance to both carbapenems and ampicillin-sulbactam on clinical outcomes. Antimicrob Agents Chemother. 2013; 57 (12):6270–6275. https://doi.org/10.1128/AAC.01520-13 PMID: 24100492

158. 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. https://doi.org/10.1093/cid/cix411 PMID: 28472416

159. Cosgrove SE. The relationship between antimicrobial resistance and patient outcomes: mortality, length of hospital stay, and health care costs. Clin Infect Dis. 2006;42(Supplement_2):S82–S89. https://doi.org/10.1086/499406 PMID: 16355321

160. Tsuzuki S, Yu J, Matsunaga N, Ohmagari N. Length of stay, hospitalisation costs and in-hospital mortality of methicillin-susceptible and methicillin-resistant Staphylococcus aureus bacteremia in Japan. Public Health. 2021; 198:292–296. https://doi.org/10.1016/j.puhe.2021.07.046 PMID: 34507134

161. Graffunder EM, Venezia RA. Risk factors associated with nosocomial methicillin-resistant Staphylococcus aureus (MRSA) infection including previous use of antimicrobials. J Antimicrob Chemother. 2002; 49(6):999–1005. https://doi.org/10.1093/jac/dkf009 PMID: 12039892

162. Ben-David D, Kordevani R, Keller N, Tal I, Marzel A, Gal-Mor O, et al. Outcome of carbapenem resistant Klebsiella pneumoniae bloodstream infections. Clin Microbiol Infect. 2012; 18(1):54–60. https://doi.org/10.1111/j.1469-0691.2011.03478.x PMID: 21722257

163. Van Boeckel TP, Gandra S, Ashok A, Caudron Q, Grenfell BT, Levin SA, et al. Global antibiotic consumption 2000 to 2010: an analysis of national pharmaceutical sales data. Lancet Infect Dis. 2014; 14 (8):742–750. https://doi.org/10.1016/S1473-3099(14)70780-7 PMID: 25022435

164. Klein EY, Van Boeckel TP, Martinez EM, Pant S, Gandra S, Levin SA, et al. Global increase and geographic convergence in antibiotic consumption between 2000 and 2015. Proc Natl Acad Sci U S A. 2018; 115(15):E3463–E3470. https://doi.org/10.1073/pnas.1717295115 PMID: 29581252

165. Qu J, Huang Y, Lv X. Crisis of antimicrobial resistance in China: now and the future. Front Microbiol. 2019; 10:2240. https://doi.org/10.3389/fmicb.2019.02240 PMID: 31611863

166. 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. https://doi.org/10.1016/j.ijid.2015.06.014 PMID: 26129972

167. Huang W, Qiao F, Zhang Y, Huang J, Deng Y, Li J, et al. In-hospital medical costs of infections caused by carbapenem-resistant Klebsiella pneumoniae. Clin Infect Dis. 2018; 67(suppl_2):S225–S230. https://doi.org/10.1093/cid/ciy642 PMID: 30423052

168. World Health Organization. Sustainable Development Goals (SDGs) AMR indicator 2022 [cited 2022 Mar 29]. Available from: https://www.who.int/data/gho/data/themes/topics/global-antimicrobial-resistance-surveillance-system-glass/sustainable-development-goals-amr-indicator.

169. MAAP: Mapping AMR and AMU partnership. Incomplete antimicrobial resistance (AMR) data in Africa: The crisis within the crisis. 2022.

170. de Kraker ME, Lipsitch M. Burden of antimicrobial resistance: compared to what? Epidemiol Rev. 2021; 43(1):53–64.

171. Pezzani MD, Tornimbene B, Pessoa-Silva C, de Kraker M, Rizzardo S, Salerno ND, et al. Methodological quality of studies evaluating the burden of drug-resistant infections in humans due to the WHO Global Antimicrobial Resistance Surveillance System target bacteria. Clin Microbiol Infect. 2021; 27 (5):687–696. https://doi.org/10.1016/j.cmi.2021.01.004 PMID: 33450389

172. De Angelis G, Murthy A, Beyersmann J, Harbarth S. Estimating the impact of healthcare-associated infections on length of stay and costs. Clin Microbiol Infect. 2010; 16(12):1729–1735. https://doi.org/10.1111/j.1469-0691.2010.03332.x PMID: 20673257

Chapter 5:

Cost-effectiveness and cost components of pharmaceutical and non-pharmaceutical interventions affecting antibiotic resistance outcomes in hospital patients: A systematic literature review

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Surname/Family Name	Allel Henriquez		
Thesis Title	Impacts of antimicrobial resistance bloodstream infections among hospital patients and potential interventions: a case study in Chile		
Primary Supervisor	Laith Yakob, Dphil		

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Date	25/March/2024

Supervisor Signature	Laith Yakob
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BMJ Global Health

Costs-effectiveness and cost components of pharmaceutical and non-pharmaceutical interventions affecting antibiotic resistance outcomes in hospital patients: a systematic literature review

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ABSTRACT

Introduction Limited information on costs and the cost-effectiveness of hospital interventions to reduce antibiotic resistance (ABR) hinder efficient resource allocation.

Methods We conducted a systematic literature review for studies evaluating the costs and cost-effectiveness of pharmaceutical and non-pharmaceutical interventions aimed at reducing, monitoring and controlling ABR in patients. Articles published until 12 December 2023 were explored using EconLit, EMBASE and PubMed. We focused on critical or high-priority bacteria, as defined by the WHO, and intervention costs and incremental cost-effectiveness ratio (ICER). Following Preferred Reporting Items for Systematic review and Meta-Analysis guidelines, we extracted unit costs, ICERs and essential study information including country, intervention, bacteria-drug combination, discount rates, type of model and outcomes. Costs were reported in 2022 US dollars ($), adopting the healthcare system perspective. Country willingness-to-pay (WTP) thresholds from Woods *et al* 2016 guided cost-effectiveness assessments. We assessed the studies reporting checklist using Drummond's method.

Results Among 20 958 articles, 59 (32 pharmaceutical and 27 non-pharmaceutical interventions) met the inclusion criteria. Non-pharmaceutical interventions, such as hygiene measures, had unit costs as low as $1 per patient, contrasting with generally higher pharmaceutical intervention costs. Several studies found that linezolid-based treatments for methicillin-resistant *Staphylococcus aureus* were cost-effective compared with vancomycin (ICER up to $21 488 per treatment success, all 16 studies' ICERs<WTP). Infection control measures such as hand hygiene and gown usage (ICER=$1160/QALY or $4949 per ABR case averted, all ICERs<WTP) and PCR or chromogenic agar screening for ABR detection were highly cost-effective (eg, ICER=$1206 and $1115 per life-year saved in Europe and the USA). Comparisons were hindered by within-study differences.

Conclusion Robust information on ABR interventions is critical for efficient resource allocation. We highlight cost-effective strategies for mitigating ABR in hospitals, emphasising substantial knowledge gaps, especially in low-income and middle-income countries. Our study

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Pharmaceutical and non-pharmaceutical interventions play a crucial role in global antibiotic resistance (ABR) control and prevention.
⇒ There is a paucity of data on the comprehensive health economic costs and outcomes, with most existing literature reviews targeting specific interventions, such as antimicrobial stewardship.

WHAT THIS STUDY ADDS

⇒ We synthesised global literature on unit costs and effectiveness of pharmaceutical and non-pharmaceutical interventions among hospitalised patients.
⇒ Despite substantial heterogeneity and some studies lacking fundamental cost and methodological considerations (eg, discounting, risk scenarios and outcomes including hospital stay or mortality), we identified several interventions with robust evidence supporting their benefit, translated into cost or utility-adjusted life years averted.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Our results aid decision-making by guiding the allocation of scarce resources for combating ABR in hospitals.
⇒ Further investigations, empirical and methodological, are essential to advance the economic evaluation of interventions to progress toward optimising antibiotic usage and reducing ABB rates in hospitals, especially in low-income and middle-income countries.

serves as a resource for guiding future cost-effectiveness study design and analyses.

PROSPERO registration number CRD42020341827 and CRD42022340064

INTRODUCTION

Antibiotic resistance (ABR) causes an enormous burden on health systems and the global economy.[1–4] According to a recent study by the Global Burden of Disease, approximately 1.27 million deaths worldwide in 2019 were attributable to ABR if all ABR infections were replaced by drug-susceptible infections.[2] The World Bank projects an annual global cost of up to $3.4 trillion by 2030 if no action is taken.[5] The US Centers for Disease Control and Prevention has estimated an annual impact of ABR infections on healthcare and societal costs of approximately $25 billion in the USA.[6] While these estimates are based on limited data, they underscore the severity of ABR. Setting-specific and population-specific strategies designed to alleviate ABR burden by reducing antibiotic usage and resistance transmission are crucial to reducing loss of life and minimising costs.

Economic evaluations provide critical insights for decision-makers about how to allocate limited healthcare budgets to optimise overall population health. Despite finances underlying healthcare management strategy,[7] economic evaluations of alternative interventions are surprisingly scarce. Those that are conducted often fail to capture key costs and outcomes required to decide whether to retain the status quo or take up a novel alternative. For example, daptomycin was the first cyclic lipopeptide with demonstrable activity against vancomycin-resistant gram-positive pathogens. It was shown to have equivalent clinical effectiveness in treating complicated skin infections compared with semi-synthetic penicillin while resulting in shorter hospital stays for patients.[8] Even in this economic evaluation of daptomycin compared with penicillin, however, treatment costs were not explicitly considered, so ambiguity remained over daptomycin's economic dominance.

Studies synthesising the economic evidence base for alternative ABR-mitigating strategies are equally rare. Previous reviews reporting on economic evaluations of interventions to prevent and control ABR are limited.[9–12] Naylor *et al* reviewed the cost-effectiveness of antimicrobial stewardship programmes, with estimates ranging from $540 in inpatient net savings to $24 231 for each prevented death.[9] In a similar review, Huebner *et al* found that targeted control of appropriate antimicrobial agents could save up to $2403 in total antibiotic costs per 100 patient-days.[12] Niewiadomska *et al* reviewed mathematical modelling studies on the population-level transmission of ABR; however, only 9% of reviewed models included details of cost-effectiveness analyses.[10] Among these, universal surveillance and decolonisation programmes were cost-saving in patients with methicillin-resistant *Staphylococcus aureus* (MRSA) infections.[12] Wilton *et al*'s review of studies of the (cost-)effectiveness of interventions for ABR control, including restricting antimicrobials use, prescriber education, use of guidelines for ABR, combination therapies and vaccination,[11] highlighted the paucity of evidence as a key limitation in delivering definitive and actionable recommendations for ABR control.[11]

Our study aims to systematically synthesise the economic evidence for pharmaceutical and non-pharmaceutical interventions to reduce, monitor and control ABR of critical or high-priority bacteria, as defined by the WHO, including colonisation, infection and antibiotic usage, in hospital settings globally from a health system or payer perspective.[13] To our knowledge, this is the first review contrasting all available economic and effectiveness components for both intervention types while focusing on key ABR pathogens. By formalising costs and effectiveness for both intervention types in hospital patients, we offer a comprehensive synthesis of ABR interventions conducted within healthcare settings.

METHODS

We conducted a systematic literature review of the costs and cost-effectiveness of pharmaceutical and non-pharmaceutical interventions to reduce, monitor and control ABR levels in hospitalised patients. We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[14] and the ISPOR (The Professional Society for Health Economics and Outcomes Research)[15] guidelines, and our study was prospectively registered with PROSPERO.[14] The search was conducted on EconLit, EMBASE and PubMed concluding on 12 December 2023.

Search strategy

We used three key concepts to perform our literature search: (1) 'Interventions for antibiotic resistance', (2) 'Hospital' and (3) 'Cost-effectiveness and Economic evaluation'. Economic evaluation filters from InterTASC Information Specialists' Sub-Group search filters were used to capture the cost-effectiveness aspect of the search. The final literature search strategy and details of studies from the initial screening are presented in online supplemental tables SM1–4.

Study selection—inclusion and exclusion criteria

We followed the Patient Population, Intervention, Comparator, Outcome, Setting, Timing (PICOST) framework to present our inclusion and exclusion criteria[16] (online supplemental tables SM1 and 2). Titles and abstracts of identified articles were screened using Rayyan (https://www.rayyan.ai) by two reviewers for eligibility, and a third reviewer checked them for final inclusion. We contrasted our results with the 'ASReview' tool for potential misclassification.[17] The study population was limited to hospital settings; community settings and acquired infections were excluded. We did not restrict our search by language and years. Studies were included

only if the intervention targeted antibiotic-resistant bacterial pathogens listed as critical or high priority by the WHO[18] (online supplemental table SM3). Bacterial pathogens not on the WHO's list were excluded. Pharmaceutical interventions were defined as those that directly involved the use of medication, while all other interventions were classified as non-pharmaceutical. Economic evaluations included only complete evaluations (eg, cost-effectiveness, cost-utility, cost-benefit) and were defined as a comparative analysis of the costs and reported the effectiveness of alternative programmes, following Drummond *et al*.[19] Only evaluations using a healthcare or payer perspective were included; very few studies used a societal perspective (n=2). While both perspectives are similar, the healthcare perspective focuses on the costs incurred by providers in delivering medical care and health services to patients and the payer perspective includes the financial aspects of healthcare from the viewpoint of the organisation that funds or reimburses costs to providers. Conference abstracts, editorials and systematic literature reviews were excluded. Papers had to present measures of costs and an incremental cost-effectiveness ratio 'ICER' or incremental net monetary and health benefit analyses (ie, a comparison between strategies presenting an ICER).

Data extraction

We extracted study characteristics and outcomes, including unit costs, effectiveness and cost-effectiveness rates following the Campbell and Cochrane Economic Methods group and a recent protocol for economic appraisal to address ABR which includes specific guidance on reporting health economic data in systematic reviews.[13 20] For study characteristics, we retrieved the study's year, author, title, perspective, country, currency, pathogen, intervention, comparator, type of economic evaluation, source of effectiveness data, source of costing and primary outcome. Implementation costs, such as training, were excluded. We also extracted information on the analytical model used, time horizon, discount rate, measure of effectiveness, results of the base-case analysis (eg, ICER) and sensitivity analyses (eg, univariate or multivariate analyses and parameter effects on outcomes). Costs were first converted to US dollars (using currency-specific exchange rates) and inflated to 2022 US dollars based on Gross Domestic Product deflators.[21] We used the reported costs year, or, if absent, using the publication year instead for exchange rate conversion and subsequent inflation.

Data synthesis and analysis

We summarise the included data by providing disaggregated unit costs and effectiveness per study and intervention type (pharmaceutical and non-pharmaceutical). Cost-effectiveness estimates were primarily characterised as ICER, including (1) $/(quality-adjusted life-years 'QALY' gained), (2) $/(disability-adjusted life-years 'DALYs' gained), (3) $/ABR infection averted or (4) $/life-year gained. A dominant strategy refers to a scenario where the incremental cost of the intervention is less than the comparator, and the incremental efficacy is greater than the comparator. Willingness-to-pay (WTP) thresholds per efficiency outcomes were also included, if provided. We identified the gap between individuals' WTP and the intervention's real cost-effectiveness to determine the feasibility of the programme in the setting where it was evaluated. Cost-effectiveness thresholds, based on countries' opportunity costs, were employed for strategy comparative purposes and to define resource gaps following Woods *et al*.[22]

Assessment of quality of reporting and risk of bias

We used Drummond *et al*'s checklist for assessing economic evaluations.[23] The checklist comprises 10 questions for evaluating reporting quality in economic evaluations, assigning a 1 (or 0) to each question if the article included the safeguard (online supplemental table SM5). The aggregate results provided an economic reporting quality appraisal of below average (1–7 points), average (8 points), and above average (9–10 points).

Microsoft Excel was used to create a database of the study characteristics, unit costs and appraisal of studies following the checklist (see https://bit.ly/SR_amrCEingredients).

Patient and public involvement

The patients and the public were not involved in the design, conduct, or reporting of our research.

RESULTS

Study identification and selection

Figure 1 describes the PRISMA chart for the results of our literature review. We found 20 958 articles in EconLit, EMBASE and PubMed, of which 1744 were duplicated. We excluded 18 811 records due to not fulfilling our inclusion criteria (figure 1). Finally, 403 studies were assessed for full eligibility and 59 (32 on pharmaceutical and 27 on non-pharmaceutical interventions) presented a complete cost-effectiveness analysis and were included in our analytical sample.

Characterisation of studies included

Most reports on pharmaceutical interventions were focused on MRSA (20 of 32 studies, 63%). The remaining studies analysed carbapenem-resistant gram-negative pathogens contrasting ceftazidime avibactam versus colistin or alternative drug-based treatments. MRSA interventions were focused on comparing linezolid, or any relatively new drug (eg, daptomycin), with vancomycin, the established treatment. Studies on non-pharmaceutical interventions were wide-ranging but most explored surveillance or screening methods. Reports included improved surveillance and wide PCR or chromogenic-based surveillance and testing (n=11), multiple surveillance schemes including testing, decolonisation and/or isolation (n=8), infection control

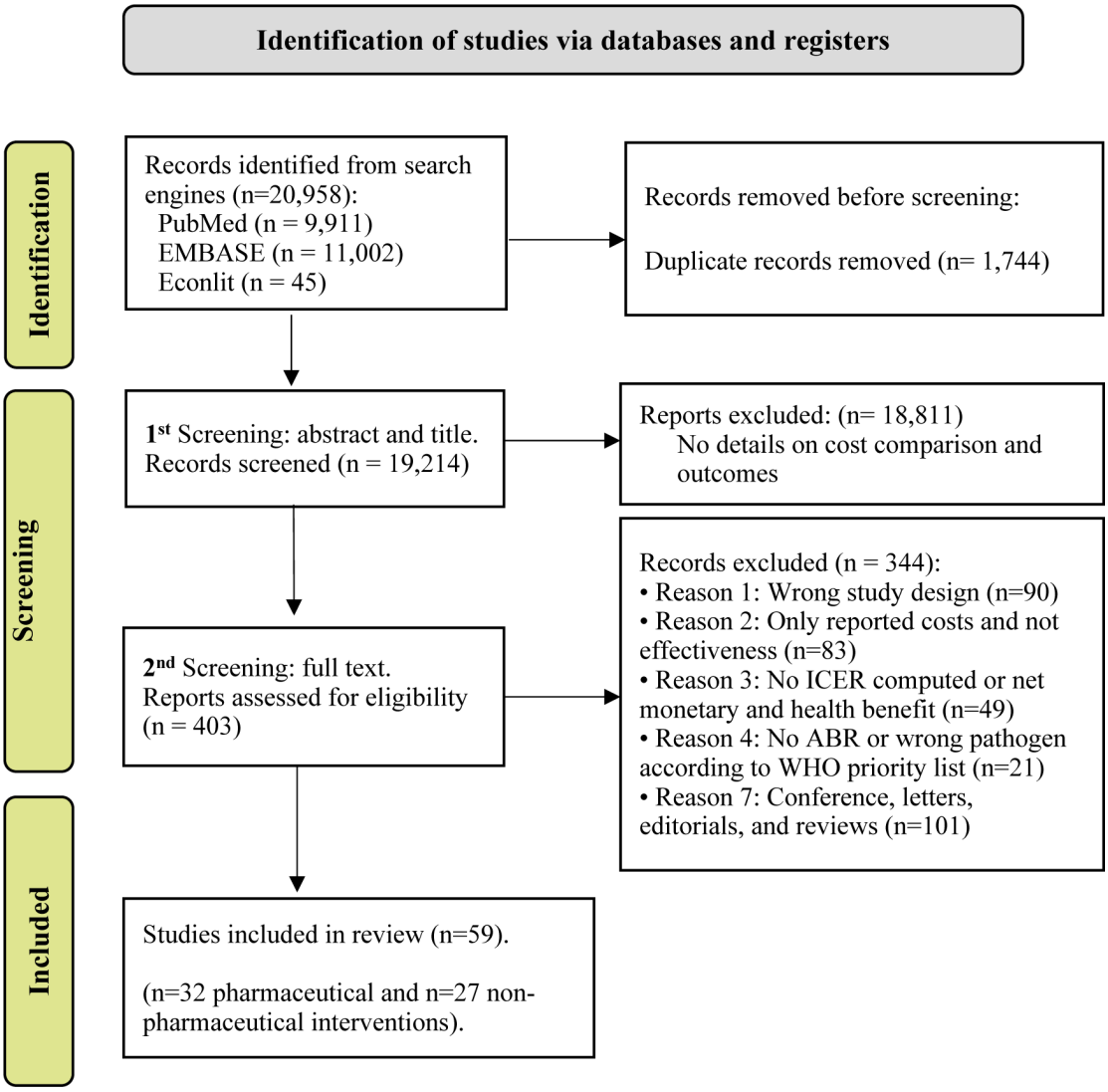

Figure 1 Preferred Reporting Items for Systematic review and Meta-Analysis flowchart for the inclusion and exclusion of relevant studies. 'n' stands for the number of articles included/excluded at each stage. ABR, antibiotic resistance; ICER, incremental cost-effectiveness ratio. Source: Moher *et al* 2009.

and hygiene including use of gowns and hand hygiene practices (n=3) and miscellaneous (n=5; eg, antibiotic stewardship, pre-emptive isolation, whole-genome sequencing). Generally, these interventions targeted MRSA (n=16, 59%), carbapenem-resistant Enterobacteriaceae (CRE) (n=4, 13%) and vancomycin-resistant Enterococci (VRE) (n=4), and compared the intervention's effectiveness with current practice, which was typically the absence of the intervention. Most studies were conducted in high-income countries, mainly the USA (n=26, 44%; see figure 2). We found two regional studies; one using European data and the second in Africa. Decision analytical models were usually employed for the analyses (eg, decision trees, Markov and stochastic simulation models), often using a one-way sensitivity analysis. Time horizons and discount rates were reported inconsistently, and target populations usually consisted of all hospital patients and patients with pneumonia. See online supplemental tables SM6 and 7 for a full description of the studies' characteristics.

Unit costs of interventions

Online supplemental table SM8 provides a cost breakdown for pharmaceutical interventions. Economic costs varied based on factors such as drug components, dosage, length of hospital stay (LOS) and study scale. Bed-day expenses, associated with admissions to general wards and intensive care unit (ICU), constituted the largest portion of total economic costs (~50%–90%). Drugs represented about 10% of total costs (adjacent therapies, rehabilitation and diagnostic were costlier), with drugs like daptomycin and linezolid being notably more expensive, approximately 200% greater than vancomycin[24 25] (online supplemental table SM8). For instance, Niederman *et al* reported the cost of intravenous linezolid (600 mg) as $107 per dose, while vancomycin costed $5.8 for 1 g intravenous administration.[26]

Online supplemental table SM9 shows an itemised breakdown of the non-pharmaceutical interventions' unit costs. Hospitalisation and additional costs were the highest cost component. Test or intervention unit costs

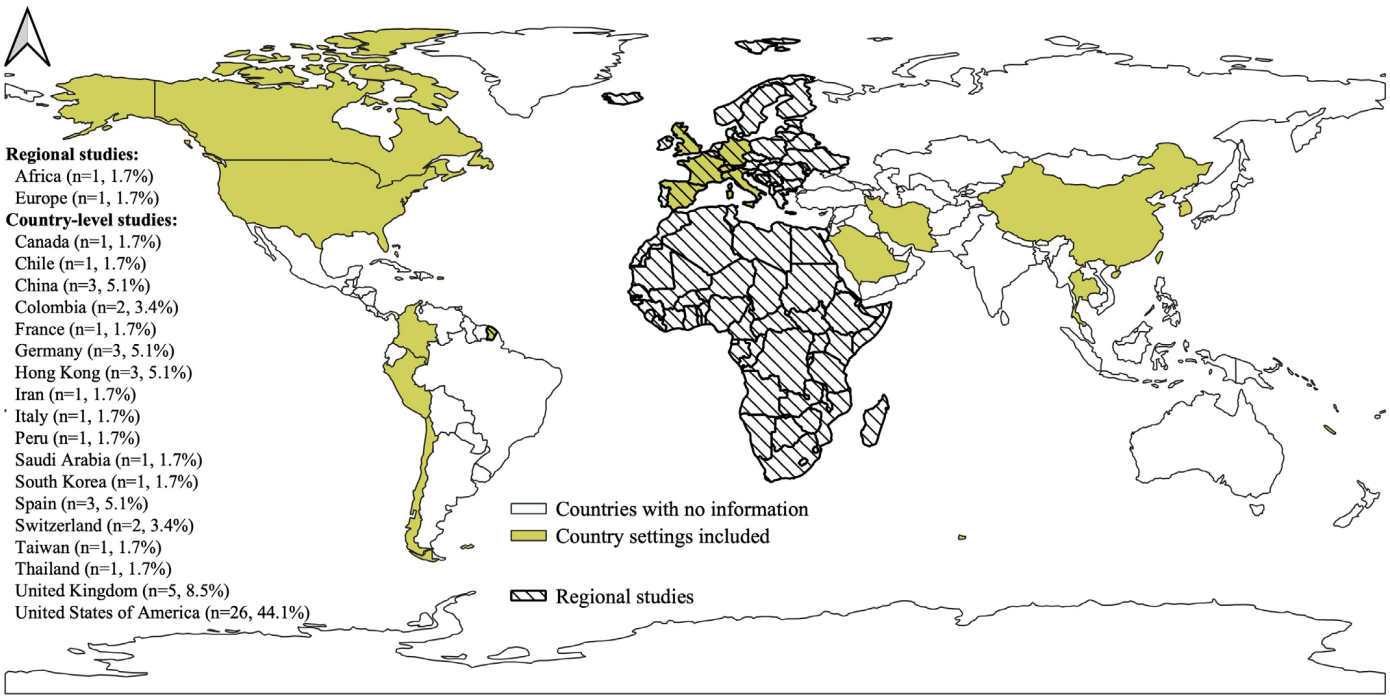

Figure 2 Geographical distribution of the included studies (N=59) Notes: Geographical Information System Open-Source Geospatial Foundation Project (QGIS) V.2022 was used for map visualisation.

varied widely, ranging from $1 per patient (eg, use of gown or gloves[27]) to as high as $108 for genome sequencing,[28] $103 for decolonisation,[29] $598 for isolation[30] and $652 for infection control bundles[31] per patient. The lowest costs among non-pharmaceutical interventions were also those involving screening or surveillance, due to their being single-step procedures incurring no overhead or operating costs (eg, PCRs, chromogenic agar or electronic registry).

Cost-effectiveness and outcomes

Online supplemental Table SM6 displays studies' strategies and cost-effectiveness (eg, ICERs) of the pharmaceutical (I) and non-pharmaceutical (II) interventions.

Pharmaceutical interventions

Linezolid versus vancomycin

For patients with complicated skin and skin structure infections (cSSSI), linezolid consistently emerged as a cost-effective and dominant strategy compared with vancomycin (online supplemental table SM6, panel I).[24 32–35] For instance, McKinnon *et al*[32] reported a mean cost of $7077 (SD=$5752) for linezolid versus $8709 (SD=$7307) for vancomycin treatment among patients with cSSSI reporting MRSA infections, with a mean cost difference of $2756 (p value=0.041) due a 2.5 days longer LOS for vancomycin-treated patients. Bounthavong *et al*.,[34] De Cock *et al*[33] and Schürmann *et al*[35] estimated lower hospitalisation costs for linezolid (incremental costs were −$7791, −$1827 and −$1749, respectively) along with higher cure rates (incremental cure rates for first-line MRSA were 13%, 10% and 10%, respectively), compared with vancomycin in patients with cSSSI. Differences were explained by reduced LOS and improved treatment failures due to linezolid oral formulation compared with intravenous vancomycin therapy.

In studies focusing on nosocomial pneumonia,[25 26 36–43] linezolid showed a dominant ICER or ICER ranging from $5726 to $84 823 per death averted or life saved, and between $3179 and $21 488 per cure or treatment success among MRSA-infected patients, compared with vancomycin (online supplemental table SM6, section I). Variations in LOS and its associated economic costs across study settings accounted for differences in ICER. Daniel Mullins *et al* predicted an ICER of $5726 for linezolid per life saved, balancing the higher acquisition costs with enhanced survival rates.[36] De Cock *et al* designed a decision–analytical model using clinical trial data that again favoured linezolid over vancomycin with greater clinical cure (+8.7%) and survival (+13.2%) rates at an additional incremental cost of $420 per treatment cycle.[37] However, Collins *et al*[25] reported a higher ICER per life saved ($84 823) due to limited variation in incremental mortality (≈1%) between linezolid and vancomycin.

Figure 3A shows that the linezolid strategy is beneficial compared with vancomycin at country-specific WTP thresholds (ICER<WTP).

Ceftazidime avibactam *versus colistin or other drugs*

Six studies evaluated the use of ceftazidime avibactam (CZA) versus colistin or other drugs (online supplemental table SM6).[44–49] ICERs ranged between $693 and $113 423 per QALY gained. Goudarzi *et al*[45] and Simon *et al*[47] calculated ICERs equal to $798 and $113 423 per QALY gained among patients infected with CRE,

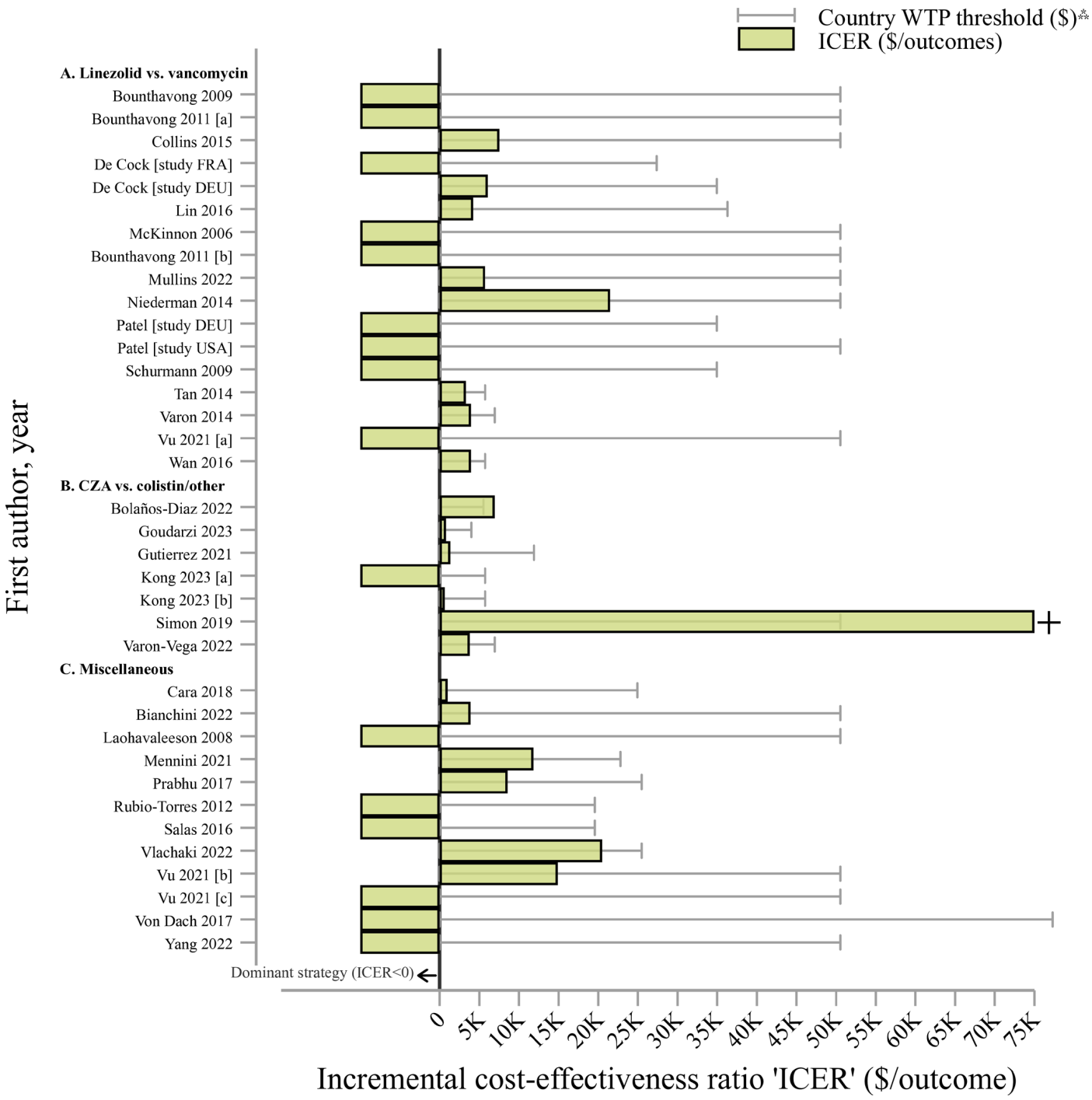

Figure 3 Incremental cost-effectiveness ratios and willingness-to-pay country thresholds among pharmaceutical interventions (in 2022 US dollars, '$'), by study†. Notes: †Studies with letters in brackets (eg, (a)) indicate different strategy evaluations, detailed in online supplemental table SM6 under the strategy column. K=thousands or 1000 units. Interpretation of the incremental cost-effectiveness ratio 'ICER' should be taken with caution as outcomes (eg, deaths averted, cured patients, quality-adjusted life years 'QALYs') used to calculate ICERs varied from study to study. Online supplemental table SM6 contains detailed information by study and outcomes used. *WTP thresholds were extracted from country estimates provided by Woods *et al*[22] and adjusted to 2022 US dollars. A dominant strategy means that interventions are more effective and less costly (ICER<0). We excluded ICER per life saved from Collins *et al*[25] and only ICER$ per QALY was included (ICER per life saved was far beyond the WTP threshold for this study, see online supplemental table SM6). + ICERs were capped at US$75 000 but values are higher (see online supplemental table SM6). CZA, ceftazidime avibactam; 'vs', versus; WTP, willingness-to-pay.

respectively, comparing CZA versus colistin therapy. Incremental QALYs were similar (≈0.5) in both studies, but costs differed. In Goudarzi *et al*, CZA therapy costs were 1.5-times greater for CZA compared with colistin according to Iran health system tariffs. Simon *et al* employed a healthcare system perspective in the USA,

estimating four times greater daily therapy costs for CZA compared with colistin after accounting for LOS, which increased the ICER. In comparison to colistin+meropenem, Gutiérrez and Fandiño[48] and Varón-Vega *et al*[49] reported ICERs of $1340 and $3797 per QALY gained for CZA, respectively. This difference is attributed to CZA showing increased incremental QALYs (+2.3 and +1.8, respectively), while incremental costs were similar ($3151 and $2886, respectively). The slight variation in additional concomitant treatments reported (amikacin+fosfomycin and tigecycline+fosfomycin) played a minor role.

Four studies presented an ICER below the WTP threshold (figure 3B), except Bolaños-Diaz *et al*[44] and Simon *et al*.[47]

Miscellaneous: other combination drug comparison types

Laohavaleeson *et al*[50] found an estimated 0.5-day shorter LOS and savings of $478 favouring telavancin (dominant strategy compared with vancomycin) among MRSA patients, regardless of sensitivity analyses on MRSA drug acquisition costs. Favourable results were shown for IMI/REL (imipenem/cilastatin/relebactam) compared with CMS+IMI (colistin plus imipenem) usage for gram-negative infections (+3.7 QALYs and lower mortality rates; 15.2% compared with 39%). However, the clinical response rate was limited among the IMI/REL group.[51] Additionally, treating patients with complicated intra-abdominal infections following ceftolozane/tazobactam+metronidazole was found to be cost-effective (ICER=$8551 per QALY gained), compared with piperacillin/tazobactam.[52] Mennini *et al*[53] and Vlachaki *et al*[54] assessed meropenem-vaborbactam versus the best available treatment for CRE patients, revealing ICERs of $11 813 and $20 486 per QALY, respectively. The disparity arises from three times higher drug costs for meropenem-vaborbactam compared with the best available therapy in the UK,[54] while in the Italy-based study,[53] it was only 1.5 times higher. Furthermore, the UK-based study attributed higher costs to long-term care tariffs associated with increased survivability among meropenem-vaborbactam.

All miscellaneous interventions presented ICERs below country-specific WTP thresholds (figure 3C).

Non-pharmaceutical interventions

Testing schemes: chromogenic-based agar or PCR

Rapid PCR testing for MRSA detection compared with standard hospital treatments was found to be cost-effective (ICER=$55 and $39 per life-year saved in Europe and the USA, respectively[55]), with ICER=$20 401 per hospital-acquired MRSA case detected in the USA,[27] ICER=$38 911 per MRSA infection averted in Switzerland[56] and ICER=$243 per life year saved in Spain.[57] Single-culture of an anterior nares specimen for universal screening of MRSA patients resulted in an ICER of $14 766 per QALY gained, compared with a 'change nothing' scenario, producing better MRSA control and lower losses attributed to hospital bed-day costs.[58] One study showed that screening for carbapenemase-producing Enterobacteriaceae was cost-saving (ICER=$32 049 per QALY gained) at prevalence levels above 0.3% or if one additional patient were exposed for every infected patient (ie, highly dependent on local transmission settings).[59] Similarly, active PCR among CRE patients, compared with do nothing, was cost-effective at $100 per QALY gained in surgical ICU patients in Hong Kong[60] due to cheaper PCR unit costs compared with an inadequate empirical antibiotic treatment for CRE. Hubben *et al*[61] found selective chromogenic-based agar cost-effective for MRSA detection compared with taking no action (ICER= $5787–$14 538, with 622 infections averted in a moderate MRSA prevalence scenario). Selective PCR was also cost-effective versus chromogenic agar (ICER= $18 349–$51 095). However, universal screening was not cost-effective, as it incurred substantial costs for screening and isolation ($9.2 million incremental costs, with only 28 infections averted; ICER= $184 902–$328 448), surpassing the country WTP threshold (figure 4A).

Hygiene and sanitation

Interventions including proactive infection control, hand hygiene and gown usage were cost-effective at country WTP thresholds (figure 4B).[62–64] For instance, Luangasanatip *et al* found that 20% compliance in healthcare hygiene protocol, versus 10%, was associated with reductions in MRSA bloodstream infections (BSIs) and ICERs of $1160 and $835 per QALY in paediatric and adult ICUs, respectively.[62] Gown usage for 18 months was linked to 58 VRE cases averted in a hospital ICU in the USA (ICER=$2939 per case averted).[64]

Using a combination of multiple surveillance schemes and other methods

Combination schemes containing decolonisation, isolation, testing and surveillance were evaluated.[29 30 65–70] Robotham *et al* combined screening, decolonisation and isolation techniques versus a do-nothing scenario.[29] Universal PCR/chromogenic agar plus decolonisation with mupirocin was cost-effective finding up to $11 005 per QALY gained; however, most interventions involving patient isolation plus PCR for identification were costly due to infrastructure requirements (online supplemental table SM6, panel II; figure 4C). Universal decolonisation for ICU patients with MRSA infections emerged as a dominant strategy in the USA[68] and in Hong Kong,[69] leading to cost savings of $737 and reductions in infection and mortality rates by 0.9% and 0.2%, respectively. Similarly, Nelson *et al*[30] estimated that PCR screening and decolonisation (dominant strategy), had cost-savings of $14 433 and $47 762 and reduced 0.38 and 3.13 MRSA infections per 100 patients compared with PCR screening alone or do-nothing scenarios, respectively. However, in the same veteran hospital in the USA, more comprehensive strategies, comprising screening, contact precautions and infection control combined were more cost-effective, particularly in scenarios with high MRSA transmission rates rather than low transmission in subsequent periods (ICER= $13 904[66] and

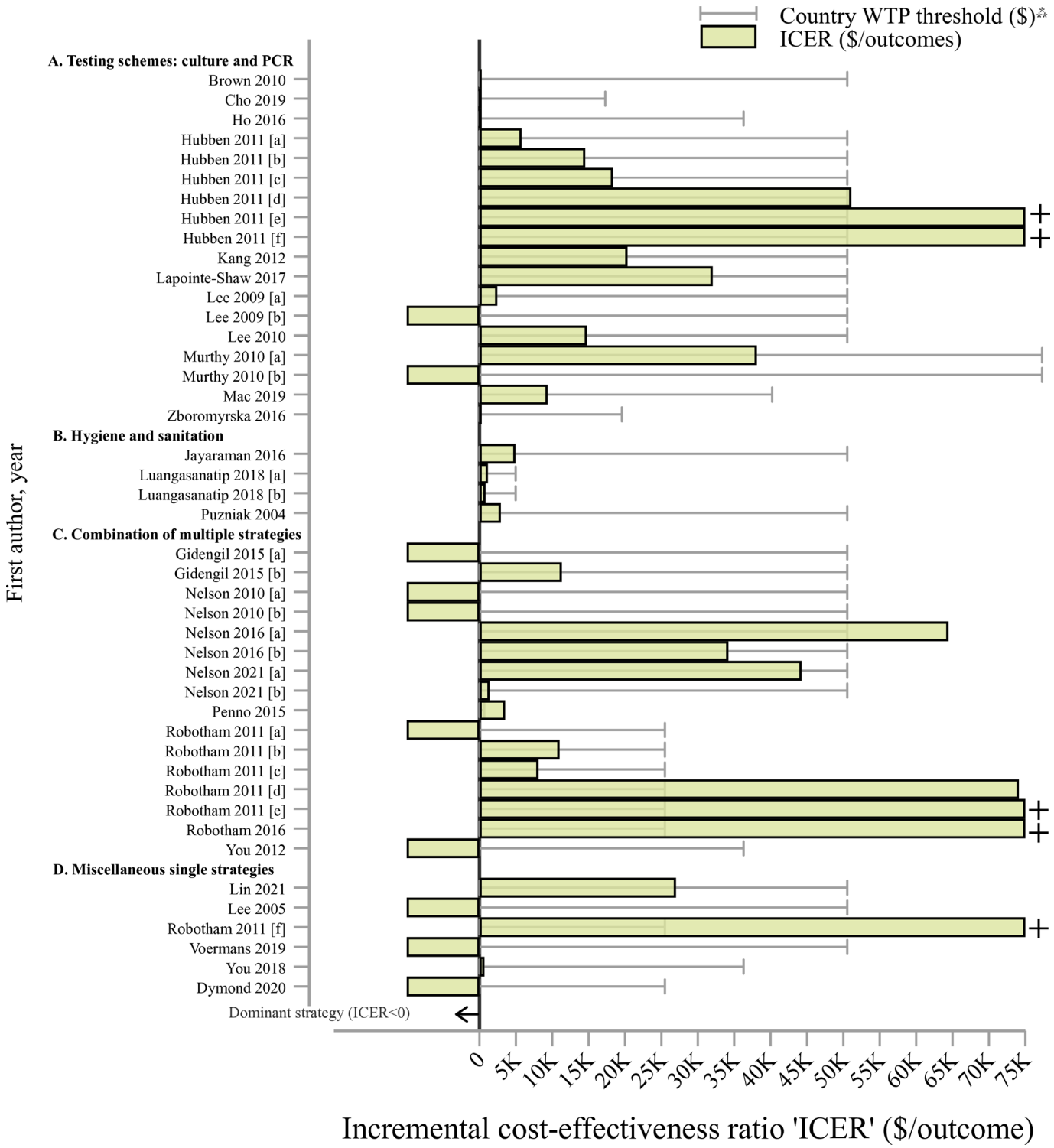

Figure 4 Incremental cost-effectiveness ratios and willingness-to-pay country thresholds among non-pharmaceutical interventions (in 2022 US dollars, '$'), by study†. Notes: †Studies with letters in brackets (eg, (a)) indicate different strategy evaluations, detailed in online supplemental table SM6 under the strategy column. K=thousands or 1000 units. Interpretation of the incremental cost-effectiveness ratio 'ICER' should be taken with caution as outcomes (eg, deaths averted, cured patients, quality-adjusted life years 'QALYs') used to calculate ICERs varied from study to study. Online supplemental table SM6 contains detailed information by study and outcomes used. ⁂WTP thresholds were extracted from country estimates provided by Woods *et al*[22] and adjusted to 2022 US dollars. A dominant strategy means that interventions is more effective and less costly (ICER<0). + ICERs were capped at US$75 000 but values are higher (see online supplemental table SM6). PCR, PCR chain reaction; 'vs', versus; WTP, willingness-to-pay.

$34 201[67] per life years gained; as shown in online supplemental table SM6, panel II, and figure 4C). Last, real-time blood culturing and evidence-based antimicrobial consumption among ampicillin-resistant *Salmonella enterica* and *Streptococcus pneumoniae* infections were cost-effective in Africa (ICER=$3531 per life saved, averting 934 deaths per 100 000 patients), compared with generic antimicrobial management.[70]

Most of these strategies were cost-effective based on country WTP thresholds (figure 3C), but consideration of local costs was essential in scenarios with low MRSA prevalence and transmission.[65]

Miscellaneous single strategies

Interventions in this category included antibiotic stewardship, single surveillance schemes, test-guided decontamination and pre-emptive isolation.[28 31 71–73] Voermans *et al* estimated that procalcitonin-led antibiotic stewardship reduced average expenses per patient, specifically, a 49% reduction from standard care for sepsis and 23% reduction for lower respiratory tract infections associated with ABR (cost savings of $29 197 and $4138 per each group).[72] Active surveillance (current standards and screening of previously hospitalised) for patients with VRE was the most medically and economically beneficial, resulting in a $4 screening cost per patient admitted, lowering admission costs ($792) and improving survival rates.[71] Whole genome sequencing as a surveillance alternative resulted in 14.3 additional QALYs gained among MRSA patients.[28] The use of a state-wide electronic registry reduced CRE by 18.8 cases per year (95% CI=5.8 to 31.7) and by 6.3% (95% CI=2.0% to 10.6%; p value<0.05) compared with the 'do nothing' scenario (ICER=$27 000 per infection averted).[31] Test-guided selective digestive decontamination among CRE patients in the ICU was cost-effective in reducing CRE (ICER=$688 per QALY, reduction of 0.2% and 0.3% in CRE cases and mortality, respectively).[73] Most strategies were cost-effective according to country-specific WTP thresholds (figure 4D), except for Robotham *et al*'s study on universal pre-emptive isolation in the UK's hospital ICU for high MRSA risk patients,[29] which reported substantial hospital costs due to necessary infrastructure investments.

Quality of reporting and risk of bias

A substantial proportion of the pharmaceutical (25%) and non-pharmaceutical studies (33%) failed to report important costs and their potential consequences (online supplemental table SM10). The type of costing methodology was dissimilar in studies, resulting in costs for drug acquisition reported, for instance, in cost per day, patient or dose. Discounting varied among studies in magnitude and usage (61% failed to report discounting online supplemental table SM10). Despite most studies achieving average high-quality scores of 8.2 and 8.0 out of 10 for pharmaceutical and non-pharmaceutical interventions,[74] time frames and years of economic evaluation were not always reported.

DISCUSSION

We identified 59 studies investigating the cost-effectiveness of pharmaceutical or non-pharmaceutical interventions reducing ABR among WHO's global priority pathogen list in hospital settings.[18] We flag the reduced data among critical pathogens, such as *Acinetobacter baumannii* and *Pseudomonas aeruginosa*, and the scarcity of standardised cost-effectiveness methods, ingredient costs and limited data from low-income and middle-income countries indicated the need for more consistent approaches in the future.

More studies found that, compared with vancomycin, linezolid was more effective and less costly for the treatment of MRSA infections. Despite pharmaceutical costs being a highly predictable line item in hospital budgets (eg, diagnostic tests, treatment), LOS often constitutes a higher proportion of the cost for hospital stay and should be considered in cost-effectiveness analyses and decisions related to formulary and drug reimbursement. For example, Kauf *et al* reported that drug costs drove 6.4% of the total inpatient cost compared with LOS accounting for 85.9% of total inpatient cost for patients with cSSSI.[75] Treatment resulting in expedited infection resolution will likely be more cost-effective even when drug costs are much higher. This is also seen with linezolid compared with vancomycin. Vancomycin can be taken orally (as opposed to intravenously) meaning that patients can be discharged earlier, potentially offsetting higher drug acquisition costs.[36] De Cock *et al* noted that in a scenario analysis between linezolid and vancomycin, when the most conservative treatment durations were applied rather than those estimated by the physician panel, linezolid was dominant over vancomycin based on the shorter LOS.[33]

The appropriateness of initial antibiotic therapy and the possibility of switching treatments during hospitalisation also play crucial roles, by affecting length of hospital stay and treatment outcome. One key question is whether being on vancomycin during hospitalisation and switching to linezolid for outpatient care is cost-saving.[36] De Cock *et al* suggest that most patients are cured after treatment with two lines of antibiotic therapy.[37] Empirical therapy with linezolid was considered most cost-effective in unconfirmed MRSA patients, as LOS for unconfirmed patients is lower.[33]

A recent meta-analysis indicates that ceftazidime-avibactam offers advantages over colistin, including lower mortality rates, improved clinical cure rates and reduced kidney deterioration in CRE infections.[76] Comparing ceftazidime-avibactam to colistin plus meropenem revealed high efficacy and lower nephrotoxicity in CRE patients in Chile[48] and Colombia[49] (ICER=$1340 and $3797 per QALY gained, both falling below the country's WTP thresholds). This finding holds relevance for a region where the kidney disease burden is substantial.[77] Moreover, considering the complex dosing requirements and close monitoring associated with colistin plus meropenem, along with the region's higher prevalence of carbapenemase-producing Enterobacterales[78 79] and

antibiotic-resistant gram-negative pathogens,[80] the potential for expanded treatment coverage is substantial.

Non-pharmaceutical interventions were generally less cost-effective than pharmaceutical interventions. For instance, one of the most expensive non-pharmaceutical interventions was a mandatory full National Health Service-level screening programme modelled by Robotham and colleagues.[65] Other infrastructure-demanding interventions, such as whole genome sequencing (WGS), were only cost-effective if applied at a specific UK tertiary research hospital where MRSA prevalence was significant and sequencing infrastructure already existed.[28] Although the effectiveness of WGS surveillance is highly dependent on infrastructure, the study's modelling estimate found that WGS was not sensitive to simulated reduced efficacy in colonisation/mortality reduction.[28] Nevertheless, the limited evidence renders universal screening strategies for reducing MRSA inconclusive.[81] Literature on MRSA demonstrates the limited capacity to account for confounding and temporal trends when assessing the burden of disease and resource utilisation associated with MRSA screening.

Costs associated with the required professional training often lead to the perception that antimicrobial stewardship is not cost-effective. However, there might be unaccounted outcomes and positive spillover effects not captured by economic evaluations. Although not specifically targeting ABR, Scheetz, *et al*[82] presented an ICER of $3219 per QALY gained in antimicrobial stewardship programmes attributed to substantial fixed operating costs required to maintain the stewardship team and the reduction in patient inflow. Antimicrobial stewardship proves more economically efficient in larger hospitals with higher inpatient volume, presenting increased risks and expanded economic returns of scale, specifically for persuasive and structural programmes.[9] Notwithstanding, some studies have shown mixed results, with increased consumption of antibiotics not targeted or restricted by the antimicrobial stewardship programme leading to higher global ABR rates and worsening patient outcomes.[83] Decreased resistance may not be expected if antimicrobial stewardships only target certain antibiotics. LOS and mortality could be affected beyond antibiotic control, changes in preintervention and post-intervention populations, including existing comorbidities and disease severity, might lead to poorer health outcomes despite the stewardship programme.[83] Comprehensive antimicrobial stewardship programmes, including physiological monitoring, therapy review and antibiotic restrictions are essential to avoid ABR and associated disease burden.

Procalcitonin (PCT) has demonstrated the ability to increase specificity and sensitivity for different bacterial infections at the point of care, even in the earliest phases of inflammation. PCT has been shown to reduce LOS and improve the appropriateness of antibiotic treatment at low costs compared with no-PCT.[72 84–86] Similar to a study in Europe avoiding antibiotic days in European settings,[85] we found support for PCT-guided healthcare in the USA, contributing to halving sepsis with cost-savings of $29 197 compared with costs for standard care.[72] These results are mainly driven by the associated reduction in ICU-admitted patients, which results in shorter antibiotic treatment and exposure time. These findings are corroborated by studies by Mewes *et al*, Harrison and Collins and Huang *et al*, showing PCT to be a cost-saving strategy in hospitalised patients with lower respiratory tract infections or suspected sepsis,[87–89] although not specifically targeting ABR pathogens. Furthermore, a recent study suggests that these interventions among emergency departments in low-resource settings are feasible if PCT is applied simultaneously with C-reactive protein through a fluorescence reader-based duplex lateral flow assay.[90] This has direct implications for applications in low-income and middle-income countries for rapid and accurate viral and bacterial infection differentiation, with an estimated rounded cost per patient below $70.[90]

Reducing the time interval between a positive test for MRSA and the implementation of appropriate infection control measures during hospitalisation is achievable using diagnostic technologies such as PCR.[91] PCR assays were cost-effective in Europe and the UK, with the lowest ICER values per life-saved, ranging from $1100 to $1200, compared with standard treatment.[55] Although the costs are low, PCR is only feasible as an intervention when the hospital has appropriate facilities and when the additional delay incurred poses little-to-no threat to patient well-being. PCR-based interventions may only be cost-effective in highly endemic settings where targeted screening is likely to detect a large number of MRSA cases.[27] Despite potential drawbacks, studies have shown that PCR may prevent adverse events and toxicity due to treating patients empirically,[92] reducing LOS and economic costs.[93 94]

Limitations

Our review has highlighted important deficiencies in the health economics literature pertaining to pharmaceutical and non-pharmaceutical interventions aimed at reducing, monitoring and controlling ABR levels, particularly concerning critical or high-priority bacteria. We included literature from three major search engines, potentially overlooking publications in interdisciplinary journals and grey literature like government reports, particularly from low-income and middle-income countries. Our primary sources were PubMed, which comprehensively indexes biomedical and life sciences literature, including health economics; Embase, which specialises in biomedical and pharmacological content, with a specific emphasis on drug and pharmaceutical research; and EconLit, which is dedicated to economics. Second, we found significant heterogeneity in the costs and effectiveness units reported across studies, which may have been affected by the lack of standardisation in analysis, illustrated by the scarcity of cost-utility analyses considering the difficulty of measuring quality of life for acute events. Therefore, comparing results was challenging given the

range of resistant bacterial types, intervention types, populations studied and the lack of consistency in study design. Our study focused on the health systems perspective to report unit costs and cost-effectiveness, which fails to take account of a societal perspective. However, most studies did not report a specific perspective of analysis. Finally, many articles failed to report discounting and a risk scenario for the associated consequences. This may be explained because due to the short time horizons used, often under a year and mostly under a month, which may not capture all relevant costs and benefits of the interventions. While we used Woods *et al's* cost-effectiveness or WTP thresholds,[22] some literature suggests wider thresholds, such as $100 000 or $150 000 per QALY, as more appropriate for evaluating interventions in the USA. This variation might impact the generalisability of our results.[95 96] It is relevant to recall that cost-effectiveness thresholds are contingent on the locally-relevant WTP thresholds.

CONCLUSION

Most economic evaluations on ABR interventions have focused on MRSA, revealing a significant gap for other priority pathogens. Even when available, most studies lack a comprehensive economic analysis, even though such analysis would require readily available components such as intervention costs, bed-day expenses and patient outcomes, such as LOS or ICU admission. Data on bed-day expenses for primary, secondary and tertiary hospitals are freely available for most countries from the WHO-CHOICE.[97] This is important because, as Nathwani *et al*[83] showed, more effective antimicrobial control does not necessarily translate into improved cost-effectiveness due to population heterogeneity and decisions in resource allocation. Many studies were based on non-randomised designs that did not adequately account for potential confounders and antimicrobial regulations or guidelines (eg, stewardship programmes could reduce antibiotic consumption of a targeted component while increasing others). This issue could be rectified by strengthening intervention designs through a priori examination of biases and ensuring consistency. We have synthesised evidence supporting pharmacological and non-pharmacological interventions from the limited available scientific literature using economic analysis. Still, for many interventions, hospital-level considerations (eg, laboratory capacity, the prevalence of resistance in the local community, therapy review and population features) need to be considered to optimise healthcare expenditure and address the costs of inaction. We recommend future economic evaluations consider the Consolidated Health Economic Evaluation Reporting Standards checklist[98] using the healthcare sector and societal perspectives simultaneously as benchmarks[99] and for consistency across studies.

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REFERENCES

1 Roope LSJ, Smith RD, Pouwels KB, *et al*. The challenge of antimicrobial resistance: what economics can contribute. *Science* 2019;364:eaau4679.
2 Murray CJL, Ikuta KS, Sharara F, *et al*. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. *The Lancet* 2022;399:629–55.
3 Naylor NR, Atun R, Zhu N, *et al*. Estimating the burden of antimicrobial resistance: a systematic literature review. *Antimicrob Resist Infect Control* 2018;7:58.
4 Ikuta KS, Swetschinski LR, Robles Aguilar G. Global mortality associated with 33 bacterial pathogens in 2019: a systematic analysis for the global burden of disease study 2019. *Lancet* 2022;400:2221–48.
5 Jonas OB, Irwin A, BertheFCJ, *et al*. Drug-resistant infections: a threat to our economic future (vol. 2): final report. HNP/Agriculture Global Antimicrobial Resistance Initiative; 2017.
6 Centres for Disease Control. Antibiotic resistance threats in the United States. 2019.
7 Amos D, Au-Yong CP, Musa ZN. The mediating effects of finance on the performance of hospital facilities management services. J Build Eng 2021;34:101899.
8 Arbeit RD, Maki D, Tally FP, *et al*. The safety and efficacy of daptomycin for the treatment of complicated skin and skin-structure infections. *Clin Infect Dis* 2004;38:1673–81.
9 Naylor NR, Zhu N, Hulscher M, *et al*. Is antimicrobial stewardship cost-effective? A narrative review of the evidence. *Clin Microbiol Infect* 2017;23:806–11.
10 Niewiadomska AM, Jayabalasingham B, Seidman JC, *et al*. Population-level mathematical modeling of antimicrobial resistance: a systematic review. *BMC Med* 2019;17:81.
11 Wilton P, Smith R, Coast J, *et al*. Strategies to contain the emergence of antimicrobial resistance: a systematic review of effectiveness and cost-effectiveness. *J Health Serv Res Policy* 2002;7:111–7.
12 Huebner C, Flessa S, Huebner N-O. The economic impact of antimicrobial stewardship programmes in hospitals: a systematic literature review. *J Hosp Infect* 2019;102:369–76.
13 Ananthakrishnan A, Painter C, Teerawattananon Y. A protocol for a systematic literature review of economic evaluation studies of interventions to address antimicrobial resistance. *Syst Rev* 2021;10:242.
14 Page MJ, McKenzie JE, Bossuyt PM, *et al*. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71.
15 Mandrik OL, Severens JLH, Bardach A, *et al*. Critical appraisal of systematic reviews with costs and cost-effectiveness outcomes: an ISPOR good practices task force report. *Value Health* 2021;24:463–72.
16 Methley AM, Campbell S, Chew-Graham C, *et al*. PICO, PICOS and SPIDER: a comparison study of specificity and sensitivity in three search tools for qualitative systematic reviews. *BMC Health Serv Res* 2014;14:579.
17 van Dijk SHB, Brusse-Keizer MGJ, Bucsán CC, *et al*. Artificial intelligence in systematic reviews: promising when appropriately used. *BMJ Open* 2023;13:e072254.
18 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;18:318–27.
19 Drummond MF, O'Brien BJ, Torrance GW, *et al*. *Methods for the economic evaluation of health care programmes*. Oxford: Oxford University Press, 1997.
20 Campbell & Cochrane Economics Methods Group. How to include economics in cochrane review protocols. part two: searches, assessing risk of bias and methodological quality, data collection and analysis. 2022. Available: https://methods.cochrane.org/economics/ [Accessed 13 Jul 2022].
21 CCEMG-EPPI. CCEMG - EPPI-centre cost converter V.1.6. 2019. Available: http://eppi.ioe.ac.uk/costconversion/default.aspx
22 Woods B, Revill P, Sculpher M, *et al*. Country-level cost-effectiveness thresholds: initial estimates and the need for further research. *Value Health* 2016;19:929–35.
23 Drummond MF, Sculpher MJ, Claxton K, *et al*. *Methods for the economic evaluation of health care programmes*. Oxford: Oxford: Oxford University Press, 2015.
24 Bounthavong M, Zargarzadeh A, Hsu DI, *et al*. Cost-effectiveness analysis of linezolid, daptomycin, and vancomycin in methicillin-resistant *Staphylococcus aureus*: complicated skin and skin structure infection using Bayesian methods for evidence synthesis. *Value Health* 2011;14:631–9.
25 Collins CD, Schwemm AK. Linezolid versus vancomycin in the empiric treatment of nosocomial pneumonia: a cost-utility analysis incorporating results from the ZEPHyR trial. *Value Health* 2015;18:614–21.
26 Niederman MS, Chastre J, Solem CT, *et al*. Health economic evaluation of patients treated for nosocomial pneumonia caused by methicillin-resistant *Staphylococcus aureus*: secondary analysis of a multicenter randomized clinical trial of vancomycin and linezolid. *Clin Ther* 2014;36:1233–43.
27 Kang J, Mandsager P, Biddle AK, *et al*. Cost-effectiveness analysis of active surveillance screening for methicillin-resistant *Staphylococcus aureus* in an academic hospital setting. *Infect Control Hosp Epidemiol* 2012;33:477–86.
28 Dymond A, Davies H, Mealing S, *et al*. Genomic surveillance of methicillin-resistant *Staphylococcus aureus*: a mathematical early modeling study of cost-effectiveness. *Clin Infect Dis* 2020;70:1613–9.
29 Robotham JV, Graves N, Cookson BD, *et al*. Screening, isolation, and decolonisation strategies in the control of meticillin resistant *Staphylococcus aureus* in intensive care units: cost effectiveness evaluation. *BMJ* 2011;343:d5694.
30 Nelson RE, Samore MH, Smith KJ, *et al*. Cost-effectiveness of adding decolonization to a surveillance strategy of screening and isolation for methicillin-resistant *Staphylococcus aureus* carriers. *Clin Microbiol Infect* 2010;16:1740–6.
31 Lin G, Tseng KK, Gatalo O, *et al*. Cost-effectiveness of carbapenem-resistant Enterobacteriaceae (CRE) surveillance in Maryland. *Infect Control Hosp Epidemiol* 2022;43:1162–70.
32 McKinnon PS, Sorensen SV, Liu LZ, *et al*. Impact of linezolid on economic outcomes and determinants of cost in a clinical trial evaluating patients with MRSA complicated skin and soft-tissue infections. *Ann Pharmacother* 2006;40:1017–23.
33 De Cock E, Sorensen S, Levrat F, *et al*. Cost-effectiveness of linezolid versus vancomycin for hospitalized patients with complicated skin and soft-tissue infections in France. *Med Mal Infect* 2009;39:330–40.
34 Bounthavong M, Hsu DI, Okamoto MP. Cost-effectiveness analysis of linezolid vs. vancomycin in treating methicillin-resistant *Staphylococcus aureus* complicated skin and soft tissue infections using a decision analytic model. *Int J Clin Pract* 2009;63:376–86.
35 Schürmann D, Sorensen SV, De Cock E, *et al*. Cost-effectiveness of linezolid versus vancomycin for hospitalised patients with complicated skin and soft-tissue infections in Germany. *Eur J Health Econ* 2009;10:65–79.
36 Daniel Mullins C, Kuznik A, Shaya FT, *et al*. Cost-effectiveness analysis of linezolid compared with vancomycin for the treatment of nosocomial pneumonia caused by methicillin-resistant *Staphylococcus aureus*. *Clin Ther* 2006;28:1184–98.
37 De Cock E, Krueger WA, Sorensen S, *et al*. Cost-effectiveness of linezolid vs vancomycin in suspected methicillin-resistant *Staphylococcus aureus* nosocomial pneumonia in Germany. *Infection* 2009;37:123–32.
38 Patel DA, Michel A, Stephens J, *et al*. An economic model to compare linezolid and vancomycin for the treatment of confirmed methicillin-resistant *Staphylococcus aureus* nosocomial pneumonia in Germany. *Infect Drug Resist* 2014;7:273–80.
39 Patel DA, Shorr AF, Chastre J, *et al*. Modeling the economic impact of linezolid versus vancomycin in confirmed nosocomial pneumonia caused by methicillin-resistant *Staphylococcus aureus*. *Crit Care* 2014;18:R157.
40 Lin P-C, Wang BCM, Kim R, *et al*. Estimating the cost-effectiveness of linezolid for the treatment of methicillin-resistant *Staphylococcus aureus* nosocomial pneumonia in Taiwan. *J Microbiol Immunol Infect* 2016;49:46–51.
41 Wan Y, Li Q, Chen Y, *et al*. Economic evaluation among Chinese patients with nosocomial pneumonia caused by methicillin-resistant

Staphylococcus aureus and treated with linezolid or vancomycin: a secondary, post-hoc analysis based on a phase 4 clinical trial study. *J Med Econ* 2016;19:53–62.
42 Varón F, Londoño D, Álvarez C, *et al*. Costo-efectividad de linezolid comparado con vancomicina en el manejo de la neumonía asociada a ventilación mecánica en Colombia. *Infectio* 2014;18:143–52.
43 Tan SC, Wang X, Wu B, *et al*. Cost-effectiveness of linezolid versus vancomycin among patients with methicillin-resistant *Staphylococcus aureus* confirmed nosocomial pneumonia in China. *Value Health Reg Issues* 2014;3:94–100.
44 Bolaños-Díaz R, Angles-Yanqui E, Pérez-Lazo G, *et al*. Cost-effectiveness of ceftazidime/avibactam for infections due to carbapenem-resistant bacteria in Peru. *J Pharm Health Serv Res* 2022;13:2–8.
45 Goudarzi Z, Danayi F, Keshavarz K, *et al*. Cost-effectiveness analysis of ceftazidime avibactam versus colistin in carbapenem-resistant enterobacteriaceae in Iran. *Cost Eff Resour Alloc* 2023;21:45.
46 Kong W, Yang X, Shu Y, *et al*. Cost-effectiveness analysis of ceftazidime-avibactam as definitive treatment for treatment of carbapenem-resistant *Klebsiella pneumoniae* bloodstream infection. *Front Public Health* 2023;11:1118307.
47 Simon MS, Sfeir MM, Calfee DP, *et al*. Cost-effectiveness of ceftazidime-avibactam for treatment of carbapenem-resistant Enterobacteriaceae bacteremia and pneumonia. *Antimicrob Agents Chemother* 2019;63:00897–19.
48 Gutiérrez A M, Fandiño C. Cost-effectiveness of ceftazidime/avibactam versus colistin+ meropenem for treatment of carbapenemic-resistant enterobacteria infections in Chile. *Rev Chilena Infectol* 2021;38:7–14.
49 Varón-Vega FA, Lemos E, Castaño GN, *et al*. Cost-utility analysis of ceftazidime-avibactam versus colistin-meropenem in the treatment of infections due to Carbapenem-resistant *Klebsiella pneumoniae* in Colombia. *Expert Rev Pharmacoecon Outcomes Res* 2022;22:235–40.
50 Laohavaleeson S, Barriere SL, Nicolau DP, *et al*. Cost-effectiveness of telavancin versus vancomycin for treatment of complicated skin and skin structure infections. *Pharmacotherapy* 2008;28:1471–82.
51 Yang J, Naik J, Massello M, *et al*. Cost-effectiveness of imipenem/cilastatin/relebactam compared with colistin in treatment of gram-negative infections caused by carbapenem-non-susceptible organisms. *Infect Dis Ther* 2022;11:1443–57.
52 Prabhu V, Foo J, Ahir H, *et al*. Cost-effectiveness of ceftolozane/tazobactam plus metronidazole compared with piperacillin/tazobactam as empiric therapy for the treatment of complicated intra-abdominal infections based on the in-vitro surveillance of bacterial isolates in the UK. *J Med Econ* 2017;20:840–9.
53 Mennini FS, Gori M, Vlachaki I, *et al*. Cost-effectiveness analysis of Vaborem in Carbapenem-resistant Enterobacterales (CRE)-*Klebsiella pneumoniae* infections in Italy. *Health Econ Rev* 2021;11:42.
54 Vlachaki I, Zinzi D, Falla E, *et al*. Cost-effectiveness analysis of vaborem for the treatment of carbapenem-resistant Enterobacteriaceae-*Klebsiella pneumoniae* carbapenemase (CRE-KPC) infections in the UK. *Eur J Health Econ* 2022;23:537–49.
55 Brown J, Paladino JA. Impact of rapid methicillin-resistant *Staphylococcus aureus* polymerase chain reaction testing on mortality and cost effectiveness in hospitalized patients with bacteraemia. *Pharmacoeconomics* 2010;28:567–75.
56 Murthy A, De Angelis G, Pittet D, *et al*. Cost-effectiveness of universal MRSA screening on admission to surgery. *Clin Microbiol Infect* 2010;16:1747–53.
57 Zboromyrska Y, De la Calle C, Soto M, *et al*. Rapid diagnosis of staphylococcal catheter-related bacteraemia in direct blood samples by real-time PCR. *PLoS One* 2016;11:e0161684.
58 Lee BY, Bailey RR, Smith KJ, *et al*. Universal methicillin-resistant *Staphylococcus aureus* (MRSA) surveillance for adults at hospital admission: an economic model and analysis. *Infect Control Hosp Epidemiol* 2010;31:598–606.
59 Lapointe-Shaw L, Voruganti T, Kohler P, *et al*. Cost-effectiveness analysis of universal screening for carbapenemase-producing Enterobacteriaceae in hospital inpatients. *Eur J Clin Microbiol Infect Dis* 2017;36:1047–55.
60 Ho K, Ng W, Ip M, *et al*. Active surveillance of carbapenem-resistant Enterobacteriaceae in intensive care units: is it cost-effective in a nonendemic region? *Am J Infect Control* 2016;44:394–9.
61 Hubben G, Bootsma M, Luteijn M, *et al*. Modelling the costs and effects of selective and universal hospital admission screening for methicillin-resistant *Staphylococcus aureus*. *PLoS One* 2011;6:e14783.
62 Luangasanatip N, Hongsuwan M, Lubell Y, *et al*. Cost-effectiveness of interventions to improve hand hygiene in healthcare workers in middle-income hospital settings: a model-based analysis. *J Hosp Infect* 2018;100:165–75.
63 Jayaraman SP, Jiang Y, Resch S, *et al*. Cost-effectiveness of a model infection control program for preventing multi-drug-resistant organism infections in critically ill surgical patients. *Surg Infect (Larchmt)* 2016;17:589–95.
64 Puzniak LA, Gillespie KN, Leet T, *et al*. A cost-benefit analysis of gown use in controlling vancomycin-resistant Enterococcus transmission is it worth the price. *Infect Control Hosp Epidemiol* 2004;25:418–24.
65 Robotham JV, Deeny SR, Fuller C, *et al*. Cost-effectiveness of national mandatory screening of all admissions to english national health service hospitals for meticillin-resistant *Staphylococcus aureus*: a mathematical modelling study. *Lancet Infect Dis* 2016;16:348–56.
66 Nelson RE, Goto M, Samore MH, *et al*. Expanding an economic evaluation of the veterans affairs (VA) methicillin-resistant *Staphylococcus aureus* (MRSA) prevention initiative to include prevention of infections from other pathogens. *Clin Infect Dis* 2021;72:S50–8.
67 Nelson RE, Stevens VW, Khader K, *et al*. Economic analysis of veterans affairs initiative to prevent methicillin-resistant *Staphylococcus aureus* infection. *Am J Prev Med* 2016;50:S58–65.
68 Gidengil CA, Gay C, Huang SS, *et al*. Cost-effectiveness of strategies to prevent methicillin-resistant *Staphylococcus aureus* transmission and infection in an intensive care unit. *Infect Control Hosp Epidemiol* 2015;36:17–27.
69 You JHS, Chan CY, Wong MY, *et al*. Active surveillance and decolonization of methicillin-resistant *Staphylococcus aureus* on admission to neonatal intensive care units in Hong Kong: a cost-effectiveness analysis. *Infect Control Hosp Epidemiol* 2012;33:1024–30.
70 Penno EC, Baird SJ, Crump JA. Cost-effectiveness of surveillance for bloodstream infections for sepsis management in low-resource settings. *Am J Trop Med Hyg* 2015;93:850–60.
71 Lee TA, Hacek DM, Stroupe KT, *et al*. Three surveillance strategies for vancomycin-resistant enterococci in hospitalized patients: detection of colonization efficiency and a cost-effectiveness model. *Infect Control Hosp Epidemiol* 2005;26:39–46.
72 Voermans AM, Mewes JC, Broyles MR, *et al*. Cost-effectiveness analysis of a procalcitonin-guided decision algorithm for antibiotic stewardship using real-world US hospital data. *OMICS* 2019;23:508–15.
73 You JHS, Li H-K, Ip M. Surveillance-guided selective digestive decontamination of carbapenem-resistant Enterobacteriaceae in the intensive care unit: a cost-effectiveness analysis. *Am J Infect Control* 2018;46:291–6.
74 Edmunds K, Ling R, Shakeshaft A, *et al*. Systematic review of economic evaluations of interventions for high risk young people. *BMC Health Serv Res* 2018;18:660.
75 Kauf TL, McKinnon P, Corey GR, *et al*. An open-label, pragmatic, randomized controlled clinical trial to evaluate the comparative effectiveness of daptomycin versus vancomycin for the treatment of complicated skin and skin structure infection. *BMC Infect Dis* 2015;15:503.
76 Chen Y, Huang H-B, Peng J-M, *et al*. Efficacy and safety of ceftazidime-avibactam for the treatment of carbapenem-resistant Enterobacterales bloodstream infection: a systematic review and meta-analysis. *Microbiol Spectr* 2022;10:e02603-21.
77 Panamerican Health Organization. Burden of kidney diseases. 2023. Available: https://www.paho.org/en/enlace/burden-kidney-diseases [Accessed 30 Dec 2023].
78 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;28:1–8.
79 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:S20–8.
80 Aguilar GR, Swetschinski LR, Weaver ND. The burden of antimicrobial resistance in the Americas in 2019: a cross-country systematic analysis. *Lancet Reg Health Am* 2023;25:100561.
81 Glick SB, Samson DJ, Huang ES, *et al*. Screening for methicillin-resistant *Staphylococcus aureus*: a comparative effectiveness review. *Am J Infect Control* 2014;42:148–55.
82 Scheetz MH, Bolon MK, Postelnick M, *et al*. Cost-effectiveness analysis of an antimicrobial stewardship team on bloodstream infections: a probabilistic analysis. *J Antimicrob Chemother* 2009;63:816–25.

83 Nathwani D, Varghese D, Stephens J, *et al*. Value of hospital antimicrobial stewardship programs [ASPs]: a systematic review. *Antimicrob Resist Infect Control* 2019;8:35.
84 Póvoa P, Salluh JIF. Biomarker-guided antibiotic therapy in adult critically ill patients: a critical review. *Ann Intensive Care* 2012;2:1–9.
85 van der Maas ME, Mantjes G, Steuten LMG. Procalcitonin biomarker algorithm reduces antibiotic prescriptions, duration of therapy, and costs in chronic obstructive pulmonary disease: a comparison in the Netherlands, Germany, and the United Kingdom. *OMICS* 2017;21:232–43.
86 Hu L, Shi Q, Shi M, *et al*. Diagnostic value of PCT and CRP for detecting serious bacterial infections in patients with fever of unknown origin: a systematic review and meta-analysis. *Appl Immunohistochem Mol Morphol* 2017;25:e61–9.
87 Mewes JC, Pulia MS, Mansour MK, *et al*. The cost impact of PCT-guided antibiotic stewardship versus usual care for hospitalised patients with suspected sepsis or lower respiratory tract infections in the US: a health economic model analysis. *PLoS One* 2019;14:e0214222.
88 Harrison M, Collins CD. Is procalcitonin-guided antimicrobial use cost-effective in adult patients with suspected bacterial infection and sepsis? Infection control & hospital epidemiology. *Infect Control Hosp Epidemiol* 2015;36:265–72.
89 Huang DT, Yealy DM, Filbin MR, *et al*. Procalcitonin-guided use of antibiotics for lower respiratory tract infection. *N Engl J Med* 2018;379:236–49.
90 Cao XE, Ongagna-Yhombi SY, Wang R, *et al*. A diagnostic platform for rapid, simultaneous quantification of procalcitonin and C-reactive protein in human serum. *EBioMedicine* 2022;76:103867.
91 Conterno LO, Shymanski J, Ramotar K, *et al*. Real-time polymerase chain reaction detection of methicillin-resistant *Staphylococcus aureus*: impact on nosocomial transmission and costs. *Infect Control Hosp Epidemiol* 2007;28:1134–41.
92 Jones BE, Ying J, Stevens V, *et al*. Empirical anti-MRSA vs standard antibiotic therapy and risk of 30-day mortality in patients hospitalized for pneumonia. *JAMA Intern Med* 2020;180:552–60.
93 Wassenberg M, Kluytmans J, Erdkamp S, *et al*. Costs and benefits of rapid screening of methicillin-resistant *Staphylococcus aureus* carriage in intensive care units: a prospective multicenter study. *Crit Care* 2012;16:R22.
94 Henson G, Ghonim E, Swiatlo A, *et al*. Cost-benefit and effectiveness analysis of rapid testing for MRSA carriage in a hospital setting. *Clin Lab Sci* 2014;27:13–20.
95 Neumann PJ, Cohen JT, Weinstein MC. Updating cost-effectiveness—the curious resilience of the $50,000-per-QALY threshold. *N Engl J Med* 2014;371:796–7.
96 Braithwaite RS, Meltzer DO, King JT, *et al*. What does the value of modern medicine say about the $50,000 per quality-adjusted life-year decision rule?. *Med Care* 2008;46:349–56.
97 World Health Organisation. World health organization. Choosing interventions that are cost effective (WHO - CHOICE). 2017. Available: http://www.who.int/choice/costs/en/ [Accessed 03 Jan 2024].
98 Husereau D, Drummond M, Petrou S, *et al*. Consolidated health economic evaluation reporting standards (CHEERS)—explanation and elaboration: a report of the ISPOR health economic evaluation publication guidelines good reporting practices task force. *Value Health* 2013;16:231–50.
99 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;316:1093–103.

Chapter 6:

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

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Thesis Title	Impacts of antimicrobial resistance bloodstream infections among hospital patients and potential interventions: a case study in Chile		
Primary Supervisor	Laith Yakob, Dphil		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

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SECTION E

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

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Summary

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

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

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

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

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

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

Research in context

Evidence before this study

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

Added value of this study

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

Implications of all the available evidence

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

Introduction

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

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

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

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

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

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

Chilean context

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

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

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

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

Methods

Study design and data

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

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

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

Analysis

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

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

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

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

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

Linear model (M1):

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

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

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

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

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

Ethics statement

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

Role of the funding source

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

Results

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

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

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

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

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

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

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

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

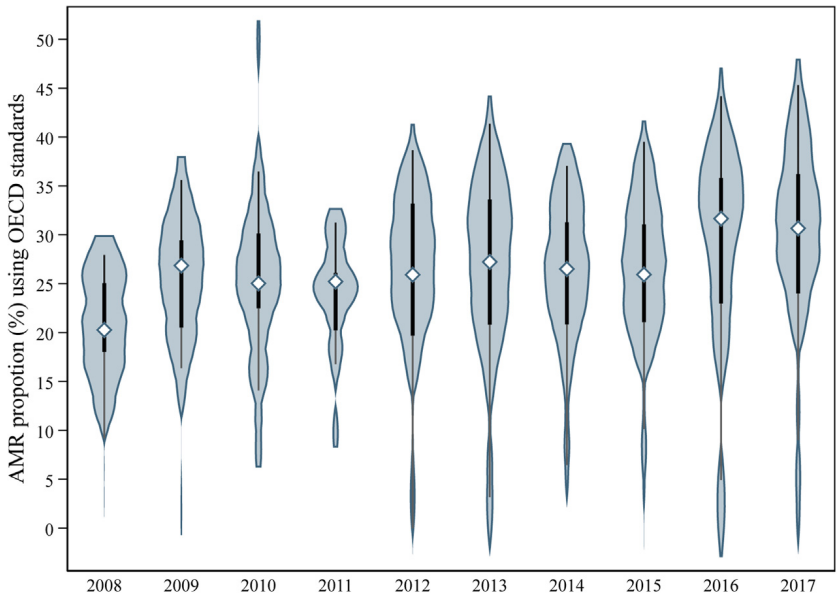

Fig. 1: **Average proportion of resistance across antibiotic-bacterium pairs, based on annual reports from 39 participating hospitals in Chile (2008–2017). Notes**: Antibiotic-bacterium pairs as defined by the OECD.[2] Violin plots present the probability density (distribution) of AMR rates at their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

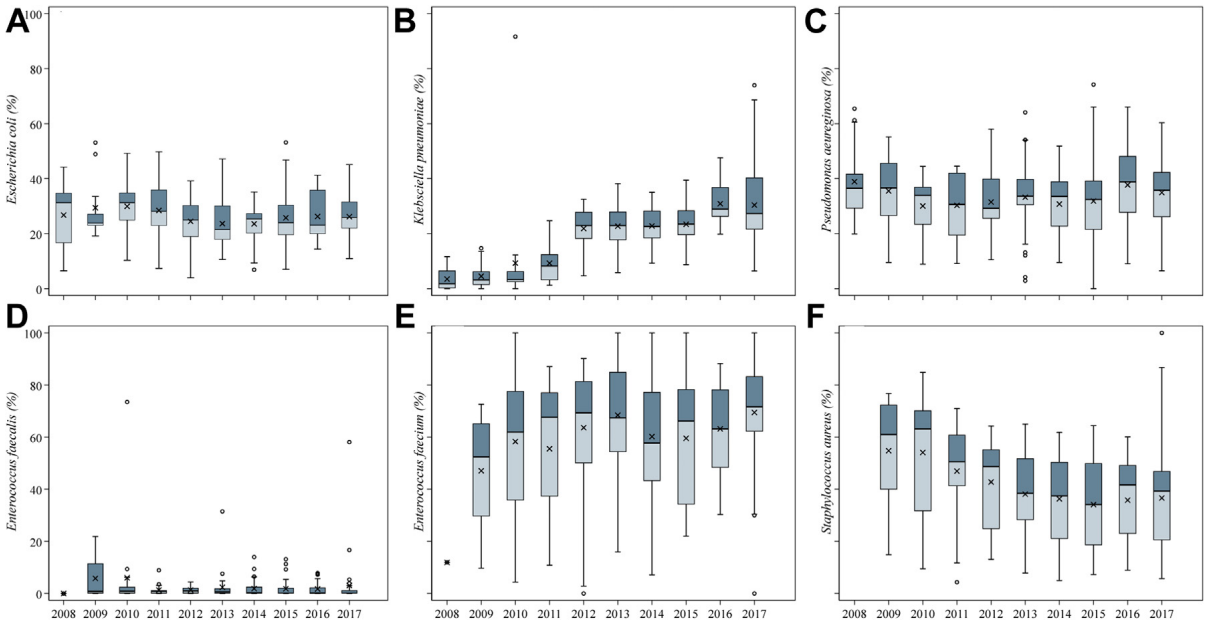

Fig. 2: **Trends in the average proportion of resistance for antibiotic-bacterium pairs (2008–2017)**. Proportion of resistant bacteria for the following antibiotics based on OECD criteria:[2] **(A)** *E. coli* resistant to third-generation cephalosporins and quinolones, **(B)** *K. pneumoniae* resistant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

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

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

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

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

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

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

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

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

Discussion

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

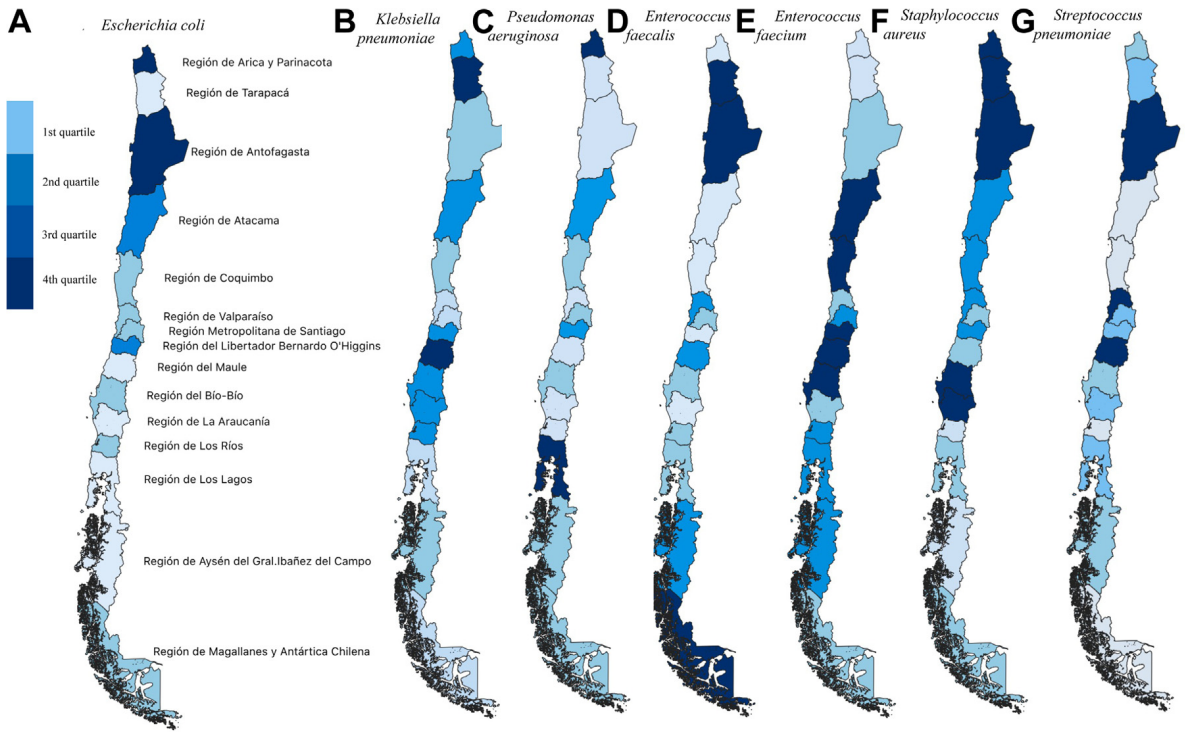

***Fig. 3*: Proportion of antibiotic resistant bacteria in 2017 according to bacterial–antibiotic combinations considered critical by OECD.** Data were aggregated by region. Graph includes expected AMR based on the characteristics of the hospitals and the population of the community. Expected values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

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

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

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

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

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

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

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

Contributors

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

Data sharing statement

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

Editor note

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Declaration of interests

The authors declare no conflict of interests.

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Appendix A. Supplementary data

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

References

1 World Health Organization. *Antimicrobial resistance: global report on surveillance*. World Health Organization; 2014.
2 Organisation for Economic Cooperation and Development OECD. *Stemming the superbug tide: just A few dollars more*. Paris, France: OECD; 2018.
3 Laxminarayan R, Duse A, Wattal C, et al. Antibiotic resistance—the need for global solutions. *Lancet Infect Dis*. 2013;13(12):1057–1098.
4 Murray CJL, Ikuta KS, Sharara F, et al. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. *Lancet*. 2022;399(10325):629–655.
5 Smith R, Coast J. The true cost of antimicrobial resistance. *BMJ*. 2013;346:f1493.
6 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):58.
7 Roope LSJ, Smith RD, Pouwels KB, et al. The challenge of antimicrobial resistance: what economics can contribute. *Science*. 2019;364(6435):eaau4679.
8 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.
9 Årdal C, Outterson K, Hoffman SJ, et al. International cooperation to improve access to and sustain effectiveness of antimicrobials. *Lancet*. 2016;387(10015):296–307.
10 Holmes AH, Moore LS, Sundsfjord A, et al. Understanding the mechanisms and drivers of antimicrobial resistance. *Lancet*. 2016;387(10014):176–187.
11 Versporten A, Zarb P, Caniaux I, et al. Antimicrobial consumption and resistance in adult hospital inpatients in 53 countries: results of an internet-based global point prevalence survey. *Lancet Global Health*. 2018;6(6):e619–e629.
12 Chatterjee A, Modarai M, Naylor NR, et al. Quantifying drivers of antibiotic resistance in humans: a systematic review. *Lancet Infect Dis*. 2018;18(12):e368–e378.
13 Klein EY, Van Boeckel TP, Martinez EM, et al. Global increase and geographic convergence in antibiotic consumption between 2000 and 2015. *Proc Natl Acad Sci USA*. 2018;115(15):E3463–E3470.
14 Van Boeckel TP, Brower C, Gilbert M, et al. Global trends in antimicrobial use in food animals. *Proc Natl Acad Sci USA*. 2015;112(18):5649–5654.
15 Fletcher S. Understanding the contribution of environmental factors in the spread of antimicrobial resistance. *Environ Health Prev Med*. 2015;20(4):243–252.
16 Collignon P, Beggs JJ, Walsh TR, Gandra S, Laxminarayan R. Anthropological and socioeconomic factors contributing to global antimicrobial resistance: a univariate and multivariable analysis. *Lancet Planet Health*. 2018;2(9):e398–e405.
17 Nellums LB, Thompson H, Holmes A, et al. Antimicrobial resistance among migrants in Europe: a systematic review and meta-analysis. *Lancet Infect Dis*. 2018;18(7):796–811.
18 Alividza V, Mariano V, Ahmad R, et al. Investigating the impact of poverty on colonization and infection with drug-resistant organisms in humans: a systematic review. *Infect Dis Poverty*. 2018;7(1):76.
19 Okeke IN, Lamikanra A, Edelman R. Socioeconomic and behavioral factors leading to acquired bacterial resistance to antibiotics in developing countries. *Emerg Infect Dis*. 1999;5(1):18.
20 Frost I, Van Boeckel TP, Pires J, Craig J, Laxminarayan R. Global geographic trends in antimicrobial resistance: the role of international travel. *J Trav Med*. 2019;26(8):taz036.
21 Laxminarayan R, Sridhar D, Blaser M, Wang M, Woolhouse M. Achieving global targets for antimicrobial resistance. *Science*. 2016;353(6302):874–875.
22 Collignon P, Athukorala P-C, Senanayake S, Khan F. Antimicrobial resistance: the major contribution of poor governance and corruption to this growing problem. *PLoS One*. 2015;10(3):e0116746.
23 Allel K, García P, Labarca J, Munita JM, Rendic M, Undurraga EA. Socioeconomic factors associated with antimicrobial resistance of Pseudomonas aeruginosa, Staphylococcus aureus, and Escherichia coli in Chilean hospitals (2008-2017). *Pan Am J Public Health*. 2020;44:e30.
24 Pehrsson EC, Tsukayama P, Patel S, et al. Interconnected microbiomes and resistomes in low-income human habitats. *Nature*. 2016;533(7602):212–216.
25 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.
26 European Centre for Disease Prevention and Control. Surveillance of antimicrobial resistance in Europe – annual report of the European antimicrobial resistance surveillance network (EARS-Net). https://www.ecdc.europa.eu/sites/default/files/documents/EARS-Net-report-2017-update-jan-2019.pdf; 2018. Accessed september 2019.
27 Hay SI, Rao PC, Dolecek C, et al. Measuring and mapping the global burden of antimicrobial resistance. *BMC Med*. 2018;16(1):78.
28 Chan M, Kazatchkine M, Lob-Levyt J, et al. Meeting the demand for results and accountability: a call for action on health data from eight global health agencies. *PLoS Med*. 2010;7(1):e1000223.
29 Frieden TR. The future of public health. *N Engl J Med*. 2015;373(18):1748–1754.
30 World Bank. World Bank open data. https://data.worldbank.org/; 2022. Accessed October 2022.
31 Lozano R, Fullman N, Mumford JE, et al. Measuring universal health coverage based on an index of effective coverage of health services in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet*. 2020;396(10258):1250–1284.
32 Aguilera X, Castillo C, Covarrubias T, et al. *Estructura y funcionamiento del sistema de salud chileno: Centro de Epidemiología y Políticas de Salud*. Universidad del Desarrollo; 2019.
33 Clínicas de Chile AG. *Dimensionamiento del sector de salud en privado en Chile*. Santiago, Chile: Actualización a cifras año 2018; 2019.
34 Ministerio de Salud Chile. *Plan nacional contra la Resistencia a los antimicrobianos Chile 2021-2025*; 2021. https://bit.ly/3CjRrrE. Accessed January 10, 2022.
35 World Health Organization. Global priority list of antibiotic-resistant bacteria to guide research, discovery, and development of new antibiotics. https://www.who.int/medicines/publications/WHO-PPL-Short_Summary_25Feb-ET_NM_WHO.pdf; 2017.
36 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.
37 Ministerio de Desarrollo Social y Familia (MDSF). *Observatorio social*. Encuesta de Caracterización Socioeconómica Nacional CASEN. http://observatorio.ministeriodesarrollosocial.gob.cl/encuesta-casen; 2020. Accessed February 2021.
38 Munita JM, Arias CA. Mechanisms of antibiotic resistance. *Microbiol Spectr*. 2016;4(2).

Chapter 7:

Excess Burden of Antibiotic-Resistant Bloodstream Infections: Evidence from a Multicentre Retrospective Cohort Study in Chile, 2018-2022

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

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ABSTRACT

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 impact of ARB BSI on 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 multivariable regressions. We stratified by community- and hospital-acquired BSI and assessed total hospital and productivity costs.

Findings

We studied 1,218 adult patients experiencing 1,349 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'). 80% of BSI were hospital-acquired. ARB was associated with IRR=1·14 (95%CI=1·05-1·24), OR=1·25 (1·07-1·46), and OR=1·42 (1·20-1·68) greater LOS, ICU admission, and mortality after index blood culture among hospital- and community-acquired infected patients. Mortality risk was 1.35-fold higher (1·16-1·58) for ARB patients, notably among hospital-acquired MRSA and CRE (1·37- and 1·48-greater hazards ratios). We found $10,300 excess hospital costs per patient for ARB and estimated a national burden of 2270 DALYs and USD53 million in hospital and productivity losses.

Interpretation

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

Funding: Agencia Nacional de Investigación y Desarrollo ANID, Chile.

Keywords: Antibiotic resistance; bloodstream infections; disease burden; mortality; Latin America.

Research in context

Evidence before this study

Antibiotic-resistant bacteria (ARB) have surged globally, demanding robust estimates of the disease and economic burden associated with ARB in hospitals. Such data are crucial for informed public health decisions, research prioritization, and program evaluation. However, evidence is scarce. We searched PubMed, SCIELO, and WHO's Global Index Medicus comprehensively from January 1, 2000, to September 14, 2023, for 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 impact of ARB on 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 (ASB) 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 was introduced to reduce the underestimation of the impact of ABR BSI due to the possibility that a proportion of patients are hospitalised because the causative bacteria are resistant, leading to biased estimates when grouping community-acquired and hospital-acquired infections. This is often named collider stratification bias, which could occur when conditioning on a variable influenced by both the exposure (e.g., AMR) and outcome (e.g., disease severity), leading to a spurious association. In our study, hospital admission is the collider, affected by both resistance phenotype and infection severity, creating a non-causal link between resistance and health outcomes. Analysing hospital-acquired infections separately avoids this bias for those types of infections. However, 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 simultaneously induces collider stratification bias. Only if antibiotic resistance had no or negligible influence on the probability of being admitted to the hospital would our results for community-acquired infections potentially be reliable; hence, estimates for community-acquired infections should be interpreted cautiously.

By analysing hospital-acquired infections separately, we can account for varying treatment histories and avoid potential comparisons between strains exclusively circulating in hospitals

and community settings. We provide empirical evidence on the impact of ARB BSIs, revealing substantially higher mortality rates, LOS, ICU admission, and economic costs among these patients compared to individually weighted patients with BSI with antibiotic-susceptible bacteria. 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, utilising patient background data collated before the BSI onset to determine the subsequent health outcomes accurately.

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.

Background

Infections produced by antibiotic-resistant bacteria (ARB) represent one of the most pressing challenges to global public health with significant clinical and economic consequences.[1-5] A recent study by Murray *et al.* estimated 1·27 million annual deaths attributable to ARB worldwide in 2019.[1] A substantial burden exists in the Americas, with an estimated annual toll of 141 thousand deaths attributed to ARB.[6] 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.[7]

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 BSI 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) BSI.[8] 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 together in one analysis, potentially removing part of the true impact of community-acquired ARB BSI by conditioning on hospital

admission, which could potentially reside on the causal pathway between ARB BSI acquired in the community and health-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.[9-11]

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 settings

We conducted a retrospective parallel matched cohort study of adult inpatients over 15 years who presented with BSIs in three major tertiary-care healthcare centres from Chile (Iquique, Santiago, and Puerto Montt) 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-S3). All centres were public hospitals and used automated blood culturing systems (i.e., BD Phoenix^{TM}) and susceptibility testing techniques and followed to the Clinical Laboratories Standard Institute (CLSI) guidelines. Enrolment in the study was defined as the date of collection of the index blood culture.

Our analysis focused on WHO's high- or critical-priority ARBs, along with their susceptible counterparts.[12] 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). All positive blood cultures more than seven days apart from the index BSI reporting a different pathogen from the first observation were considered a separate BSI episode.[13] We excluded polymicrobial BSIs.

Data sources

Patient data were retrieved from hospital's clinical records and included two sets of variables: baseline information and time-varying attributes. Baseline variables included 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 during the 3 months previous to the current admission were also recorded. Variables related to the BSI episode encompassed source of the BSI (e.g., primary, catheter, respiratory, gastrointestinal, as defined by the primary team[14]), hospital- or community-acquired infections (i.e. cultures obtained <48 or >48 hours after admission, respectively[14]), mechanical ventilation (yes/no), and antibiotic usage, measured in daily defined doses (DDD per 1,000 hospital bed-days) per antibiotic family adhering to WHO ATC/DDD index standards and adjusted for frequency and dosage.[15] BSI treatment followed the Infectious Diseases Society of America clinical protocols.[16-18]

Clinical outcomes

Main outcomes included in-hospital mortality, hospital LOS (in days), and ICU admission; all of which were 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 S4-5). Hospital costs considered hospital bed-day in general wards and the ICU, 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.[19] Antibiotic costs, homologated to DDDs, were extracted from the Central de Abastecimiento (CENABAST)[20], 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).[21] 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.[22] 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 impacts of ARB BSIs on mortality.[23] We generated pathogen-specific cumulative incidence graphs using cause-specific hazard models, considering discharge alive and in-hospital mortality as endpoints.[24,25] We analysed the impact of IPW-adjusted single ARB effects on in-hospital mortality (a), and then incorporated (b) year and pathogen fixed-effects, and (c) time-varying covariates such as surgery and ICU admissions post-AMR culture. Although ICU admissions could mediate the effect between AMR and mortality, we included them because they often dictate subsequent treatment specifics—type, intensity, and timing—that directly affect patient outcomes. Moreover, ICU admissions indicate patient severity, closely linked to mortality risk. We analysed these variables in a separate model to distinguish between main AMR effects and ICU adjustments that may(not) potentially lie in the causal pathway. We analysed BSI episodes as independent events and applied clustered standard errors at the individual level. For missing data (15% missingness tolerance), we used predictive mean matching to preserve raw's 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.[26] Hospital-day costs included all inpatient admission (i.e., ICU and non-ICU wards 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 are presented in the Supplementary Material S10). Second, we estimated disease burden based on disability-adjusted life years (DALYs). Last, we estimated the excess burden attributable to ARB BSI deaths in Chile, extrapolating our results to the national level using Monte Carlo simulations (n=1,000 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.[6] We present upper and lower bound uncertainty estimates following mortality incidences CIs. See details in Supplementary Material S5-S6.

Results

I. Description of BSI events and incidence

We identified 1,218 patients experiencing a BSI, resulting in 1,349 BSI episodes (47·3% of which fulfilled our definition of an ARB) from 2018 until 2022 in the three hospitals (23·3%, 32·7 and 44·0% in each hospital). Table S4 shows sample details by pathogen and resistance pattern. A total of 1,072 BSI episodes (80%) were categorised as hospital-acquired and only 277 as community-acquired (Table S4). Figure 1 shows the overall incidence of BSI over time, revealing a significant peak in 2021, primarily driven by Enterobacterales and *Staphylococcus aureus*. Gram-negative bacteria (Figure 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%).

2. 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 Figure S5).

Table 1 shows that ARB BSI patients showed higher mortality (37·5%, vs. 29·4%; p<0·001), full LOS (47·3 (8-125), vs. 34·2 (5-95)) and full ICU admission (62·7% versus 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 (Figure 2) when compared to ASB BSIs, regardless of BSI acquisition (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 (Figure 2).

In the context of hospital- and community-acquired infections, we noted a less detrimental 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), although we found the opposite among community-acquired BSIs (Tables S4, S5). Patients with hospital-acquired ARB BSIs were more exposed to catheter usage before index culture (61·3 vs. 40·7% among ASB, compared to 19·5% and 25·5% among ASB and ARB community-acquired BSIs, respectively) (Table S4).

Overall, antibiotic consumption was greater among ARB patients, compared to ASB (260·3 and 196·4 DDDs per 1,000 hospital bed-days, respectively, Table 1). MRSA, VRE, 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 (Figure S5). Tables S4-5 illustrate that community-acquired BSIs exhibited greater antibiotic consumption (358·2 vs. 248·8 DDDs per 1,000 hospital bed-days) for ARB, compared to hospital-acquired BSIs.

3. 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 impact of hospital-acquired ARB BSIs on mortality was OR=1·38 (1·14-1·65, p=0·001), with the most substantial impacts 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 impact of ARB on LOS after BSI diagnostic was IRR=1·14 (1·05-1·24, p=0·001) among all bacteria, but predominantly among Gram-positive (IRR=1·22, 1·09-1·36, p=0·015). The impact of ARB BSIs on LOS indicated a 1·25-fold prolonged stay among patients with community-acquired BSIs.

Pathogen-specific analyses (Table S23) revealed MRSA and CRE-associated overall mortality were among the highest (OR=1·59, 1·2-2·2, p=0·003; OR=1·44, 1·1-1·9, p=0·018, respectively). Although MRSA and CRE impacts on 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, but most significant impact were found 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 impact estimates among hospital-acquired infections (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 (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 impacts of CRPA on LOS among hospital-acquired BSIs were more significant (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 impacts on mortality, ICU admission, and LOS were found among the remaining pathogens. Models with added fixed effects (i.e., hospital, pathogen, and year) were mostly consistent with the main estimates. (Full model results in Supplementary Material S7-S8).

4. Survival analysis using the competing risk model

Table 3 shows the impact of ARB on 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). Figure 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 (Figure 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 (Figure 3). Non-significant results were found among

community-acquired ARB BSIs. Tables 24.1-24.3 and Figures S9-S10 contain the complete results among all stratified models.

5. Costs and morbidity losses associated with ARB hospitalisation and premature mortality

Average direct hospital costs per patient ranged from $3,373 to $7,691 among all ARB and ABS BSIs (Table S26.1). The highest average excess costs related to ARB BSIs were found among CRPA ($2,564 excess), followed by CRE ($2,301 excess; $5,674-$3,373) and MRSA ($1,682 excess; $4,848-$3,167). Hospital bed-day costs usually represented 98% of total healthcare spending per patient. Excess hospital costs associated with ARB accounted for $2,244 ($123-$3,792) per patient in our sample.

In our study cohort, indirect or total ARB excess costs associated with premature mortality across pathogens were estimated at $10,313 per patient (Table S26.2). MRSA presented the most significant excess cost per patient associated with premature mortality, $14,288, followed by VRE and CRE ($10,169 and $9,933 per patient, respectively).

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 (Table S26.2).

6. DALYs and economic burden at the national level

The societal economic burden attributable to ARB BSI deaths (hospital costs+ productivity loss) was projected at about $53,725,000 ($27,914,566-$91,178,230), with hospitalisation costs accounting for $13,406,500 (Table S26.2). DALYs were projected at 2,270 (1,179-3,853) 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. The economic burden associated with BSIs, including hospital spending and productivity losses, were substantial.

We found that 65% of BSI episodes in our study were associated with *S. aureus* and Enterobacterales, consistent with recent findings from GBD 2019.[1] Our results suggest that hospital patients with ARB BSIs are 1·42 times more likely to die, with the most substantial mortality attributable burdens produced by hospital-acquired MRSA and CRE (1·60 and 1·44, respectively). Our results are comparable to those produced by a recent global meta-analysis that found 1·52 (0·76-2·28) and 1·49-times (1·09-1·90) greater mortality.[8]

Our estimates are lower than those from studies in Europe[24] (OR=1·80, 1·04-3·2) and Latin America[27] (RR=1·94, 1·38-2·73) for MRSA BSIs. Research on CRE-infected patients has generally reported approximately twice the mortality rate when compared to CSE.[28,29] Several factors may explain these differences. We stratified our sample based on BSI acquisition, whereas previous studies[8,27] have grouped hospital patients without considering potential cofounders influencing ARB acquisition and development.[9,10] Consistent with previous studies, we found substantial mortality impacts associated with hospital-acquired ARB BSIs compared to community-acquired ARB BSIs.[30] This difference could be explained by the epidemiological characteristics of the pathogens included, limited data for community-

acquired BSIs, and unobservable accumulated vulnerability (i.e., exposure to complex and toxic treatments and high disease severity) among patients with hospital-acquired BSIs.[30] 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. Only if ARB had a negligible influence on the probability of hospital admission would our results for community-acquired infections be accurate.

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.[8] 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.[8,31]

ARB infections have been associated with longer LOS, typically 2-12 days longer than ASB infections.[8,32] We observed crude median differences in hospital LOS between ARB and ASB BSIs after BSI diagnostic, ranging between 3-10 days among CRPA, MRSA, VRE, and CRE. After utilising 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.[33] MRSA was not associated with longer LOS, as in previous research.[24] This null finding may relate to factors such as BSI complications, which can vary across populations.[27] 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 hospitalization, consistent with previous findings.[34]

Excess hospital (direct) costs attributed to ARB BSIs were estimated at $10,313 compared to ASB BSIs,[8] consistent with recent studies. Researchers in Colombia found excess hospitalisation costs of $10,212 associated with MRSA BSIs, and estimates for CRAB in China and CRE in Italy and Turkey have been reported at $10,763,[35] $19,300,[36] and $10,002,[37] respectively. However, prior studies did not include costs associated with therapy, treatment, and professional staff.[4,5] Our estimates based on FONASA and CENABAST reflect health-system opportunity costs for BSI treatment. However, we believe our estimates are conservative because health outcomes related to disease severity, such as invasive device replacement, need for physical therapy, and vasoactive drug, among others, could increase economic costs but could not be included due to data availability.[38]

Following Daroudi et al.'s[39] approach for monetising DALYs based on GDP per capita (1·2 times GDP per capita times DALYs), our estimate of 2,270 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 cost of $53·7 million attributed to ARB BSI-related mortality, representing an substantial economic burden. The estimated DALYs attributed to ARB surpass those previously calculated for HIV (n=149), tuberculosis (n=65), lower respiratory infections (n=375), mounting to ~9% (2270 out of 24,829) of the total estimated DALYs in Chile in 2019.[40]

Heightened host vulnerability, inadequate empirical antibiotic treatment, excessive antibiotic usage following culture results, and reduced efficacy of reserve antibiotics contribute to this

ARB burden.[28,41] A meta-analysis reported that CRE patients were consistently less likely to receive appropriate initial antibiotic therapy.[28] We found that ARB patients had more substantial DDDs per 1,000 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 hours 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 versus 39·1% among ARB (χ^2 test p<0.001), with the largest differences among MRSA and CRE, compared to MSSA and CSE, respectively (14·0% versus 42·9%, χ^2 test p<0·001; and 26·4% versus 37·8%, χ^2 test p<0·001, Table S27). Early identification of BSI pathogens, especially Enterobacterales and *S. aureus*, could improve outcomes in patients with BSIs at a population level.[42]

Consistent with previous studies,[43-45] 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 1,000 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,[11] rather than solely by resistance to vancomycin.[46,47] In contrast, although *A. baumannii* is recognized for its high pathogenicity[48] and is notably prevalent in colonization in tertiary care hospitals in Chile,[49] 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.[6]

This study has some shortcomings. We used IPW methods, which may reduce the efficiency of our estimates and rely on observed variables, potentially concealing results. However, we included a wide range of host risk factors, encompassing LOS before the onset of infection, underlying health conditions, and sociodemographic factors, which might help mitigate the increased vulnerability following BSI diagnosis in hospital wards. We found large confidence intervals and small pathogen-specific analytical sample sizes. Additionally, hospitals can exhibit variations in blood culture sampling techniques and clinical management, which could affect the comparability of our estimates. We sought to mitigate this risk by selecting hospitals with similar equipment and infrastructure (e.g., automated blood culture system and antimicrobial susceptibility guidelines). Nevertheless, other factors, such as operational staff and day-to-day practices, may have introduced some unobserved data variability. Last, we did not perform genomic analyses. For instance, new lineages of MRSA clones harbouring enhanced pathogenicity[50] and emerging prevalence of carbapenemases among Enterobacterales[51,52] in Latin America could have hampered appropriate treatments. We did not include COVID-19 infections. However, our analysis revealed a surge in BSIs during 2020 and 2021, likely due to the pandemic's influence, manifesting in increased antibiotic usage and possibly relaxed stewardship practices, as supported by literature.[52,53] Finally, the virulence of strains (specifically MSSA)[54] and definition for community-acquired BSIs[55] may impact health-status and true prevalence of individuals with community-acquired BSIs, thus warranting cautious interpretation of these estimates.

Our study evaluated the health and economic impact of ARB BSIs in Chile, offering comprehensive estimates that underscore the need for improved prevention and surveillance strategies. This should include molecular epidemiology, monitoring selective pressure, and implementing rigorous control measures for patients colonised with ARB upon hospital admission (hygiene, contact precaution and isolation, stewardship of antimicrobials

protocols).[56-58] Emphasizing these practices is essential to mitigate the severe health and economic consequences associated with ARB in hospital settings.

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Ethical consideration

The study has already been approved by the Pontificia Universidad Catolica Chile Human Research Ethics Committee (Protocol ID: 200706001). 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.

Author contributions

Conceptualization, KA, PG, JM, EU; methodology, KA, LY, KP, JM, EU; data collation and extraction, AP, MS, JC; formal analysis, KA; writing—original draft preparation, KA; writing—review and editing, LY, AP, MS, PG, JM, EU; supervision, LY, JM, EU. KA, AP, MS, JC, PG, JM, 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

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, anonymized data are available from the corresponding author upon request.

Declaration of interest

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References

1. Murray CJ, Ikuta KS, Sharara F, et al. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. *The Lancet* 2022; **399**(10325): 629-55.

2. Jee Y, Carlson J, Rafai E, et al. Antimicrobial resistance: a threat to global health. *The Lancet Infectious Diseases* 2018; **18**(9): 939-40.

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. *Antimicrobial Resistance & Infection Control* 2018; **7**: 1-17.

5. Gandra S, Barter D, Laxminarayan R. Economic burden of antibiotic resistance: how much do we really know? *Clinical microbiology and infection* 2014; **20**(10): 973-80.

6. Aguilar GR, Swetschinski LR, Weaver ND, et al. The burden of antimicrobial resistance in the Americas in 2019: a cross-country systematic analysis. *The Lancet Regional Health–Americas* 2023.

7. Co-operation OfE, Staff D. Stemming the superbug tide: just a few dollars more: OECD; 2019.

8. 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 Medicine* 2023; **20**(6): e1004199.

9. 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. *Journal of Hospital Infection* 2018; **99**(1): 42-7.

10. 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. *Clinical Infectious Diseases* 2020; **71**(9): e415-e20.

11. 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. *Journal of Global Antimicrobial Resistance* 2021; **24**: 198-204.

12. 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. *The Lancet infectious diseases* 2018; **18**(3): 318-27.

13. Daneman N, Fridman D, Johnstone J, et al. Antimicrobial resistance and mortality following E. coli bacteremia. *Eclinicalmedicine* 2023; **56**.

14. 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. *Clinical Microbiology and Infection* 2010; **16**(9): 1408-13.

15. World Health Organization. ATC/DDD Index 2023. 2023. https://www.whocc.no/atc_ddd_index/?code=J01CR01 (accessed 13th of July 2023).

16. Tamma PD, Aitken SL, Bonomo RA, Mathers AJ, van Duin D, Clancy CJ. Infectious Diseases Society of America 2023 guidance on the treatment of antimicrobial resistant gram-negative infections. *Clinical Infectious Diseases* 2023: ciad428.

17. Liu C, Bayer A, Cosgrove SE, et al. Clinical practice guidelines by the Infectious Diseases Society of America for the treatment of methicillin-resistant Staphylococcus aureus infections in adults and children. *Clinical infectious diseases* 2011; **52**(3): e18-e55.

18. Infectious Diseases Society of America. IDSA Practice Guidelines. 2024. https://www.idsociety.org/practice-guideline/practice-guidelines/#/+/0/date_na_dt/desc/ (accessed 29 March 2024).

19. Fondo Nacional de Salud. Aranceles mai. 2023. https://www.fonasa.cl/sites/fonasa/prestadores/modalidad-atencion-institucional#aranceles-mai-2023) (accessed 13th of July 2023).

20. Central de abastacemiento (CENABAST) Chile. Reporte de compras historicas de CENABAST. 2023. https://www.cenabast.cl/compras-cenabast/ (accessed 13th of July 2023).

21. Organization WH. GLASS method for estimating attributable mortality of antimicrobial resistant bloodstream infections. 2020.

22. 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. *Journal of Antimicrobial Chemotherapy* 2011; **66**(2): 398-407.

23. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *Journal of the American statistical association* 1999; **94**(446): 496-509.

24. 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. *Antimicrobial agents and chemotherapy* 2011; **55**(4): 1598-605.

25. Lau B, Cole SR, Gange SJ. Competing risk regression models for epidemiologic data. *American journal of epidemiology* 2009; **170**(2): 244-56.

26. 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): 1093-103.

27. Seas C, Garcia C, Salles MJ, et al. Staphylococcus aureus bloodstream infections in Latin America: results of a multinational prospective cohort study. *Journal of Antimicrobial Chemotherapy* 2018; **73**(1): 212-22.

28. 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. *infection control & hospital epidemiology* 2017; **38**(11): 1319-28.

29. Xu L, Sun X, Ma X. Systematic review and meta-analysis of mortality of patients infected with carbapenem-resistant Klebsiella pneumoniae. *Annals of clinical microbiology and antimicrobials* 2017; **16**: 1-12.

30. Diekema D, Beekmann S, Chapin K, Morel K, Munson E, Doern G. Epidemiology and outcome of nosocomial and community-onset bloodstream infection. *Journal of clinical microbiology* 2003; **41**(8): 3655-60.

31. Ben-David D, Kordevani R, Keller N, et al. Outcome of carbapenem resistant Klebsiella pneumoniae bloodstream infections. *Clinical Microbiology and Infection* 2012; **18**(1): 54-60.

32. 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. *Clinical Infectious Diseases* 2017; **65**(4): 644-52.

33. Page DB, Donnelly JP, Wang HE. Community-, healthcare-and hospital-acquired severe sepsis hospitalizations in the University HealthSystem Consortium. *Critical care medicine* 2015; **43**(9): 1945.

34. Bai AD, Lo CK, Komorowski AS, et al. Staphylococcus aureus bacteraemia mortality: a systematic review and meta-analysis. *Clinical Microbiology and Infection* 2022; **28**(8): 1076-84.

35. Huang W, Qiao F, Zhang Y, et al. In-hospital medical costs of infections caused by carbapenem-resistant Klebsiella pneumoniae. *Clinical Infectious Diseases* 2018; **67**(suppl_2): S225-S30.

36. Tumbarello M, Spanu T, Di Bidino R, et al. Costs of bloodstream infections caused by Escherichia coli and influence of extended-spectrum-β-lactamase production and inadequate initial antibiotic therapy. *Antimicrobial agents and chemotherapy* 2010; **54**(10): 4085-91.

37. Gulen TA, Guner R, Celikbilek N, Keske S, Tasyaran M. Clinical importance and cost of bacteremia caused by nosocomial multi drug resistant Acinetobacter baumannii. *International Journal of Infectious Diseases* 2015; **38**: 32-5.

38. 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.

39. 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 Effectiveness and Resource Allocation* 2021; **19**(1): 1-9.

40. 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. *The Lancet* 2020; **396**(10258): 1204-22.

41. Holland TL, Bayer AS, Fowler Jr VG. Persistent methicillin-resistant Staphylococcus aureus bacteremia: resetting the clock for optimal management. *Clinical Infectious Diseases* 2022; **75**(9): 1668-74.

42. 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. *The Lancet Infectious Diseases* 2021; **21**(2): 241-51.

43. Shay DK, Maloney SA, Montecalvo M, et al. Epidemiology and mortality risk of vancomycin-resistant enterococcal bloodstream infections. *Journal of Infectious Diseases* 1995; **172**(4): 993-1000.

44. Salgado CD, Farr BM. Outcomes associated with vancomycin-resistant enterococci: a meta-analysis. *Infection Control & Hospital Epidemiology* 2003; **24**(9): 690-8.

45. Carmeli Y, Eliopoulos G, Mozaffari E, Samore M. Health and economic outcomes of vancomycin-resistant enterococci. *Archives of internal medicine* 2002; **162**(19): 2223-8.

46. 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. *Antimicrobial resistance & Infection control* 2018; **7**: 1-9.

47. Piezzi V, Marschall J, Buetti N. Are vancomycin-resistant enterococcal bloodstream infections associated with decreased survival? *Clinical infectious diseases* 2020; **71**(6): 1586-.

48. 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. *Microbiology Spectrum* 2022; **10**(5): e02463-22.

49. 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. *The Lancet Regional Health–Americas* 2023; **21**.

50. 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. *Antimicrobial agents and chemotherapy* 2017; **61**(10): 10.1128/aac. 00816-17.

51. 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. *Emerging Infectious Diseases* 2022; **28**(11).

52. 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. *Clinical Infectious Diseases* 2023; **77**(Supplement_1): S20-S8.

53. Langford BJ, Soucy J-PR, Leung V, et al. Antibiotic resistance associated with the COVID-19 pandemic: a systematic review and meta-analysis. *Clinical Microbiology and Infection* 2023; **29**(3): 302-9.

54. Cheung GY, Bae JS, Otto M. Pathogenicity and virulence of Staphylococcus aureus. *Virulence* 2021; **12**(1): 547-69.

55. 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. *Journal of Hospital Infection* 2005; **60**(4): 329-32.

56. Rice S, Carr K, Sobiesuo P, et al. Economic evaluations of interventions to prevent and control health-care-associated infections: a systematic review. *The Lancet Infectious Diseases* 2023.

57. Salvador BC, Lucchetta RC, Sarti FM, et al. Cost-effectiveness of molecular method diagnostic for rapid detection of antibiotic-resistant bacteria. *Value in Health Regional Issues* 2022; **27**: 12-20.

58. 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 Global Health* 2024; **9**(2): e013205.

59. Brown LD, Cai TT, DasGupta A. Interval estimation for a binomial proportion. *Statistical science* 2001; **16**(2): 101-33.

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

Variables	**ASB** (N= 711)			**ARB** (N= 638)			χ^2 or M-WU‡ test
	Mean (%)	95%CI	IQR	Mean	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	<0·001
LOS before BC (days)	11·55	0—36	12	21·28	0—61	21	<0·001
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	-	<0·001
ICU admission (%) before BC	6·33	5—8	-	1·88	1—3	-	<0·001
ICU admission (%) after BC	41·49	38—45	-	55·96	52—60	-	<0·001
Full ICU LOS (days)	10·27	0—42	15	18·87	0—63	30	<0·001
ICU LOS after BC (days)	9·46	0—42	14	18·50	0—63	30	<0·001
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	-	0·119
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	<0·001
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							<0·001
Primary (%)	31·67	28—36	-	38·38	34—43	-	0·021
Catheter (%)	16·12	13—20	-	14·23	11—17	-	0·388
Pneumonia/respiratory (%)	23·80	20—28	-	20·00	17—24	-	0·132

Gastrointestinal (%)	9·02	7—12	-	8·65	6—11	-	0·830
Abdomen (%)	13·24	10—16	-	12·97	10—16	-	0·896
Bones and joints (%)	2·88	2—5	-	1·98	1—4	-	0·339
Skin and soft tissue (%)	2·69	1—4	-	3·24	2—5	-	0·592
Meningitis (%)	0·58	0—2	-	0·54	0—2	-	0·938
Community-acquired infection (%)	27·75	24—31	-	12·32	10—15	-	<0·001
Indwelling catheter (%)	36·43	33—40	-	56·27	52—60	-	<0·001
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	-	<0·001
Mechanical ventilation before BC (%)	4·64	3—6	-	5·33	4—7	-	0·562
Mechanical ventilation after BC (%)	28·83	26—32	-	53·92	50—58	-	<0·001
Surgery previous BC (%)	0·70	0—2	-	0·63	0—2	-	0·864
Surgery after BC (%)	6·47	5—9	-	15·05	12—18	-	<0·001
Antibiotic consumption in daily defined doses 'DDDs' per treatment course after BC (in 1,000 hospital bed-days)							
Total consumption	196·44	0—645	273·9	260·34	0—765	253·87	<0·001
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	0·643
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	0·554
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	<0·001
Penicillin	3·43	0—21	1·73	3·08	0—15	3·66	0·471
Glycopeptides	2·75	0—14	3·85	5·15	0—20	6·64	<0·001
LOT (days)	16·11	0—64	22	36·26	0—6	2	<0·001
NOA (number)	2·60	0—9	4	5·18	0—101	39	<0·001

Notes: ARB= Antibiotic resistance. ASB= Antibiotic sensitive. 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[59]. BC= index Blood culture. ID= Infectious disease. ICU= Intensive care unit. LOS= Length of hospital stay. IQR= 75^{th} percentile – 25^{th} percentile. [b]χ^2 or Mann-Whitney U-test were employed according to each variable's distribution (α=0.05). Descriptive statistics among community and hospital-acquired infections are shown in Supplementary Material, section 3. ‡ Mann-Whitney U statistics were used to test differences between two independent groups among continuous variables.

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

Outcome	Model†	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 (N=1,349 all hospital patients, N=1,072 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	<0·001	1·37	1·13—1·66	0·001	1·40	0·87—2·24	0·170
	(B) A + $FE_{H,Y,P}$	1·43	1·20—1·71	<0·001	1·39	1·15—1·69	0·001	1·57	0·95—2·60	0·078
Overall mortality after index blood culture	**(A)** ARB only	1·42	1·20—1·68	<0·001	1·38	1·14—1·65	0·001	1·27	0·80—2·00	0·305
	(B) A + $FE_{H,Y,P}$	1·44	1·22—1·71	<0·001	1·41	1·17—1·70	0·000	1·38	0·86—2·23	0·187
ICU admission after index blood culture	**(A)** ARB only	1·25	1·07—1·46	0·005	1·04	0·87—1·24	0·668		‡ Omitted	
	(B) A + $FE_{H,Y,P}$	1·05	0·89—1·25	0·560	0·88	0·73—1·07	0·192		‡ Omitted	
LOS after index blood culture	**(A)** ARB only	1·14	1·05—1·24	0·001	1·08	0·99—1·19	0·088	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	0·326	1·31	1·08—1·59	0·005
Gram-positive (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	0·069	1·76	0·87—3·55	0·115
	(B) A + $FE_{H,Y,P}$	1·41	1·07—1·85	0·015	1·31	0·98—1·77	0·071	1·19	0·53—2·67	0·669
Overall mortality after index blood culture	**(A)** ARB only	1·45	1·13—1·86	0·003	1·30	0·99—1·70	0·058	1·55	0·81—2·95	0·188
	(B) A + $FE_{H,Y,P}$	1·46	1·12—1·91	0·005	1·40	1·04—1·87	0·024	1·00	0·48—2·08	0·999
	(A) ARB only	0·96	0·76—1·22	0·738	0·80	0·62—1·04	0·093		‡ Omitted	

ICU admission after index blood culture	**(B)** A + $FE_{H,Y,P}$	0·83	0·64—1·09	0·188	0·71	0·53—0·95	0·023		‡ Omitted	
LOS after index blood culture	**(A)** ARB only	1·22	1·09—1·36	0·015	1·04	0·91—1·19	0·547	1·21	0·91—1·6	0·189
	(B) A + $FE_{H,Y,P}$	1·14	1·01—1·29	0·030	1·07	0·94—1·23	0·304	1·69	1·26—2·25	0·000
Gram-negative (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	0·711
	(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	0·673
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	0·839
	(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	0·778
ICU admission after index blood culture	**(A)** ARB only	1·41	1·14—1·75	0·001	1·20	0·94—1·54	0·138		‡ Omitted	
	(B) A + $FE_{H,Y,P}$	1·46	1·15—1·86	0·002	1·32	0·99—1·75	0·049		‡ Omitted	
LOS after index blood culture	**(A)** ARB only	1·08	0·95—1·22	0·237	1·11	0·98—1·25	0·115	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	0·959	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. †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); *Gram-positive bacteria included *Staphylococcus aureus* and Enterococcus spp.; Gram-negative bacteria included *Acinetobacter baumannii*, Enterobacterales, and *Pseudomonas aeruginosa*. See Tables S13-S20 for the full models of mortality, LOS, and ICU admission. Table S23 summarizes the pathogen-specific analysis. . ‡ 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. BSI= Bloodstream infection. CI= Confidence interval. FE= Fixed effect. ICU= Intensive care unit. BC= blood culture. LOS= Length of hospital stay.

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

Pathogen	Model†	IPW-adjusted survival model		
		HR	95% CI	p
All hospital patients				
(A) All bacteria (N=1,349)	**1.A** ARB only	1·34	1·15—1·55	<0·001
	1.B 1.A + $FE_{H,Y,P}$	1·37	1·18—1·59	<0·001
	1.C 1.B + IV	1·35	1·16—1·58	<0·001
(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=1,072)	**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	<0·001
	1.C 1.B + IV	1·34	1·14—1·58	<0·001
(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	<0·001
	3.C 3.B + IV	1·49	1·17—1·92	<0·001
Community-acquired BSIs				
(A) All bacteria (N=277)	**1.A** ARB only	1·21	0·81—1·81	0·349
	1.B 1.A + $FE_{H,Y,P}$	1·28	0·85—1·91	0·239
	1.C 1.B + IV	1·38	0·90—2·10	0·139
(B) Gram-positive	**2.A** ARB only	1·45	0·83—2·56	0·195

(N=139)	**2.B** 2.A + $FE_{H,Y,P}$	1·04	0·61—1·76	0·886
	2.C 2.B + IV	1·12	0·65—1·93	0·693
(C) Gram-negative (N=138)	**3.A** ARB only	1·03	0·59—1·81	0·919
	3.B 3.A + $FE_{H,Y,P}$	0·98	0·54—1·80	0·956
	3.C 3.B + IV	1·04	0·55—1·98	0·894

Notes: ARB= Antibiotic-resistant bacteria. ASB= Antibiotic-sensitive bacteria. IPW= Inverse-probability weighting. HR= Hazard ratios. †Three (A, B, C) models were performed: **(A)** only considered ARB as an independent variable, compared to ASB BSIs; **(B)** considered ARB versus 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. 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.

1

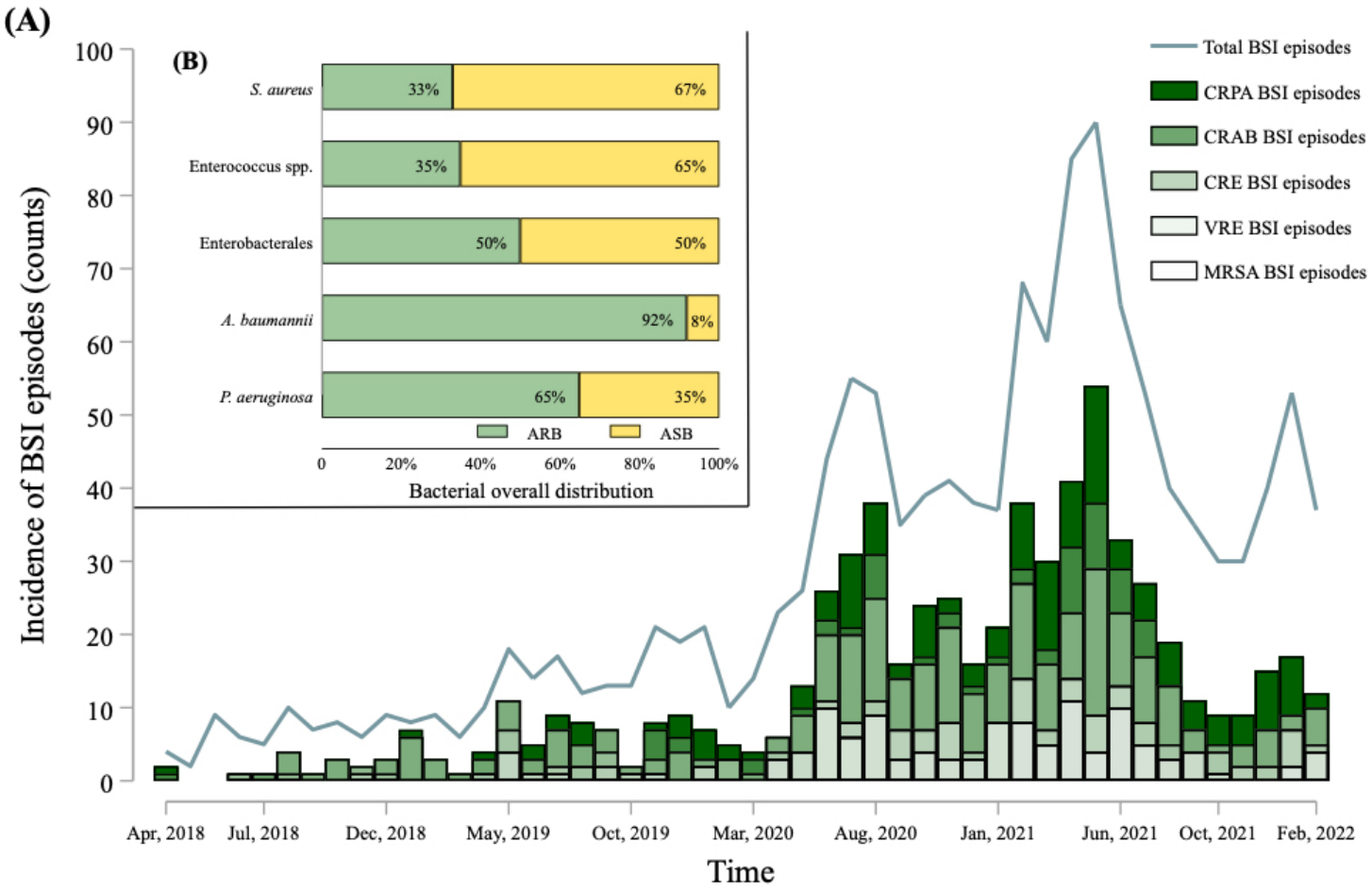

Figure 1. Incidence of ARB and ASB BSI episodes and resistance levels over time by pathogen.

(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.

Notes: ARB= Antibiotic resistance. ASB= Antibiotic sensitive. 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.

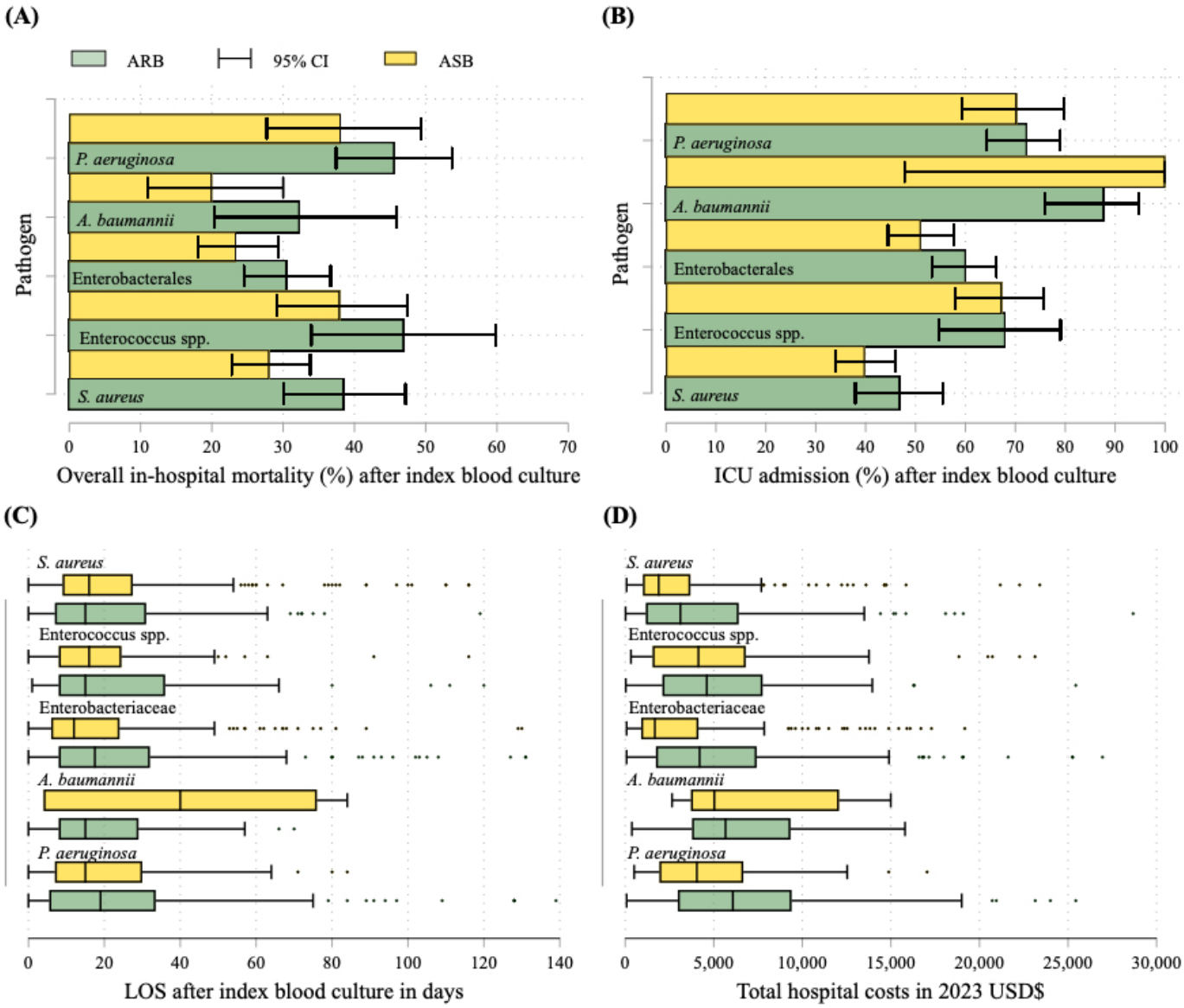

Figure 2. Unadjusted distribution of the main outcomes by pathogen and resistance levels. **(A)** Mortality proportions by pathogen and resistance level among sampled patients. **(B)** ICU admission proportions by pathogen and resistance level among sampled patients. **(C)** Length of hospital stay by pathogen and resistance level among sampled patients. **(D)** Total hospital economic costs by pathogen and resistance levels.

Notes: LOS= Length of hospital stay. ICU= Intensive care unit. ARB= Antibiotic resistance. ASB= Antibiotic sensitive. 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.

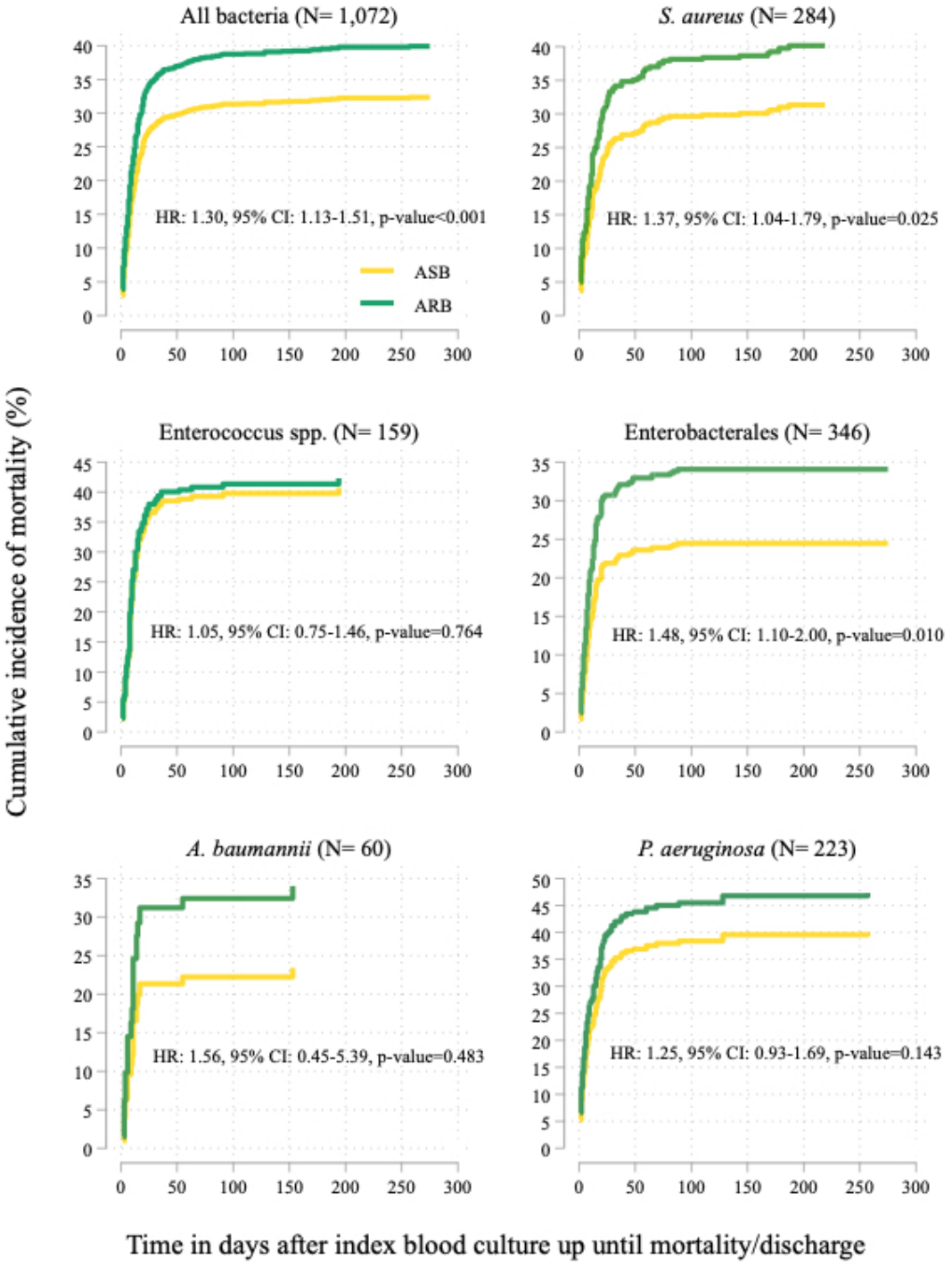

Figure 3. Cumulative incidence of in-hospital mortality over time among hospital-acquired blood stream infections using an adjusted competing-risk model by pathogen.

Notes: 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 *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. 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.

Chapter 8:

Cost-effectiveness of Screening, Decolonisation and Isolation Strategies for Carbapenem-resistant Enterobacterales and Methicillin-resistant Staphylococcus aureus Infections in hospitals: A Sex-stratified Mathematical Modelling Study

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Student ID Number	1807578	**Title**	Mr
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Surname/Family Name	Allel		
Thesis Title	Impacts of antimicrobial resistance bloodstream infections among hospital patients and potential interventions: a case study in Chile		
Primary Supervisor	Laith Yakob		

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SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	I have conceptualised the study, collated and extracted the data, performed formal analysis, drafted the paper and validated data, and compiled the final manuscript.

SECTION E

Student Signature	Kasim Allel
Date	25/March/2024

Supervisor Signature	Laith Yakob
Date	25/March/2024

Cost-effectiveness of Screening, Decolonisation and Isolation Strategies for Carbapenem-resistant Enterobacterales and Methicillin-resistant *Staphylococcus aureus* Infections in hospitals: A Sex-stratified Mathematical Modelling Study

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Abstract

Background. Methicillin-resistant *Staphylococcus aureus* (MRSA) and carbapenem-resistant Enterobacterales (CRE) incur greatest burden among WHO critical pathogens. Evidence for sex differences among antibiotic resistant bacterial infections, including MRSA and CRE, is burgeoning but its influence on policy remains nascent.

Methods. We assessed excess length of hospital stay, ICU admission and mortality burdens by sex from CRE/MRSA from a cohort study of 469 patients with Enterobacterales and 404 with *Staphylococcus aureus* symptomatic infections in Chilean hospitals, 2018-2021. We used propensity scores to balance patient characteristics and inverse-probability weighting combined with descriptive, logistic, and competing-risks analyses. Next, we developed a sex-stratified deterministic compartmental model to analyse hospital transmission dynamics and the cost-effectiveness of nine interventions against CRE and MRSA, including pre-emptive measures for new admissions and chromogenic agar and PCR tests, alongside decolonisation and contact precautions. Parametrizing the model with the hospital data, we estimated the projected benefit of targeting interventions. We assessed these interventions based on the incremental cost-effectiveness ratio (ICER) per quality-adjusted life year (QALY) gained, setting the ICER threshold at $16,230 per QALY over one year. Net benefits (NB) across varying hospital-bed coverage rates were calculated using estimated ICERs and willingness to pay (WTP).

Findings. After accounting for underlying health-conditions, the probability of women presenting CRE and MRSA were 0·44 (95% CI= 0·48-1·01, p=0·050) and 0·73 (95% CI= 0·28-0·70, p=0·001), respectively. Competing-risk models indicated higher mortality rates among women, compared to men. Mathematical model projections showed that pre-emptive isolation across all newly admitted high-risk men was the most cost-effective intervention (ICER=$1,366 and 1,083/QALY for CRE and MRSA model, respectively). Chromogenic agar coupled with MRSA decolonisation was second most cost-effective with $2,099/QALY,

followed by screening plus isolation or pre-emptive isolation strategies (ICER ranging between $2,411 and $4,216/QALY across CRE and MRSA models). Probabilistic sensitivity analysis showed that strategies were ICER<WTP in 80% of simulations, except for testing plus digestive decolonisation for CRE. At a 20% national hospital coverage, the healthcare system could save at least $12·2 million under any of the intervention scenarios.

Interpretation. Targeted infection control strategies are urgently needed to address rising CRE and MRSA rates. The greatest health-economic gains can be expected from prioritising burden reduction in women, which, counterintuitively, requires targeting men with interventions as they contribute disproportionately to transmission.

Keywords: Mathematical modelling, Antibiotic resistance, Transmission dynamics, Interventions, Cost-effectiveness

Research in context

Evidence before this study

Studies have established the effectiveness of various interventions, such as screening, isolation, and decolonisation, in controlling the spread of Methicillin-resistant *Staphylococcus aureus* (MRSA) and carbapenem-resistant Enterobacterales (CRE). Interventions are typically applied to whole hospital populations, failing to take advantage of our understanding that risk factors for CRE/MRSA stem from local, epidemiologically driven processes. The literature on tailoring interventions to these specific risk factors remains limited.

Added value of this study

Using the most comprehensive CRE/MRSA survey conducted in Chilean hospitals to date, we identified significantly fewer infections among women but showed that their infection burden was higher than men's. Accounting for these important sex differences in a new mathematical model of both CRE and MRSA, we used the hospital data to inform the projected benefit of a suite of alternative interventions. Our model demonstrates a clear advantage to targeting men with pre-emptive interventions and the level of gains achievable are 519 QALYs per year in a 1,000-bed hospital, compared to standard-of-care. Our analysis highlights substantial net benefits at the national level, scaling from $12·12 million with 20% of hospital-beds targeted with the least cost-effective strategy to $346·15 million when 100% hospital-beds are covered with the most cost-effective strategy. Additionally, in determining sensitivity trade-offs with timeliness of diagnosis, we developed a target product profile for future development of diagnostics.

Implications of all the available evidence

This study's findings are pivotal for shaping public health policies and refining hospital infection control measures. Implementing strategies customised to the unique risk profiles, health impacts, transmission dynamics, and intervention responses across diverse patient cohorts promises to amplify the efficacy of infection control efforts, thereby enhancing net monetary benefits.

Introduction

Antibiotic-resistant bacteria (ARB) represent a pressing global health challenge.[1] Sociodemographic and anthropogenic factors are key in facilitating their spread.[2] Limited information on costs and the cost-effectiveness of hospital interventions to reduce antibiotic resistance (ABR) hinders efficient resource allocation.[3] Recent evidence suggests that, in certain contexts, pharmaceutical and non-pharmaceutical interventions have emerged as the most cost-effective measures.[4] Decolonisation (e.g., using topical agents or selective digestive decontamination)[5-9], diagnostics (e.g., chromogenic agar, polymerase chain reaction)[10-15], and isolation via contact precaution (e.g., use of gowns and gloves)[7,9,16,17] were primary measures for infection control, with numerous interventions outperforming standard care by being both less costly and more efficient.[6-9,17] However, the majority of the literature has concentrated on unit-based or whole-hospital populations. This approach is likely suboptimal, given the existing heterogeneities in ARB infections and the risk factors associated with higher rates.[7,15,18,19] Accommodating heterogeneity in ARB infections requires adapting control to local demographics and disease ecologies.[4] Importantly, variations have been reported in terms of disease impact and dynamics between sexes[20-24] but these have not translated into optimising cost-effective interventions.[20-22] Despite men typically having higher ARB incidence, women generally have a worse prognosis—attributable to hormonal, behavioural, and genetic characteristics affecting the expression of virulence factors.[22-26] Comprehensive sex-based analyses of ARB are needed for improved infection control and health outcomes.[27-39]

In South America, Methicillin-resistant Staphylococcus aureus (MRSA) and carbapenem-resistant Enterobacterales (CRE), constitute 22·0% (12·2 per 100,000) and 33·9% (19·1 per 100,000) of ARB cases, respectively.[1] While these rates align with worldwide prevalence, mortality rates are particularly high in this region, with age-standardised deaths reported at 56·3 (40·2–76·3) per 100,000 individuals.[40] Our study was conducted in Chile including

1,218 infected patients, either associated with ARB or antibiotic-susceptible bacteria, and their clinical (e.g., mortality, intensive care unit admission), and sociodemographic data (e.g., age and sex). Full details have been described in a previous study.[41] In this setting, CRE and MRSA infections demonstrated notable prevalence rates of 49·8% and 33·1%, respectively, responsible for $10,300 excess hospital costs per patient.[41] Yet, Chile's National Action Plan (NAP[42]) for ARB currently provides insufficient guidance on screening, decolonisation treatments and isolation at the point of care. The plan primarily focuses on embracing standard precautions, such as early identification and the prompt implementation of additional safety measures, including the use of personal protective equipment and hand hygiene. However, this hinders effective prevention of CRE/MRSA transmission and falls short in stating specific screening tools and decolonisation treatments.[43]

This study aims to identify differences between sexes in terms of incidence and health outcomes in Chilean hospitals, and to capitalise on these differences to inform optimised health-economic targeting of interventions for CRE and MRSA.

Methods

We used a pathogen-specific sex-structured deterministic model of MRSA and CRE, adapted from previous literature[27-37,44], to assess in-hospital transmission dynamics. We computed parameters from statistical analyses of patient data collected from three large Chilean hospitals (first stage), then integrated these into a novel compartmental model to determine the impact of alternative approaches and targeting strategies in reducing disease burden (second stage).

First stage: Statistical analyses of CRE/MRSA data

Drawing upon data from a retrospective matched-parallel cohort study in tertiary hospitals[41,45], we used descriptive analysis (subgroup means and standard deviations) and inverse probability weighting (IPW) techniques[46] to analyse the burden of MRSA or CRE in symptomatic hospital patients with positive blood cultures (469 and 404 for CRE and MRSA, respectively). We estimated a propensity score to match MRSA with MSSA and CRE with CSE populations according to their baseline characteristics prior to infection (e.g., antibiotic consumption, prior hospitalisation, community-acquired infection, age). These characteristics were selected upon improved Bayesian Information Criterion (BIC), correlation analysis (using Pearson X^2), while keeping a Variance Inflation Factor (VIF) <10. Subsequently, we computed pathogen-specific IPW-adjusted logistic regressions for ICU admission, and survival regressions accounting for competing-risks (i.e., mortality and discharge)[47] to determine the co-hazards associated with sex, ARB (e.g., MRSA/MSSA or CRE/CSE) and disease severity (e.g., general wards or ICU admission). Marginal effects were computed for sex-specific estimates. Additionally, we collated data on prior antibiotic usage (i.e., methicillin or carbapenems), and length of hospital stays, across pathogens and patient sex. A more detailed description of the study is found in Supplementary Box A1.[41]

Second stage: Mathematical model

We created two deterministic models, each separately capturing the progression of CRE or MRSA transmission in hospitals through epidemiological states. We included men and women patients uncolonised (U), colonised but asymptomatic (by either carbapenem/methicillin-resistant 'C^R' or -susceptible 'C^S' Enterobacterales/*S. aureus*), symptomatic with mild or severe infections (I^R_{Mil} and I^R_{Sev} for CRE/MRSA and I^S_{Mil} and I^S_{Sev} for CSE/MSSA) and dead or recovered (D^R or D^S and R^R or R^S, repectively, and depending upon antibiotic susceptibility) (Supplementary Figure A1). Dual-carriage of susceptible and resistant strains was not incorporated following the assumption that mixed carriage is predominantly sensitive-colonised (CSE or MSSA) and do not further transmit the resistant

strain in the absence of antibiotics.[48] A stable hospital inpatient population was maintained by adjusting daily admissions to daily deaths and discharges. Recovery and treatment were adjusted to the pathogen-specific data. Treatment metrics showed the proportion of patients receiving antibiotics in compliance with pathogen's susceptibility guidelines.[29] Risk-group specific length of hospital stay, discharge rates, and patient's movement between risk-severity groups within healthcare setting were also included. Individuals could transition health states daily. See Supplementary Tables A1-2 for full description of the baseline conditions and parameters used to calibrate the model. The ordinary differential equations used to describe system dynamics are in Supplementary Text.

Computational simulations

We computed the transmission parameter by fitting our model to the most recent prevalence rates for CRE/MRSA[49] utilising the Runge-Kutta[50] optimisation method. Relative transmission from men and women was informed by the propensity score estimates obtained from the first stage (in the form of odds ratios; OR comparing men relative to women). We did a global sensitivity analysis to identify the parameters that had greatest influence on both CRE/MRSA transmission. Parameter uncertainty was incorporated using the Latin hypercube sampling method with 1,000 simulations[51] and calculated the partial rank correlation coefficient (PRCC).[51]

Intervention strategies

We evaluated screening (using chromogenic agars and polymerase chain reaction methods 'PCR'[52]), isolation via enhanced contact precaution (e.g., monitoring and use of gloves and gowns[16,53]), and decolonisation strategies (mupirocin[54] and digestive decontamination[55] for MRSA and CRE, respectively) per pathogen model (see Supplementary Table A3), informed from a recent systematic literature review of the most cost-effective testing-treatment

combination strategies.[4] After computing our base scenario with no intervention (S0), we simulated 9 strategies for transmission prevention (S1-S9). S1, S2, and S3 included screening all newly admitted patients using chromogenic agar 48 hours, chromogenic agar 24 hours, and PCR, respectively, + decolonisation among CRE/MRSA+. S4, S5 and S6 comprised the same screening diagnostics plus isolation (contact precaution) among CRE/MRSA positives. S7, S8 and S9 involved pre-emptive isolation among all new admissions, and only men or women, respectively. Efficiency parameters for diagnostics, isolation and treatments are detailed in Supplementary Table A4. We simulated a range of intervention coverage levels. We accommodated differential risk of infection between sexes by adjusting the success rates of pre-emptive isolation. For example, pre-emptively isolating only men would isolate 1·37-fold more MRSA infectious individuals relative to isolating an equivalent number of mixed-sex patients because the OR of MRSA infections among women was 0·73 (equivalent to 1·37 among men, if reference group was reversed, i.e., 1/0.73).

Health economics

We evaluated cost-effectiveness by calculating the incremental cost-effectiveness ratio (ICER) comparing the 9 strategies versus a 'do-nothing' base scenario using the healthcare perspective. We followed the WHO best practices for AMR prevention and control and the Consolidated health economic evaluation reporting standards (CHEERs).[56,57] We also evaluated the number of averted infected and dead patients associated with CRE/MRSA , and quality-adjusted life years (QALYs) associated with health states. Economic costs included diagnostic, hospital bed-days (general wards, intermediate care and intensive care units 'ICU') and drug (i.e., colistin, gentamicin, mupirocin, and chlorhexidine). Hospital bed-days and diagnostic tests' costs were sourced from Chile's public health insurance program.[58] Antibiotic costs for decolonisation schemes were extracted from Chile's government unit in charge of acquiring and distributing drugs and medical supplies.[59] All

costs were expressed in 2022 USDs and no discount rate was applied due to 1-year time horizon. We reported the ICER per QALY gained for each strategy. See Supplementary Tables A4-5 for more information. Finally, we extrapolated our results to the national level accounting for 37,397 hospital beds in the country.[60] Willingness-to-pay 'WTP' was defined following Chile's gross-domestic product (GDP) per capita ($16,265). We calculated the net benefit ('NB'= (WTP per QALY – cost per QALY)*QALYs gained) of each intervention, compared to base scenario, and following coverage at 20, 40, 60, 80 and 100% of total country's hospital beds (n=30,000 beds, those used for psychiatric care were excluded).[60] Uncertainty intervals for QALYs gained and NB were computed adjusting our models to pathogen's prevalence lower and upper bounds.[49]

Probability sensitivity analyses were performed for intervention parameters using 1,000 random samples. We varied diagnostic sensitivities, test turnaround time, isolation and decolonisation efficiency, and health utilities, utilising a beta distribution for rates and gamma distribution for costs and turnaround time. Due to uncertainty in parameter's confidence interval, we assumed a sample size of N=100 for parameters reporting rates, allowing us to derive the alpha (α) and beta (β) parameters of a beta distribution to approximate the confidence interval based on the known mean. For modelling economic costs and turnaround times, we selected a k parameter of 0.5 for the gamma distribution, appropriate due to the skewness observed in cost distribution, with a high concentration of values near the lower end. We estimated the percentage of cost-effective (ICER<WTP) simulations per strategy at different WTP thresholds.

All statistical analyses were performed in R version 3.3.4. Full code is available at https://bit.ly/3sgnmrU.

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. Authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

First stage: Epidemiology of sex-stratified CRE/MRSA

Supplementary Tables A6-7 and Figure 1 display the sex-stratified incidence and main characteristics of symptomatic infection for Enterobacterales (56·1% and 40·8% with CRE among 278 men and 157 women, respectively; χ^2 p<0·001) and *Staphylococcus aureus* (35·2% and 29·3% with CRE among 247 men and 157 women, respectively, χ^2 p=0·042). Higher mortality and ICU admissions after diagnosis were found among women with MRSA, compared to men (45·6% versus 34·5%, χ^2 p=0·034; and 45·7% versus 37·9%, χ^2 p=0·038, respectively). Although similar mortality rate was experienced, extended length of hospital stay (LOS) was found among women with CRE, compared to men (29·9 versus 24·3, respectively; χ^2 p=0·049). Our propensity score estimation indicated that women were 0·44 (95% CI= 0·48-1·01, p=0·050) and 0·73 (95% CI= 0·28-0·70, p=0·001) times less likely to acquire CRE and MRSA under baseline conditions , respectively (Supplementary Tables A8-9 and Figures A3-4 for density checks). Our IPW-adjusted models suggested greater ICU admissions among women with MRSA and men with CRE, compared to men and women with their susceptible counterparts (Supplementary Table A10 and Figures A5-6 for sex-marginal effects). Supplementary Table A11 and Figures A7-8 show that women had the highest mortality rate associated with CRE and MRSA in survival models with competing risks (hazard ratio 'HR'=2·40, 95% CI= 1·5-3·9, p<0·001 and HR=2·34, 95% CI=1·3-4·1,

p=0·003 for women in the ICU if compared to the lowest mortality rate exhibited in men with CSE or MSSA in general wards, respectively).

Second stage: Mathematical model

Pre-emptive isolation and testing + isolation strategies improved health outcomes and reduced costs the most, regardless of pathogen (Figure 2 and Supplementary Figures A9-11). The best strategy for CRE was pre-emptively isolating men, averting 1,700 infections and 36 CRE-associated deaths per year, producing an ICER equal to $1,366 per QALY gained. The most cost-effective CRE-screening strategy used PCR (ICER=3,156) and chromogenic agar enriched with carbapenems (ICER=3,157), although the former strategy averted double the number of infections and associated deaths. All CRE decolonisation strategies had ICER>WTP due to the low efficacy of this treatment coupled with its prolonged duration. For MRSA, chromogenic agar enriched with salt and oxacillin was preferred for screening carriers and resulted in better value for money. Testing plus MRSA decolonisation among all new admissions, totalled ICERs of $2,099, $1,900, and $1,850 per QALY gained, respectively, reducing annual deaths per 1,000 hospital beds (i.e., [number of deaths/1,000 hospital beds]*365) by 9·9, 3·7, and 5·8, respectively. This strategy was cost-effective and preferred to all test + isolation interventions because isolated patients continue to contribute to within-hospital transmission (e.g. via healthcare workers) whereas decolonised patients do not. The most cost-effective strategy for MRSA was pre-emptive isolation of newly admitted men (ICER=$1,083, saving 32·1 deaths per 1,000 hospital beds annually).

PCR testing combined with isolation strategies led to a 22·2% and 30·8% decrease in CRE infections per 100 admissions and deaths per 100,000 hospital-bed days, respectively, compared to a do-nothing scenario (Figure 2, panel A and B). Similarly, MRSA infections decreased by 46·2% and deaths by 41·5 % (Figure 2, panel C and D). Isolating men pre-emptively led to similar figures.

Health benefits per new admission were greatest when pre-emptively isolating men, with 0·0121 and 0·014 incremental QALYs and $14·9 and $16·8 incremental costs per new admission among CRE and MRSA, respectively, compared to a do-nothing scenario (Supplementary Figure A12).

PSA analysis and WTP

Supplementary Figures A13-4 display the PSA analysis per pathogen and strategy intervention suggesting consistent increased effectiveness in 100% scenarios and positive average incremental costs. Utilising PSA results, the ICER fell below the WTP thresholds of $8,000 and $16,000 per QALY gained in 80% and 100% of simulations, respectively, for pre-emptive isolation strategies (covering all new admissions and high-risk men) and the PCR plus isolation approach in CRE/MRSA models (Supplementary Figure A15). Agar-based screening combined with isolation was deemed cost-effective in over 81% of simulations at WTP=$16,265 per QALY. Notably, for MRSA, strategies involving 48-hour agar screening and PCR combined with decolonisation were cost-effective in more than 80% of simulations, using the national WTP threshold. However, decolonisation schemes for CRE only reached cost-effectiveness in 55% of simulations at country WTP.

Analysis of the intervention strategies impact at national scale

Health-economic gains were best following pre-emptive isolation of high-risk individuals (specifically males) or all new admissions, or PCR screening of new admissions followed by isolation of those testing positive for CRE/MRSA (Table 2). Implementing these strategies in at least 20% of national hospital beds could yield monetary benefits exceeding $47·4 millions per year. Increasing this coverage to 40% shows the most substantial incremental gain more than doubling monetary savings, while extending to 80% coverage produces net benefits ranging between $189·7 and $276·8 million, depending on strategy. Conversely,

widespread adoption of digestive decolonisation approaches for CRE could result in financial deficits across all levels of hospital-bed coverage, as indicated by a negative NB.

Global sensitivity analysis of the model

Supplementary Figure A16 displays global sensitivity analysis results. For the CRE model, key factors included the transmission parameter (PRCC = 0·37, p<0·001), discharge rates for uncolonized individuals (men: PRCC = 0·38, women: PRCC = 0·31, p<0.001 and p=0·007, respectively), and rates of CRE clearance and treatment (PRCC = -0·52 and -0·38, p<0·001). In the MRSA model, significant parameters were the clearance rate and treatment rate among men (PRCC = -0·47 and -0·32, p<0·001), while transmission rate, discharge rate among women, and progression to infection from MRSA colonisation had significant positive influence on MRSA burden (PRCC = 0·58, 0·35, 0·31; p<0·001, p=0·001, and p=0·004, respectively). Sensitivity of diagnostic tests and result delays were also analysed, showing that a 10% increase in test sensitivity could prevent 164 to 72 CRE and 183 to 125 MRSA infections (Supplementary Figures A17-8), if test turnaround was kept constant at three or one day, respectively. Reducing turnaround from three days to one day could prevent up to 1,242 CRE and 1,713 MRSA infections, assuming constant test sensitivity.

Discussion

We evaluated the sex-specific epidemiology of CRE and MRSA, demonstrating distinct patterns in infection rates and clinical outcomes. We used mathematical modelling to test a combination of strategies to reduce the burden of CRE/MRSA in hospitals, capitalising on these patterns to improve projected health-economic gains..

We showed significant sex-based differences in both incidence and clinical outcomes. Higher CRE/MRSA incidence rates have also been found among males in the wider region[61] and elsewhere, including Europe.[22,61-63] Reasons for these differences are uncertain but could be due to sex-specific risk factors that predispose men to CRE/MRSA acquisition (e.g., diabetes, indwelling devices, etc.).[20-24,61,62] Our data suggested that observed sex differences were associated with elevated antibiotic consumption and increased prior hospitalisations (CRE and MRSA), and higher rates of kidney therapy and mechanical ventilation prior to infection diagnosis (CRE) among men. After accounting for major confounders, we found that mortality was higher among women. This result is consistent with prior findings,[64-67] but does not specifically pertain to Chile. A meta-analysis revealed that, considering adjusted estimates for confounding factors, women exhibited a 1·18-fold increase in *Staphylococcus aureus* mortality across 95,469 patients.[66] Additionally, women have demonstrated higher mortality rates in conditions such as endocarditis,[68] hospital-acquired bloodstream infections,[67] and severe sepsis.[69] Potential reasons include behavioural factors like delayed care-seeking, treatment postponements, and lower quality of acute care compared to men, as indicated by a US-based study examining care quality across sociodemographic groups.[70] However, our observed survival disadvantages for women could also be small due to limited information on multiple organ dysfunction of non-infectious origin among severe infections,[71] which we could not test.

Chile's NAP does not accommodate these differences,[72] and this is generally the case for other countries as well.[73] While Denmark's NAP recognises risk and vulnerability assessments among high-risk groups, including women with urinary tract infections, and acknowledges potential differences in antibiotic usage, infections, and burdens, these have not translated into sex-specific intervention targeting.[74] We could not identify any country which currently includes this as an explicit consideration in their NAP.

We contribute important advocacy for accounting for sex differences when strategizing control that goes beyond addressing inequities. Pre-emptive isolation or contact precaution, particularly of men and all new admissions, emerged as a significantly impactful measure, reducing CRE and MRSA[75] transmissions and presenting the lowest ICER when compared to the standard care. Some studies suggest the opposite due to extensive resource implications,[7] but it improves health outcomes efficiently if patients are in critical care or high-CRE/MRSA prevalence settings,[76-78] like Chile.[41,49] We found that isolating high-risk male carriers of CRE/MRSA can indirectly protect women's health by curbing pathogen spread in healthcare environments. Supporting evidence from a qualitative study suggests men typically exhibit greater acceptance in response to hospital isolation, bolstering the case for this targeted intervention.[79] Additionally, PCR testing coupled with contact precaution demonstrated best value for money among CRE and MRSA individuals. For instance, ICERs have ranged from $13,904/life year saved[80] and $80,159/QALY[7] gained for MRSA if same strategy was applied.[8,17] We observed lower ICERs due to increased costs associated with bed-days and personnel in the UK- and US-based studies, where MRSA prevalence is notably low (≈2%).[7,80] These results underly the efficacy of combining rapid diagnostic techniques with strict isolation protocols. However, results should be taken with caution as poorer compliance and hospital-specific risks could affect transmissibility and therefore the effectiveness of such interventions locally and state-wide.[81] For instance, a study noted that contact precaution strategies for extended-spectrum beta-lactamase (ESBL)-producing CRE had a limited effect in high-income European countries like Germany, Spain, Switzerland, and the Netherlands, particularly in settings with extensive surveillance.[98] While findings vary in other regions,[99-100] it's crucial to recognise that the effectiveness of contact precautions can differ significantly across different hospital environments and countries.

In line with our study results, the use of mupirocin for MRSA has demonstrated to be a cost-effective strategy coupled with PCR screening,[82] with ICERs ranging from dominant

strategies (ICER<0) to $11,005/QALY gained.[5,7,8,83] Yet, one study suggested an association between decolonisation with nasal mupirocin and a rise in infections by alternative microorganisms; however, the causal relationship remains to be definitively established.[54] Moreover, Martinez *et al* found different MRSA genetic lineages using whole-genome sequencing (WGS), replacing most traditional *ChC* MRSA clones (i.e., MRSA subtype based on their genetic lineage, often called community-associated MRSA clonal complex), which could impact the disease prevalence and death rates among Chilean populations.[84] Yet, WGS may not be a viable strategy considering limited national infrastructure and 3-fold higher prices compared to PCR (WGS cost per isolate>$100).[85] However, incorporating disease evolution in future mathematical models and economic evaluations should be acknowledged.

Decolonisation strategies for CRE were the least cost-effective. We modelled gentamicin and colistin selective digestive decontamination for CRE decolonisation treatment, but literature is limited and there is no consensus over its applicability and safety due to posterior selection for resistance, toxicity, mutation, and disruption of gut microbiota.[86,87] Also, whether it is a viable strategy in high-resistance settings is not conclusive.[101]In our modelling, CRE decolonisation failed to meet ICER< country WTP, in concordance with recent European Committee on Infection Control guidelines which cautioned against its usage.[88] One study found an ICER=$665/QALY gained in Hong Kong,[6] but they used a significant daily reduction in transmission (≈35%) if under decolonisation treatment, compared to do-nothing. The study's treatment duration visualised daily changes, whereby outcomes are evaluated at least 7 days after treatment imitation following a recent systematic literature review.[86] Alternative strategies, including faecal microbiota transplantation, use of probiotics or bacteriophages, could be helpful, although with limited evidence and costlier to contact precaution strategies.[89-92] New treatments among individuals with CRE could help better dissuade its transmission using new compounds not

yet available in Chile, such as ceftazidime/avibactam. A recent meta-analysis found it to produce 0.48-times lower 30-day mortality compared to colistin-based regimen (95%CI=0·33-0·69, p<0·001).[93] This could be crucial in Chile where carbapenemase-producing *Klebsiella pneumoniae* was reported to increase from 12·8% pre–COVID-19 to 51·9% after pandemic onset, suggesting an increment in ARB dissemination.[94]

Our cost effectiveness estimates reported here are believed to be conservative: true net monetary benefits are likely to be more significant due to our interventions could also impact other healthcare-associated infections and associated burdens. Expanding on a national scale, implementing universal screening and isolation or pre-emptive strategies in at least 20% of national hospital beds could lead to substantial financial benefits, exceeding $60 million per year and gaining at least 2,000 QALYs. This suggests a strong case for the nationwide adoption of such strategies, following examples from other countries.[95] Additionally, we underscore the critical balance between test sensitivity and timely results in controlling infection rates; a 1% reduction in sensitivity marginally decreases infections (0·19-0·36%), but 1 day delay in obtaining test results significantly exacerbate the spread (21-29%), especially under optimal sensitivity conditions.

Our study has limitations, primarily the reliance on simplified assumptions and questions about model generalisability. Employing some non-Chile-specific literature parameters, untested in local contexts, may obscure the actual effects of interventions and overlook the nuances of epidemiological dynamics. Also, the model's exclusion of re-occurrence or co-infection or rehospitalizations, might lead to an underestimation of the full health benefits and cost savings achievable through CRE/MRSA control interventions. However, to mitigate these limitations, we used a two-stage approach, integrating best available epidemiological data from Chile. Furthermore, we did not test universal topical decolonisation among new admissions as other studies have done.[7,9] However, we believe such strategies could select

for resistance in the long-run.[96] We did not include within-host dynamics and interactions between susceptible and resistant strains, or relative growths when dual carriage is present.[48] However, we used fitness costs for resistance strains and assumed that individuals had CRE/MRSA loads predominantly, making transmissibility by dual-strain carriage limited in the absence of antibiotics. Furthermore, the potential emergence of colistin resistance could negate any benefits from SSD among CRE carriers. Future research must consider the broader consequences of resistance development and its impact on the treatment of multidrug-resistant bacteria in model assessments. Finally, we acknowledge that our study did not differentiate gender-specific transmission rates; instead, we applied a uniform transmission parameter across the entire population, but utilised different gender-specific burden parameters based on our retrospective study. This approach underscores a critical area for future research enhancement, including the application of genomic data to deepen our understanding of these processes.

In conclusion, our study accentuates the need for sex-, context-, and pathogen-specific strategies in managing hospital infections to optimise resource allocation and patient's health outcomes. We must prioritise women's health by focusing control efforts on men for CRE/MRSA due to the higher transmission rates from men, indirect protection benefits for women, and addressing sex-disparate impacts of these infections. However, reduced availability of treatments remains as an essential gap as WHO alternative approach for governments should be prioritised including other potentially applicable diagnostic tests tailored to pathogen specifics.[86,97]

Data Materials and software availability. Data are available in previous literature and full code used for analyses is available in Github at www.bit.ly/3sgnmrU.

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Ethical approval. The study has been already approved by the Pontificia Universidad Catolica Chile Human Research Ethics Committee (Protocol ID: 200706001).

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Table 1. Base-case scenario and cost-effectiveness per strategy over a year's time in a 1,000-beds hospital[†]

Pathogen	Strategy	Population	Scheme	Costs ($)	QALYs	ICER ($/QALY)	Number of CRE/MRSA infections averted	Number of CRE/MRSA deaths averted
CRE	Do-nothing	N/A	**-**	17,857,343 (17·56; 18·1 million)	349,173 (348,380; 350,124)	Ref.	Ref.	Ref.
	Testing + decolonisation	All new admissions	**i)** Chromogenic agar 48h	18,949,142 (18·66; 19·19 million)	349,232 (348,442; 350,177)	18,586 (17,505; 20,783)	957 (786; 1,068)	190 (166; 206)
			ii) Chromogenic agar 24h	19,125,883 (18·84; 19·36 million)	349,247 (348,457; 350,190)	17,270 (16,279; 19,263)	1,168 (960; 1,306)	237 (207; 257)
			iii) PCR	20,152,344 (19·87; 20·39 million)	349274 (348,486; 350,216)	22,745 (21,515; 25,182)	1499 (1231; 1677)	325 (286; 350)
	Testing + isolation (contact precaution)	All new admissions	**i)** Chromogenic agar 48h	18,669,352 (18·41; 18·88 million)	349,366 (348,677; 350,206)	4,216 (2,611; 10,334)	4,401 (1,801; 7,012)	641 (262; 1,021)
			ii) Chromogenic agar 24h	18,815,998 (18·58; 19·06 million)	349,477 (348,845; 350,255)	3,157 (1,942; 7,738)	6942 (2,877; 10,989)	1,011 (419; 1,600)
			iii) PCR	19,760,327 (19·58; 19·90 million)	349,776 (349,279; 350,396)	3,157 (2,003; 7,396)	13,793 (5,959; 21,297)	2008 (867; 3,102)
	Pre-emptive isolation (contact precaution)	All and sex-specific new admissions	**i)** All new admissions	19,928,113 (19·75; 20·07 million)	349,776 (349,279; 350,396)	3,435 (2,189; 8,014)	13,792 (5,959; 21,297)	2,008 (867; 3,102)
			ii) Men newly admitted	18,743,732 (18·55; 18·92 million)	349,822 (349,232; 350,451)	1,366 (960; 3,029)	11,680 (5,629; 16,232)	1,700 (819; 2,364)
			iii) Women newly admitted	18,924,151	349,525	3,034 (2,586; 5,812)	5,563 (2,983; 6,559)	809 (434; 955)

				(18·69; 19·15 million)	(348,784; 350,317)			
MRSA	Do-nothing	N/A	**-**	17,718,562 (17·38; 17·94 million)	347,290 (346,165; 349,123)	Ref.	Ref.	Ref.
	Testing + decolonisation	All new admissions	**i)** Chromogenic agar 48h	18,224,547 (17·93; 18·32 million)	347,531 (346,676; 349,256)	2,099 (746; 4,154)	6,699 (3,060; 17,206)	996 (476; 2,401)
			ii) Chromogenic agar 24h	18,445,419 (18·13; 18·61 million)	347,459 (346,474; 349,223)	4,287 (2,156; 7,603)	4,442 (2,079; 9,807)	685 (347; 1,416)
			iii) PCR	19,483,761 (19·18; 19·59 million)	347,567 (346,759; 349,285)	6,357 (2,779; 11,145)	7,153 (3,267; 19,544)	1,118 (562; 2,756)
	Testing + isolation (contact precaution)	All new admissions	**i)** Chromogenic agar 48h	18,439,084 (18·18; 18·49 million)	347,588 (346,850; 349,198)	2,411 (806; 10,859)	8,643 (1,850; 22,860)	1,248 (269; 3,250)
			ii) Chromogenic agar 24h	18,616,308 (18·37; 18·66 million)	347,621 (346,917; 349,207)	2,709 (956; 11,874)	9,590 (2,077; 25,175)	1,384 (302; 3,581)
			iii) PCR	19,576,302 (19·39; 19·62 million)	347,993 (347,381; 349,337)	2,641 (1,379; 9,447)	20,495 (5,307; 40,933)	2,960 (772; 5,886)
	Pre-emptive isolation (contact precaution)	All and sex-specific new admissions	**i)** All new admissions	19,801,550 (19·62; 19·86 million)	348,044 (347,413; 349,361)	2,760 (1,538; 9,454)	22,014 (5,901; 41,977)	3,180 (858; 6,042)
			ii) Men newly admitted	18,542,668 (18·41; 18·42 million)	348,050 (347,725; 349,338)	1,083 (307; 4,828)	22,209 (5,330; 53,858)	3,206 (775; 7,682)
			iii) Women newly admitted	18,802,155 (18·54; 18·93 million)	347,630 (346,726; 349,228)	3,185 (1,773; 11,198)	9,302 (2,462; 17,304)	1,349 (359; 2,512)

Notes: CRE= Carbapenem-resistant Enterobacterales. MRSA= Methicillin-resistant *Staphylococcus aureus*. ICER= Incremental cost-effectiveness ratio. N/A= Not applicable. Ref.= Reference. PCR= polymerase chain reaction. [†]Model estimations specify upper and lower bounds within brackets (uncertainty intervals), calibrated to the national prevalence extremes of the pathogen.

Table 2. National scale cost savings and potential health benefits among selected strategies

Pathogen	Strategy	Scheme	National coverage (total hospital beds)	QALYs gained	95% UI_{QALYs}	NB ($)	95% UI_{NB} (in 1,000s $)
CRE	Testing + decolonisation, all new admissions	**i)** Chromogenic agar 48h	20%	354	318; 372	-821,634	-1,437; -461
			40%	708	636; 744	-1,643,268	-2,873; -923
			60%	1,062	954; 1,116	-2,464,902	-4,310; -1,384
			80%	1,416	1,272; 1,488	-3,286,536	-5,747; -1,845
			100%	1,770	1,590; 1,860	-4,108,170	-7,184; -2,306
		ii) Chromogenic agar 24h	20%	444	396; 462	-446,220	-1,187; -6
			40%	888	792; 924	-892,440	-2,374; -13
			60%	1,332	1,188; 1,386	-1,338,660	-3,562; -19
			80%	1,776	1,584; 1,848	-1,784,880	-4,749; -26
			100%	2,220	1,980; 2,310	-2,231,100	-5,936; -32
		iii) PCR	20%	606	552; 636	-3,926,880	-4,922; -3,339
			40%	1,212	1,104; 1,272	-7,853,760	-9,844; -6,678
			60%	1,818	1,656; 1,908	-11,780,640	-14,767; -10,017
			80%	2,424	2,208; 2,544	-15,707,520	-19,689; -13,356
			100%	3,030	2,760; 3,180	-19,634,400	-24,611; -16,695
	Testing + isolation (contact precaution), all new admissions	**i)** Chromogenic agar 48h	20%	1,158	492; 1,782	13,952,742	2,918; 24,331
			40%	2,316	984; 3,564	27,905,484	5,836; 48,663
			60%	3,474	1,476; 5,346	41,858,226	8,754; 72,994
			80%	4,632	1,968; 7,128	55,810,968	11,672; 97,326
			100%	5,790	2,460; 8,910	69,763,710	14,590; 121,657
		ii) Chromogenic agar 24h	20%	1,824	786; 2,790	23,908,992	6,702; 39,961
			40%	3,648	1,572; 5,580	47,817,984	13,404; 79,922
			60%	5,472	2,358; 8,370	71,726,976	20,107; 119,884
			80%	7,296	3,144; 11,160	95,635,968	26,809; 159,845
			100%	9,120	3,930; 13,950	119,544,960	33,511; 199,806
		iii) PCR	20%	3,618	1,632; 5,394	47,424,744	14,474; 76,929
			40%	7,236	3,264; 10,788	94,849,488	28,948; 153,858

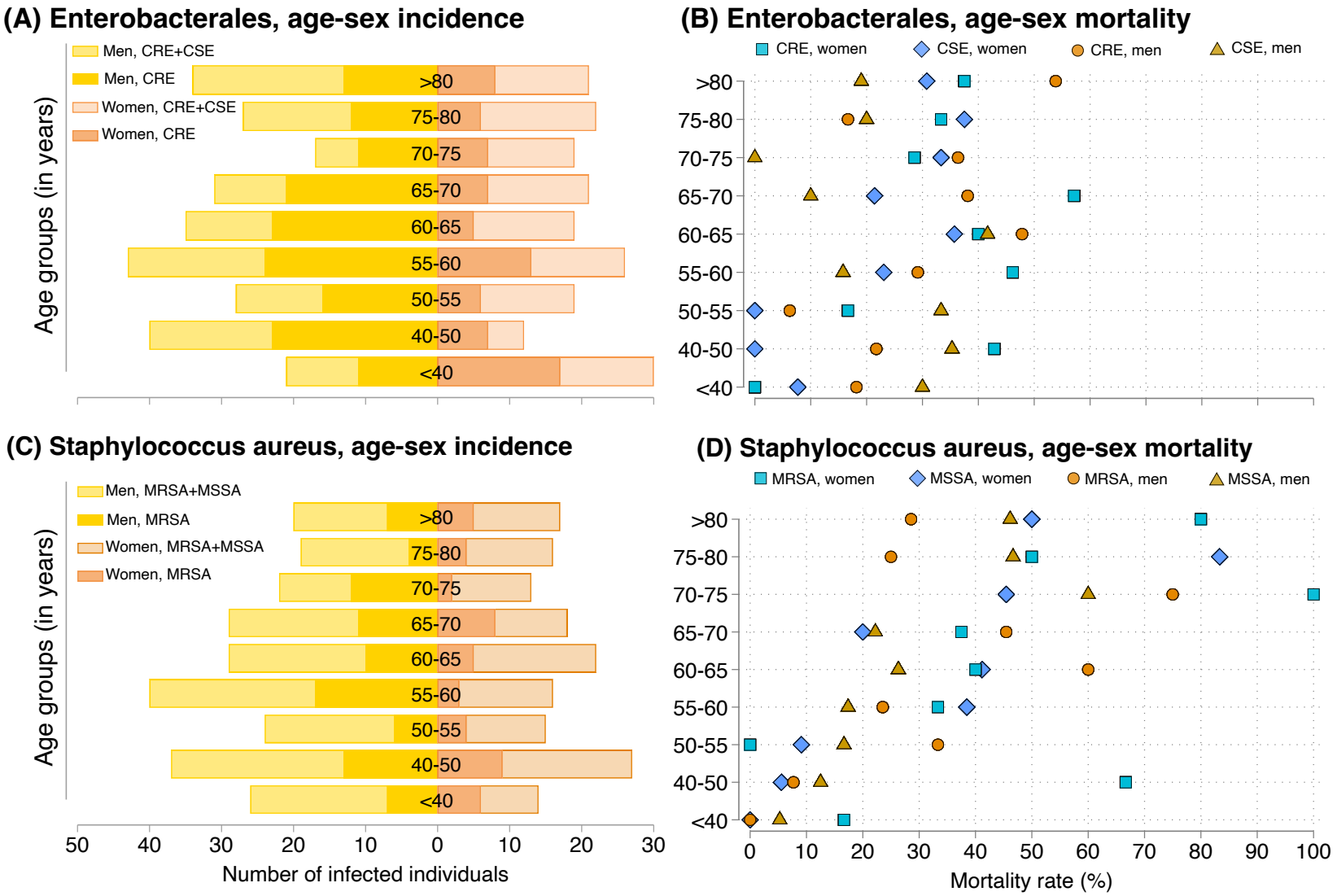
		60%	10,854	4,896; 16,182	142,274,232	43,423; 230,788
		80%	14,472	6,528; 21,576	189,698,976	57,897; 307,717
		100%	18,090	8,160; 26,970	237,123,720	72,371; 384,646
Pre-emptive isolation (contact precaution), all new admissions and sex-specific	**i)** All new admissions	20%	3,618	1,632; 5,394	46,418,940	13,466; 75,926
		40%	7,236	3,264; 10,788	92,837,880	26,931; 151,852
		60%	10,854	4,896; 16,182	139,256,820	40,397; 227,778
		80%	14,472	6,528; 21,576	185,675,760	53,863; 303,704
		100%	18,090	8,160; 26,970	232,094,700	67,328; 379,630
	ii) Men newly admitted	20%	3,894	1,962; 5,112	58,016,706	25,969; 78,239
		40%	7,788	3,924; 10,224	116,033,412	51,938; 156,478
		60%	11,682	5,886; 15,336	174,050,118	77,907; 234,717
		80%	15,576	7,848; 20,448	232,066,824	103,876; 312,957
		100%	19,470	9,810; 25,560	290,083,530	129,845; 391,196
	iii) Women newly admitted	20%	2,112	1,158; 2,424	27,943,872	12,105; 33,158
		40%	4,224	2,316; 4,848	55,887,744	24,209; 66,316
		60%	6,336	3,474; 7,272	83,831,616	36,314; 99,474
		80%	8,448	4,632; 9,696	111,775,488	48,418; 132,632
		100%	10,560	5,790; 12,120	139,719,360	60,523; 165,789
Testing + decolonisation, all new admissions	**i)** Chromogenic agar 48h	20%	1,446	798; 3,066	20,484,036	9,665; 47,581
		40%	2,892	1,596; 6,132	40,968,072	19,329; 95,163
		60%	4,338	2,394; 9,198	61,452,108	28,994; 142,744
		80%	5,784	3,192; 12,264	81,936,144	38,658; 190,325
		100%	7,230	3,990; 15,330	102,420,180	48,323; 237,906
		20%	1,014	600; 1,854	12,145,692	5,197; 26,158

		ii) Chromogenic agar 24h	40%	2,028	1,200; 3,708	24,291,384	10,394; 52,316
			60%	3,042	1,800; 5,562	36,437,076	15,592; 78,474
			80%	4,056	2,400; 7,416	48,582,768	20,789; 104,632
			100%	5,070	3,000; 9,270	60,728,460	25,986; 130,790
		iii) PCR	20%	1,662	972; 3564	16,467,096	4,977; 48,064
			40%	3,324	1,944; 7,128	32,934,192	9,953; 96,128
			60%	4,986	2,916; 10,692	49,401,288	14,930; 144,192
			80%	6,648	3,888; 14,256	65,868,384	19,907; 192,256
			100%	8,310	4,860; 17,820	82,335,480	24,883; 24,0321
MRSA	Testing + isolation (contact precaution), all new admissions	**i)** Chromogenic agar 48h	20%	1,788	450; 4,110	24,770,952	2,433; 63,536
			40%	3,576	900; 8,220	49,541,904	4,865; 127,073
			60%	5,364	1,350; 12,330	74,312,856	7,298; 190,609
			80%	7,152	1,800; 16,440	99,083,808	9,731; 254,146
			100%	8,940	2,250; 20,550	123,854,760	12,164; 317,682
		ii) Chromogenic agar 24h	20%	1,986	504; 4,512	26,922,216	2,213; 69,074
			40%	3,972	1,008; 9,024	53,844,432	4,426; 138,148
			60%	5,958	1,512; 13,536	80,766,648	6,639; 207,223
			80%	7,944	2,016; 18,048	107,688,864	8,852; 276,297
			100%	9,930	2,520; 22,560	134,611,080	11,065; 345,371
		iii) PCR	20%	4,218	1,284; 7,296	57,466,032	8,754; 108,608
			40%	8,436	2,568; 14,592	114,932,064	17,509; 217,217
			60%	12,654	3,852; 21,888	172,398,096	26,263; 325,825
			80%	16,872	5,136; 29,184	229,864,128	35,017; 434,433

		100%	21,090	6,420; 3,6480	287,330,160	43,772; 543,041
Pre-emptive Isolation (contact precaution), all new admissions and sex-specific	**i)** All new admissions	20%	4,524	1,428; 7,488	61,096,620	9,726; 110,276
		40%	9,048	2,856; 1,4976	122,193,240	19,452; 220,552
		60%	13,572	4,284; 22,464	183,289,860	29,178; 330,827
		80%	18,096	5,712; 29,952	244,386,480	38,904; 441,103
		100%	22,620	7,140; 37,440	305,483,100	48,631; 551,379
	ii) Men newly admitted	20%	4,560	1,290; 9,360	69,229,920	14,754; 149,367
		40%	9,120	2,580; 18,720	138,459,840	29,507; 298,734
		60%	13,680	3,870; 28,080	207,689,760	44,261; 448,101
		80%	18,240	5,160; 37,440	276,919,680	59,015; 597,468
		100%	22,800	6,450; 46,800	346,149,600	73,769; 746,834
	iii) Women newly admitted	20%	2,040	630; 3,366	26,683,200	3192; 48,780
		40%	4,080	1,260; 6,732	53,366,400	6,384; 97,560
		60%	6,120	1,890; 10,098	80,049,600	9,577; 146,340
		80%	8,160	2,520; 13,464	106,732,800	12,769; 195,120
		100%	10,200	3,150; 16,830	133,416,000	15,961; 243,900

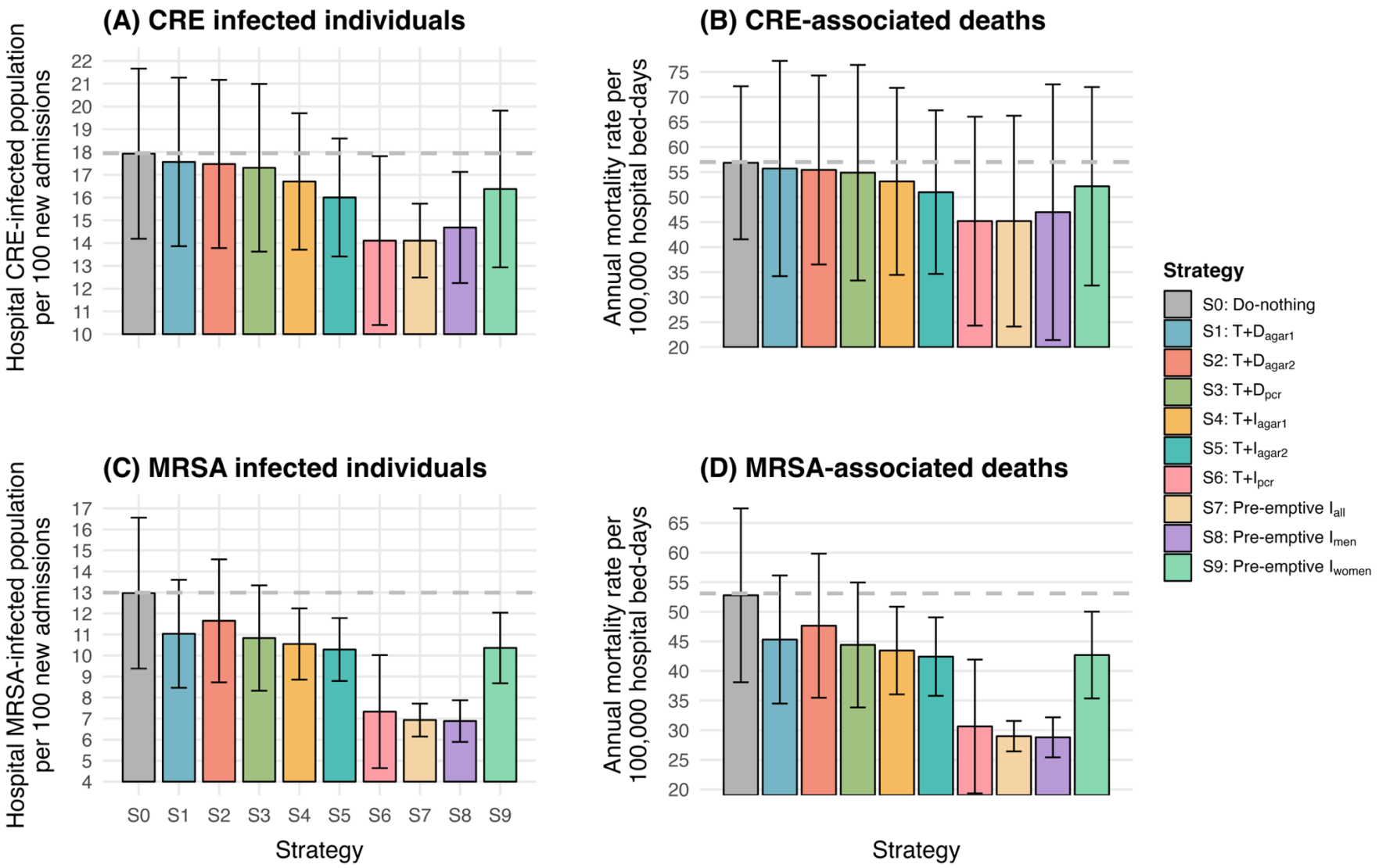
Notes: NB= Net benefit. NB is calculated as (WTP per QALY – cost per QALY) *(QALYs gained compared to S0). CRE= Carbapenem-resistant Enterobacterales. MRSA= Methicillin-resistant *Staphylococcus aureus*. PCR= polymerase chain reaction. UI=Uncertainty intervals. 95% UIs were estimated using pathogen-specific prevalence and their upper and lower bounds.

Figure 1. Number of infections among Enterobacterales and *Staphylococcus aureus* species in three representative hospitals in Chile, 2018-2021



Notes: MRSA= Methicillin-resistant *Staphylococcus aureus*. MSSA= Methicillin-susceptible *Staphylococcus aureus*. CRE= Carbapenem-resistant Enterobacterales. CSE= Carbapenem-susceptible Enterobacterales. Infections were confirmed with blood-cultures.

Figure 2. CRE/MRSA impacts in number of infected individuals and number of deaths from the mathematical model, by strategy scheme



Notes: CRE= Carbapenem-resistant Enterobacterales. MRSA= Methicillin-resistant *Staphylococcus aureus*. Dashed line sets the maximum according to S0 strategy for comparison purposes. 95% uncertainty intervals (brackets) were computed utilising pathogen's prevalence upper and lower bounds. T+D= testing + decolonization treatment. T+I= Testing + isolation (contact precaution). Pre-emptive I= Pre-emptive solation (contact precaution).

References

1. Murray CJ, Ikuta KS, Sharara F, et al. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. *The Lancet* 2022; **399**(10325): 629-55.

2. Ikhimiukor OO, Odih EE, Donado-Godoy P, Okeke IN. A bottom-up view of antimicrobial resistance transmission in developing countries. *Nature Microbiology* 2022: 1-9.

3. World Health Organization. Sustainable Development Goals (SDGs) AMR indicator. 2024. https://www.who.int/data/gho/data/themes/topics/global-antimicrobial-resistance-surveillance-system-glass/sustainable-development-goals-amr-indicator (accessed 27 February 2024).

4. 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 Global Health* 2024; **9**(2): e013205.

5. You JH, Chan C, Wong M, Ip M. Active surveillance and decolonization of methicillin-resistant Staphylococcus aureus on admission to neonatal intensive care units in Hong Kong: a cost-effectiveness analysis. *Infection Control & Hospital Epidemiology* 2012; **33**(10): 1024-30.

6. You JH, Li H-k, Ip M. Surveillance-guided selective digestive decontamination of carbapenem-resistant Enterobacteriaceae in the intensive care unit: A cost-effectiveness analysis. *American Journal of Infection Control* 2018; **46**(3): 291-6.

7. Robotham JV, Graves N, Cookson BD, et al. Screening, isolation, and decolonisation strategies in the control of meticillin resistant Staphylococcus aureus in intensive care units: cost effectiveness evaluation. *Bmj* 2011; **343**.

8. Nelson R, Samore M, Smith K, Harbarth S, Rubin M, Program CPE. Cost-effectiveness of adding decolonization to a surveillance strategy of screening and isolation for methicillin-resistant Staphylococcus aureus carriers. *Clinical microbiology and infection* 2010; **16**(12): 1740-6.

9. Gidengil CA, Gay C, Huang SS, Platt R, Yokoe D, Lee GM. Cost-effectiveness of strategies to prevent methicillin-resistant Staphylococcus aureus transmission and infection in an intensive care unit. *infection control & hospital epidemiology* 2015; **36**(1): 17-27.

10. Hubben G, Bootsma M, Luteijn M, et al. Modelling the costs and effects of selective and universal hospital admission screening for methicillin-resistant Staphylococcus aureus. *PloS one* 2011; **6**(3): e14783.

11. Kang J, Mandsager P, Biddle AK, Weber DJ. Cost-effectiveness analysis of active surveillance screening for methicillin-resistant Staphylococcus aureus in an academic hospital setting. *Infection Control & Hospital Epidemiology* 2012; **33**(5): 477-86.

12. Zboromyrska Y, De la Calle C, Soto M, et al. Rapid diagnosis of staphylococcal catheter-related bacteraemia in direct blood samples by real-time PCR. *PLoS One* 2016; **11**(8): e0161684.

13. Ho K-w, Ng W-t, Ip M, You JH. Active surveillance of carbapenem-resistant Enterobacteriaceae in intensive care units: Is it cost-effective in a nonendemic region? *American Journal of Infection Control* 2016; **44**(4): 394-9.

14. Lee BY, Bailey RR, Smith KJ, et al. Universal methicillin-resistant Staphylococcus aureus (MRSA) surveillance for adults at hospital admission: an economic model and analysis. *Infection Control & Hospital Epidemiology* 2010; **31**(6): 598-606.

15. Murthy A, De Angelis G, Pittet D, Schrenzel J, Uckay I, Harbarth S. Cost-effectiveness of universal MRSA screening on admission to surgery. *Clinical microbiology and infection* 2010; **16**(12): 1747-53.

16. Cooper BS, Stone S, Kibbler C, et al. Systematic review of isolation policies in the hospital management of methicillin-resistant Staphylococcus aureus: a review of the literature with epidemiological and economic modelling. *Health Technology Assessment (Winchester, England)* 2003; **7**(39): 1-194.

17. Nelson RE, Stevens VW, Khader K, et al. Economic analysis of Veterans Affairs initiative to prevent methicillin-resistant Staphylococcus aureus infections. *American journal of preventive medicine* 2016; **50**(5): S58-S65.

18. Robotham JV, Deeny SR, Fuller C, Hopkins S, Cookson B, Stone S. Cost-effectiveness of national mandatory screening of all admissions to English National Health Service hospitals for meticillin-resistant Staphylococcus aureus: a mathematical modelling study. *The Lancet Infectious Diseases* 2016; **16**(3): 348-56.

19. Lin G, Tseng KK, Gatalo O, et al. Cost-effectiveness of carbapenem-resistant Enterobacteriaceae (CRE) surveillance in Maryland. *Infection Control & Hospital Epidemiology* 2022; **43**(9): 1162-70.

20. Scully EP. Sex, gender and infectious disease. *Nature Microbiology* 2022; **7**(3): 359-60.

21. Lipoldová M, Demant P. Gene-specific sex effects on susceptibility to infectious diseases. *Frontiers in immunology* 2021; **12**: 712688.

22. Waterlow NR, Cooper BS, Robotham JV, Knight GM. Antimicrobial resistance prevalence in bloodstream infection in 29 European countries by age and sex: An observational study. *PLoS medicine* 2024; **21**(3): e1004301.

23. Kupfer M, Jatzwauk L, Monecke S, Möbius J, Weusten A. MRSA in a large German University Hospital: Male gender is a significant risk factor for MRSA acquisition. *GMS Krankenhaushygiene interdisziplinär* 2010; **5**(2).

24. Humphreys H, Fitzpatick F, Harvey BJ. Gender differences in rates of carriage and bloodstream infection caused by methicillin-resistant Staphylococcus aureus: are they real, do they matter and why? *Clinical Infectious Diseases* 2015; **61**(11): 1708-14.

25. Harbarth S, Sax H, Fankhauser-Rodriguez C, Schrenzel J, Agostinho A, Pittet D. Evaluating the probability of previously unknown carriage of MRSA at hospital admission. *The American journal of medicine* 2006; **119**(3): 275. e15-. e23.

26. Sahuquillo-Arce JM, Selva M, Perpinán H, et al. Antimicrobial resistance in more than 100,000 Escherichia coli isolates according to culture site and patient age, gender, and location. *Antimicrobial agents and chemotherapy* 2011; **55**(3): 1222-8.

27. Austin D, Anderson R. Studies of antibiotic resistance within the patient, hospitals and the community using simple mathematical models. *Philosophical Transactions of the Royal Society of London Series B: Biological Sciences* 1999; **354**(1384): 721-38.

28. Knight GM, Costelloe C, Deeny SR, et al. Quantifying where human acquisition of antibiotic resistance occurs: a mathematical modelling study. *BMC medicine* 2018; **16**(1): 1-11.

29. Niewiadomska AM, Jayabalasingham B, Seidman JC, et al. Population-level mathematical modeling of antimicrobial resistance: a systematic review. *BMC medicine* 2019; **17**(1): 1-20.

30. Levin BR, Baquero F, Johnsen PJ. A model-guided analysis and perspective on the evolution and epidemiology of antibiotic resistance and its future. *Current opinion in microbiology* 2014; **19**: 83-9.

31. Austin D, Kakehashi M, Anderson R. The transmission dynamics of antibiotic–resistant bacteria: the relationship between resistance in commensal organisms and antibiotic consumption. *Proceedings of the Royal Society of London Series B: Biological Sciences* 1997; **264**(1388): 1629-38.

32. Blanquart F, Lehtinen S, Lipsitch M, Fraser C. The evolution of antibiotic resistance in a structured host population. *Journal of The Royal Society Interface* 2018; **15**(143): 20180040.

33. Elettreby MF, Ahmed E. Multi-drug antimicrobial resistance model. *Mathematical Methods in the Applied Sciences* 2020; **43**(18): 10462-73.

34. Lipsitch M, Bergstrom CT, Levin BR. The epidemiology of antibiotic resistance in hospitals: paradoxes and prescriptions. *Proceedings of the National Academy of Sciences* 2000; **97**(4): 1938-43.

35. Kouyos RD, Abel zur Wiesch P, Bonhoeffer S. On being the right size: the impact of population size and stochastic effects on the evolution of drug resistance in hospitals and the community. *PLoS pathogens* 2011; **7**(4): e1001334.

36. Drummond MF, Sculpher MJ, Claxton K, Stoddart GL, Torrance GW. Methods for the economic evaluation of health care programmes: Oxford university press; 2015.

37. Birkegård AC, Halasa T, Toft N, Folkesson A, Græsbøll K. Send more data: a systematic review of mathematical models of antimicrobial resistance. *Antimicrobial Resistance & Infection Control* 2018; **7**(1): 1-12.

38. Godijk NG, Bootsma MC, Bonten MJ. Transmission routes of antibiotic resistant bacteria: a systematic review. *BMC Infectious Diseases* 2022; **22**(1): 1-15.

39. Knight GM, Davies NG, Colijn C, et al. Mathematical modelling for antibiotic resistance control policy: do we know enough? *BMC Infectious Diseases* 2019; **19**(1): 1-9.

40. Aguilar GR, Swetschinski LR, Weaver ND, et al. The burden of antimicrobial resistance in the Americas in 2019: a cross-country systematic analysis. *The Lancet Regional Health–Americas* 2023.

41. Allel K, Peters A, Haghparast-Bidgoli H, et al. Excess Burden of Antibiotic-Resistant Bloodstream Infections: Evidence from a Multicentre Retrospective Cohort Study in Chile, 2018-2022. *Available at SSRN 4676961* 2024.

42. Chilean Ministry of Health. Plan nacional contra la resistencia a los antimicorbianos, Chile 2021-2025, 2021.

43. Fabre V, Secaira C, Cosgrove SE, et al. Deep dive into gaps and barriers to implementation of antimicrobial stewardship programs in hospitals in Latin America. *Clinical Infectious Diseases* 2023; **77**(Supplement_1): S53-S61.

44. Spicknall IH, Foxman B, Marrs CF, Eisenberg JN. A modeling framework for the evolution and spread of antibiotic resistance: literature review and model categorization. *American journal of epidemiology* 2013; **178**(4): 508-20.

45. Allel K, Peters A, Furuya-Kanamori L, et al. Impact of Inappropriate Empirical Antibiotic Therapy on Mortality: A Retrospective Multicentre Cohort Study of Patients with Bloodstream Infections in Chile, 2018-2022. *Available at SSRN 4677015* 2024.

46. Huber M. Identifying causal mechanisms (primarily) based on inverse probability weighting. *Journal of Applied Econometrics* 2014; **29**(6): 920-43.

47. Wolbers M, Koller MT, Witteman JC, Steyerberg EW. Prognostic models with competing risks: methods and application to coronary risk prediction. *Epidemiology* 2009: 555-61.

48. Davies NG, Flasche S, Jit M, Atkins KE. Within-host dynamics shape antibiotic resistance in commensal bacteria. *Nature ecology & evolution* 2019; **3**(3): 440-9.

49. 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. *The Lancet Regional Health–Americas* 2023; **21**.

50. Audet C. Tuning Runge-Kutta parameters on a family of ordinary differential equations. *International Journal of Mathematical Modelling and Numerical Optimisation* 2018; **8**(3): 277-86.

51. Marino S, Hogue IB, Ray CJ, Kirschner DE. A methodology for performing global uncertainty and sensitivity analysis in systems biology. *Journal of theoretical biology* 2008; **254**(1): 178-96.

52. Malhotra-Kumar S, Haccuria K, Michiels M, et al. Current trends in rapid diagnostics for methicillin-resistant Staphylococcus aureus and glycopeptide-resistant enterococcus species. *Journal of clinical microbiology* 2008; **46**(5): 1577-87.

53. Kypraios T, O'Neill PD, Huang SS, Rifas-Shiman SL, Cooper BS. Assessing the role of undetected colonization and isolation precautions in reducing methicillin-resistant Staphylococcus aureus transmission in intensive care units. *BMC infectious diseases* 2010; **10**: 1-10.

54. van Rijen M, Bonten M, Wenzel R, Kluytmans J. Mupirocin ointment for preventing Staphylococcus aureus infections in nasal carriers. *Cochrane database of systematic reviews* 2008; (4).

55. Saidel-Odes L, Polachek H, Peled N, et al. A randomized, double-blind, placebo-controlled trial of selective digestive decontamination using oral gentamicin and oral polymyxin E for eradication of carbapenem-resistant Klebsiella pneumoniae carriage. *Infection Control & Hospital Epidemiology* 2012; **33**(1): 14-9.

56. Organization WH. Guidelines for the prevention and control of carbapenem-resistant Enterobacteriaceae, Acinetobacter baumannii and Pseudomonas aeruginosa in health care facilities. 2017.

57. Husereau D, Drummond M, Petrou S, et al. Consolidated health economic evaluation reporting standards (CHEERS) statement. *Bmj* 2013; **346**.

58. Fondo Nacional de Salud. Aranceles mai 2023. https://www.fonasa.cl/sites/fonasa/prestadores/modalidad-atencion-institucional#aranceles-mai-2023 (accessed 28 February 2024).

59. Central de abastacemiento (CENABAST) Chile. Reporte de compras historicas de CENABAST. 2023. https://www.cenabast.cl/compras-cenabast/ (accessed 28 February 2024).

60. Organization for Economic Cooperation and Development. Hospital beds. 2024. https://data.oecd.org/healtheqt/hospital-beds.htm (accessed 26 February 2024).

61. Zhang Y, Wang Q, Yin Y, et al. Epidemiology of carbapenem-resistant Enterobacteriaceae infections: report from the China CRE Network. *Antimicrobial agents and chemotherapy* 2018; **62**(2): 10.1128/aac. 01882-17.

62. Brandl M, Hoffmann A, Willrich N, et al. Bugs that can resist antibiotics but not men: gender-specific differences in notified infections and colonisations in Germany, 2010–2019. *Microorganisms* 2021; **9**(5): 894.

63. Wang M, Earley M, Chen L, et al. Clinical outcomes and bacterial characteristics of carbapenem-resistant Klebsiella pneumoniae complex among patients from different global regions (CRACKLE-2): a prospective, multicentre, cohort study. *The Lancet Infectious Diseases* 2022; **22**(3): 401-12.

64. Aizen E, Ljubuncic Z, Ljubuncic P, Aizen I, Potasman I. Risk factors for methicillin-resistant Staphylococcus aureus colonization in a geriatric rehabilitation hospital. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences* 2007; **62**(10): 1152-6.

65. Kempker RR, Farley MM, Ladson JL, Satola S, Ray SM. Association of methicillin-resistant Staphylococcus aureus (MRSA) USA300 genotype with mortality in MRSA bacteremia. *Journal of Infection* 2010; **61**(5): 372-81.

66. Westgeest AC, Lambregts MMC, Ruffin F, et al. Female Sex and Mortality in Patients with Staphylococcus aureus Bacteremia: A Systematic Review and Meta-analysis. *JAMA Network Open* 2024; **7**(2): e240473-e.

67. Leibovici L, Paul M, Weinberger M, et al. Excess mortality in women with hospital-acquired bloodstream infection. *The American journal of medicine* 2001; **111**(2): 120-5.

68. Barca LV, Vidal-Bonnet L, Fariñas M, et al. Analysis of sex differences in the clinical presentation, management and prognosis of infective endocarditis in Spain. *Heart* 2021; **107**(21): 1717-24.

69. Pietropaoli AP, Glance LG, Oakes D, Fisher SG. Gender differences in mortality in patients with severe sepsis or septic shock. *Gender medicine* 2010; **7**(5): 422-37.

70. Asch SM, Kerr EA, Keesey J, et al. Who is at greatest risk for receiving poor-quality health care? *New England Journal of Medicine* 2006; **354**(11): 1147-56.

71. Papathanassoglou E, Middleton N, Benbenishty J, Williams G, Christofi MD, Hegadoren K. Systematic review of gender-dependent outcomes in sepsis. *Nursing in Critical Care* 2017; **22**(5): 284-92.

72. Ministerio de Salud. Plan nacional contra la resistencia a los antimicrobianos Chile, 2021-2025, 2021.

73. Organization WH. Tackling antimicrobial resistance (AMR) together: working paper 5.0: enhancing the focus on gender and equity: World Health Organization, 2018.

74. Ministry of Health. National action plan on antibiotics in human healthcare. 2017. https://cdn.who.int/media/docs/default-source/antimicrobial-resistance/amr-spc-npm/nap-library/denmark-national-action-plan-on-antibiotics-in-human-healthcare-2017.pdf?sfvrsn=98102e2b_1&download=true (accessed 22 March 2024).

75. Kavanagh KT, Calderon LE, Saman DM, Abusalem SK. The use of surveillance and preventative measures for methicillin-resistant staphylococcus aureus infections in surgical patients. *Antimicrobial resistance and infection control* 2014; **3**: 1-7.

76. Arena F, Vannetti F, Di Pilato V, et al. Diversity of the epidemiology of carbapenemase-producing Enterobacteriaceae in long-term acute care rehabilitation settings from an area of hyperendemicity, and evaluation of an intervention bundle. *Journal of Hospital Infection* 2018; **100**(1): 29-34.

77. Harbarth S, Masuet-Aumatell C, Schrenzel J, et al. Evaluation of rapid screening and pre-emptive contact isolation for detecting and controlling methicillin-resistant Staphylococcus aureus in critical care: an interventional cohort study. *Critical care* 2006; **10**: 1-8.

78. Richter SS, Marchaim D. Screening for carbapenem-resistant Enterobacteriaceae: who, when, and how? *Virulence* 2017; **8**(4): 417-26.

79. Madsen A. Experience of source isolation during hospitalization–a qualitative study. *Antimicrobial Resistance and Infection Control* 2015; **4**(Suppl 1): P95.

80. Nelson RE, Goto M, Samore MH, et al. Expanding an economic evaluation of the veterans affairs (VA) methicillin-resistant Staphylococcus aureus (MRSA) prevention initiative to include prevention of infections from other pathogens. *Clinical infectious diseases* 2021; **72**(Supplement_1): S50-S8.

81. McLaws M-L. The relationship between hand hygiene and health care-associated infection: it's complicated. *Infection and drug resistance* 2015: 7-18.

82. Popovich KJ, Aureden K, Ham DC, et al. SHEA/IDSA/APIC Practice Recommendation: Strategies to prevent methicillin-resistant Staphylococcus aureus transmission and infection in acute-care hospitals: 2022 Update. *Infection Control & Hospital Epidemiology* 2023; **44**(7): 1039-67.

83. Organization WH. Global guidelines for the prevention of surgical site infection. Web Appendix 3 Summary of a systematic review on decolonization with mupirocin ointment with or without chlorhexidine gluconate body wash for the prevention of Staphylococcus aureus infection in nasal carriers undergoing surgery: World Health Organization; 2016.

84. Martínez JR, Planet PJ, Spencer-Sandino M, et al. Dynamics of the MRSA Population in a Chilean Hospital: a Phylogenomic Analysis (2000–2016). *Microbiology Spectrum* 2023: e05351-22.

85. Price V, Ngwira LG, Lewis JM, et al. A systematic review of economic evaluations of whole-genome sequencing for the surveillance of bacterial pathogens. *Microbial genomics* 2023; **9**(2): 000947.

86. Mascolo A, Carannante N, di Mauro G, et al. Decolonization of drug-resistant Enterobacteriaceae carriers: A scoping review of the literature. *Journal of Infection and Public Health* 2023; **16**(3): 376-83.

87. Langdon A, Crook N, Dantas G. The effects of antibiotics on the microbiome throughout development and alternative approaches for therapeutic modulation. *Genome medicine* 2016; **8**: 1-16.

88. Tacconelli E, Mazzaferri F, de Smet AM, et al. ESCMID-EUCIC clinical guidelines on decolonization of multidrug-resistant Gram-negative bacteria carriers. *Clinical microbiology and infection* 2019; **25**(7): 807-17.

89. Wynn AB, Beyer G, Richards M, Ennis LA, Richards MC. Procedure, Screening, and Cost of Fecal Microbiota Transplantation. *Cureus* 2023; **15**(2).

90. Hitchcock NM, Devequi Gomes Nunes D, Shiach J, et al. Current clinical landscape and global potential of bacteriophage therapy. *Viruses* 2023; **15**(4): 1020.

91. Bonnet M, Eckert C, Tournebize R. Decolonization of asymptomatic carriage of multi-drug resistant bacteria by bacteriophages? *Frontiers in Microbiology* 2023; **14**: 1266416.

92. Hung Y-P, Lee C-C, Lee J-C, Tsai P-J, Hsueh P-R, Ko W-C. The potential of probiotics to eradicate gut carriage of pathogenic or antimicrobial-resistant Enterobacterales. *Antibiotics* 2021; **10**(9): 1086.

93. Chen Y, Huang H-B, Peng J-M, Weng L, Du B. Efficacy and safety of ceftazidime-avibactam for the treatment of carbapenem-resistant Enterobacterales bloodstream infection: a systematic review and meta-analysis. *Microbiology Spectrum* 2022; **10**(2): e02603-21.

94. 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. *Clinical Infectious Diseases* 2023; **77**(Supplement_1): S20-S8.

95. Performance NF. The Operating framework for 2010/11 for the NHS in England. Crown, Department of Health London; 2009.

96. Batra R, Cooper BS, Whiteley C, Patel AK, Wyncoll D, Edgeworth JD. Efficacy and limitation of a chlorhexidine-based decolonization strategy in preventing transmission of methicillin-resistant Staphylococcus aureus in an intensive care unit. *Clinical infectious diseases* 2010; **50**(2): 210-7.

97. Tolley A, Bansal A, Murerwa R, Howard Dicks J. Cost-effectiveness of point-of-care diagnostics for AMR: a systematic review. *Journal of Antimicrobial Chemotherapy* 2024: dkae067.

98. Maechler F, Schwab F, Hansen S, et al. Contact isolation versus standard precautions to decrease acquisition of extended-spectrum β-lactamase-producing Enterobacterales in non-critical care wards: a cluster-randomised crossover trial. The Lancet infectious diseases 2020; 20(5): 575-84.

99. Kim N-H, Han W-D, Song K-H, et al. Successful containment of carbapenem-resistant Enterobacteriaceae by strict contact precautions without active surveillance. American journal of infection control 2014; 42(12): 1270-3.

100. Kardaś-Słoma L, Fournier S, Dupont J-C, et al. Cost-effectiveness of strategies to control the spread of carbapenemase-producing Enterobacterales in hospitals: a modelling study. Antimicrobial Resistance & Infection Control 2022; 11(1): 117.

101. Bonten M. Selective decontamination of the digestive tract: an answer at last? Jama 2022; 328(23): 2310-1

Chapter 9:

Discussion

The complex interplay between human and animal sectors, socioeconomic factors, and governance in shaping AMR trends are described in **Chapter 3**.[27,66-68] This analysis was fundamental to the One-Health paradigm[7] by showing, for the first time, bidirectionality in the consumption of antibiotics associated with AMR between humans and animals at the global scale. Governance quality also emerged as a key factor linked to AMR,[18] suggesting that stronger institutional frameworks could mitigate AMR spread.[69] Comprehensive national action plans could go further than antibiotic stewardship, as models might suggest, incorporating robust political frameworks and socioeconomic factors for effective structural reform, particularly in high-AMR regions like Asia.[70] An important step in this direction will involve improving data coverage, particularly in animal health and LMIC contexts. Furthermore, ecological analyses, while valuable for identifying broad patterns and generating hypotheses, have significant limitations in establishing causal conclusions. The primary issue is the ecological fallacy, where inferences about individual behaviour are drawn from group-level data, potentially leading to incorrect conclusions.[71] Additionally, confounding variables that vary across groups can distort associations, making it difficult to isolate specific causal relationships. Despite these limitations, ecological analysis plays a crucial role in public health research by highlighting trends and disparities that warrant further investigation through more precise, individual-level studies.

The meta-analysis study (**Chapter 4**) revealed the significant impact of ARB BSIs in LMICs, associated with increased mortality, longer hospital stays, and higher ICU admission rates, particularly due to *A. baumannii* and Enterobacteriaceae infections. The study corroborated global findings,[70] highlighting the pronounced impacts of ARB BSIs, and identifies disparities between LMICs, suggesting differing geographical levels of antibiotic consumption and resistance development.[19] However, challenges such as data paucity, particularly in LMICs, and methodological limitations like inconsistent data collection and analysis, underscore the need for enhanced surveillance and data quality.[72] Additionally, economic analyses show considerable excess hospital costs associated with ARB BSIs, underlining the financial strain

on healthcare systems in LMICs. Future research should aim to provide clearer distinctions between pre- and post-BSI lengths of stay and account for confounding factors more comprehensively with enhanced data granularity. Addressing these issues will enable more precise estimates and better-informed control strategies. Moreover, post-ICU patients face significantly higher mortality rates than the general population, enduring long-term impacts from their critical illnesses.[73] Residual effects like organ dysfunction, infections, and cognitive impairments contribute to this elevated risk.[74] This disparity highlights the urgent need for targeted post-ICU care and monitoring to improve their long-term outcomes.

Chapter 5 showed the quite limited health-economic evidence developed for interventions targeting ARB in healthcare settings. Non-pharmaceutical interventions, such as whole-genome sequencing were found to be costly and potentially only applicable in settings with pre-existing sequencing infrastructure and with high ARB prevalence.[75] Several studies indicated linezolid's superiority over vancomycin in MRSA treatment for cost and efficacy, and underscored the importance of explicit consideration of hospital stay duration (and not just drug costs) in overall healthcare expenditure.[76] Findings from this systematic review also emphasized the critical role of appropriate initial antibiotic therapy and the nuanced cost-effectiveness of antimicrobial stewardship programs, often overlooked due to perceived high operational costs.[77] Additionally, emerging treatments like ceftazidime-avibactam showed promise against CRE infections,[78] suggesting potential regional benefits, notably in areas with high carbapenemase-producing Enterobacterales prevalence, such as Chile.[79,80] Finally, assumptions about utility weights are crucial in health economic evaluations and should vary by country to reflect local preferences and values. Most studies refer to literature-based utility weights, most often quantified in high-income countries, which may not be appropriate as countries' populations and health statuses differ.[81] Country-specific weights ensure accurate assessments and relevant policy decisions, avoiding misleading conclusions and suboptimal resource allocation.

Our study conducted in Chile demonstrated a high AMR prevalence of 27.8% to 28.5% for critical and high-priority antibiotic-bacterium pairs (**Chapter 6**), with significant increases particularly in *K. pneumoniae* between 2008 and 2018. This prevalence aligns with other South American countries and the G20 average,[1] but challenges persist, including incompleteness of data and a lack of prioritisation for certain antibiotic-bacterium combinations, deemed critical by the WHO.[82] In line with high health inequalities in the country,[83,84] we found that hospital complexity and socioeconomic factors were significant predictors of AMR necessitating refined approaches in AMR surveillance and control. Despite a comprehensive hospital network reporting data, limitations include a non-probabilistic sample that may not fully represent national trends, and potential biases due to the inclusion of different bacterial ecological niches and hospital types, including disease-severity prompted testing, which might mask real estimates. Enhancing AMR surveillance, particularly in high- and medium-complexity healthcare centres, should be prioritised for consistency in reporting.

Significant burdens were demonstrated from hospital-acquired ARB BSIs including increased mortality, extended hospital stays, and elevated ICU admissions, particularly with CRE and MRSA in Chile (**Chapter 7**), in line with previous reports.[1,85,86]. Economic ramifications included considerable hospital spending and lost productivity.[87] The substantial overall burden of resistant infections, perhaps intermediated by the dangers of inappropriate antibiotic therapy,[88] underline the necessity for effective timely diagnostics and precise treatments. Enhancing molecular epidemiology studies, monitoring antibiotic usage, and implementing strict control measures for ARB colonisation at hospital admission can mitigate ARB's adverse effects.[89-91] Considering increasing AMR rates from **Chapter 6** coupled with substantial CRE burdens in Chile, it is urged to find effective solutions, especially among *Klebsiella pneumoniae*, and an accelerated appearance of resistance mechanisms, including the production of carbapenemases, after the COVID-19 pandemic.[80]

Additionally, while propensity score methods are popular for reducing bias in observational studies (**Chapter 7**), they could present several limitations in causal inference.[92] They rely heavily on correct model specification, and any misspecification can bias results. Propensity scores do not account for unmeasured confounders, a significant issue for community-acquired infections with limited data. The overlap assumption could also be problematic, as propensity scores near 0 or 1 lead to extreme weights and increased variance, making IPW estimates unreliable. However, we did not estimate extreme values and presented substantial overlap between AMR/AMS groups. Also, we minimised unmeasured confounding by incorporating characteristics after hospital admission (i.e., reporting less unbiased results for hospital-acquired infections). Recent methodologies, such as those described by Pouwels *et al.,*[93] have utilised IPW and Kaplan-Meier curves to adjust for time-varying confounding. This adjustment is essential in studies where both the exposure and outcomes evolve over time, which could be applicable to our study as well. While this approach enhances the accuracy of excess LOS estimates and effectively mitigates biases like collider stratification, it is constrained by the availability of data on time-varying confounders. Consequently, our analysis predominantly relies on accurately measured baseline exposures.

Model-based projections (**Chapter 8**) showed considerable health-economic benefits from using identified risk factors to target interventions.. Focusing on testing plus isolation strategies or isolation of high-risk patients optimised resource utilization and reduced the spread of infections, ultimately leading to better healthcare outcomes and decreased healthcare costs.[94] National scale, targeted isolation/testing schemes were estimated to curtail enormous costs posed by AMR, while increasing quality of life. Limitations included the fact that type of infection (e.g., urinary, skin, blood) were all considered together potentially masking sex differences per infection type. Future model developments can build on these models to include additional complexities, such as infection type as well as alternative transmission routes (e.g. via healthcare personnel). [95,96]

For future directions, I advocate the integration of methodologies that refine our causal understanding within epidemiological studies, such as instrumental variables or negative controls.[97,98] These methods offer a robust framework for distinguishing causal relationships from non-causal associations, a critical aspect in observational studies where direct control over experimental conditions is not possible. Furthermore, incorporating regularisation techniques in regression modelling can enhance the precision of our estimates by mitigating the risk of overfitting.[98] By adopting these advanced statistical approaches, future studies can achieve more accurate and reliable causal inferences, leading to better-informed public health interventions.

In my thesis, I primarily compared health outcomes between patients with antibiotic-resistant and sensitive infections, using a susceptible-infection counterfactual to assess the added burden of resistance. However, this method is not always ideal, particularly for evaluating hypothetical interventions like vaccines.[99] In such scenarios, employing a no-infection counterfactual—estimating the total potential harm averted if drug-resistant infections were entirely prevented—proves more fitting. This approach is vital for thoroughly evaluating strategies designed to completely stop these infections, offering a complete perspective on their potential public health benefits. Future studies should incorporate both counterfactuals to more accurately reflect the impact of antibiotic resistance on mortality in the context of potential interventions.

Finally, enhancing Chile's National Action Plan Against AMR,[100] by fostering interdisciplinary collaboration and analysing the interplay between geographic, sociodemographic factors, antimicrobial use, and AMR, is crucial for effective disease surveillance and management.[101] Recent analyses have highlighted monitoring, evaluation, and equity in policy design as critical barriers to AMR control in Chile.[102] Adopting cost-effective approaches[103] could bolster AMR intervention decisions, leading to smarter, fairer, and more impactful allocation of healthcare resources.

Chapter 10:

Conclusion

This thesis explored the global link between AMR and primary risk factors, assessing the significant impacts on patients with BSIs in LMICs and specifically in Chile using detailed patient data. It highlights the multifaceted drivers of AMR across One Health domains. Findings revealed that LMICs bear a disproportionate burden of AMR-related BSIs, indicating a critical need for improved data collection, early detection, risk reduction, and AMR management, aligning with SDG target 3.d. The best evidence available to date on the health and economic impacts of AMR compared to drug-sensitive infections within a Chilean cohort was generated employing competing risks in mortality analysis and adjusting for factors like bacterial acquisition (community or hospital) and patient health background. These data informed transmission models of CRE and MRSA in Chile and determined that interventions such as testing plus isolation and pre-emptive isolation of high-risk groups, notably men, are most effective in reducing infections and fatalities. Prior to this PhD research, there was no comprehensive study that systematically evaluated the temporal trends in AMR, nor assessed the associated disease and economic burdens at either the individual hospital or national level in Chile, crucial for policymaking.

Collectively, these findings emphasise the need for integrated, context-specific strategies to curb AMR, leveraging both global and local insights to improve health outcomes and address health disparities. It underscores the critical role of comprehensive data in shaping effective AMR management and infection control policies to enhance public health and reduce inequalities.

References

1. Organisation for Economic Cooperation and Development. Stemming the Superbug Tide: Just a Few Dollars More: OECD; 2019.

2. Laxminarayan R, Duse A, Wattal C, et al. Antibiotic resistance—the need for global solutions. *The Lancet infectious diseases* 2013; **13**(12): 1057-98.

3. Laxminarayan R, Sridhar D, Blaser M, Wang M, Woolhouse M. Achieving global targets for antimicrobial resistance. *Science* 2016; **353**(6302): 874-5.

4. Okeke IN, Laxminarayan R, Bhutta ZA, et al. Antimicrobial resistance in developing countries. Part I: recent trends and current status. *The Lancet infectious diseases* 2005; **5**(8): 481-93.

5. Control CfD, Prevention. Antibiotic resistance threats in the United States. Atlanta, GA: US Department of Health and Human Services. *Center for Disease Control and Prevention https://doi org/1015620/cdc* 2019; **82532**.

6. Hay SI, Rao PC, Dolecek C, et al. Measuring and mapping the global burden of antimicrobial resistance. *BMC medicine* 2018; **16**(1): 1-3.

7. Collignon P. The importance of a One Health approach to preventing the development and spread of antibiotic resistance. *One health: The human-animal-environment interfaces in emerging infectious diseases* 2012: 19-36.

8. Robinson TP, Bu D, Carrique-Mas J, et al. Antibiotic resistance is the quintessential One Health issue. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 2016; **110**(7): 377-80.

9. Jee Y, Carlson J, Rafai E, et al. Antimicrobial resistance: a threat to global health. *The Lancet Infectious diseases* 2018; **18**(9): 939-40.

10. O'Neill J. Tackling drug-resistant infections globally: final report and recommendations. 2016.

11. Hampton T. Report reveals scope of US antibiotic resistance threat. *Jama* 2013; **310**(16): 1661-3.

12. Versporten A, Zarb P, Caniaux I, et al. Antimicrobial consumption and resistance in adult hospital inpatients in 53 countries: results of an internet-based global point prevalence survey. *The Lancet Global Health* 2018; **6**(6): e619-e29.

13. Chatterjee A, Modarai M, Naylor NR, et al. Quantifying drivers of antibiotic resistance in humans: a systematic review. *The Lancet Infectious Diseases* 2018; **18**(12): e368-e78.

14. Holmes AH, Moore LS, Sundsfjord A, et al. Understanding the mechanisms and drivers of antimicrobial resistance. *The Lancet* 2016; **387**(10014): 176-87.

15. Klein EY, Van Boeckel TP, Martinez EM, et al. Global increase and geographic convergence in antibiotic consumption between 2000 and 2015. *Proceedings of the National Academy of Sciences* 2018; **115**(15): E3463-E70.

16. Roope LS, Smith RD, Pouwels KB, et al. The challenge of antimicrobial resistance: what economics can contribute. *Science* 2019; **364**(6435).

17. Årdal C, Outterson K, Hoffman SJ, et al. International cooperation to improve access to and sustain effectiveness of antimicrobials. *The Lancet* 2016; **387**(10015): 296-307.

18. Rochford C, Sridhar D, Woods N, et al. Global governance of antimicrobial resistance. *The Lancet* 2018; **391**(10134): 1976-8.

19. Browne AJ, Chipeta MG, Haines-Woodhouse G, et al. Global antibiotic consumption and usage in humans, 2000–18: a spatial modelling study. *The Lancet Planetary Health* 2021; **5**(12): e893-e904.

20. Van Boeckel TP, Brower C, Gilbert M, et al. Global trends in antimicrobial use in food animals. *Proceedings of the National Academy of Sciences* 2015; **112**(18): 5649-54.

21. Ikhimiukor OO, Odih EE, Donado-Godoy P, Okeke IN. A bottom-up view of antimicrobial resistance transmission in developing countries. *Nature Microbiology* 2022; **7**(6): 757-65.

22. Weldon I, Hoffman SJ. Bridging the commitment-compliance gap in global health politics: lessons from international relations for the global action plan on antimicrobial resistance. *Global Public Health* 2021; **16**(1): 60-74.

23. Kelbrick M, Hesse E, O'Brien S. Cultivating antimicrobial resistance: how intensive agriculture ploughs the way for antibiotic resistance. *Microbiology* 2023; **169**(8): 001384.

24. Andleeb S, Majid M, Sardar S. Environmental and public health effects of antibiotics and AMR/ARGs. Antibiotics and antimicrobial resistance genes in the environment: Elsevier; 2020: 269-91.

25. Wilkinson JL, Boxall AB, Kolpin DW, et al. Pharmaceutical pollution of the world's rivers. *Proceedings of the National Academy of Sciences* 2022; **119**(8): e2113947119.

26. Collignon P, Beggs JJ, Walsh TR, Gandra S, Laxminarayan R. Anthropological and socioeconomic factors contributing to global antimicrobial resistance: a univariate and multivariable analysis. *The Lancet Planetary Health* 2018; **2**(9): e398-e405.

27. Littmann J, Viens AM, Silva DS. The super-wicked problem of antimicrobial resistance. *Ethics and drug resistance: Collective responsibility for global public health* 2020; **5**: 421-43.

28. Smith R, Coast J. The true cost of antimicrobial resistance. *Bmj* 2013; **346**.

29. Gandra S, Barter D, Laxminarayan R. Economic burden of antibiotic resistance: how much do we really know? *Clinical microbiology and infection* 2014; **20**(10): 973-80.

30. Naylor NR, Atun R, Zhu N, et al. Estimating the burden of antimicrobial resistance: a systematic literature review. *Antimicrobial Resistance & Infection Control* 2018; **7**(1): 1-17.

31. Howard D, Cordell R, McGowan Jr JE, Packard RM, R Douglas Scott I, Solomon SL. Measuring the economic costs of antimicrobial resistance in hospital settings: summary of the Centers for Disease Control and Prevention-Emory Workshop. *Clinical infectious diseases* 2001: 1573-8.

32. Eliopoulos GM, Cosgrove SE, Carmeli Y. The impact of antimicrobial resistance on health and economic outcomes. *Clinical infectious diseases* 2003; **36**(11): 1433-7.

33. Founou RC, Founou LL, Essack SY. Clinical and economic impact of antibiotic resistance in developing countries: a systematic review and meta-analysis. *PloS one* 2017; **12**(12): e0189621.

34. 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. *Journal of Antimicrobial Chemotherapy* 2011; **66**(2): 398-407.

35. de Kraker ME, Wolkewitz M, Davey PG, Grundmann H. Clinical impact of antimicrobial resistance in European hospitals: excess mortality and length of hospital stay related to methicillin-resistant Staphylococcus aureus bloodstream infections. *Antimicrobial agents and chemotherapy* 2011; **55**(4): 1598-605.

36. Lambert M-L, Suetens C, Savey A, et al. Clinical outcomes of health-care-associated infections and antimicrobial resistance in patients admitted to European intensive-care units: a cohort study. *The Lancet infectious diseases* 2011; **11**(1): 30-8.

37. Stewardson A, Fankhauser C, De Augelis G, et al. Burden of bloodstream infection caused by extended-spectrum β-lactamase–producing Enterobacteriaceae determined using multistate modeling at a Swiss University Hospital and a nationwide predictive model. *Infection Control & Hospital Epidemiology* 2013; **34**(2): 133-43.

38. De Angelis G, Murthy A, Beyersmann J, Harbarth S. Estimating the impact of healthcare-associated infections on length of stay and costs. *Clinical microbiology and infection* 2010; **16**(12): 1729-35.

39. Drummond MF, Sculpher MJ, Claxton K, Stoddart GL, Torrance GW. Methods for the economic evaluation of health care programmes: Oxford university press; 2015.

40. 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): 1093-103.

41. Lopez AD, Murray CC. The global burden of disease, 1990–2020. *Nature medicine* 1998; **4**(11): 1241-3.

42. Dicker D, Nguyen G, Abate D, et al. Global, regional, and national age-sex-specific mortality and life expectancy, 1950–2017: a systematic analysis for the Global Burden of Disease Study 2017. *The lancet* 2018; **392**(10159): 1684-735.

43. Frieden TR. The future of public health. *New England Journal of Medicine* 2015; **373**(18): 1748-54.

44. Viscoli C. Bloodstream infections: the peak of the iceberg. Taylor & Francis; 2016.

45. World Health Organization. Antimicrobial resistance: global report on surveillance: World Health Organization; 2014.

46. Temkin E, Fallach N, Almagor J, et al. Estimating the number of infections caused by antibiotic-resistant Escherichia coli and Klebsiella pneumoniae in 2014: a modelling study. *The Lancet Global Health* 2018; **6**(9): e969-e79.

47. Rudd KE, Johnson SC, Agesa KM, et al. Global, regional, and national sepsis incidence and mortality, 1990–2017: analysis for the Global Burden of Disease Study. *The Lancet* 2020; **395**(10219): 200-11.

48. Akova M. Epidemiology of antimicrobial resistance in bloodstream infections. *Virulence* 2016; **7**(3): 252-66.

49. Hotchkiss RS, Karl IE. The pathophysiology and treatment of sepsis. *New England journal of medicine* 2003; **348**(2): 138-50.

50. Organization WH. Global report on the epidemiology and burden of sepsis: Current evidence, identifying gaps and future directions. 2020.

51. Nagarjuna D, Mittal G, Dhanda RS, Gaind R, Yadav M. Alarming levels of antimicrobial resistance among sepsis patients admitted to ICU in a tertiary care hospital in India-a case control retrospective study. *Antimicrobial Resistance & Infection Control* 2018; **7**(1): 1-11.

52. Cole KA, Rivard KR, Dumkow LE. Antimicrobial stewardship interventions to combat antibiotic resistance: an update on targeted strategies. *Current infectious disease reports* 2019; **21**: 1-10.

53. Mudenda S, Chabalenge B, Daka V, et al. Global strategies to combat antimicrobial resistance: a one health perspective. *Pharmacology & Pharmacy* 2023; **14**(8): 271-328.

54. Dar OA, Hasan R, Schlundt J, et al. Exploring the evidence base for national and regional policy interventions to combat resistance. *The Lancet* 2016; **387**(10015): 285-95.

55. Niewiadomska AM, Jayabalasingham B, Seidman JC, et al. Population-level mathematical modeling of antimicrobial resistance: a systematic review. *BMC medicine* 2019; **17**: 1-20.

56. Trotter AJ, Aydin A, Strinden MJ, O'grady J. Recent and emerging technologies for the rapid diagnosis of infection and antimicrobial resistance. *Current opinion in microbiology* 2019; **51**: 39-45.

57. Salgado CD, O'Grady N, Farr BM. Prevention and control of antimicrobial-resistant infections in intensive care patients. *Critical care medicine* 2005; **33**(10): 2373-82.

58. Simor AE. Staphylococcal decolonisation: an effective strategy for prevention of infection? *The Lancet infectious diseases* 2011; **11**(12): 952-62.

59. World Bank. World Bank Country and Lending Groups. 2024. https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-country-and-lending-groups#:~:text=For%20the%20current%202024%20fiscal,those%20with%20a%20GNI%20per (accessed 26 March 2024).

60. Co-operation OfE, Development. Does Inequality Matter?: How People Perceive Economic Disparities and Social Mobility: OECD Publishing; 2021.

61. Bossert TJ, Leisewitz T. Innovation and change in the Chilean health system. *N Engl J Med* 2016; **374**(1): 1-5.

62. Paraje G, Vásquez F. Health equity in an unequal country: the use of medical services in Chile. *International journal for equity in health* 2012; **11**: 1-16.

63. Ministerio de Salud Chile. Plan Nacional Contra la Resistencia a los Antimicrobianos. https://diprece.minsal.cl/wrdprss_minsal/wp-content/uploads/2017/08/Plan-Nacional-contra-la-resistencia-a-los-antimicrobianos.pdf. (accessed March 26 2024).

64. Otaíza F, Orsini M, Pohlenz M, Tarride T. Informe de Vigilancia de Infecciones Asociadas a la Atención en Salud. *Ministerio de Salud, Departamento de Calidad y Formación Control de IAAS; Minsal: Santiago, Chile* 2017.

65. Bonten M. Selective decontamination of the digestive tract: an answer at last? *Jama* 2022; **328**(23): 2310-1.

66. Woolhouse M, Ward M, Van Bunnik B, Farrar J. Antimicrobial resistance in humans, livestock and the wider environment. *Philosophical Transactions of the Royal Society B: Biological Sciences* 2015; **370**(1670): 20140083.

67. Graham DW, Bergeron G, Bourassa MW, et al. Complexities in understanding antimicrobial resistance across domesticated animal, human, and environmental systems. *Annals of the New York Academy of Sciences* 2019; **1441**(1): 17-30.

68. Booton RD, Meeyai A, Alhusein N, et al. One Health drivers of antibacterial resistance: quantifying the relative impacts of human, animal and environmental use and transmission. *One Health* 2021; **12**: 100220.

69. Byarugaba D. Antimicrobial resistance in developing countries and responsible risk factors. *International journal of antimicrobial agents* 2004; **24**(2): 105-10.

70. Murray CJ, Ikuta KS, Sharara F, et al. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. *The Lancet* 2022; **399**(10325): 629-55.

71. Sedgwick P. Understanding the ecological fallacy. *Bmj* 2015; **351**.

72. Joh HS, Yeats C, Shaw A, et al. Methodological approach to identify and expand the volume of antimicrobial resistance (AMR) data in the human health sector in low-and middle-income countries in Asia: implications for local and regional AMR surveillance systems strengthening. *Clinical Infectious Diseases* 2023; **77**(Supplement_7): S507-S18.

73. Luangasanatip N, Hongsuwan M, Lubell Y, et al. Long-term survival after intensive care unit discharge in Thailand: a retrospective study. *Critical Care* 2013; **17**: 1-10.

74. Williams TA, Dobb GJ, Finn JC, et al. Determinants of long-term survival after intensive care. *Critical care medicine* 2008; **36**(5): 1523-30.

75. Painter C, Faradiba D, Chavarina KK, et al. A systematic literature review of economic evaluation studies of interventions impacting antimicrobial resistance. *Antimicrobial Resistance & Infection Control* 2023; **12**(1): 69.

76. Li J, Zhao Q, Huang K, et al. Linezolid vs. vancomycin in treatment of methicillin-resistant staphylococcus aureus infections: a meta-analysis. *Eur Rev Med Pharmacol Sci* 2017; **21**(17): 3974-9.

77. Coulter S, Merollini K, Roberts JA, Graves N, Halton K. The need for cost-effectiveness analyses of antimicrobial stewardship programmes: A structured review. *International journal of antimicrobial agents* 2015; **46**(2): 140-9.

78. Chen Y, Huang H-B, Peng J-M, Weng L, Du B. Efficacy and safety of ceftazidime-avibactam for the treatment of carbapenem-resistant Enterobacterales bloodstream infection: a systematic review and meta-analysis. *Microbiology Spectrum* 2022; **10**(2): e02603-21.

79. 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. *Emerging Infectious Diseases* 2022; **28**(11).

80. 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. *Clinical Infectious Diseases* 2023; **77**(Supplement_1): S20-S8.

81. Gold MR, Franks P, McCoy KI, Fryback DG. Toward consistency in cost-utility analyses: using national measures to create condition-specific values. *Medical care* 1998; **36**(6): 778-92.

82. 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. *The Lancet Infectious Diseases* 2018; **18**(3): 318-27.

83. Rotarou ES, Sakellariou D. Neoliberal reforms in health systems and the construction of long-lasting inequalities in health care: A case study from Chile. *Health policy* 2017; **121**(5): 495-503.

84. Núñez A, Manzano CA, Chi C. Health outcomes, utilization, and equity in Chile: an evolution from 1990 to 2015 and the effects of the last health reform. *Public Health* 2020; **178**: 38-48.

85. 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. *The Lancet Regional Health–Americas* 2023; **21**.

86. Aguilar GR, Swetschinski LR, Weaver ND, et al. The burden of antimicrobial resistance in the Americas in 2019: a cross-country systematic analysis. *The Lancet Regional Health–Americas* 2023.

87. 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.

88. Allel K, Peters A, Furuya-Kanamori L, et al. Impact of Inappropriate Empirical Antibiotic Therapy on Mortality: A Retrospective Multicentre Cohort Study of Patients with Bloodstream Infections in Chile, 2018-2022. *Available at SSRN 4677015* 2024.

89. Chindelevitch L, Jauneikaite E, Wheeler NE, et al. Applying data technologies to combat AMR: current status, challenges, and opportunities on the way forward. *arXiv preprint arXiv:220804683* 2022.

90. Majumder MAA, Rahman S, Cohall D, et al. Antimicrobial stewardship: Fighting antimicrobial resistance and protecting global public health. *Infection and drug resistance* 2020: 4713-38.

91. Sharma A, Singh A, Dar MA, et al. Menace of antimicrobial resistance in LMICs: Current surveillance practices and control measures to tackle hostility. *Journal of infection and public health* 2022; **15**(2): 172-81.

92. King G, Nielsen R. Why propensity scores should not be used for matching. *Political analysis* 2019; **27**(4): 435-54.

93. 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. *Clinical Infectious Diseases* 2020; **71**(9): e415-e20.

94. Reddy P, Malczynski M, Obias A, et al. Screening for extended-spectrum β-lactamase-producing Enterobacteriaceae among high-risk patients and rates of subsequent bacteremia. *Clinical infectious diseases* 2007; **45**(7): 846-52.

95. Nadimpalli G, O'Hara LM, Pineles L, et al. Patient to healthcare personnel transmission of MRSA in the non–intensive care unit setting. *Infection Control & Hospital Epidemiology* 2020; **41**(5): 601-3.

96. Su C-p, de Perio MA, Cummings KJ, McCague A-B, Luckhaupt SE, Sweeney MH. Case investigations of infectious diseases occurring in workplaces, United States, 2006–2015. *Emerging infectious diseases* 2019; **25**(3): 397.

97. Hernan M, Robins J. Causal inference: What if. boca raton: Chapman & hill/crc. 2020.

98. Lipsitch M, Tchetgen ET, Cohen T. Negative controls: a tool for detecting confounding and bias in observational studies. *Epidemiology* 2010; **21**(3): 383-8.

99. de Kraker ME, Lipsitch M. Burden of antimicrobial resistance: compared to what? *Epidemiologic reviews* 2021; **43**(1): 53-64.

100. Ministry of Health. PLAN NACIONAL CONTRA LA RESISTENCIA A LOS ANTIMICROBIANOS

CHILE 2021-2025, 2020.

101. Organization WH. Antimicrobial resistance and the United Nations sustainable development cooperation framework: Guidance for United Nations Country teams: World Health Organization; 2021.

102. Patel J, Harant A, Fernandes G, et al. Measuring the global response to antimicrobial resistance, 2020–21: a systematic governance analysis of 114 countries. *The Lancet Infectious Diseases* 2023; **23**(6): 706-18.

103. 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 Global Health* 2024; **9**(2): e013205.